

Hazard Analysis and Risk-Based Preventive Controls for Human Food: Draft Guidance for Industry¹

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or we) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact FDA's Technical Assistance Network by submitting your question at <https://www.fda.gov/food/food-safety-modernization-act-fsma/fsma-technical-assistance-network-tan>.

Chapter 12: Control of Chemical Hazards

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¹ This guidance has been prepared by the Human Foods Program at the U.S. Food and Drug Administration.

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12.1 Purpose of this Chapter

This chapter addresses controls for known or reasonably foreseeable ("potential") chemical hazards. These hazards include radiological hazards, pesticide and drug residues, natural toxins, decomposition, unapproved food or color additives, and food allergens,² as specified in 21 CFR 117.130(b)(1)(ii), as well as environmental contaminants (such as toxic elements and dioxin), and hazardous chemicals that can form during food production (process-related contaminants). Depending on the outcome of a hazard analysis, a known or reasonably foreseeable ("potential") chemical hazard could be addressed by a program that includes:

² This chapter does not address preventive controls for those chemical hazards that are food allergen hazards. For specific guidance on control of food allergen hazards, see Chapter 11.

- CGMP³ measures and other prerequisite programs;
- One or more preventive controls (and associated preventive control management components (i.e., monitoring, corrective actions and corrections, verification, and associated records). Preventive controls for chemical hazards could include, as appropriate to the facility and its food products:
 - Process controls – i.e., procedures, practices, and processes to ensure the control of parameters during operations including the maximum or minimum value, or combination of values, to which any parameter must be controlled to significantly minimize or prevent a hazard requiring a process control (see 21 CFR 117.135(c)(1)); and
 - A supply-chain program for those raw materials and other ingredients for which you have identified a chemical hazard that is controlled before receipt of the raw material or other ingredient (see part 117, subpart G),⁴ or
- A combination of CGMP measures and other prerequisite programs and one or more preventive controls (and associated preventive control management components).

Several chapters in this guidance address the chemical hazards that are the subject of this guidance as follows:

- For background and details about chemical hazards, see section 3.4 of draft Chapter 3.⁵
- For help in identifying known or reasonably foreseeable (“potential”) chemical hazards for each type of food manufactured, processed, packed, or held at your facility, see Appendix 1.
- For help in determining, through a hazard analysis, which known or reasonably foreseeable (“potential”) chemical hazards require a preventive control, see draft Chapter 2.
- For a preliminary discussion of preventive controls for chemical hazards, see Chapter 4.
- For an overview of preventive control management components, see Chapter 5.

12.2 General Information About Terms, Abbreviations, and Resources

See the following sections in the “Introduction and General Information Applicable to This Guidance” (hereinafter “Introduction”) of this guidance for terms, abbreviations, and resources as follows:

- Section III.A: Glossary of terms that are used in this guidance and are defined in 21 CFR 117.3;

³ See the Introduction of this guidance and section 12.2 of this chapter for information about abbreviations used in this guidance.

⁴ For comprehensive guidance on how to comply with the requirements of part 117, subpart G for a supply-chain program, including the applicable recordkeeping requirements, see Chapter 15.

⁵ Comments from interested parties on the draft chapters that we made available for public comment in 2016 asked us to discuss the subject matter of draft Chapter 3 (Potential Hazards Associated with the Manufacturing, Processing, Packing, and Holding of Human Food) before discussing the subject matter of draft Chapter 2 (Conducting a Hazard Analysis). Thus, the sequence of these chapters could change when we finalize these chapters. In this draft chapter, when we refer to information published in draft Chapter 2 and draft Chapter 3, we specifically refer to “draft Chapter 2” and “draft Chapter 3.”

- Section III.B: Glossary of terms that are defined for use in this guidance but are not defined in 21 CFR 117.3;
- Section IV: Table of Abbreviations that are used in this guidance,⁶ and
- Section VI: Resources that could be useful in developing and implementing your food safety plan.

We organized the resources in section VI in the Introduction of this guidance in a series of tables as shown in Table 12-1:

Table 12-1 Resource Tables in Section VI in the Introduction of This Guidance

Table No. in Section VI of the Introduction	Table Title
3	FDA Compliance Policy Guides Cited as a Resource in This Guidance
4	FDA Guidance for Industry Cited as a Resource in This Guidance
5	FDA Compliance Programs and Import Alerts Cited as a Resource in This Guidance
6	Standards, Codes of Practice, and Guidelines of the Codex Alimentarius Commission (CAC or “Codex”) Cited as a Resource in This Guidance
7	Resources for Designing Validation Studies
8	Additional Resources Cited in This Guidance

When we cite a resource that is listed in one of the tables in section VI of the Introduction of this guidance, we refer you to the applicable Table in the Introduction for information on how to access the resource. For example, if we cite to “Closer to Zero: Reducing Childhood Exposure to Contaminants from Foods,” we refer you to the additional resources in Table 8 in section VI of the Introduction.

These resources are available as of the date that we make this guidance available. We have verified the website addresses listed for these resources, as of the date that we make the Introduction of this guidance available, but websites are subject to change over time. In addition, the policies, recommendations, and information in these resources can change over time. We recommend that you periodically review websites listing FDA’s Compliance Policy Guides (CPGs), FDA’s Guidance for Industry, FDA’s Compliance Programs and Import Alerts, and relevant international sources, specifically Codex Alimentarius Standards, Codes of Practice, and Guidelines, for new or modified policies, recommendations, and information.

⁶ Examples of common abbreviations that are used within this chapter without describing them when they are first used are CGMP (current good manufacturing practice), HACCP (Hazard Analysis Critical Control Point), PCHF (preventive controls for human food), PCQI (preventive controls qualified individual), and USDA (U.S. Department of Agriculture).

See section 12.16 for a list of resources that are cited in this chapter but not yet included in the draft Introduction of this guidance. We intend to include these resources in the Introduction when we next update it.

12.3 Understand the Chemical Hazard Requiring a Preventive Control

12.3.1 Known or Reasonably Foreseeable (“Potential”) Chemical Hazards

Chemical contamination can occur at any stage in the production of a food. Known or reasonably foreseeable (“potential”) chemical hazards that could be present in raw materials and other ingredients or that could form during food production include:

- Environmental contaminants that can result from natural sources or industrial contamination or be accidentally released during or following a natural or industrial disaster, including:
 - Toxic elements (such as arsenic, cadmium, and lead);⁷ and
 - Substances such as dioxins, perchlorates, per- and polyfluoroalkyl substances (PFAS),⁸ and radionuclides;
- Natural toxins, such as:
 - Mycotoxins, which are toxic metabolites produced by molds that can infect and proliferate on agricultural commodities such as grains (e.g., wheat and corn), peanuts, fruits, and tree nuts in the field and during storage;
 - Hypoglycin A, which is a plant-produced toxin that is found in the unripe fruit of the tropical ackee tree;
- Unlawful pesticide residues;
- Drug residues in food derived from an animal (such as milk and honey);
- Unapproved food or color additives (e.g., due to the use of a food ingredient outside the established conditions of safe use or due to a process contaminant that forms under certain manufacturing processes).
- Chemicals that are intentionally introduced for purposes of economic gain. Known examples include:
 - Lead salts (such as lead chromate in cinnamon and turmeric and lead oxide in paprika) added to spices to increase their weight and enhance their color, in an attempt to increase the monetary value of the adulterated spices;
 - Melamine in milk to increase the apparent protein content; and
 - Sudan I in chili powder to enhance color;

⁷ Mercury is another environmental contaminant that is a toxic element. This chapter does not address mercury, which is principally a hazard in seafood products that are not covered by this guidance.

⁸ The draft Chapter 3 that we made available for public comment in 2016 did not discuss perchlorates and PFAS. When we finalize that chapter, we intend to include perchlorates and PFAS as examples of environmental contaminants. We also intend to discuss the requirement of section 410(b)(1) of the FD&C Act (21 U.S.C. 349(b)(1)) that, not later than 180 days before the effective date of a National Primary Drinking Water Regulation issued by EPA for a contaminant under section 1412 of the Safe Drinking Water Act (42 U.S.C. 300g-1), FDA is required to issue a standard of quality regulation for that contaminant in bottled water, or make a finding that such a regulation is not necessary to protect the public health because the contaminant is contained in water in public water systems but not in water used for bottled water. For additional requirements applicable to bottled water, see 21 CFR 165.110.

- Process-related chemical hazards that have the potential to be produced during food production, particularly at high temperature, such as:
 - 3-monochloropropane-1,2-diol esters (3-MCPDEs) and glycidyl esters (GEs) formed in certain refined oils;
 - 3-monochloropropane-1,2-diol (3-MCPD)⁹ in acid-hydrolyzed protein and Asian-style sauces;
 - 4-methylimidazole (4-MEI) formed as a byproduct during the manufacturing of certain types of caramel coloring (known as Class III and Class IV caramel coloring); and
 - acrylamide in certain plant-based foods; and
- Facility-related chemical hazards (e.g., cleaning chemicals).

12.3.2 FDA Resources Applicable to Chemical Hazards

We recommend that you periodically review our websites that provide new or updated information about current and emerging chemical contaminants. These resources are available for your use in supporting decisions made in your hazard analysis (including decisions about whether a chemical hazard could be managed through CGMPs and other prerequisite programs) as well as your identification and implementation of preventive controls for a chemical hazard in your food or facility. These resources include:

- Tables 3 and 4 in section VI of the Introduction of this guidance identify CPGs and Guidances for Industry that are most relevant to chemical hazards and are available as of the date that this chapter is made available. Some CPGs and Guidances for Industry that FDA has made available specific contaminant levels, such as “action levels,”¹⁰ for specific chemical hazards in specific commodities.¹¹ An action level is a level of contamination at

⁹ Another chemical name for 3-MCPD is 3-chloro-1,2-propanediol (see CPG Sec. 500.500 Guidance Levels for 3-MCPD(3-chloro-1,2-propanediol) in Acid-Hydrolyzed Protein and Asian-Style Sauces; Table 3 in section VI of the Introduction of this guidance).

¹⁰ In this chapter, “contaminant levels” include action levels, guidance levels, advisory levels, or other levels FDA has established through guidance. For example, our guidance for industry regarding inorganic arsenic in rice cereals for infants uses the term “action level,” whereas our guidance for industry regarding the mycotoxin deoxynivalenol (DON) uses the term “advisory level” to discuss levels of DON in wheat and wheat-derived products that would not appear to present a public health hazard (see Table 4 in section VI of the Introduction of this guidance). In other cases, a guidance document describes a policy in which FDA may regard food as adulterated within the meaning of section 402(a)(1) of the FD&C Act (21 U.S.C. 342(a)(1)) due to the presence of a chemical contaminant without specifying that the level is an “action level” (see, e.g., our CPG Sec. 555.400 for aflatoxins in human food in Table 3 in section VI of the Introduction of this guidance). We also refer to “maximum levels (MLs)” set by the CAC for chemical hazards; Codex MLs for contaminants and natural toxicants in food and feed are levels recommended by the CAC to be applied to commodities moving in international trade.

¹¹ FDA has not established contaminant levels for toxic elements in most foods. FDA assesses the safety of contaminants in foods on a case-by-case basis. Under the FD&C Act, a food is deemed to be adulterated if it bears or contains any added poisonous or deleterious substance which may render it injurious to health (21 U.S.C. 342(a)(1)). If a chemical contaminant, such as a toxic element, is detected in a food, FDA will review the relevant information to determine whether the levels of that contaminant found in that food may pose a health hazard, such that the food is deemed to be adulterated under the

which a food may be regarded as adulterated within the meaning of section 402(a)(1) of the FD&C Act (see 21 CFR 109.6(d)). FDA considers action levels, in addition to other factors and scientific evidence, when considering whether to bring enforcement action in a particular case.

- Our website titled “Chemical Contaminants & Pesticides” (see Table 8 in section VI of the Introduction of this guidance) describes our efforts to help safeguard the U.S. food supply (domestic and import) by monitoring chemical contaminants. Some of these chemical contaminants (such as mycotoxins in some raw agricultural commodities (RACs), and environmental contaminants such as dioxins and PCBs) have been the subject of scientific research and monitoring for many years. We include information about emerging chemical contaminants on this website or related websites when we begin to monitor such chemical contaminants.
- Our website titled “Closer to Zero - Reducing Childhood Exposure to Contaminants from Foods” (abbreviated in the remainder of this chapter as “Closer to Zero”; see Table 8 in section VI of the Introduction of this guidance) identifies actions FDA will take to reduce exposure to toxic elements from foods eaten by babies and young children to as low as possible. FDA prioritized babies and young children because their smaller body sizes and metabolism make them more vulnerable to the harmful effects of these contaminants. “Closer to Zero” builds on actions, by FDA and our stakeholders, that already have led to meaningful reductions in exposure to toxic elements and outlines a science-based, iterative approach for achieving continual improvements over time. Over time, the steps described in “Closer to Zero” could lead to setting additional action levels for toxic elements.
- Our website titled “FDA Total Diet Study (TDS)” (see Table 8 in section VI of the Introduction of this guidance) describes a longstanding program to monitor levels of nutrients (e.g., calcium and iron) and contaminants (e.g., toxic elements and pesticide residues) in foods eaten by people in the United States. We buy the foods from the same retail outlets as U.S. consumers and prepare the foods as consumers typically would, to provide realistic estimates of what is in the foods consumers eat. The ongoing nature of the study enables us to track trends in the average U.S. consumer’s diet and inform the development of interventions to reduce or minimize risks, when needed.
- Tables 3 and 8 in section VI of the Introduction of this guidance identify resources applicable to pesticide residues.
- Table 5 in section VI of the Introduction of this guidance identifies examples of Import Alerts as resources, applicable to chemical hazards, regarding food produced outside of the United States and offered for import. Import alerts inform the FDA’s field staff and the public that the Agency has enough evidence to allow for Detention Without Physical Examination (DWPE) of products that appear to be in violation of the FDA’s laws and regulations. These violations could be related to the product, manufacturer, shipper, and/or other information.
- Table 5 in section VI of the Introduction of this guidance identifies resources, applicable to chemical hazards, that are available in FDA’s current Compliance Programs. FDA’s

FD&C Act and subject to enforcement actions (e.g., seizure of domestic foods in interstate commerce and refusal of entry for imported foods). As part of this case-by-case assessment, FDA typically considers information such as:

- the levels of the contaminant found in that food;
- the type of food;
- the consumption of that food; and
- the most currently available toxicological information for that contaminant.

Compliance Programs provide instructions to FDA personnel for conducting activities to evaluate industry compliance with the FD&C Act, its implementing regulations, and other laws administered by FDA. We make our Compliance Programs available to the public on our website.

- Table 8 in section VI of the Introduction of this guidance identifies our website that is a resource regarding animal drug residues and enables you to search for approved animal drugs.
- Draft Chapter 3 discusses the statutory framework for lawful use of food ingredients. Resources that are available to you if you have questions about the regulatory status of a particular food substance when formulating your food products include:
 - Food and color additive regulations. The most relevant regulations are in:
 - 21 CFR part 70: Color Additives
 - 21 CFR part 73: Listing of Color Additives Exempt from Certification
 - 21 CFR part 74: Listing of Color Additives Subject to Certification
 - 21 CFR part 170: Food Additives
 - 21 CFR part 172: Food Additives Permitted for Direct Addition to Food for Human Consumption
 - 21 CFR part 173: Secondary Direct Food Additives Permitted in Food for Human Consumption
 - The Color Additive Status List and the Food Additive Status List (see Table 8 in section VI of the Introduction of this guidance).
 - Lists of substances that are used in food under the GRAS provisions of the FD&C Act, including:
 - 21 CFR part 182: Substances Generally Recognized as Safe
 - 21 CFR part 184: Direct Food Substances Affirmed as Generally Recognized as Safe
 - GRAS Notice Inventory (see Table 8 in section VI of the Introduction of this guidance).
 - Regulations identifying food and color additives that are specifically prohibited from use in food:
 - 21 CFR part 189: Substances Prohibited from Use in Human Food
 - 21 CFR 81.10: Termination of Provisional Listings of Color Additives.
 - Our website “Post-market Determinations that the Use of a Substance is Not GRAS” (see Table 8 in the Introduction of this guidance)
 - Our website “Human Food Made with Cultured Animal Cells Inventory” (see Table 8 in the Introduction of this guidance);
 - “Guidance for Industry: Antimicrobial Food Additives” in section VI of the Introduction of this guidance, which discusses FDA’s jurisdiction over antimicrobials that are used in or on food.

12.3.3 International Resources Applicable to Chemical Hazards

The CAC was formed in 1963 to develop food standards, guidelines, and related texts such as Codes of Practice, and is recognized under the World Trade Organization Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) as the international standards organization for food safety. The CAC receives scientific advice in reports from standing and ad hoc committees. These documents could be helpful resources in supporting decisions made in your hazard analysis (including decisions about whether the chemical hazard could be managed through CGMPs) as well as your identification and implementation of preventive controls for a chemical hazard in your food, particularly if FDA has not provided relevant information for that chemical hazard-food pair.¹²

See Table 6 in section VI of the Introduction of this guidance for those international documents (such as Codes of Practice) that are most relevant to the prevention and reduction of chemical contaminants in food. For example, these Codes of Practice provide recommendations for the prevention and/or reduction of chemical contaminants such as acrylamide, arsenic, cadmium, lead, 3-MCPDE, and GE, and mycotoxins (such as aflatoxin, deoxynivalenol (DON), and ochratoxin) in certain foods. These Codes of Practice could supplement guidances and other information FDA has provided with respect to supporting measures (such as preventive controls) that significantly minimize or prevent chemical hazards.

See Table 6 in section VI of the Introduction of this guidance for the Codex General Standard for Contaminants and Toxicants in Food and Feed, CXS 193-1995. This general standard may be helpful for use as a guide for determining your specifications for levels of chemical contaminants in foods when FDA has not established a contaminant level for a particular chemical contaminant in a particular food or group of foods. Importantly, a contaminant level for a particular chemical contaminant in a particular food or group of foods established by FDA is the relevant contaminant level rather than a maximum level (ML) established by the CAC.

12.3.4 Factors to Consider in Evaluating Whether a Known or Reasonably Foreseeable (“Potential”) Chemical Hazard Can Be Effectively Managed Through Application of CGMPs or Is a Hazard Requiring a Preventive Control

Following CGMPs is sometimes called a “prerequisite program” (NACMCF, 1998) to signify that the measures that you take to comply with the CGMP requirements should be in place before you conduct your hazard analysis and identify risk-based preventive controls to address specific hazards. The preventive controls that you identify and implement to control chemical hazards should complement and enhance the measures you have in place to comply with the CGMP requirements to protect against contamination of food with chemical hazards. CGMP measures can be enhanced by the addition of preventive control management components to function as a preventive control.

Your hazard analysis should consider which known or reasonably foreseeable (“potential”) hazards can be effectively managed through the application of CGMPs and other prerequisite programs, and which hazards require one or more preventive controls. Factors that you should consider during your hazard analysis include:

¹² Reference to these documents is provided for informational purposes only. These documents are not incorporated by reference into this guidance and are not FDA guidance.

- information about the known or reasonably foreseeable (“potential”) hazards;
- information about the food and the production process, including:
 - association of the type of food with illness or injury due to the hazard (e.g., outbreaks or recalls associated with the food);
 - the sources of raw materials and other ingredients (e.g., knowledge or experience with a supplier’s history and performance);
 - information about the manufacturing process, including:
 - formulation of the food;
 - handling of the food during production;
 - the condition, function, and design of the facility and equipment;
 - the steps followed to prepare the finished product, the control measures applied during those steps, and the impact of those control measures on the hazard; and
 - the reasonably foreseeable use of the food, including consumption by vulnerable populations; and
 - the PCQI’s judgement about whether and how control of the hazard would benefit from preventive control management components (i.e., monitoring, corrective actions and corrections, verification, and associated records);
- the probability that a known or reasonably foreseeable (“potential”) hazard will occur in the absence of preventive controls, which may be informed by:
 - knowledge of the history of the production of the food at the facility, e.g., past lapses¹³ in the application of control measures (such as CGMPs or other prerequisite programs);
 - testing results related to identification of a hazard in the food;
 - an understanding of actions taken to comply with other applicable requirements, such as:
 - USDA’s marketing orders pertaining to mold in general, or mycotoxin hazards in particular, in several RACs; and
 - regulations issued by FDA’s Center for Veterinary Medicine (CVM) pertaining to chemical hazards in feed for food-producing animals; and
 - an understanding of participation in programs such as:
 - the Grade “A” Pasteurized Milk Ordinance (PMO) under the FDA program of the National Conference on Interstate Milk Shipments (NCIMS) pertaining to chemical hazards in dairy products; and
 - USDA’s voluntary programs for grading grain RACs relevant to quality defects, including those consistent with a higher probability of mycotoxin presence (e.g., mold-, insect- or weather-damaged kernels); and
- the severity of the illness or injury if the hazard were to occur.

During reanalysis of your food safety plan in accordance with 21 CFR 117.170, we recommend that you consider any regulatory action by FDA (e.g., regarding contaminant levels) that could lead to changes in the specifications that you set for contaminants and whether such changes impact your evaluation of which known or reasonably foreseeable (“potential”) hazards can be

¹³ Measures that you could use to assess past lapses in the application of CGMP measures include the frequency of reprocessing, reworking, diverting to a use that does not present a safety concern, or destroying the food and the frequency of product recalls.

effectively managed through the application of CGMPs and other prerequisite programs, and which hazards require one or more preventive controls.

12.3.5 Evaluating Environmental Contaminants

Environmental contaminants (such as toxic elements (e.g., arsenic, cadmium, and lead), dioxins, perchlorates, PFAS, and radionuclides) generally are geographically localized as a result of natural occurrence, industrial contamination, or accidental release during or following a natural or industrial disaster.

We recommend that you address environmental contaminants through avoidance whenever possible. For example, you should be able to avoid sourcing food ingredients from geographically localized sites that have been contaminated following a natural or industrial disaster or as a result of limited industrial contamination (e.g., industrial contamination that affected a limited geographic area). When the location of these sites is well known, you could avoid sourcing an ingredient from the affected areas without identifying the environmental contaminant as a hazard requiring a supply-chain program as a preventive control.

In some cases, environmental contaminants are present over a relatively wide geographic area due to natural occurrence and ongoing industrial contamination, including contamination from multiple sources. For example, this is the case for toxic elements in some areas where RACs are grown. In evaluating whether an environmental contaminant in a RAC used as an ingredient could be a hazard requiring a preventive control, we recommend that you consider:

- the factors we identified in section 12.3.4; and
- the intended consumer. A priority for FDA is reducing dietary exposure to contaminants to as low as possible, while maintaining access to nutritious food (see our Closer to Zero website, Table 8 in section VI of the Introduction of this guidance). FDA has prioritized foods commonly eaten by babies and young children because their smaller body sizes and metabolism make them more vulnerable to the harmful effects of these contaminants. If you manufacture foods intended for babies and young children, we recommend that you identify applicable toxic elements that are known or reasonably foreseeable (“potential”) hazards in ingredients of such foods as hazards requiring a supply-chain program as a preventive control. See sections 12.10 and 12.11 for examples of how to do so.

12.3.6 Evaluating Natural Toxins

The PCHF requirements specify that you must consider, as part of your hazard identification, known or reasonably foreseeable (“potential”) chemical hazards that include natural toxins (see 21 CFR 117.130(b)(1)(ii)).

12.3.6.1 Evaluating mycotoxins

Mycotoxins are toxic metabolites produced by molds that can infect and proliferate on RACs such as grains (e.g., wheat and corn), peanuts, fruits, and tree nuts in the field and during storage. Mycotoxin hazards are generally addressed through a combination of modern agricultural and processing practices, particularly during storage (on farms and in food processing facilities). For several RACs, marketing orders established by USDA’s Agricultural Marketing Service (AMS) include provisions to assess the potential presence of mold in general

or aflatoxin in particular and restrict the marketing of commodities that do not satisfy mold-related criteria or aflatoxin-related criteria in the marketing order. For example:

- For domestic and imported peanuts marketed in the United States, the marketing order in 7 CFR part 996 includes outgoing quality standards for shelled peanuts (see 7 CFR 996.31) requiring results certified as “negative” for aflatoxin following laboratory analysis before shipping or otherwise disposing of shelled peanuts for human consumption.
- Marketing orders and import regulations applicable to pistachios do not allow shipment for domestic human consumption of pistachios that exceed a specified aflatoxin level and require all shipments to be covered by an aflatoxin inspection certificate (see 7 CFR 983.150 for “aflatoxin regulations” for pistachios grown in California, Arizona, and New Mexico and 7 CFR 999.600 for import regulations applicable to aflatoxin in imported pistachios).
- For almonds grown in California, the marketing order in 7 CFR part 981 includes a definition (see 7 CFR 981.8) for an inedible kernel, in part, as a kernel, piece, or particle of almond kernel with any defect scored as damage due to mold. Additional provisions of 7 CFR part 981 establish quality control requirements for determining and disposing of inedible kernels (see 7 CFR 981.42 and 981.442).
- For hazelnuts grown in Oregon and Washington, the marketing order in 7 CFR part 982 includes grade requirements (see 7 CFR 982.101) specifying that hazelnut kernels or portions of hazelnut kernels must be free from mold.

For grains, applicable control measures include collection of samples for evaluation of grain quality and for the potential for contamination with mycotoxins. The Federal Grain Inspection Service (FGIS) of the USDA AMS sets standards for U.S. grain grades and grade requirements and oversees a voluntary (fee-for-service) national inspection system applicable to grains (see 7 CFR part 810).¹⁴ Grades and grade requirements for grains address defects that are consistent with a higher probability of mycotoxin presence (such as the presence of kernels that have been damaged by mold, insects, or weather). Under the voluntary national inspection system, food producers can request grading of grain and specify a certain grade in purchase agreements. For example, U.S. No. 1 grade wheat has the lowest maximum percent limits for damaged kernels (see 7 CFR 810.2204). In addition, under the authority of the United States Grains Standards Act (7 U.S.C. 71-87k), as amended, and the Agricultural Marketing Act of 1946 (7 U.S.C. 1621-1627), as amended, AMS provides official mycotoxin testing services throughout the United States for domestic and export grains, oilseeds, and processed-grain commodities. Official testing services are provided for aflatoxins, DON, fumonisins, ochratoxin A, and zearalenone.¹⁵

¹⁴ See also “Overview of U.S. Wheat Inspection,” a booklet printed in 2021 by U.S. Wheat Associates in cooperation with USDA/AMS/FGIS to provide information on the national, official grain inspection and weighing system used in the United States. Available at <https://www.uswheat.org/wp-content/uploads/Overview-of-U.S.-Wheat-Inspection.pdf>.

¹⁵ Testing at field locations requires rapid, inexpensive, and accurate methods to effectively assess U.S. grain quality. An essential part of ensuring the quality of official mycotoxin testing is the AMS test kit evaluation program, through which test kits are evaluated and certified for conformance to specific criteria. Only test kits having AMS certification are approved for official mycotoxin testing. AMS establishes the test kit performance criteria and periodically updates them to improve testing accuracy and to meet the official mycotoxin testing program's operational needs (87 FR 67859, November 10, 2022).

In evaluating whether a mycotoxin hazard in a RAC ingredient could be a hazard requiring a preventive control, we recommend that you consider factors such as the factors we identified in section 12.3.4.

12.3.6.2 Evaluating plant-produced toxins

Some plants naturally produce toxins. For example, the toxin hypoglycin A is found at high levels in the unripe fruit of the tropical ackee tree. Ingestion of hypoglycin A may result in no symptoms or symptoms that range from mild (e.g., some vomiting) to severe (e.g., vomiting with profound hypoglycemia, drowsiness, muscular exhaustion, prostration, and possibly coma and death). When ackee is fully ripe, the hypoglycin A drops to negligible levels in the fruit (other than the rind and seeds, which should not be consumed). If the fruit is not properly processed, the finished product could contain more than a negligible level of hypoglycin A and could pose a health risk. In a CPG issued in 2014, FDA determined that canned ackee, frozen ackee, or other ackee products containing concentrations of hypoglycin A above 100 ppm have not been processed properly and that finished product may be injurious to health. For more information about the processing of ackee, see our CPG 550.050 Canned Ackee, Frozen Ackee, and Other Ackee Products – Hypoglycin A Toxin (see Table 3 in section VI of the Introduction of this guidance). As discussed in that CPG, key control measures for hypoglycin A begin with selection of fruit that is ripe, followed by removal of rind, seeds, and raphe before processing.

In evaluating whether a plant-produced toxin in an ingredient could be a hazard requiring a preventive control, we recommend that you consider the factors we identified in section 12.3.4.

12.3.7 Evaluating Pesticide Residues

The PCHF requirements specify that you must consider, as part of your hazard identification, known or reasonably foreseeable (“potential”) chemical hazards that include pesticide residues (see 21 CFR 117.130(b)(1)(ii)). Pesticide residues could be present in food crops and in foods of animal origin (e.g., as a result of pesticide residues in animal food) (see draft Chapter 3). The U.S. EPA registers the use of pesticides and may establish tolerances for pesticide chemical residues that could remain in or on food (see 40 CFR part 180). A detailed description of how FDA enforces pesticide tolerances in human and animal food is available in our 1995 CPG Sec. 575.100 Pesticide Residues in Food and Feed – Enforcement Criteria¹⁶ (see Table 3 in section VI of the Introduction of this guidance) and on FDA’s pesticide monitoring website (see Table 8 in section VI of the Introduction of this guidance)¹⁷. FDA monitors levels of pesticide residues in the U.S. food supply and publishes an annual report summarizing the findings from this monitoring each year (see Table 8 in section VI of the Introduction of this guidance).

¹⁶ The regulation of food containing pesticide chemical residues is governed by sections 201, 402, and 408 of the FD&C Act (21 U.S.C. 321, 342, and 346a, respectively). These sections of the FD&C Act were amended by the passage of the Food Quality Protection Act of 1996 (FQPA, Pub. Law 104–107). In 2008, FDA issued as draft guidance a revised CPG Sec. 575.100 that, when finalized, will represent FDA’s current thinking on enforcement criteria for pesticide residues in food and feed, taking into account the provisions of the FQPA.

¹⁷ See also our 2009 Memorandum of Understanding with USDA (FSIS and AMS) and EPA regarding regulatory activities concerning residues of drugs, pesticides, and environmental contaminants in foods (MOU 225-85-8400). Available at <https://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm116368.htm>.

In evaluating whether a pesticide hazard in a food ingredient could be a hazard requiring a preventive control, we recommend that you consider:

- the factors we identified in section 12.3.4; and
- whether the food has a history of violative pesticide residues. For commodities associated with violative pesticide residues in domestic and imported foods, see:
 - U.S. Food and Drug Administration regulatory pesticide residue monitoring of human foods: 2009-2017, Food Additives & Contaminants: Part A (Liang et al., 2021);
 - FDA's Pesticide Residue Monitoring Program Reports and Data (Table 8 in section VI of the Introduction);
 - Import Alert 99-05 Detention Without Physical Examination of Raw Agricultural Products for Pesticides (which applies to specific growers) (Table 5 in section VI of the Introduction¹⁸);
 - Import Alert 99-08 Detention without Physical Examination of Processed Human and Animal Foods for Pesticides (which applies to specific commercial entities) (Table 5 in section VI of the Introduction);
 - Import Alert 99-14 Countrywide Detention Without Physical Examination of Raw Agricultural Products for Pesticides (which applies to countries rather than to specific commercial entities) (Table 5 in section VI of the Introduction); and
 - Import Alert 99-15 (Countrywide Detention Without Physical Examination of Processed Foods for Pesticides) (Table 5 in section VI of the Introduction).

12.3.8 Evaluating Residues of Animal Drugs

The PCHF requirements specify that you must consider, as part of your hazard identification, known or reasonably foreseeable ("potential") chemical hazards that include drug residues (see 21 CFR 117.130(b)(1)(ii)). A hazard analysis for drug residues should consider factors such as whether a tolerance has been established for the particular drug-food combination, and whether a tolerance level has been exceeded (see draft Chapter 3). Animal drugs used according to label directions, regulations, and veterinary directives should not result in residues that exceed the tolerances established for the drugs in animal-derived food products such as meat, milk, or egg products. Note that extra-label uses of certain drugs (e.g., the use of antibiotics such as chloramphenicol, nitrofurantoin drugs, or fluoroquinolone drugs in honeybees) are prohibited for therapeutic purposes and only allowed in narrow circumstances.¹⁹ Such antibiotics have been detected in honey and blended syrup products (see Import Alert 36-04).

In evaluating whether a drug residue in an animal-derived ingredient could be a hazard requiring a preventive control, we recommend that you consider:

- the factors we identified in section 12.3.4; and

¹⁸ Table 5 in the draft Introduction that we made available for public comment in 2024 did not include Import Alerts 99-05, 99-08, 99-14, and 99-15. We intend to include these import alerts in that table when we next update the Introduction. To find a list of FDA import alerts, please visit Search for Import Alerts at <https://www.fda.gov/industry/import-alerts/search-import-alerts>.

¹⁹ See 21 CFR 530.21, 530.25, and 530.41.

- Import Alert 36-04 Detention Without Physical Examination of Honey and Blended Syrup Due to Unsafe Drug Residues.

12.3.9 Evaluating Unapproved Food Additives or Color Additives

The PCHF requirements specify that you must consider, as part of your hazard identification, known or reasonably foreseeable (“potential”) chemical hazards that include unapproved food additives or color additives (see 21 CFR 117.130(b)(1)(ii)). See draft Chapter 3 for a discussion of the statutory framework for lawful use of food ingredients. Generally, the safety of food ingredients is established under specific conditions of use, such as a maximum level of use or use only in certain food categories, before the ingredients are used in the manufacturing or processing of human food in accordance with part 117. With certain exceptions, substances used in the manufacturing or processing of food that are not authorized for their use as food additives by FDA or are not generally recognized by qualified experts as safe (GRAS) for their use (as demonstrated through either scientific procedures or, for substances used in food before 1958, through either scientific procedures or experience based on common use in food) are unapproved food additives. In some cases, FDA has determined that a substance is not GRAS for use as an ingredient in food (see, e.g., FDA’s memorandum “Regulatory status and review of available information pertaining to tara protein/flour derived from the seed germ of the plant, *Caesalpinia spinosa*: lack of general recognition of safety for its use in foods” (FDA, 2024b)). In other cases, FDA has determined that a process contaminant that forms above a specified level in a food product during production causes the original ingredient to not be GRAS and, therefore, it is an unsafe food additive (see, e.g., CPG 500.500, Guidance Levels for 3-MCPD (3-chloro-1,2-propanediol) in Acid-Hydrolyzed Protein and Asian-Style Sauces, Table 3 in section VI of the Introduction of this guidance).²⁰

In evaluating whether the potential for an unapproved food additive or color additive is a hazard requiring a preventive control, we recommend that you consider the resources we identified in section 12.3.2 and factors we identified in section 12.3.4.

12.3.10 Evaluating Biogenic Amines in Animal-derived Foods

The PCHF requirements specify that you must consider, as part of your hazard identification, known or reasonably foreseeable (“potential”) chemical hazards that include decomposition (see 21 CFR 117.130(b)(1)(ii)). Biogenic amines, such as histamine produced from the breakdown of the amino acid histidine, are the most common example of a decomposition product. Biogenic amines are most commonly associated with seafood (which is generally covered by the Seafood HACCP regulation²¹ and not covered by preventive controls requirements in part 117). In foods other than seafood, biogenic amines are principally associated with certain cheeses (particularly aged cheeses) and generally managed through practices that minimize the potential for growth and histamine production by undesirable microorganisms.

In evaluating whether biogenic amines in a cheese product could be a hazard requiring a preventive control, we recommend that you consider the factors we identified in section 12.3.4.

²⁰ Note that we also discuss 3-MCPD as a process contaminant in acid-hydrolyzed protein and Asian-style sauces in section 12.3.12, which discusses process contaminants more broadly.

²¹ 21 CFR Part 123; Procedures for the Safe and Sanitary Processing and Importing of Fish and Fishery Products (Seafood HACCP regulation).

12.3.11 Evaluating Substances Introduced for 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)).

In evaluating whether a chemical contaminant introduced for economic gain could be a hazard requiring a preventive control, we recommend that you:

- consider the factors we identified in section 12.3.4; and
- 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.²² For example:
 - Lead salts have been illegally added to certain spices to increase their weight and enhance their color, in an attempt to increase the monetary value of the adulterated spices (Cowell et al., 2017). In 2023, FDA, along with CDC and state and local partners, began investigating reports of elevated blood lead levels in individuals with reported exposure to certain cinnamon-containing applesauce products (CDC, 2024). Investigations pointed to cinnamon used in these products as the likely source of contamination. In FDA's testing of affected products and the cinnamon used in the products, FDA found very high levels of lead and chromium and determined that the lead and chromium are from lead chromate (FDA, 2024a). As of the date of this guidance, FDA's leading hypothesis is that this was likely an act of economically motivated adulteration.
 - Milk firms in one country added melamine, a nitrogen-rich industrial by-product, to diluted dairy products to increase the apparent protein content (see Table 8 in section VI of the Introduction of this guidance).
 - The United Kingdom Food Standards Agency has documented a timeline (ranging from May 2003 through February 2005) for adulterated chili products containing Sudan I, an orange-red solid organic chemical, classified as an azo dye, that has carcinogenic properties (United Kingdom Food Standards Agency, 2005).

12.3.12 Evaluating Process-related Contaminants

12.3.12.1 3-MCPDEs and GEs

The process-related chemical hazards 3-MCPDEs and GEs are contaminants that can occur in edible oils and foods made from these oils (see Table 8 in section VI of the Introduction of this guidance).²³ Refined oils are often a major component of infant formula. Following a risk

²² See the resources applicable to "food fraud" that we list in Table 8 in section VI of the Introduction of this guidance. See also Import Alert 99-47 (Detention Without Physical Examination of Human Food Products That Appear to be Adulterated for Economic Gain; Table 5 in section VI of the Introduction). In addition, Table 3-8 in draft Chapter 3 of this guidance is a quick reference guide listing circumstances where there has been a pattern of such adulteration in the past.

²³ The draft Chapter 3 that we made available for public comment in 2016 did not discuss 3-MCPDE and

assessment by JECFA, the CAC, in which FDA participates, developed recommendations for industry on reducing 3-MCPDE and GE in refined oils, particularly when used in infant formula (see Table 6 in section VI of the Introduction). In evaluating 3-MCPDE and GE levels in refined oils and foods that include refined oils as ingredients, FDA has focused much of its testing efforts on infant formula because infants are a vulnerable population, infant formula contains relatively large amounts of oil (about 25-30%) to support infants' nutritional needs, and, for some infants, infant formula is a sole food source. Because of the combined efforts of industry and FDA, average 3-MCPDE and GE levels in infant formula in the United States have declined over the last several years.

In evaluating whether 3-MCPDEs or GEs could be a hazard requiring a preventive control (e.g., a process control for a food that you manufacture, or a supply-chain control for a food that you use as a raw material or other ingredient), we recommend that you consider:

- the factors identified in section 12.3.4; and
- the potential that your refined oil could be used as an ingredient in infant formula.

12.3.12.2 3-MCPD in acid-hydrolyzed protein and Asian-style sauces

The process-related chemical hazard 3-MCPD²⁴ is a contaminant that can occur in acid-hydrolyzed protein and Asian-style sauces (see section 12.3.9 and CPG Sec. 500.500; Table 3 in section VI of the Introduction of this guidance).

- Acid-hydrolyzed protein (acid-HP) is prepared by the hydrolysis of proteins by heat and food-grade acids. During the production of acid-HP, the reaction of hydrochloric acid (HCl) with residual fat in the protein starting material may form 3-MCPD, a member of a group of chemicals known as chloropropanols, which have been identified as carcinogens. The manufacturing process for acid-HP can be modified to reduce the levels of 3-MCPD that are formed (see Codex Code of Practice for the Reduction of 3-Monochloropropane-1,2-Diol During the Production of Acid-HVPs and Products That Contain Acid-HVPs, CXC 64-2008, Table 6 in section VI of the Introduction of this guidance).
- Acid-HP can be added to soybeans and other ingredients to produce soy sauce that does not undergo a traditional fermentation process, added to fermented sauces to enhance the flavor of the sauce, and used as an ingredient in other Asian-style sauces. In some cases, HCl may be added directly to soybeans to make soy sauce, so that acid-HP is formed during production of the soy sauce. Adding HCl directly to soybeans can result in reactions with residual fat to generate chloropropanols unless the processing conditions are well controlled. A range of techniques can be used in the manufacture of soy sauces. Generally, products made exclusively by means of fermentation do not contain chloropropanols, or, if present, they only occur in trace amounts (see Codex Code of Practice for the Reduction of 3-Monochloropropane-1,2-Diol During the Production of Acid-HVPs and Products That Contain Acid-HVPs, CXC 64-2008, Table 6 in section VI of the Introduction of this guidance).

GE. When we finalize that chapter, we intend to reference the information on FDA's website regarding 3-MCPDE and GE.

²⁴ Chemical names for 3-MCPD include 3-chloro-1,2-propanediol (as specified in CPG Sec. 500.500), 3-monochloropropane-1,2-diol, and 3-chloropropane-1,2-diol.

In evaluating whether 3-MCPD is a hazard requiring a preventive control (e.g., a process control for a food that you manufacture, or a supply-chain control for a food that you use as a raw material or other ingredient), we recommend that you consider the factors identified in section 12.3.4.

12.3.12.3 4-methylimidazole (4-MEI)

The chemical 4-MEI can form as a byproduct during the manufacturing of certain types of caramel coloring (known as Class III and Class IV caramel coloring), which are commonly used color additives. The results of toxicological studies conducted in rodents using levels of 4-MEI that far exceed current estimates of human exposure to 4-MEI from the consumption of food have shown that 4-MEI can cause adverse effects when present at high levels (NTP, 2007). These studies include a 2-year study in rats (which was inconclusive regarding carcinogenicity), a 2-year study in mice (which showed an increased incidence of certain lung tumors), and a multi-generation reproductive and developmental study on 4-MEI in rats (which showed reproductive and developmental effects in male and female rats) (see List of Select Chemicals in the Food Supply Under FDA Review, Table 8 in section VI of the Introduction of this guidance).

FDA is currently reviewing all available data on the safety of 4-MEI. In 2018, FDA published an assessment of potential consumer exposure to 4-MEI from the use of Class III and Class IV caramel coloring in food products (Folmer et al., 2018). FDA's current review, along with this exposure assessment, will help FDA determine what, if any, regulatory action needs to be taken. Such actions could include setting a limit on the amount of 4-MEI that can be present in Class III and IV caramel coloring.

In evaluating whether 4-MEI can be a hazard requiring a preventive control (e.g., a process control for a food that you manufacture, or a supply-chain control for a food that you use as a raw material or other ingredient), we recommend that you consider:

- the factors identified in section 12.3.4; and
- current information about manufacturing controls to reduce exposure to 4-MEI due to its presence in Class III and IV caramel coloring.

12.3.12.4 Acrylamide

The process-related chemical hazard 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. Acrylamide in food is a concern because it can cause cancer in laboratory animals at high doses and is “reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals” (National Toxicology Program, 2011). In 2010, an international evaluation of acrylamide by JECFA concluded that acrylamide may be “a human health concern” (JECFA, 2011b). Reducing acrylamide levels in foods may mitigate potential human health risks from exposure to acrylamide. For additional information about acrylamide and measures to reduce acrylamide in food, see our “Acrylamide” website and “Fact Sheets” regarding reducing acrylamide in cereal-based foods and in potato-based foods (see Table 8 in section VI of the Introduction of this guidance).

See also our “Guidance for Industry: Acrylamide in Foods” (Table 4 in section VI of the Introduction of this guidance). In that guidance, 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.

In evaluating whether acrylamide could be a hazard requiring a preventive control (e.g., a process control for a food that you manufacture, or a supply-chain control for a food that you use as a raw material or other ingredient), we recommend that you consider the factors we identified in section 12.3.4.

12.3.13 Evaluating Facility-related Chemicals

Facility-related chemical hazards such as cleaning chemicals have long been addressed through application of CGMPs. We are not aware of circumstances in which these chemical hazards would be a hazard requiring a preventive control.

12.4 Examples of Control Measures for Chemical Hazards

See Table 12-2 for examples of control measures for chemical hazards. As discussed in section 12.3.4, you determine through your hazard analysis whether a hazard can be effectively managed through the application of control measures, such as CGMPs or other prerequisite programs, or whether a hazard requires one or more preventive controls.

Table 12-2 Examples of Control Measures for a Chemical Hazard

Chemical Hazard	Example of a Control Measure
Mycotoxins	- Physical sorting of peanuts, tree nuts, or grains to remove affected materials (e.g., using equipment such as screen separators, aspirators, disc separators, washers, and electronic optical sorters) - Blanching* peanuts or tree nuts to remove the seed coat (skin), followed by physical color sorting (e.g., using an electronic optical sorter) to remove discolored kernels (Whitaker, 1997)
Hypoglycin A in processed ackee fruit	- Selection of fruit that is ripe** - Removal of rind, seeds, and raphe before processing

Chemical Hazard	Example of a Control Measure
3-MCPDEs and GEs in refined oils	See the Codex Code of Practice for the Reduction of 3-Monochloropropane-1,2- Diol Esters (3-MCPDEs) and Glycidyl Esters (GEs) in Refined Oils and Food Products Made with Refined Oils, CXC 79-2019 (Table 6 in section VI of the Introduction of this guidance) for CAC's recommendations for procedures, practices, and processes that could be used with production of your food product, such as: - Application of mitigation measures for oil milling and refining, which could include measures at crude oil production and treatment, degumming, neutralization, bleaching, and deodorization; - Treatment post refining (such as additional bleaching and deodorization); or - Processing modifications (such as reducing the amount of refined oils used).
Chloropropanols (3-MCPD) in acid-hydrolyzed protein intended for use in soy sauce and as ingredients in other Asian-style sauces (e.g., oyster sauce, black bean sauce)	See the Codex Code of Practice for the Reduction of 3-monochloropropane-1,2-diol (3-MCPD) During the Production of Acid-HVPs and Products That Contain Acid-HVPs, CXC 64-2008 (Table 6 in section VI of the Introduction of this guidance) for CAC's recommendations for procedures, practices, and processes that could be used to minimize 3-MCPD, such as: - Control of the acid hydrolysis step; - Subsequent neutralization to minimize 3-MCPD formation; or - Substitution of sulfuric acid for hydrochloric acid in the hydrolysis step.
Toxic elements, chemicals that are intentionally introduced for purposes of economic gain, unlawful pesticide and drug residues	Controls on incoming raw materials and other ingredients - e.g., setting specifications in supplier programs and purchase agreements and confirming that specifications are met.

* Although some blanching processes used by food manufacturers/processors could be designed and validated as a kill step for bacterial pathogens, the blanching process used to remove the skin of a peanut or tree nut typically is not designed as a kill step for bacterial pathogens.

** Most processors buy fruit that is unopened or just beginning to split along the seams and then spread the fruit out on ripening racks to let it finish ripening. Processing staff monitor the fruit, looking for ackee that has split wide open and is ready for processing. If the fruit does not ripen by splitting fully open within three to four days, the fruit is discarded.

12.5 Considerations If You Identify and Implement a Preventive Control for a Chemical Hazard

This chapter focuses on supply-chain programs for incoming raw materials and other ingredients, and process controls that you identify and implement to produce your food product, because these preventive controls are most relevant to chemical hazards requiring a preventive control. Based on your hazard analysis, there may be other preventive controls to consider.

A food safety plan is facility specific. However, a corporation may designate an individual at the corporate level as the owner, operator, or agent in charge of a particular facility, and an employee of the corporation, whether at headquarters or at another facility owned by the

corporation, may provide input into a particular facility's food safety plan (80 FR 55908 at 56022, September 17, 2015). Examples of aspects of a food safety plan for a chemical hazard that can be handled at the corporate²⁵ level include:

- written procedures that will be included in the food safety plan (see section 12.8.1); and
- a supply-chain program for those raw materials and other ingredients for which a manufacturing/processing facility has identified a chemical hazard that is controlled before its receipt (see section 12.7 and Chapter 15 of this guidance).

Other aspects of a food safety plan for a chemical hazard are not suitable for handling at the corporate level. For example, process controls and associated preventive control management components (monitoring, verification, corrective actions and corrections, and associated records) are conducted at an individual facility (see section 12.6).

In the remainder of this chapter, we discuss preventive controls for chemical hazards from the perspective of an individual facility, without repeating within each discussion that certain aspects of a food safety plan that includes preventive controls for chemical hazards could be handled at the corporate level.

Part 117 requires that certain activities either be performed, or overseen by, a PCQI. When a PCQI oversees (rather than performs) these activities, the activity could be performed by a designee of the PCQI. For simplicity, when discussing the role of the PCQI within the examples in this chapter we describe the activity as performed by a PCQI, without specifying each time that the activity could be performed by a designee of the PCQI.

12.6 Identify and Implement a Process Control and Associated Preventive Control Management Components for a Chemical Hazard

12.6.1 Identify a Process Control

See Table 12-2 in section 12.4 for examples of control measures that you could identify and implement as a process control for a chemical hazard.

12.6.2 Develop a Strategy for Preventive Control Management Components

With some exceptions, part 117 specifies that preventive controls are subject to the following preventive control management components as appropriate to ensure the effectiveness of the preventive controls, taking into account the nature of the preventive control and its role in the facility's food safety system: (1) monitoring; (2) corrective actions and corrections; and (3) verification²⁶ (see 21 CFR 117.140). We discuss each of these preventive control management components as they relate to a process control for chemical hazards in section 12.6.3 through 12.6.5.

²⁵ In some cases, programs handled by corporate are managed as prerequisite programs rather than as preventive controls.

²⁶ Verification includes validation (see 21 CFR 117.155(a)(1)).

12.6.3 Design and Validation of a Process Control for a Chemical Hazard

With some exceptions,²⁷ part 117 requires that you validate that the preventive controls are adequate to control the hazard as appropriate to the nature of the preventive control and its role in your food safety system (see 21 CFR 117.160(a)). The validation of the preventive controls must be performed (or overseen) by a PCQI (see 21 CFR 117.160(b)(1)). “Validation” means obtaining and evaluating scientific and technical evidence that a control measure, combination of control measures, or the food safety plan as a whole, when properly implemented, is capable of effectively controlling the identified hazards (see 21 CFR 117.3).

In general, based on the nature of the preventive controls discussed in this chapter, the validation of preventive controls for chemical hazards will involve approaches such as obtaining scientific or technical information from credible sources and obtaining experimental data. This could include collection of data during operating conditions (e.g., monitoring results, measurements, test results) to support that process controls are scientifically sound, can effectively control the chemical hazard, and function as intended on a day-to-day basis.

12.6.4 Establish, Implement, and Document Monitoring and Verification for a Process Control

12.6.4.1 Requirements for monitoring

Part 117 requires that, as appropriate to the nature of the preventive control and its role in your food safety system, you establish and implement written procedures, including the frequency with which they are to be performed, for monitoring the preventive control. You must monitor the preventive controls with adequate frequency to provide assurance that they are consistently performed (see 21 CFR 117.145).

What you monitor depends on the process control you have identified as a preventive control. See Table 12-3 for examples of what you could monitor. In general, what you monitor could be associated with:

- the food;
- the chemical hazard; or
- the processing equipment.

12.6.4.2 Requirements for verification

Part 117 requires that verification activities include, as appropriate to the nature of the preventive control and its role in your food safety system: (1) validation; (2) verification that monitoring is being conducted; (3) verification that appropriate decisions about corrective actions are being made; (4) verification of implementation and effectiveness; and (5) reanalysis (see 21 CFR 117.155). See section 12.6.3 for a discussion of validating a process control for a chemical hazard.

²⁷ See the exceptions in 21 CFR 117.160(c). In general, the type of preventive controls that are validated are process controls.

Part 117 also requires that you verify that the preventive controls are consistently implemented and are effectively and significantly minimizing or preventing the hazards. To do so you must conduct certain activities as appropriate to the facility, the food, and the nature of the preventive control and its role in the facility's food safety system (see 21 CFR 117.165(a)). Among the verification activities listed, those most relevant to process controls for a chemical hazard are:

- calibration of process monitoring instruments and verification instruments (or checking them for accuracy) (see 21 CFR 117.165(a)(1));
- product testing (see 21 CFR 117.165(a)(2)); and
- review of certain records by (or under the oversight of) a PCQI at specified intervals (which depend on the record), to ensure that the records are complete, the activities reflected in the records occurred in accordance with the food safety plan, the preventive controls are effective, and appropriate decisions were made about corrective actions (see 21 CFR 117.165(a)(4)).

Part 117 also requires, as appropriate to the facility, the food, the nature of the hazard and preventive control, and the role of the preventive control in the facility's food safety system, that you establish and implement written procedures for certain verification activities (see 21 CFR 117.165(b)). Among the written procedures listed, those most relevant to this chapter are:

- the method and frequency of calibrating process monitoring instruments and verification instruments (or checking them for accuracy) (see 21 CFR 117.117.165(b)(1)); and
- product testing (see 21 CFR 117.165(b)(2)).

12.6.4.3 Flexibility in complying with the requirements for monitoring and verification

The requirements for monitoring provide flexibility for you to establish and implement written procedures for monitoring preventive controls as appropriate to the nature of the preventive control and its role in your food safety system (see 21 CFR 117.145). Likewise, the requirements for verification provide flexibility for you to conduct verification activities that are appropriate to the facility, the food, and the nature of the preventive control and its role in the facility's food safety system (see 21 CFR 117.165). In some cases (such as instrument calibration, product testing²⁸, and review of records), part 117 specifically identifies an activity as a verification activity. In other cases (such as measurement of refrigeration temperature), part 117 mentions records of the activity as records of monitoring. However, part 117 does not specifically mention all activities that could be conducted as a preventive control management component for a preventive control, and some activities (such as visual observation) could be classified as either monitoring or as verification. In light of the flexibility that part 117 provides for monitoring and verification, it generally makes little difference whether you consider some activities (such as visual observation) to be monitoring or verification for the purposes of your process control as long as you comply with requirements applicable to monitoring or verification. Regardless of what you call them, your preventive control management component(s) must be appropriate to ensure the effectiveness of the preventive controls (see 21 CFR 117.140(a)).

²⁸ In some cases, in-process testing of a batch can be classified as either monitoring or verification. For example, continuous measurement of a batch for pH would generally be classified as monitoring, and measurement of representative samples of a batch for pH could be classified as either monitoring or verification.

12.6.4.4 Examples of monitoring and verification activities for a process control for a chemical hazard

See Table 12-3 for examples of monitoring or verification activities that could apply to a control measure that you identify and implement as a process control for a chemical hazard. Table 12-3 focuses on the examples of control measures for chemical hazards that we listed in Table 12-2 in section 12.4. The examples shown are not all-inclusive of the types of processes or the methods for monitoring and verification and do not illustrate all the information that you could include on Form 2-C (Process Controls)²⁹ if you classify the activity as monitoring. We recommend that your procedures identify “who conducts the activity” (e.g., a line operator, QC personnel, the vendor of equipment that is being calibrated, or laboratory personnel who have the knowledge, skills, and experience to conduct analytical tests).

Part 117 identifies review of certain records within specified timeframes (see 21 CFR 117.165(a)(4) and section 12.6.4.2). Because review of records as a verification activity generally would apply to any preventive control, we do not specify it for each listing in Table 12-3.

²⁹ See Appendix 2 of this guidance for Food Safety Plan forms, including Form 2-C (Process Controls).

Table 12-3 Examples of Monitoring and Verification for a Process Control for a Chemical Hazard

Hazard	Preventive Control	Example(s) of Monitoring Activity	Example(s) of Verification Activity	Example of Activity That Could Be Either Monitoring or Verification	Example of How Often to Monitor or Verify	Example of Record(s)* of the Monitoring or Verification
Mycotoxins in grain	Physical cleaning using equipment such as screen separators, aspirators, disc separators, washers, and electronic optical sorters	Observation that the equipment is on and functioning as intended	- Testing for level of applicable mycotoxin - Calibration of electronic optical sorter (if used)	Observation of the sorted grain for discolored or moldy grain	- Periodic visual observation of equipment several times per shift - Periodic testing for level of applicable mycotoxin - Testing every lot when there is evidence of levels that are higher than internal specification - Calibration frequency of electronic optical sorter (if used) according to manufacturer's instructions	- Record of any indication that equipment is not functioning as intended - Results of analytical tests for applicable mycotoxin - Calibration records (if any)
Aflatoxin in tree nuts	Physical sorting of tree nuts (such as almonds, pistachios, and walnuts) (e.g., based on color, using an electronic optical sorter)	Observation that the sorter is on and functioning as intended	- Calibration of electronic optical sorter - Testing for level of aflatoxin	Observation of the sorted tree nuts for nuts that are discolored	- Periodic visual observation of sorter several times per shift - Periodic visual observation of sorted tree nuts several times per shift - Calibration frequency of sorter according to manufacturer's instructions - Periodic testing for level of aflatoxin	- Record of any indication that electronic optical sorter is not functioning as intended - Records of visual observation of sorted tree nuts - Calibration records - Results of the analytical testing
3-MCPDEs and GEs in refined oils	Process control to significantly minimize or prevent formation of 3-MCPDEs and GEs	Depends on the production process and efficacy of the associated process control	Testing of refined oil		- Depends on the production process and efficacy of the associated process control - Periodic testing of refined oil	- Records appropriate to the process control measure applied. - Record of test results

Hazard	Preventive Control	Example(s) of Monitoring Activity	Example(s) of Verification Activity	Example of Activity That Could Be Either Monitoring or Verification	Example of How Often to Monitor or Verify	Example of Record(s)* of the Monitoring or Verification
3-MCPD in acid-hydrolyzed protein and Asian-style sauces	Process control to significantly minimize or prevent formation of 3-MCPD	Depends on the production process and efficacy of the associated process control	Testing product		- Depends on the production process and efficacy of the associated process control - Periodic testing of product	- Records appropriate to the process control measure applied - Record of test results

*Records of monitoring activities can in some cases be exception records (21 CFR 117.145(c)(2)).

12.6.5 Establish and Implement Corrective Action Procedures and Document Corrective Actions for a Process Control for a Chemical Hazard

Part 117 includes requirements, as appropriate to the nature of the hazard and the nature of the preventive control, for:

- written corrective action procedures that must be taken if preventive controls are not properly implemented (see 21 CFR 117.150(a)(1));
- corrective actions in the event of an unanticipated food safety problem (such as when there are no corrective action procedures in place) (see 21 CFR 117.150(b)); and
- reanalysis when appropriate in the event of an unanticipated food safety problem (see 21 CFR 117.150(b)(2)(ii) and 117.170).

However, part 117 provides for corrections (rather than corrective actions) if you take action, in a timely manner, to identify and correct a minor and isolated problem that does not directly impact product safety. We expect there to be limited circumstances that would lead to a correction for a process control of a chemical hazard, but this would depend on your facility's application of a particular process control (see 21 CFR 117.150(c)).

When your preventive control is a process control, your corrective action procedures could describe the steps you will take when a critical parameter/critical factor for the process control does not achieve the specified critical value/critical limit.

Examples of steps that could be identified in corrective action procedures applicable to a process control for a chemical hazard include:

- determine root cause of the problem and take actions to address the problem (e.g., repair or replace malfunctioning equipment, re-train personnel, revise the written procedures for the process control);
- evaluate the product for safety;
- based on the evaluation, determine disposition of the product, e.g.:
 - divert the product to a different use, e.g., divert a root vegetable with a level of lead that exceeds the specifications set for use of that root vegetable in foods for babies and young children but is safe for the general population to a product (such as a fully or partially cooked adult entrée) that is unlikely to be consumed by babies and young children);
 - divert the product to animal food (usually for animals other than pets)³⁰ (e.g., when a CPG for a chemical hazard establishes different levels for a chemical hazard in an intended species/class of animals and the food is below that level and an ingredient appropriate for use in the diet of the intended animal); or

³⁰ In 2016, FDA issued for public comment a draft guidance for industry (GFI #239) titled “Human Food By-Products For Use As Animal Food” (see Table 4 in section VI of the Introduction of this guidance and 81 FR 58521, August 25, 2016). In determining whether it is appropriate to divert a food product to animal food use, we recommend that you consult the final guidance on this subject when it becomes available. We expect this guidance to provide recommendations for circumstances in which you should contact CVM before diverting a human food for use as animal food, and recommendations for circumstances in which you could divert a human food to use as animal food without contacting CVM. We also expect this guidance to include applicable contact information within CVM.

- destroy the product.

What you document in records of corrective actions depends on the applicable corrective action situation. In general, records of corrective actions should describe the problem, explain what you did to address the problem (including any applicable root cause investigation), steps you will take to prevent the problem from happening again, and the evaluation and disposition of any affected food), and be reviewed by the PCQI as a verification that appropriate decisions about corrective actions are being made.

When you determine that it is appropriate to document a correction, what you document in records of corrections likewise depends on the applicable correction situation.

12.7 Establish and Implement a Supply-Chain Program When a Chemical Hazard That Requires a Preventive Control Is Controlled Before Receipt

See section 12.3.1 for examples of chemical hazards. When one or more of these chemical hazards has the potential to be present in raw materials and other ingredients that you use in your food products, the presence of that chemical hazard would generally be controlled before receipt. If the outcome of your hazard analysis is that the chemical hazard requires a preventive control, the appropriate control would be a supply-chain control in accordance with part 117, subpart G. For detailed guidance on how to comply with the requirements of part 117, subpart G, see Chapter 15.

Briefly, key elements of a supply-chain program as required by part 117, subpart G, include:

- approving suppliers before you use them;
- determining and conducting appropriate supplier verification activities, such as:
 - onsite audits;
 - sampling and testing of the raw material or other ingredient (e.g., to determine compliance with a specification that you establish for a chemical hazard);
 - review of the supplier's relevant food safety records;
 - other appropriate supplier verification activities based on supplier performance, such as review of:
 - the supplier's procedures, processes, and practices related to the safety of the raw material and other ingredients;
 - applicable FDA food safety regulations and information relevant to the supplier's compliance with those regulations; and
 - the supplier's food safety history relevant to the raw materials or other ingredients that you receive from the supplier, including available information about results from testing raw materials or other ingredients for hazards, audit results relating to the safety of the food, and responsiveness of the supplier in correcting problems; and
 - other appropriate supplier verification activities based on the risk associated with the raw material or other ingredients;
- documenting supplier verification activities; and
- documenting corrective actions.

Some guidance that FDA has made available regarding some chemical hazards recommends that amounts of specific chemical hazards in specific commodities do not exceed a certain level (see section 12.3.2). When a recommended contaminant level is available, you can use that recommended contaminant level as a factor in developing a specification for the maximum level of a chemical hazard in a raw material or other ingredient.

See sections 12.10 through 12.13 for examples of supply-chain programs for raw materials and other ingredients with a chemical hazard.

12.8 Required Records

12.8.1 Requirement for a Food Safety Plan

Your food safety plan is a record that is subject to the requirements of part 117, subpart F, including the requirement to promptly make it available for official review and copying upon oral or written request (see 21 CFR 117.320).

Your hazard analysis must be written and included in your food safety plan (see 21 CFR 117.130(a) and 117.126(b)(1)). Additionally, information that you rely on to determine, through your hazard analysis, that a chemical hazard does not require a preventive control would be considered part of the hazard analysis and must be made available for official review and copying. For example, if your hazard analysis includes a determination that a chemical hazard does not require a preventive control because the hazard is addressed through your CGMPs or other “prerequisite programs” (such as the terms of purchase agreements with suppliers), you would include the information that you rely on to make that determination as part of the documentation of your hazard analysis (see 21 CFR 117.130(a)(2)), which must be available for official review and copying upon request. Similarly, if you determine that a chemical hazard does not require a preventive control because the history of analytical testing for the contaminant demonstrates that your prerequisite programs are adequate to control the hazard, those analytical testing results would be part of the hazard analysis and must be made available for official review and copying upon request. Likewise, if your hazard analysis of a raw material or other ingredient with unclear regulatory status determines that it is not an unapproved food additive, you would include the information that you rely on to make that determination in your hazard analysis, which must be available for official review and copying upon request.

Preventive controls must be written and included as records in your food safety plan (see 21 CFR 117.135(b) and 117.126(b)(2) and (c)). Procedures for monitoring, corrective actions, and verification also must be written and included in your food safety plan (see 21 CFR 117.126(b)(5), (6), and (7)).

12.8.2 Requirement for Implementation Records

Part 117 includes requirements for records documenting the monitoring of preventive controls, all corrective actions (and, when appropriate, corrections), and all verification activities (see 21 CFR 117.145(c), 117.150(d), and 117.155(b)).

See Table 12-3 in section 12.6.4.4 for examples of what you could document in monitoring records or verification records applicable to a process control for a chemical hazard.

See section 12.6.5 for a discussion of records applicable to corrective actions.

12.9 Examples Used in This Chapter

Sections 12.10 and 12.11 provide examples that illustrate how to establish and implement a supply-chain program for a chemical hazard. These examples are:

- a supply-chain program established and implemented by Manufacturer A for the control of toxic elements during production of shelf-stable baby food (section 12.10);³¹ and
- a supply-chain program established and implemented by Manufacturer B for the control of toxic elements during production of dry infant cereal (section 12.11).

Sections 12.12 through 12.14 provide examples that illustrate a hazard analysis in which the conclusion is that a chemical hazard generally does not require a preventive control because the hazard is controlled through CGMPs or other prerequisite programs (such as terms of a purchase agreement with suppliers). These examples are:

- a hazard analysis and program established and implemented by Miller C for the control of DON during production of milled wheat products (section 12.12);
- a hazard analysis and program established and implemented by Baker D for the control of DON during production of products that are made from wheat flour or from products containing wheat flour (section 12.13); and
- a hazard analysis conducted by Sandwich Maker F for the control of DON during production of sandwiches made with bread produced with wheat flour (see section 12.14).

In reviewing these examples, keep in mind that:

- In each example, we provide only a brief description of the manufacturing process. Additional details would have limited relevance to the preventive controls described in the example.
- The examples only address certain chemical hazards and the manufacturer's determination, through its hazard analysis, of whether those particular chemical hazards are hazards requiring a preventive control. These examples do not describe the hazard analysis that could have identified other chemical hazards requiring a preventive control nor do they identify other preventive controls that could be used to significantly minimize or prevent the applicable chemical hazards. Likewise, the examples do not describe the hazard analysis that could have identified biological or physical hazards requiring a preventive control nor do they identify preventive controls that could be used to significantly minimize or prevent biological or physical hazards requiring a preventive control.
- In one example (see section 12.12), the manufacturer identifies circumstances (related to crop characteristics during a growing/harvesting season) in which its control program for a chemical hazard (i.e., the mycotoxin DON in wheat) will be implemented as a preventive control rather than through its CGMP measures and other prerequisite programs.

³¹ In the example in section 12.10, Manufacturer A produces a fruit or vegetable purée and then uses that fruit or vegetable purée as an ingredient in a baby food product that also contains water as an ingredient and is not used as a beverage. Such a product is subject to the PCHF requirements (unless an exemption applies) rather than to our juice HACCP regulation in part 120. The juice HACCP regulation applies to any juice sold as such or used as an ingredient in beverages, where "juice" means the aqueous liquid expressed or extracted from one or more fruits or vegetables, purées of the edible portions of one or more fruits or vegetables, or any concentrates of such liquid or purée (21 CFR 120.1(a)).

- Our purpose in providing multiple, detailed recommendations in each example in which the manufacturer identifies a chemical hazard requiring a preventive control is to provide several illustrative examples so that you can develop your own preventive controls as appropriate to your operations, not to imply that such a preventive control should have all the elements that we describe in each example.
- For a process control, you have flexibility to determine what monitoring and verification activities, and how many monitoring and verification activities, are appropriate for your operation as long as they are adequate to ensure the effectiveness of the process control (see 21 CFR 117.140(a)). For the purpose of these examples, we specified how each manufacturer classified an activity as either monitoring or verification and retained that classification throughout the examples. This does not imply that similar operations would classify monitoring and verification activities the same way.

12.10 Example of a Program Established and Implemented by Manufacturer A for the Control of Toxic Elements During Production of Shelf-Stable Baby Foods

12.10.1 Manufacturer A's Products, Production Process, and Hazard Analysis

Manufacturer A makes shelf-stable baby food – i.e., puréed apples (i.e., applesauce), carrots, sweet potatoes, and blends of these ingredients. Some of these baby food products are flavored by the addition of cinnamon. Briefly, Manufacturer A's production process is as follows:

- Receive vegetables and fruit and store them under refrigeration;
- Receive ground cinnamon in bulk packaging and store it at room temperature;
- Grind the vegetables and fruit to produce a coarse purée;
- Blend vegetable and fruit purées per recipe, add ground cinnamon per recipe, add water, and pump the mixture to batch tanks for filling in glass jars; and
- Process the filled jars in accordance with specific recommendations from its process authority for acid (fruit) and low-acid (vegetables) foods.

Purchase agreements with suppliers of fruit and vegetables and ground cinnamon include specifications for three toxic elements (i.e., arsenic, cadmium, and lead) in these ingredients.

- When the outcome of the hazard analysis is that a specific toxic element in a specific ingredient is a hazard requiring a preventive control, Manufacturer A implements a supply-chain program as described in 12.10.2.
- When the outcome of the hazard analysis is that a specific toxic element in a specific ingredient is not a hazard requiring a preventive control, Manufacturer A's program for the control of chemical hazards includes the review of test results for the ingredient as an appropriate quality control operation to ensure that food is suitable for human consumption (i.e., by babies and young children) (see 21 CFR 117.80(a)(2)) and as data to inform reanalysis of the food safety plan as a whole, including information about toxic element hazards in ingredients and whether Manufacturer A's food safety plan is effective at controlling toxic element hazards (see 21 CFR 117.170(b) and (d)):

- Manufacturer A reviews results from testing for the specific toxic element (whether Manufacturer A's testing or the supplier's testing) before accepting the first shipment from the supplier; and
- Manufacturer A's purchase agreements require the supplier to develop and implement a periodic testing program for the specific toxic element and provide the results of this testing program annually.

To inform reanalysis of the food safety plan as a whole, including information about toxic element hazards in ingredients and whether Manufacturer A's food safety plan is effective at controlling toxic element hazards, Manufacturer A tests finished product for arsenic, cadmium, and lead on a quarterly basis (see 21 CFR 117.170(b) and (d)).

During the hazard analysis, Manufacturer A's PCQI considered that:

- The toxic elements arsenic, lead, and cadmium can occur in the environment naturally (as elements in the earth's crust) and from human activities. Levels in the air, water, and soil used to grow crops can vary depending on natural geographical differences and proximity to past or current pollution. The amount of arsenic, lead, or cadmium in plant-based foods depends on the amount in the environment and how much the plant "takes up" from the environment. Babies and young children are more vulnerable to the harmful effects of these contaminants due to their smaller body sizes and metabolism.
- FDA's "Closer to Zero" approach (see Table 8 in section VI of the Introduction of this guidance) outlines a science-based, iterative approach for achieving continual improvements in reducing the levels of these toxic elements in foods intended for babies and young children over time. As part of this approach, FDA has:
 - issued "Guidance for Industry: Action Levels for Lead in Processed Food Intended for Babies and Young Children" (see Table 4 in section VI of the Introduction of this guidance) that specifies action levels achievable by industry when control measures are taken to minimize the presence of lead; and
 - announced "Planned Action Items," including development of action levels for arsenic and cadmium in foods intended for babies and young children.
- Appendix 1 of this guidance identifies lead (but not arsenic or cadmium) as a known or reasonably foreseeable ("potential") chemical hazard in carrots and sweet potatoes;
- Appendix 1 did not identify arsenic, cadmium, or lead as a known or reasonably foreseeable ("potential") chemical hazard for apples;
- A publication in 2017 described a historical pattern of economically motivated adulteration in which lead salts are added to certain spices to increase their weight, enhance their color, and attempt to increase their monetary value (Cowell et al., 2017). Beginning in 2023, CDC reported on elevated blood lead levels in individuals with exposure to certain applesauce products that contained cinnamon with very high levels of lead and chromium from lead chromate (CDC, 2024). In 2024, FDA announced its leading hypothesis that this was likely an act of economically motivated adulteration (FDA, 2024a).
- A review of the literature did not provide any additional information regarding toxic elements in raw materials or other ingredients used by Manufacturer A.

The outcome of Manufacturer A's hazard analysis is that:

- For fruit and vegetables received from a supplier:

- The toxic element lead is a chemical hazard requiring a preventive control in the baby food products due to the potential contamination of growing areas with lead and the intended consumer of the products (i.e., babies and young children).
- A supply-chain program is the appropriate preventive control to significantly minimize or prevent the chemical hazard of lead.
- In addition to identified preventive controls, as part of a quality control operation under CGMPs to ensure that food is suitable for the intended consumer (i.e., babies and young children), it is appropriate to set specifications in purchase agreements for arsenic and cadmium (in addition to the lead specification in the supply-chain program) in incoming fruits and vegetables to minimize toxic elements in finished products.
- For ground cinnamon received from a supplier:
 - The toxic element lead is a chemical hazard requiring a preventive control in cinnamon due to the known prevalence of lead in cinnamon, the potential for economically motivated adulteration, and the intended consumer of the applesauce product (i.e., babies and young children).
 - A supply-chain program is the appropriate preventive control to significantly minimize or prevent the presence of lead in cinnamon used to make the baby food products.
 - In addition to identified preventive controls, as part of a quality control operation under CGMPs to ensure that food is suitable for the intended consumer (i.e., babies and young children), it is appropriate to set specifications in purchase agreements for arsenic and cadmium (in addition to the lead specification in the supply-chain program) in cinnamon to minimize toxic elements in finished products.

12.10.2 Manufacturer A's Supply-Chain Program

Manufacturer A establishes a supply-chain program to significantly minimize or prevent the presence of toxic elements in fruits, vegetables, and other ingredients used to make shelf-stable food for babies and young children. Based on current scientific information and applicable recommendations from FDA regarding toxic elements in processed foods intended for babies and young children, Manufacturer A's PCQI sets specifications for lead in cinnamon, carrots, and sweet potatoes.

Manufacturer A's PCQI reviews FDA's "Closer to Zero" website for updates to applicable FDA recommendations on a semi-annual basis and whenever Manufacturer A's PCQI receives a communication from FDA regarding such updates.

Manufacturer A:

- Approves suppliers by:
 - reviewing a supplier's procedures, processes, and practices related to the presence of lead in the raw materials and other ingredients it produces, potentially including periodic testing of soil and water used for growing RACs (if applicable) for lead and, when practicable, the use of cultivars that are less likely to accumulate a toxic element such as lead;
 - reviewing information relevant to a supplier's compliance with applicable FDA food safety regulations, including an FDA warning letter or import alert relating to the safety of

food and other FDA compliance actions related to food safety³² (or, when applicable, relevant laws and regulations of a country whose food safety system FDA has officially recognized as comparable or has determined to be equivalent to that of the United States, and information relevant to the supplier's compliance with those laws and regulations);

- reviewing “food fraud” resources identified in Table 8 in section VI of the Introduction of this guidance;
- obtaining historical data from the supplier of carrots, sweet potatoes, and cinnamon related to lead testing in its operation (e.g., in products, and/or in soil and water, as appropriate); and
- obtaining several lots of carrots, sweet potatoes, and cinnamon and testing them for lead prior to final approval of the supplier.
- Conducts supplier verification activities as follows:
 - On a quarterly basis, conducts analytical tests on samples from incoming carrots and sweet potatoes to verify the ongoing program of the supplier is adequately controlling lead. Depending on the circumstances, Manufacturer A either does not use the carrots and sweet potatoes until test results are available or uses the carrots and sweet potatoes but holds finished product until the test results are available.
 - Obtains a certificate of analysis (COA) from the supplier for each lot of ground cinnamon and conducts periodic analytical tests for lead on samples from incoming ground cinnamon to confirm the results on the COA as verification that the supplier is not intentionally introducing a substance such as lead chromate for purposes of economic gain.³³
- Makes corrections or takes corrective action(s) as appropriate if levels of lead in incoming carrots, sweet potatoes, or ground cinnamon exceed specifications. Examples include:
 - Correction: If Manufacturer A's verification test results on a specific shipment of incoming carrots, sweet potatoes, or ground cinnamon indicate levels of lead exceed specifications, and that specific shipment has not been used in production, Manufacturer A concludes that the problem is likely an isolated problem (due to supplier history of no previous problems) that does not directly impact the safety of any product because the ingredient has not been used in production. Manufacturer A returns the shipment to the supplier and discusses the problem with the supplier to determine the likely cause of the problem and obtain the supplier's agreement to correct the problem in a timely manner. Manufacturer A determines whether to increase testing on incoming carrots, sweet potatoes, or ground cinnamon from that supplier based on the likely cause and correction of the problem. Based on the discussions with the supplier and (when applicable) the results of any additional testing, Manufacturer A determines whether to discontinue use of the supplier.
 - Corrective action: Supplier notifies Manufacturer A that carrots, sweet potatoes, or ground cinnamon has exceeded specification limits for lead, Manufacturer A determines whether the applicable ingredient has been used in any of its products. If so, Manufacturer A tests the products and determines appropriate disposition, including

³² FDA warning letters, import alerts describing products that may be subject to detention without physical examination, and other FDA actions (such as public warnings) could be particularly useful in determining whether any suppliers have been associated with food fraud.

³³ Analytical testing to verify supplier control of toxic elements and to confirm the results in the supplier's COA are conducted on every lot until Manufacturer A develops confidence in the supplier's program; at that point, verification testing is reduced to quarterly.

disposition of any product that has entered commerce. Manufacturer A discusses the problem with the supplier to determine the likely cause of the problem and obtains the supplier's agreement to correct the problem. Manufacturer A determines whether to increase testing on ingredients from that supplier based on the likely cause and correction of the problem. Manufacturer A discontinues use of a supplier if the supplier is not responsive to correcting the problem.

- Takes specific corrective action(s) if levels of lead in an incoming shipment of ground cinnamon exceed specifications at a level that suggests the possible addition of lead (e.g., as lead chromate) to ground cinnamon for purposes of economic gain. Examples include:
 - Stopping production of any product that would use ground cinnamon from this shipment until the results of the analytical tests for lead are confirmed in that shipment, and either disposing of the shipment or returning it to the supplier if the analytical results are confirmed;
 - Segregating any product already made with this shipment to assess it for safety, and determining appropriate disposition, including disposition of any product that has entered commerce;
 - Notifying the supplier;
 - Immediately discontinuing use of the supplier; and
 - Performing or repeating analytical tests for lead on available inventory of ground cinnamon to confirm that the previous shipments were not contaminated with levels of lead that exceeded specifications, and taking appropriate corrective actions if the results of analytical testing are consistent with elevated levels of lead.

12.10.3 Manufacturer A's Verification

As verification of control of toxic elements, Manufacturer A tests finished products for lead on a quarterly basis. If the level of a toxic element exceeds internal specifications for a finished product, Manufacturer A:

- conducts a root cause investigation to determine the source ingredient of the toxic element;
- assesses whether changes should be made to the supply-chain program for the applicable ingredient; and
- determines appropriate disposition of the finished product after evaluating the affected food for safety, including preventing affected food from entering into commerce if Manufacturer A cannot ensure that the affected food is not adulterated under section 402 of the FD&C Act (21 U.S.C. 342).

12.10.4 Manufacturer A's Records

Manufacturer A establishes and maintains records of:

- specifications that it establishes for levels of lead in incoming carrots, sweet potatoes, and cinnamon;
- implementation of the supply-chain program as required by 21 CFR 117.475 (including records related to analytical test results);
- results of any analytical testing to detect lead in finished products;
- disposition of carrots, sweet potatoes, and ground cinnamon in which lead was detected and shipments refused or returned; and

- disposition of finished product if the level of lead exceeds internal specifications for a finished product.

Each record includes a line for Manufacturer A's PCQI to document review of the records by signing and dating the records.

12.11 Example of a Program Established and Implemented by Manufacturer B for the Production of Dry Infant Rice Cereal

12.11.1 Manufacturer B's Products, Production Process, and Hazard Analysis

Manufacturer B makes dry infant rice cereal. Briefly, Manufacturer B's production process for dry infant rice cereal is as follows:

- Receive husked, milled rice and store it at room temperature;
- Cook the rice into a slurry;
- Add a vitamin and mineral premix to the slurry; and
- Dry the slurry and grind it into small flakes.

Purchase agreements with suppliers of rice and suppliers of vitamin and mineral premixes include specifications for three toxic elements (i.e., arsenic, cadmium, and lead) in these ingredients.

- When the outcome of the hazard analysis is that a specific toxic element in a specific ingredient is a hazard requiring a preventive control, Manufacturer B implements a supply-chain program as described in 12.11.2.
- When the outcome of the hazard analysis is that a specific toxic element in one of these ingredients is not a hazard requiring a preventive control, Manufacturer B's program for the control of chemical hazards includes the review of test results for the ingredient as an appropriate quality control operation to ensure that food is suitable for human consumption (i.e., by babies and young children) (see 21 CFR 117.80(a)(2)) and as data to inform reanalysis of the food safety plan as a whole, including information about toxic element hazards in ingredients and whether Manufacturer B's food safety plan is effective at controlling toxic element hazards (see 21 CFR 117.170(b) and (d)):
 - Manufacturer B reviews results from testing for the specific toxic element (whether Manufacturer B's testing or the supplier's testing) before accepting the first shipment from the supplier; and
 - Manufacturer B's purchase agreements require the supplier to develop and implement a periodic testing program for the specific toxic element and provide the results of this testing program annually.

To inform reanalysis of the food safety plan as a whole, including information about toxic element hazards in ingredients and whether Manufacturer B's food safety plan is effective at controlling toxic element hazards, Manufacturer B tests finished product for arsenic, cadmium, and lead on a quarterly basis (see 21 CFR 117.170(b) and (d)).

During the hazard analysis, Manufacturer B's PCQI considered that:

- Toxic elements can occur in the environment naturally (as elements in the earth's crust) and from human activities. Levels in the air, water, and soil used to grow crops can vary depending on natural geographical differences and proximity to past or current pollution. The amount of a toxic element in plant-based foods depends on the amount in the environment and how much the plant "takes up" from the environment. Babies and young children are more vulnerable to the harmful effects of toxic element contaminants due to their smaller body sizes and metabolism.
- FDA's "Closer to Zero" approach (see Table 8 in section VI of the Introduction of this guidance) outlines a science-based, iterative approach for achieving continual improvements in reducing the levels of these toxic elements in foods intended for babies and young children over time. As part of this approach, FDA has:
 - issued "Guidance for Industry: Action Level for Inorganic Arsenic in Rice Cereals for Infants" (see Table 4 in section VI of the Introduction of this guidance);
 - issued "Guidance for Industry: Action Levels for Lead in Processed Food Intended for Babies and Young Children" (see Table 4 in section VI of the Introduction of this guidance) that specifies action levels achievable by industry when control measures are taken to minimize the presence of lead; and
 - announced "Planned Action Items," including development of action levels for arsenic and cadmium in foods intended for babies and young children;
- Both arsenic and cadmium are known or reasonably foreseeable ("potential") contaminants of rice (Appendix 1 of this guidance; Han et al., 2023; Horiguchi, 2012; Tatah Mentan et al., 2020; Zhao and Wang, 2020);
- A 2022 review of toxic heavy metal content of infant and toddler foods (Bair, 2022) noted that ingredients such as vitamin premixes have tested positive for toxic elements; and
- Manufacturer B has a testing program for arsenic, cadmium, and lead in vitamin and mineral premixes. Manufacturer B has a history of periodically detecting arsenic and lead in incoming vitamin and mineral premixes and a history of changing suppliers to reduce the amount of arsenic and lead in incoming vitamin and mineral premixes.

The outcome of Manufacturer B's hazard analysis is that:

- For rice received from a supplier:
 - The toxic elements arsenic and cadmium are chemical hazards requiring a preventive control in rice due to the well-established potential for rice to accumulate arsenic and cadmium from the growing area and the special vulnerability of babies and young children to the harmful effects of toxic element contaminants; and
 - A supply-chain program is the appropriate preventive control to significantly minimize or prevent the presence of these toxic elements in rice used to make the dry infant rice cereals.
 - In addition to identified preventive controls, as a quality control operation under CGMPs to ensure that food is suitable for the intended consumer (i.e., babies and young children), it is appropriate to set specifications in purchase agreements for lead in rice (in addition to the arsenic and cadmium specifications in the supply-chain program) to minimize toxic elements in finished products.
- For vitamin and mineral premixes received from a supplier:
 - The toxic elements arsenic and lead are chemical hazards requiring a preventive control based on the history that Manufacturer B has with testing vitamin and mineral premixes for arsenic and lead, and the special vulnerability of babies and young children to the

harmful effects of toxic elements. A supply-chain program is the appropriate preventive control to significantly minimize or prevent the presence of these toxic elements in vitamin and mineral premixes.

- In addition to identified preventive controls, as a quality control operation under CGMPs to ensure that food is suitable for the intended consumer (i.e., babies and young children), it is appropriate to set specifications in purchase agreements for cadmium in vitamin and mineral premixes (in addition to the arsenic and lead specifications in the supply-chain program) to minimize toxic elements in finished products.

12.11.2 Manufacturer B's Supply-Chain Program

Manufacturer B establishes a supply-chain program to significantly minimize or prevent the presence of arsenic and cadmium in rice, vitamins, and premixes used to make dry infant rice cereals. Based on current scientific information and applicable recommendations from FDA regarding toxic elements in foods intended for babies and young children, Manufacturer B's PCQI sets specifications for the toxic elements arsenic (specifically inorganic arsenic) and cadmium in rice that it uses to make its dry infant rice cereal. Manufacturer B's PCQI also sets specifications for the toxic elements arsenic and lead in vitamin and mineral premixes. Manufacturer B's PCQI reviews FDA's "Closer to Zero" website for updates to applicable FDA recommendations on a semi-annual basis and whenever Manufacturer B's PCQI receives a communication from FDA regarding such updates.

Manufacturer B:

- Approves suppliers by:
 - reviewing the rice supplier's procedures, processes, and practices related to the presence of the toxic elements arsenic and cadmium in the husked, milled rice it produces, including, as appropriate, testing of product, soil, and water at the grower for inorganic arsenic and cadmium and, when practicable, the use of cultivars that are less likely to take up these toxic elements;
 - reviewing the vitamin and mineral premix supplier's procedures, processes, and practices related to the presence of inorganic arsenic and lead in the vitamin and mineral premix;
 - reviewing information relevant to each supplier's compliance with applicable FDA food safety regulations, including an FDA warning letter or import alert relating to the safety of food and other FDA compliance actions related to food safety (or, when applicable, relevant laws and regulations of a country whose food safety system FDA has officially recognized as comparable or has determined to be equivalent to that of the United States, and information relevant to the supplier's compliance with those laws and regulations);
 - obtaining historical data from the suppliers of rice related to testing for inorganic arsenic and cadmium and from the suppliers of vitamin and mineral premixes for inorganic arsenic and lead in the applicable operation (e.g., in its products and in soil and water, as appropriate); and
 - obtaining several lots of husked, milled rice and vitamin and mineral premix and testing them for applicable toxic elements prior to final approval of the supplier.
- Conducts supplier verification activities, on a quarterly basis, by conducting analytical tests on samples from incoming husked, milled rice and incoming vitamin and mineral premix to verify the ongoing program of the supplier is adequately controlling applicable toxic

elements; depending on the circumstances, Manufacturer B either does not use the incoming husked, milled rice and incoming vitamin and mineral premix until test results are available, or uses the incoming husked, milled rice and incoming vitamin and mineral premix but holds finished product until the test results are available.

- Takes corrections or corrective action(s) as appropriate if levels of an applicable toxic element exceed specifications. Examples include:
 - Correction: If Manufacturer B's verification test results indicate levels of an applicable toxic element exceed specifications in a specific shipment of husked, milled rice or in a vitamin and mineral premix, and that specific shipment has not been used in production, Manufacturer B concludes that the problem is an isolated problem that does not directly impact the safety of any product. Manufacturer B returns the shipment to the supplier and discusses the problem with the supplier to determine the likely cause of the problem and obtain the supplier's agreement to correct the problem in a timely manner. Manufacturer B determines whether to increase testing on incoming husked, milled rice or in a vitamin and mineral premix from that supplier based on the likely cause and correction of the problem. Based on the discussions with the supplier and (when applicable) the results of any additional testing, Manufacturer B determines whether to discontinue use of the supplier.
 - Corrective action: If Manufacturer B's verification test results on shipments of incoming husked, milled rice or vitamin and mineral premix indicate ongoing problems with levels of an applicable toxic element that exceed specifications for that toxic element, the shipments are returned to the supplier and Manufacturer B discusses the problem with the supplier to determine the likely cause of the problem and obtain the supplier's agreement to correct the problem. Manufacturer B determines whether to increase verification testing from that supplier based on the likely cause and correction of the problem. Manufacturer B also assesses whether products made with lots of husked, milled rice or vitamin and mineral premix that were not tested could have excessive levels of an applicable toxic element, for example by requesting additional information from the supplier about testing of previously supplied ingredients.
 - Corrective action: If notified by the supplier that a lot of husked, milled rice or vitamin and mineral premix has exceeded specification limits for an applicable toxic element, Manufacturer B determines if that lot has been used in any of its products. If so, Manufacturer B tests the products and determines appropriate disposition, including disposition of any product that has entered commerce. Manufacturer B discusses the problem with the supplier to determine the likely cause of the problem and obtains the supplier's agreement to correct the problem. Manufacturer B determines whether to increase verification testing from that supplier based on the likely cause and correction of the problem.
 - Corrective action: Manufacturer B discontinues use of a supplier if the supplier is not responsive to correcting a problem.

12.11.3 Manufacturer B's Verification

As verification, Manufacturer B tests finished products for inorganic arsenic, cadmium, and lead on a quarterly basis. If the level of a toxic element exceeds internal specifications for a finished product, Manufacturer B:

- conducts a root cause investigation to determine the source ingredient of the toxic element (i.e., husked, milled rice or vitamin and mineral premix);

- assesses whether changes should be made to the supply-chain program for the applicable ingredient; and
- determines appropriate disposition of the finished product after evaluating the affected food for safety, including preventing affected food from entering into commerce if Manufacturer B cannot ensure that the affected food is not adulterated under section 402 of the FD&C Act.

12.11.4 Manufacturer B's Records

Manufacturer B establishes and maintains records of:

- specifications that it establishes for levels of toxic elements in incoming husked, milled rice and vitamin-mineral premix;
- implementation of the supply-chain program as required by 21 CFR 117.475;
- results of any analytical testing to detect toxic elements in finished products; and
- disposition of finished product if the level of a toxic element exceeds internal specifications for a finished product.

Each record includes a line for Manufacturer B's PCQI to document review of the records by signing and dating the records.

12.12 Example of a Hazard Analysis by Miller C for the Control of DON During Production of Milled Wheat Products

Miller C makes milled wheat products including patent flour (i.e., a high-quality flour made from the center part of the endosperm), whole wheat flour, wheat bran, and other milled wheat products. Miller C sells some of its milled wheat products for use in human foods (e.g., patent flour and whole wheat flour) and others for use in animal foods (e.g., wheat bran). Briefly, Miller C's production process includes:

- **Wheat Receiving** – Miller C typically receives wheat RACs by truck or rail from grain elevators where the wheat RACs are stored in silos. Periodically, Miller C receives wheat RACs from entities that have stored the wheat RACs in ground piles. Miller C specifies that entities in its supply chain provide wheat RACs that meet the grade requirements for U.S. No. 1 in the U.S. Standards for Wheat as established by the FGIS (see 7 CFR part 810, Subpart M). These standards for wheat address quality defects, including those consistent with a higher probability of mycotoxin presence (e.g., mold-, insect- or weather-damaged kernels). U.S. No. 1 grade has the lowest maximum percent limits for damaged kernels.
- Miller C collects samples from each shipment for evaluation of wheat quality and for compliance with the grade requirements for U.S. No. 1.³⁴
- For shipments that do not meet the grade requirements for U.S. No. 1, Miller C:
 - Rejects that shipment; or
 - When the mill has sufficient processing capacity to make use of an electronic color sorter, Miller C:

³⁴ Miller C collects samples from incoming trucks using an automated sampling device and a sampling pattern designed to be representative of the shipment before trucks are unloaded. Miller C collects samples from wheat RACs in railcars using an autosampler that is on the receiving line and is programmed to collect samples at preset time intervals during unloading.

- separates that shipment from the main product stream by diverting it to a separate holding silo;
- conducts the physical cleaning steps applied to all wheat RACs; and
- uses an electronic optical sorter (i.e., a color sorter) to identify and remove wheat kernels potentially contaminated with mycotoxins using sorting parameters (e.g., wavelength, feed rate, and rejection rate) previously shown to be effective with the particular type of wheat; or
- When the mill does not have sufficient processing capacity to make use of the electronic color sorter, Miller C:
 - diverts the shipment to animal feed if the level of DON is within acceptable range for animals in “Guidance for Industry and FDA: Advisory Levels for Deoxynivalenol (DON) in Finished Wheat Products for Human Consumption and Grains and Grain By-Products used for Animal Feed” (Table 4 in section VI of the Introduction of this guidance);
 - diverts the shipment to domestic or foreign non-food/feed industrial applications; or
 - destroys the shipment.
- Storage of wheat RACs – Miller C stores received wheat RACs in silos that keep the wheat dry and suitable for processing into milled wheat products. Miller C uses fans to circulate air through the silo to control excessive heat and humidity and minimize the potential for growth of mold.
- Physical Cleaning – Miller C removes sticks, stones, metal fragments, non-wheat grains, chaff, and other material from the field from the wheat grains, as well as broken and damaged kernels, using a series of equipment such as screen separators, aspirators, disc separators, scourers, and washers (de-stoners). Miller C uses an insect destroyer (i.e., equipment that applies centrifugal force to grains, thereby killing live insects and their eggs) to kill any insects and their eggs. Miller C immediately moves cleaned wheat to the tempering process.
- Tempering – Miller C adds a measured amount of water to cleaned wheat to prepare the outer bran layers for easier separation in the milling process. Miller C stores the wetted wheat in bins until the tempering process is complete, typically less than 24 hours.
- Milling – Miller C passes the tempered wheat through a roller mill with corrugated rolls designed to break the grains into coarse particles. The remainder of the milling process consists of a repeated series of sifters, purifiers, and reducing rolls from which the various milled wheat products are collected and stored in silos.
- Periodic testing – Technicians who participate in an annual proficiency program (which is administered by a third-party laboratory) test inbound wheat RACs and milled wheat products for the levels of DON.³⁵ The frequency of testing varies and is increased for circumstances such as:

³⁵ FDA has issued Guidance for Industry with an advisory level for DON on finished wheat products (see Table 4 in section VI of the Introduction of this guidance). That guidance does not identify an advisory level for wheat RACs, explaining that significant variability in manufacturing processes applicable to wheat RACs does not make it practical to do so. Based on Miller C’s experience in testing in-bound wheat RACs and finished wheat products, Miller C’s PCQI determines and establishes an internal specification for a level of DON in inbound wheat RACs that is adequate to ensure that the levels of DON in its milled wheat products will not exceed FDA advisory levels for DON in milled wheat products destined for use in human foods (such as patent flour and whole wheat flour) or for use in animal foods (such as wheat bran).

- the initial receipt of “new crop” wheat RACs (i.e., wheat RACs from the initial shipments for current harvest season) to develop information on expected prevalence and levels of DON in the new crop;
- USDA’s weekly reports³⁶ of the overall condition of the wheat crop that include any specific information about the elevated prevalence and/or levels of DON in wheat RACs from a geographic region supplying Miller C;
- receipt of wheat RACs that were stored in ground piles; and
- increased detection of DON in incoming wheat RACs or milled wheat products, with verification testing conducted on every milled wheat product from wheat RACs that were processed using electronic color sorting.
- Specification for DON – Miller C considers FDA’s advisory level for DON in milled wheat products when setting internal specifications for DON in wheat RACs and milled wheat products.
- Packaging and Shipping – Miller C packages some of the finished milled wheat products in 50-pound bags that are palletized and shipped in trucks to customers or distributors. Miller C loads the remainder of the finished milled wheat products into bulk trucks for direct delivery to customers.

During the hazard analysis, Miller C’s PCQI considered that:

- Toxigenic fungi are associated with both pre-harvest and post-harvest mycotoxin contamination in cereal grain RACs such as wheat. The mycotoxin of greatest significance for wheat RACs is DON (also referred to as vomitoxin) produced by certain *Fusarium* species.
- The occurrence of DON in wheat RACs is not entirely avoidable and, thus, small amounts of DON may be detected on wheat RACs. The degree of fungal and DON contamination of the wheat RACs can vary greatly from year to year due to variability in weather conditions and damage caused by insects and fungi.
- Outbreaks of illness in humans (e.g., in China in 1984/85 and in India in 1987) resulted in nausea, vomiting, gastrointestinal upset, dizziness, diarrhea, and headache (see “Guidance for Industry and FDA: Advisory Levels for Deoxynivalenol (DON) in Finished Wheat Products for Human Consumption and Grains and Grain By-Products used for Animal Feed” (Table 4 in section VI of the Introduction of this guidance)). The toxic effects of DON in animals include vomiting and anorexia, alteration of intestinal and immune functions, reduced absorption of nutrients, as well as increased susceptibility to infection and chronic diseases (Payros et al., 2016). There is limited information on the health effects of chronic exposure in humans, but studies indicate long-term effects could include growth suppression in children (Pieters et al., 2002 and Mishra et al., 2019). FDA has an advisory level for DON on finished wheat products (e.g., flour, bran, and germ) that may potentially be consumed by humans (see Table 4 in section VI of the Introduction of this guidance). In setting that advisory level, FDA considered the available reports of acute illness, which occurred outside the United States; and
- The CGMP measures that Miller C has in place to control DON in wheat RACs include:

³⁶ See <https://grains.org/markets-tools-data/reports/usda-reports/>. The USDA Crop Production Progress Report is issued weekly during the U.S. growing season (April to November), listing planting, fruiting, and harvesting progress and overall condition of selected crops in major producing states. Videos are available as a subscription service (<https://www.neogen.com/mycotoxin-crop-report/>).

- specifying that entities in its supply chain provide wheat RACs that meet the grade requirements for U.S. No. 1 (which has the lowest maximum percent limits for damaged kernels that have a higher probability of mycotoxin presence);
- physical cleaning processes for wheat RACs, including removal of broken and damaged kernels;
- sampling and visually inspecting inbound wheat RACs for compliance with the grade requirements for U.S. No. 1; for shipments that do not meet the grade requirements for U.S. No. 1, either:
 - rejecting that shipment; or
 - separating that shipment from the main product stream and using electronic vision equipment (i.e., a color sorter) in addition to physical cleaning processes to identify and remove wheat kernels potentially contaminated with mycotoxins from the product stream, and sampling and testing milled wheat products for levels of DON;
- control of heat and humidity during storage; and
- periodic sampling and testing of incoming wheat RACs and milled wheat products for the levels of DON.

Miller C concludes that the procedures, practices, and processes that the Miller already employs to address mycotoxin hazards during the manufacturing/processing of wheat RACs into milled flours are such that it would be unlikely that DON would be present at levels that could cause illness or injury, unless seasonal information about incoming wheat RACs indicate the potential for higher levels of DON than expected. The outcome of Miller C's hazard analysis is that the hazard of DON in wheat RACs is not a hazard requiring a preventive control unless the available information (such as the test results for incoming RACs and milled wheat products associated with "new crop" wheat or USDA's weekly reports) indicate the potential for higher levels of DON than expected.

When the potential for higher than expected levels of DON is indicated, Miller C:

- implements its physical cleaning processes as a preventive control and maximizes use of the electronic color sorter (with monitoring through observation that the equipment used for cleaning and the electronic color sorter are on and functioning);
- conducts increased sampling and testing of milled wheat products as verification of its preventive control;
- takes corrective actions on milled wheat products that have levels of DON that exceed Miller C's specifications to divert those milled wheat products to animal feed or to non-food/feed industrial applications or destroy them; and
- maintains records of the monitoring, verification, and corrective actions taken.

12.13 Example of Hazard Analysis by Baker D for the Control of DON in Bread Products Made with Wheat Flour

Baker D receives wheat flour from Miller C and from Miller E and uses the flour to make bread products that include pre-sliced sandwich breads and artisanal breads.

- Miller C is a small business as defined in 21 CFR 117.3 and receives relatively large shipments of wheat RACs by truck or railcar. Miller C's procedures, processes, and practices for the production of flour from wheat RACs include specifying that entities in its

supply chain provide wheat RACs that meet the grade requirements for U.S. No. 1; physical cleaning processes for wheat RACs; sampling and visually inspecting inbound wheat RACs for compliance with the grade requirements for U.S. No. 1; control of heat and humidity during storage; and periodic sampling and testing of incoming wheat RACs and milled wheat products for the levels of DON. Miller C implements its procedures, processes, and practices for the production of flour from wheat RACs as a CGMP program. However, when the potential for higher than expected levels of DON is indicated, Miller C implements its physical cleaning processes as a preventive control (i.e., process control), with increased testing of milled wheat products as verification of the process control.

- Miller E is a very small business as defined in 21 CFR 117.3. Miller E receives relatively small shipments of heritage wheat RACs by truck and does not specify that entities in its supply chain provide wheat RACs that meet the grade requirements for U.S. No. 1. Miller E's procedures, processes, and practices for the production of flour from wheat RACs include physical cleaning processes for wheat RACs and control of heat and humidity during storage. Miller E does not have a program for periodic sampling and testing of incoming wheat RACs or the flour that Miller E produces for the levels of DON. However, Miller E checks USDA's weekly reports and samples and tests some lots of its flour for DON when abnormally cool, wet conditions during a growing season could produce higher than normal levels of DON in wheat RACs.

During the hazard analysis, the PCQI for Baker D considered that:

- Toxigenic fungi are associated with mycotoxin contamination in cereal grain RACs such as wheat. The mycotoxin that is of greatest significance for wheat RACs is DON, produced by certain *Fusarium* species. FDA has identified an advisory level for DON on finished wheat products (see Table 4 in section VI of the Introduction of this guidance). The presence of DON in milled wheat products is controlled by the miller through appropriate storage of wheat RACs and the overall milling process. Although DON is sometimes found in wheat grown under normal weather conditions, the fungus that produces DON thrives in cool, wet conditions and, thus, abnormally cool, wet conditions during a growing season could produce higher than normal levels of DON in wheat RACs.
- As part of its process for entering into purchase agreements with suppliers of flour, Baker D reviews each miller's applicable procedures, processes, and practices for receiving, storing, cleaning, and milling wheat.
 - When the miller's procedures, processes, and practices include a program for analytical testing for DON (which is the case for Miller C), Baker D reviews those test results to confirm that the levels of DON are consistent with the FDA advisory level before entering into a purchase agreement. Baker D's purchase agreement with Miller C specifies that the miller inform Baker D when the potential for higher than expected levels of DON is indicated in wheat RACs, and that Baker D may request a COA (which includes the results of analytical testing for the presence of DON) from Miller C for each shipment of flour under such circumstances.
 - When the miller's procedures, processes, and practices do not include a program for analytical testing for DON (which is the case for Miller E), Baker D arranges for analytical testing on several shipments of flour from that miller to confirm that the levels of DON are consistent with the FDA advisory level before entering into a purchase agreement. Baker D's purchase agreement with Miller E specifies that the miller inform Baker D when the potential for higher than expected levels of DON is indicated in wheat RACs. Baker D's purchase agreement with Miller E also specifies that Baker D may add an acceptance criterion to its purchase agreement for each shipment of flour under such

circumstances. That additional acceptance criterion specifies that Baker D's decision to accept a shipment of flour is conditional on the results of analytical tests for the presence of DON, with the tests conducted by either Miller E or Baker D.

Baker D concludes that the procedures, practices, and processes that the Baker includes in its purchase agreements are adequate to provide assurance that DON is unlikely to be present at levels that could cause illness or injury, unless information about a growing season indicates the potential for higher levels of DON than expected. The outcome of Baker D's hazard analysis is that the hazard of DON in wheat RACs is not a hazard requiring a preventive control. When the potential for higher than expected levels of DON is indicated during a growing season, Baker D uses the conditions specified in its purchase agreements (e.g., requesting a COA from Miller C for each shipment with a potential for higher than expected levels of DON; and analytical testing for the presence of DON by either Miller E or Baker D) to verify that each miller continues to control DON in the flour it produces from wheat under such circumstances.

12.14 Example of a Hazard Analysis by Sandwich Maker F for the Control of DON in Sandwiches Made with Bread Produced with Wheat Flour

Sandwich Maker F receives pre-sliced wheat bread from Baker D and uses it to make sandwiches for distribution to retail food establishments.

During the hazard analysis, the PCQI for Sandwich Maker F considered that:

- Toxigenic fungi are associated with mycotoxin contamination in cereal grain RACs such as wheat. The mycotoxin that is of greatest significance for wheat RACs is DON, produced by certain *Fusarium* species. FDA has identified an advisory level for DON on finished wheat products (see Table 4 in section VI of the Introduction of this guidance). The presence of DON in milled wheat products is controlled by the miller through selection of incoming wheat RACs, appropriate storage of wheat RACs, and the overall milling process.
- As part of its process for entering into purchase agreements with suppliers of pre-sliced bread, Sandwich Maker F reviews the procedures, processes, and practices applicable to the supplier's evaluation of the adequacy of the miller's program to control the level of DON in milled wheat products, including whether and how the miller adapts its program when the potential for higher than expected levels of DON in wheat RACs is indicated.

Sandwich Maker F concludes that the procedures, practices, and processes that it includes in its purchase agreements are adequate to provide assurance that DON is unlikely to be present at levels that could cause illness or injury. The outcome of Sandwich Maker F's hazard analysis is that the hazard of DON in pre-sliced bread is not a hazard requiring a preventive control.

12.15 References

Section VII in the Introduction of this guidance intends to include all references cited in this guidance, including most references cited in this chapter. When a reference listed in section VII of the Introduction of this guidance includes a website address, FDA has verified the website address, as of the date the notice of availability for the Introduction of this guidance publishes in the *Federal Register*, but websites are subject to change over time.

See below for additional references that are cited in this chapter but not yet included in the Introduction of this guidance. We intend to include these references in the Introduction when we next update it.

CDC, 2024. Lead and Chromium Poisoning Outbreak Linked to Cinnamon Applesauce Pouches. Update. Available at <https://www.cdc.gov/nceh/lead/news/lead-poisoning-outbreak-linked-to-cinnamon-applesauce-pouches.html>.

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12.16 Resources

See section 12.2 for a description of resources that we have included in section VI in the Introduction of this guidance. See below for additional resources that are cited in this chapter but not yet included in the Introduction. We intend to include these resources in the Introduction when we next update it.

Addition to Table 5: Import Alert 99-05 Detention Without Physical Examination Of Raw Agricultural Products for Pesticides

Addition to Table 5: Import alert 99-14 Countrywide Detention Without Physical Examination Of Raw Agricultural Products for Pesticides

Addition to Table 5: Import Alert 99-14 Countrywide Detention Without Physical Examination Of Raw Agricultural Products for Pesticides

Addition to Table 5: Import Alert 99-08 Detention without Physical Examination of Processed Human and Animal Foods for Pesticides

Addition to Table 5: Import Alert 99-47 Detention Without Physical Examination of Human Food Products That Appear to be Adulterated for Economic Gain

Addition to Table 8: FDA. 2009. Memorandum of Understanding with USDA (FSIS and AMS) and EPA regarding regulatory activities concerning residues of drugs, pesticides, and environmental contaminants in foods (MOU 225-85-8400). Available at <https://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm116368.htm>.

Addition to Table 8: FDA website "Food Chemical Safety." Available at <https://www.fda.gov/food/food-ingredients-packaging/food-chemical-safety>.

Addition to Table 8: "Human Food Made with Cultured Animal Cells Inventory." Available at <https://www.fda.gov/food/human-food-made-cultured-animal-cells/inventory-completed-pre-market-consultations-human-food-made-cultured-animal-cells>

Addition to Table 8: FDA website “Post-market Determinations that the Use of a Substance is Not GRAS.” Available at <https://www.fda.gov/food/generally-recognized-safe-gras/post-market-determinations-use-substance-not-gras>

Addition to Table 8: Overview of U.S. Wheat Inspection. This booklet was printed by U.S. Wheat Associates in cooperation with the USDA/AMS/FGIS to provide information on the national, official grain inspection and weighing system used in the United States of America. Revised 2021. Available at <https://www.uswheat.org/wp-content/uploads/Overview-of-U.S.-Wheat-Inspection.pdf>

Addition to Table 8: USDA Crop Production Progress Report. Available at <https://grains.org/markets-tools-data/reports/usda-reports/>

Addition to Table 8: USDA Crop Production Progress Report Available at <https://www.neogen.com/mycotoxin-crop-report/>