Economically motivated adulteration:
implications for food protection and alternate approaches to detection

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DEDICATION

This dissertation is dedicated to Tim, my parents, and my brother.

ABSTRACT

The food supply system is vulnerable to various types of contamination and adulteration. This research focuses on economically motivated adulteration (often called "food fraud"). Economically motivated adulteration (EMA) refers to the knowingly selling a food product that is not up to standards in order to gain economic advantage. There is a long history of EMA in a wide variety of food products. The food safety paradigm is not sufficient for food defense, or for prevention and deterrence of EMA. The goal of this research was to develop methods to improve capabilities for preventing and detecting EMA incidents.

First, the food ingredient monographs in the United States Pharmacopeial (USP) Convention Food Chemicals Codex (FCC) were evaluated for susceptibility to EMA. These evaluations can be used to help target the most susceptible ingredients for monograph modernization within USP, and for inspection and laboratory testing resources by regulatory agencies. Second, economic and production data for dairy products in China leading up to the melamine adulteration event was analyzed to evaluate the utility of this data for alerting to the potential for EMA in a food commodity. This analysis shed insight on variables that may be useful for tracking the production of global commodities for early indications of EMA. Finally, a surveillance technique for trade data was evaluated using melamine adulteration of wheat gluten as a case study. This biosurveillance-like methodology can be applied to food import data to identify supply chain shifts that could indicate changes in the market for food products and a heightened risk of EMA.

Regulatory agencies have an enormous burden of responsibility for regulating the food supply for both domestically-produced and imported food products. Given the constrained resources of these agencies, they need improved methods for targeting those resources towards the riskiest food products. These preliminary efforts to shed light on EMA vulnerabilities and potential mitigation efforts can contribute to efforts in that area. An integrated, systems-based approach to food protection that encompasses both food safety and food defense is imperative for ensuring the integrity of our food supply.

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CHAPTER 1: Introduction

The food supply system is vulnerable to various types of contamination and adulteration. The vulnerability of the food system to unintentional contamination is well-known and has been repeatedly demonstrated by large-scale foodborne outbreaks. Recent outbreaks include *E. coli* O104:H4 contamination of sprouts that infected thousands of people in multiple European countries in 2011 *(118)*; *Salmonella* Typhimurium contamination of peanut products that caused illness in more than 700 people in 46 states in 2008-9, and resulted in the recall of thousands of food products *(64)*; and *Salmonella* Montevideo contamination of imported pepper-coated salami that infected almost 300 people in 44 states in 2009-10 *(70)*. Incidents of intentional adulteration of the food supply with intent to cause harm are rarer. Examples include *Salmonella* Typhimurium adulteration of restaurant salad bars in Oregon by a religious cult in 1984 in an effort to affect voter turnout, which caused illness in over 700 people *(188)*; and *Shigella dysenteriae* adulteration of food items in a work place by a disgruntled laboratory worker in Texas in 1996, which caused illness in 12 people *(122)*. More recently, in 2004, trace amounts of ricin were detected in two jars of brand-name baby food, but a perpetrator was not identified *(146)*. The vulnerability of the food system to intentional adulteration for economic gain, with the intent not to cause harm or be detected, is less understood. This type of adulteration, economically-motivated adulteration (EMA), was most strikingly demonstrated by the melamine adulteration of dairy products in 2008, which resulted in illness in thousands of infants in China and the deaths of at least six *(104,*

179).

Large-scale foodborne outbreaks and EMA incidents cost society millions in medical care, lost wages, and lost industry profit *(174, 176, 200, 214)*. They also illustrate vulnerabilities in the food supply system that could potentially be exploited by people intent on causing widespread illness, death, or economic damage. A successful attack on the food supply could result in significant morbidity and mortality, economic and trade consequences, a strain on our public health systems, and political instability *(221)*. Homeland Security Presidential Directive 9 declared the U.S. food and agriculture sector to be a critical infrastructure that should be protected from intentional harm *(62)*. The World Health Organization (WHO) World Health Report 2007 identified unintentional and intentional contamination of food as one of the global public health threats in the 21st century *(221, 222)*. Public health and regulatory agencies, academia, and industry have spent decades implementing and refining food safety efforts. In the past ten years, the increasing importance of implementing food defense strategies has become evident. Under the Food Safety Modernization Act (FSMA), passed in 2011, the food industry will be held increasingly accountable for mitigating both food safety and food defense risks.

Food safety, food defense, and food protection

The term "food security" refers to sufficiency in the food supply, or access by people to sufficient quantities of nutritionally adequate food *(63)*. "Food safety" refers to the reliability of the food system in terms of reducing exposure to expected and unintentional hazards. "Food defense" refers to the resiliency of the food system to

intentional attacks *(63)*. These attacks may be motivated by the desire to inflict physical or economic harm *(77)*, or the desire for economic gain. Intentional attacks on the food supply may involve the use of known food safety hazards, recognized biological, chemical, or radiological terrorism agents, or novel agents *(71, 72, 127)*. "Food protection" broadly covers both the safety and defense of the food supply. A comprehensive food protection plan relies on integrated food safety and food defense control methods.

Food safety: laboratory-based surveillance and outbreak detection

Foodborne contamination incidents are most often unintentional, resulting from environmental contamination during growth, harvest, or processing, or contamination by infected food handlers. The true number of foodborne illnesses experienced in the U.S. every year is unknown, but the Centers for Disease Control and Prevention (CDC) estimates that approximately 48 million people per year experience foodborne illness *(172, 173)*. Surveillance for foodborne pathogens in food, and human illnesses resulting from those pathogens, is conducted by multiple stakeholders, including food production companies, public health agencies, and regulatory agencies. Surveillance and sampling for specific foodborne pathogens routinely happens during many food production processes; for example, *E. coli* spp. in ground beef and *Listeria* spp. in many ready-to-eat foods. A very limited amount of testing by federal agencies of imported food products occurs at the ports of entry.

There are approximately 1,100 documented foodborne disease outbreaks nationwide per year in the U.S. *(65)*. Detection of foodborne outbreaks of bacterial

pathogens most often occurs through surveillance of laboratory-confirmed human infections by state and local public health departments. In Minnesota (as in many other states), human infections with certain pathogens are reportable to the state health department *(139, 182)*. This enables the health department to conduct follow-up interviews with case patients to identify possible common causes *(135)*. Confirmed foodborne illnesses and potential outbreaks are then voluntarily reported to the CDC by state and local health departments. Pulsed-field gel electrophoresis (PFGE) subtyping of bacterial isolates at the state public health laboratory, combined with the nationwide CDC PulseNet system *(73)* has resulted in the identification of multiple nationwide foodborne outbreaks over the past few years *(66, 67, 69)*. PFGE can be a particularly effective means of identifying widespread foodborne outbreaks of *Salmonella* and *E. coli* when testing is conducted in real time. Real-time PFGE subtyping at public health laboratories refers to the practice of conducting PFGE testing quickly enough for the results to be actively used in identifying and investigating foodborne outbreaks - typically, within a few days of receiving isolates. Many state public health laboratories are unable to perform real-time PFGE due to budget constraints. Prioritization of PFGE subtyping of *Salmonella* and *E. coli* isolates by the Minnesota Department of Health (MDH) Public Health Laboratory is one reason MDH is so proficient at identifying and quickly investigating foodborne outbreaks of these pathogens. Foodborne disease surveillance and PFGE subtyping of isolates are powerful tools. However, successful surveillance for bacterial foodborne pathogens depends on many factors, and the number of reported cases of any given foodborne pathogen is widely considered to be merely the tip of the

iceberg.

In addition to bacterial subtype identification and coordination among multiple health agencies *(73)*, foodborne outbreaks are also detected through consumer complaint systems *(131, 140)*, and reports from medical providers or poison control centers *(131)*. Once a possible outbreak is identified, epidemiologic methods can confirm the outbreak and enable identification of the implicated food vehicle in many cases. These epidemiologic methods typically include detailed patient interviews combined with laboratory data and statistical methods where appropriate.

Foodborne disease surveillance, outbreak detection, and outbreak investigations are inherently reactive processes. Ideally, the results of thorough outbreak investigations are able to prevent further cases of illness and inform food safety measures with the ultimate goal of preventing future outbreaks.

Food safety: complaint-based surveillance and outbreak detection

Many state and local health departments across the country conduct complaint-based surveillance for foodborne illness, in addition to laboratory-based surveillance. Complaint-based surveillance has the potential to detect foodborne outbreaks from any number of foodborne pathogens, but is particularly useful for detecting outbreaks caused by non-reportable pathogens such as norovirus. In 2007, 82% of the 61 confirmed foodborne outbreaks identified in Minnesota were initially reported by a complaint call from the public, whereas 16% were initially identified through routine laboratory-based surveillance of reportable pathogens *(138)*. The remaining outbreak (2%) was identified through a report from Poison Control. Complaint surveillance systems can also help

identify outbreaks due to reportable pathogens earlier than they would have been detected through routine laboratory-based surveillance *(131)*. There can be a lag time of 2-3 weeks from onset of illness to report of laboratory results to the state health department. MDH has a well-developed and successful centralized foodborne illness complaint surveillance system *(131)*, including a hotline that receives calls from the public about suspected foodborne illness. The Minnesota Food Code *(141)* also requires that restaurant managers report any consumer complaints about possible foodborne illness to the local or state health department.

Information collected from callers to the MDH foodborne illness hotline *(140)* includes a detailed illness history (including onset dates and times), detailed information about the suspected meal and others who shared the meal, as well as a four-day food history. Data collected from all complaint reports are entered into a complaint database, which aids in the ability to quickly identify and respond to potential outbreaks *(131)*. Complaint surveillance systems exist in various forms at state and local health departments across the country. In a recent survey of local health departments, 81% reported using complaint-based surveillance for foodborne illness *(130)*. Most health departments with a complaint system collected at least some of the same data types listed above. Health departments without complaint-based surveillance systems indicated that cost, lack of resources, and lack of personnel were the leading barriers. The survey also found that use of an electronic complaint database and systematic review of complaints for common exposures was associated with higher rates of outbreak detection *(130)*.

Food defense: intentional adulteration

Intentional food adulteration takes two basic forms: adulteration with the intent to cause physical or economic harm (such as terrorist attacks) or adulteration with a goal of not causing harm or being detected (for economic gain). Intentional adulteration for economic gain will be referred to as economically-motivated adulteration (EMA). The term "intentional adulteration" will therefore refer to incidents that were intended to cause harm; this may be either physical harm to those consuming the food products or harm with the goal of competitive business advantage.

Fewer than thirty incidents of intentional adulteration of food, water, or over-the counter medications have been documented in the United States since 1960 *(146)*. With few exceptions, these incidents were localized and involved fewer than 50 cases of illnesses. Noted exceptions include: the widely-publicized contamination of salad bars with *Salmonella* Typhimurium in 1984 that resulted in more than 700 illnesses, which was politically motivated *(188)*; ground beef contamination with nicotine sulfate by a disgruntled store employee in 2002 that resulted in more than 110 illnesses *(68)*; and contamination of coffee and snacks at a church group function with arsenic in 2003 that resulted in a handful of illnesses plus one death (this was perpetrated by a single actor who may have been motivated by personal relationship conflicts) *(146)*.

Detection of incidents of intentional adulteration of food generally happens in the same way detection of foodborne illness happens, through clinical or laboratory reporting routes, or consumer complaints. If the adulterant is also a common pathogen, as in the example of *Salmonella* Typhimurium contamination of salad bars, it may be unknown at the beginning of the outbreak investigation whether the contamination was intentional or

unintentional.

Food defense: the history of economically motivated adulteration (EMA)

The Food and Drug Administration (FDA) "working definition" of EMA is the "fraudulent, intentional substitution or addition of a substance for the purpose of increasing the apparent value of the product or reducing the cost of its production" *(28)*. The FDA definition of EMA encompasses food products as well as products such as dietary supplements, tobacco, cosmetics, pharmaceuticals, and medical device equipment. The more general term "food fraud" encompasses EMA, and is used to explicitly include economically-motivated misbranding, theft, diversion, simulation, smuggling and counterfeiting which are considered "adulteration" under FD&C, but may not contain a substituted material *(180)*. For the purposes of these studies, we focus only on food products, and define EMA as knowingly selling a product that is not up to standards in order to gain economic advantage. This includes addition of a fraudulent ingredient, dilution, substitution, simulation, and mislabeling.

In contrast to intentional adulteration of food, there are many documented instances of EMA that have occurred in a wide variety of food products both domestically and globally. We defined an incident as a "documented, isolated occurrence of EMA within a defined time frame with a distinct group of perpetrators" *(82)*. Systemic occurrences that could not be easily assigned to a defined time frame or perpetrator were considered to be one incident (for example, melamine adulteration of dairy products in China). Our literature and media search of incidents since 1980 resulted in 137 unique EMA incidents that were categorized into 11 food categories (see Figure 1).

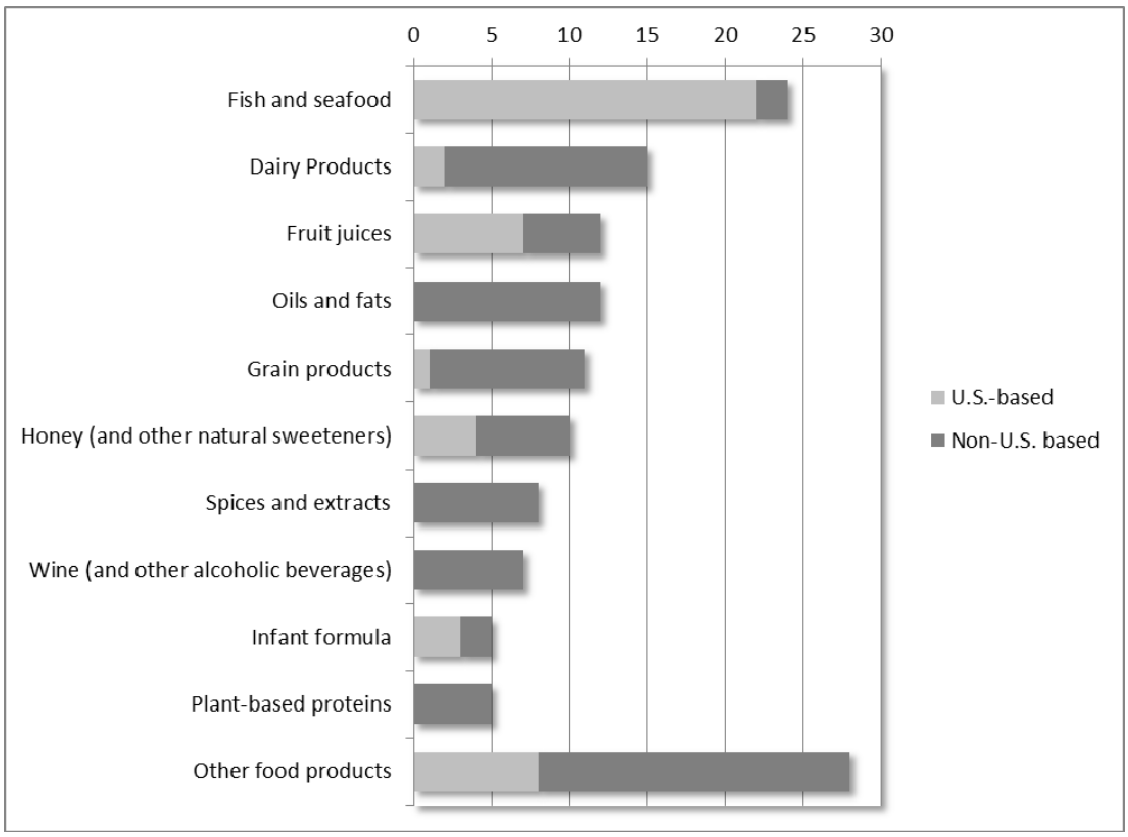


Figure 1. Number of EMA incidents in each food category, by location of adulteration (N=137).

Fish and seafood products accounted for the largest number of EMA incidents. Species substitution is the most common form of EMA in seafood products. A survey conducted in 2008-9 took 500 retail fish samples and matched them to the Barcode of Life DNA database at the University of Guelph *(4)*. The samples were collected from supermarkets, fish markets, and restaurants, and about 25% of the samples were found to be misidentified or mislabeled *(171)*. All the substituted fish were species of lower market value than the species for which they were substituted. Multiple seafood fraud surveys have been conducted over the years with similar results: the National Seafood

Inspection Laboratory found 37% of fish samples collected over a nine-year period were mislabeled *(187)*; the mislabeling of red snapper in the U.S. has been a widespread and ongoing problem *(110, 111, 134)*; inexpensive domestic fish eggs were substituted for imported Russian beluga caviar in Maryland *(97, 105)*; sales of fake grouper have been pervasive in Florida *(41, 166)*; and 10-15% of "wild-caught" salmon, sea bass, and sea bream sampled in the U.K. were actually farmed *(81)*. Other forms of seafood EMA include artificially increasing the weight of the product, misrepresenting the country of origin, and using illegal chemicals in production.

Most of the EMA incidents in dairy products originated outside of the U.S. In 2008, close to 300,000 children became ill and six died because at least 22 Chinese food companies sold milk products, including baby formula, containing melamine *(112)*. The adulteration was detected after an unusually high number of infants became ill and developed kidney stones *(12, 54)*. The two main tests to determine the protein content of dairy products at the time relied on determining total nitrogen content as a proxy for protein *(149)*. Since the tests did not distinguish between nitrogen from protein sources and nitrogen from non-protein sources, the addition of nitrogen-rich melamine artificially inflated protein test results *(104)*. This enabled dairy producers to dilute their milk but maintain admissible protein-level readings. There was no established quality assurance mechanism for the detection of melamine in dairy products at the time because it was not an expected additive. The addition of melamine to dairy products in China was widespread and, reportedly, dated back a number of years *(55, 128, 189)*. The extent of the product recalls illustrated the long and complicated supply chains that existed for

products made with liquid milk, the original point of adulteration. At least 47 countries received melamine-contaminated products. The adulteration of milk with substances intended to artificially inflate protein readings has already proven to be an ongoing problem. In 2009, Chinese dairy products were found to contain hydrolyzed leather protein, which is derived from animal skin and may be processed with harmful chemicals *(2)*.

Pure and fresh-squeezed fruit juices are relatively expensive to produce, making the prospect of even partial dilution an attractive one because producers can gain a distinct market advantage. According to FDA, the most common forms of juice adulteration are the addition of some form of sugar and water, the addition of pulpwash solids, the substitution of a less expensive juice, the addition of unapproved preservatives, and labeling reconstituted juice as fresh-squeezed *(193)*. There are many documented instances of juice companies "extending" or otherwise adulterating juice *(50, 170)*. A 1995 report by the U.S. General Accounting Office (GAO) estimated the rate of adulteration of orange juice in the U.S. was from 1% to 20% *(204)*. Apple juice has also been a problem; in November 1986, Beech-Nut Nutrition Corporation and its suppliers were indicted on charges of conspiring to sell adulterated and misbranded apple juice *(123)*. Reportedly, in 1978, Beech-Nut became aware that the apple juice concentrate they were buying from a supplier for 20-25% below market price was likely adulterated with various sugars, artificial colors and flavorings, and contained little if any apple juice *(59, 123, 143)*. However, the company continued to buy the product and market it as "100% apple juice." In June 1982, an investigator tracked a shipment of counterfeit apple

juice concentrate from a supplier to the Beech-Nut plant and informed the company of the findings *(144, 190)*. In July, state and federal investigators informed Beech-Nut that they had tested apple juice at retail sale and found it to be adulterated. Beech-Nut agreed to a recall of apple juice in October 1982, but continued to add the implicated concentrate to mixed juices and other products after the recall *(145, 190)*. Beech-Nut eventually pleaded guilty to selling fraudulent apple juice, including more than 200 felony counts and food and drug law violations *(220)*. The company paid a $2 million fine, and two executives were found guilty of violating federal laws *(59)*. The sharp increase in the demand for pomegranate juice in recent years has made it an attractive target for adulteration. In 2008, Pom Wonderful, LLC won a case against a smaller beverage company, Purely Juice, Inc., for false advertising *(107, 203)*. Purely Juice had advertised their product as "100% pomegranate juice" when it contained only small amounts of juice along with high fructose corn syrup. Purely Juice reportedly sourced pomegranate juice concentrate from suppliers in the Middle East at prices that were far below the market rate for pure juice.

Olive oil is prone to EMA due to its high demand and potential profit margin. According to the International Olive Oil Council (IOOC), extra virgin olive oil must be extracted only through physical means and have a strictly defined amount of free acidity *(26)*. Free acidity is a quality parameter that indicates chemical degradation (or rancidity). Trade associations such as the North American Olive Oil Association (NAOOA) have argued that the opportunity for fraud has existed because the U.S. did not have strict quality standards for olive oil until recently. In October 2010, the United States adopted

olive oil standards similar to the IOOC standards *(27, 152)*. However, more than 99% of the olive oil consumed in the U.S. is produced in other countries *(9)*, and is therefore subject to the quality assurance and regulatory systems of those countries. There are multiple analytical testing methods for olive oil, and new methods are continually being developed *(86, 96)*. Producers of fraudulent oil have kept pace with new testing methods by altering the characteristics of the adulterated oil to evade detection *(45)*. In 1992, the FDA received a report claiming that a vegetable oil distributor in Ohio was blending canola oil into oil labeled as olive oil *(108)*. A sample analyzed by the FDA contained 42-68% canola oil. The FDA collected evidence of widespread EMA by the distributor, including adulteration of various grades of olive oil with less expensive oils. They also found evidence that the company adulterated the products that were least likely to be tested by industry trade group or grocery chain product testing programs. Reports of internationally-produced adulterated or counterfeit olive oil are common. Lower grades of olive oil (non-virgin or olive pomace oil) have been sold as extra virgin olive oil, and other types of oils have been mixed in with olive oil (such as canola, hazelnut, sunflower, or colza oil) *(10, 18, 103, 199)*. Low-grade olive oils have also been imported from other countries and repackaged as locally-produced *(13)*. In a particularly tragic case in 1981, denatured oil that was intended for industrial use was sold door-to-door as olive oil in Spain and resulted in almost 20,000 illnesses and more than 300 deaths *(162)*. Although olive oil appears to be the most commonly adulterated oil, other food oils and fats have also been adulterated. In 2000, large-scale fraud involving fake butter was uncovered by the European Commission *(87, 132)*. Nigeria has had problems with the adulteration of

palm oil with water and a chemical colorant *(212)*. Finally, more recently, the illegal reuse of potentially carcinogenic discarded kitchen oil, dubbed "gutter oil," has been a widespread problem in China *(225)*.

Grain products have been adulterated in a variety of ways. In 1990, the owners of a Minnesota grain company pleaded guilty to adding urea (a nitrogen-rich chemical used in fertilizer) to wheat before selling it to flour companies because it increased the price per bushel due to the higher apparent protein content *(88)*. Prior to this, urea had routinely been added to animal feeds for nitrogen-enrichment before routine urea testing was implemented *(43)*. In 2004, a survey by the Food Standards Agency in the U.K. found 63 (17%) of 196 samples of Basmati rice at retail contained non-Basmati rice in a proportion greater than 20% *(95)*. As a result, they updated the Code of Practice for Basmati rice in 2005 *(48, 56)*. In 2011, a food company in China was shut down for producing steamed corn buns that were actually produced with wheat flour (a potential allergen), artificial colorings, and artificial corn flavoring *(3)*. The same year, Italy uncovered a so-called "food fraud ring" that involved false certification of foods as organic; the seized products included grains that were falsely labeled as organic *(29)*.

EMA in imported honey has been a big problem in recent years, typically involving false country-of-origin labeling, corn syrup adulteration, and illegal antibiotic use. There is no national U.S. standard of identity for honey, although Florida, California, Wisconsin, and North Carolina have all adopted state standards over the past two years that prohibit additives to natural honey *(7)*. Before the development of high-fructose corn syrup in the 1970s, the adulteration of honey typically involved invert syrup, glucose

syrup, or corn syrup, and was easily detectable *(76, 154)*. Since the sugar profile of high-fructose corn syrup is similar to honey, it is generally more difficult to detect. A survey of U.S. honey packers reported that 71% of the firms that tested for economic adulteration in their honey supplies had found adulterated honey *(83)*. The average detected level of adulterant ranged from about 6% to 43% from 1996 through 1998. Of the adulterated honey detected, China and Argentina were the sources of more than 90% of the adulterated honey in all three survey years. The use of chloramphenicol in bees in China resulted in a two-year ban of Chinese honey in the EU and Canada beginning in 2002 *(125)*. Chloramphenicol is an antibiotic that was used on bee populations in China following an epidemic of foulbrood in the late 1990s. It is prohibited for use in food production animals in the U.S. Although Chinese honey is not currently banned in the U.S., it is subject to additional testing for chloramphenicol at the borders *(129)*, as well as high tariffs to prevent dumping on the market *(161)*. Adding to the demand for imported honey has been a recent decrease in the domestic production of honey in the U.S. due to colony collapse disorder *(116)*. So-called "honey laundering" is a problem that has emerged in recent years *(80, 129)*. In 2010, eleven people and six companies were indicted on conspiracy charges of illegally importing Chinese honey, thereby avoiding almost eighty million dollars in anti-dumping tariffs *(192)*. There has been widespread documentation that Chinese honey has been shipped to other countries, re-packaged, and re-exported for shipment to the U.S., in order to avoid taxes and inspections *(40, 129)*.

Spices are particularly susceptible to adulteration because they are often sold in powdered form, they have long and complicated supply chains, and quality or

performance losses in final food products can be difficult to detect *(151)*. Dyes may be added to make a spice look fresher, older spices may be mixed with freshly ground ones *(51)*, non-spice material may be added as an extender, or "spent" spices with valuable constituents removed may be sold as whole spices *(36)*. In 1994, domestic sales and exports of paprika were banned in Hungary because lesser-grade powdered paprika had been imported from Romania and mixed with lead oxide for color, resulting in more than 60 hospitalizations *(19, 20)*. In 2005, contamination of chili powder with the dye Sudan 1 caused recalls of hundreds of food products worldwide. Sudan 1 is an industrial dye classified as a category 3 carcinogen *(17)*. A British company imported the contaminated chili powder from India and added it to Worcestershire sauce, which was subsequently used in the manufacturing of hundreds of food products *(164)*. The chili powder was originally imported from India and passed through the hands of at least seven different companies in India and Britain before being bought by the makers of the Worcestershire sauce *(79, 126, 136)*.

Wine has a long history of containing additives and adulterants *(160, 219)*. Consequently, multiple regulatory systems have been established for quality control, including the Appellation D'origine Controlée (AOC) system in France, the Denominazione di Origine Controllata in Italy, the EU Protected Designation of Origin (PDO), and the American Viticultural Area (AVA) system in the U.S. Wine is an attractive target for adulteration because desirable varieties are very profitable and identifying adulteration can be difficult. In July 1985, West German authorities announced that some Austrian dessert wines were contaminated with diethylene glycol

(DEG), a solvent with multiple industrial and commercial applications. By December of 1985, the U.S. Bureau of Alcohol, Tobacco and Firearms (BATF) had detected DEG in 81 different brands of wine sold in the U.S. *(205)*. The adulteration was discovered after an Austrian tax inspector noticed that a wine producer was claiming tax refunds on large quantities of DEG *(24)*. Many Austrian wines were sold in bulk to West Germany *(21)*, for blending with wines produced domestically. Indeed, multiple wines labeled as West German were found to be contaminated with DEG, indicating they had been blended with the Austrian wine *(23, 102)*. At the time, neither BATF nor FDA routinely tested wine for the presence of contaminants, and had no reason to test wine for DEG *(205)*. The adulterated Austrian wines were sold as expensive white dessert wines. The theory at the time was that DEG was added specifically to increase sweetness. However, the quantity of DEG found in some wines apparently was not large enough to affect taste *(22)*. A more compelling argument was that DEG was used to add body to the wine, and possibly to mask the addition of sugar for sweetness *(177)*. The use of DEG in Austrian wine was advantageous because it could be added in small quantities to have the desired effect and, as a novel wine adulterant, did not have routine QA tests associated with it. In addition, the chemical did not have any short-term health effects in the typical quantities being ingested. Presumably, the wine fraud could have continued for much longer had it not been discovered by the tax inspector. In 2008 and 2009, Italian officials removed the varietal classification from almost two million liters of high value wine from five wineries because it was made with unauthorized grapes *(38)*. In 2002 in the Bordeaux region of France, large-scale fraud was discovered as producers were importing cheaper

wine from other regions and selling it with the Bordeaux label *(159)*. Other alcoholic beverages have also been prone to adulteration. Methanol is commonly used to boost alcohol content because of its similarity to ethanol, although it is toxic. In 2000, more than 100 people died in El Salvador after consuming liquor that was contaminated with methanol *(124)*. At least 20 people died in another methanol-adulterated liquor incident in the Czech Republic in 2012 *(181)*.

The U.S. has had ongoing problems with counterfeit infant formula due to its high cost and steady demand *(74)*. The FDA considers counterfeit formula to include "products that have been diverted from normal distribution channels and relabeled" *(5)*. Relabeled products may not have the age, quality, or ingredients accurately represented, and diverted products may be diluted or adulterated. In 1995, the FDA seized 45,000 pounds of counterfeit formula in California, and uncovered ten operations that were producing formula and packaging it with false labels *(61)*. The counterfeiting was discovered when parents of infants began calling the maker of Similac brand infant formula to complain that the formula they had purchased looked and smelled unusual; the formula company then contacted the FDA *(6, 61)*. The Food Marketing Institute (FMI) documented eleven separate instances of infant formula theft related to organized retail crime from 2005 through 2006 in ten states *(92, 93)*. In 2004, FMI ranked baby formula fourth in the list of items that were most frequently shoplifted from grocery stores. China has had multiple problems with sub-standard infant formula. In 2004, parents of malnourished infants in China sent samples of formula they were using to feed their children to the local Centre for Disease Control and Prevention. Tests on the formula

indicated it contained very low levels of protein, fat, calcium, and magnesium *(153, 213)*. High numbers of malnourished infants were showing up in hospitals and clinics in China for at least a year prior *(226)* and at least 55 brands of formula were found not to meet nutritional standards *(115, 178)*. Hundreds of babies were malnourished as a result of the sub-standard formula and more than ten died. In 2006, ministry inspectors in China again found baby formula on the market in rural China that was dangerously low in nutrients *(15)*.

Similar to milk and some grains, plant-based proteins have been susceptible to non-protein nitrogen enrichment. A year prior to the outbreak of melamine in dairy products, wheat gluten and other vegetable proteins from China used in the production of pet foods and animal feed were found to be contaminated with melamine *(216, 218)*. More than 150 brands of pet food were recalled *(8)*. The outbreak was identified after the deaths of cats during feeding trials of pet foods, and resulted in the deaths of hundreds of dogs and cats in the U.S. due to renal failure *(57)*. Melamine alone is not highly toxic to animals, but the combination of melamine with cyanuric acid caused the formation of insoluble crystals in the kidneys *(58, 215)*. As with dairy products, melamine was added to vegetable proteins to make them appear to be more protein-rich. There were no routine QA standards in place for melamine in vegetable proteins or pet food at the time. Supplementing animal feeds with melamine was reportedly a long-standing practice in China; there was evidence that feed producers looking to purchase melamine scrap had advertised on the Internet *(44)*. Melamine was detected in the feed supply of food

production animals in the U.S., and some food production animals that consumed melamine in their feed most certainly entered the human food supply *(8, 35, 46, 217)*.

Various other food products have been susceptible to EMA, including meat products, coffee, and tea. Meat products have been prone to adulteration with alternate meats or non-meat protein sources. In 1986, a beef supplier that served New York City schools was found to have adulterated its products with vegetable filler and water over at least a five-year period *(169)*. The company was sold to a group of investors who reported the adulteration to the FBI upon finding evidence in company records. In the UK in 2009, the Food Standards Agency (FSA) detected denatured bulking agents made from porcine and bovine products that were injected into chicken products to bind water and increase weight; multiple firms were engaging in this practice *(109)*. Because the non-chicken material was denatured, it would have passed traditional DNA tests; however, the FSA used novel scientific techniques to detect the bulking agents *(109, 165)*. In 2011, pork in China was found to be contaminated with clenbuterol, a drug that promotes growth and reduces the percentage of fat in animals but can cause adverse human health effects *(157, 224)*. Tea adulteration has been a widespread, ongoing problem in India, with much of it happening at a local level *(14, 16)*. Adulterants have included plant stalks, used tea leaves, and other organic material to extend the leaves. A decade-long survey conducted by the Brazilian Coffee Industry Association (ABIC), reported in 1998, concluded that many companies sold adulterated coffee which was commonly bulked up with corn, barley, rye, caramel, or coffee bean husks *(168)*. Reportedly, the rate of adulteration dropped after the ABIC introduced a quality seal program. In the mid-1990s,

Britain reportedly uncovered problems with instant coffee manufactured in other countries and imported in bulk; remnants of the coffee plant and caramel were being added to increase profits *(78)*.

Food defense: implications of EMA incidents

EMA incidents present a particular challenge to the food industry, regulators, and consumers. Food safety incidents are unintentional acts with unintentional harm, whereas food defense incidents are intentional acts with intentional harm. EMA incidents, on the other hand, are intentional acts with unintentional harm, designed specifically not to be detected. For this reason, they typically involve unconventional adulterants or dilution with cheaper, benign food ingredients *(148)*. Regulatory food safety and QA systems are not designed to detect novel adulterants or low levels of dilution. Moreover, regulatory agencies such as the FDA operate with limited resources, and therefore have to target those resources to the most serious threats to the food system *(194)*. Since most EMA incidents involve "indirect" or "technical" health risks *(180)*, EMA has generally been viewed as less important than food safety incidents or incidents of bioterrorism. However, recent large-scale incidents have raised the concern about EMA incidents among regulatory agencies. Also, FDA traditionally has not distinguished among different motives for adulteration since it can conduct an investigation when it detects any form of adulteration *(206)*. Regardless of whether or not the adulterant is a public health threat, EMA incidents reveal vulnerabilities and gaps in our food production and distribution system that could potentially be exploited for intentional harm.

The EMA incidents described above illustrate some important concepts related to

detection and deterrence of future incidents. First, quality assurance methods for food products need to be specific and effective. Multiple EMA incidents involving evasion of the Kjeldahl test for protein with various non-protein nitrogen sources have illustrated this point. Furthermore, since EMA incidents are economically motivated and do not typically result in illnesses, detection of these incidents requires the use of non-traditional data sources (i.e., data that is not typically used for public health surveillance). Finally, EMA incidents illustrate that there are fraud opportunities created by long and complicated supply chains; therefore, industry and regulatory agencies should be monitoring those supply chains for anomalies that could indicate EMA potential.

Food safety and food defense: food imports are increasing

The U.S. imports enormous and increasing quantities of food products. From 2000-2010, the U.S. imported (on average, per year) 1.6 million metric tons (MMT) of meats, 2.2 MMT of fish and shellfish, 1.8 MMT of coffee and tea, 3.5 MMT of vegetable oils, and 7.5 MMT of cereals and bakery products *(202)*. The number of food import lines increased from 5.6 million to 10.7 million between 2002 and 2009 *(194)*. More than 16% of food products currently consumed in the U.S. are imported , compared to 11-12% in 1995 *(49, 207)*. Eighty-four percent of the seafood consumed in the U.S. is imported. Importation rates of agricultural products from China have increased even more rapidly; they increased fourfold between 1997 and 2007. Regulation of imported foods is a burdensome and growing task. In FY1997, FDA-regulated products represented approximately 2.8 million imported food shipments; this number had risen to 8.2 million shipments by FY2007 *(49)*. In 2011, FDA physically examined only about 2% of

imported food shipments, and performed testing on samples from less than 0.5% of shipments *(207)*. In addition, they performed inspections of less than 0.5% of the 270,000 registered foreign food facilities.

The United States Department of Agriculture Food Safety Inspection Service (USDA FSIS) employs a concept known as "equivalence" for meat and poultry products imported to the U.S. from other countries. Equivalence refers to the concept that the sanitary measures applied in another country achieve the same level of public health protection as those applied in the U.S., even if those specific measures are different *(201)*. Foreign meat and poultry producers, under the FSIS equivalency program, are subject to document analysis, on-site audits, and port-of-entry re-inspections *(201)*. FDA is responsible for regulating about 80% of the U.S. food supply *(113)*; however, they have a more limited function in terms of operations and inspections in foreign countries than does FSIS *(49)*. While FDA can visit foreign facilities to inspect their operations *(49)*, foreign inspection coverage was only about 1% between 2002 and 2007 *(194)*. Under the FSMA, FDA will have an increased responsibility to verify that foreign suppliers have adequate preventive controls in place in their facilities *(194)*.

<u>The food safety paradigm is not sufficient for food defense</u>

The effectiveness of testing for foodborne pathogens in food products and clinical samples, the identification of foodborne outbreaks, and the identification of outbreak vehicles all depend on well-characterized pathogens with readily-available laboratory testing methods. The food safety model relies on knowledge of the range of pathogens that will most likely be responsible for any given foodborne outbreak. Intentional

contamination of food products has certainly happened with known foodborne pathogens (e.g., *Salmonella* Typhimurium *(188)*), and the well-described pathogenicity of these agents could motivate the use of a common foodborne pathogen in an attack. However, an intentional attack on the food system could very likely involve a chemical or biological agent that is not considered to be a foodborne pathogen. Contamination with an alternate agent would make identification of both the agent and the contaminated food item more difficult, potentially increasing the public health response time and, subsequently, the morbidity/mortality caused by the incident *(191)*. Furthermore, EMA incidents never involve the intentional introduction of foodborne pathogens, since the goal of EMA is to avoid detection. Reliance on routine testing for known foodborne pathogens is not sufficient for detecting adulteration with non-conventional agents. However, implementing widespread testing for the range of potential biological or chemical terrorism agents would be expensive and unrealistic *(120)*. Therefore, the food safety model of outbreak identification through laboratory-based surveillance is not an adequate strategy for detecting intentional contamination or EMA.

Another weakness of the current food safety system, from both a food safety and food defense perspective, is the lack of a detailed understanding of supply networks for food products. A better understanding of supply chain structures and networks for food products could improve our ability to conduct quick and accurate traceback investigations, and could contribute to epidemiologic data for hypothesis-generating at the beginning of an outbreak investigation.

The complexity and scale of supply chain distribution networks was illustrated in

the 2009 *Salmonella* outbreak involving peanut-containing products *(69)*. The contaminated peanut paste originated at one facility, but resulted in the recall of almost 4000 products *(195)*. The process of tracing the contaminated ingredients to the final food products took many months. More recently, the outbreak of *E. coli* O104:H4 in Germany illustrated how an understanding of supply chain dynamics could have assisted in an outbreak investigation. The initial hypothesis focused on Spanish cucumbers, although it turned out that the distribution of cases did not fit with the distribution pattern of the cucumbers *(119)*.

Finally, an analysis of the 2008 outbreak of *Salmonella* Saintpaul *(66)* supported the assertion that understanding supply chain networks is important for outbreak investigations. While the epidemiology initially pointed to Roma and round red tomatoes as the source of the outbreak, the initial trace-back investigations did not converge to a common source. After clusters of restaurant-associated cases were investigated, jalapeño peppers were implicated as the most likely source. Almost seven weeks elapsed from the time CDC was notified of the first cases of *Salmonella* Saintpaul in the New Mexico until the first consumer warning about jalapeño peppers was issued *(186)*. It is very likely this time frame could have been shortened by improved traceability within the produce industry, as well as a more thorough understanding of the supply chain dynamics within the tomato industry. Following this outbreak, the FDA and CDC conducted an examination of entry data from the Operation and Administrative System for Import Support (OASIS), which tracks imports of foreign-origin FDA-regulated products. The examination of OASIS data demonstrated a statistical association between a state's

Salmonella Saintpaul infection rate and the combined quantity of Mexican-grown jalapeño and Serrano peppers that were imported into that state *(121)*. The same association was not seen with Mexican-grown Roma and round red tomatoes. More importantly, OASIS entry data helped explain the pattern of *Salmonella* Saintpaul cases seen in the U.S. For example, California saw very few human cases associated with the outbreak. This made sense based on the "geographic lanes of commerce" that Mexican peppers followed into the U.S. Furthermore, the OASIS data indicated that the production and flow of jalapeño and Serrano peppers was very different from that of tomatoes. Had this supply chain information been available and analyzable during the early stages of the outbreak investigation, it is conceivable that the identification of peppers as the more likely outbreak source could have happened more quickly. FDA and CDC concluded that the analysis of the spatial and temporal flow of agricultural products early in an outbreak investigation could help identify foods "worthy of careful scrutiny." If a large-scale intentional contamination incident were to occur, we likely would not be able to rely on PFGE subtyping to help identify the contaminated food vehicle. In this case, the spatial and temporal flow of food products could be even more critical for helping to identify potential food vehicles.

Food supply chains: complexity and global scope increase vulnerabilities

The food supply and distribution system is becoming increasingly globalized and complex *(63)*. Globalization of the food supply, specifically, consolidation in sourcing and complexity in distribution, can complicate outbreak investigations and magnify food safety and food defense problems. This was evident in recent outbreaks of foodborne

illness in jalapeño peppers *(66)*, peanut-containing products *(69)*, and pepper-coated salami *(70)*. These outbreaks illustrated various aspects of complexity with regards to food supply chains. The outbreak of *Salmonella* Saintpaul in jalapeño peppers was originally attributed to tomatoes. The outbreak investigation was hampered by difficulties in the traceability of fresh tomato products throughout the supply chain *(47, 175)*. In addition to the complexity of the distribution chain, tomatoes were often commingled, repacked, and sold singly at retail without labeling, which added to the difficulty of the traceback investigations. The two outbreaks of *Salmonella* Typhimurium in peanut-containing products and pepper-coated salami products, respectively, illustrated how widespread the distribution of food ingredients can be, even from a single, relatively small producer.

Some of the recent incidents of EMA described above have also demonstrated the complexity and globalized nature of supply chains that exist within the food supply. Chili powder contaminated with Sudan 1 was sold numerous times to different suppliers and brokers over a period of multiple years, and was eventually used as an ingredient in name brand Worcestershire sauce in the U.K. The Worcestershire sauce was subsequently used as an ingredient in hundreds of food items which had to be recalled when the contamination was discovered *(164)*. At least 300 food companies were involved in tracing the affected products *(126)*. The 2008 incident of melamine adulteration of milk products in China also resulted in the recall of hundreds of food products in at least 47 countries *(49, 104)*. The adulteration of milk resulted in the recall of many types of products, including powdered infant formula and other powdered milk products, yogurt,

frozen dairy products, snack foods, candies, and instant coffee.

Traditionally, food producers have been somewhat reluctant to provide what is considered to be proprietary data about production processes and ingredient sources to regulatory agencies. Furthermore, the FDA has a history of requesting limited amounts of data from the food industry during investigations, and sharing even less of that information with outside groups *(186)*. During the *Salmonella* Saintpaul investigation, for example, members of the tomato industry reportedly did not feel that they were permitted to provide information to regulatory agencies that might have absolved U.S. tomatoes earlier in the investigation *(186)*. Public health, regulatory agencies, and academia do not typically have access to detailed information about food supply chains unless there is a traceback investigation conducted as part of a foodborne outbreak or other food adulteration incident. These investigations tend to focus on tracing back food products consumed by geographically-separated cases to determine if the supply chains for those products converge to a common source. These investigations are useful and necessary during the course of an outbreak investigation, and improving our ability to conduct these investigations is an important area of work. However, these investigations do not give us the full picture of how global supply networks for different food products function. This type of characterization is necessary for understanding the risk present in these networks, as well as informing foodborne outbreak investigations.

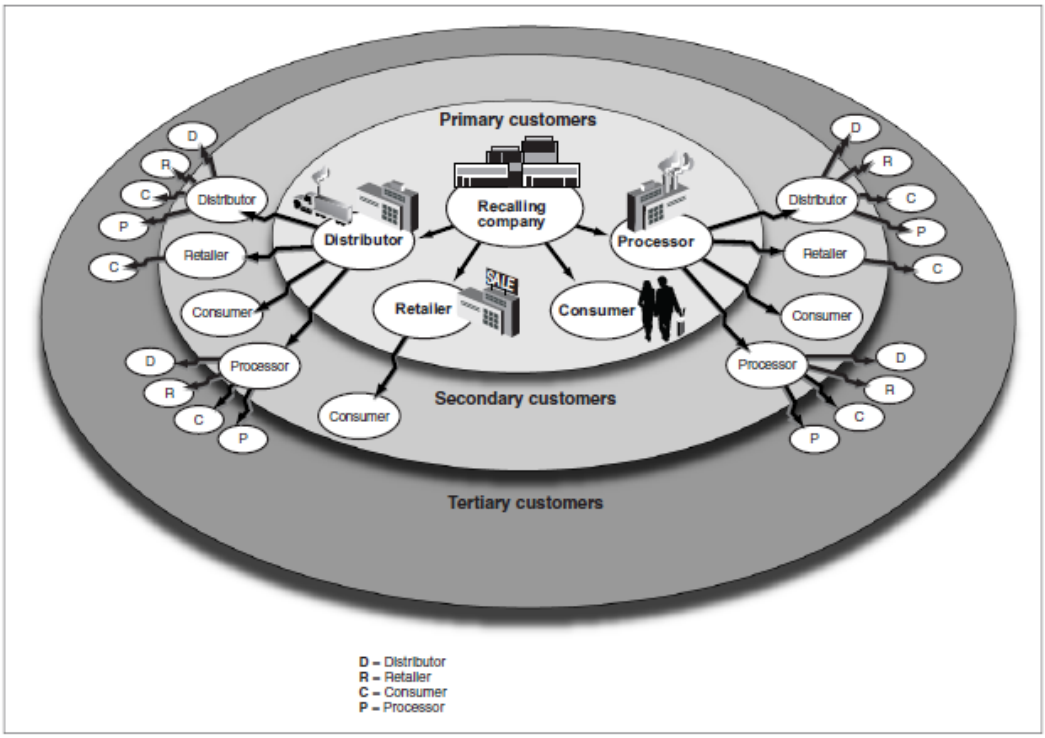


Figure 2. A supply network with multiple levels of distributors, processors, and retailers before the food reaches consumers. (Source: GAO-05-51).

Supply chains for food products are becoming increasingly complex; they are better described as supply networks than supply chains *(117)*. Figure 2 illustrates a simple supply network for a hypothetical recalled product. "Complex networks" refer to supply networks with a structure that is complex, irregular, and dynamic *(117)*. Supply networks for many imported food commodities would certainly be classified as complex. As the complexity in supply networks increases, so does the risk *(106, 223)*. Supply chain management practices such as globalization, decentralization, and outsourcing, which are all common within the food sector, increase vulnerability by increasing the number of exposure points and increasing the distance and time that the product must travel *(184)*.

The supply chain for a product such as canned tuna is a good example of a globalized supply chain for a product that travels long distances (Figure 3.)

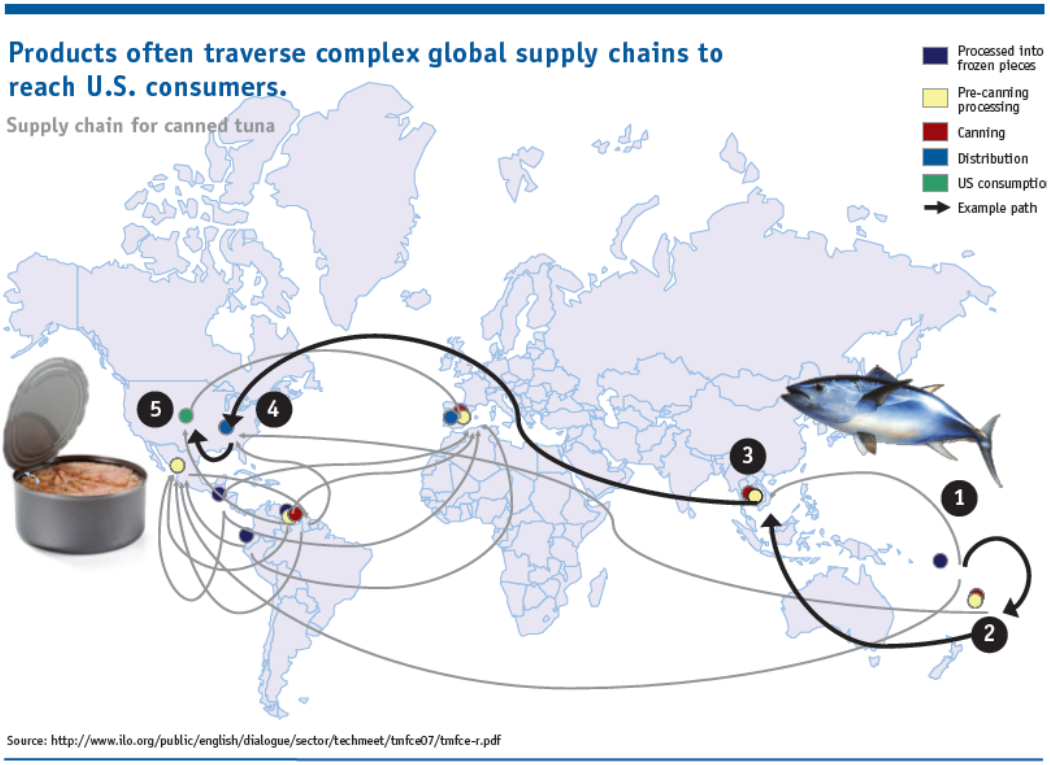


Figure 3. An example supply chain for canned tuna, from harvest in East Asia to finished product in the U.S.

Non-traditional data sources for food protection

As noted above, supply networks for food products are globalized, complex, and dynamic, which increases their vulnerability. FDA has noted that globalization presents challenges for regulators, and that the agency "does not – nor will it - have the resources to adequately keep pace with the pressures of globalization" *(194)*. FDA's main tools for

product safety have traditionally been inspections (at facilities or at the borders) and laboratory testing. By FDA's own admission, scaling the current FDA operating model for an increasingly globalized food supply is not a viable option, especially given the fact that foreign facility inspections cost more than twice as much as domestic facility inspections. The foreign facility inspection rate is about 1% (see Figure 4).

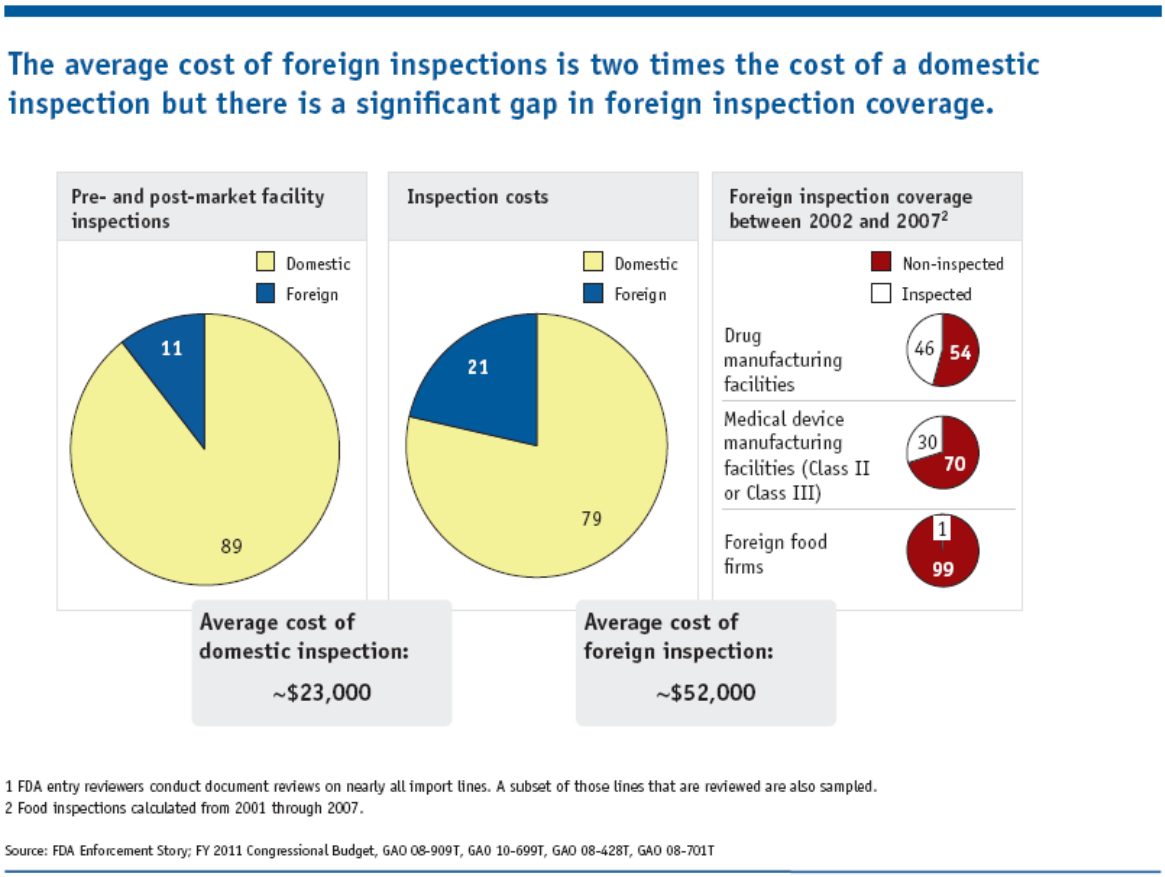


Figure 4. Comparison of foreign and domestic facility inspections by FDA.

In order to ensure the safety and quality of food products, FDA recommends aggregating and utilizing "multiple sources of information as inputs to intelligence and

regulatory analysis to identify potential threats" *(194)*. FDA recommends integration of multiple data sources to gain a better understanding of potential threats within the food supply system (as well as the supply systems for other FDA regulated products), and for developing a type of warning system for potential risks in order to better target scarce regulatory resources towards those products which represent the "greatest potential harm to public health." Many of these data sources will be ones that are not traditionally associated with public health surveillance or regulatory efforts.

Multiple EMA incidents have illustrated the potential utility of non-traditional data sources for identifying adulteration. As noted above, contamination of Austrian wines with diethylene glycol in the mid-1980s was discovered by a tax inspector who noticed that a wine producer was claiming tax refunds on large quantities of diethylene glycol *(1)*. Since the adulteration did not cause immediate health effects, and there was no reason to test for diethylene glycol in wine at the time, presumably the adulteration could have continued if the suspicious tax records had not been noticed. Beech-Nut was indicted around the same time for selling fake apple juice. The company was having financial troubles, and switched juice suppliers when they were offered concentrate at 25% below typical market prices *(60, 142)*. Below-market pricing is a potential red flag for adulteration or dilution of food products; saffron and olive oil are two additional examples of products that are often adulterated and sold at cheaper-than-market prices *(150, 155)*.

Implications of the Food Safety Modernization Act

Protecting the food supply from multiple types of threats requires a shift in thinking

from merely "food safety" or "food defense" to a comprehensive "food protection" strategy. Most companies and regulatory agencies are well-versed in food safety measures such as HACCP plans and laboratory testing. However, widespread implementation of food defense strategies is still a work in progress. The Food Safety Modernization Act (FSMA) was the first major change to U.S. food laws in more than 70 years. FSMA requires food defense planning on the part of all parties along the food supply chain. Specifically, FSMA requires that all food production facilities "identify and evaluate known or reasonably foreseeable hazards" including those that are naturally or intentionally introduced: "biological, chemical, physical, and radiological hazards, natural toxins, pesticides, drug residues, decomposition, parasites, allergens, and unapproved food and color additives…" *(167)*. Food facilities will be required to identify and evaluate these hazards, implement preventive controls to minimize those hazards, monitor the performance of the preventive controls, and maintain records of this monitoring process *(137)*. FSMA compels the food industry to operate more proactively and less reactively, and to consider the system as a whole.

Given the large-scale scope of the legislation, FSMA rules and regulations are currently being developed. In January 2013, FDA released the first two proposed FSMA rules: "Current Good Manufacturing Practice and Hazard Analysis and Risk-Based Preventive Controls for Human Food" and "Standards for the Growing, Harvesting, Packing, and Holding of Produce for Human Consumption" *(196)*. In the Preventive Controls proposed rule, the FDA requested comment on whether or not to include EMA in the rule, dependent upon whether it can be considered "reasonably likely to occur."

Implementing FSMA regulations will require increased levels of collaboration among suppliers, producers, distributors, and government regulators. This will be particularly challenging to achieve for imported food products and food ingredients with complex supply chains. Effective identification and minimization of the various types of hazards will require a greater understanding of complex supply chains by both food companies and regulatory agencies. Industry will be held increasingly responsible for knowing the origin of all the food ingredients they use and for preventing contamination at any point of the supply chain. Government and academia will need a more in-depth understanding of food supply networks to better understand the vulnerabilities present in those networks and reduce them.

As mentioned earlier, food producers have a history of being reluctant to share proprietary data regarding ingredient sources and production practices, and FDA tends to request very limited amounts of data from producers. If this continues to be the situation in the future, academia could potentially bridge the information gap between industry and regulatory agencies to work toward a better understanding of supply chain dynamics and other issues that will be crucial to preventing future contamination incidents.

The Congressional Budget Office estimated that implementation of FSMA would cost about $1.4 billion over the next 5 years *(75)*. Along with new requirements for food defense efforts under FSMA, there has been an ongoing national discussion about the need to improve foodborne outbreak response - a discussion that tends to intensify whenever there is a large-scale foodborne outbreak *(37, 53, 185)*. It is not realistic to expect that funding for FDA, USDA, and state and local health departments will be

increased to the full extent necessary to fully implement FSMA as well as increase foodborne disease surveillance and laboratory capacities over the next few years. Improving food protection will require collaboration among government, industry, and academia to take advantage of the best expertise and resources available to each of them. This type of collaboration is not unprecedented; following the large-scale outbreak of *E. coli* in spinach, government and academia collaborated on an industry-funded project to better understand the mechanisms of contamination *(158)*. Centers like NCFPD provide an environment where academia, government, and industry actively collaborate to understand and mitigate food defense risks. In addition to collaboration, implementation of FSMA and improved foodborne outbreak response will require creative solutions. One of these creative solutions is the analysis of non-traditional data sources to enhance detection of contamination incidents.

The focus of the research described in the following chapters is methods to improve our capability to prevent and detect EMA incidents in food. First, food ingredients and related quality assurance testing methodologies will be evaluated for EMA susceptibility, and the ingredients will be clustered into groups based on susceptibility characteristics. Subsequently, Chinese dairy production data from will be analyzed for anomalies, using the years surrounding the melamine adulteration event as a case study. Finally, a modeling technique used in biosurveillance will be applied to U.S. import data for food products to detect anomalies in the supply chains for those products.

CHAPTER 2

An evaluation of the monographs in the United States Pharmacopeial Convention Food Chemicals Codex for susceptibility to EMA to improve quality assurance methodologies for food ingredients

Introduction

In 2007, wheat gluten and other plant-based proteins adulterated with melamine and related compounds caused illnesses and deaths in thousands of dogs and cats in the U.S. *(57)*. The adulteration resulted in the recall of more than 150 brands of pet food *(8)*. Subsequently, melamine was detected in the feed supply of food production animals in the U.S., and some of those food production animals most certainly entered the human food supply *(8, 35, 46, 217)*. The following year, adulteration of milk with melamine in China resulted in illnesses in hundreds of thousands of infants in China and six known deaths *(104)*. At least 47 countries recalled adulterated products. Melamine contamination of both wheat gluten and dairy products was effective and successful because the industry-standard quality assurance (QA) test for protein used at the time (the Kjeldahl method) was non-specific; it relied on measuring nitrogen content as a proxy for protein content. QA testing methodologies are used at different points in the supply chain for food ingredients to check for the authenticity, purity, functionality, and conformance to specifications of ingredients. The addition of nitrogen-rich melamine evaded the industry standard tests for protein content. Furthermore, there was no analytical method designed specifically for the detection of melamine in either wheat gluten or dairy products at the time because it was not an expected adulterant.

The United States Pharmacopeia (USP) Food Chemicals Codex (FCC) provides written reference standards (monographs) for each of over 1,100 food ingredients *(208)*. The monographs are intended, among other things, to describe quality assurance testing methodologies that can be used during supply chain transactions for food ingredients. Generally, these methodologies are used as part of buyer/seller relationships for food ingredients at various steps in the supply chain. The food ingredients addressed in the FCC include food-grade chemicals, processing aids, flavoring agents, vitamins, functional food ingredients, and some finished foods (such as oils, fructose, and whey). The monographs describe the form and function of each ingredient, information such as the chemical structure and labeling requirements, and detail the suggested industry-standard analytical methods for the identity and purity of the ingredients. The testing methodology is given as both identification tests and assays. Identification tests are generally qualitative tests intended to substantiate the identity of an ingredient, whereas assays are generally quantitative and intended to evaluate the purity or concentration of an ingredient. Many of the monographs give multiple identification and/or assay tests. Multiple tests are designed to work orthogonally; in other words, there is more power in the use of multiple tests that measure different characteristics of an ingredient. At the time of the melamine EMA incidents, there was no FCC monograph for milk, and the monograph for wheat gluten listed “Nitrogen Determination” as the assay test.

The National Center for Food Protection and Defense undertook a project in collaboration with USP to determine which of the ingredients in the FCC may have an increased susceptibility to EMA based on the inherent attributes of the ingredient and the

attributes of the associated identification and assay tests. Food scientists from around the world were recruited to review a representative subset of the monographs using an online questionnaire, and then we performed a cluster analysis on the resulting scores. Cluster analysis is a method for grouping similar entities together to result in a meaningful structure in the data set *(183)*. Clustering methodology relies on using dissimilarities or distances between the entities to result in useful groupings. The result of our analysis was groups of FCC ingredients that were similar based on EMA susceptibility. EMA susceptibility can then be mitigated differently depending on cluster characteristics.

Methods

Individual electronic files for all FCC monographs and appendices were transferred from USP to NCFPD for use during this project. Links between each monograph file and its associated appendices were rebuilt and the files were individually loaded into Google Documents. Monograph attributes relevant to EMA susceptibility were determined based on expert elicitation of a small group of food scientists very familiar with the FCC, including one food scientist directly associated with USP. Relevant monograph attributes included the complexity of the ingredient ("complexity"), the variability of the ingredient ("variability"), the selectivity of each identification test listed in the monograph ("selectivity"), the specificity of each assay test listed in the monograph ("specificity"), and an assessment of EMA detectability based on a loss of function in the final food product ("function"). A questionnaire template was constructed using the monograph attributes (see Table 1 for the questions used to evaluate each

attribute). Individual online questionnaires were then created for each ingredient based on the number and type of identification tests and assays. A 5-point Likert-type scale was applied to each of the attributes for simplicity with regards to reviewer response. Attributes and the associated response options are shown in Table 2. Higher scores represented less susceptibility to EMA. An individual online questionnaire was created for each monograph based on the number and types of identification tests and assay tests. Each online questionnaire was assigned to a unique URL and was linked directly to the URLs that displayed the associated monograph and appendices.

The 443 monographs with associated Flavor and Extract Manufacturers Association (FEMA) numbers were excluded from analysis *(30)*. These flavor chemicals are used in very small concentrations in food products, and the composition of these chemicals is generally very well-characterized and standardized. Of the remaining 677 monographs without FEMA numbers, we selected a representative sample of the ingredients based on ingredient function, in order to represent 98% of the monographs in terms of the function in the final food product.

Volunteer reviewers were solicited through a variety of means, including direct email communication to contact lists maintained at NCFPD and USP, presentations at professional conferences and resulting contact information, and in-person visits to food companies. Food scientists directly associated with USP were precluded from being reviewers due to potential conflicts of interest. Due to the technical expertise necessary to effectively assess the monographs for EMA susceptibility, reviewers were asked to establish their familiarity with the FCC and provide either a current or prior association

with a stakeholder organization (such as academia, a government regulatory agency, or the food industry). Reviewers were able to select which monograph(s) they were able to review based on their knowledge of the monographs and associated QA methodologies.

Reviewer responses to each of the monograph attributes were scored (see Table 1) and the resulting scores were used to perform a cluster analysis. Missing data were re-coded as a score of 1 (the lowest, or most susceptible, score) since cluster analysis cannot be performed on observations with missing data. A sensitivity analysis was conducted by assigning a score of 5 (the highest, or least susceptible, score) to each missing observation to determine the degree to which cluster membership was affected by the missing data. For monographs that were reviewed by multiple reviewers, the lowest (or most susceptible) score was used. To take into account the additional EMA "protection" offered by multiple orthogonal methods, selectivity and specificity scores for monographs with multiple identification and/or assay tests, respectively, were assigned as follows: the highest score was used, plus half the value of the score for each additional test. For example, a monograph with 3 identification tests that were assigned scores of 2, 3, and 5, respectively, would be assigned an overall selectivity score of 7.5. Data manipulation and descriptive statistics were performed in Stata Version 12. Cluster analyses were performed on the scores from the 5 monograph attributes using the "flexclust" package in R and k-means clustering using Euclidean distances. Since k-means clustering requires defining the desired number of clusters, the results of analyses performed by assigning ingredients to each of 2, 3, and 4 clusters, respectively, were

explored. The analysis that provided the most intuitive and useable information was chosen as the final resulting set of clusters.

Results

A total of 449 monographs were evaluated by 46 reviewers based on the 5 attributes related to EMA susceptibility. Monograph attributes, questionnaire response choices, and the associated scores used for the cluster analysis are shown in Table 2. There were 14 total missing responses that were assigned a score of 1 (the score that corresponded to the highest susceptibility). Most (12 or 86%) of the missing responses were non-responses to the function question, the selectivity question had 1 (7%) missing response, and the specificity question had 1 (7%) missing response. There were no ingredient evaluations with missing responses on more than 1 attribute. The analysis that assigned ingredients to each of 3 clusters yielded the most meaningful and useful results. The assignment of ingredients to only 2 clusters did not provide adequate differentiation in terms of EMA susceptibility. The extension of the analysis to 4 clusters did not provide sufficient additional useful information about the ingredient characteristics as only 5 ingredients were assigned to the fourth cluster.

Histograms of the distribution of frequencies for overall responses to each attribute question are shown in Figure 5. The scores for complexity and variability were fairly broadly distributed, with about half of the scores in each category being greater than 3 (the “neutral” score): 49% (221) of complexity scores and 57% (257) of variability scores were greater than 3. Sixty-three percent (281) of the calculated selectivity scores

were greater than 3. Only 21% (91) of the calculated specificity scores were greater than 3, as well as only 13% (60) of the function scores. Table 3 shows the mean scores for each attribute in each of the 3 resulting clusters. There was a high susceptibility cluster comprised of ingredients that generally scored lower on all 5 attributes, and a low susceptibility cluster that generally scored higher on all 5 attributes. In addition, there was an intermediate susceptibility cluster comprised of ingredients that scored high, on average, in terms of the complexity and variability scores (attributes inherent to the ingredient), and lower in terms of the selectivity, specificity, and function scores (attributes related to the associated QA testing methodologies and use in the final food ingredient). Ingredient names and cluster assignments are described in the Appendix. The sensitivity analysis, which assigned a value of 5 to all missing responses, resulted in a change of cluster assignment for only one ingredient: calcium lignosulfate would have been assigned to the low susceptibility cluster instead of the high susceptibility cluster if function were assigned a score of 5 instead of 1.

Although the primary intent of this study was to have each ingredient monograph reviewed by 1 expert, there was some replication as 11 monographs were reviewed by 2 reviewers and 1 monograph was reviewed by 3 reviewers. These additional reviews resulted in 72 pairwise comparisons of scores of the same ingredient and attribute between two different reviewers. Of those 72 comparisons, 31 resulted in a scoring difference of 0, 26 comparisons had a scoring difference of 1, 8 had a scoring difference of 2, 6 had a scoring difference of 3, and 1 had a scoring difference of 4.

Discussion

QA testing methodologies for food ingredients have been evaded a number of times for economic gain. Many stakeholders, including USP, academia, regulatory agencies, and industry, have a vested interest in identifying those ingredients and methodologies that are the most susceptible to EMA. Our analysis identified 3 clusters of food ingredients based on EMA susceptibility. The low susceptibility cluster included ingredients that were generally less susceptible to EMA based on all 5 attributes that measured characteristics inherent to the ingredients (complexity and variability), characteristics of the associated analytical methods (selectivity and specificity), and function in the final food product. An example of an ingredient assigned to the low susceptibility cluster is caffeine. The composition of caffeine was determined to be very simple and highly consistent. Two identification tests are given in the monograph for caffeine, one of which was determined to be moderately selective and the other selective. The assay given in the monograph was determined to be specific. EMA of caffeine was determined to be detectable based on a loss of function in the final food product. The high susceptibility cluster included ingredients that were generally more susceptible to EMA based on all 5 attributes. One example of an ingredient assigned to the high susceptibility cluster is bay oil, the composition of which was classified as complex and variable. One of the two identification tests was classified as highly selective and the other as having low selectivity. EMA of bay oil was classified as moderately detectable based on a loss of function in the final food product. Finally, the intermediate susceptibility cluster included ingredients that were generally less susceptible to EMA based on characteristics inherent to the ingredient (complexity and variability), but more

susceptible based on analytical methods and function in the final food product (selectivity, specificity, and function). An example of an ingredient assigned to the intermediate susceptibility cluster is dextrose, which was determined to have a very simple and highly consistent composition. However, the identification test was classified as having low selectivity and the assay as being not specific. EMA of dextrose was classified as moderately detectable based on a loss of function in the final food product.

The complexity and variability questions appeared to be adequate in terms of discrimination among monographs. Responses to the complexity and variability questions were fairly well distributed. The calculation method applied to selectivity and specificity scores, for monographs with multiple analytical methods, were also somewhat broadly distributed. However, the specificity scores skewed right, with a high proportion of scores of 1 or 2. This indicates that, overall, the assay tests given in FCC monographs were not determined by reviewers to be very specific. This could be a potential area of focus by USP and industry. Finally, a high proportion of the scores on the function question were also a 1 or a 2. The function of an ingredient is not an attribute over which USP has control. In addition, the function question was not useful in helping to further discriminate among monographs since the mean function score in each of the 3 clusters was very similar. The function question had the highest number of missing responses, indicating reviewers may have had difficulty evaluating monographs based on that attribute. Therefore, future evaluations of EMA susceptibility should re-evaluate whether this is a necessary attribute to evaluate.

EMA vulnerability can and should be managed differently for each cluster of ingredients. Just fewer than 40% of the monographs were assigned to the high susceptibility cluster. Food ingredients falling in the highest susceptibility cluster should be considered priority ingredients for review by USP and its stakeholders for monograph modernization. Ingredients that are susceptible to EMA based on inherent characteristics should have selective identification tests and specific assay tests associated with them, especially if there is a strong economic incentive for adulteration. These susceptible ingredients may also deserve additional scrutiny by regulatory agencies at ports of entry into the U.S., such as an increased physical inspection or sampling frequency. The most susceptible ingredients may also warrant additional testing by industry during supply chain transactions, and development of more selective and specific methods that can inform future monograph updates. The largest cluster was the intermediate susceptibility cluster, comprising about 40% of the monographs reviewed. Additional supply chain verification by industry may also be advisable for these ingredients. The 20% of reviewed ingredients that were determined to have the lowest susceptibility to EMA should not be discounted; however, with the resource-constraints faced by regulatory agencies and industry alike, prioritization of resources towards the highest risk ingredients is a necessity.

This analysis had several challenges and limitations. Recruitment of expert reviewers was difficult and extended the projected timeline for data collection. Scoring for each attribute relied on expert opinion; therefore, scores assigned by multiple reviewers may potentially not agree. Indeed, in the examination of 13 ingredients that

were reviewed by 2 or 3 reviewers, 7 of the 72 pairwise comparisons between scores had a difference of 3 or 4 between the scores. To assure the most robust and reliable results, future analyses should incorporate an analysis of averaged scores assigned by at least 3 independent reviewers for each monograph. Lastly, the attributes chosen to represent EMA susceptibility may not represent all attributes related to that susceptibility, due to the fact that our understanding of EMA incidents and vulnerability is still evolving. An analysis based on additional attributes could result in different cluster memberships.

This analysis of the EMA susceptibility of the food ingredients represented by the USP FCC monographs should be incorporated into internal monograph modernization efforts at USP. Regulatory agencies can also make use of the results of this analysis in their targeting efforts for inspections at the border. Finally, industry should incorporate the results of this analysis into their risk assessments of supply chains for the food ingredients they purchase.

Table 1. Monograph attributes and associated reviewer questions.

Attribute	**Question**				
Complexity	Please rank the compositional complexity of this ingredient using the scale below:				
	Very simple	Simple	Neither simple nor complex	Complex	Very complex
Variability	Please rank the variability of this ingredient using the scale below:				
	Highly consistent	Consistent	Neither consistent nor variable	Variable	Highly variable
Selectivity	Please review each test procedure listed in the "identification" section of the monograph and use your knowledge of analytical chemistry to determine the selectivity of the procedure. Please rank the selectivity of each procedure using the scale below:				
	Highly selective	Selective	Moderately selective	Low selectivity	Not selective
Specificity	Please review each test procedure listed in the "assay" section of the monograph to determine the specificity of the procedure. Please rank the specificity of each procedure using the scale below:				
	Highly specific	Specific	Moderately specific	Low specificity	Not specific
Function	In your experience with the most common function of this ingredient in a final food product, how detectable would its adulteration be based on a loss of function in the final food product?				
	Highly detectable	Detectable	Moderately detectable	Low detectability	Not detectable

Table 2. Monograph attributes, questionnaire responses, and associated scores.

Attribute	5-point Likert-type scale responses and associated scores				
	5	**4**	**3**	**2**	**1**
Complexity	Very simple	Simple	Neither simple nor complex	Complex	Very complex
Variability	Highly consistent	Consistent	Neither consistent nor variable	Variable	Highly variable
Selectivity	Highly selective	Selective	Moderately selective	Low selectivity	Not selective
Specificity	Highly specific	Specific	Moderately specific	Low specificity	Not specific
Function	Highly detectable	Detectable	Moderately detectable	Low detectability	Not detectable

Table 3. Mean scores for 5 attributes for each cluster (N=449).

Cluster membership (n)	Mean score	Std. deviation
High susceptibility (179)		
Complexity	1.7	0.7
Variability	1.8	0.8
Selectivity	3.6	1.4
Specificity	1.6	1.0
Function	2.4	0.8
Low susceptibility (89)		
Complexity	3.7	1.2
Variability	4.1	1.0
Selectivity	6.0	1.6
Specificity	4.5	1.6
Function	2.5	1.2
Intermediate susceptibility (181)		
Complexity	4.5	0.7
Variability	4.5	0.6
Selectivity	3.2	1.3
Specificity	1.8	0.9
Function	2.0	0.9

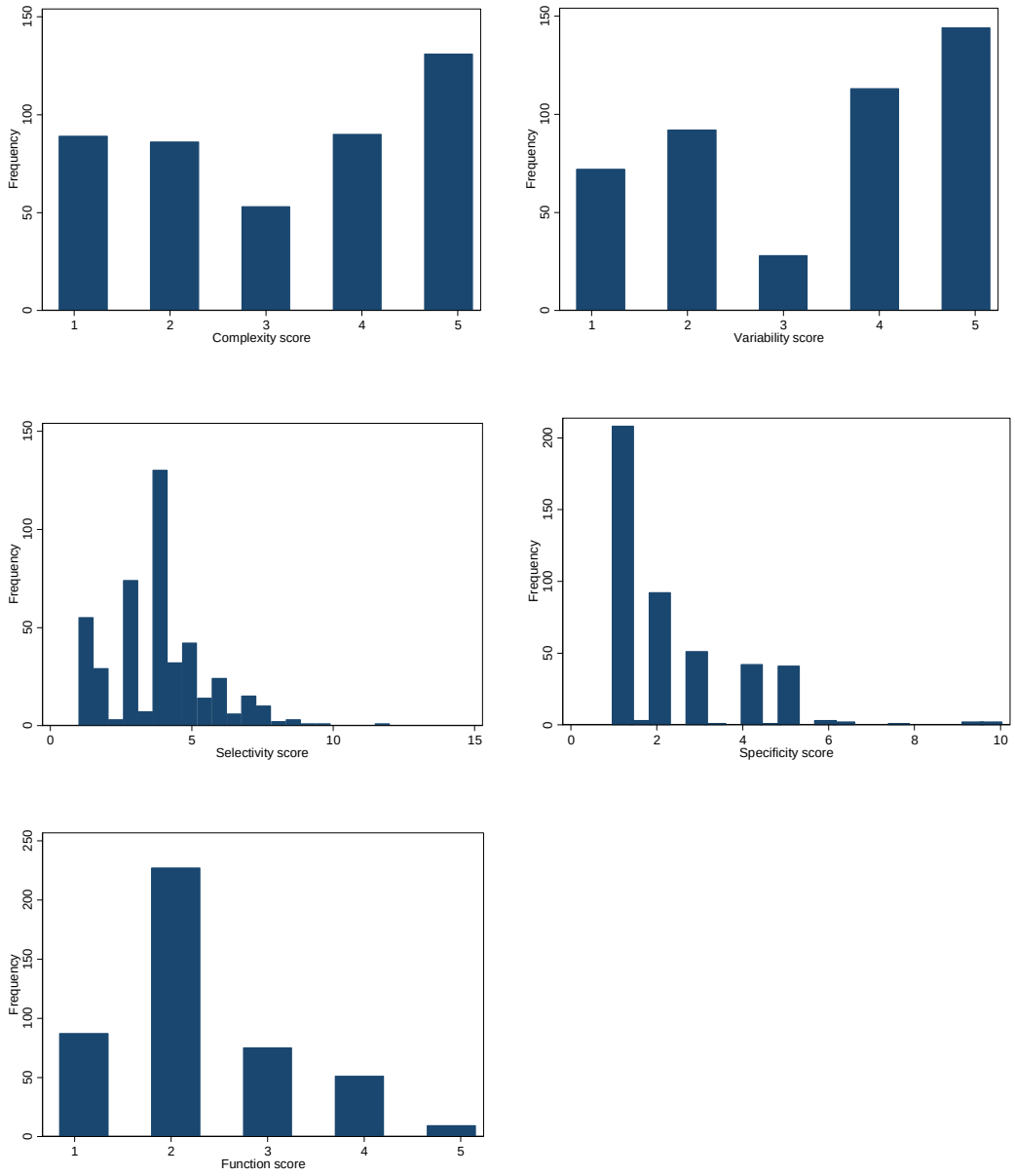


Figure 5. Histograms of response frequencies for 5 monograph attributes (N=449).

CHAPTER 3

Monitoring a food system using commodity production data to identify anomalies: analysis of Chinese dairy production data in the years surrounding the melamine adulteration event

Introduction

In 2008, widespread systemic adulteration of Chinese milk supplies with melamine was exposed *(112)*. The adulteration was discovered after months of reports of illnesses and kidney stones in Chinese infants who were consuming infant formula *(25, 54)*. After a cluster of cases of kidney illnesses in infants was associated with Sanlu brand infant formula in July 2008, a health advisory was issued in China in September. Apparently, Sanlu had received the first complaints of illnesses in December 2007 (see Figure 6). At the time of the adulteration, the standard quality tests for milk in China were based on determining the nitrogen content as a proxy for protein. Melamine is a chemical compound that contains a high percentage of nitrogen and is used in the production of polymers, composite wood products, and various plastics. Melamine contains a high percentage of nitrogen; therefore, it artificially inflated the results of the test for protein content in milk. The addition of so-called "protein powders" to milk was reportedly a widespread practice in China that had been ongoing for years *(84, 101)*. Common ingredients in these protein powders included urea and vegetable proteins. The use of melamine in protein powders may have dated back to 2006. There has not been a definitive assessment of the point in the Chinese milk supply chain where adulteration most likely occurred. However, reports indicate adulteration may have happened at

multiple stages in the supply chain: by farmers, operators of village milk supply stations, milk traders, and drivers who delivered raw milk for processing *(84, 101)*.

World milk production is divided almost evenly between developing regions and developed regions of the world *(89)*. In 2006, the global production of milk was about 664 million metric tons *(90)*. In most countries, the vast majority of the milk produced is consumed within the country (see Table 4). For example, although the United States was responsible for about 12% of world production of milk in 2009, the U.S. accounted for just over 1% of dairy imports and less than 6% of dairy exports that same year. China produced about 6% of global milk supplies in 2009, whereas the country is typically responsible for less than 1% of world exports of milk. EU countries and New Zealand are responsible for the majority of the global trade in dairy products.

Global per capita milk consumption has increased over the past five years and was estimated to be about 107 kg per year in 2011 *(114)*. Per capita consumption of milk products, especially liquid milk, varies greatly by region. Consumption is generally highest in countries in North America, Europe, and Oceania, and lowest in African and Asian countries *(114)*. There has been a general growth trend in African and Asian countries, as well as in South America. Per capita consumption of milk in China is one of the lowest in the world; however it has been increasing over the past decade. Figure 7 shows the growth in per capita consumption of milk in China along with the growth of gross national income per capita. Although per capita milk consumption is relatively low, there is a high demand for infant formula in China. This is due in part to the widespread perception that infant formula is nutritionally superior to breast milk *(39)*. Infant formula

is typically produced using skim milk powder (SMP) and vegetable fats, with the addition of specific starches and nutrients that are crucial for infant development. In 2006, about 50% of raw milk delivered to dairies in China was used to produce liquid milk, while about 5% was used to produce SMP *(91)*. China is a major producer of whole (WMP) and semi-skimmed milk powder, and a major importer of SMP, WMP, and semi-skimmed milk powder (see Table 5).

Dairy production systems around the world vary substantially in terms of farm size and ration composition. Large farms with thousands of dairy cows are common in the U.S., whereas smaller farms with fewer than ten cows are common in many developing countries. On average, worldwide, there are only 2.5 cows maintained per farmer *(114)*. Countries with many small dairy farm operations generally require collection centers for consolidation of milk for further processing. This is common in many developing countries, including China. The dairy production system in China consists of many small milk farmers and milk collection stations *(210)*. There are more than 2 million small farmers in China, many of whom are located in remote and underdeveloped areas of the country *(101)*. In 2006, 35% of milk produced in China originated from farms with 5 or fewer cows and 60% from farms with 20 or fewer cows. The Chinese system of milk production based on contributions from many small farmers benefits from increased flexibility and lower costs. This is especially true at the farmer level since family members are generally responsible for most of the labor. However, as a result there is less regulatory and quality assurance oversight throughout the supply chain.

Leading up to the discovery of melamine adulteration of milk in China, milk production had increase substantially. Overall yield increased by 300% between 2000 and 2007 *(101)*. Demand was also increasing during this time, spurred by increasing incomes among the Chinese population, government subsidies for milk for school children, ultra-high temperature (UHT) milk production that increased shelf-life and transportability, and general investments in the dairy industry. Dairy production has been concentrated in northern and northwestern China for many decades, but farmers in those areas were not able to link into commercial supply chains until UHT technology was adapted for milk *(101)*. Incorporation of these small farmers into the commercial supply chain for milk by large producers in China was one of the main contributors to the rapid increase in milk production in the late 1990s and 2000s. Incorporation of milk from numerous small farms in the provinces of Inner Mongolia, Heilongjiang, and Hebei was instrumental to dairy industry growth. By 2006, those three provinces accounted for about half of milk production *(101, 211)*. In China, unit production costs are much lower for small-scale farms than large-scale farms, and large Chinese dairy companies have indicated that sourcing milk from these provinces where natural sources of cattle feed are plentiful is much more cost effective *(101)*. However, incorporation of small farmers from remote regions of China into milk supply chains required the use of intermediate collection points, including village milking stations and intermediary milk consolidation stations. At the time of discovery of the melamine incident, Hebei province had more than 350 such stations. An extensive network of traders, agents, and truck drivers facilitated transfer of milk supplies between collection points and the processors.

Although production costs were lower, cows on small farms in China often had poorer nutrition due to the predominant foraging and feeding practices, resulting in milk with lower protein and fat content *(101)*. Reportedly, quality standards enforced by milk processing companies tended to change along with market demand. In 2007, an increase in demand for milk products combined with lower production capacity and increasing prices resulted in considerable competition for raw milk supplies. This may have resulted in lax enforcement of quality standards by milk processors. Subsequently, in 2008, feed prices rose, while the prices paid to farmers for milk fell *(101, 210)*. Reportedly, the use of melamine-containing protein powders intensified and became more prevalent during this time.

Melamine adulteration of dairy products in China illustrated that the quality and safety of a food product can be affected by the supply chain structure and economic conditions. Increased demand for milk by processors combined with price constraints at the level of the farmer provided incentive. A decentralized supply chain that included multiple intermediary parties resulted in less quality assurance oversight. Additionally, the standard quality assurance methodology for milk was not specific enough to differentiate between nitrogen from protein or non-protein sources. Finally, a viable and economical method for increasing the apparent protein content was made widely available to farmers and milk collectors, resulting in a system-wide adulteration practice. Standard quality assurance methodologies for milk at the time did not include an analytical method for melamine, since it was not an “expected” adulterant.

Melamine addition to milk was motivated by a desire for economic gain. It allowed an increase in milk supplies through acceptance of lower-quality milk by processors, and dilution of milk by farmers and intermediaries. Therefore, reported milk supplies should have increased beyond what was expected given the number of dairy cattle and average yield per head. The goal of this chapter was to describe and assess economic production data for milk in China in the years surrounding the melamine adulteration event to evaluate the utility of economic and production data for alerting to the potential for EMA in a food commodity.

Methods

National- and province-level data describing Chinese dairy industry production and economic variables were acquired from the Dairy Association of China (http://www.dac.com.cn/) as multiple Microsoft Excel spreadsheets. Communication with a representative of the Dairy Association of China was facilitated by an interpreter. Spreadsheet titles, variable labels, province labels, units of measurement, and other relevant non-numerical information were translated from Chinese to English using Google translate as well as an interpreter. Data fields included raw milk purchase price, raw milk production, liquid milk production, production of finished dairy products, number of cattle, average yield per cow, fat content, and protein content.

Descriptive plots of the data were visually examined to identify patterns among provinces and across time. Specifically, the distribution of cattle across provinces was described, as well as raw milk production and average milk yield per cow. The

relationship between reported yields and calculated yields was assessed, as well as reported raw milk production and calculated raw milk production. The ratio of fat to protein content over time was explored. The trend in national raw milk purchase price and national production of milk products was evaluated. To quantify the relationship between average milk yield and time, a linear model was developed with average milk yield as the dependent variable and year as the independent variable. A Bayesian approach with non-informative priors was used to permit random intercepts and slopes for each province and to obtain posterior distributions of average milk yield. A spaghetti plot of average milk yield over time indicated widespread variability among provinces and fluctuations over time within provinces. Therefore, year was coded as three indicator variables using 2006 as the referent year:

$$avg\_yield_{ij} = \beta_{0i} + \beta_{1i}*2007_j + \beta_{2i}*2008_j + \beta_{3i}*2009_j$$

Formatting and merging of the data sets was performed in Excel, and subsequent data analyses were performed in Stata version 12. A map of Chinese provinces and cattle distribution was created in ArcGIS version 10. The Bayesian linear model was fit in WinBUGS v1.4.3.

Results

National-level Chinese dairy production data was available for 2006-2011 and province-level data was available for 2006-2010. The distribution of cattle was

concentrated in the north of the country in 2007, with the highest number of cattle in Inner Mongolia ("Neimongol") (see Figure 8). The cattle distribution was nearly identical in 2008, and similar in 2009 and 2010. Figure 4 shows the national monthly raw milk purchase price and the national monthly production amounts of milk products. The raw milk purchase price dropped steadily beginning in April 2008 through August 2009. The monthly production weight of milk products shows cyclical trends, with a localized peak in June 2008. Least squares regression lines for 3 province-level dairy products volumes are shown in Figure 10. The average yearly production of raw milk and liquid milk both show a general parallel upward trend. The average yearly production of dairy products (other than liquid milk) demonstrates a steeper upward trend.

Raw milk production in the top 5 producing provinces increased each year from 2006 to 2008, and then showed more gradual increases and one decrease between 2008 and 2009 (see Figure 11). Raw milk production was more variable in the remaining 26 provinces. Raw milk production compared to the number of cattle in each of the 3 top producing provinces was explored. From 2006 to 2008 raw milk production in Hebei appeared to increase at a greater rate than did the number of cattle in that province (Figure 12). The average yields per cow for the top 3 provinces are shown in Figure 13. All 3 provinces showed a substantial increase in the average yield per cow from 2006 to 2007, but Inner Mongolia and Hebei both showed decreases in average yield between 2007 and 2008. These decreases in average yield per cow combined with slight decreases in the number of cattle in Inner Mongolia and Hebei appear inconsistent with the modest increases reported in raw milk production.

Calculated values of raw milk production for each province were plotted against reported raw milk production in Figure 14. Calculated raw milk production was defined as:

(number of cattle per province) x (average yield per cow per province)

While the two variables show a linear relationship, they are not perfectly correlated. Calculated raw milk production was nearly always higher than reported milk production for a given province and year. Similarly, the relationship between reported average milk yield per cow was similarly plotted, where calculated average yield was defined as:

(raw milk production per province) / (number of cattle per province)

The reported average yield per cow was nearly always higher than the calculated average yield. Figure 15 shows the comparison of fat content and protein content reported from each province from 2007 to 2009. A visual inspection of the plot shows a higher average protein percentage relative to fat percentage in 2008. The average ratio of protein to fat (defined as protein_percentage/fat_percentage) was 0.89 in 2007, 0.91 in 2008, 0.88 in 2009, and 0.89 in 2010.

The Bayesian linear model was fit using reported average yields from 2006-2009 in each province to compare average trends over time. The fitted values for each coefficient are given below:

Variable	Coefficient (country level)	95% confidence interval
β_0 (intercept)	4268	3820 – 4718
β_1 (2007)	153.5	-112.8 – 424.8
β_2 (2008)	293.7	33.13 – 556.9
β_3 (2009)	409.0	162.4 – 658.7

Country level average yield was not significantly different in 2007 compared to 2006 but was significantly higher in 2008 and 2009. Plots of posterior medians and 95% CIs of avg_yield_{ij} are shown in Figures 16 and 17. In 2006, the average yields per cow for 3 of the 4 top producing provinces were at or below the national average among all provinces (indicated by the dotted line). There were no significant differences among the average yields in Inner Mongolia, Heilongjiang, and Hebei. In 2007, the average yields for those same 3 provinces were above the national average, and the average yield in Inner Mongolia was significantly higher than that of Heilongjiang and Hebei. Inner Mongolia was below the national average in 2006, 2008, and 2009, but above the national average in 2007. Heilongjiang was at or above the national average in all 4 years.

Discussion

Numerous factors led to the adulteration of milk supplies in China in 2007-8. These factors included a decentralized supply chain with multiple intermediate parties,

economic pressures, lack of quality assurance oversight, and high demand for raw milk supplies. Melamine was identified as an adulterant in milk only after large numbers of infants developed kidney problems. Since EMA incidents are economically motivated and intended not to be detected through traditional food safety measures, economic and other data sources may potentially be more useful for signaling ongoing incidents.

The goal of this chapter was to describe and examine national- and province-level dairy production data maintained by a Chinese dairy trade association for trends and anomalies in the years surrounding the melamine adulteration event. The data showed a localized peak in production of finished dairy products in June 2008, the month that a cluster of infant illnesses was identified that led to an association with Sanlu brand infant formula. This localized peak in production occurred 3 months after the first decrease in raw milk purchase prices in almost a year. The decrease in raw milk purchase price put economic pressures on dairy farmers in China. It is likely that these three events led to an increased intensity in the use of melamine-containing protein powders.

The data indicated that from 2007 to 2010, there was a greater average increase in production of finished dairy products than the increase in either raw milk production or liquid milk production. Melamine addition to milk would have helped farmers and producers meet the increased demand for milk products, including whole milk powder (China was the top producer of whole milk powder in 2011). Melamine adulteration could account for an imbalance between raw milk supplies and the volume of finished products, although this study was not able to confirm that.

Since milk production varies greatly by province in China, an examination of dairy production variables at the province level was necessary. The top provinces showed an expected increase in production from 2006-2008. However, there were some apparent inconsistencies in the amount of raw milk produced, the number of cattle, and the average yield per cow in Inner Mongolia and Hebei in 2007 and 2008. This is not definitive evidence of adulteration, but it provides some insight into variables that may be potentially useful for tracking commodity production over time to detect imbalances in the supply chain. Also, the average ratio of protein to fat was 0.02-0.03 higher in 2008 than 2007, 2009, or 2010; 2008 was the year when melamine adulteration likely intensified.

The numbers reported for raw milk production were almost universally lower than the calculated value of raw milk production. Presumably, this is due in part to losses after collection or data sampling methods. Similarly, the reported average yield per cow was generally higher than the calculated average yield per cow. This could be due to sampling methods for cow yields as wells as losses along the supply chain. The Bayesian linear model indicated average yield per cow increased significantly in 2008 and 2009 over baseline (2006). An increase in average yields would be realistic with improved feed and farming practices, but this could also be due in part to melamine adulteration. The top 3 producing provinces showed variation in average yields over the 4 years examined in the model. The top 3 provinces all had above-average yields in 2007, but only 1 had above-average yields in 2008.

While various anomalies were observed in these data, there did not appear to be one obvious imbalance in raw milk production numbers when compared to other dairy production variables. This could indicate that raw milk production numbers were recorded after melamine and other adulteration and dilution substances had been added to the milk supply.

There were numerous challenges and limitations in this exploratory analysis. It has historically been challenging to obtain detailed, meaningful, and accurate market data from China, and this was no exception. The language barrier inhibited communication with the representative from the Chinese dairy trade association. Since the data was compiled and collected by a third party, the validity and accuracy of the data cannot be guaranteed. Furthermore, details on data collection methods were not available for each of the variables in the data set. This analysis sheds insight on variables that may be useful for tracking the production of global commodities for early indications of EMA. Future analyses should validate these types of methods in other food products originating in other countries. This would require detailed and reliable data sets with variables describing multiple steps in the supply chain. These types of data sets could then be used to prospectively monitor multiple variables for changes to a food production system over time.

Research into EMA incidents is a growing field. Detection of these incidents cannot be achieved through public health surveillance systems alone. Economic and other market data has the potential to provide insight into the incentive for EMA, as well as the evolution of an incident. We examined Chinese dairy production data in the years

surrounding melamine adulteration of milk products to identify potentially useful variables and trends. Surveillance of these types of data sources for food commodities can be a useful tool in food defense efforts moving forward.

Table 4. Major global producers, importers, and exporters of dairy products.

Statistic	Major countries/regions (%)*
Milk production	EU (21)
	India (16)
	U.S. (12)
	China (6)
Dairy imports	EU (51)
	China (6)
	Mexico (3)
	Algeria (3)
Dairy exports	EU (60)
	New Zealand (15)
	U.S. (6)
	Australia (4)

*Statistics for milk production are reported for 2010; statistics for imports and exports are reported for 2009. Source: FAO.

Table 5. Major global producers, importers, and exporters of skim milk powder, semi-skimmed milk powder, and whole milk powder.

Product	**Major producers (1,000 metric tons)***	**Major exporters (% total world exports)***	**Major importers (% total world imports)***
Skim milk powder	EU (1,220)	EU (30)	Mexico (11)
	U.S. (893)	U.S. (25)	China (7)
	New Zealand (440)	New Zealand (21)	Indonesia (7)
	India (410)	Australia (10)	Algeria (7)
Whole and semi-skimmed milk powder	China (1,045)	New Zealand (50)	China (14)
	New Zealand (1,000)	EU (18)	Algeria (9)
	EU (725)	Argentina (9)	Venezuela (5)
	Brazil (510)	Australia (5)	Saudi Arabia (4)

*All figures are reported for 2011. Source: International Dairy Federation.

Timeline of melamine adulteration incident, dairy products, 2008

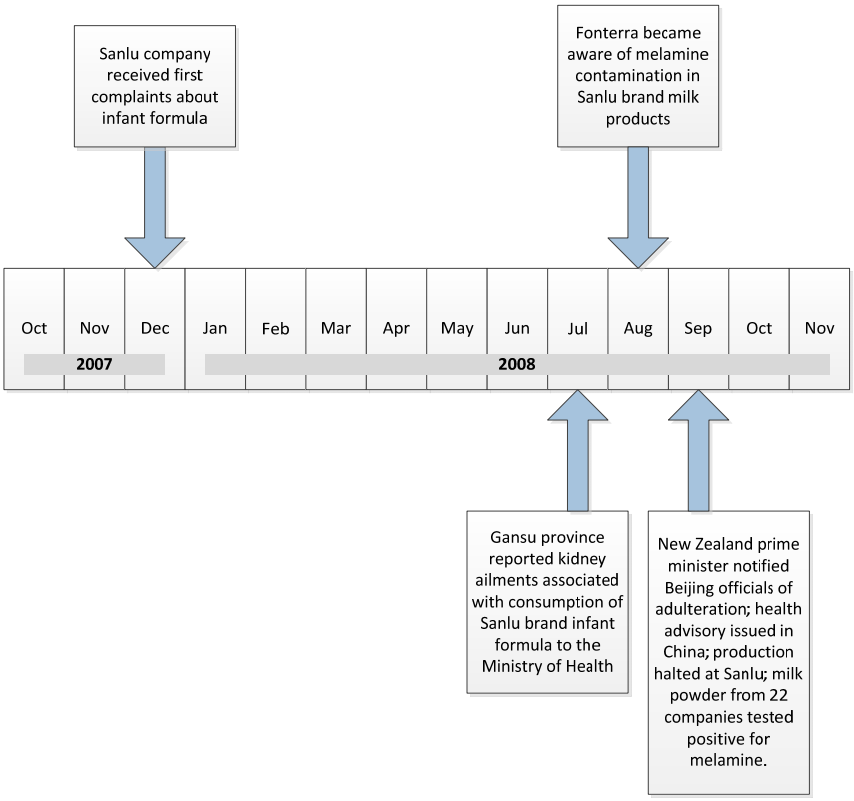


Figure 6. Timeline of incident of melamine adulteration of dairy products in China.

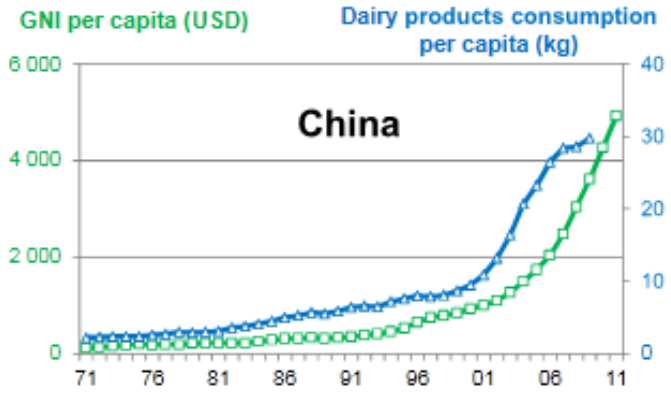


Figure 7. Gross national income (GNI) and consumption of dairy products per capita in China, from 1971 projected through 2011. (Source: International Dairy Federation).

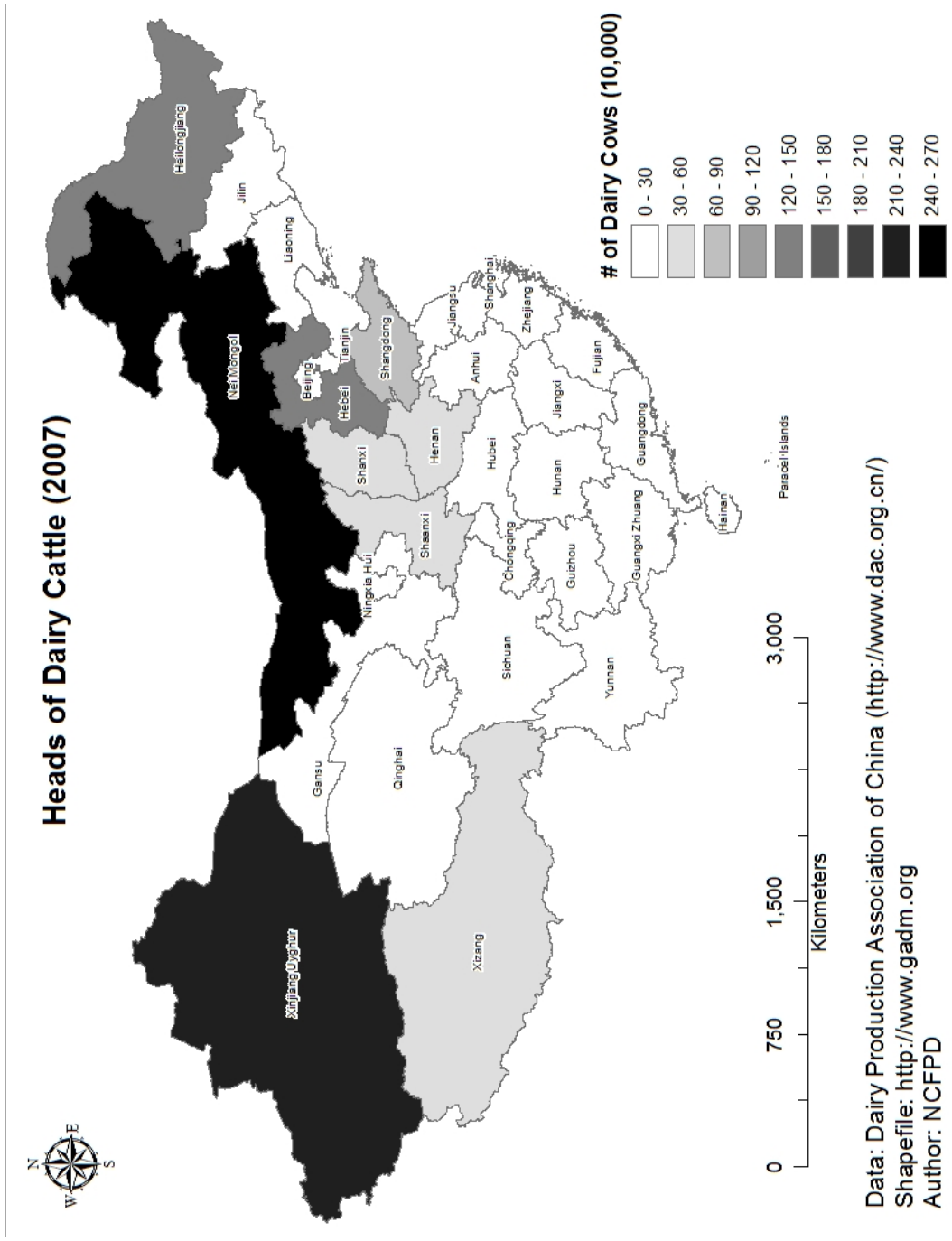


Figure 8. Number of dairy cattle in each of 31 Chinese provinces, 2007.

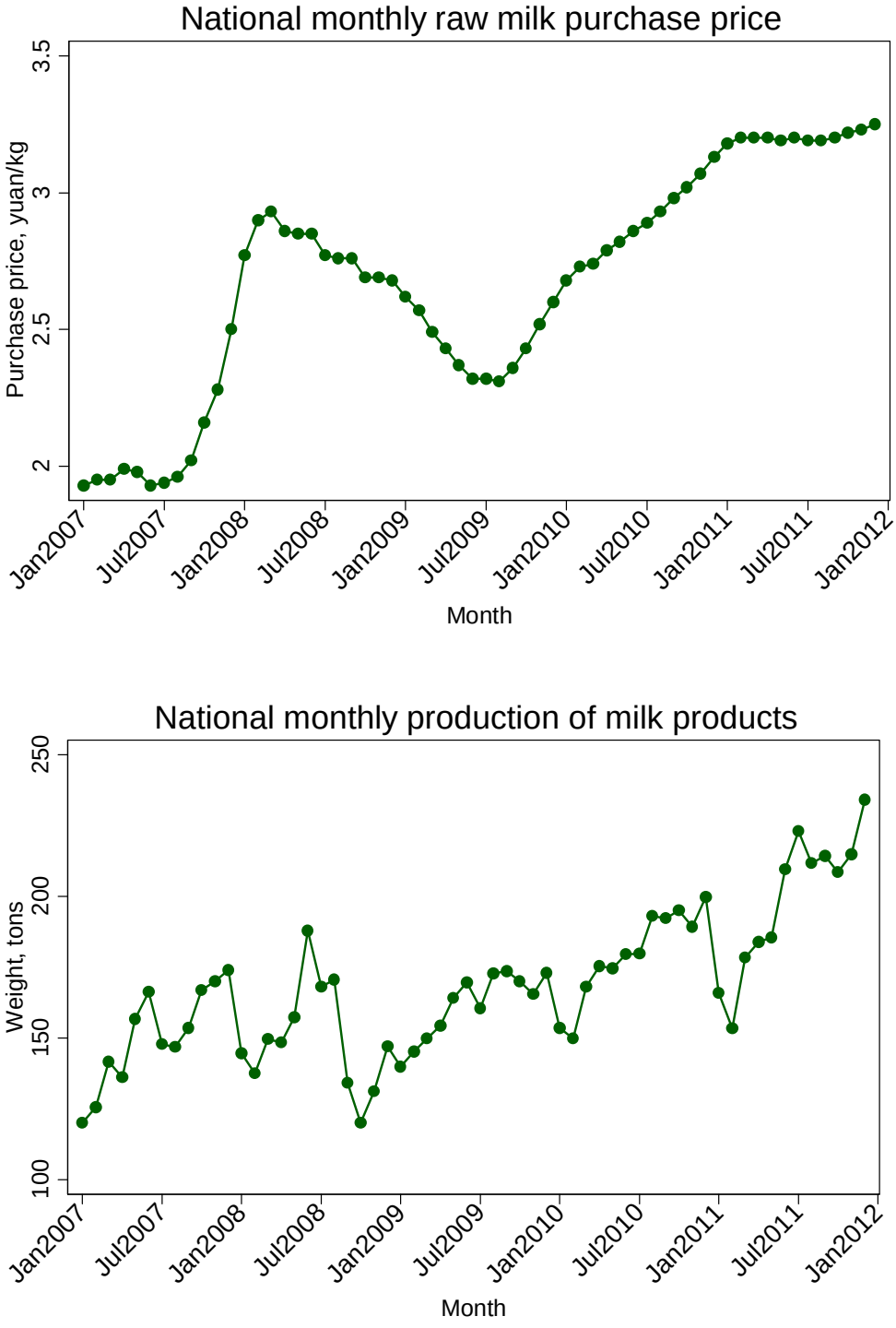


Figure 9. Raw milk purchase prices and national production of milk products, by month, in China, 2007-2011.

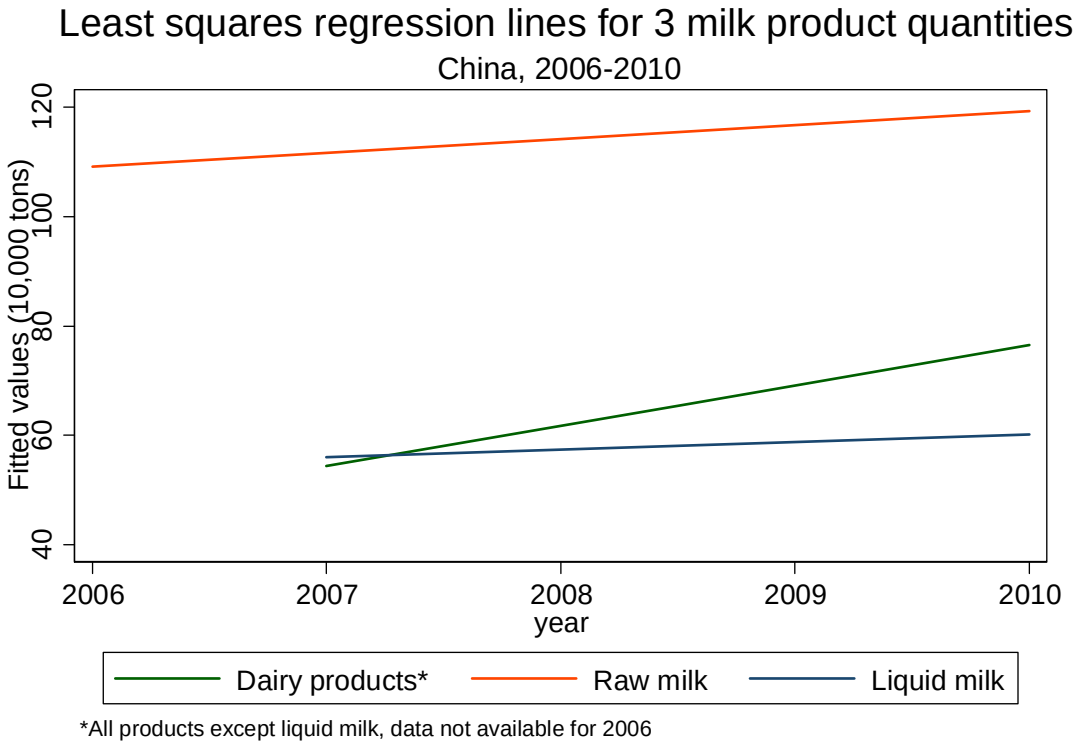
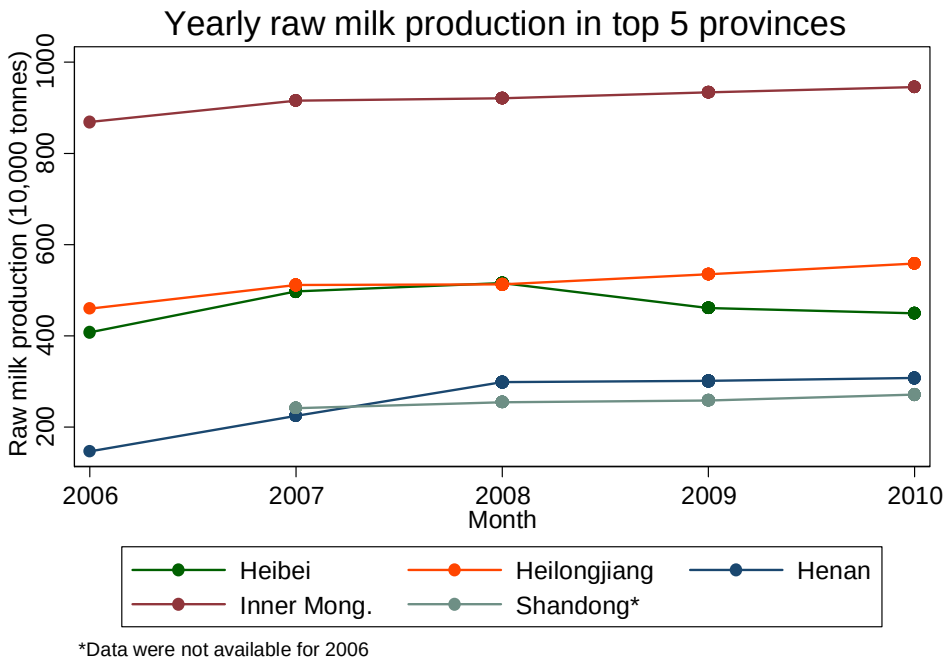


Figure 10. Fitted least squares regression lines for raw milk production, liquid milk production, and production of finished dairy products in 31 provinces, 2006-2010.



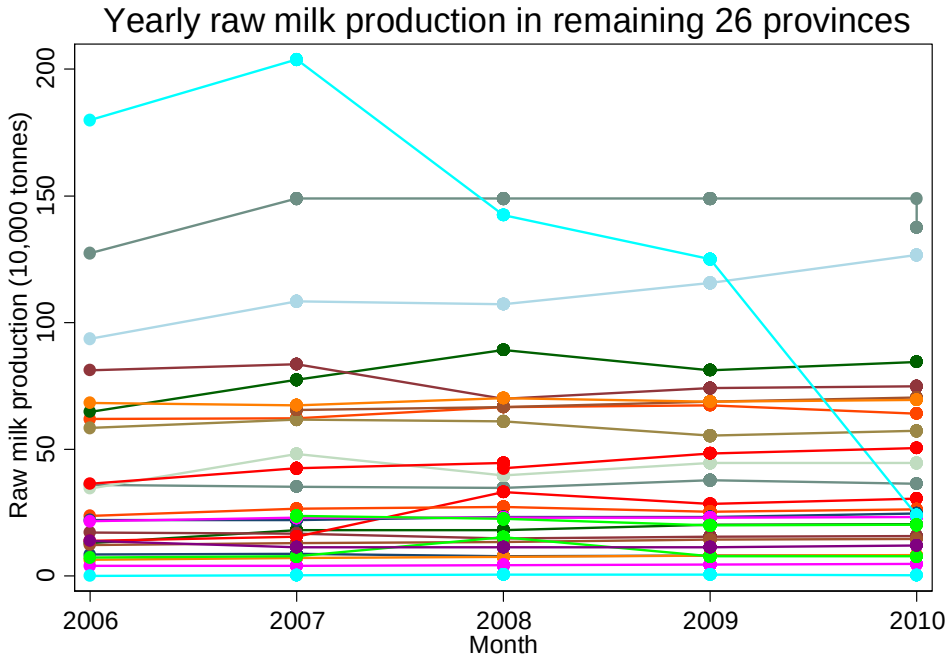
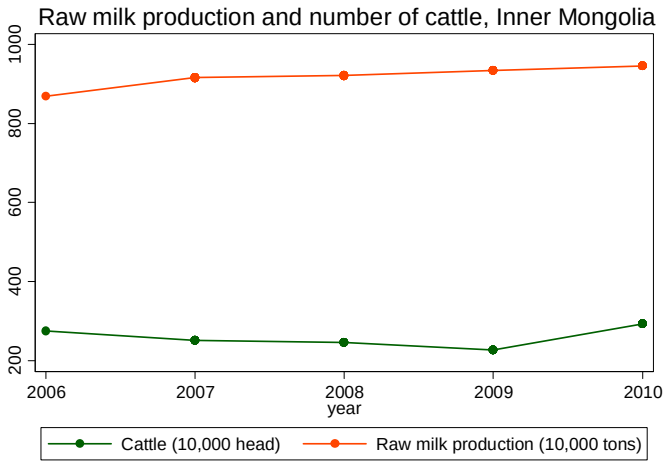
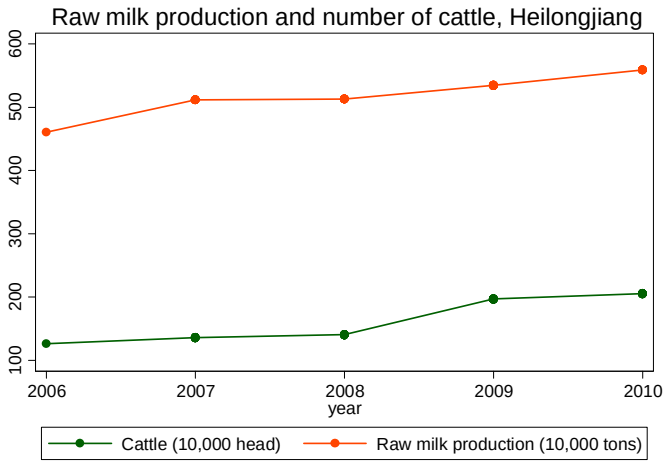


Figure 11. Yearly milk production quantities in top 5 provinces and remaining 26 provinces in China, 2006-2010.





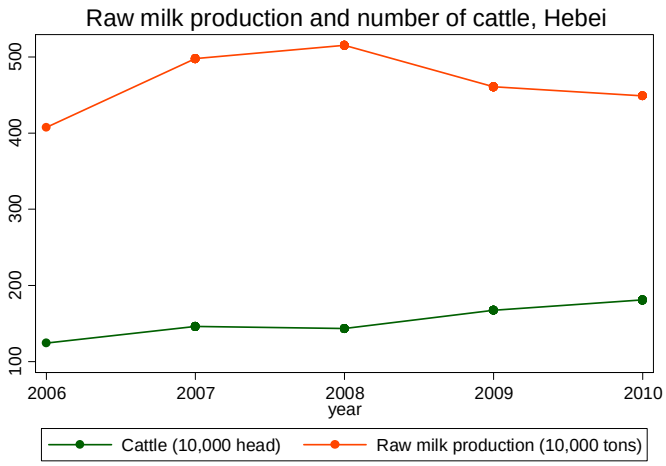


Figure 12. Raw milk production and number of cattle for top 3 milk-producing provinces in China, 2006-2010.

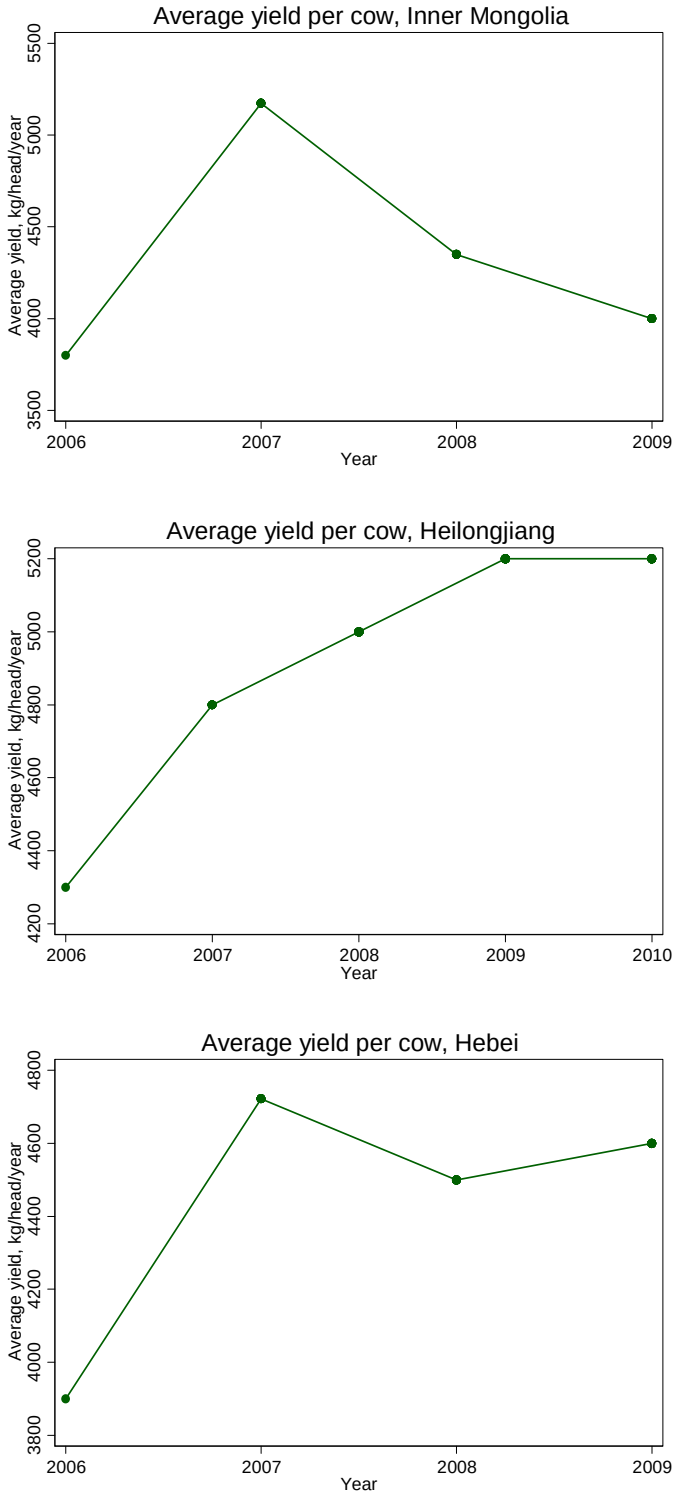


Figure 13. Average milk yield per cow for top 3 milk-producing provinces, 2006-2009.

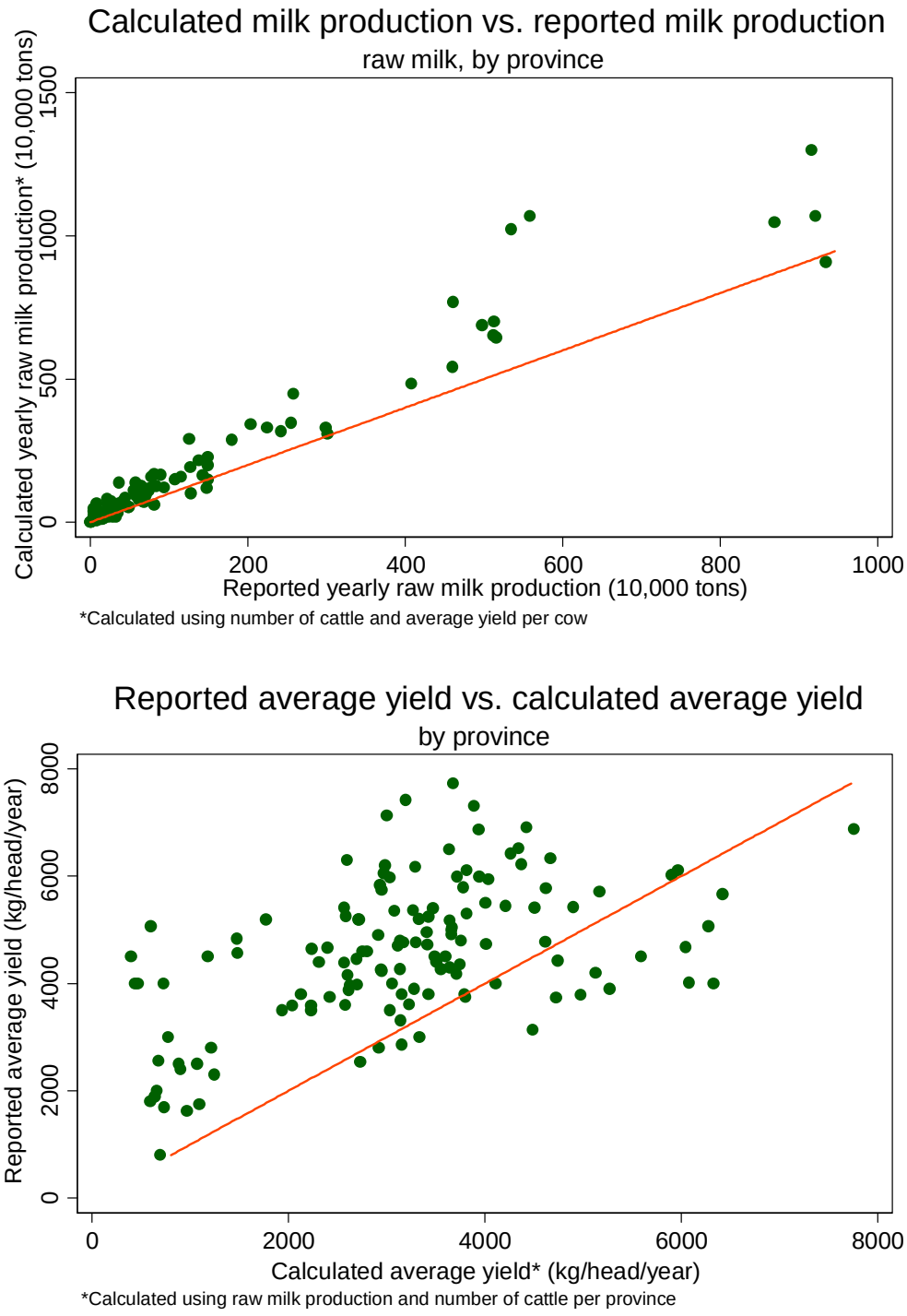


Figure 14. Calculated yearly raw milk production vs. reported yearly raw milk production (top) and reported average yield per cow vs. calculated average yield per cow (bottom) for 31 provinces, 2006-2010, with a reference line (y=x).

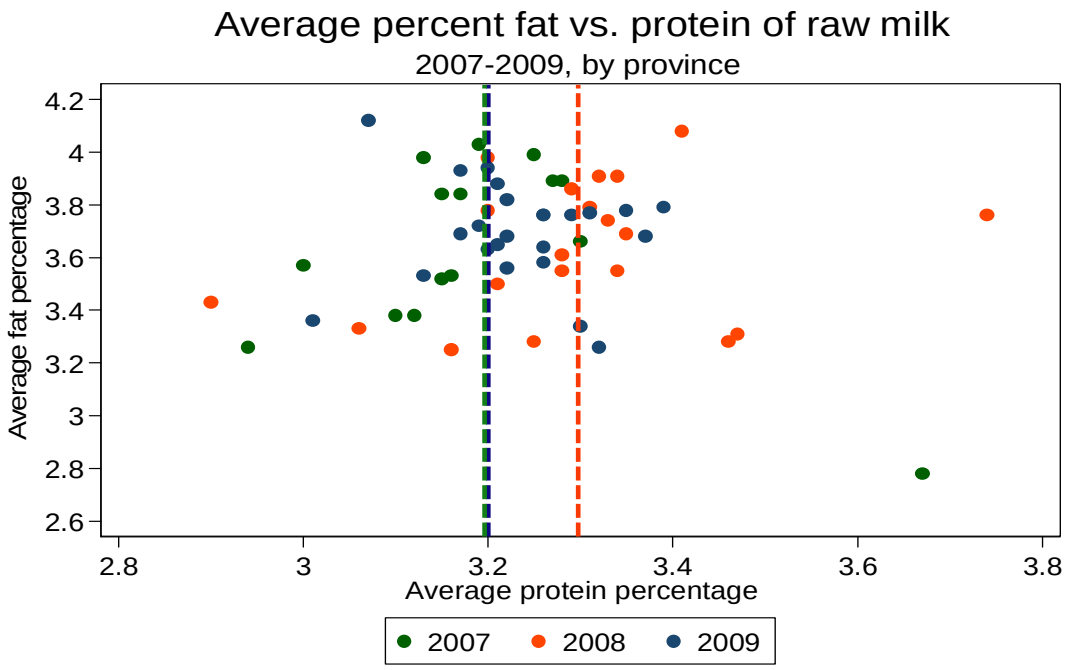
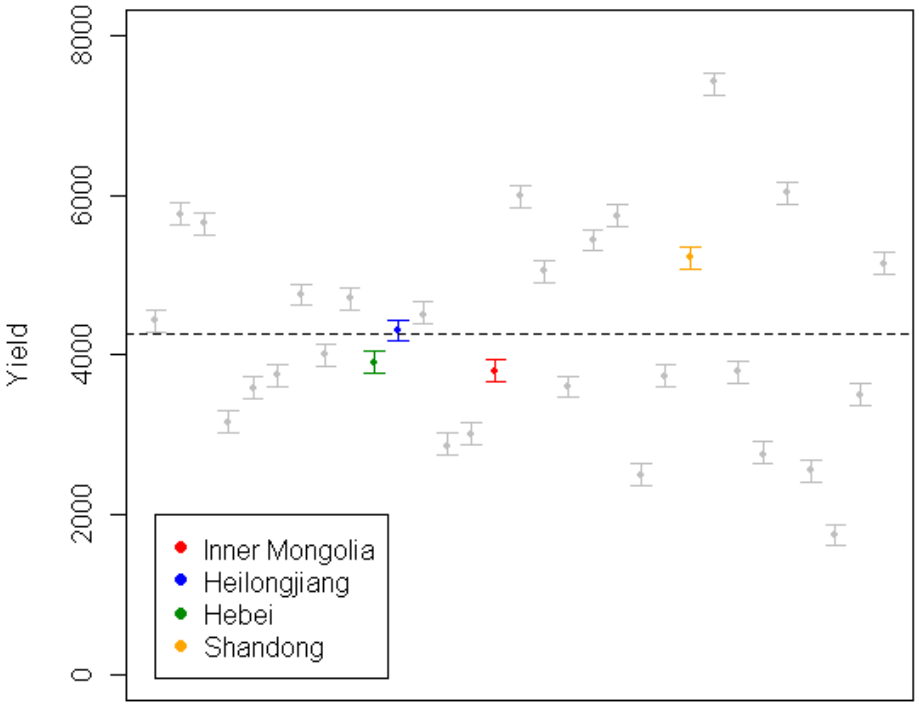


Figure 15. Average percentage of fat vs. average percentage of protein in raw milk supplies for 31 provinces, 2007-2009.

a.



b.

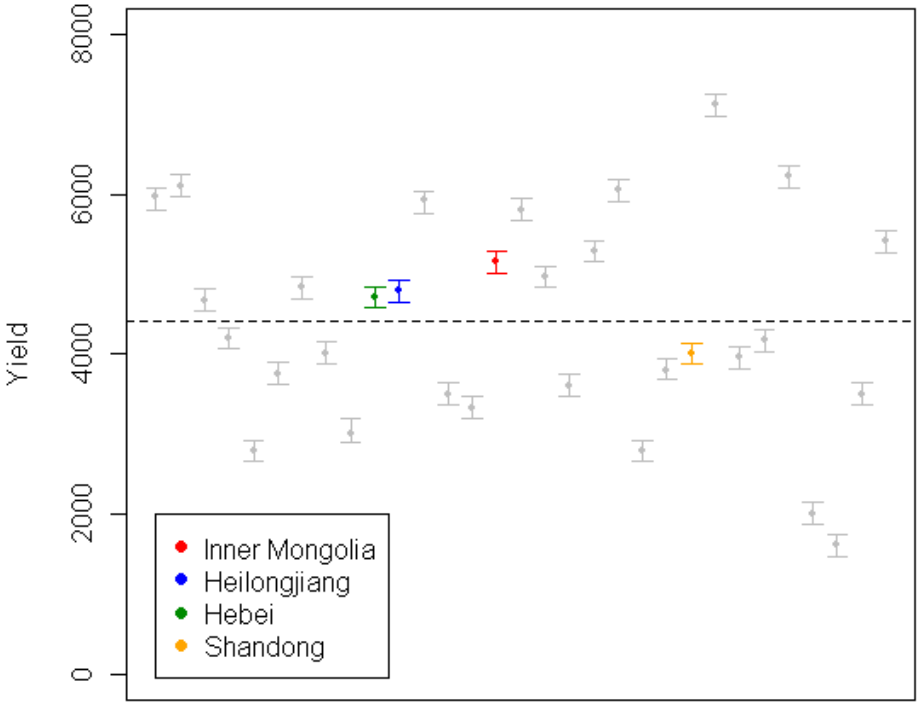
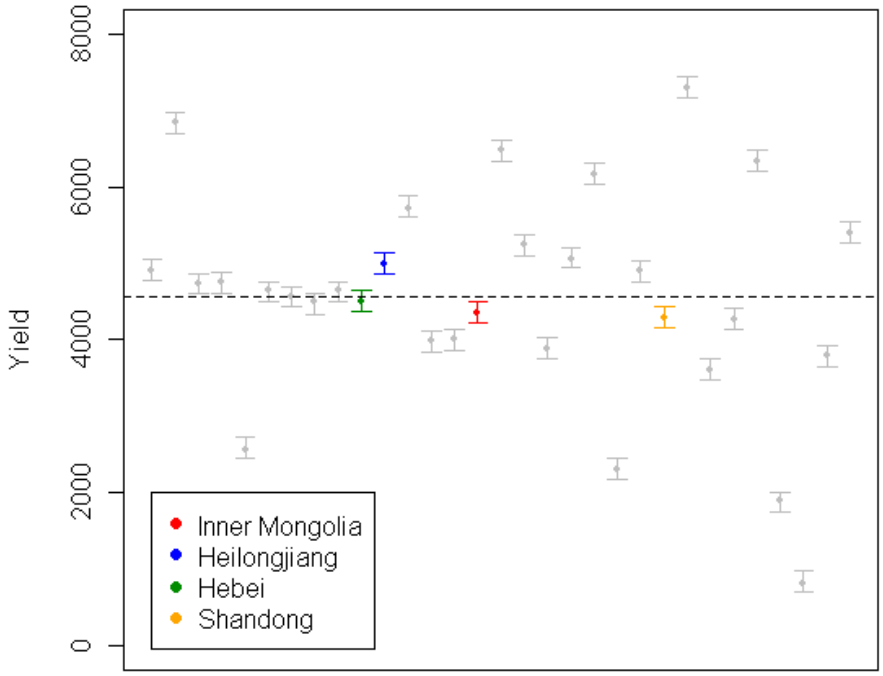


Figure 16. Posterior distributions of average milk yields in each of 31 provinces, 2006 (a.) and 2007 (b.). Dotted line represents the overall yearly average.

a.



b.

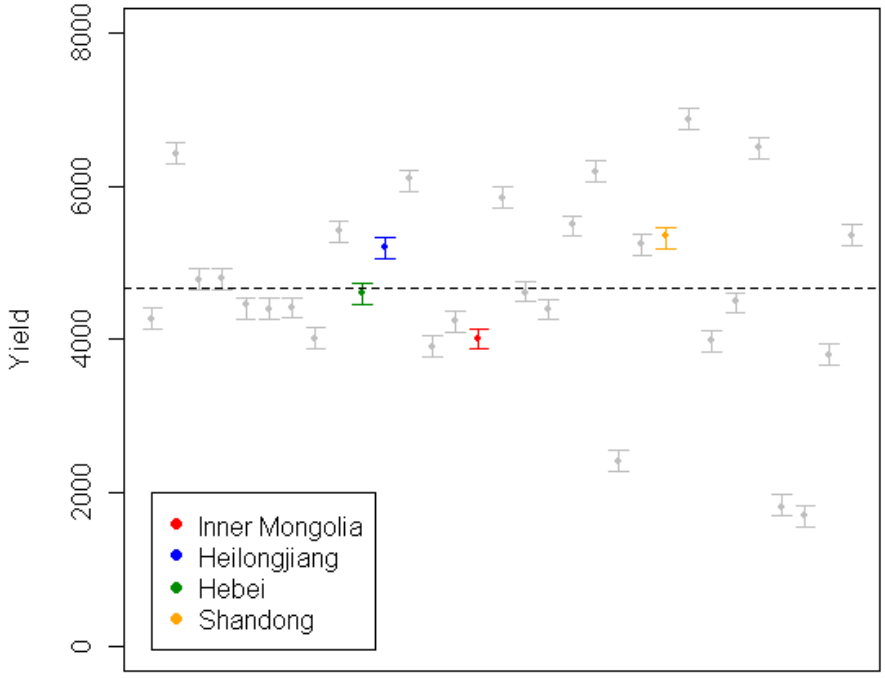


Figure 17. Posterior distributions of average milk yields in each of 31 provinces, 2008 (a.) and 2009 (b.). Dotted line represents the overall yearly average.

CHAPTER 4

Early event detection methods for surveillance of imported food products: a case study of melamine adulteration of plant-derived proteins

Introduction

U.S. Customs and Border Protection (CBP), within the Department of Homeland Security (DHS), has primary responsibility for administering U.S. laws related to imports and exports. CBP collects and maintains data for all import shipments that enter the U.S., including food products. Products are classified according to Harmonized Tariff System (HTS) codes which are published by the U.S. International Trade Commission (USITC) in the Harmonized Tariff Schedule of the United States *(31)*. The Harmonized Tariff Schedule is consistent with the convention in the Harmonized System that is administered by the World Customs Organization (WCO) *(156)*. The WCO Harmonized system was developed to standardize the codes used for goods in international trade, and covers more than 98% of world trade. The HTS details the rates of duty as legally established in the U.S. It is intended for use by importers, customs brokers, CBP officers, and other stakeholders to determine the correct classification for imported articles, the amount of duty that applies to those articles, and the relevant information that must be reported for each shipment. Data fields collected and compiled by CBP for import shipments include: HTS code; quantity of shipment; value of shipment; dates of export, import, and release into the U.S.; country of origin; country of export; manufacturer and exporter demographic information; importer and consignee demographic information; and method

of transportation. There are approximately 5,400 HTS codes in the first 24 chapters of the Harmonized Code which address food and agricultural products.

Although CBP holds primary responsibility for imports, The Food and Drug Administration (FDA) and the United States Department of Agriculture Food Safety and Inspection Service (FSIS), as the regulatory agencies for food, share responsibility with CBP in terms of monitoring the entry of food imports at the border. FDA and FSIS are responsible for determining whether or not imported food products within their purview are in regulatory compliance *(85)*. FSIS generally requires what is called "re-inspection" of all imports of FSIS-regulated products at an import inspection facility *(32)*. The process is referred to as "re-inspection," since FSIS-regulated products have already been subject to what is termed "continuous inspection" at multiple steps during production. FSIS requires that countries that export meat to the U.S. have inspection systems that are equivalent to those in the U.S. *(209)*. FSIS uses the "Automated Import Information System" to determine the type of re-inspection required for each import shipment. This system bases re-inspection parameters in part on the compliance history of the establishment and country from which the product originated. FSIS also performs random sampling of products at the border for drug and chemical residue analysis. In 2011, 2.9 billion pounds of FSIS-regulated meat and poultry products were presented for import into the U.S.; almost 90% of those products originated in Canada, Australia, New Zealand, or Mexico *(94)*. An additional 17.8 million pounds of egg products were imported, all of which originated in Canada.

FDA has a much more cumbersome burden of responsibility for regulation of imported food products than FSIS. In 2011, there were almost 10.5 million import lines for FDA-regulated food products that arrived from almost every country in the world *(33)*. Unlike FSIS-regulated products, the vast majority of FDA-regulated products are not physically inspected. FDA-regulated products are not subject to "continuous inspection"-type regulations as FSIS-regulated products are. FDA does perform inspections of foreign food facilities, but at a relatively low rate. In 2011 FDA performed inspections at 995 (0.4%) of 254,088 active registered foreign food and feed facilities. FDA electronically screens all import entries with an automated system ("PREDICT") that is intended to target the highest-risk imports based, in part, on violative histories. In 2011, FDA physically examined 2.3 percent of food import lines.

In February and March 2007, consumer complaints about pet illnesses as well as animal deaths that occurred during a premarket palatability study for a pet food manufacturer prompted an investigation into contaminated pet food ingredients *(163)*. Thousands of dogs and cats were eventually affected with reduced renal function, renal failure, or death. The adulterated ingredients were determined to be wheat gluten and other plant-derived protein products (PDP) and the identified adulterants were melamine, cyanuric acid, and melamine analogues. FDA eventually determined that products that were being imported as wheat gluten and rice protein consisted primarily of wheat flour adulterated with melamine (and related chemicals) *(163)*. The interaction between melamine and cyanuric acid caused the formation of insoluble crystals in the kidneys of dogs and cats, leading to renal injury, renal failure, and death. Another ramification of the

adulterated pet food ingredients was the incorporation of pet food waste into the feed of production animals in the U.S. At least 56,000 swine, 2.5 million chickens, and fish at 160 hatcheries and 2 aquaculture farms consumed melamine-contaminated feed *(163)*. FDA indicated that some people most likely consumed meat from animals fed melamine-contaminated feed; however, the human health risk was ultimately determined to be minimal *(197)*. A timeline of the adulteration incident is shown in Figure 18.

Melamine was added to plant proteins specifically due to its high nitrogen content, whereas cyanuric acid and melamine analogues were likely unintentional co-adulterants of lower quality melamine scrap *(11)*. At the time of the melamine adulteration event, protein content in wheat gluten was typically measured with a nitrogen determination method *(208)*. Melamine is comprised of 67% nitrogen; therefore, the addition of melamine to PDP artificially inflated the interpretation of the analytical method for protein content in those products. The addition of non-protein nitrogen sources, including nitrogen-rich melamine, to animal feeds was reportedly a long-standing and common practice in China prior to this EMA incident *(44)*. Previously unattributed outbreaks of renal failure in animals that had occurred years prior to the 2007 incident were retrospectively attributed to melamine adulteration after the 2007 incident was discovered *(57)*.

Wheat gluten is a cream or light tan, free-flowing powder that is manufactured through water extraction of wheat flour ("wet-milling") *(208)*. Wet-milling of wheat produces about ¼ wheat gluten and ¾ wheat starch, by weight *(42)*. Wheat gluten is often added to bread products to enhance protein content, and therefore the elasticity and rise

of the products. During years when the intrinsic protein content of the wheat crop in the U.S. is low, wheat gluten is added to wheat flour to make up the deficiency *(42)*. In addition to incorporation into animal feed for protein content, wheat gluten may be added to food products for protein content without the need for its leavening and structure-enhancing functions. Since melamine adulteration would inhibit the functional properties of wheat gluten in bread products, adulteration of gluten that was subsequently used in the production of bread products would have theoretically been detected through a loss of ingredient function. However, a loss of function (and subsequent detection of adulteration) would not have occurred with gluten that was incorporated into non-bread products for nutritional content.

The market value of wheat gluten and other PDP, such as rice or corn proteins, is based on protein content. Increasing market demand for non-animal protein sources such as wheat gluten, combined with an increase in wheat gluten prices and a viable method for evading the common analytical methods for protein content, would provide both the incentive and the means for large-scale fraud in the market for PDP intended for incorporation into animal feeds (and, in theory, non-bread food products). The relatively low yield of gluten per pound of wheat flour made the sale of adulterated flour marketed as gluten a lucrative endeavor.

There are 4 U.S. HTS code classifications for wheat gluten and other PDP:

- 1109001000: wheat gluten, whether or not dried: to be used as animal feed
- 1109009000: wheat gluten, whether or not dried, “other” (this code would include wheat gluten intended for incorporation into human food products)

- 2106100000: protein concentrates and textured protein substances
- 3504001000: protein isolates *(34)*

The general rates of duty for feed gluten and food gluten imports in 2007 were 1.8% and 6.8%, respectively *(34)*. Other than the classifications for wheat gluten to be used as animal feed ("feed gluten") and wheat gluten "other" ("food gluten"), non-wheat PDP ("protein concentrates" and "protein isolates") are not differentiated by plant origin. Therefore, shipments of rice protein and corn protein could not be evaluated separately through analysis of data collected by CBP.

There is a large market for wheat starch in the EU. Since wheat gluten is produced along with wheat starch during the wet-million process, the EU has historically been a net exporter of wheat gluten *(52)*. Therefore, EU countries have traditionally supplied the bulk of wheat gluten imports to the U.S., and from 1983 to 1995, imports of wheat gluten from EU countries increased, on average, 47% each year *(42)*. However, beginning in 2003, imports of feed gluten from China increased considerably: from 2.6 million kg in 2002 to 7.0 million kg in 2003 (see Figure 19). Imports again increased dramatically from 2005 to 2006, from 6.5 million kg to 13.0 million kg.

Although, in retrospect, melamine was probably not a novel adulterant in wheat gluten, at the time there was not a recognized risk of melamine adulteration of PDP and, therefore, no routine analytical methods existed for detecting melamine in these products. However, as noted above, the quantities of wheat gluten imported into the U.S. from China increased dramatically in the years preceding the adulteration incident. The addition of melamine to wheat flour to pose as wheat gluten or other plant proteins would

have allowed Chinese production of higher-valued gluten to increase substantially without the need for a corresponding increase in wheat production. This increase in production and exports of wheat gluten without a corresponding increase in wheat production could have been viewed as an anomaly in the supply chain for wheat gluten that warranted investigation.

Biosurveillance has two main objectives, per Homeland Security Presidential Directive 21: early event detection (EED) and situational awareness (SA) *(98)*. EED involves eliciting early warning of possible disease incidents - for example, indication of an outbreak prior to the diagnostic case confirmation that would occur as part of epidemiologic surveillance. SA involves ongoing analysis during an outbreak for monitoring purposes. Some commonly used data sources in biosurveillance include emergency department data or other clinical visit information, medication sales, calls to poison control centers, and school absenteeism rates. Whereas epidemiologic outbreak investigations are inherently retrospective, the goal of biosurveillance is to be a prospective monitoring tool and, therefore, biosurveillance cannot be accomplished with traditional epidemiologic methodologies.

Statistical process control (SPC) refers to a set of techniques that have been used for decades to monitor and improve quality in manufacturing processes *(147)*. More recently, SPC methods have been applied to biosurveillance and EED research as a method of prospective monitoring for potential disease outbreaks *(98)*. The concept of SPC involves establishing upper and/or lower statistical control limits for time-series data monitoring. If data points fall outside these pre-determined limits, the system is

determined to be "out of control" and warrants attention. The control limits are intended to differentiate between variations in data values that are attributable to random noise, versus those that have an assignable cause that can be remedied. A sample control chart is shown in Figure 20. This sample chart includes only an upper control limit (illustrated by the dotted line), and the red data points are those that fall outside of the limit based on a sample statistic (typically, the process mean) *(133)*.

SPC plots, also known as "control charts," take various forms. Shewhart charts monitor the values of sample statistics, such as the mean or variance, of sampled data values from a process, and are useful for detecting one large deviation from those statistics *(100, 133)*. Exponentially weighted moving average (EMWA) charts monitor an exponentially weighted average of current and past statistics. EMWA charts were designed to monitor mean shifts and can be useful for detecting smaller shifts and gradual deviations from the statistic. Finally, cumulative sum (CUSUM) charts monitor the cumulative sums of observation deviations from target statistics (mean and/or variance). CUSUM charts can also detect more gradual shifts in the target statistics, but they have a longer "expected time-to-signal" than EMWA charts. This means that, for a given out-of-control situation, an EMWA chart is likely to signal slightly earlier than a CUSUM chart. However, since both EMWA and CUSUM charts detect more gradual shifts in data processes, they are generally more applicable to biosurveillance-type data than Shewhart charts (this will be discussed further below). All control chart methodologies require specifying control limits based on the characteristics of the data set and the type of shifts to be detected.

In SPC terminology, ARL_0 is the expected number of observations between false signals. It is therefore advantageous for ARL_0 to be large. In EED terminology, this is usually referred to as the average time between false signals (ATFS) *(99)*. ARL_1 is the expected number of observations before a true signal is detected when a legitimate out of control condition is present; therefore, it is advantageous for ARL_1 to be small. In EED, this would be analogous to the number of time periods that would elapse after the beginning of an outbreak before the method signaled, and it is called the conditional expected delay (CED).

A CUSUM method (assuming normally distributed, standardized distributions) plots one or both of the following two statistics *(100)*:

$$C^+_t = \max [0, C^+_{t-1} + (Y_t - \mu_0)/\sigma - k] \text{ and}$$

$$C^-_t = \min [0, C^-_{t-1} + (Y_t - \mu_0)/\sigma + k],$$

where Y is the value of the observed data at time t, μ_0 is the process mean of the in-control (or non-outbreak) distribution, σ is the shared standard deviation of both the in-control and out-of-control distributions, k is the chosen reference value, and C_0 is 0. C^+_t is the statistic used to detect positive shifts in the process, and C^-_t is used to detect negative shifts in the process. Both statistics are bounded by zero. For EED, it is usually only necessary to monitor positive shifts; however, both may be monitored simultaneously. Positive signals occur when $C^+_t > h$, where h is a chosen threshold

(sometimes referred to as the "decision interval"). Both *k* and *h* are chosen based on the desired ATFS.

In EED, the choice of k and h are based on a desire for outbreak detection sensitivity, combined with the smallest ATFS that is reasonable given resources that are available for investigating signals *(100)*. Therefore, there is an inherent tradeoff between sensitivity of shift detection, and the ability to respond to false signals. Commonly chosen values for *h* and *k* for a CUSUM based on the normal distribution are 4 and 0.5, respectively. When h=4 and k=0.5, the CUSUM will generally detect a shift of 1 standard deviation from the in-control (non-outbreak) distribution. The two values may be adjusted to increase or decrease the sensitivity of signal detection, depending on the attributes of the data source and the type of shift to be detected.

SPC (as applied to data resulting from manufacturing processes) requires certain assumptions that do not necessarily apply to biosurveillance-type data sets *(99)*. Some of these assumptions include:

- the data are stationary and observations are independent,
- the expected distribution of the data is known (and, generally, normal), and
- temporal detection is the main focus.

Data sets that lend themselves to biosurveillance or EED tend to violate these assumptions. For example, disease incidence data are almost never stationary; time-series observations are usually correlated and, therefore, not independent; the distribution of the data may not be known, and therefore statistical tests based on a specific distribution are

not useful; and both spatial and temporal deviations may be indicative of an incident *(98)*. In short, systematic effects need to be taken into consideration with EED. In order to apply SPC methods to EED, preprocessing is required so that the data better meets the assumptions implicit in SPC. Pre-processing is involves using a modeling technique that removes systematic trends in the data (such as seasonality and autocorrelation) to result in a data set of residuals which are approximately normally distributed. These residuals can then be used with EED methods such as the CUSUM method.

When implementing EED for biosurveillance, the question arises of whether or not the statistic should be re-set after it signals, given that an outbreak will continue to occur for multiple time periods. When the statistic is not re-set, the method will often continue to signal for multiple time periods. A study that examined EED methodologies using hospital-based GI syndrome data indicated that re-setting the statistic after the first signal did result in fewer signals *(99)*. However, intermittent subsequent signals continued to occur and confirmed the outbreak was still ongoing. On the other hand, re-setting the statistic after a signal adds complexity to an automated system, and does not necessarily result in additional useful information. Therefore, it was determined that it may be preferable not to re-set after signals, but to consider a "signal event" to be the "consecutive time period during which a method signals".

Our goal was to determine whether ongoing EED-type monitoring of import data for food products could potentially alert us to anomalies in the supply chains for those products. Similar to the biosurveillance goal of identifying "any anomalous deviation from the usual incidence of a disease or syndrome" *(98)*, we would like to prospectively

apply the concepts of EED to food trade data to detect unusual deviations from the norm. As a proof-of-concept exercise, we retrospectively analyzed import data provided by CBP for shipments of wheat gluten and two other PDP prior to the melamine adulteration incident that was identified in 2007.

Methods

We acquired import data for all line entries (units of recordkeeping for assessing duties on imported products) from CBP for all shipments of products classified under 4 HTS codes for plant-derived proteins (PDP) over a 12 year period: 2000-2011. The HTS code classifications encompassed wheat gluten for animal feed ("feed gluten"), wheat gluten for human food ("food gluten"), protein concentrates, and protein isolates. We assessed aggregated import quantities by weight and HTS code for each country of origin. Analysis was performed on the top countries of origin, as determined by aggregated weight over the 12-year period, so that at least 80% of imports for each respective HTS code was included in the analysis. Additionally, China was included in the food gluten category, due to the known history of adulteration of Chinese wheat gluten.

The data were visually explored with monthly and yearly time-series and autocorrelation plots to detect the presence of seasonality or other trends. Trends in the data were removed through simple exponential smoothing (SES) methods to achieve residuals that were approximately normally distributed. Although ideally we would tailor the smoothing technique to the specific distribution of data for each food product

category, for our exploratory purposes we applied a consistent methodology to all the data. SES was determined to be a sufficient generalized smoothing method based on inspection of residual plots after smoothing. We then applied cumulative sum (CUSUM) control chart methodology to the standardized residuals of aggregated monthly quantities of imports from each country. CUSUM analysis was determined to be the most applicable to detecting gradual and sustained supply chain shifts that would be characteristic of artificial market inflation due to EMA in food products. Since shipments from multiple countries were monitored for each product, we focused only on positive CUSUM signals. Negative shifts in imports from a particular country would most likely coincide with positive shifts from another country; therefore, it was determined to be unnecessary to monitor both. Reference value and decision interval parameters were chosen to optimize the balance between sensitivity of signal detection and minimization of false signals, and were based on values recommended by the literature as effectively detecting a shift of 1 standard deviation from the process mean. We defined a signal event as a group of consecutive or semi-consecutive positive signals (separated by no more than 2 non-signaling time periods).

Descriptive statistics for the data are presented in each food category, as well as aggregated yearly and monthly graphs by country and one region (EU). Plots that illustrate the data pre-processing steps are provided for feed gluten from China: raw monthly quantities and the associated autocorrelation function, the residuals after SES as well as a histogram and quantile-quantile plot, and the autocorrelation function of the residuals. CUSUM was applied to all 12 years of data; however, positive signal events

were only reported from 2002-2011 since the small amount of data available in the early time periods was not sufficient to establish a mean. CUSUM charts are presented for Chinese imports in all 4 food categories. Finally, results that detail the number of signal events per year are presented for all top countries of origin and food products.

Data were transferred from CBP as Microsoft Access databases, and extracted into Microsoft Excel. They data set was imported into Stata version 12, which was used for all data cleaning, re-formatting, and descriptive tables and graphs. Subsets of the data set were exported for further analysis in the R environment. Simple exponential smoothing and standardization of residuals was performed in R, as well as the CUSUM method using the "qcc" package.

Results

More than 85,000 total line entries for PDP imports were recorded over the 12-year period from 2000 through 2011, totaling more than 2 billion kg of products (see Table 6). The top countries of origin in each product category, accounting for at least 80% of imports by weight in each category, are also shown in Table 6. Total yearly import quantities in each of the 4 product categories are shown in Figure 21. Food gluten accounted for the vast majority of imports per year, by weight. Plots of aggregated import quantities per country were explored on yearly, monthly, and weekly time-series plots. For the purposes of supply chain shift detection, weekly and monthly biosurveillance-type CUSUM analyses were explored. Monthly analyses were determined to have the most utility. Aggregating quantities by week resulted in many weeks without shipments,

and accounting for many observations with "0" quantities complicated the analytical techniques. Graphs of aggregated monthly quantities of feed gluten imports are shown in Figure 22. The graphs illustrate the amount of variability in import quantities over time.

A time-series plot of aggregated monthly quantities of feed gluten from China over the 12-year period (144 months) is shown in Figure 23, along with an autocorrelation plot of the same data. The autocorrelation plot looks as expected for an AR(1) correlation structure; months with the fewest number of lags between them are the most correlated, and the correlation decays with increasing lag time. After SES, a time-series plot of the resulting residuals, as well as a histogram of the residuals and a quantile-quantile (Q-Q) plot are shown in Figure 24. The three residual plots demonstrate an approximately normal distribution. An autocorrelation plot of the residuals is shown in Figure 25, and illustrates that almost all of the autocorrelation was removed through smoothing. Similar plots of Chinese import data for the remaining 3 PDP products indicated that systematic trends were similarly removed and the residuals were approximately normally distributed.

CUSUM analysis was applied to the standardized residuals of the monthly Chinese feed gluten import data, the primary implicated product. The threshold (h) and reference value (k) were assigned as 4 and 0.5, respectively. The CUSUM control chart (Figure 26) shows 6 positive signals during the year preceding the identification of melamine-adulterated gluten: April, May, June, September, October, and December 2006. Since none of the signals are separated by more than 2 signal-less months, this was classified as one signal event. The first known implicated shipment occurred in August

2006; the first positive signal occurred 4 months prior to this shipment. Figure 10 presents CUSUM charts for the remaining 3 HTS codes for Chinese imports of PDP. Food gluten, similar to feed gluten, showed a positive signal 5 months preceding the identification of melamine-adulterated gluten from China. Both protein concentrates and protein isolates were imported in relatively low quantities from China before 2007, and CUSUM charts of both indicated positive signals after 2007.

Pre-processing and CUSUM analysis were applied to import data from all top countries in the 4 product categories. Table 7 provides detail on the number of signal events in each product category that were detected per year for imports from each of the top countries of origin. On average, 0.9 signal events were detected per year per food product category. For feed gluten, prior to 2006 signal events only occurred for 2 EU countries. The first signal event for China occurred in 2006. Following the identification of melamine adulteration in 2007, there were again signal events for EU countries as well as Australia. Food gluten shows a similar pattern. The highest number (12 or 33%) of signal events occurred in the category of protein concentrates. Protein isolates showed the highest number of signal events in a single year, with 4 signal events in 2010 among three countries of origin.

Discussion

EED methodologies, which have been applied to biosurveillance data for detection of possible disease outbreaks, can alert us to shifts in the supply chains for food products that could indicate the potential for EMA. CUSUM methods applied to import data

resulted in a total of 36 positive signal events among 4 PDP products from the top countries of origin over 10 years. An examination of the pattern of signal events provides insight into the supply chains for those imported products.

Historically, wheat gluten was imported mainly from EU countries. Prior to 2006 in in feed gluten, signal events occurred only for EU countries, which is consistent with market conditions at the time. The first signal event for China occurred in 2006, 4 months prior to the first implicated shipment, indicating an upward shift in import quantities beyond what was expected based on historical trends in the data. However, we do not know with certainty when the adulteration of gluten began. Since the adverse health effects in animals occurred as a result of the interaction between melamine and cyanuric acid, it is possible that adulteration of PDP with purer sources of melamine was occurring earlier and was not detected because melamine in its pure form is not highly toxic. Although the signal event could not have provided conclusive evidence of EMA, it did indicate a substantial change in the supply chain for imported wheat gluten that could have triggered additional investigation. After 2007, signal events for EU countries and Australia indicated that they filled in the gap left in the market by the halt of Chinese shipments.

CUSUM analysis of Chinese food gluten imports also signaled in early 2006 (one month prior to feed gluten). Adulteration of food gluten was never publicly confirmed; however, it is plausible that supplies of food-grade wheat gluten out of China were also adulterated with alternate nitrogen sources such as melamine.

The highest number of signal events occurred in the category of protein concentrates, with signal events occurring for all of the top countries of origin. This could be the result of an overall increase in market demand for these products and competition in pricing. Protein isolates had 4 signal events in 2010 alone, which is consistent with an overall substantial increase in imports of that product that year. A significant increase in market demand for a particular product is another situation that could present EMA incentive and would warrant further investigation.

This analysis faced several challenges and limitations. Adulteration of Chinese wheat gluten is the largest EMA incident in recent years to affect the U.S.; however, there is still little known about the details of the timeline of melamine adulteration. Therefore, it was not possible to further adjust the threshold based on the known timeline of events. Furthermore, there are no other recent large EMA events involving imported food products; therefore, validation of this technique with another comparable EMA incident was not possible. SPC methods were developed for monitoring manufacturing data which has very different characteristics from disease data or trade data. EED methods have been used with varying levels of success with biosurveillance data due to violations of the assumptions inherent in SPC, and those same assumption violations would apply to trade data.

Moving forward, analysis of additional food commodities is necessary to determine the general frequency of signals that occurs in a larger data set, and to potentially adjust the sensitivity of the threshold. Automation of data import and analysis could be accomplished with relatively few resources. Case studies should then be

conducted for a set number of food commodities to investigate the signals that occur for market-based explanations. FDA has already implemented a risk-based screening system for imported food products, which is aimed at using multiple data sources to assign a risk "score" to shipments entering the U.S. *(198)*. Shipments with a higher risk score are then targeted for examination at the border. Supply chain shifts could be incorporated into this type of risk-based scoring system for targeting imports. This signaling methodology would then be combined with other sources of data about supply chains to make the signals more meaningful. Thresholds could be further adjusted depending on performance and resource availability.

Automated, continuous analysis of import data streams combined with analytical methods that can adapt to normal shifts in trade behavior have the potential to inform food protection systems utilizing relatively few resources. EED methods can be used to alert when unusual shifts occur in the supply chains for food products. Advantages of these methods include the fact that they can be automated, thresholds can be adjusted, and the methods can adapt to changes in background behavior over time. It is important to note that many supply chain shifts will be attributable to current market conditions, or other situations such as adverse weather events or political unrest. Therefore, these EED methods need to be combined with other data streams and background research, where appropriate, to elicit a meaningful picture around a given supply chain situation. Use of EED methods combined with additional data streams can be useful to further inform ongoing import targeting efforts at FDA, FSIS, and CBP to reduce the potential for public health harm caused by EMA.

Table 6. Number of line entries and total weight of all imports of plant proteins into the U.S. and top countries of origin, by HTS code, from 2000-2011.

Product	Number of line entries	Total weight (kg)	Top countries of origin* (%)
Food gluten	44,931	1,630,000,000	Australia (34), France (20), Poland (12), Netherlands (10), Germany (9), China (3)*
Feed gluten	6,902	340,000,000	Netherlands (32), France (17), China (13), Poland (9), Australia (8), Germany (6)
Protein concentrates	16,421	89,000,000	Israel (18), Netherlands (18), China (14), Canada (9), Denmark (8), Taiwan (7), Mexico (6)
Protein isolates	16,747	48,000,000	China (44), France (14), Australia (11), New Zealand (9), Belgium (7)
Total	85,001	2,107,000,000	

*The top countries of origin were selected from those countries that exported the most product to the U.S., by weight and HTS code, aggregated over the 12 year period, to account for at least 80% of total imports. China did not meet these specifications for food gluten, but was included due to the known history of adulteration.

Table 7. Number of signal events resulting from the CUSUM method applied to monthly quantities of import shipments for 4 plant-derived protein products, by product, year, and country of origin.

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Total
Feed gluten											
Netherlands	0	1	0	0	0	0	0	0	0	0	
France	1	0	0	0	0	1	0	0	0	0	
China	0	0	0	0	1	0	0	0	0	0	
Poland	0	0	0	0	0	1	0	0	0	0	
Australia	0	0	0	0	0	0	1	1	1	1	
Germany	0	0	0	0	0	0	0	0	0	1	
Subtotal	**1**	**1**	**0**	**0**	**1**	**2**	**1**	**1**	**1**	**2**	**10**
Food gluten											
Australia	0	0	0	0	0	0	0	1	1	0	
France	0	0	1	0	0	0	0	0	0	0	
Poland	0	0	0	0	0	0	1	0	0	0	
Netherlands	0	0	1	0	0	0	0	0	0	0	
Germany	0	0	0	0	0	0	0	0	0	0	
Canada	0	0	0	0	0	0	0	0	0	0	
China	0	0	0	0	2	0	0	0	0	0	
Subtotal	**0**	**0**	**2**	**0**	**2**	**0**	**1**	**1**	**1**	**0**	**7**
Protein concentrates											
Israel	0	0	0	0	0	0	0	0	1	0	
Netherlands	0	1	1	1	0	0	0	0	0	0	
China	0	0	0	0	0	0	1	0	1	0	
Canada	0	0	0	0	0	0	0	0	1	0	
Denmark	0	0	0	1	0	1	1	0	0	0	
Taiwan	1	0	0	0	0	0	0	0	0	0	
Mexico	0	0	0	1	0	0	0	0	0	0	
Subtotal	**1**	**1**	**1**	**3**	**0**	**1**	**2**	**0**	**3**	**0**	**12**
Protein isolates											
China	0	0	0	0	0	0	0	0	1	0	
France	0	0	0	0	0	0	0	0	2	0	
Australia	0	0	1	0	0	0	0	0	0	0	
New Zealand	0	0	0	0	0	0	0	0	1	0	
Belgium	1	0	0	0	0	0	0	0	0	1	
Subtotal	**1**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**4**	**1**	**7**
Total	**3**	**2**	**4**	**3**	**3**	**3**	**4**	**2**	**9**	**3**	**36**

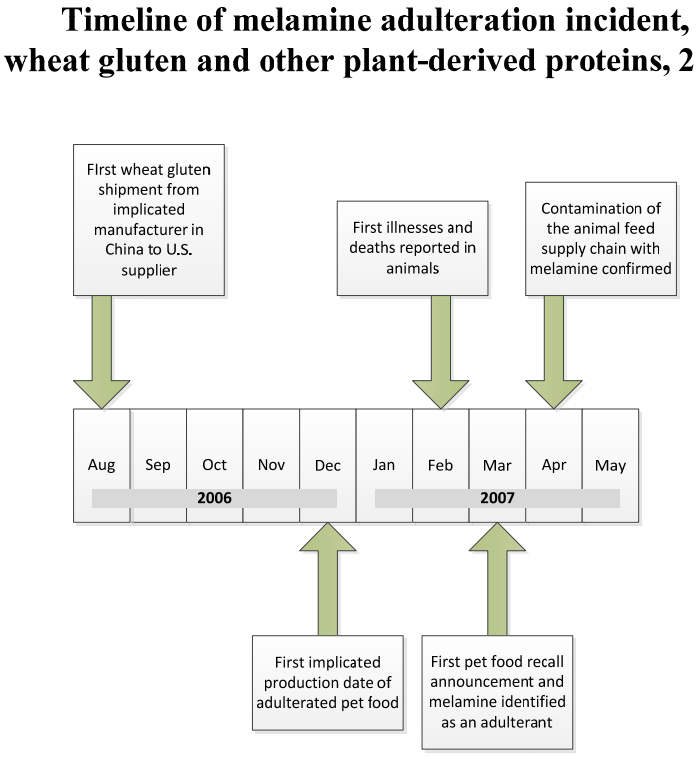


Figure 18. Timeline of incident of melamine adulteration of wheat gluten and other plant-derived proteins.

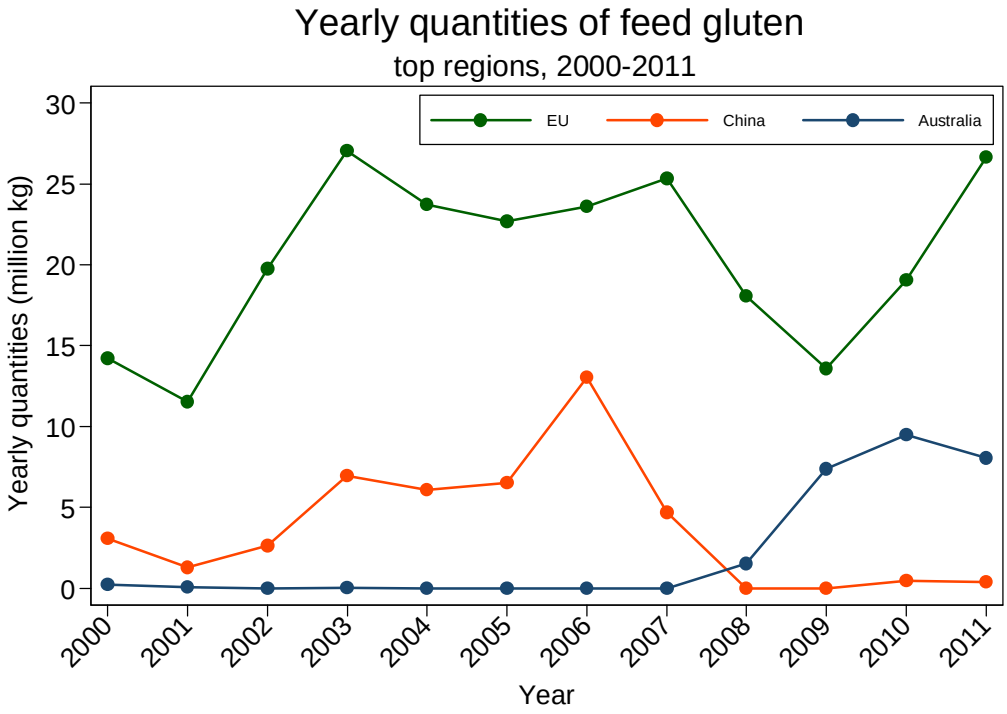


Figure 19. Yearly quantities, by weight, of wheat gluten for animal feed imported into the U.S. from EU countries, China, and Australia.

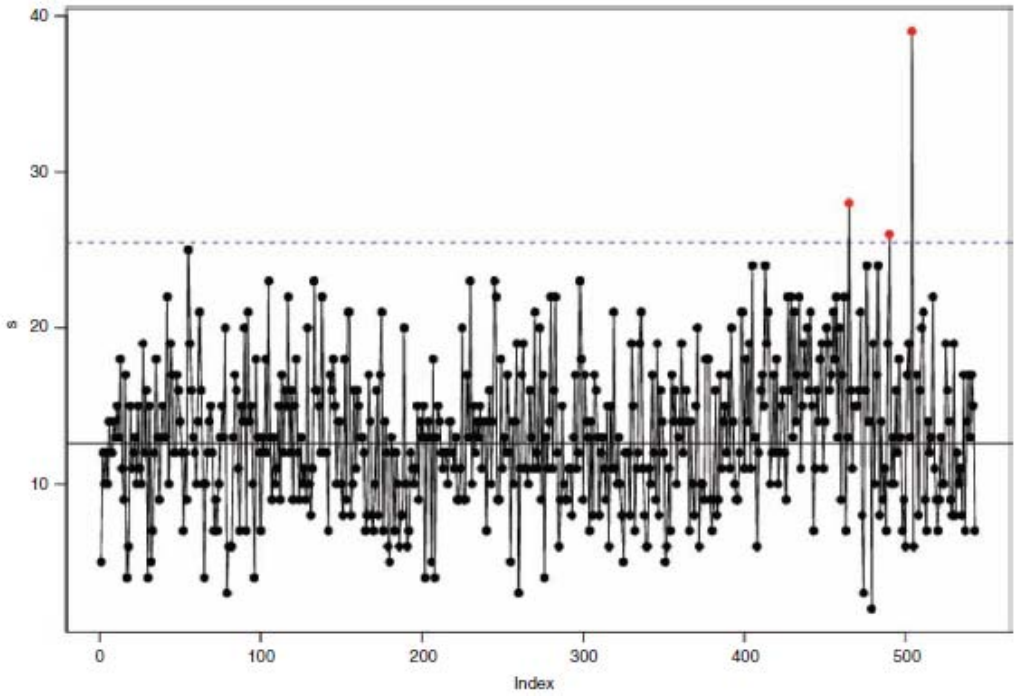


Figure 20. Sample control chart (Source: Lotze, T., S. Murphy, and G. Shmueli. 2008. Implementation and Comparison of Preprocessing Methods for Biosurveillance Data. *Advances in disease surveillance* 6:1-19).

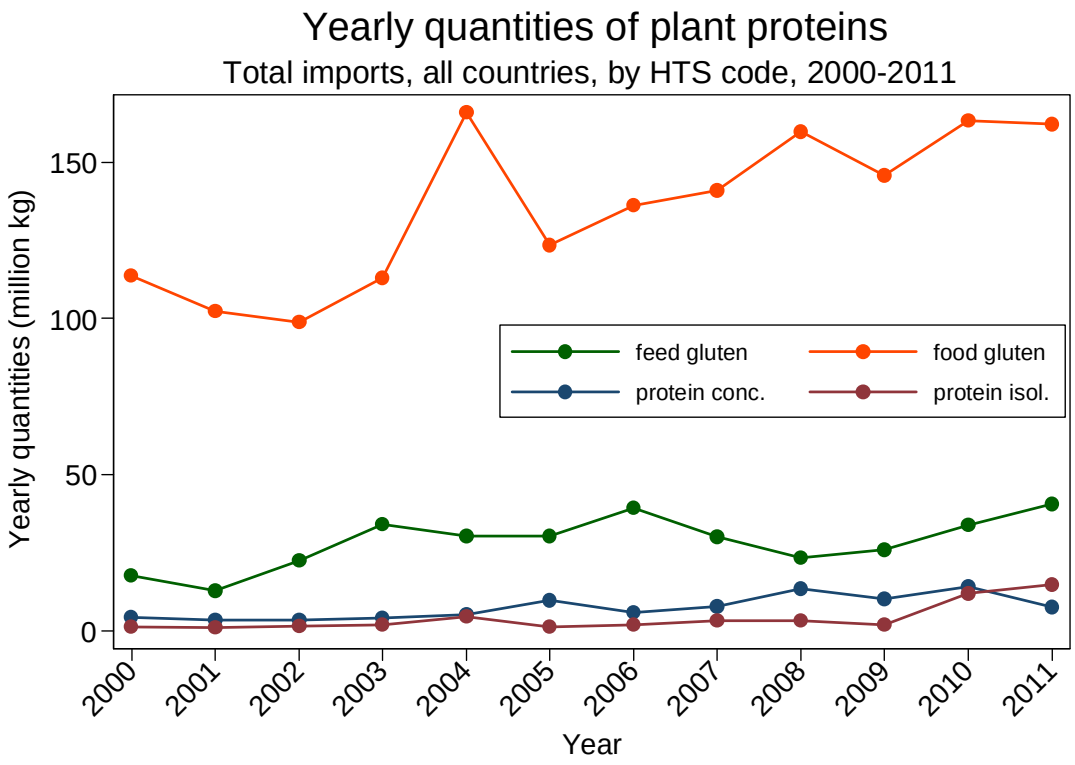
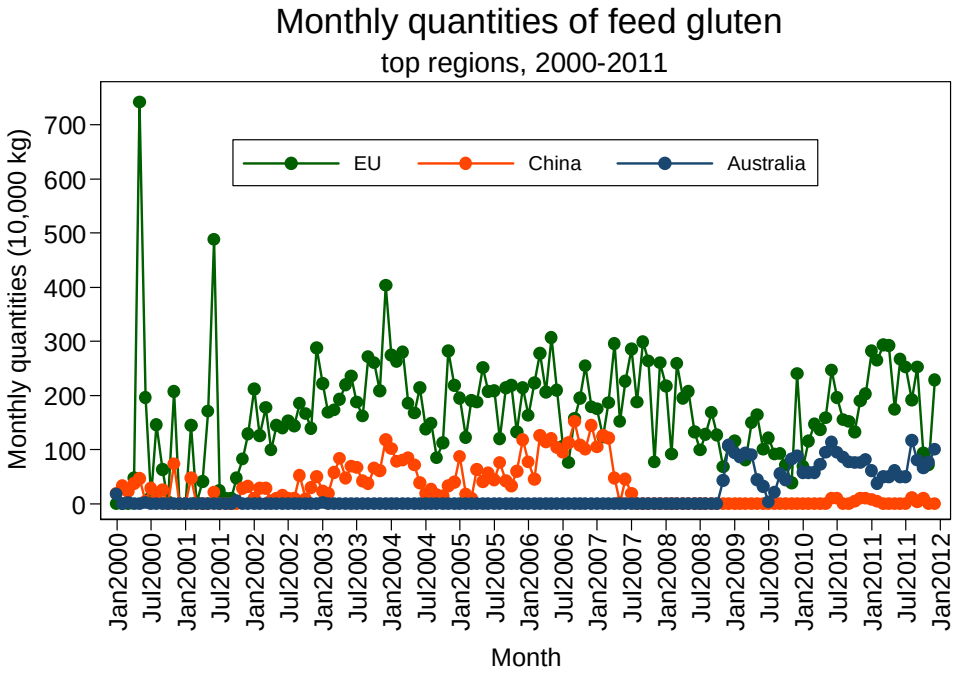


Figure 21. Yearly import quantities of each of 4 HTS codes for plant proteins.

a.



b.

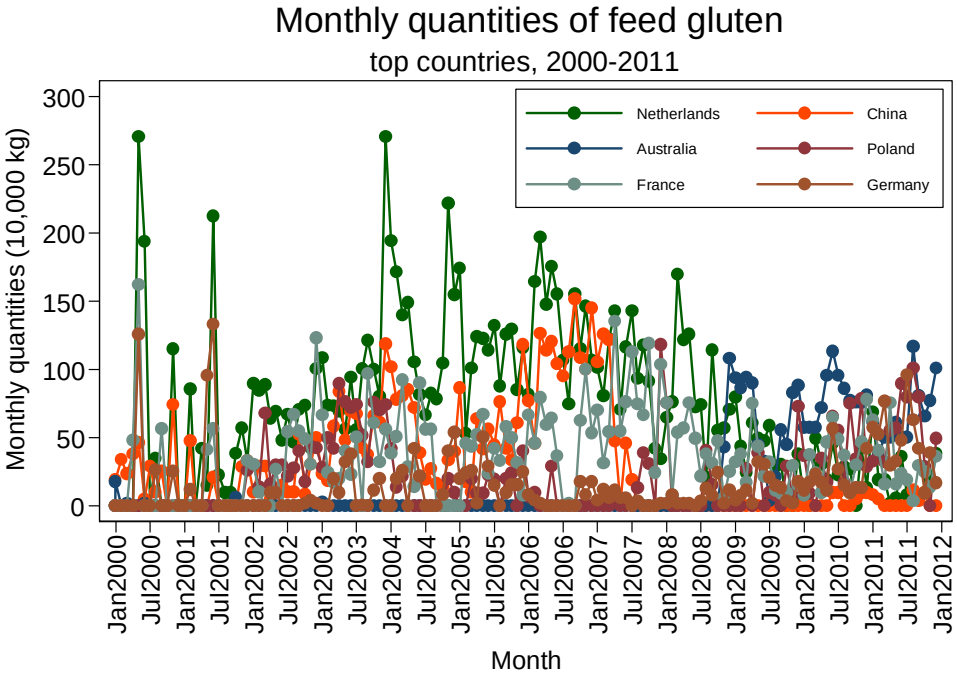


Figure 22. Monthly import quantities of feed gluten, by top regions with EU countries aggregated (a.) and top countries (b.).

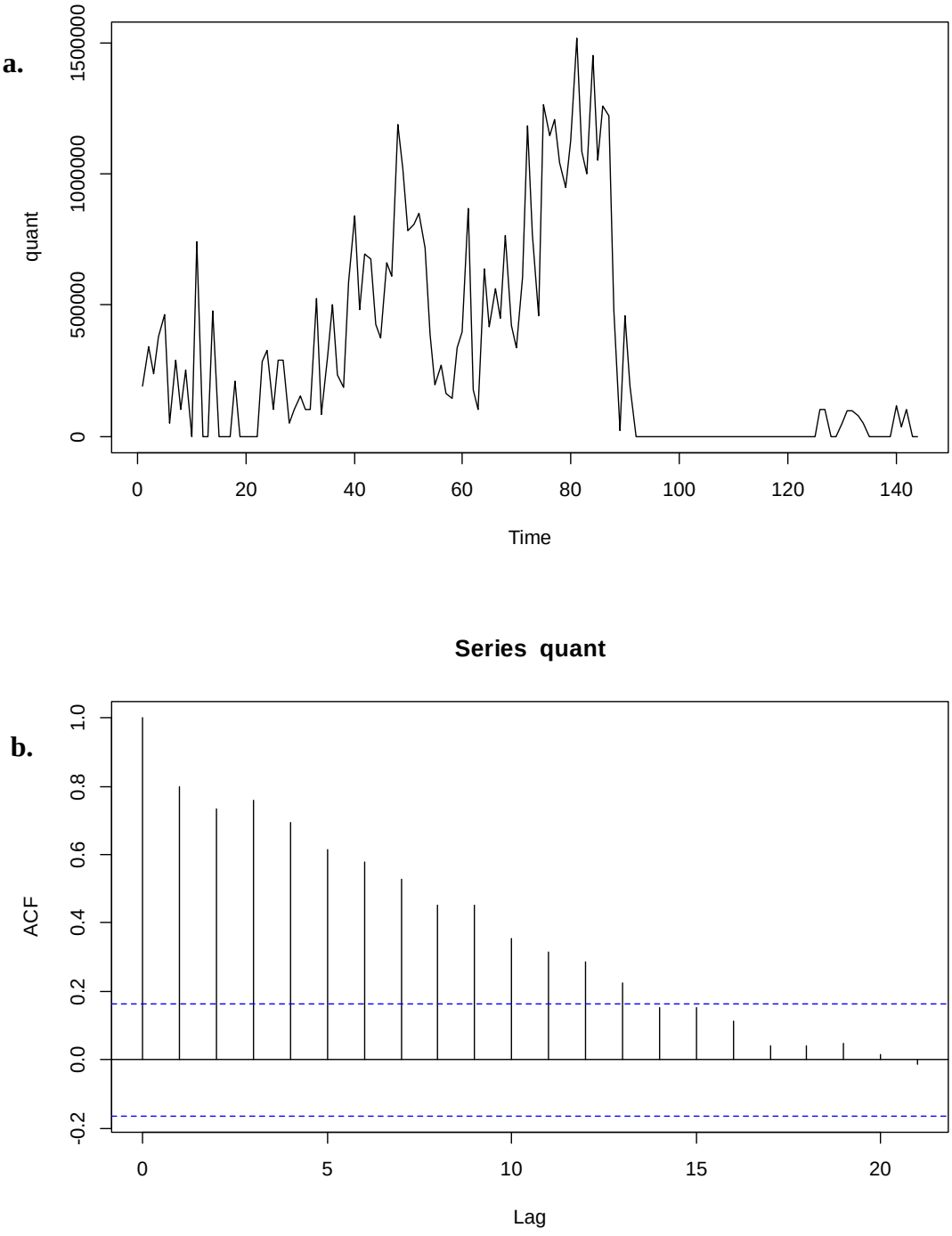
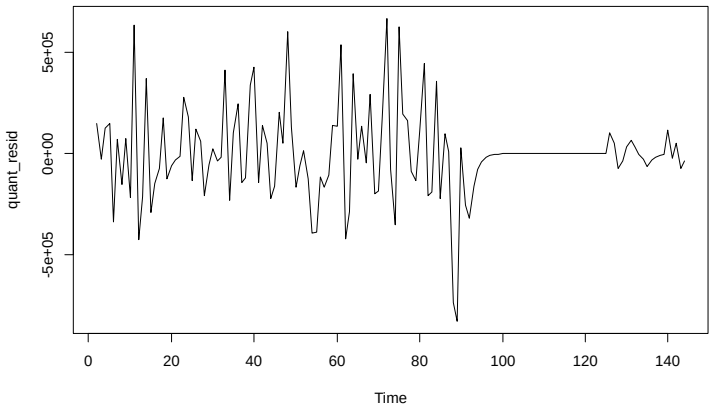
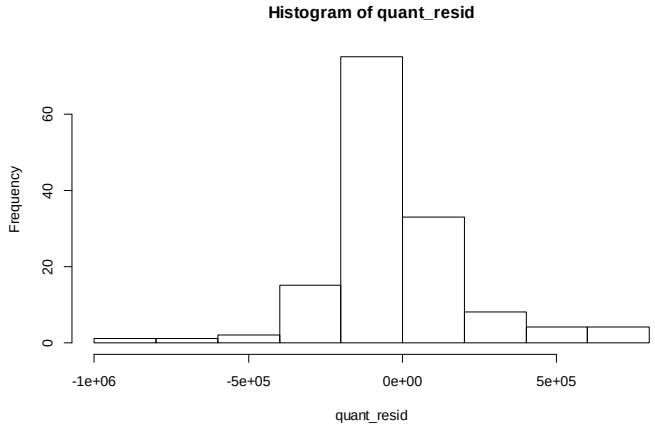


Figure 23. Time-series plot (a.) and plot of autocorrelation function (b.) for aggregated monthly quantities of imports of Chinese feed gluten.

a.



b.



c.

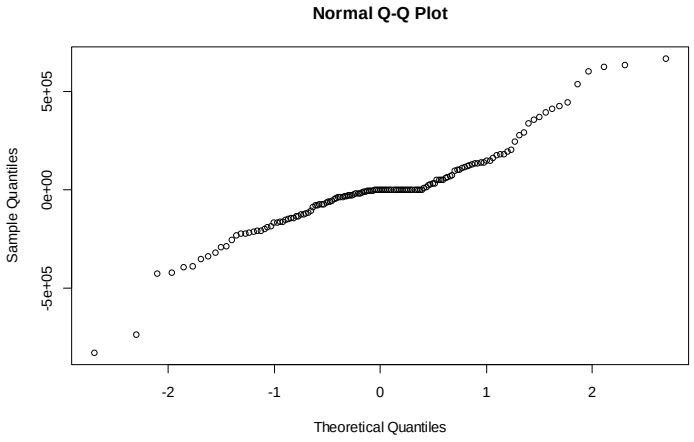


Figure 24. Time-series plot of residuals (a.), histogram of residuals (b.), and quantile-quantile plot of residuals (c.) for aggregated monthly quantities of imports of Chinese feed gluten.

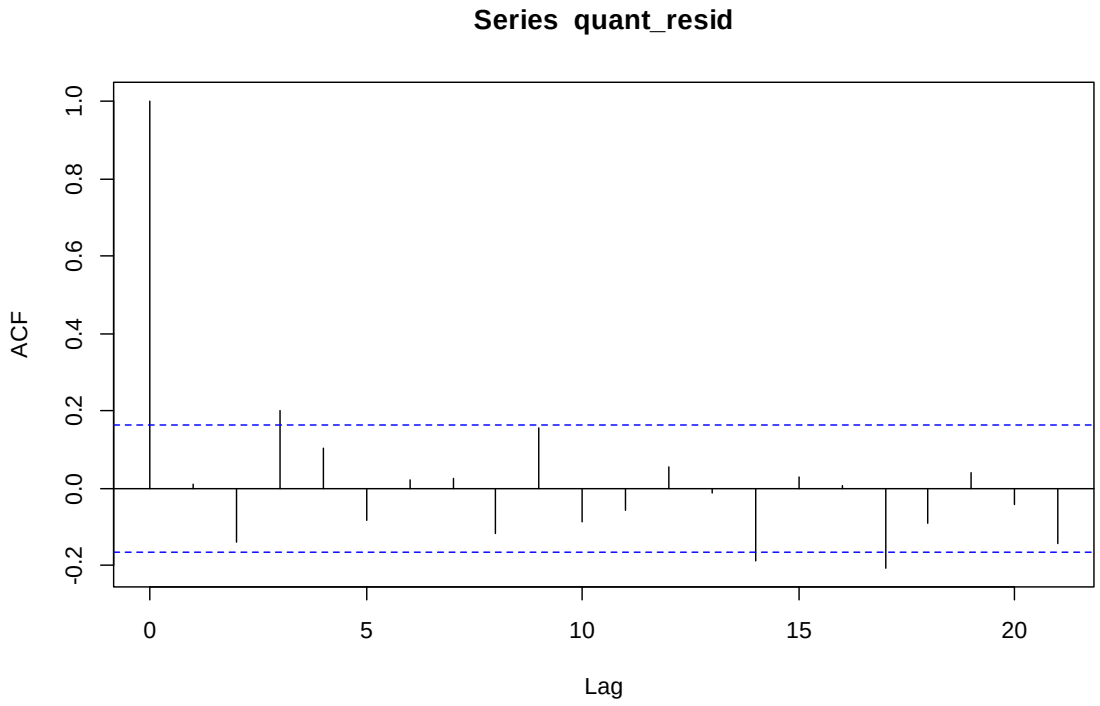


Figure 25. Autocorrelation plot of residuals after smoothing for aggregated monthly quantities of imports of Chinese feed gluten.

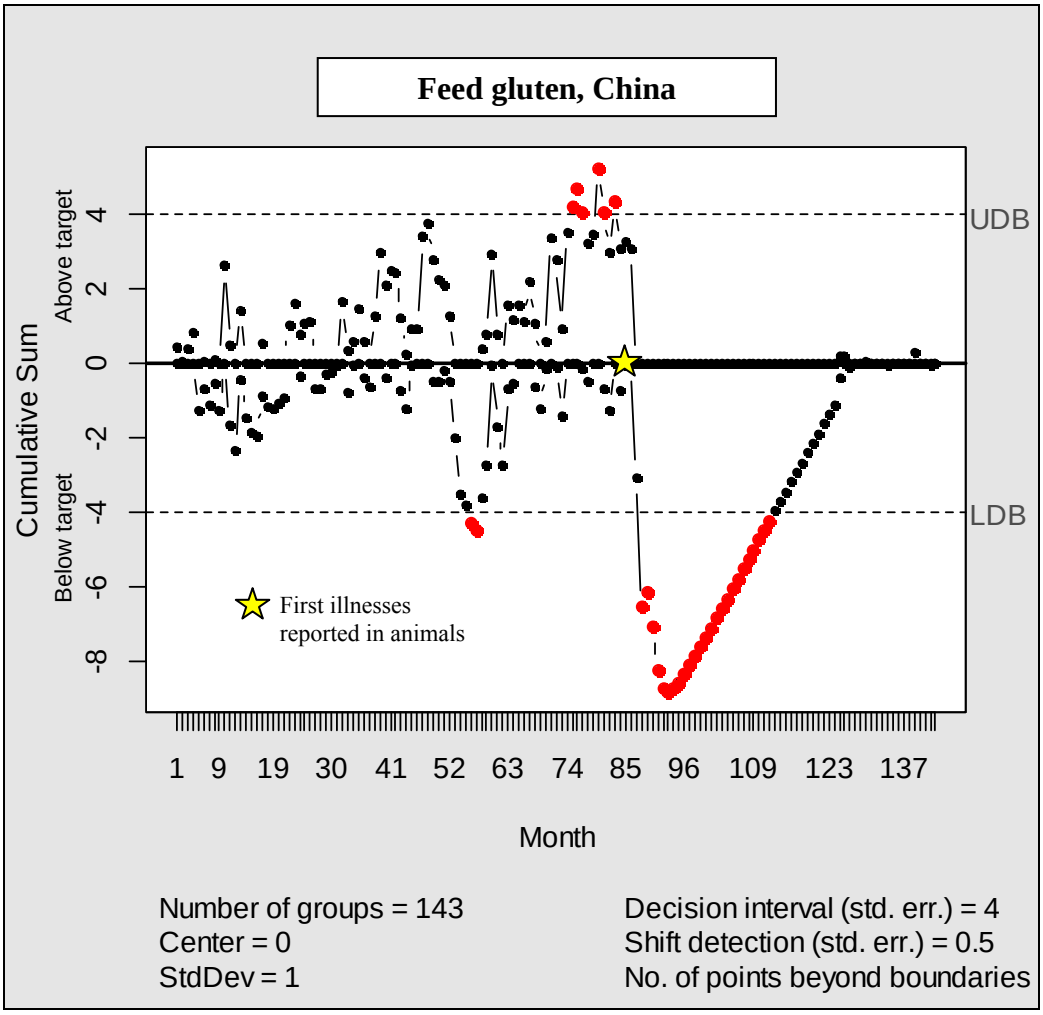
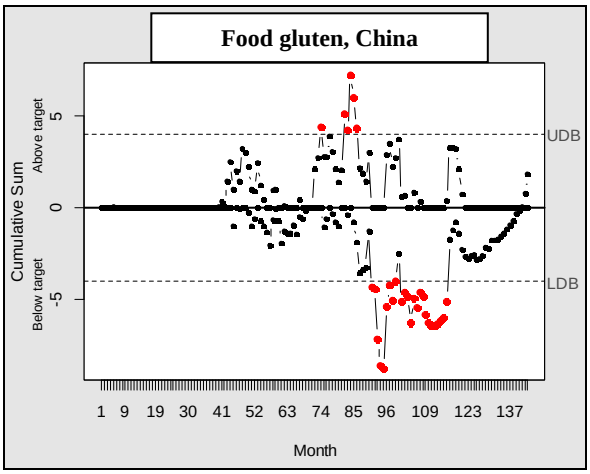


Figure 26. CUSUM chart for food gluten imports from China, 2000-2011.

Prior to detection of melamine in Chinese food gluten, positive signals occurred in April, May, June, September, October, and December of 2006 (months 75-77, 80, 81, and 83). The first illnesses and deaths were reported in animals in February of 2007 (month 85).

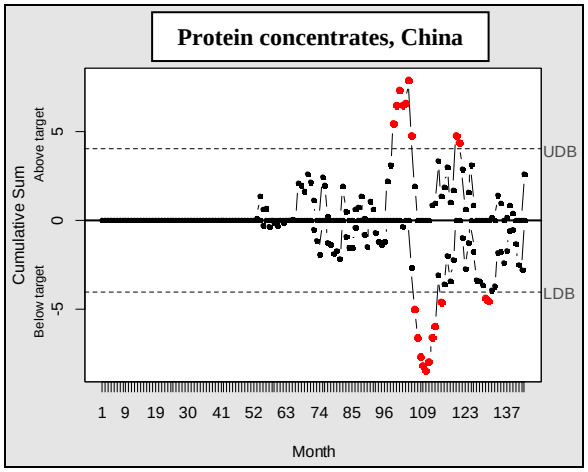
a.



High signals:
Mar 06,
Nov 20-Mar 07

Low signals:
Beginning Aug 07

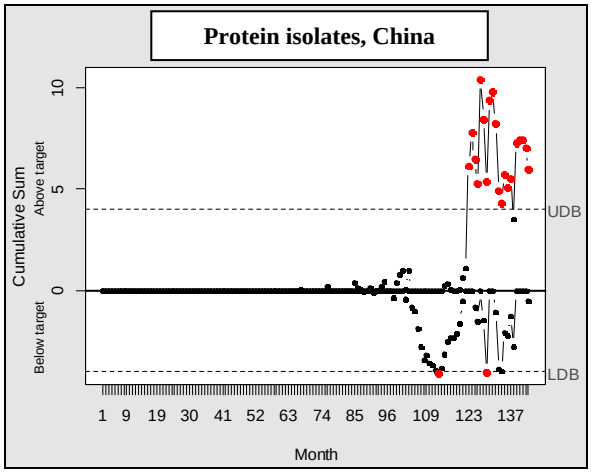
b.



High signals:
Apr-Oct 08,
Jan-Feb 10

Low signals:
Nov 08-Jan 09,
Nov-Dec 10

c.



High signals:
Beginning Apr 10

Low signals:
Jun 09, Oct 10

Figure 27. CUSUM charts for imports of food gluten (a.), protein concentrates (b.), and protein isolates (c.) from China, 2000-2011.

CONCLUSION

Our understanding of the scope of EMA incidents, and the vulnerability of our food supply and distribution systems to EMA, is still evolving. EMA is not a new concern; however, the increasingly globalized food supply, recent large-scale EMA events, and the first major change to food laws in more than 70 years have increased EMA mitigation efforts by industry, regulators, and academia. The food system is globalized and complex, and this complexity increases vulnerabilities. FSMA requires increased responsibility on the part of industry for identification and mitigation of all "reasonably foreseeable" hazards. According to the recently-released proposed rule for preventive controls for human food, FDA is soliciting comment about whether EMA should be considered a "reasonably foreseeable" hazard. Regardless of the decision on that issue, EMA incidents result in substantial profit and reputation losses for industry. They also can result in serious public health consequences, and illustrate vulnerabilities in our regulatory and QA systems for foods that could be exploited for intentional harm.

EMA presents a particular challenge to industry, regulators, and customers because it is designed not to be detected, and public health consequences are rare. Therefore, detection and deterrence of EMA incidents must be approached differently from that of food safety incidents. The use of specific and effective analytical methods for assuring the quality and purity of foods is important, as is knowledge about supply chain structure and the utilization of non-traditional data sources for supply chain surveillance.

The work described in this dissertation was aimed at better understanding the

vulnerabilities of food ingredients to EMA, and proposing methods to use two different types of data sources for EMA surveillance. USP FCC monographs for food ingredients were evaluated and assigned to groups based on EMA susceptibility. EMA susceptibility can be mitigated differently in each of the groups. One of the data sources used for EMA surveillance focused on food products imported into the U.S. (plant-derived proteins), while the other focused on a global food commodity not imported into the U.S. in large quantities (milk products). In both instances, there was a tightening in the market for the product prior to the EMA incident, which likely increased incentive. There was also an increase in either production or import quantities preceding identification of the adulteration event. In addition, a technique for evading the standard analytical method for quality assurance provided a viable technique for adulteration. The methods for analyzing both import data and commodity-level production data should be combined with additional data streams to provide context to the analysis, and should be evaluated further with additional case studies.

Since EMA is motivated by economic gain and often takes advantage of novel adulterants, mitigation efforts should be focused in part on the economic factors and market conditions that may increase the incentive for a particular food product. In addition, updates to analytical methodologies outlined in the Food Chemicals Codex can provide further assurance of the quality and purity of food ingredients. Finally, surveillance of food supply chains for unexplained shifts can help regulators and academia target efforts towards those foods.

FDA and USDA FSIS have an enormous burden of responsibility for regulating the

food supply for both domestically-produced and imported food products. The resources of both agencies are constrained. Effective allocation of regulatory resources requires improved methods for targeting those resources towards the riskiest food products. These preliminary efforts to shed light on EMA vulnerabilities and potential mitigation efforts can contribute to ongoing work in that area. An integrated, systems-based approach to food protection that encompasses both food safety and food defense is imperative for ensuring the integrity of our food supply.

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APPENDIX

Intermediate susceptibility cluster

1,3-BUTYLENE GLYCOL
ACETONE
ACETONE PEROXIDES
ACIDIFIED SODIUM CHLORITE SOLUTIONS
ADIPIC ACID
ALUMINUM AMMONIUM SULFATE
ALUMINUM POTASSIUM SULFATE
ALUMINUM SODIUM SULFATE
AMMONIA SOLUTION
AMMONIUM BICARBONATE
AMMONIUM CARBONATE
AMMONIUM CHLORIDE
AMMONIUM CITRATE, DIBASIC
AMMONIUM PHOSPHATE, DIBASIC
AMMONIUM PHOSPHATE, MONOBASIC
AMMONIUM SACCHARIN
AMMONIUM SULFATE
AMYRIS OIL, WEST INDIAN TYPE
ANGELICA SEED OIL
ASCORBYL PALMITATE
ASPARTAME-ACESULFAME SALT
BASIL OIL, EUROPEAN TYPE
BEESWAX, YELLOW
BENTONITE
BENZOIC ACID
BETA-APO-8'-CAROTENAL
BIOTIN
BRILLIANT BLUE
BUTYLATED HYDROXYMETHYLPHENOL
CALCIUM ACETATE
CALCIUM ACID PYROPHOSPHATE
CALCIUM BROMATE
CALCIUM CHLORIDE
CALCIUM CHLORIDE SOLUTION
CALCIUM CITRATE
CALCIUM DISODIUM EDTA
CALCIUM GLUCONATE
CALCIUM GLYCEROPHOSPHATE
CALCIUM HYDROXIDE
CALCIUM IODATE
CALCIUM LACTATE
CALCIUM LACTOBIONATE
CALCIUM OXIDE
CALCIUM PEROXIDE
CALCIUM PHOSPHATE, DIBASIC
CALCIUM PHOSPHATE, MONOBASIC
CALCIUM PHOSPHATE, TRIBASIC
CALCIUM PYROPHOSPHATE
CALCIUM SACCHARIN
CALCIUM SILICATE
CALCIUM SORBATE
CALCIUM STEAROYL LACTYLATE
CALCIUM SULFATE
CANTHAXANTHIN
CARBON DIOXIDE
CARDAMOM OIL
CARMINE
CASSIA OIL
CASTOR OIL
CEDAR LEAF OIL
CHAMOMILE OIL, ENGLISH TYPE
CHOLIC ACID
COPOVIDONE
COPPER GLUCONATE
COPPER SULFATE
DECANOIC ACID
DEHYDROACETIC ACID
DESOXYCHOLIC ACID
DEXTROSE
DHA FROM ALGAL (CRYPTHECODINIUM) OIL
DIMETHYL DICARBONATE
DISODIUM GUANYLATE
DL-ALANINE
DL-ASPARTIC ACID
DL-LEUCINE
DL-METHIONINE
DL-PHENYLALANINE
DL-SERINE
DL-TRYPTOPHAN
ERYTHORBIC ACID
ERYTHROSINE
ETHYL ALCOHOL
ETHYLENE DICHLORIDE
FAST GREEN
FD&C BLUE NO. 1
FD&C BLUE NO. 2
FD&C RED NO. 3
FD&C RED NO. 40
FD&C YELLOW NO. 6

Intermediate susceptibility cluster (continued)

FERRIC AMMONIUM CITRATE, BROWN
FERRIC CITRATE
FERRIC PHOSPHATE
FERRIC PYROPHOSPHATE
FERROUS CITRATE
FERROUS SULFATE
FERROUS SULFATE, DRIED
FORMIC ACID
FUMARIC ACID
GARLIC OIL
GIBBERELLIC ACID
GLUCONO DELTA-LACTONE
GLYCERYL MONOSTEARATE
GLYCERYL TRISTEARATE
GLYCERYL-LACTO ESTERS OF FATTY ACIDS
GLYCINE
HELIUM
HEPTYLPARABEN
HEXANES
HYDROCHLORIC ACID
HYDROGEN PEROXIDE
HYDROXYLATED LECITHIN
INOSITOL
IRON, CARBONYL
IRON, ELECTROLYTIC
ISOPROPYL ALCOHOL
L-ARGININE
L-ARGININE MONOHYDROCHLORIDE
L-ASPARAGINE
L-ASPARTIC ACID
L-CYSTEINE MONOHYDROCHLORIDE
L-GLUTAMIC ACID HYDROCHLORIDE
L-GLUTAMINE
L-HISTIDINE
L-HISTIDINE MONOHYDROCHLORIDE
L-ISOLEUCINE
L-PHENYLALANINE
L-PROLINE
L-SERINE
L-THREONINE
L-TRYPTOPHAN
L-TYROSINE
L-VALINE
LABDANUM OIL
LACTIC ACID
LACTOSE
LAURIC ACID
LIMESTONE, GROUND
MAGNESIUM CARBONATE
MAGNESIUM CHLORIDE
MAGNESIUM GLUCONATE
MAGNESIUM LACTATE
MAGNESIUM PHOSPHATE, DIBASIC, MIXED HYDRATES
MAGNESIUM PHOSPHATE, DIBASIC, TRIHYDRATE
MAGNESIUM SILICATE
MAGNESIUM STEARATE
MALIC ACID
METHYLENE CHLORIDE
MONOAMMONIUM GLYCYRRHIZINATE
MONOAMMONIUM L-GLUTAMATE
MONOPOTASSIUM L-GLUTAMATE
MYRISTIC ACID
MYRRH OIL
N-ACETYL-L-METHIONINE
NIACIN
NIACINAMIDE ASCORBATE
OCTANOIC ACID
OLEIC ACID
OZONE
PARTIALLY HYDROLYZED PROTEINS
PHOSPHORIC ACID
POLYETHYLENE GLYCOLS
POTASSIUM CITRATE
QUININE HYDROCHLORIDE
QUININE SULFATE
RIBOFLAVIN
SODIUM FUMARATE
SODIUM LAURYL SULFATE
SODIUM NITRITE
SODIUM POTASSIUM TARTRATE
SODIUM THIOSULFATE
SUCCINIC ACID
SUCCINYLATED MONOGLYCERIDES
TARTARIC ACID
TITANIUM DIOXIDE
TRIACETIN
TRICHLOROETHYLENE
TRIETHYL CITRATE
UREA
WHEAT PROTEIN ISOLATE
ZINC OXIDE
ZINC SULFATE

Low susceptibility cluster

4-HEXYLRESORCINOL
5'-ADENYLIC ACID
ACESULFAME POTASSIUM
ACONITIC ACID
ALITAME
ALL-RAC-ALPHA-TOCOPHEROL
ALL-RAC-ALPHA-TOCOPHERYL ACETATE
ALLURA RED
ALPHA-CYCLODEXTRIN
AMMONIUM CITRATE, TRIBASIC
ASCORBIC ACID
BETA-CAROTENE
BETA-CYCLODEXTRIN
BHA
BUTANE
CAFFEINE
CALCIUM ASCORBATE
CALCIUM BENZOATE
CALCIUM CARBONATE
CALCIUM LIGNOSULFONATE (40-65)
CALCIUM PANTOTHENATE
CALCIUM PANTOTHENATE, CALCIUM CHLORIDE DOUBLE SALT
CALCIUM PANTOTHENATE, RACEMIC
CHLORINE
CHOLINE BITARTRATE
CITRIC ACID
D-TAGATOSE
DEXPANTHENOL
DISODIUM 5'-URIDYLATE
DISODIUM EDTA
DISODIUM INOSINATE
DL-PANTHENOL
ERYTHRITOL
FERROUS FUMARATE
FRUCTOSE
GAMMA-CYCLODEXTRIN
GLYCERIN
GLYCERYL MONOOLEATE
ISOBUTANE
ISOMALTULOSE
L-METHIONINE
L-SELENOMETHIONINE
LACTITOL
LINOLEIC ACID
LUTEIN
LYCOPENE EXTRACT FROM TOMATO
MALTITOL
MALTITOL SYRUP
MANNITOL
MESO-ZEAXANTHIN
METHYL ETHYL CELLULOSE
MONOSODIUM L-GLUTAMATE
NATAMYCIN
NICKEL
NONCRYSTALLIZING SORBITOL SOLUTION
OLESTRA
POLYVINYL ACETATE
POTASSIUM SORBATE
PROPANE
PROPYLENE GLYCOL
PROPYLENE OXIDE
RRR-ALPHA-TOCOPHEROL CONCENTRATE
RRR-ALPHA-TOCOPHERYL ACID SUCCINATE
RRR-TOCOPHEROLS CONCENTRATE, MIXED
SALATRIM
SEAWEED-DERIVED CALCIUM
SODIUM ALUMINOSILICATE
SODIUM BISULFITE

Low susceptibility cluster (continued)

SODIUM CARBOXYMETHYL CELLULOSE, ENZYMATICALLY HYDROLYZED

SODIUM CHLORIDE

SODIUM CITRATE

SODIUM DIACETATE

SODIUM LACTATE SOLUTION

SODIUM MAGNESIUM ALUMINOSILICATE

SODIUM PHOSPHATE, DIBASIC

SORBITOL

SORBITOL SOLUTION

SUCRALOSE

TALC

THIAMINE HYDROCHLORIDE

TREHALOSE

VEGETABLE OIL PHYTOSTEROL ESTERS

VITAMIN A

VITAMIN B12

VITAMIN D2

VITAMIN D3

VITAMIN K

XYLITOL

ZINC GLUCONATE

High susceptibility cluster

ACID HYDROLYSATES OF PROTEINS
AGAR
ALGINIC ACID
ALMOND OIL, BITTER, FFPA
ALPHA-LACTALBUMIN
AMBRETTE SEED OIL
AMMONIATED GLYCYRRHIZIN
AMMONIUM ALGINATE
ANGELICA ROOT OIL
ANISE OIL
ANNATTO EXTRACTS
ARABINOGALACTAN
ASPARTAME
BALSAM PERU OIL
BASIL OIL, COMOROS TYPE
BAY OIL
BEESWAX, WHITE
BERGAMOT OIL, COLDPRESSED
BHT
BIRCH TAR OIL, RECTIFIED
BLACK PEPPER OIL
BOHENIN
BOIS DE ROSE OIL
BROMINATED VEGETABLE OIL
BUTADIENE-STYRENE RUBBER
CALCIUM ALGINATE
CALCIUM LIGNOSULFONATE
CANANGA OIL
CARAMEL
CARAWAY OIL
CARBON, ACTIVATED
CARNAUBA WAX
CARRAGEENAN
CASCARILLA OIL
CASEIN AND CASEINATE SALTS
CELERY SEED OIL
CELLULOSE GEL
CELLULOSE GUM
CELLULOSE, POWDERED
CHAMOMILE OIL, GERMAN TYPE
CLARY OIL
CLOVE LEAF OIL
CLOVE OIL
CLOVE STEM OIL
COCOA BUTTER SUBSTITUTE
COCONUT OIL (UNHYDROGENATED)
COGNAC OIL, GREEN
COPAIBA OIL
CORIANDER OIL
CORN OIL (UNHYDROGENATED)
COSTUS ROOT OIL
COTTONSEED OIL (UNHYDROGENATED)
CROSPOVIDONE
CUBEB OIL
CUMIN OIL
CURDLAN
DAMMAR GUM
DHA FROM ALGAL (SCHIZOCHYTRIUM) OIL
DIACYLGLYCEROL OIL
DIATOMACEOUS EARTH
DILL SEED OIL, EUROPEAN TYPE
DILL SEED OIL, INDIAN TYPE
DILLWEED OIL, AMERICAN TYPE
DIMETHYLPOLYSILOXANE
DIOCTYL SODIUM SULFOSUCCINATE
ENZYME-MODIFIED FATS
ETHOXYLATED MONO- AND DIGLYCERIDES
ETHOXYQUIN
ETHYL CELLULOSE
EUCALYPTUS OIL
FD&C GREEN NO. 3
FENNEL OIL
FERRIC AMMONIUM CITRATE, GREEN
FERROUS GLYCINATE
FIR NEEDLE OIL, CANADIAN TYPE
FIR NEEDLE OIL, SIBERIAN TYPE
FOOD STARCH, MODIFIED
FOOD STARCH, UNMODIFIED
FRUCTOOLIGOSACCHARIDES, SHORT CHAIN
FURCELLERAN
GELATIN
GELLAN GUM
GERANIUM OIL, ALGERIAN TYPE
GINGER OIL
GLUCOSE SYRUP
GLUCOSE SYRUP, DRIED

High susceptibility cluster (continued)

GLYCEROL ESTER OF PARTIALLY DIMERIZED ROSIN
GLYCEROL ESTER OF PARTIALLY HYDROGENATED GUM ROSIN
GLYCEROL ESTER OF PARTIALLY HYDROGENATED WOOD ROSIN
GLYCEROL ESTER OF POLYMERIZED ROSIN
GLYCEROL ESTER OF WOOD ROSIN
GRAPE SKIN EXTRACT
GUAR GUM
GUM ARABIC
GUM GHATTI
GUM GUAIAC
HIGH-FRUCTOSE CORN SYRUP
HOPS OIL
HYDROGENATED STARCH HYDROLYSATE
HYDROXYPROPYL METHYLCELLULOSE
INULIN
INVERT SUGAR
ISOBUTYLENE-ISOPRENE COPOLYMER
ISOMALT
JUNIPER BERRIES OIL
KAOLIN
KARAYA GUM
KONJAC FLOUR
LACTYLATED FATTY ACID ESTERS OF GLYCEROL AND PROPYLENE GLYCOL
LACTYLIC ESTERS OF FATTY ACIDS
LANOLIN, ANHYDROUS
LARD (UNHYDROGENATED)
LAVENDER OIL
LECITHIN
LEMON OIL, COLDPRESSED
LEMON OIL, DESERT TYPE, COLDPRESSED
LEMON OIL, DISTILLED
LEMONGRASS OIL
LIME OIL, COLDPRESSED
LIME OIL, DISTILLED
LINALOE WOOD OIL
LOVAGE OIL
MALTODEXTRIN
MONO- AND DIGLYCERIDES
NUTMEG OIL
ONION OIL
ORRIS ROOT OIL
OX BILE EXTRACT
PALMAROSA OIL
PEANUT OIL (UNHYDROGENATED)
PECTINS
PENTAERYTHRITOL ESTER OF WOOD ROSIN
PETROLATUM
PETROLEUM WAX, SYNTHETIC
PINE NEEDLE OIL, SCOTCH TYPE
POLYSORBATE 80
PORK COLLAGEN
POTASSIUM ALGINATE
PROPYLENE GLYCOL ALGINATE
RAPESEED OIL, FULLY HYDROGENATED
RAPESEED OIL, SUPERGLYCERINATED
ROSE OIL
ROSEMARY OIL
RUE OIL
SAGE OIL, DALMATIAN TYPE
SAGE OIL, SPANISH TYPE
SANDALWOOD OIL, EAST INDIAN TYPE
SAVORY OIL (SUMMER VARIETY)
SODIUM ALGINATE
SODIUM LIGNOSULFONATE
SORBITAN MONOLAURATE
SORBITAN MONOOLEATE
SORBITAN MONOPALMITATE
SORBITAN TRISTEARATE
SOY PROTEIN CONCENTRATE
SPEARMINT OIL
SPIKE LAVENDER OIL
STEARYL CITRATE
SUNFLOWER OIL (UNHYDROGENATED)
TAGETES EXTRACT
TANGERINE OIL, COLDPRESSED
TARA GUM
TARRAGON OIL
TERPENE RESIN, NATURAL
THAUMATIN
THYME OIL
TRAGACANTH
WHEAT GLUTEN
WHEY
WHEY PROTEIN CONCENTRATE
WHEY PROTEIN ISOLATE
WHEY, REDUCED LACTOSE
WHEY, REDUCED MINERALS
WINTERGREEN OIL
XANTHAN GUM
YEAST EXTRACT
YEAST, AUTOLYZED
YEAST, DRIED
ZEIN