Intentional and Inadvertent Chemical Contamination of Food, Water, and Medication

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**KEYWORDS**
- Chemical terrorism
- Food contamination
- Water contamination
- Medication contamination
- Risk communication
- Supply chain

**KEY POINTS**
- Food, water, and medication production, processing, and distribution involve multiple potential points of entry for chemical contamination.
- Developing a clinical case definition based on toxidrome recognition is the most important epidemiologic step early in a chemical contamination event.
- Laboratory investigation and identification of a chemical compound as the cause can be time and labor intensive, expensive, and frustrating, with attendant problems of confounding or associated noncausal substances.
- The number and location of affected individuals can facilitate identification of the likely point of entry of a chemical contaminant through the use of bow-tie modeling.
- Risk communication is an important aspect of the response to potential chemical contamination of food, water, or medication.
- The resources of a regional poison control center or medical toxicologist can be used as an entry to the public health system and considerations regarding tracking potential contamination of food, water, or medication.
- Following large-scale contamination events, the public health impact associated with an outbreak of mass epidemic illness must also be addressed, especially in the absence of an available biological marker to differentiate stress response from toxic injury.

Disclosures: None.

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INTRODUCTION

The delivery of toxins or contaminants via food supply, water, or medications has a long history, particularly as a means of altering political futures. In 585 BC, the city of Kirra in modern-day Greece was besieged by attacking clans in the First Sacred War. The attackers discovered a buried pipe bringing fresh water to Kirra and reportedly poisoned it with hellebore, weakening the city occupants by inducing vomiting and diarrhea.\(^1\) Recordings of other targeted terroristic poisonings at feasts or other gatherings date back several millennia.\(^2,3\) Technological, legislative, and regulatory efforts to forestall terrorist goals of targeted or widespread poisoning by contamination of food, water, or medication supplies continue. This article uses examples of contamination of these critical supply chains to highlight the production and distribution components that provide common points of vulnerability for attack, and the resources and measures to counter such attempts.

**Production and Distribution Systems as a Framework**

Most modern societies have developed highly specialized production and distribution methods to deliver large quantities of goods such as medications to populations that are both congregated in large cities and more widely dispersed, while maintaining standards of uniform composition and potency. The same is true for food and water. Separation of the many steps and multiple components required to produce, package, and widely distribute these critical entities affords numerous opportunities for inadvertent or intentional contamination; this complexity can also create barriers and delays in identification of, and notification about, contamination. Production and distribution systems can be depicted as a bow-tie model, as shown in Fig. 1. Many raw materials or tributaries combine to make a processed or finished product, which is then collected, stored, and distributed via a series of outlets until eventually reaching a large number of consumers. This simple unidirectional flow example of network theory has been used to model the impact of introduction of a small amount of the potent botulinum toxin into the milk supply.\(^4\)

**Using Bow-tie Analysis to Identify the Point of Introduction of Chemical Contaminant**

From an epidemiologic point of view, the in-flow/out-flow concept is critically important in determining the need and location for investigations, recalls, testing, and communications. These same issues need to be addressed in individual patient encounters. For

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**Fig. 1.** (A) Bow-tie production and distribution. (B) Insertion of a large amount of a compound early in the production can have a widespread but diluted effect for many consumers. (C) Insertion of a smaller amount of a compound late in the distribution process requires less substance for effect, but affects fewer individuals. (From Centers for Disease Control. CDC estimates of foodborne illness in the United States: overview of attribution of foodborne illness. Available at: www.cdc.gov/foodborneburden/attribution/overview.html.)
example, symptoms of palpitations or light-headedness that are associated by the individual with eating at a restaurant may be coincidental, attributable to underlying medical illness, environmental heat, or emotional stress. However, they could also represent early symptoms of food toxicity or foodborne illness from a variety of preformed biological toxins or chemical contaminants, such as the sodium azide poisoning of iced tea drinkers at a Texas restaurant in 2010. When several people rapidly became ill while still at the restaurant, it might reasonably be assumed that there was a shared exposure, but was it in the air, the food, or the water? Because not everyone in the restaurant at one time was affected, a shared airborne exposure (eg, carbon monoxide) was unlikely. In the same way, not all victims were present at exactly the same time, making the problem of line-of-sight transmission of psychogenic reactions unlikely. Investigation in this event quickly focused on the common iced tea urn, with analysis for cardiovascular toxins eventually identifying hydrazoic acid as a reaction product of sodium azide and water. However, although the clinical syndrome of rapid onset of hypotensive symptoms was quickly identified and appropriate supportive care initiated, the analysis and identification of the causative chemical agent took months. Interviews of other restaurant patrons and evaluation of contemporaneous emergency department visits identified only 1 additional victim, confirming the far right side (distribution) of the bow-tie model intrusion of a contaminant. Epidemiologic response tools, such as the Electronic Surveillance System for the Early Notification of Community-based Epidemics (ESSENSE), which tracks emergency department visits or poison center calls, were also used to screen for other cases.

Early access to clinical partners such as regional poison control centers or medical toxicologists can assist in developing a clinical picture based on toxidrome recognition, determining which, if any, laboratory tests should be obtained and where to obtain this testing, and contacting public health entities for further investigation or intervention. The nature and extent of any needed public communication and involvement of law enforcement can also be better ascertained when properly applying the bow-tie tool.

**TYPES OF FOODBORNE ILLNESS**

The term foodborne illness is used to describe illness resulting from the consumption of food products. This term is preferred to the term food poisoning because it encompasses a broader range of food source contaminants and is technically more appropriate. Foodborne illness needs to be distinguished from coincidental onset of symptoms while a person is eating, or noncausal food-associated illness.

Foodborne illness may be the result of bacterial, viral, or parasitic contamination, or noninfectious toxins such as ciguatera. Illness can also be the result of toxins produced by bacterial contamination (eg, botulism). Although foodborne illness from infectious contamination is usually the result of improper food preparation or handling practices, bacterial contamination has also been the means of terrorist acts. Foodborne illness may also be the result of foreign body contamination, insect infestation, or the introduction of nonfood substances. Foreign body contamination or other non–foreign body contaminants (eg, chemicals) can be introduced inadvertently or deliberately, based on a desire to substitute a less expensive compound, circumvent a regulatory restriction or standard, or to cause harm. State public health laboratories have increased capabilities and capacities to address these issues through the Food Emergency Response Network (FERN).

**FOOD CONTAMINATION**

The US Centers for Disease Control and Prevention (CDC) tracks a variety of foodborne illnesses. More than 1 in every 6 Americans becomes ill from some food they
eat every year. Because these under-report the scope of the problem, some investigators have explored using social media as a more robust means of monitoring foodborne illness outbreaks, at least those associated with dining out. Fig. 2 shows the broad categories of food commodities tracked by the CDC and the relative attribution of reported diseases. Although most people recover, 1 in 300 people with symptoms are treated in a hospital and more than 3000 people die. Most of these cases reflect identified microorganism contamination; much of this biocontamination occurs during food handling or prepreparation of complex food items (containing multiple food items/commodity categories). In some instances, the food may have originated from outside the country, and therefore may not have been subjected to the preparation practices guiding food production in the United States.

**Contaminant Identification**

Of nearly 200 chemical contamination events involving US food in the last 30 years, as reported by one consumer advocacy group, with each event affecting 2 to 133 people, more than one-half were characterized as “suspected or unknown chemical.”

![Hierarchy of 17 Food Commodities Used in Outbreak Analysis](image)

**Fig. 2.** Food categories and attribution of foodborne disease outbreaks in the United States. Commodity groups appear in orange cells; 17 commodities are italicized and appear in green cells. *(From Centers for Disease Control. CDC estimates of foodborne illness in the United States: overview of attribution of foodborne illness. Available at: www.cdc.gov/foodborneburden/attribution/overview.html; and From Painter JA, Ayers T, Woodruff R, et al. Recipes for foodborne outbreaks: a scheme for categorizing and grouping implicated foods. Foodborne Pathog Dis 2009;6:1259–64, with permission.)*
highlighting the analytical challenges noted earlier. Although regulations focus on ensuring food safety and quality based on accidental contamination by biological organisms, these same principles apply to intentional chemical contamination. Chemical regulatory focus by the Center for Food Safety and Applied Nutrition (CFSAN) has been on pesticide residues, heavy metals, and natural toxins such as mycotoxins, although several other biopersistent chemicals are also monitored. The US Food and Drug Administration (FDA) and the Department of Agriculture (USDA) have primary responsibility for regulating food quality and safety, although the number of agencies with some involvement is much larger. The USDA is responsible through the Food Safety Inspection Service (FSIS) for meat, poultry, and egg safety, whereas the FDA is responsible for all other food products. Recognizing the need for improved oversight and coordination, Congress passed the Food Safety Modernization Act in 2010 and FDA published its draft approach to designating high-risk foods in 2014. Analytical capabilities have increased within many state departments of health and other cooperative laboratories following the 2001 terrorist attacks. This Laboratory Response Network (LRN) may be able to assist when questions of chemical contamination arise.

**Impact of Site of Contamination**

As depicted in Table 1, chemical contamination or threat thereof on the food production/processing side of the bow tie have much greater impact than when they occur on the distribution side. Production of large batches with uniform mixing increases the extent of spread of an introduced contaminant. Multiple points of access exist from farm to storage to shipment to processing and manufacture, as well as throughout the distribution network. From a chemical terrorism point of view, products with short shelf lives are preferred vehicles, because they are less likely to be stored away unused and be available for removal or recall once a source of symptoms is recognized. The psychological impact of a contamination event can spread greatly beyond the physically affected individuals. As noted earlier, many complex food products are composed of raw materials from other countries. The extent of this outsourcing was highlighted in 2008 by the melamine scare (and the previous 2007 melamine-attributable animal deaths from contaminated pet food). Melamine is an industrial compound widely used to form plastics; another related and potentially contaminating compound (cyanuric acid) is used to stabilize pool water disinfectants (Fig. 3). Melamine is 66% nitrogen by weight; this characteristic was used by unscrupulous farmers and dairy companies in China to falsely increase the apparent protein content of milk and milk powder when measured by total nitrogen content. During late 2008, as many as 300,000 Chinese children (most less than 3 years old) were evaluated for exposure and resulting crystalluria/hematuria. Thousands were hospitalized with acute kidney injury; at least 6 died. Although there were no significant illnesses in the United States, the identification of melamine in several products with dairy ingredients sourced from China caused widespread public concern. The US problem was more of a risk communication issue, in that mere identification of melamine did not indicate risk.

**WATER CONTAMINATION**

Safe and plentiful water, available at the turn of a handle, has been the assumed status quo for almost all Americans for decades. More than 84% of the US population is served by public water systems, defined by the Environmental Protection Agency
<table>
<thead>
<tr>
<th>Bow-Tie Site of Introduction</th>
<th>Chemical Exposure (Intentional or Inadvertent)</th>
<th>Site/Date</th>
<th>Number of People Affected</th>
<th>Health Effects</th>
<th>Acute vs Chronic Health Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw material: harvested fruit in Chili</td>
<td>Cyanide-tainted fruit</td>
<td>US imports/1989</td>
<td>All US Chilean fruit imports for 3 wk; $300,000,000 loss to Chile</td>
<td>None; hoax with telephone alert; 3 µg of cyanide identified in 2 punctured grapes</td>
<td>Acute (economic)</td>
</tr>
<tr>
<td>Production: substitution of 225–450 kg (500–1000 pounds) of PBB flame retardant for magnesium oxide cattle feed</td>
<td>PBB (inadvertent)</td>
<td>Michigan/1973</td>
<td>Potentially 9 million Michigan residents; quarantine &gt;500 farms; ~30,000 cattle, 4500 swine, 1500 sheep, and 1.5 million chickens and food products destroyed</td>
<td>Emotional impact of biopersistent contamination; constitutional and depressive symptoms; abnormal immunologic studies of uncertain significance</td>
<td>Chronic</td>
</tr>
<tr>
<td>Production: inappropriate use of carbamate insecticide on melons</td>
<td>Aldicarb-contaminated watermelons (inadvertent)</td>
<td>California and 10 other states, provinces/1985</td>
<td>1350 cases (California) with 483 cases elsewhere; 17 hospitalized; clusters of 1–13 people affected</td>
<td>Cholinergic symptoms including seizures, coma, hypotension</td>
<td>Acute</td>
</tr>
<tr>
<td>Processing: addition of nonbioavailable high-nitrogen-content chemical to milk and/ or animal feed</td>
<td>Melamine-adulterated milk/powdered milk (inadvertent)</td>
<td>Multiple provinces, China/2008 (repeat events continue)</td>
<td>~300,000 infants and children with urinary stones of 22,384,000 examined; &gt;50,000 hospitalized; 6 known deaths (impact on United States considered minimal)</td>
<td>Crystalluria with hematuria and obstruction; renal tubular injury</td>
<td>Subacute to chronic</td>
</tr>
<tr>
<td>Processing: refined aniline denaturant in rapeseed oil (illicit use as cooking oil)</td>
<td>TOS$^{23}$ (inadvertent)</td>
<td>Madrid, Spain/1981</td>
<td>19,904 people; ~400 of 1224 deaths attributed to TOS</td>
<td>Systemic nonnecrotizing vasculitis usually presenting as noncardiogenic pulmonary edema, eosinophilia, myalgia, and rash</td>
<td>Acute and chronic</td>
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<tr>
<td>Processing: undercooked chili sauce at plant in Georgia</td>
<td>Botulinum-contaminated chili sauce$^{24}$ (inadvertent)</td>
<td>Three US states (Indiana, Texas, Ohio)/2007</td>
<td>At least 8 people in 3 states</td>
<td>Bulbar dysfunction with motor paralysis</td>
<td>Acute to subacute</td>
</tr>
<tr>
<td>Distribution: nicotine insecticide added to 115 kg (250 pounds) of ground beef in single store</td>
<td>Nicotine-contaminated ground beef$^{25}$ (intentional)</td>
<td>Detroit, MI/2003</td>
<td>At least 92 people</td>
<td>Nausea and vomiting, other cholinergic symptoms</td>
<td>Acute</td>
</tr>
<tr>
<td>Distribution: preserved bamboo shoots served at local festival</td>
<td>Botulism-contaminated bamboo shoots$^{26}$ (inadvertent)</td>
<td>Thailand/2006</td>
<td>209 people; 42 with respiratory failure requiring mechanical ventilation for as long as 1 mo</td>
<td>Bulbar dysfunction with motor paralysis and autonomic instability</td>
<td>Acute</td>
</tr>
<tr>
<td>Local distribution: arsenic placed in church coffee pot by member</td>
<td>Arsenate-contaminated water$^{27}$ (intentional)</td>
<td>New Sweden, ME/2003</td>
<td>15 people sickened; 1 death</td>
<td>Vomiting/diarrhea; hemodynamic shock; persistent neuropathy</td>
<td>Acute and chronic</td>
</tr>
<tr>
<td>Consumer: single container</td>
<td>Cyanide-contaminated yogurt$^{28}$ (intentional)</td>
<td>New Jersey/1989</td>
<td>One death</td>
<td>Rapid collapse</td>
<td>Acute</td>
</tr>
</tbody>
</table>

Note that the number of people affected generally decreases as the site of contaminant introduction moves from the production to the distribution side. 

*Abbreviations: PBB, polybrominated biphenyls; TOS, toxic oil syndrome.*
EPA) as those systems that regularly (60 or more days per year) supply drinking water to at least 25 persons or 15 separate connections. Two-thirds of the approximately 160,000 public drinking water systems use surface water (rivers, lakes, and reservoirs), whereas one-third have a groundwater source (wells and aquifers). For those relying on private water systems, most water comes from small wells.29 Using the bow-tie model, rain, runoff, and groundwater flow can be considered the raw materials, potentially picking up chemical solutes as the water is collected together at 1 point. The distribution network for water is both extensive and vulnerable. Although most public water systems serve fewer than 3300 people each, some large systems service more than 100,000 people (Fig. 4). Most of the millions of miles of distribution system pipes have been in place for more than 30 to 100 years and are vulnerable to leaking and accidental contamination. The EPA has estimated that there is an average of 1 line break per year for every 1000-person system, leading to a high likelihood of cross-connections in water flow.30 The greatest vulnerability for intentional introduction of a chemical contaminant to the water system is

Fig. 3. Chemical structures of (A) melamine, (B) cyanuric acid, and (C) melamine–cyanuric acid complex.

![Chemical structures](image)

Fig. 4. Comparison of community water systems: number of systems versus number of people served by those systems. (Data from Kongsaengdao S, Samintarapanya K, Rusmeechan S, et al. An outbreak of botulism in Thailand: clinical manifestations and management of severe respiratory failure. Clin Infect Dis 2006;43(10):1247–56.)
by creating backflow and overcoming the low pressure at the end of a water distribution network.

**Contamination Identification**

The EPA, in most cases via state environmental agencies, has regulatory responsibility for the safety of public drinking water systems. National Primary Drinking Water Regulation (NPDWR) standards, first codified in the Safe Drinking Water Act in 1974 (last revised in 1996) include maximum contaminant levels for more than 80 elements and chemical compounds, as well as several micro-organisms. Municipal and private water companies are required to test and report on the status of their water product relative to these standards. However, the EPA does not regulate the testing methodology; most systems use intermittent rather than continuous monitoring for chemical contaminants. In addition, testing requirements are limited to those identified contaminants listed in the Safe Drinking Water Act. This potential vulnerability is being addressed as a portion of the critical infrastructure assessment pursuant to Executive Order 13636; several routine and innovative techniques are being considered.

Note that systems that do not qualify as public water systems are not under EPA regulations, and homeowners are usually responsible for their own testing. In areas of the country with significant groundwater contribution from mountain ranges, arsenic and radon contamination of private water sources is a matter of concern. Several regions and states provide information for homeowners.

Millions of people in the United States drink bottled water, many as their sole source of drinking water. As opposed to tap water, bottled water is considered a food product and is regulated by the FDA under the Food, Drug, and Cosmetic Act; Title 21 of the Code of Federal Regulations part 129 covers the regulations relating to the Processing and Bottling of Bottled Drinking Water. The plastic containers are regulated as a food contact substance; they are governed by food additive regulations. Contaminant standards set by NPDWR may apply to bottled water or the standard may be different if the contaminant is not found in water used for bottled water (eg, allowed lead levels are lower in bottled water because there is no likely contribution by lead in public water system pipes). Recalls of bottled water products are common and testing of bottled water for some contaminants, like coliform bacteria, differs from that for public water systems.

The CDC tracks reported water-borne illness outbreaks. In 2009 to 2010, there were 33 outbreaks affecting 1040 people reported. Almost all of the serious cases and all of the deaths were attributable to legionella infection. Contamination is not only from biological sources. One chemical exposure affecting 3 people was attributed to sodium hydroxide–contaminated water. Over an 18-year period, 459 events with more than 12,000 associated illnesses have been reported. Fifteen of these outbreaks (679 associated illnesses) were caused by chemical contaminants. Many water-associated events are not reported and ascertaining the cause is often difficult. As listed in Table 2, obvious odor or visible changes to water can be quickly recognized, but analytical analysis for compounds other than the chemical compound $\text{H}_2\text{O}$ can be complicated by natural minerals and introduced disinfectants, as well as the increasing sophistication of laboratory equipment, resulting in the problem of the so-called receding zero: it has become technologically possible to detect extremely small concentrations of chemicals (parts per trillion), whereas the corresponding knowledge on the public health implications of these (very) low-level exposures, if there are any, is lacking. It further complicates investigations that the mere identification of a compound does not indicate that it is responsible for observed symptoms and signs.
Table 2
Examples of chemical contamination of the water supply

<table>
<thead>
<tr>
<th>Bow-Tie Site of Introduction</th>
<th>Chemical Exposure</th>
<th>Site/Date</th>
<th>Number of People Affected</th>
<th>Health Effects</th>
<th>Acute vs Chronic Health Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw material: Yippie political theater threat to introduce LSD into drinking water supply at 1968 Democratic National Convention</td>
<td>LSD\textsuperscript{43} (and other intentional threats\textsuperscript{44})</td>
<td>Lake Michigan, Chicago, IL/1968</td>
<td>None directly; large security presence at convention with riots</td>
<td>None; threat only</td>
<td>None</td>
</tr>
<tr>
<td>Raw material: Elk River contamination from above-ground storage tank</td>
<td>4-Methylcyclohexane methanol\textsuperscript{45} (inadvertent)</td>
<td>Charleston, WV/2014</td>
<td>300,000 no-use water warning</td>
<td>Odor, skin rashes, nonspecific complaints</td>
<td>Acute</td>
</tr>
<tr>
<td>Raw material: 4.1 million cubic meters of wet ash released into Tennessee River tributaries</td>
<td>Coal ash\textsuperscript{46} (inadvertent)</td>
<td>Harriman, TN/2008 (and other sites: North Carolina\textsuperscript{47})</td>
<td>22 residents evacuated; 165 properties sold to TVA</td>
<td>None; concern about heavy metal contamination and particulate-related respiratory irritation</td>
<td>—</td>
</tr>
<tr>
<td>Production: waste off site: dry cleaning plant. On site: industrial spills, leaking underground storage tanks, waste disposal sites</td>
<td>Trichloroethylene, perchloroethylene, vinyl chloride, benzene, multiple other chemicals (VOCs)\textsuperscript{48} (inadvertent)</td>
<td>Camp Lejeune Marine Corps Base, North Carolina/1953–1987 (investigation started in 2009)</td>
<td>Up to 750,000 (service members and families) exposed to contaminated tap water</td>
<td>Concerns for higher cancer rates, birth defects (neural tube defects), amyotrophic lateral sclerosis</td>
<td>Chronic with delayed identification of contamination</td>
</tr>
<tr>
<td>Processing: security fence cut at 12 million gallon reservoir</td>
<td>Unknown(^49) (intentional)</td>
<td>Seattle, OR/2002</td>
<td>None; cost of emptying reservoir; increased water security</td>
<td>None identified</td>
<td>NA</td>
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<tr>
<td>Distribution: 60 gallons of foam accidentally pumped into hydrant</td>
<td>Fire retardant foam(^50) (inadvertent)</td>
<td>Charlotte, NC/1997</td>
<td>40,000 households; no water use for 1.5 d</td>
<td>None</td>
<td>NA</td>
</tr>
<tr>
<td>Distribution: (cross-connection): water for soup contaminated by boiler additive</td>
<td>Nitrites(^51) (inadvertent)</td>
<td>New Jersey/1992</td>
<td>49 children; 14 with MetHb &gt;20%</td>
<td>Cyanosis, nausea, abdominal pain, vomiting, dizziness</td>
<td>Acute</td>
</tr>
<tr>
<td>Distribution: possible plot to introduce 4 kg (9 pounds) of a cyanide compound into US embassy water supply</td>
<td>Potassium ferrocyanide(^52) (intentional)</td>
<td>Rome, Italy/2002</td>
<td>None</td>
<td>None; plot disrupted</td>
<td>NA</td>
</tr>
</tbody>
</table>

Note that the number of people affected generally decreases as the site of contaminant introduction moves from the production to the distribution side.

*Abbreviations:* LSD, lysergic acid diethylamide; MetHb, methemoglobinemia; NA, not applicable; TVA, Tennessee valley authority; VOC, volatile organic compounds; Yippie, Youth International Party.
**Impact of Site of Contamination**

From a terrorist viewpoint, characteristics of the ideal water contaminant include an agent that causes illness and is:

- Odorless and tasteless
- Colorless
- Resistant to water treatment procedures
- Water stable (not subject to hydrolysis)
- Water soluble
- Low LD$_{50}$ (median lethal dose; ie, high toxicity)

Several compounds have been assessed and ranked for relative water toxicity, using the ratio of solubility in water to lethal dose.$^{38}$ As with the milk vehicle model mentioned earlier, botulinum toxin leads the list of theoretic water toxins. Many other chemical compounds that are of significant acute toxicity would be diluted beyond effect if introduced into a large water supply, or potentially removed or inactivated by water treatment procedures. Most water systems (particularly those that use surface water, which is most of them) process water by flocculation and sedimentation to remove large particulates, then filtration through sand, gravel, or charcoal (removing micrometer-sized particles), then disinfection (using a halide such as chlorine) as depicted in Fig. 5. Only after this is the water distributed to end users, usually with free residual chlorine content of considerably more than 0.2 mg/L.$^{39}$

The January 2014 Elk River chemical spill just upstream from Charleston, West Virginia, provides an example of the impact of water contamination on a large scale.

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**Fig. 5.** Community water treatment steps. (From United States Environmental Protection Agency. Water treatment process. Available at: http://water.epa.gov/learn/kids/drinkingwater/watertreatmentplant_index.cfm.)
An above-ground storage tank containing approximately 37,855 L (10,000 gallons) of a coal flotation product containing a mixture of 88.5% 4-methylcyclohexane methanol (MCHM), 7.3% propylene glycol phenyl ether (PPH), and water leaked into the Elk River at a point 2.5 km (2.4 km) above the sole intake valve for a public water system serving 300,000 people in 9 counties. A do-not-use order was announced the evening of the spill; water was to be used for firefighting and toilet flushing only. The water was cleared for use in zones beginning 4 days later, with all sections cleared 8 days after the spill. During the 2 weeks after the spill, hospitals recorded 369 water contamination–related hospital visits, the WV Poison Center recorded 2000 human exposures, and (according to the CDC Community Assessment for Public Health Emergency Response survey), 21.7% of households reported someone having symptoms they thought were related to water contamination. No hospital admissions were determined to be related to water contamination. Although the environmental health screening value was set by the CDC at 1 ppm for MCHM and 1.2 ppm for PPH (below which water was cleared for use), it was determined after the water crisis ended that the odor threshold was even lower. The noxious licorice smell of MCHM was detectible down to 0.022 ppm (22 parts per billion). The lingering water odor and the ability to taste MCHM led to persisting distrust of water safety long after water zones had reopened; the state of emergency was not lifted until 42 days after the last zone was opened for use. During the water crisis, more than 19.5 million bottles of water, 8.7 million liter containers of water, and 3 million gallons of bulk water were distributed by the National Guard; more than 3000 water samples were tested (Elizabeth Scharman, PharmD 2014). Public schools in the area were closed for weeks and businesses lost thousands of dollars. It caused outrage in the community that a company was allowed to store such large quantities of a chemical with no human health exposure information, and no previously established test to detect its presence in water, in such proximity to the intake valve of a public water system. The lack of extensive human health effect information for MCHM, the inability of the water company to shut off water coming into the intake valve following the spill, the lack of regulations applying to the chemicals involved, and the distrust of state public health partners fueled fear in the community. Multiple instances of social media postings of untrue or misleading information helped to spread the fear quickly. This incident brings to light several potential vulnerabilities in the public water drinking system:

- Available filtration systems may be overwhelmed by a large volume of contaminant
- Backup storage capacity in a water system is an important safety redundancy
- Consideration of the odor and taste of a contaminant can be a serious public health issue (even in the absence of clinically significant toxicity of that contaminant at the levels present)
- Unregulated above-ground storage tanks near public water supplies are a vulnerability for a large number of communities (eg, 800,000 people in Charlotte, NC, are downstream of coal ash waste located just 3 miles from the public water source intake)

Because of the critically important role played by water in daily life, and its often limited access, many organizations and governmental authorities have provided public health educational and response tools to address concerns about water quality. One of these, the physician online reference guide to water-borne disease and health effects of water pollution developed by the American College of Preventive Medicine, provides continuing medical education and a tool kit for clinicians.
MEDICATION CONTAMINATION

The FDA is responsible for ensuring that prescription and over-the-counter medications in the United States are safe and effective. To that end, the FDA regulates all steps in the process of manufacture under the concept of current good manufacturing practice regulations. This authority came in a series of acts precipitated by the substitution of diethylene glycol for the more expensive glycerin solvent in the liquid formulation of an early antibiotic, sulfanilamide, in 1937. This substitution resulted in the deaths of 105 people of the known 353 people exposed. The Food, Drug, and Cosmetic Act of 1938 increased regulatory authority of the FDA for medication safety. However, substitution of diethylene glycol in several medications and consumer products continues to result in poisoning outbreaks in different parts of the world. The ongoing problem of intermittent medication shortages is partially caused by production halts by the FDA because of identified lack of pharmaceutical manufacturers’ compliance with regulatory standards for documenting purity or sterility or other good manufacturing processes. Additional problems with compounding pharmacies, which traditionally have been regulated by the state in which the entity is sited, have become apparent when these entities have done large-scale production and distribution. The multistate outbreak of fungal meningitis and other closed-space infection from methylprednisolone acetate contaminated at the site of processing in 2013 highlighted a problem with use and regulation of these entities.

Given the frequency with which all of these problems occur, the potential for intentional and inadvertent contamination is even greater with products marketed outside the FDA’s usual regulatory oversight. These products include dietary supplements, which occupy a legislated limbo by the 1994 Dietary Supplement Health and Education Act. They are regulated as food, but routinely illegally promoted as active medications; foreign products brought into the United States, such as Chinese patent medicines, Ayurvedic medication, or other culturally based medical practices that frequently make use of heavy metals; and counterfeit medications, a market considered larger than the illicit drug of abuse market.

Contamination Identification

Identification of chemically adulterated medication can be difficult. In contrast with the situations described for food and water, in which small or large segments of the general population may be affected, medications are often given to individuals who are already ill. Thus, additional clinical symptoms or death could be attributed to the underlying medical condition, intercurrent medical illness, or drug-drug interactions, resulting in a missed or delayed identification of drug adulteration. The major postmarketing mechanism for identification of adverse medication reactions, FDA’s MedWatch program, is a voluntary reporting system, and causality may be difficult to determine. Voluntary reporting via regional poison control centers to the National Poison Data System has similarly been used to identify illicit drug supply adulteration because of the increased number of emergency department visits, but incoming calls depend on the clinician recognizing the potential for drug-related adverse events. Other surveillance mechanisms, such as health insurance–based monitoring, the standards-setting organization, US Pharmacopeia, or organ-specific programs such as the Drug-Induced Liver Injury Network can play an important role, but are not well coordinated centrally and may have significant time lags in identifying signals. Analytical testing by chromatographic techniques is an excellent mechanism to identify contaminants, but has been largely applied only to confiscated and black market drug analysis. For solid medication preparations, comparison of potential counterfeit
tablets with infrared spectra of a known branded product has been used as an accurate screening method.67

**Impact of Site of Contamination**

The frequent occurrence of manufacturing errors provides a window into the multinational sourcing of medication components, with active pharmaceutical ingredients being manufactured in one place and shipped with other ingredients to another site for batch processing and addition of excipients for medication delivery or aesthetics, labeling, and distribution to third parties for delivery to pharmacies and other retail outlets. As examples, star anise, in addition to its use as a flavoring agent, was the major source of shikimic acid, itself the major precursor of the anti-influenza medication, oseltamivir. Until a process for *Escherichia coli*–mediated synthesis of shikimic acid was developed, China was the major source of star anise.68 Such international dependence for a raw material is not only strategically unwise, it also provides opportunity for product adulteration. This opportunity was seen recently with a large number of allergic reactions reported with use of one brand of heparin. The ultimate cause was identified as the substitution of a cheaper, but less active and allergenic, raw material (active pharmaceutical ingredient [API]) from multiple Chinese suppliers.69,70

At the other end of the production-distribution chain, the batching process used by most pharmaceutical manufacturers allows errors at switchover transition from one product to another, resulting in one API being packaged and labeled as another. Still further down the chain, individual pharmacies can mislabel product, affecting a single or small number of individuals. The most famous example of end-distribution medication tampering was the so-called Chicago Tylenol murders in 1982.71 Substitution of several capsules in multiple drug stores resulted in 7 deaths from cyanide poisoning. The response to this included legislation making drug tampering a federal offense and an industry response that resulted in the standard of triple-sealed tamper-evident packaging for over-the-counter medications (now amended to 2 tamper-evident seals).72 Table 3 lists some examples of medication adulteration along this supply chain.

**RECOGNIZING CLINICAL MANIFESTATIONS**

As outlined in Tables 1–3 listing examples of past food, water, and medication contamination, identification of the causative agent or even the existence of a contamination event is not always easy or rapid. Clinicians face competing challenges: identify toxic symptoms and reassure those with unrelated symptoms while all are facing a stressful situation. Local and national experts, as appropriate, can assist by providing alerts to emergency and primary care providers, and by formulating clinical case definitions. However, these definitions often undergo revisions as more information becomes available and may take some time to develop; clinicians must depend on obtaining a good history of associated events and timing, while being aware of symptom clusters that may identify toxidromes. The importance of a system-wide approach, making use of all available resources, has been emphasized previously both here and elsewhere.79 The CDC has provided a symptom-based approach to some agents, as listed in Table 4.80 The American College of Emergency Physicians and other organizations have prepared graphic material to display in emergency departments to assist in toxidrome recognition in the mass casualty situation. Although these resources can be outdated, the National Library of Medicine has incorporated several resources and expert input into an online interactive Chemical Hazards Emergency Medical Management (CHEMM).81 This resource is valuable because it allows a clinical picture to be built of a potentially poisoned patient using the CHEMM Intelligent
### Table 3
**Examples of chemical contamination of the medication supply**

<table>
<thead>
<tr>
<th>Bow-Tie Site of Introduction</th>
<th>Chemical Exposure</th>
<th>Site/Date</th>
<th>Number of People Affected</th>
<th>Health Effects</th>
<th>Acute vs Chronic Health Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw ingredient (API): Chinese suppliers substituted animal cartilage–based oversulfated chondroitin sulfate for pig intestine–based product</td>
<td>Baxter Healthcare brand heparin&lt;sup&gt;70&lt;/sup&gt; (intentional)</td>
<td>United States and at least 10 other countries/2008</td>
<td>Thousands; &gt;100 reported deaths in United States</td>
<td>Allergic reactions (angioedema, hypotension, dyspnea, gastrointestinal symptoms)</td>
<td>Acute</td>
</tr>
<tr>
<td>Production: substitution of DEG for glycerin or propylene glycol in an acetaminophen elixir</td>
<td>DEG&lt;sup&gt;73&lt;/sup&gt; (intentional)</td>
<td>Haiti/1995–1996 (and multiple other events&lt;sup&gt;46&lt;/sup&gt;)</td>
<td>106 children with renal failure, 93 of whom died</td>
<td>Vomiting, mental status changes, renal failure</td>
<td>Acute</td>
</tr>
<tr>
<td>Production: aegeline substituted for illegal stimulant (DMAA) in OxyElite Pro dietary supplement</td>
<td>Aegeline&lt;sup&gt;74–76&lt;/sup&gt; (intentional)</td>
<td>Hawaii/2013</td>
<td>Approximately 30 cases; 1 death</td>
<td>Loss of appetite, jaundice consequent to hepatic injury</td>
<td>Acute to subacute</td>
</tr>
<tr>
<td>Production: 200 times indicated selenium and 17 times indicated chromium content added to dietary supplements Total Body Formula and Total Body Mega Formula</td>
<td>Selenium (and chromium)&lt;sup&gt;77&lt;/sup&gt; (inadvertent)</td>
<td>9 US states/2008</td>
<td>At least 43 people</td>
<td>Muscle cramps, diarrhea, joint pain, fatigue, hair loss, and nail changes days to weeks while using product</td>
<td>Subacute</td>
</tr>
<tr>
<td>End distribution: tampering of Tylenol brand acetaminophen capsules on pharmacy shelves</td>
<td>Cyanide&lt;sup&gt;71&lt;/sup&gt; (intentional)</td>
<td>Chicago, IL/1982 (and numerous copycat events&lt;sup&gt;78&lt;/sup&gt;)</td>
<td>7 people died</td>
<td>Sudden cardiovascular collapse</td>
<td>Acute</td>
</tr>
</tbody>
</table>

Note that the number of people affected generally decreases as the site of contaminant introduction moves from the production to the distribution side.

Abbreviations: DEG, diethylene glycol; DMAA, 1,3-dimethylamylamine.
<table>
<thead>
<tr>
<th>Category</th>
<th>Clinical Syndrome</th>
<th>Potential Chemical Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinergic crisis</td>
<td>Salivation, diarrhea, lacrimation, bronchorrhea, diaphoresis, and/or urination</td>
<td>Nicotine&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
|                                | Miosis, fasciculations, weakness, bradycardia or tachycardia, hypotension or hypertension, altered mental status, and/or seizures | Organophosphate insecticides<sup>b</sup>  
|                                |                                                                                |   ○ Decreased acetylcholinesterase activity  
|                                |                                                                                |   ○ Carbamate insecticides  
|                                |                                                                                |   ○ Medicinal carbamates (eg, physostigmine)  
| Generalized muscle rigidity    | Seizurelike, generalized muscle contractions or painful spasms (neck and limbs) and usually tachycardia and hypertension | Strychnine  
|                                |                                                                                |   ○ Intact sensorium  
| Oropharyngeal pain and ulcerations | Lip, mouth, and pharyngeal ulcerations and burning pain | Paraquat<sup>b</sup>  
|                                |                                                                                |   ○ Dyspnea and hemoptysis secondary to pulmonary edema or hemorrhage; can progress to pulmonary fibrosis over days to weeks  
|                                |                                                                                |   ○ Diquat  
|                                |                                                                                |   ○ Caustics (ie, acids and alkalis)  
|                                |                                                                                |   ○ Inorganic mercuric salts  
|                                |                                                                                |   ○ Mustards (eg, sulfur)  
| Cellular hypoxia               | Mild: nausea, vomiting, and headache  
|                                | Severe: altered mental status, dyspnea, hypotension, seizures, and metabolic acidosis | Cyanide<sup>b</sup>  
|                                |                                                                                |   ○ Bitter almond odor<sup>c</sup>  
|                                |                                                                                |   ○ Sodium monofluoroacetate<sup>b</sup>  
|                                |                                                                                |   ○ Hypocalcemia or hypokalemia  
|                                |                                                                                |   ○ Carbon monoxide  
|                                |                                                                                |   ○ Hydrogen sulfide  
|                                |                                                                                |   ○ Sodium azide  
|                                |                                                                                |   ○ Methemoglobin-causing agents  
| Peripheral neuropathy and/or neurocognitive effects | Peripheral neuropathy signs and symptoms: muscle weakness and atrophy, glove-and-stocking sensory loss, and depressed or absent deep tendon reflexes | Mercury (organic)<sup>b</sup>  
|                                | Neurocognitive effects: memory loss, delirium, ataxia, and/or encephalopathy   |   ○ Visual disturbances, paresthesias, and/or ataxia  
|                                |                                                                                |   ○ Arsenic (inorganic)<sup>b</sup>  
|                                |                                                                                |   ○ Delirium and/or peripheral neuropathy  
|                                |                                                                                |   ○ Thallium  
|                                |                                                                                |   ○ Delirium and/or peripheral neuropathy  
|                                |                                                                                |   ○ Lead  
|                                |                                                                                |   ○ Encephalopathy  
|                                |                                                                                |   ○ Acrylamide  
|                                |                                                                                |   ○ Encephalopathy and/or peripheral neuropathy  

(continued on next page)
Differentiating fear response from toxic exposure can be particularly difficult. Even for suspected substances that are often considered all or none in their clinical presentation, such as cyanide salts, patient and provider fear or lack of understanding can interfere with good medical care. Recognizing that people respond to the unknown with uncertainty can be the first step toward formulating a reasonable approach that involves them in the solution.

**MANAGEMENT**

The axiom that supportive care forms the basis of emergency medical care is also true in settings of mass exposure events. One of the issues that arise during mass casualty events is the problem of limited resources, which can include difficulty in determining a diagnosis and initiating treatment, as well as mobilizing adequate numbers of personnel, supplies, and treatment modalities. A recently published systematic review of the disaster medicine literature evaluated response strategies in mass casualty events; it identified little evidence for effective, proven strategies to manage or allocate scarce resources, particularly for chemical exposure events. Hospital-based antidote supplies have long been recognized as deficient; a consensus panel recently reviewed the rationale for immediate availability of several antidotes. However, maintaining stocks of infrequently used, and sometimes expensive, medications encounters the problem of the often arbitrary out-date for these agents. Although the Medical Letter and professional organizations such as the American College of Medical Toxicology and the American Academy of Clinical Toxicology have called for a resolution to this largely bureaucratic problem, there has only been limited success, as exemplified by the Department of Defense’s Shelf Life Extension Program regulating the ongoing extensions of the out-dates for nerve agent antidotes regionally located in the Chem-Pack program. Regional poison control centers maintain lists of antidote availability at regional hospitals and can be accessed through their toll-free number of 1-800-222-1222. In contrast with most other acute emergencies, individual cases of potential contamination of food, water, or medication require immediate notification of relevant regulatory agencies and careful crafting of messages to the public. The local or state health department is the point of first contact; this too can sometimes be facilitated by the regional poison control center and its toxicology directors.

<table>
<thead>
<tr>
<th>Category</th>
<th>Clinical Syndrome</th>
<th>Potential Chemical Cause</th>
</tr>
</thead>
</table>
| Severe gastrointestinal illness, dehydration | • Abdominal pain, vomiting, profuse diarrhea (possibly bloody), and hypotension, possibly followed by multisystem organ failure | • Arsenic<sup>b</sup>  
  • Ricin<sup>b</sup>  
  ○ Inhalation an additional route of exposure; severe respiratory illness possible |
|                                 |                                                        | • Colchicine                                                         |
|                                 |                                                        | • Barium                                                             |
|                                 |                                                        | ○ Hypokalemia common                                                  |

<sup>a</sup> Not intended as a complete differential diagnosis for each syndrome or a list of all chemicals that might be used in a covert chemical release.

<sup>b</sup> Potential agents for a covert chemical release based on historical use (ie, intentional or inadvertent use), high toxicity, and/or ease of availability.

<sup>c</sup> Unreliable sign.

Box 1
Assistance in identification of a potential food, water, or medication contamination event

- Obtain a history of onset of symptoms and any association with new medication refills or purchases, or eating/drinking.
- Identify any concerns regarding food, water, or medication appearance or taste.
- Query as to others who shared these items and their condition.
- Identify any prominent organ effects or laboratory findings of concern.
- If possible, obtain sample of potentially contaminated material.
- If assessment raises concern regarding contamination, contact the regional poison control center (PCC) at 1-800-222-1222 and report concerns.
- If a toxidrome with a specific antidote is being considered, the PCC can assist in identifying and/or locating these medical countermeasures. The PCC can also identify additional resources, such as medical toxicologists, if the hospital does not have a medical toxicologist on staff.
- If other reports from regional caregivers, or consistent with notices on American Association of Poison Control Centers (AAPCC) listserv, Epi-X, or other reporting sources, the PCC directors may draft a press release for dissemination to hospitals in conjunction with state department of public health notification to assist in defining the clinical picture, possible diagnostic studies, and treatment.
- Incorporate additional public health, laboratory, and investigative resources as appropriate.

some commonsense management points that may assist in the early recognition and response to potentially contaminated food, water, or medication supplies.

SPECIAL CONSIDERATIONS

As noted earlier in this article, children were at particular risk in the modeling of poisoning of the milk supply by botulinum toxin because of their larger intake of milk compared with adults and their smaller mass and increased respiratory rate.4 In general, this same principle can apply to other toxins and toxicants delivered via food or water in terms of at-risk populations. As noted earlier, medication tampering has the potential for asymmetric impact on those with underlying health issues for which the medications were indicated in the first place.

SUMMARY

Food, water, and medication production, processing, and distribution involve multiple potential points of entry for chemical contamination. These points of entry can be inadvertent or intentional. Past experience indicates that these issues will continue to present challenges in prevention, rapid identification, and response. Several regulatory agencies have ultimate responsibility for each of these areas, but early recognition of introduced contamination will continue to be based on clinical suspicion. Given that analytical testing can be delayed, a complete history of travel and medication use (including specific questioning about supplements, over-the-counter products, and ethnic products), timing of onset and nature of symptoms, inquiries about others with symptoms, and recognition of potential toxidromes forms the foundation for subsequent investigation. Regional poison control centers are a valuable resource for assistance and potential case finding, and they can serve as an entry point to additional medical toxicology and public health resources. State public health laboratories
participate in a national LRN, with specific capabilities to deal with potential food issues via the FERN.

The number and location of affected individuals can facilitate identification of the likely point of entry of a chemical contaminant through the use of bow-tie modeling. In general, the earlier in the production-distribution chain the contamination occurred, the more widely dispersed and greater in number will be the impact. This epidemiologic tool can be important when crafting a public response, which may include recalls or no-use warnings. Appropriate and ongoing risk communication is an important aspect of the overall response to potential chemical contamination of food, water, or medication, in order to avoid inappropriate responses based on fear or inaccurate information.

REFERENCES

13. Food and Drug Administration. FDA’s draft approach for designating high-risk foods as required by section 204 of FSMA. Available at: http://www.fda.gov/


