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## Food Safety Lessons from the Field

A mysterious outbreak of sleeping sickness in Angola

Gerald G. Moy, Ph.D.

A public health outbreak is the occurrence of disease cases in excess of normal expectancy. Disease outbreaks are caused either by infectious agents, such as bacteria, viruses, fungi, parasites, and noxious agents, such as chemicals and toxins. As a consequence, an outbreak investigator is faced with the formidable task of solving the true cause of the outbreak not only with the time pressure of appropriately treating the victims, but also the prevention of spread in the community and beyond. Perhaps the initial key is knowing if the agent is spread via the inhalation, dermal absorption, or ingestion. This is not always clear, as exposure can be through multiple pathways.

The difficulty and uncertainty in the investigation of disease outbreaks of unknown cause illustrates the importance of how food should be considered as a possible route to transmission until it is effectively ruled out based on evidence. The U.S. Centers of Disease Control and Prevention has stated that researchers have identified more than 250 foodborne infectious agents.<sup>1</sup> The number of possible noxious chemical agents is much higher because, in principle according to Paracelsus, “All things are poison, and nothing is without poison; the dosage alone makes it so a thing is not a poison.”<sup>2</sup> Besides the thousands of chemicals approved for use in food, such as food additives, pesticides, and veterinary drugs, many naturally occurring toxins, like heavy metals and mycotoxins, can pose a risk to health. The present paper describes an outbreak that was ultimately determined to be foodborne and the need for explicitly considering this possibility in any investigation.

### A Mysterious Outbreak of “Sleeping Sickness”

An outbreak of acute neurological disease of unknown origin occurred from October to December 2007 in Cacuaco Municipality, Angola. A suburb of the capital Luanda, Cacuaco has a population of about 1.3 million. The most distinguishing symptom was that victims were falling asleep and could only be aroused with painful stimulation. Other symptoms include extreme somnolence, persistent drowsiness, blurred vision, difficulty speaking, and loss of muscle control. It was reported that some dogs and chickens were also falling asleep. Patients recovered slowly over a number of days, but many still had difficulty walking. The disease would ultimately affect 467 individuals—a majority of whom were children. Fortunately, no deaths were reported. The original “sleeping sickness” is caused by a parasite transmitted by the Tsetse fly, but this disease was clearly not East African trypanosomiasis.

The first cases occurred on October 2 and were officially reported on October 24 to the Angolan Ministry of Health (AMOH). Shortly thereafter, the World Health Organization (WHO) country

office with the AMOH conducted initial investigations. Although the cause could not be identified, the symptoms suggested that this was an intoxication rather than an infection. On October 30, 2007, the AMOH officially requested WHO to provide experts to investigate this outbreak. Most of the information in this paper is taken from the Executive Summary of the report prepared by this team of experts.<sup>3</sup> The WHO team arrived in the country on November 2, consisting of a clinical toxicologist, an epidemiologist, an environmental investigator, a laboratory specialist, and a team coordinator. In collaboration with the national authorities, some members of the team set about identifying the cause of the outbreak through the clinical and neurological examinations of more than 50 patients. This included taking blood and urine samples that were shipped to laboratories in Europe. The neurological examination reported:

“Patients had extreme somnolence. On awakening they had ataxia,<sup>4</sup> lasting several days. The central nervous system was affected, particularly the cerebellum (altered balance and coordination). All other vital parameters were normal. In particular, there was no sign of peripheral neuropathy. No vomiting nor diarrhea were consistently reported. Differential diagnosis supported a toxic origin, likely through a substance affecting the gamma-aminobutyric acid receptors.”

Other team members conducted an epidemiological investigation to identify the source of the outbreak, including the collection of food and water samples, which were also sent to laboratories in Europe for analysis. Children under 15 years of age were the largest group affected (64%) followed by females (62%). Some evidence indicated household clusters, but not all members were affected. Bacterial or viral infections were not indicated by the epidemiological curve, and interviews did not point to a common source of exposure. Samples of blood and urine were taken and sent to laboratories in Germany and the United Kingdom. The samples were tested for more than 7,000 substances, including benzodiazepines, gamma-hydroxybutyrate and its analogues, pharmaceuticals and metabolites, organic solvents, and heavy metals.

On November 19, the laboratory in Germany detected very high concentrations of bromide, ranging from 1,000 to 2,450 mg/L in six out of seven blood samples, which were 20–50 times higher than normal physiological levels. On November 21, the laboratory in the United Kingdom confirmed these findings in a different set of blood samples, which showed similarly high bromide levels. It should be noted that although three deaths were reported earlier, the cause of these deaths were later determined to be unrelated to bromide. Food and water samples collected on the field were then tested for bromide in Germany and Switzerland. In particular, analysis of four out of six table salt samples were shown to contain at least 80 percent sodium bromide. Two other food items that were in contact with this salt were also found positive for bromide. Altogether, these laboratory results strongly indicated that ingestion of “table salt” (that actually was mostly sodium bromide) produced the neurological symptoms observed among cases.

As a result of these findings, risk management activities were initiated including informing the public about the potential risk of “table salt” and providing healthcare facilities advice on treatment. In addition, testing of salt was initiated using a simple analytical method. The WHO team made recommendations to prevent and respond to further incidents, including the strengthening of national chemical and food safety programs and establishing a national poison center with associated clinical and analytical toxicological capacities. Even with these capabilities, it is uncertain if such an unusual outbreak could be quickly resolved given its unusual features.

Although sodium bromide is used in Angola in the oil industry to make a heavy clear brine for drilling, it is still unknown how sodium bromide came to be substituted for salt. However, if this incident would have occurred 100 years earlier, it would have been solved almost immediately.

### **Elementary, My Dear Watson**

In 1887, the English writer, Sir Arthur Conan Doyle, created the popular detective novel and character of Sherlock Holmes known for his powers of observation, forensic science, and deduction. Among his eccentricities, he occasionally used morphine and cocaine, which were legally marketed at the time.<sup>5</sup> But the real key to this outbreak was another drug widely marketed to the public at the time. Potassium bromide was used as an anticonvulsant and sedative as well as other claims. It was also widely used in the medical community. For example, one hospital was reported to use several tons a year. However, it should be noted that potassium bromide only tastes salty at high concentrations while sodium bromide tastes salty at all concentrations. Perhaps, Sherlock would have needed a clue, like finding an empty bag labeled “sodium bromide” as was alleged in the Angola outbreak. To be fair, mass bromide intoxication was never reported before and the clinical presentations did not fully fit with acute single dose nor with chronic intoxication. The drug is especially bioavailable and has long half-life of 12 days in the blood.<sup>6</sup>

### **Bromide Today**

In a reflection of the widespread usage of potassium bromide, the American humorist Gelett Burgess in 1906 published pamphlet entitled “Are you a bromide?” that describes a “bromide” as a sedate, dull person who said boring things. This definition can still be found today in Merriam-Webster dictionary, but it also includes another definition, namely “a commonplace or hackneyed statement or notion.” One of the landmarks in the city of Baltimore is the Emerson Bromo-Seltzer Tower, which was built in 1907. At that time, the tower was capped with a 16-m replica of a the distinctive blue Bromo-Seltzer bottle that glowed and rotated. While the bottle weighing 20 tons was removed in 1936 because of structural problems, the tower remains. The product with potassium bromide remained on the market until 1975, when the product was reformulated without bromide because of concerns for chronic toxicity. In Germany, a prescription drug containing potassium bromide is still approved as an antiepileptic drug, particularly for children and adolescents.

In a related matter, brominated vegetable oil (BVO) is an approved food additive in the U.S. that is used as an emulsifier in citrus flavored soft drinks. It is not approved in the European Union or Japan. Anecdotal reports have surfaced of individuals experiencing memory loss and skin and nerve problems after drinking excessive amounts (more than 2 L/day). This has been ascribed to the buildup of bromine due to its long half-life.<sup>7</sup> In 1984, the U.S. Food and Drug Administration changed the status of BVO from “generally recognized as safe” to more restrictive upper limit of 15 parts per million pending further toxicological studies.<sup>8</sup> Nothing much happened until 2012 when a teenager in Hattiesburg, Mississippi, Sarah Kavanagh, started an online petition on Change.org to get PepsiCo to drop BVO from its Gatorade products, which gathered about 200,000 signatures. In January 2013, PepsiCo announced that it would replace the ingredient with sucrose acetate isobutyrate in Gatorade, but it continues to use it in some varieties of Mountain Dew and Amp Energy. Ms. Kavanagh then petitioned Coca-Cola to eliminate BVO from Powerade, which

gathered about 60,000 signatures. In 2014, Coca-Cola announced that they would also remove BVO from all of their products.<sup>2</sup> In an April 24, 2017 Facebook post, Betsy Ball Clark claimed that Pepsi had not removed BVO from her favorite product, Mountain Dew, which subsequently received 1.1 million hits. On May 9, 2020, Pepsi confirmed to Ms. Ball that their products no longer contained BVO.<sup>10</sup>

On the other hand, a 2014 study has shown that bromide is essential for tissue development in all life, including humans.<sup>11</sup> Bromine was found to be important by providing collagen IV scaffolds for all tissues, including the kidney's filtering units. This finding has important implications for human disease as many patient groups have been shown to be bromine deficient. In particular, bromine supplementation may improve the health of patients on dialysis or total parenteral nutrition. The typical daily dietary intakes of bromide in the European Union were estimated to be between 1.6 and 9.4 percent (lower and upper bound) of the acceptable daily intake for bromide of 1 mg/kg body weight.<sup>12</sup> The main sources of bromide in the diet are cereals and grains, nuts and fish. However, a recommended daily intake for bromide has not yet been established.<sup>13</sup>

## Lessons Learned

The lesson from this unusual outbreak is that in all investigations of unknown etiology, food should be considered as a potential vehicle until it can be explicitly ruled out. Another lesson is that information from the past is being lost as the cause might have been readily determined 100 years ago. There is a need for an international database of individual outbreaks, including summarized (a) location of the event, (b) clinical data, (c) epidemiologic data, (d) laboratory findings, and (e) results of on-site investigations.<sup>14</sup>

The other important lesson is that with social media, individual consumers can exert considerable influence on food manufacturers. As BVO was already approved by FDA, the onus was on the government to demonstrate that the additive was unsafe, which is both difficult and expensive. However, given that trust in government institutions has eroded, the food industry is now being subject to greater scrutiny and may even heed to unwarranted consumer demands, especially in highly competitive markets.

## References

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*Gerald G. Moy, Ph.D., is the principal at Food Safety Consultants International and former staff member of the WHO Department of Food Safety and Zoonoses.*