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Perspective

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Melamine and the Global Implications of Food Contamination

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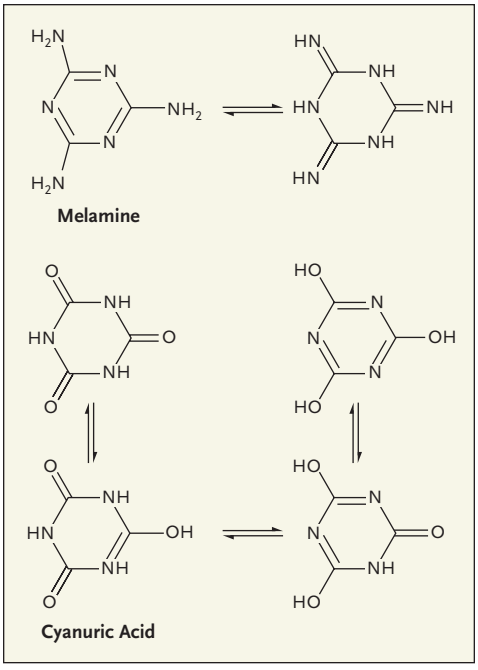
Food contamination, whether accidental or intentional, has been a sad, recurrent theme throughout recorded history, going back some 8000 years and described in the Old Testament.

However, a new dimension has been added in this new millennium: globalization and international agribusiness allow problems with the food supply to spread around the planet all too quickly. The most recent, and still evolving, example is the epidemic of melamine poisoning stemming from tainted infant formula in China. More than 294,000 children in China have reportedly been affected by adulterated formula. Over 50,000 were hospitalized, and at least 6 died. Some are said to remain in the hospital. There are also reports that children in other parts of Asia — such as Taiwan, Singapore, and Vietnam — were also affected. Those who became ill had ingested melamine-contaminated powdered infant formula; some 22 brands were implicated. In the wake of this stunning discovery, the contaminated formula was taken off the market, but the story of melamine contamination is far from over.

In addition to its catastrophic health effects, the contamination has had major economic effects, with the United States and other countries banning the importation of milk and other food products from China. Recent news reports note that China has asked the United States to lift its ban on milk products and that the U.S. Food and Drug Administration (FDA) has opened an office in Beijing (and will open others in Shanghai and Guangzhou and in other countries) that will examine food exports destined for the United States.

Now melamine is being discovered in other foods, which are turning up worldwide. Melamine (1,3,5-triazine–2,4,6-triamine, or $C_3H_6N_6$) (see diagram), a chemical developed in the 1830s, has had varied and widespread legitimate uses. China is not the only country producing melamine; millions of kilograms are synthesized annually in the United States and elsewhere in the Western world. The compound is a component in many plastics, adhesives, glues, laminated products such as plywood, cement, cleansers, fire-retardant paint, and more. But melamine does not always remain



Chemical Structures of Melamine and Its Metabolite Cyanuric Acid.

where it is placed. For example, melamine in plasticware may be leached from the product by acid and thus can migrate into food, though — at least as measured — not in amounts considered toxic. Fortunately, melamine-containing plasticware becomes discolored or fractures, so it is used less often than it once was. A greater concern is that melamine is frequently added to crop fertilizer, from which it is absorbed into the soil and then, most likely, into crops themselves, though any uptake has been largely unmeasured. Thus, there is melamine in many products throughout the world, and we do not know what problems it may cause in the future.

But why would one intentionally add a nonnutritious substance such as melamine to food? Nitrogen content has long been used as a surrogate for assessing the protein content of foods, and melamine contains a substantial amount of nitrogen — 66% by mass. Before the current melamine disaster, the marked dilution of infant formula in China had resulted in marasmus in some infants,[1] which led to government directives to increase the protein content of such preparations or risk severe penalties. Thus, it is possible that the adulteration was conceived in response to a well-intentioned government directive. The fact that melamine could increase the apparent protein content and, furthermore, make the product look milky may have been irresistible to those who would adulterate.

That melamine and its congeners have toxic effects has been known for decades. These compounds are toxic to humans and animals, though the amount leading to adverse effects depends on the rate of exposure. The 2007 melamine adulteration of pet food resulted in many deaths of cats and dogs in the United States and elsewhere.[2,3] This epidemic of illness in pets should have reinforced the understanding that melamine ingestion might be very harmful to humans. Moreover, the melamine congener hexamethylmelamine was tested as an anticancer medication in the 1960s, and again in the late 1990s for advanced ovarian cancer and other conditions.[4] Side effects of this congener were mainly gastrointestinal, not renal, but the chemotherapeutic use of hexamethylmelamine and other melamine congeners has largely been abandoned.

How much melamine must food contain to pose a risk to humans? Given the lack of data, regulatory bodies such as the FDA and international agencies such as the World Health Organization (WHO) are trying hard to develop useful recommendations. An early December meeting of experts took place in Ottawa, Canada, sponsored by the WHO and Health Canada. The experts recommended considering melamine in food as having a baseline level, the level not resulting from adulteration or misuse, and an adulteration level, the level resulting from purposeful addition of melamine. Since there are insufficient data from humans, the WHO meeting recommended a tolerable daily intake (TDI) of 0.2 milligrams per kilogram of body weight for melamine and 1.5 milligrams per kilogram of body weight for cyanuric acid. The executive summary stated that the TDI is "applicable to the whole population, including infants." However, exposure to both melamine and cyanuric acid may confer a higher risk, and there are unknowns about long-term renal and other risks. The current limit set by the FDA for melamine in food is 2.5 parts per million, calculated on the basis of ingestion by a person weighing 60 kg. The FDA initially stated that no melamine is permitted in infant formula but in late November changed that to 1 part per million being permitted.[5] It is not clear how much melamine in other food would be "safe" for children, particularly young children, especially since they ingest far more food for their size than do adults, rendering the dose per kilogram of any toxin potentially higher. Furthermore, initial signs and symptoms may be subtle and non-

Products Withdrawn from the U.S. Market because of Melamine Contamination.

Product	Brand	Distribution	Distributor and Location	Reason for Withdrawal
Candy	White Rabbit	CA, GA, HI, IL, MN, NY, OR, TX, WA	QFCO, Burlingame, CA	According to distributor, melamine contamination found
Biscuits	Fresh and Crispy Jacobina Biscuits	Nationwide	Everlasting Distributors, Bayonne, NJ	Melamine found on FDA testing
Cookies	Koala March	Nationwide	Lotte USA, Battle Creek, MI	Melamine contamination possible because cookie is produced in China
Milk	Yili Pure Milk and Yili Sour Milk	Nationwide	HUA XIA Food Trade USA, Flushing, NY	Melamine found on FDA testing
Drink	Blue Cat Flavor Drink (Lanmao)	Nationwide	Tristar Food, Jersey City, NJ	Melamine found on FDA testing
Coffee	Mr. Brown	Wholesale distributors and retail stores in CA, FL, GA, IA, IN, KS, KY, MA, MI, MN, NC, NM, NV, OH, PA, RI, TN, TX, VA, WA, and WI	Sunny Maid, Monterey Park, CA	Manufacturer says may contain melamine
Chocolate	Sweet Time Christmas Dressy Bear with Chocolate Bar	Not specified	Wal-mart, Bentonville, AR	Possible melamine contamination
Candy	Topaz Hazelnut Wafer Rolls with Hazelnut Chocolate Flavored Creme Filling	Not specified	Topaz	FDA says may contain melamine

specific in very young children, who typically cannot describe how they feel. Thus, although the onset of illness, as in the current epidemic, may be insidious and unanticipated in the very young, it is far more likely to result in a catastrophic outcome.

The present epidemic illness resulted from melamine's tendency to form stones and gravel in the urinary system. Young children exposed to the median level of the brand with the highest melamine content, according to the executive summary from the WHO meeting, received approximately 40 to 200 times the TDI. Stones can cause obstructive uropathy, and marked obstruction may cause acute renal failure. In the children who died, acute renal failure was discovered too late. The available data suggest that melamine stones are not fully radiopaque, often formed by melamine and its metabolite cyanuric acid (see figure), in complex with uric acid or in a matrix with protein, uric acid, and phosphate. Once the source of these unusual stones and the contamination of powdered formula were uncovered in the present epidemic, the care given to severely affected children became more effective. Many stones could be dissolved with hydration, alkalinization, or lithotripsy, and the renal failure, if present, could be managed with supportive care, including dialysis, if needed. However, many studies indicate that the long-term sequelae of acute renal failure in children, irrespective of its cause, are often serious and include hypertension, albuminuria, and chronic kidney disease. Whether children who had melamine-induced acute renal failure will have long-term consequences is unknown.

A further problem is that melamine food contamination is more pervasive than was originally thought. Since melamine is in animal feed in China, it has now been detected in eggs; it has also been found in wheat gluten and other foods. After the discovery of the melamine contam-

ination of pet food, a detection method involving liquid chromatography–mass spectrometry became widely available and reliably identifies both cyanuric acid and melamine. A number of suspect foods from China tested by the FDA were found to contain melamine (see table), and more are being reported around the world each week. Furthermore, the FDA has found trace levels of melamine in several U.S. infant formulas and, as of the end of November, states that 1 part per million is permitted.

Yet it is not certain what should be done going forward. In the United States, commonsense suggestions have been posted on the Web sites of both the FDA (www.fda.gov/oc/opacom/hottopics/melamine.html) and the Centers for Disease Control and Prevention (http://emergency.cdc.gov/agent/melamine/chinafood.asp), and similar content is available on the WHO Web site (www.who.int/foodsafety/fs_management/infosan_events/en/index.html). The pediatric nephrology community, the American Society of Pediatric Nephrology, and the International Pediatric Nephrology Association recommend vigilance without panic (www.aspneph.com/ASPNStatement%20Melamine%20Oct22_cbl%20(3).pdf). All these organizations suggest examining at-risk children exposed to the brands of infant formula, such as Sanlu, that are known to have been heavily contaminated by melamine.

The bottom line, however, is that nobody knows the true extent of the present epidemic or the risks to come. No more deaths have been reported since the Chinese government and the international public health community became aware of the problem. Yet the long-term health effects remain unknown.

In today's world, it is crucial to understand and deal with the global implications of foodborne diseases if problems like the melamine epidemic are to be prevented. In 2006, the WHO launched an ambitious project to estimate and understand the global burden of foodborne disease, and the Foodborne Disease Burden Epidemiology Reference Group appears to be well on its way to achievement of its initial goals. In addition, the group will be developing much-needed user-friendly tools so that outbreaks, be they due to organisms or chemical substances, can be studied more rapidly and the causes identified, reported, and eliminated.

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Culture Shock — Patient as Icon, Icon as Patient

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On my first day as an attending physician in a new hospital, I found my house staff and students in the team room, a snug bunker filled with glowing monitors. Instead of sitting down to hear about the patients, I suggested we head out to see them. My team came willingly, though they probably felt that everything I would need to get up to speed on our patients — the necessary images, the laboratory results — was right there in the team room. From my perspective, the most crucial element wasn't.

For the next few weeks, I ensured that we spent as little time as possible in the bunker. These were excellent residents who cared enormously about patients' welfare. They enjoyed being shown common findings — white nails of liver disease, an accessory nipple, Dupuytren's contracture, parotid enlargement, spider angiomas, café au lait spots, the paradoxical splitting of the second heart sound in left bundle-branch block, signs of pseudo-