Melamine Contamination of Infant Formula in China: The Causes, Food Safety Issues and Public Health Implications

Commentary

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Background

Melamine - an industrial chemical - was recently found in infant formula in China but it has since spiralled to other food categories that use milk powder as an ingredient, such as chocolate, biscuits and eggs. As of September 21, 2008, a total of 52,857 cases of nephrolithiasis (and, in some instances, renal failure) had been reported in China linked to consumption of this contaminated powdered formula. There have been approximately 13,000 hospitalizations, and at least 4 deaths confirmed to date. The vast majority of illnesses involved children under the age of 3 years (82% < 2 years; 17% 2-3 years; 0.8% > 3 years; and no cases involved adults) [1]. The results of an investigation conducted in China indicated that Chinese-produced powdered infant formula was linked to these illnesses; no cases were associated with liquid infant formula. An investigation of powdered formulas was conducted nationally by China's General Administration of Quality Supervision, Inspection and Quarantine (AQSIQ) and revealed contamination of powdered formulas produced by 22 companies. Test results conducted in China on samples of the powdered infant formula showed that they contained a wide range of concentrations (0.1 ppm to greater than 2,500 ppm melamine powder (Fig. 1). In addition, other countries have
reported detection of melamine in other product categories, such as confections and beverages. Generally, there are available analytical methods that can reliably detect a level of 1 ppm melamine in some food matrices.

![Figure 1: Typical melamine powder](image)

Following consumption of melamine-contaminated milk powdered products, illnesses were reported in ten (10) different regions in China, including Ganzu, Shaanxi, Ningxia, Jiangsu, Henan, Jiangxi, Hubei, Shandong, Anhui and Hunan. A press release from the Ganzu Health Bureau on September 11, 2008 stated that during the first half of 2008, one hospital in Ganzu treated 16 infants who had kidney stones. The 16 infants varied in age from 5 months to 11 months; some of the cases reportedly developed renal insufficiency. In a record review conducted for the period 2006 to date, hospitals in Ganzu identified a total of 59 cases of kidney stones in infants, including one death. The cases were located in 24 Ganzu counties and most of the cases were from rural areas. All of the cases occurred in 2008; none were identified in 2006 and 2007 [2]. Medical authorities in China indicated that there were 14 cases in which information was available regarding the composition of kidney stones. Twelve of these cases had stones reportedly composed of dihydrate uric acid and urine ammonium. Stones of this composition were reportedly visualized by ultrasound and CT scan, but not by routine x-ray, indicating that some cases may have not been diagnosed [3].

Why melamine contamination of foods?

Melamine is an organic base and a trimer of cyanamide, with a 1,3,5-triazine skeleton (Fig. 2). Like cyanamide, it contains 66% nitrogen by mass and, if mixed with resins, has fire retardant properties due to its release of nitrogen gas when burned or charred, and has several other industrial uses. Melamine is also a metabolite of cyromazine, a pesticide. It is formed in the body of mammals that have ingested cyromazine. It has been reported that cyromazine can also be converted to melamine in plants. It
combines with cyanuric acid to form melamine cyanurate, which has been implicated in the Chinese food export contaminations.

Figure 2: Chemical formula of melamine

Melamine, in its chainlike "polymerized" form, is an industrial chemical and has been used for decades in manufacturing of dishes, plastic resins, flame-retardant fibers, components of paper and paperboard and industrial coatings (Fig. 3). It has only very limited exposure in foods from these food contact substance uses. The estimated level of melamine in food resulting from all of these uses is less than 15 µg/kg (0.015 ppm) [4]. Additionally, trichloromelamine is approved for use as a sanitizing agent on food processing equipment and utensils, except for milk containers and equipment. Trichloromelamine readily decomposes to melamine during its use as a sanitizer.

Figure 3: Typical products for industrial applications of melamine

Only very low levels of melamine in food would be expected to result from this use. There is no approved melamine use in direct addition to human or animal foods, nor is it permitted to be used as a fertilizer anywhere in the world.
Melamine was illegally added to food products in order to increase the apparent protein content. Standard tests such as the Kjeldahl and Dumas tests estimate protein levels by measuring the nitrogen content and multiply the value by either 5.27 or 6.25, depending on the food product to obtain the protein content. Melamine was thus added to mislead government protein content tests after water was added to fraudulently dilute the milk. Because of melamine’s high nitrogen content (66% by mass versus approx. 10-12% for typical protein), it can cause a food to appear to have more protein than it really has. Officials estimate that about 20 percent of the dairy companies tested in China sell products tainted with melamine [2]. It is therefore believed that the Chinese food companies used the nitrogen-based compound in milk products, wheat flour and in other food products to make them appear to have high protein than their true value, hence the contaminations.

**Quality inspection on powdered milk**

After sampling infant powdered milk and liquid milk products, China’s state quality inspection organ expanded its sampling of general and other formula powdered milk products. The results showed that melamine contamination levels in Sanlu’s high iron and zinc formula exceeded 6,196 ppm. According to results released by China’s Administration of Quality Supervision, Inspection and Quarantine (AQSIQ), the sampling was performed on the products from 154 manufacturers, equivalent to 70 percent of the market, and melamine contamination was found in 13 percent of the sampled manufacturers. Besides the Sanlu brand, other products of another two manufacturers were also found to contain over 5,000 ppm melamine [3]. Although the above results were only announced recently, general powdered milk products have already been taken off the shelves after the infant formula contamination was publicly announced.

**Results of toxicological studies**

The observed toxic effects of melamine alone in animals in controlled studies occur only following high-dose exposures. All information thus far indicates that melamine appears to be metabolically inactive or inert (in that it does not readily undergo any type of metabolic change). This information supports a reasonable probability that all species eliminate the originally ingested substance, melamine or its analogues, and not a metabolite. Some species excrete melamine more slowly than other species. For example, fish excrete melamine more slowly than rodents. In addition, whether adverse effects are observed in some species and not others may vary depending on the level of exposure and which melamine analogues are present. Additionally, one of the bases for differential toxicity to these substances is species-specific rates of elimination.

Melamine and its analogues - cyanuric acid, ammelide and ammeline - are assumed to be of equal potency and are referred to collectively as melamine-analogues. Since there is limited information about the toxicity or pathology of the analogues compared
to melamine, it is deemed prudent to make an assumption that these analogues have equal effects. There is evidence available now that when these melamine analogues, especially cyanuric acid, are available in the kidney simultaneously, they can combine to cause renal pathology [4]. The actual extent of renal injury associated with different melamine analogues and the relative concentrations leading to toxicity is still under experimental study.

Preliminary work suggests that lattice crystals composed of melamine and cyanuric acid, and possibly other substances, form in the kidney. This has been shown to take place at various dose levels and is a threshold- and concentration-dependent phenomenon that would not be relevant to low levels of exposure to single melamine-type compounds. The combination of melamine and cyanuric acid has been linked to acute renal failure in cats and dogs. Crystals from cats that died from pet food containing melamine and cyanuric acid were comprised of melamine combined with cyanuric acid.

Melamine-cyanurate crystals have been shown to develop in mice, pigs, cats and fish kidneys when dosed with the combination of both melamine and cyanuric acid. The crystals that form in the pigs and fish are identical to those seen in cats. The crystals are a lattice of six molecules - three of melamine and three of cyanuric acid - held together by hydrogen bonds.

In mammals, the toxicity of melamine alone is low, with a half-life of approximately three to four hours. Available publications report that the most sensitive value for oral 50% lethal dose (LD₅₀ is the amount that kills one-half of the tested animals) is 3,161 mg/kg bw/d in rats. The most recently reported no-observed-adverse-effect-levels (NOAELs) are 63 mg/kg bw/d (13 weeks, oral with feed, in rats); 240 mg/kg bw/d (28 days, oral with feed, in rats); 417 mg/kg bw/d (14 days, oral with feed, in rats); and 1,600 mg/kg bw/d (13 weeks, oral with feed, in mice). In addition, the most sensitive calculated NOAELs for oral reproductive and developmental toxicity in rats are 400 mg/kg bw/d (maternal) and 1,060 mg/kg bw/d (fetal), respectively. The most commonly observed toxic effects in animal experiments where melamine was administered orally include: reduced food consumption, body weight loss, bladder stones, crystalluria, epithelial hyperplasia of urinary bladder, and lowered survival rate. However, no kidney failure or clinical symptoms of kidney failure were observed from these studies [4, 5].

**Melamine safety and risk assessment**

The U.S. Food and Drug Administration (FDA) recently issued the results of its interim safety and risk assessment of melamine and melamine-related compounds in food, including infant formula [6].

A safety/risk assessment is a scientifically based methodology used to estimate the risk to human health from exposure to specified compounds. It is based on available
data and certain scientific assumptions in the absence of data. The purpose of the FDA interim assessment was to identify the level of melamine and melamine-related compounds in food which would not raise public health concerns. The assessment evaluated the melamine exposure in infant formula and in other foods. The safety/risk assessment, prompted by reports of melamine contamination of milk-derived ingredients and finished food products containing milk manufactured in China, was conducted by scientists from FDA’s Center for Food Safety and Applied Nutrition, and the Center for Veterinary Medicine. The FDA reviewed scientific literature on melamine toxicity. The FDA is in the process of identifying a group of experts that would be charged with the task of reviewing the risk assessment and providing guidance regarding the current gaps in scientific knowledge relating to the toxicity of melamine and its analogues [7].

**Infant formula**

The FDA is currently unable to establish any level of melamine and melamine-related compounds in infant formula that does not raise public health concerns. In large part, this is because of gaps in our scientific knowledge about the toxicity of melamine and its analogues in infants, including:

i. the consequences of the continuous use of infant formulas as the sole source of nutrition;
ii. the uncertainties associated with the possible presence and co-ingestion of more than one melamine analogue; and
iii. for premature infants with immature kidney function, the possibility that they may be fed these formulas as the sole source of nutrition and thus on a body weight basis experience greater levels of intake for a longer time than is experienced by term infants [6].

There is too much uncertainty to set a level in infant formula and rule out any public health concern. However, it is important to understand that this does not mean that any exposure to any detectable level of melamine and melamine–related compounds in formula will result in harm to infants.

In food products other than infant formula, the FDA concludes that levels of melamine and melamine-related compounds below 2.5 parts per million (ppm) do not raise concerns. This conclusion assumes a worst case exposure scenario in which 50% of the diet is contaminated at this level, and applies a 10-fold safety factor to the Tolerable Daily Intake (TDI) to account for any uncertainties [7]. The TDI is an estimate of the maximum amount of an agent to which an individual could be exposed on a daily basis over the course of a lifetime without an appreciable health risk.
Other food products affected

The ramifications of the melamine contamination incident continue to reverberate beyond China. Early October, Lotte Koala biscuits were withdrawn from sale in Europe due to raised levels of melamine, after tests in the Netherlands found them to contain 4.98 mg per kilogram, almost twice as much as the EU’s 2.5 mg limit. This prompted the UK government to also recall the biscuits, which had been distributed to Chinese supermarkets and other independent retailers across the country. Meanwhile, the Dutch Food Safety Authority (VWA) released a statement which stressed that the chances of becoming ill from consuming the biscuits were very slim, explaining that “only with daily consumption of two kilograms of the biscuits will children enter the danger zone”. This conclusion is based on a theoretical study conducted by the European Food Safety Authority (EFSA) to test the EU’s established tolerated daily intake level of melamine. The EFSA stated that in its opinion it is safe to consume up to 0.5 mg of melamine per kilogram of bodyweight daily [5].

As a precautionary measure, chocolate manufacturer Cadbury has also recalled 11 Chinese-made products from China, Hong Kong, Taiwan and Australia. The UK's Food Standards Agency announced that certain batches of White Rabbit products from China containing up to 60 times the melamine limit were found on UK shop shelves and had been recalled.

In the United States, the chemical has been found in White Rabbit Creamy Candy imported from China, as well as Blue Cat Flavour Drinks, Mr. Brown instant coffee and milk tea products all of which have been recalled from the market. FDA continues to screen products, collaborate with foreign governments and their regulatory agencies, and monitor reports of contamination from international sources to help ensure that potentially contaminated products from foreign sources are examined if imported into the United States [8]. If products are adulterated because they contain melamine and/or a melamine-related compound, the agency will take appropriate actions to prevent the products from entering commerce.

China is taking steps to reassure countries that are banning its imports following the melamine crisis with the introduction of new safety levels for food and drink. The Chinese government has announced the first rules for allowable levels of melamine considered safe at one part per million for infant formula and 2.5 parts per million for liquid milk, milk powder and food products that contain more than 15 percent milk, stressing that any items containing higher levels will be "prohibited from sale" [9].

Consequences of melamine consumption

Once consumed with any food product, melamine remains inside the kidney, and transforms into stones blocking the tubes (Fig. 4). As a result, pain will be eminent as contaminated persons cannot urinate, leading to swelling of the kidneys. Although
surgery can remove the stones, its presence in the kidney causes irreversible damage, and can lead to loss of kidney function and consequently would require kidney dialysis or lead to death because of uremia. Dialysis, also known as "blood washing" is done by filtering all of the body's blood into a machine and then returning back to the body [4]. The entire diuretic process takes 4 hours and it is necessary to undergo dialysis once for every 3 days for the rest of your life, which is practically impossible no matter the support available.

![Figure 4: Illustration of kidney stones in human ureter and calyces](image)

**Public health advice**

Since the toxicity levels of melamine consumption in foods and its complex compounds formations and derivatives in human organs are still not very well understood, it does not matter how much melamine one consumes in any product, approved or unapproved - the important public health advice to the general public is that “melamine is NOT a food ingredient and therefore foods suspected or identified to contain the chemical should not be CONSUMED”.

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[Image of kidney stones in human ureter and calyces]
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