2008 Chinese Milk Products Crisis

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Abstract

Milk is one of the most important food products for children’s growth and overall health. Melamine (2,4,6-triazine-1,3,5-triamino) is an organic compound used in the manufacture of pesticides, plastics, sanitizers, and disinfectants. Melamine when added to milk increases the overall amount of nitrogen in the milk thus fooling common tests for protein content. Melamine is also extremely harmful when ingested, especially for young children. Sanlu, one of China's largest dairy producers, diluted their milk products with water and added then added melamine to fool the protein tests. Consumption of milk containing melamine in amounts greater than 1 mg/kg can cause kidney failure, bladder cancer and death. Testing milk using the LC-MS/MS and GC-MS/MS methods can reveal melamine contamination. Further actions that can be implemented to reduce milk adulteration include product traceability, corporate transparency, 100% product testing procedures and consistent enforcement of the law.

Keywords: Melamine, milk, renal failure, food safety

2008 Krisis Produk Susu China

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Abstrak

Susu merupakan salah satu produk pangan yang paling penting untuk pertumbuhan anak-anak dan kesehatan. Melamin (2,4,6-triazina-1,3,5-triamino) adalah senyawa organik yang digunakan dalam pembuatan pestisida, plastik, pembersih, dan disinfektan. Melamin ketika ditambahkan ke susu meningkatkan jumlah keseluruhan nitrogen dalam susu sehingga mengelabui tes umum untuk kandungan protein. Melamin juga sangat berbahaya bila tertelan, terutama untuk anak-anak. Sanlu, salah satu produsen susu terbesar di China, mengencerkan produk susu mereka dengan air dan menambahkan melamin untuk mengelabui tes protein. Konsumsi susu yang mengandung melamin dalam jumlah yang lebih besar dari 1 mg/kg dapat menyebabkan gagal ginjal, kanker kandung kemih dan kematian. Pengujian susu menggunakan LC-MS/MS dan metode GC-MS/MS dapat mengungkapkan kontaminasi melamin. Tindakan lebih lanjut yang dapat diterapkan untuk mengurangi pemalsuan susu antara lain penelusuran produk, transparansi perusahaan, 100% prosedur pengujuan produk dan penegakan hukum yang konsisten.

Kata kunci: Melamin, susu, gagal ginjal, keamanan pangan
The 2008 milk products crisis was an illegal food adulteration scandal in the People’s Republic of China involving the addition of melamine to milk and milk products. In December of 2008 the Chinese official media outlet, Xinhua, reported that the Chinese Health Ministry has released information declaring that there have been 300,000 victims of the melamine adulteration including 8 infant fatalities and 865 infant hospitalizations in China alone (“China admits tainted milk victim numbers greater than first reported,” 2008). There are reports that children in other parts of Asia fell ill from ingesting Chinese milk products marketed under 22 different brands (Ingelfinger, 2008). Prior to these disclosures the Chinese government attempted to deny the scandal and then downplay the extent of the problem, which first became publicly known in July of 2008 (Moore, 2008). Four years earlier a similar incident involving watered down milk killed 13 infants as a result of malnutrition (Wikipedia, 2008). The Chinese government, having been disgraced by the earlier incident and the national pride associated with hosting the Olympic Games in August of 2008, was motive to avoid negative attention. Prior to the final admission of the true extent of the problem the government stopped reporting data saying it was not necessary "because it is not an infectious disease, so it's not absolutely necessary for us to announce it to the public" (Wikipedia, 2008).

In an attempt to continue the sale of watered down milk the producers used melamine to increase the apparent protein content of the milk thereby escaping detection based on nitrogen content testing and maximize their profit. Additionally, Sanlu, the largest of the milk product producers involved lobbied the Chinese government to cover up the scandal and to deflect the blame to dairy farmers and milk collection facilities so as to buy time to deal with the impacts of the contamination (Wu, 2008). This contamination event stands as one of the largest intentional food adulteration incidents (Gossner et al., 2009). In spite of the fact that three prominent business leaders were executed and five others jailed, melamine contaminated milk continues to be produced and sold in China (Wikipedia, 2008).

**Melamine**

Melamine (2,4,6-triamino-1,3,5-triazine) is an organic compound with the chemical formula C₃H₆N₆. It was first prepared in 1834 by Liebig. Large scale manufacturing of melamine is done by heating dicyandiamide or urea in the presence of ammonia (Tyan et al., 2009). Most producers use a process based on the following chemical reaction:
Melamine is typically combined with formaldehyde to produce melamine resin, a synthetic polymer that is a fire retardant and heat tolerant (Wise Geek, n.d.). It is used as a fire retardant because its high nitrogen content is released as flame-stifling nitrogen gas when the compound is burned or charred (Sharma & Paradakar, 2010). Other uses include: laminates, plastics, coatings, commercial filters, glues or adhesives, and molded compounds such as dishware and kitchenware (Sharma & Paradakar, 2010). Trichloromelamine (CAS No. 7673-09-8), which decomposes to melamine, is regulated in the USA for use in sanitizing solutions used on food-processing equipment, utensils and other food contact articles, with the exception of milk containers or equipment (21 CFR section 178.1010). The Environmental Protection Agency (EPA) in the US allows for the use of trichloromelamine as a sanitizer and disinfectant on hard surfaces and as a component of a wash solution for fruit and vegetables (Tolleson et al., 2008).

Melamine is also a metabolite of cyromazine which is used as a pesticide and a veterinary drug. Melamine can be degraded via deamination reactions to ammeline, ammelide and cyanuric acid (Sharma & Paradakar, 2010; Tolleson et al., 2008).

\[ 6 \text{NH}_2\text{CO} \rightarrow \text{C}_3\text{H}_6\text{N}_6 + 6 \text{NH}_3 + 3 \text{CO}_2 \]

First, urea decomposes into cyanic acid and ammonia in an endothermic reaction:

\[ (\text{NH}_2\text{CO}) \rightarrow \text{HCNO} + \text{NH}_3 \]

Then, cyanic acid polymerizes to form melamine and carbon dioxide:

\[ 6 \text{HCNO} \rightarrow \text{C}_3\text{H}_6\text{N}_6 + 3 \text{CO}_2 \]

(Wikipedia, n.d.)

Figure 1 - Melamine and it's analogs (Sharma & Paradakar, 2010)
Its legitimate uses and its very low solubility in water can account for the occurrence of trace amounts of melamine in the environment (Wikipedia, n.d.). The United Nations’ food standards body has defined the acceptable amount of melamine in infant formula as 1 mg/kg and 2.5 mg/kg in other foods and animal feeds (Wikipedia, n.d.). In China melamine is also produced using coal as the raw ingredient. The resultant Melamine has few legitimate uses and is commonly called melamine scrap. Melamine scrap is the most common type used for food adulteration because of its low cost and the same 66% nitrogen content as the more common melamine (Wikipedia et al., 2007).

**Melamine as a Protein Mimic**

“Researchers say the adulteration was nothing short of a wholesale re-engineering of milk. Weeks ago, investigators established that workers at Sanlu and at a number of milk-collection depots were diluting milk with water; they added melamine to dupe a test for determining crude protein content” (Xin & Stone, 2008). It is this crude protein testing that is at the root of the problem with melamine adulteration in milk products. The test, known as the Kjeldahl nitrogen analysis, measures the total nitrogen. The results of that test are then multiplied by 6.38 to give the protein equivalent (Barbano & Lynch, 1999). The total amount of nitrogen in milk comes from both protein and non-protein nitrogen (NPN) sources. True protein reflects only the nitrogen associated with protein (Barbano & Lynch, 1999). This

<table>
<thead>
<tr>
<th>Chemical formula</th>
<th>Melamine</th>
<th>Cyanuric acid</th>
<th>Ammelide</th>
<th>Ammeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight (g/mol)</td>
<td>126.12</td>
<td>129.07</td>
<td>128.09</td>
<td>127.10</td>
</tr>
<tr>
<td>% nitrogen (w/w)</td>
<td>66.6</td>
<td>32.6</td>
<td>43.7</td>
<td>55.1</td>
</tr>
<tr>
<td>Appearance</td>
<td>Fine white crystalline powder</td>
<td>White crystalline solid</td>
<td>White powder</td>
<td>White powder</td>
</tr>
<tr>
<td>Melting point (°C)</td>
<td>345–347</td>
<td>360</td>
<td>Decomposes</td>
<td>Decomposes</td>
</tr>
<tr>
<td>Aqueous solubility (mg/l)</td>
<td>3240</td>
<td>2000</td>
<td>70.9</td>
<td>75</td>
</tr>
<tr>
<td>$pK_a$ (dissociation constant)</td>
<td>5.35 (25 °C)</td>
<td>4.74 (25 °C)</td>
<td>9.65 (40 °C)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2 - The physical and chemical properties of melamine and its analogues (Tolleson et al., 2008)
would appear to be a severe limitation but the amount of NPN in milk varies naturally, just like any other milk component. On average NPN represents approximately 6% of the total nitrogen. NPN accounts for about 0.19% of the “protein” in a crude protein value, but may range at the extremes between 0.12-0.25% (Barbano & Lynch, 1999).

Investigators found that workers at Sanlu and at a number of milk-collection depots were diluting the milk with water; they added melamine to fool the test for determining crude protein content. Researchers have since learned that the emulsifier used to suspend melamine, a compound that resists going into solution, also boosted apparent milk-fat content. Sanlu baby formula contained a whopping 2,563 mg/kg of melamine, adding 1% of apparent crude protein content to the formula, says Jerry Brunetti, managing director of Agri-Dynamics in Easton, Pennsylvania. Milk, he notes, is only 3.0% to 3.4% protein. Chen says a dean of a school of food science told him that it would take a university team 3 months to develop this kind of concoction (Xin & Stone, 2008). Compared to the UN standard of 1 mg/kg the amount of protein found in the milk this is nothing short of staggering. Investigators have concluded that unidentified individuals invented a protocol for a premix, a solution designed to fortify foods with vitamins or other nutrients. In this case, it was deadly. Several milk collecting companies were using the same premix, so someone with technical skill had to be training them (Xin & Stone, 2008).

**Health Impacts of Melamine Ingestion**

Pure melamine is not toxic. It is the combination of melamine and cyanuric acid and the resultant melamine – cyanuric salts that are harmful (Moodie, 2008). This simple statement has become something of a controversy. Chinese scientists have fingered only melamine as the toxic agent. Published studies on cats and rats indicate that melamine reacts with cyanuric acid to form melamine cyanurate crystals found in kidney stones. Both melamine and cyanuric acid were present in wheat gluten imported from China during the North American pet-food recall last year; the mixture killed dozens of cats and sickened thousands of other pets. In the tainted milk products, however, Chinese researchers have found only trace amounts of cyanuric acid, a few parts per billion, or roughly 1% of the amount of melamine in the samples. It can be concluded that melamine by itself caused the kidney stones. But one unresolved issue is how high the melamine levels have to be for this to happen (Xin & Stone, 2008). It remains to be seen if the exceedingly high levels of melamine alone caused the kidney stones via the degradation of melamine into cyanuric acid or the similarity of the two molecules caused misleading test results. U.S. chemists found
melamine but not cyanuric acid in their initial attempts to identify the contaminant in pet food, additional testing uncovered significant amounts of cyanuric acid. To answer all the questions about the new melamine cases, we need more data (Xin & Stone, 2008). Later testing utilizing Liquid chromatography-tandem mass spectrometry (LC-MS/MS) points to, but has not been widely reproduced, cyanuric acid being present in the milk (United States Food and Drug Administration, 2008a).

All of the primary hospitalizations and deaths resulted from the formation of melamine-cyanuric acid crystals forming large kidney stones.

Figure 3 - (A) Molecular structure of cyanuric acid, noted for its structural similarity with melamine. (B) Melamine can interact with the isomeric form of cyanuric acid to form melamine cyanurate, explaining the increase in stone formation and toxicity (Hau, Kwan, & Li, 2009)

Acute renal toxicity is best illustrated by a study done in 1953. When sheep were fed a single 100-g oral dose of melamine, all of them died by the 11th day. When a daily dose of 25 to 50 g of melamine was given for 7 to 9 days, again all of the sheep died. They experienced acute renal failure with elevation in blood urea nitrogen and creatinine followed by oliguria preceding death. Examinations revealed crystals in the kidney tubules, nephrosis, and hemorrhagic cystitis. When the exposure was reduced to 10 g/d melamine for 16 to 31 days, two thirds of the sheep died. Again, they experienced loss of appetite, oliguria, and elevation of blood urea nitrogen and creatinine before their death. Postmortem analyses under these conditions also revealed crystal deposition in the kidney (Hau et al., 2009). It is clear that the predominate cause of hospitalization and death was as a result of the formation of
these kidney stones. Melamine stones are soft in nature and those less than 4 mm usually pass spontaneously. Those larger than 4 mm are easily treated medically with ultrasonography (Hau et al., 2009).

The difficulty with the treatment of these stones generally and the lack of precedent during the height of the 2008 crisis and that melamine stones do not show up on plain x-ray films was a deadly combination. Newer diagnostic imaging equipment such as CAT scanners, which easily find the stones, is often not found in rural hospitals in China. According to a report from the Chinese Ministry of Health in December of 2008, 22,384,000 examinations were conducted in infants in China with suspected melamine exposure. By November, 294,000 infants were diagnosed as having urinary tract stones and 51,900 infants were hospitalized in Beijing, a total of 32,530 children were examined by ultrasound. Of all the screened children, 2.9% had urinary tract calculi, of which 4.2% were hospitalized, and 25 of the hospitalized children were subsequently diagnosed as urolithiasis with complication of acute obstructive renal failure. All of the 25 children had consumed the same brand of infant formula, Sanlu, which was contaminated with melamine. The aim of the current study was to describe the clinical and laboratory features, the composition of calculi, the treatment and outcome of the 25 patients with melamine-induced kidney stones complicated by acute obstructive renal failure (Sun et al., 2010). Other hospitals recorded similar experiences. 15,577 infants and children fed with the milk products were screened using ultrasonography. For those found with urinary tract calculi on ultrasonography, urinalysis was done. Among them, 846 with detailed data screened from September 17 to 25 were enrolled for further analysis in this study. They were divided into calculus group (326 children) and non-calculus group (520 children) according to the results of ultrasonography. They included 429 boys and 417 girls, aged from 1 month to 5 years (median, 18 months). Their clinical and laboratory data, ultrasonograms, and treatment results were analyzed (Zhang et al., 2009). There is no mystery as to the cause and the health effect of melamine ingestion, especially amongst those less than 3 years old. Unexpected pathologies and new diseases that afflict mankind are occasionally recognized and can be attributed to a defined causative agent, be it infectious or chemical in nature. Recently, four deaths from exposure to melamine, have been reported in China (Yang & Batlle, 2008). Given the large number of children screened and diagnosed with acute obstructive renal failure it is a small miracle that there were only 8 fatalities in the short term. Long term deaths due to other causes such as bladder cancer remain to be seen (Hau et al., 2009).
Testing for Melamine Contamination

The gold standard for melamine testing in milk products is LC-MS/MS. The test is fast and very accurate (Ibáñez, Sancho, & Hernández, 2009). The United States Food and Drug Administration recommended a similar testing procedure, GC-MS Screen for the presence of melamine, ammeline, ammelide, and cyanuric acid, which is also fast and accurate but costly and involves equipment not found in the typical rural Chinese food distribution center or industry testing lab (United States Food and Drug Administration, 2008b). Commercial Enzyme-Linked Immunosorbent Assay Technology is a less cumbersome test and has been developed into two commercially available test kits. An atrazine ELISA test kit is produced by Abraxis and the EnviroGard Triazine Plate kit was developed by Strategic Diagnostics, Inc. (Garber, 2008). Recently (Mauer et al. 2009) have developed NIR and FTIR based rapid methods of detecting melamine in infant formula powder at a level of 1 ppm (Sharma & Paradakar, 2010). It is evident that the surprising audacity of this contamination scandal had caught the government authorities and public health agencies unprepared for such a massive contamination event. Data for melamine toxicity in humans is still incomplete. However, some success has been achieved in developing analytical methods for melamine estimation in different food products. Several laboratories worldwide are working on various methods for the screening, confirmation and quantitative analysis of melamine and its analogues. LC-MS/MS and GC-MS/MS are the techniques of choice because of their high selectivity and sensitivity (Sharma & Paradakar, 2010).
China, Politics and the Globalization of the Food Supply Chain

Figure 4 - Global distribution of melamine-contaminated products as reported to INFOSAN and published on national official web sites. Light shading indicates countries that reported melamine findings in products originating from China or in products containing ingredients from China. The positive results were transmitted to WHO directly by the country, or by another relevant authority, or via the country’s official web site (Australia, Austria, Belgium, Canada, China, Hong Kong, Macao, Taiwan, Czech Republic, Denmark, France, Germany, Hungary, Indonesia, Ireland, Italy, Japan, Malaysia, Malta, Netherlands, New Zealand, Nigeria, Poland, Republic of Korea, Singapore, Slovakia, Slovenia, Solomon Islands, South Africa, Spain, Switzerland, Thailand, United Kingdom, Tanzania, and United States). Dark shading indicates countries to which import of contaminated products occurred, as declared by the exporting country, and countries that reported the import of contaminated products (Bangladesh, Brunei, Burkina Faso, Burundi, Cambodia, Gabon, Ghana, Lebanon, Myanmar, Palau, Philippines, Russian Federation, Seychelles, Viet Nam, Yemen). Data from WHO Map Production, by public health information and geographic health information systems, WHO 2009; all rights reserved. The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city, or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement (Gossner et al., 2009)

As the map above indicates the reach of melamine contaminated products originating in China is global in nature and has affected both developed and developing nations. The 2008 scandal is obviously not the only large scale food contamination event. However, it does stand out as the one event that was intentional and directly driven by the desire to
artificially raise the value of the food product involved. The following table lists some of the large scale food contamination events occurring in the last few centuries.

<table>
<thead>
<tr>
<th>Year</th>
<th>Incident</th>
<th>Description</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>E. coli contamination of bean sprouts</td>
<td>As of this printing, an outbreak of a rare form of E. coli killed 37 people and sickened more than 3600 in Europe. European Union approved 210 million euros ($288.78 million) in emergency aid for vegetable farmers affected by the crisis.</td>
<td>Sprout farm in northern Germany near Hamburg</td>
</tr>
<tr>
<td>2008-2009</td>
<td>Salmonella outbreak in peanut butter paste</td>
<td>Contaminated peanut butter paste is linked to nine deaths and 637 cases of Salmonellosis in the U.S. and Canada with thousands more illnesses suspected. The incident triggered the largest product recall in U.S. history affecting nearly 4000 products (Layton and Mirull, 2009).</td>
<td>Peanut Corporation of America</td>
</tr>
<tr>
<td>2008</td>
<td>Dioxin in Irish pork dioxin</td>
<td>Large international recall of Irish pork products due to contamination with dioxin. Pork supplies to a total of 23 countries was affected, 13 within the European Union (EFSA, 2008; Hornibrook et al., 2005).</td>
<td>Millstream Power Recycling Limited</td>
</tr>
<tr>
<td>2008</td>
<td>Melamine in Chinese milk products, including milk powder</td>
<td>Contamination of milk and infant formula, as well as other milk-based products due to adulteration with melamine. An estimated 300,000 illnesses were reported and six infants died (Roth et al., 2008).</td>
<td>Chinese milk producers Sanlu Menghai, Yili, and Yaziili</td>
</tr>
<tr>
<td>1986-1987</td>
<td>Mad cow disease</td>
<td>Epidemic of Bovine Sporadic Encephalopathy (BSE) or “Mad Cow” disease in U.K. was suspected to be the cause of variant Creutzfeldt-Jakob Disease (CJD) which affected hundreds of people (Colchester and Colchester, 2005).</td>
<td>Multiple producers in U.K.</td>
</tr>
<tr>
<td>1858</td>
<td>Arsenic poisoning in sweets</td>
<td>An accidental contamination of sweets with arsenic poisoned more than 200 people and resulted in about 20 deaths. This incident led to the passage of the Pharmacy Act 1858 in the UK and legislation regulating the adulteration of foodstuffs (Sheeran, 1992).</td>
<td>Bradford, England</td>
</tr>
</tbody>
</table>

Figure 5 - Selected high profile food safety incidents. (Marucheck, Greis, Mena, & Cai, 2011)

The number of end products that resulted from this single event is displayed in the following flow chart:
Given the singularly disturbing nature of this event and the history of similar Chinese government cover-ups or denials such as the SARS outbreak, the impossibility of economically testing all food products flowing through the global food supply chain, and the reach that a single raw material can have across multiple food products presents massive challenges to food safety. Corporate responsibility, accountability, and government investment in surveillance and monitoring programs is most promising approach to reduce the risk of similar far reaching and intentional food adulteration events and improve food safety generally on both national and international levels.

In China, this presents certain challenges as the very nature of corporate responsibility involves not only private business entities but also the Chinese government at all levels. In China, the boundaries between the state and business are not clear. Corporate Social Responsibility (CSR) must therefore take a broader view in its purview of application when addressing recommendations for China (Dellios, Yang, & Yilmaz, 2009). This applies not only to China but also to all countries, developed or developing, were corporate interests, profit motives, investor pressure, and the “flexible” (corrupt) nature of governments all conspire to place public safety low on the priority list. The antidotes to such things are...
product traceability, corporate transparency, product testability, time, trust, and training. These are common sense ideals that are necessary for the preservation of public welfare through a safe food supply.

CONCLUSION

The safety of our food supply in the era of globalization is too complicated and too distributed to be insured by national level standards and procedures. The fact that stands out loud and clear is that a trust relationship between all entities: producers, distributors, retailers, and oversight agencies is the key element. Without this trust, greed and corruption will from time to time combine to bring about other severe and intentional food safety events.

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