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REVIEW ARTICLE

Melamine Toxicity

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Abstract Melamine contamination of infant formula in China and its health effects highlight the safety of the global food supply especially as it relates to formula-fed infants. Melamine is a widely used industrial chemical not considered acutely toxic with a high LD_{50} in animals. The data available on acute and chronic human exposure to melamine have been limited and extrapolated from animal data. Pet food contamination in 2004 and 2007 showed stone formation and illness in animals when melamine was co-ingested with cyanuric acid. The recent outbreak in infants showed that melamine ingested in large doses may cause stones and illness without significant ingestion of cyanuric acid or other melamine-related chemicals. This may be due to increased uric acid excretion in infants and formation of melamine–uric acid stones. Diagnosis and treatment of infants exposed to melamine requires further study. Clinical signs and symptoms in infants are nonspecific. The stones may be radiolucent and are not consistently seen on ultrasound. The use of alkalinization of the urine for treatment has been proposed, but is of unproven benefit. The FDA and other regulatory agencies have recommended acceptable levels of melamine in foods for consumption. Melamine ingestion has been implicated in stone formation when co-ingested with cyanuric acid, but will cause urinary stones in infants when large amounts of melamine alone are ingested.

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Introduction

The exposure of Chinese infants to melamine-adulterated formula and the resulting health effects draw critical attention to food production safety and its importance in an increasingly global and interactive market. This incident also reinforces Paracelsus' famous caveat, "the dose makes the poison," in that neither significant exposure nor toxicity would have been foreseen from common melamine exposure. For example, in 2004 and 2007, outbreaks of crystalluria and death in animals were caused by contamination of animal feeds with a combination of the stone-forming synergists melamine and cyanuric acid [1–3]. Early animal studies had shown stone formation and bladder carcinogenicity at high doses of melamine [4–9]. In the wake of the illness in animals, new studies suggested little toxicity of melamine or cyanuric acid when ingested individually, but showed that co-ingestion, even at far lower doses than either alone, led to crystal formation [10, 11].

Infants in China fell ill when fed formula containing large amounts of melamine [12–15] without evident co-ingestion of cyanuric acid or other melamine-related compounds (MRCs). This illness was characterized by urinary tract crystals and stones and, less frequently, by renal impairment from tubular injury and obstructive uropathy. The formula contamination event revealed that melamine alone could cause its own toxicity when ingested at larger doses—doses as large as or larger than those of some early animal studies [8]—likely because the melamine combined with endogenous urate to form calculi [14, 15].

These incidents focused attention on melamine, a common chemical previously regarded as safe, and its toxicity when combined with other melamine-like compounds such as cyanuric acid and its health effects alone in formula-fed infants. The outbreaks led to regulatory recommendations concerning melamine and highlighted the fragile nature of food safety, regulation, and oversight in a global economy.

Chemistry and Toxicology

Developed in the 1830s, melamine has widespread uses. It is used in thermoplastics to produce a wide variety of durable and useful products, including dinnerware such as plates and cups. Melamine from these products may migrate to food in trace, nontoxic amounts [16–18]. Melamine is also used in paint and coatings on automobiles, laminates for furniture, and glues for wood and particle board [19]. Cyanuric acid is used as a precursor to make trichlortriazine for swimming pool chlorination, or it is added to pool water to stabilize existing chlorination [20, 21].

Melamine and cyanuric acid are simple molecules (see Fig. 1) produced from urea [6, 19]. Cyanuric acid and the other MRCs ammeline and ammelide may be by-products when melamine is formed [19]. Melamine is high in nitrogen and allegedly was added to animal feeds to increase the apparent protein content in assays that measure nitrogen as a surrogate for protein content [1, 2]. In the tainting of Chinese infant formula, melamine, without cyanuric acid, may have been added to compensate for intentional dilution (to increase saleable amounts) of the market-bound products [13, 14].

Melamine and cyanuric acid or other MRCs may complex when combined. When examining melamine and cyanuric acid together on a slide, a rosette crystal pattern is seen, which may result from hydrogen bonding between melamine and cyanuric acid [10, 22]. It is possible that a similar reaction with urate was the cause of the Chinese formula illnesses. These patterns are also most likely related to the increased crystal formation at sufficient concentrations in the kidney [22–26] (see Figs. 2 and 3).

Human exposure data on melamine are limited, and the available toxicology and toxicokinetic data come from animal studies. In general, melamine and cyanuric acid are considered not acutely toxic because of their large lethal doses (LD_{50}'s). For melamine, these LD_{50}'s range from

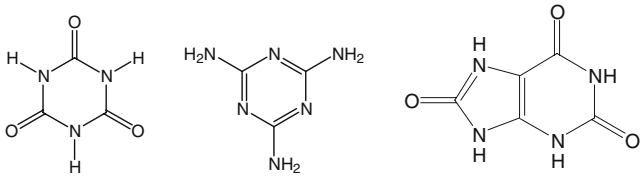

Fig. 1 Cyanuric acid, melamine, and uric acid

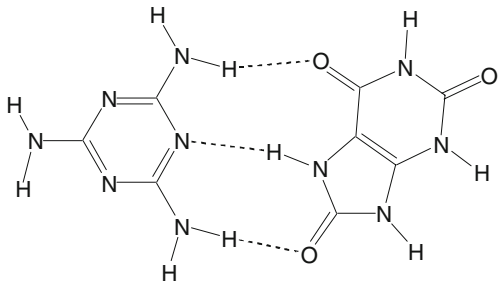

Fig. 2 Possible hydrogen-bonded structure of melamine and urate which may have resulted in stone formation in infants ingesting contaminated formula (redrawn from suggested structures in [15, 22–26])

3.1 g/kg to more than 6.4 g/kg in rats and from 3.2 g/kg to 7.0 g/kg in mice [5, 6]. For cyanuric acid, the LD_{50} is estimated to be 7.7 g/kg in rats [27]. Melamine has a low volume of distribution (0.61 L/kg), a half-life of 4.0 h in pigs and 2.7 h in rats, and little metabolism with substantial renal excretion of unchanged melamine [4, 28]. Cyanuric acid is similarly rapidly eliminated [21].

Several early studies on rats found that melamine (95% to 99.9% pure) can be carcinogenic in high doses when added to their feed. Cancer formed exclusively in the bladder of animals that developed stones, suggesting that the tumors grew as a result of bladder epithelial irritation and hyperplasia, not because of a genotoxic effect of the chemical itself [5, 7–9, 29, 30]. When stones were analyzed in one of the studies, melamine and urate were demonstrated in equal molar amounts [8].

Also of interest are experiments reported in 1966 on sheep, which were conducted to determine whether melamine was a safe, nitrogen-containing feed additive [31]. In these experiments, the sheep were fed moderately high doses (10 g/day) up to 39 days. Investigators concluded that

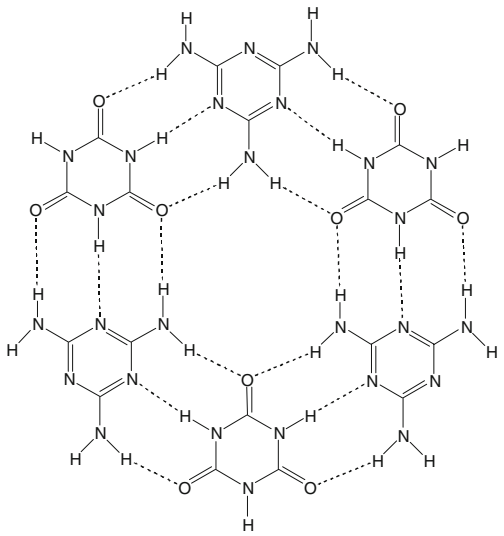

Fig. 3 Hydrogen-bonded structure of melamine and cyanuric acid which may lead to crystal and stone formation in the kidneys (redrawn from suggested structures in [15, 22–26])

melamine was not safe because of the frequent formation of stones resulting from both subacute and chronic administration of melamine.

Two multigenerational studies on animals showed no significant reproductive or developmental effects when melamine was administered, either in doses of 70 mg/kg body weight intraperitoneally on two different days during gestation or in doses up to approximately 1,060 mg/kg body weight in maternal feed during organogenesis (maternal feed concentration 15,000 ppm). However, these studies were very limited and further investigation is needed [6, 32]. Few other data exist in regard to the chronic and reproductive toxicity of melamine.

Pet Food Contamination

In 2004 in Asia, an outbreak of renal failure occurred in many dogs following consumption of a specific dog food. Melamine was later implicated as the source of the outbreak [1]. In the USA during early 2007, the Food and Drug Administration (FDA) recalled certain pet foods after they caused many dogs and cats to become sick or die after developing urinary crystals. More than 100 potentially contaminated products were recalled [1–3]. Contaminated vegetable protein products imported from China were sold as "wheat gluten" and used as ingredients in pet foods. Non-toxic amounts were also consumed by some livestock used for human consumption. The feed was recalled and destroyed [2]. The pet food tested from this outbreak contained melamine and cyanuric acid [33, 34]. The amounts of melamine found in some tested food ranged from 10 to 3,200 ppm (1 ppm is equivalent to 1 mg/kg food source); animals received an estimated dose of 360 to 430 mg kg^{-1} day^{-1} from the contaminated food [11, 33]. Histological investigations showed that melamine and cyanuric acid were present in the tissues of animals fed these products [1, 33, 34]. Stones in the distal tubules of affected animals also contained melamine and cyanuric acid.

Several animal studies were performed to determine the safety of melamine and cyanuric acid. In one study, cats were fed melamine, cyanuric acid, or both at increasing doses. The cats fed only one compound had no renal failure or urine crystals at doses of 181 mg/kg body weight for melamine or at doses of 243 mg/kg body weight for cyanuric acid. However, the cats fed both compounds developed urinary stones at a dose of 32 mg/kg body weight of melamine and cyanuric acid [11]. Two other animal studies showed that melamine and cyanuric acid when administered together at 400 mg kg^{-1} day^{-1} produced renal stones, but when they were administered separately, no stones formed [10, 33]. Based on these studies, melamine and cyanuric acid appeared to be relatively safe in low doses when administered individually, but when combined caused stone formation.

Infant Formula Contamination

In the 2008 outbreak of illness in China, high melamine levels in infant formulas were implicated as the cause for urinary stones in formula-fed infants [12]. An estimated 294,000 infants in China were affected, with more than 51,900 hospitalizations and six deaths [13]. Of the affected children, 99% were younger than 3 years old and developed symptoms 3 to 6 months after ingesting the formula [35], with formula being their sole or major food source. Stones that were later analyzed showed melamine–urate crystals in near equimolar amounts with no evidence of cyanuric acid [14, 36, 37]. Compared with adults, infants excrete five to eight times the amount of uric acid, a potential predisposing factor toward melamine–urate stone formation [38–41]. Infants with inborn errors of metabolism, leukemia, lymphoma, or other illness that increases uric acid secretion potentially may have increased risk of stone formation from melamine.

Levels of melamine in one company's line of infant milk formula products were up to 6,197 ppm of melamine, which was much higher than levels found in other milk products and secondarily contaminated foods [13, 35]. Comparatively, melamine was found in one US infant formula at 0.137 ppm and cyanuric acid in another at 0.247 ppm [42]. The levels in the two US products were below the 1 ppm current standard for infant formula and were <1/10,000 of the melamine concentrations in many of the contaminated Chinese infant formulas. After the outbreak in China, a Hong Kong study of 3,170 patients younger than 12 years who were ingesting an estimated dose of 0.01–0.21 mg kg^{-1} day^{-1} of melamine did not show an increased incidence of kidney stones [41].

Acceptable Melamine Consumption

Large amounts of melamine were found in the tainted Chinese infant formula. A typical infant weighs 3 kg and ingests about 0.15 kg of dry formula per day [42]. Assuming this formula is tainted with the highest reported melamine level of 6,197 ppm, the infant would ingest approximately 930 mg/day, or 310 mg kg^{-1} day^{-1}.

Based on 50 healthy participants aged 6 years and older, approximate background human intakes of melamine were estimated from a median urinary concentration of 3.9 μg/L (Centers for Disease Control and Prevention preliminary data reported to FDA). Assuming no metabolism and steady state, the estimated daily intake would compute to

be about 4 μg, or only about 0.00006 mg kg^{-1} day^{-1}, for a 60-kg person.

Based on a 13-week rat study, the FDA determined a tolerable daily intake (TDI) of 0.63 mg kg^{-1} day^{-1} of melamine, or 2.5 ppm in food, as a safe level of consumption for adults. This TDI includes a 100-fold safety factor [42]. FDA has set a tenfold lower limit for infants, making a total of a 1,000-fold safety factor for a TDI of 0.063 mg kg^{-1} day^{-1} of melamine. Based on a 3-kg infant ingesting 0.15 kg of powdered formula per day, the concentration in formula equivalent to the TDI would be 1.26 ppm melamine. This number was rounded to1 ppm melamine as a tolerance limit for US infant formulas. Other countries have adopted similar levels (see Table 1) [14, 43–45].

Stone Formation

Urinary tract stones in infants are generally rare (1/1,000 to 1/7,600 of hospital admissions). Genetics may be a risk factor because 40% of pediatric patients who develop stones have a relative who also develops kidney stones. Other risk factors may include dehydration, increased dietary intake of calcium or oxalate products, or infections [46, 47].

Common calculi include calcium oxalate, uric acid, struvite (Mg ammonium phosphate), and cystine stones [46]. Approximately 30% to 50% of urinary tract stones in children are calcium stones attributable to familial and specific inborn causes of hypercalciuria. Calcium oxalate stones are usually due to increased secretion of oxalate in the urine, which can occur in about 20% of pediatric patients with stones and may have a variety of etiologies, including malabsorption, increased vitamin C intake, increased intake of oxalate containing foods, or an autosomal recessive disorder in which oxalate is over-produced by the liver. Children who have increased urinary tract infections may be at an increased risk of developing struvite stones. Citrate is a urinary stone inhibitor and prevents precipitation of many calcium-based stones. Low dietary citrate intake may be a risk factor in some pediatric patients and can be treated with potassium citrate to increase the urinary amount of citrate excreted and increase the pH [46, 47]. Cystine stones are usually the result of an autosomal recessive condition of abnormal renal tubular transport of cystine and account for about 6% of kidney stones in pediatric patients.

Table 1 Melamine TDI doses and tolerance levels for food set by the US and other countries and the World Health Organization [14, 43–45]

Organization	TDI (mg/kg body weight/day)	Tolerance limit in food (ppm)[a]
Federal Drug Administration (USA)	0.063	1
World Health Organization	0.2	
Health Canada	0.2	0.5
European Food Safety Authority	0.5	

[a] 1 ppm=1 mg/kg food source per day

Increased uric acid secretion predisposes patients to stone formation, especially in acidic urine. Pediatric patients with uric acid stones often have a disproportionately lower urine pH and may have increased uric acid production from an inborn error of metabolism or other etiology. Urinary pH<5.5 increases the risk of uric acid stones because of insolubility of uric acid at this lower pH. Alkalinizing urine tends to be more effective in decreasing crystallization from uric acid in the urine than does lowering the uric acid concentration. Urine alkalinization has been performed using potassium citrate [48].

Diagnosis based on physical exam and presentation of the effected Chinese infants was often problematic. Signs and symptoms ranged from vague and nonspecific to those more typical of stone presentations. Unexplained crying, vomiting, dysuria, passing of stones or crystals in the urine, high blood pressure, anuria, oliguria, and edema were reported [13]. Hematuria was not consistently noted [37].

Multiple imaging modalities including CT and ultrasound were used during the outbreak with mixed results. Calcium oxalate stones are radiopaque, struvite and cystine stones are less so, and uric acid stones are radiolucent. Melamine stones also appear to be radiolucent [49]. Evaluated stones ranged in size from small and sand-like to as large as 9 mm [37, 41, 50]. Ultrasound for detection of stones in China and Taiwan yielded mixed results [37, 49, 50].

Treatment for stones includes stopping the source of exposure, increasing fluid intake, and controlling pain. Standard treatments, including dialysis, may be needed for acute renal failure. Surgical removal or invasive procedures may be necessary for larger stones [51]. As melamine stones were associated with urate, alkalinization of the urine has been suggested to help prevent or dissolve current stones as described above [13, 37, 52]. Others have reported that increasing or decreasing the urine pH may increase risk of stone formation [36]. Further study is needed to define optimal management.

Conclusion

Melamine, an industrial compound, was added to animal feed and infant formula allegedly to boost their nitrogen level and apparent protein content. Melamine causes stone formation when ingested chronically in excessive doses. Pediatric patients, due to relatively increased uric acid

excretion, may be at increased risk when formula is their sole or major source of food. When combined with cyanuric acid, melamine causes stones at low doses. FDA and other regulatory agencies have published advisories of the acceptable levels of melamine in foods.

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