

- Consumption of melamine-contaminated infant formula has been linked to urinary tract ailments in nearly 300,000 infants and the deaths of six infants in China in 2008. The high melamine content of certain brands of Chinese infant formula (e.g. Sanlu) has been implicated as the prime causative agent in the outbreak of pediatric renal disease. Since September 2008, no more child deaths have been reported from melamine-contaminated milk products. Melamine causes crystalluria which may lead to irritation of the urinary tract epithelium, kidney stones, and acute kidney failure.

QUICK FACTS

- Infant formula manufactured in China and available for purchase at Asian markets in the US could still pose a risk to infants.
- U.S. manufactured formula is considered safe for consumption at this time.
- Infants who recently emigrated from China and have a clinical picture suggestive of melamine-induced nephrotoxicity should be evaluated and referred to a pediatric nephrologist.
- Avoid milk and milk containing products that could originate from China.
- An expert body from the American Society of Pediatric Nephrologists does not recommend testing on asymptomatic infants who may have been living in the areas where infant exposure and disease occurred in China.
- An environmental health consultation can be obtained from a pediatric environmental health specialty unit by calling 888-347-2632 or going to www.pehsu.net

What kinds of food may be contaminated with melamine?

Prior to August 6, 2008 melamine was illegally added to milk in China to fraudulently inflate the protein content. Melamine contaminated milk was used in the manufacture of infant formula and as an ingredient in various dairy products and other foods.

Food produced in China found to have melamine contamination:

- Infant Formula (before Aug 6, 2008)
- Foods with milk-derived ingredients
- Eggs
- Pet Food

The detection of melamine in a variety of human and animal foods suggests that melamine contamination of Chinese food products may still exist. Recent testing of infant formula manufactured in the U.S. has identified only trace concentrations. These are up to 10,000 times lower than concentration in Chinese formula associated with infant illness and ten-fold lower than the FDA acceptable level for melamine in infant formula.

What is melamine?

Melamine is a synthetic compound used in plastic tableware, flame retardants, paper, paperboard, and industrial coatings. Melamine is a metabolite of a pesticide (cryomazine) and a decomposition product of a food equipment sanitizer (trichloromelamine). These are estimated to contribute negligible amounts of melamine to food. Melamine is not approved in the U.S. as a fertilizer, as it is in some other

countries, nor is it approved for use in human or animal food.

Why are infants a high risk group for melamine-related health effects?

Infants may consume contaminated formula as their primary food source. Older children and adults who consume a variety of foods will receive less melamine per unit of body weight (i.e. lower dose) from a contaminated source. The smaller lumens of the infant urinary tract, tubules and blood vessels may lead to easier irritation of tubular and urinary tract walls, easier occlusion by uroliths, and proportionately greater compression of blood vessels by urinary stones. This may explain why the risk of renal disease was greatest among premature infants in the Chinese epidemic.

Infants have a lower glomerular filtration rate than older children and adults. This may decrease the flow of urine through the tubules thus predisposing crystals to bump together and co-crystallize. Lastly, it is possible that uric acid may co-crystallize with melamine in infants (Ogasawara 1995). The kidney stones analyzed in affected Chinese children were primarily co-crystals of melamine and uric acid. Uric acid is excreted into the urine at a much higher rate in infants relative to older children and adults. The fractional excretion rate of uric acid is 61% in 29-33 week old infants and decreases to 12% at 3-4 years of age (Baldree and Stapleton, 1990).

What are the health effects of ingesting melamine?

- **Acute**
The acute toxicity of melamine is low. In the presence of its analogue and common co-contaminant, cyanuric acid, toxicity is much higher. Both are excreted via the kidneys without metabolism with half-lives estimated to be a few hours. Each may form crystals in

urine. When both are present in urine, they can combine as melamine cyanurate complexes. This results in highly insoluble, larger, and more numerous calculi than either of the two chemicals alone. These irritate the urinary tract lining and may lead to obstruction and uremia. Melamine cyanurate crystals have been implicated as the cause of renal toxicity in cats and dogs resulting from contaminated pet food in 2007.

The signs and symptoms of acute melamine exposure (high dose over several days) and presumably in the presence of a co-crystallizing substance, are related to acute urolithiasis or cystitis (e.g. anorexia, hematuria, abdominal pain, oliguria, uremia).

- **Chronic**
Longer-term exposure (weeks to months or years) to melamine results in the same adverse effects but the presenting signs may be less severe. Animal studies suggest that long-term exposure can also result in urinary tract cancer due to epithelial irritation, and subsequent inflammation, from crystals and stones.

Retrospective studies of children suspected of ingesting melamine-contaminated milk in Beijing, Taiwan and Hong Kong report that most children with confirmed nephrolithiasis had normal renal function tests. Similarly, urinalysis was not an adequate screening test for melamine-associated urinary stones. Finally, children with melamine-related nephrolithiasis often did not display classic signs and symptoms and were largely asymptomatic.

The long-term effects from exposure to melamine in the asymptomatic child and the long term health consequences of early life melamine related kidney disease are unknown. These are key data gaps that need to be addressed.

What is an appropriate medical evaluation for melamine exposure?

The most important action is to stop any ongoing exposure and continue evaluation based on symptoms.

The need for medical evaluation of asymptomatic but potentially melamine-exposed infants and children, such as those who have recently emigrated from China to the United States, is not clear. Currently, an expert committee from the American Society of Pediatric Nephrologists does not recommend testing on asymptomatic infants who may have been living in the areas where infant exposure and disease occurred in China (reference below).

While screening tests for renal function in internationally adopted children are not uniformly recommended, a complete physical examination including measurement of blood pressure, assessment of general nutritional status and hydration should be considered. Tests for melamine in blood serum and urine are investigational, not commercially available, and of limited clinical utility given the rapid elimination from the body once exposure has ceased.

Melamine toxicity should be evaluated in any infant or young child with the appearance of urinary system signs or symptoms AND suspected or known exposure to melamine-contaminated formula/food products.

The medical assessment of the affected child might include the following studies:

- renal function test - serum electrolytes, urea nitrogen and creatinine
- urinalysis (microscopic evaluation of hematuria)
- renal imaging - ultrasound (to rule out obstruction)
- consultation with a pediatric nephrologist for those children in whom melamine exposure and potential renal injury are confirmed.

Evidence to date suggests that ultrasound is the most sensitive diagnostic test for detecting stones in symptomatic and asymptomatic patients with a history of exposure to tainted milk products. Recommendations and more detailed information are available from the American Society of Pediatric Nephrologists.

What about melamine found in domestic food products?

The widespread use of melamine in applications involving food (pesticides, food-packaging materials such as plastics, adhesives and melamine-formaldehyde resins) has resulted in a near ubiquitous presence of trace amounts of melamine throughout the food-chain. This includes trichloromelamine, used in the USA in sanitizing solutions for food-processing equipment, which readily decomposes to melamine. However, the conservative estimated intake from all sources due to migration from plastics that come in contact with food is well below the tolerable daily intake (TDI) of 0.2 mg/kg body weight/day set for the whole population including infants (WHO, 2008). In contrast, the dietary exposure that occurred from intentionally contaminated infant formulas in China was 40 to 120 times the TDI, explaining the dramatic health outcomes in Chinese infants.

What regulatory actions are being taken?

Using standard and similar risk assessment approaches the food regulatory agencies in Canada, the European Union, Australia / New-Zealand and Hong Kong established a tolerance for melamine in

infant formula varying from 0.5 to 2.5 parts per million (ppm). FDA has established a new infant formula tolerance of melamine alone or cyanuric acid alone, at or below 1 ppm. Updates and revisions will continue. For more information on public health reference levels and guidelines, see the resources listed below.

References and Resources for More Information

American Society of Pediatric Nephrologists. Statement: Kidney Disease from Powdered Infant Formula-based Melamine Exposure in Chinese Infants.

[http://www.aspneph.com/ASPStatement%20Melamine%20Oct22_cbl%20\(3\).pdf](http://www.aspneph.com/ASPStatement%20Melamine%20Oct22_cbl%20(3).pdf)

Baldree LA, Stapleton FB. Uric acid metabolism in children. *Pediatr Clin North Am* 1990; 37:391-418.

Brown CA et al. Brief communications. Outbreaks of renal failure associated with melamine and cyanuric acid in dogs and cats in 2004 and 2007. *J Vet Diagn Invest* 19:525–531 (2007)

University of Washington Center for Adoption Medicine. Melamine and Chinese adoptees.

<http://www.adoptmed.org/topics/melamine-and-chinese-adoptions.html>

CDC - Melamine in Chinese-Manufactured Infant Formula Oct. 2, 2008

<http://wwwn.cdc.gov/travel/contentMelamineChina.aspx>

US Food and Drug Administration web page on Melamine Contamination in China – contains a listing of product recalls related to melamine contamination

<http://www.fda.gov/oc/opacom/hottopics/melamine.html#company>

FDA Advisory on Melamine contamination. September 26, 2008

<http://www.fda.gov/bbs/topics/NEWS/2008/NEW01891.html>

FDA Interim Melamine and Analogues Safety/Risk Assessment May 25, 2007

<http://www.cfsan.fda.gov/~dms/melamra.html>

FDA Updates Health Information Advisory on Melamine Contamination September 23, 2008.

<http://www.fda.gov/bbs/topics/news/2008/new01889.html>

FDA Update Interim Safety and Risk Assessment of Melamine and its Analogues in Food for Humans.

November 28, 2008. <http://www.cfsan.fda.gov/~dms/melamra4.html>

IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer. 73: 329-338, 1999

<http://monographs.iarc.fr/ENG/Monographs/vol73/mono73-17.pdf>

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Ogasawara H, Imaida K, Ishiwata H, et al. Urinary bladder carcinogenesis induced by melamine in F344 male rats: correlation between carcinogenicity and urolith formation. *Carcinogenesis* 1995; 16:2773-7

WHO Melamine-contamination event, China, September - October 2008
http://www.who.int/foodsafety/fs_management/infosan_events/en/index.html

World Health Organization. Melamine and Cyanuric acid: Toxicity, Preliminary Risk Assessment and Guidance on Levels in Food 25 September 2008
http://www.who.int/foodsafety/fs_management/Melamine.pdf

World Health Organization. Toxicological and health aspects of melamine and cyanuric acid: report of a WHO expert meeting in collaboration with FAO, supported by Health Canada, Ottawa, Canada, 1-4 December 2008.
http://www.who.int/foodsafety/fs_management/infosan_events/en/index.html.

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