



Intentional and Economically Motivated Adulteration – Melamine Paradigm

Comments by
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Science Board to the FDA Advisory Committee
October 31, 2008



Outline

- How we first learned about melamine
- Current situation – melamine contamination of milk-derived ingredients and finished food products containing milk manufactured in China
- What have we learned about melamine and melamine + cyanuric acid
- Information needs



How we Learned About Melamine

Spring 2007

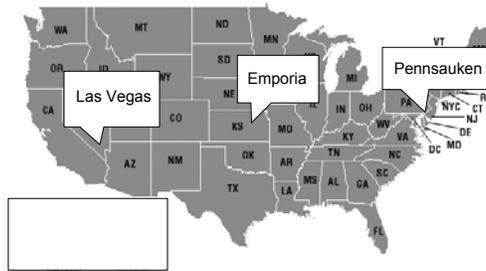


Public Attention

- Consumers turned to FDA/CVM for advice
- 18,700 calls for FDA Complaint Coordinators in 11 weeks
 - typically 4,600-6,000 a **year** on all FDA-regulated products
- FDA held 13 media teleconferences

The Recall Facts

- March 16, Menu Foods begins recall
 - 60 million containers, “cuts and gravy”
- Small number of cat, dog deaths
- Wheat gluten suspected

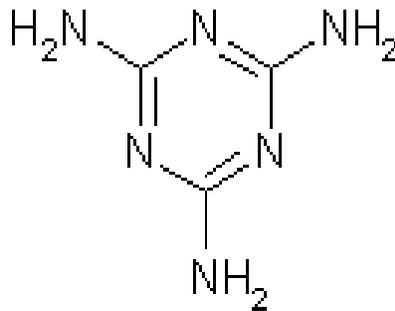


Discovering Melamine

- FDA announced finding on March 30
- Melamine in food, kidneys/urine of cats that died
 - presence of melamine causes food to be adulterated
- Second importer found melamine in rice protein
 - April 18, 2007: Began recall of 155 metric tons of rice protein

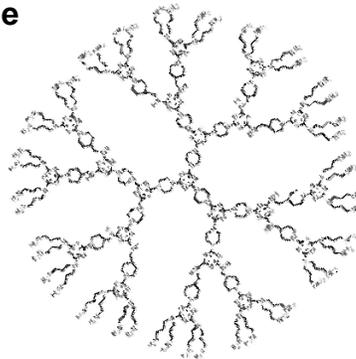
Mela Who?

- **1,3,5-triazine-2,4,6-triamine**



Industrial uses of Melamine

- **Slow acting fertilizer?**
- **Melamine resin**
 - Combined with formaldehyde
 - Plastics
 - Resins
 - Glues
 - Textile dyes
- **Yellow colorant**
- **Pharmaceuticals**



Neerman et al 2004

Melamine Method

- No method to detect melamine in pet food
- Several components of FDA jointly developed method
 - gas chromatography/mass spectrometry
 - most labs can do



Spilling Over to Food-Animals

- Pet food scraps to hog, poultry feed
 - contained melamine, creating food safety concern



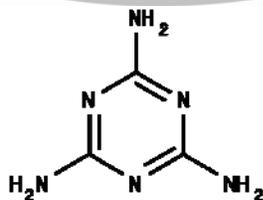


Risk Assessment

- **USDA/FDA developed risk assessment**
- **Low human food safety risk**
 - due to dilution factors
 - 132 lb. person must eat 800 lb. of contaminated meat daily for risk
- **Peer reviewed**
- **Subject to public comment**
- **Presented to the Science Board on 6/07**



The Current Situation



http://www.telegraph.co.uk/telegraph/multimedia/archive/00980/CHINA-MILK-460summa_980965c.jpg

2008 – China – MELAMINE



Infant
Formula

<http://www.nytimes.com/2008/09/13/world/asia/13milk.html?ref=world>

Current Situation*

- ~ 53,000 ill infants, most < 2 yrs old
- ~ 13,000 hospitalizations
- 4 deaths (1 unconfirmed as melamine - caused)

* According to Chinese government officials



China arrests 6 for role in contaminating milk; more than 3,600 kids still hospitalized

By HENRY SANDERSON | Associated Press Writer 10:27 AM CDT, October 23, 2008



<http://www.chicagotribune.com/news/nationworld/sns-ap-as-asia-tainted-milk,0,781111.story>



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Candy with melamine, chemical in Chinese milk, found in Conn.

THE ASSOCIATED PRESS

Updated Wednesday, October 1st 2008, 4:48 PM

HARTFORD, Conn. — An industrial chemical blamed for sickening thousands of infants in China has been found in candy in four Connecticut stores this week, a state official said Wednesday.

Connecticut Consumer Protection Commissioner Jerry Farrell Jr. said Wednesday that tests on White Rabbit Creamy Candy found melamine in two New Haven stores, a West Hartford market and an East Haven store, days after the



Chinese food safety personnel check on the



1,500 Chinese raccoon dogs die from tainted feed

By GILLIAN WONG
ASSOCIATED PRESS WRITER, October 20, 2008



http://seattlepi.nwsource.com/national/1104ap_as_china_tainted_milk.html?source=mypi



New methods posted Oct 8, 2008 Melamine and Cyanuric Acid



U.S. Food and Drug Administration



CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

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Determination of Melamine and Cyanuric Acid Residues in Infant Formula using LC-MS/MS

Sherri Turnipseed¹, Christine Casey¹, Cristina Nochetto², David N.
Heller²



FDA News

FOR IMMEDIATE RELEASE
October 3, 2008

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888-INFO-FDA

FDA Issues Interim^{*} Safety and Risk Assessment of Melamine and Melamine-related Compounds in Food

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

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 safety/risk assessment was to identify the level of melamine and melamine-related compounds in food which would not raise public health concerns. The interim safety/risk 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.

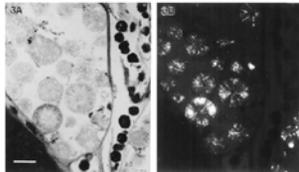
^{*}Subject to peer review.



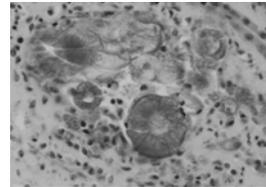
What Have We Learned about Melamine and Melamine + Cyanuric Acid

Cause of Injury

- Working hypothesis – similar to human acute urate nephropathy
 - crystals similar to uric acid crystals
 - made of melamine, cyanuric acid



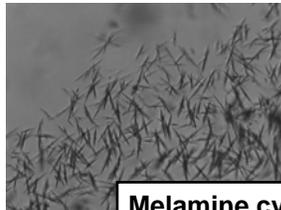
Urate crystals formed in a worm
Photo courtesy of Charles C. Lambert
Department of Biological Science, California State
University Fullerton, and Friday Harbor Laboratories,
Friday Harbor, Washington



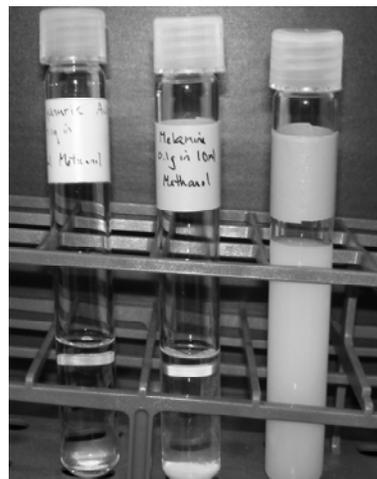
From case involving dog
Photo courtesy of DOPAH, MSU

Crystal Formation

- Combining melamine, cyanuric acid in laboratory
- Instantly forms crystals

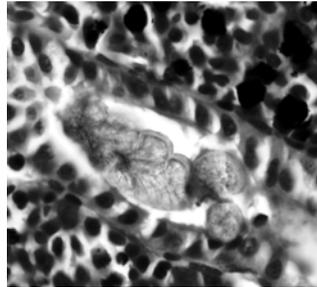


Melamine cyanurate



Hypothesis

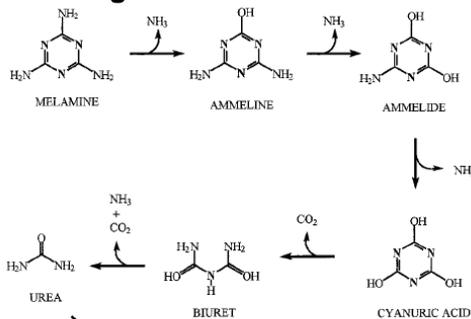
- Melamine:cyanurate crystal nephropathy similar to uric acid nephropathy in humans
 - crystals create obstructions
- Similar morphology



Gold-brown crystals in trout kidney tubule

Cyanuric Acid

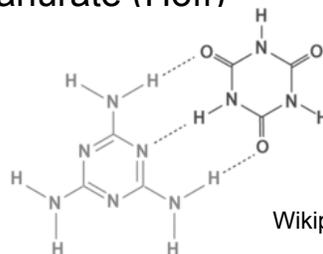
- Melamine analogue
 - Incomplete manufacture?
 - Bacterial degradation?
 - Reaction during manufacture?



Shelton et al. 1997

Cyanuric Acid

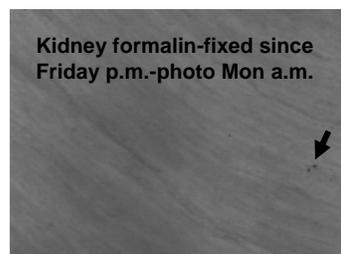
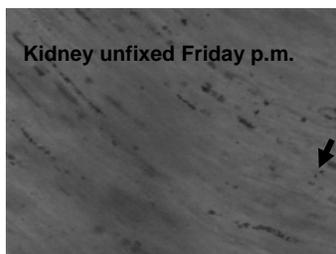
- Polymerizes with melamine
 - pH = 5.8
 - 50.58% cyanuric acid
- Detected in urinary crystals
 - ≈ 30% melamine/70% cyanurate (Hoff)



Wikipedia

Response to Formalin

- Unfixed sample on Friday shows crystals
- Tissue flooded with formalin, left on microscope
- Crystals not visible on Monday





J Vet Diagn Invest 19:616-624 (2007)

Assessment of melamine and cyanuric acid toxicity in cats

Birgit Puschner,¹ Robert H. Poppenga, Linda J. Lowenstine, Michael S. Filigenzi,
Patricia A. Pesavento

Abstract. The major pet food recall associated with acute renal failure in dogs and cats focused initially on melamine as the suspect toxicant. In the course of the investigation, cyanuric acid was identified in addition to melamine in the offending food. The purpose of this study was to characterize the toxicity potential of melamine, cyanuric acid, and a combination of melamine and cyanuric acid in cats. In this pilot study, melamine was added to the diet of 2 cats at 0.5% and 1%, respectively. Cyanuric acid was added to the diet of 1 cat at increasing doses of 0.2%, 0.5%, and 1% over the course of 10 days. Melamine and cyanuric acid were administered together at 0%, 0.2%, 0.5%, and 1% to 1 cat per dose group. No effect on renal function was observed in cats fed with melamine or cyanuric acid alone. Cats dosed with a combination were euthanized at 48 hours after dosing because of acute renal failure. Urine and touch impressions of kidneys from all cats dosed with the combination revealed the presence of fan-shaped, birefringent crystals. Histopathologic findings were limited to the kidneys and included crystals primarily within tubules of the distal nephron, severe renal interstitial edema, and hemorrhage at the corticomedullary junction. The kidneys contained estimated melamine concentrations of 496 to 734 mg/kg wet weight and estimated cyanuric acid concentrations of 487 to 690 mg/kg wet weight. The results demonstrate that the combination of melamine and cyanuric acid is responsible for acute renal failure in cats.



Information Needs

Information Needs

- **Toxicology studies that investigate the synergistic action of combinations of melamine, cyanuric acid and possibly other analogs on kidney crystal formation in mammalian species**
- **Pharmacokinetic studies in mammalian species that investigate the clearance rates and potential for kidney melamine cyanurate crystal formation upon ingestion of melamine and cyanuric acid feed separately at varying time intervals**

Information Needs – cont'd

- **Information from the Chinese medical authorities on the estimated levels of exposure to melamine and cyanuric that caused renal failure, death and/or hospitalization in Chinese infants**
- **Development of rapid ELISA test kits, lateral flow devices or other tests that can rapidly and inexpensively screen for both melamine and cyanuric acid**
- **Identifying and surveying for other likely economic adulterants such as urea and urea ammonium nitrate fertilizers that may be used to replace melamine and cyanuric acid as cheap, readily available and profitable nitrogen containing adulterants that can be used to boost the apparent protein content of products.**

Information Needs – cont'd

- **Data on “background” amounts of melamine in a wide variety of food products and raw materials.**
- **Ongoing surveillance of a wide variety of protein commodities and a database of test results from both industry and regulatory laboratories**

Conclusion

- **Global connections make safeguarding food supply more complex**
- **FDA showed how capable it was during pet food recall, investigation**
 - **in uncovering new syndrome**
- **We welcome the Science Board’s assistance/ feedback as we continue to address issues related to contamination of food and ingredients with melamine and its analogues**