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Melamine and the History of Adulteration of Food

Comments by

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Government-University-Industry Research Roundtable Meeting

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Outline

- History of food adulteration
- 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



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History of Food Adulteration



Adulteration

- Adulterate is defined by Merriam-Webster Dictionary as “to make impure by the addition of a foreign or inferior substance or element; *especially*: to prepare for sale by replacing more valuable with less valuable or inert ingredients” [which thus leads to **adulteration**].
- In relation to food, we can take this to mean the unintentional or deliberate addition of foreign substances; being contaminated with bacteria, viruses, parasites, toxins, chemical contaminants, and metals.



Adulteration of Food

- Throughout history food has been subject to adulteration, most often by people and corporations that prize profits above the health of consumers
- Modern science has both helped and hindered food fraudsters – increasing the sophistication of scams but also the means to detect them



Adulteration of Food

- The deliberate adulteration of food was a common and, until 1860, virtually an unrestricted practice
- Typically, conditions for the processing and sale of foods were unsanitary
- One of the most prominent cases of adulteration in the 19th century was the swill milk affair



Food Adulteration

Common Examples in the 19th Century

- **Cinnamon** that was a mixture of cassia, almond shells, corn, wheat, allspice, and beans
- **Yellow colored candies** poisoned with lead
- **Ground allspice** mixed with breadcrumbs, woody tissues, and tumeric
- **Sugar** adulterated with glucose
- **Lard** preserved with caustic lime and alum
- **Cheese** containing mercury salts
- **Ground coffee** thinned with chicory powder
- **Honey** cleverly disguised as glucose (with just a hint of the real stuff left in to give the right smell)
- **Milk** was watered down (often with contaminated water)



Post-Civil War

- Shift from predominantly agricultural society to an industrial nation
- With big industry came new technologies – new ways of tampering with food
- Industrial chemists were hired to invent new aids to deception (e.g., flavors, crispers for flabby foods, softeners for hard food)



Significant Legislation that Addressed Food Adulteration

- 1860 – Britain passed its first General Administration Act making it illegal to sell adulterated food as pure
- 1872 – Britain passed an Act making it an offense to sell a mixture containing ingredients designed to add weight or bulk, unless explicitly stated as such
- 1875 – The Sale of Food and Drugs Act prevented the addition of harmful ingredients to foods and drugs



Towards the End of the Century...

- Antifederalists opined that food regulation was a local matter belonging to the states
- Federalists, like **Harvey Wiley**, believed that safe food could not be guaranteed unless there were federal laws to regulate trade in food between states
- Eventual triumph of the federalists led to the Pure Food and Drug Act of 1906



Even Today....

Consumers and governments must recognize that there is still continuous pressure on companies to make money by substituting nutritious, genuine ingredients with adulterants



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How we Learned About Melamine

Spring 2007



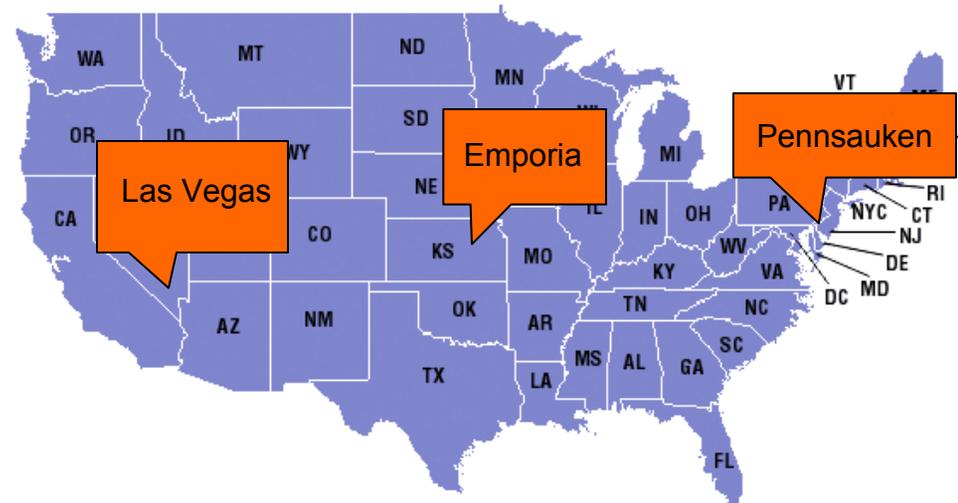
Public Attention

- 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





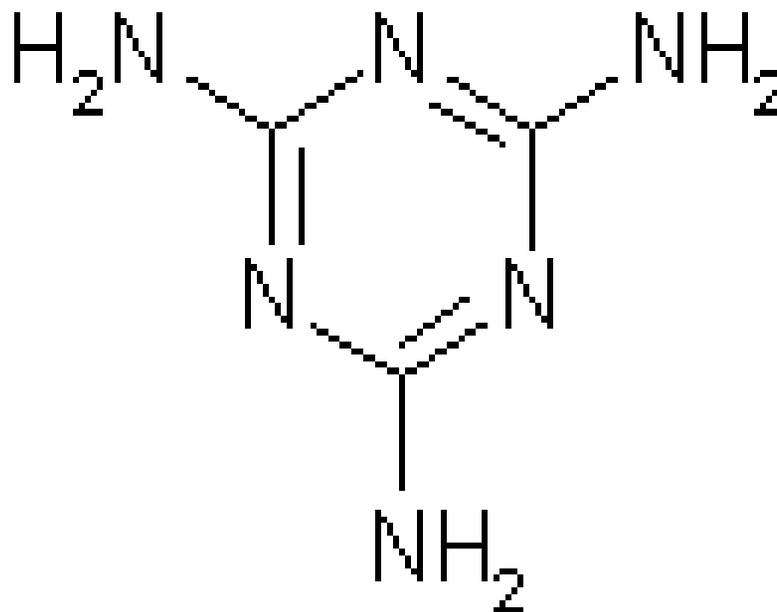
Discovering Melamine

- 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



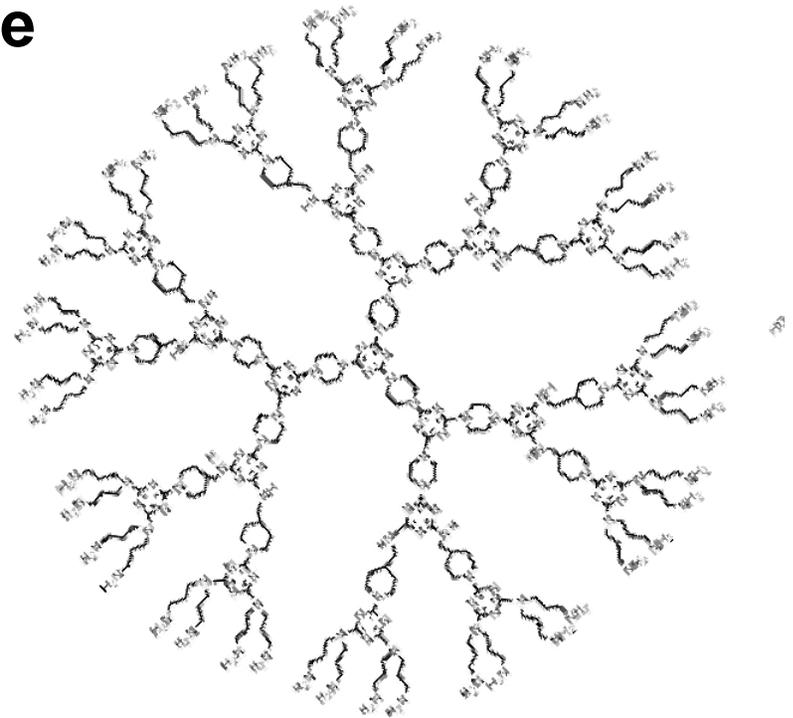
Mela Who?

- **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

The screenshot shows the website for the Center for Veterinary Medicine (CVM) under the U.S. Food and Drug Administration. The page is titled "Office of Research" and includes a search bar, a table of contents, and several research updates. The table of contents lists various sections such as "About CVM", "Mission Statement", "Guiding Principles", "CVM Organization Chart", "Introduction", "A Brief History of CVM", "Structure/Responsibility", "CVM Annual Report", "Safeguarding Animal Health", "Office of the Director (OD)", "Office of Management", "CVM & Budget", "CVC of New Animal Drugs", "Surveillance/Compliance", "Office of Research", and "Minor Use/Minor Species". The "Office of Research" section includes a quote: "The Office of Research conducts applied research in support of current and evolving FDA regulatory issues. We work with our customers to provide research solutions that ensure the safety of animal derived food and animal health products. We seek to develop an internationally recognized research program in these areas." Below this, there are several research updates, including "GC-MS Screen for the Presence of Melamine, Ammelide, Ammelide and Cyanuric Acid (Version 2.1), May 16, 2007 NEW", "GC-MS Method for Screening and Confirmation of Melamine and Related Analogs (Version 2), May 7, 2007 NEW", "Interim GC-MS Method for Screening and Confirmation of Melamine and Related Analogs (PRLNW), April 25, 2007 NEW", "GC-MS Screen for the Presence of Melamine and Cyanuric Acid (Adapted from FDA/ORA Forensic Chemistry Center SOP T015) revised April 25, 2007 NEW", and "Updated FCC Developmental Melamine Quantitation (HPLC-LV), April 2, 2007 NEW". The "Division of Animal Research (DAR)" section includes a quote: "The Division of Animal Research (DAR) conducts applied and basic research using animals and animal systems in support of current and evolving regulatory issues. We provide research solutions to issues of animal health, food safety of animal derived products, and other animal industry associated technologies." The "Division of Food and Animal Microbiology (DAFM)" section includes a quote: "The mission of the Division of Animal and Food Microbiology (DAFM) is to conduct basic and applied research to support regulatory decision-making by the Center for Veterinary Medicine. This research involves the isolation, identification and characterization of microorganisms potentially harmful to animals and humans. In particular, DAFM research explores the effects of antimicrobial use in animals on: 1) efficacy against pathogens, 2) changes in the environmental microbial ecology, and 3) the development of antimicrobial resistance in pathogenic and commensal microorganisms." At the bottom, there is a paragraph stating: "CVM is fortunate to have a state-of-the-art research complex containing offices, laboratories, animal buildings, and pastures. This facility includes a mass spectrometry laboratory, analytical instrument rooms, a radioactive materials laboratory, and specialized laboratories designed for multi-disciplinary studies. The animal research buildings accommodate beef cattle, dairy cattle, calves, swine, sheep, dogs, poultry, and a variety of aquatic species."



Spilling Over to Food-Animals

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





Risk Assessment

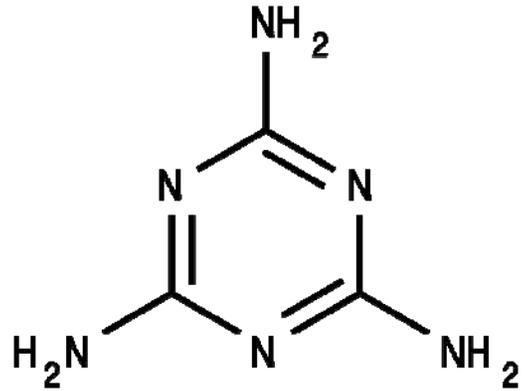
- **USDA/FDA developed risk assessment**
- **Low human food safety risk**
 - **due to dilution factors**
 - **132 lb. person must eat 800 lb. of contaminated meat daily for risk**
- **Peer reviewed**
- **Subject to public comment**
- **Presented to the Science Board on 6/07**



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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*

- ~ 294,000 ill infants, most < 2 yrs old
- > 50,000 infants hospitalized
- 6 confirmed deaths

* 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



AP

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



seattlepi.nwsourc.com/national/1104ap_as_china_tainted_milk.html?source=myspi



New methods posted Oct 8, 2008 Melamine and Cyanuric Acid



Laboratory Information Bulletin No. 4421
October 2008

Laboratory Information Bulletin
LIB No. 4421
Volume 24, October 2008

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

Media Inquiries:

Stephanie Kwisnek, 301-827-0955

Consumer Inquiries:

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.

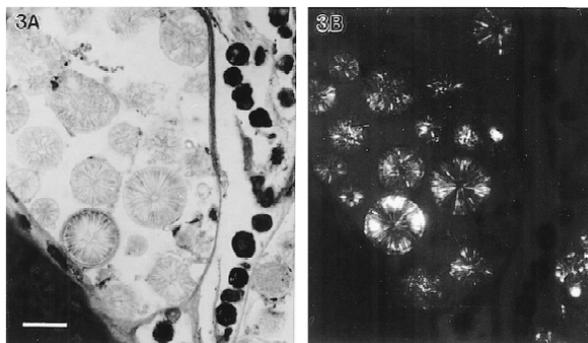
*Subject to peer review.



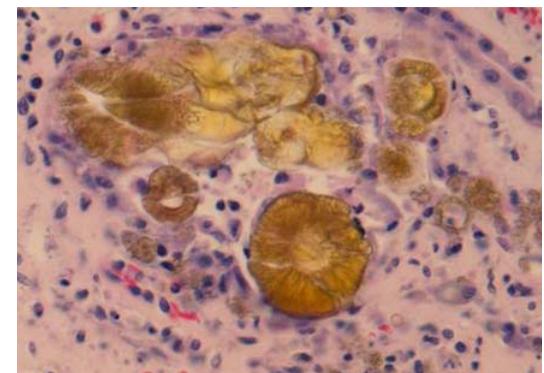
What Have We Learned about Melamine and Melamine + Cyanuric Acid

Cause of Injury

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



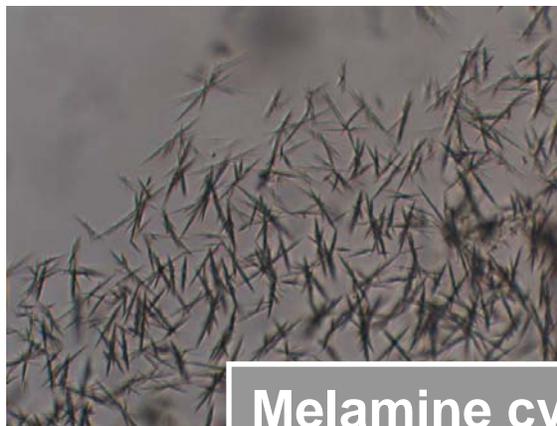
Urate crystals formed in a worm
 Photo courtesy of Charles C. Lambert
 Department of Biological Science, California State
 University Fullerton, and Friday Harbor Laboratories,
 Friday Harbor, Washington



From case involving dog
 Photo courtesy of DOPAH, MSU

Crystal Formation

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



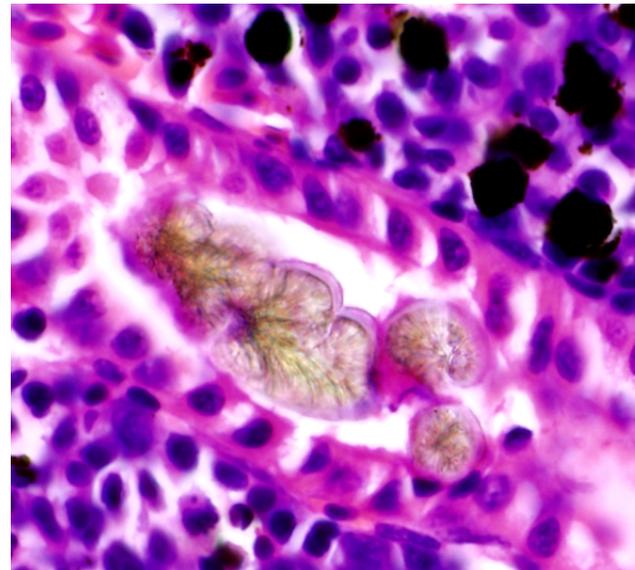
Melamine cyanurate



Hypothesis

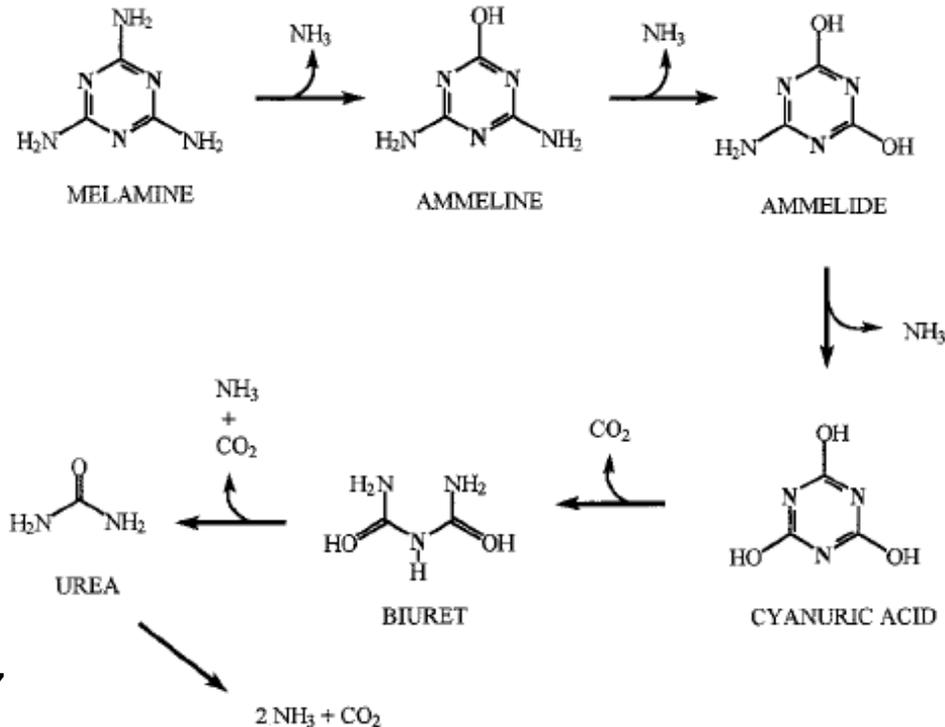
- Melamine:cyanurate crystal nephropathy similar to uric acid nephropathy in humans
 - crystals create obstructions
- Similar morphology

Gold-brown crystals in trout kidney tubule



Cyanuric Acid

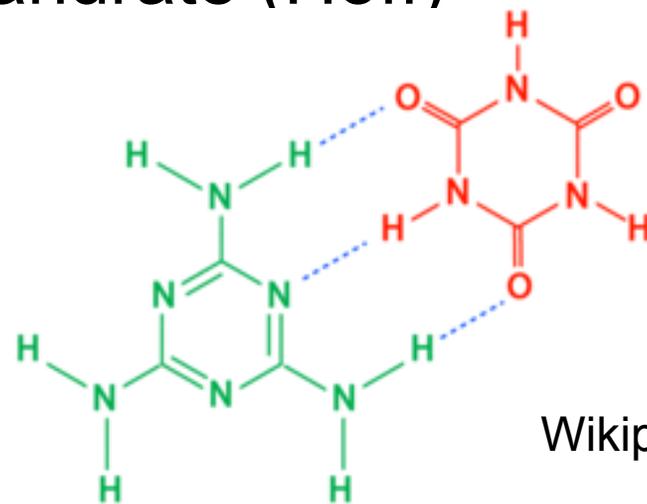
- Melamine analogue
 - Incomplete manufacture?
 - Bacterial degradation?
 - Reaction during manufacture?



Shelton et al. 1997

Cyanuric Acid

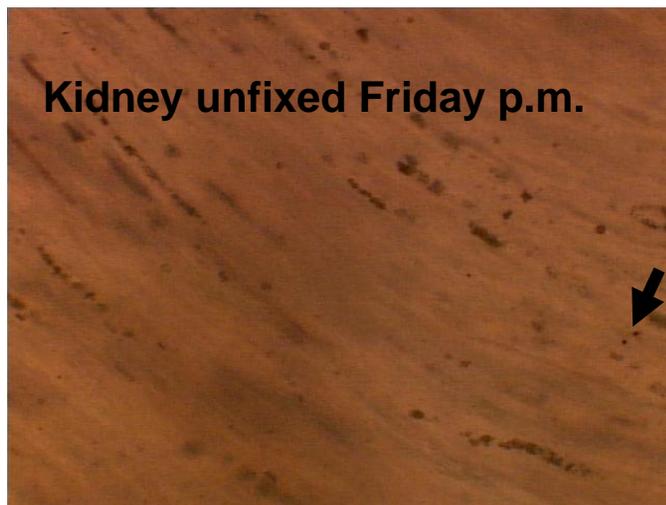
- Polymerizes with melamine
 - pH = 5.8
 - 50.58% cyanuric acid
- Detected in urinary crystals
 - \approx 30% melamine/70% cyanurate (Hoff)



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.



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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**