



# ***Melamine: The cause of the Pet Food and Infant Formula Recalls***

Renate Reimschuessel VMD PhD  
Center for Veterinary Medicine, FDA

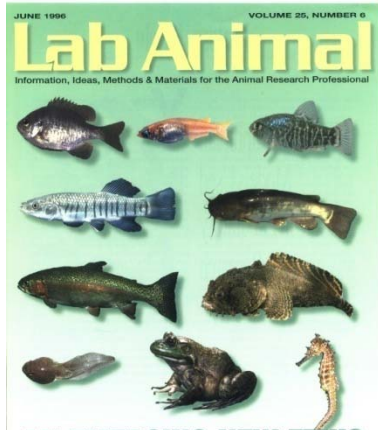
**MANY OTHERS CONTRIBUTED TO  
THE WORK I AM PRESENTING TODAY  
(within FDA and outside the Agency  
in academia and industry)**

# Renate Reimschuessel VMD, PhD

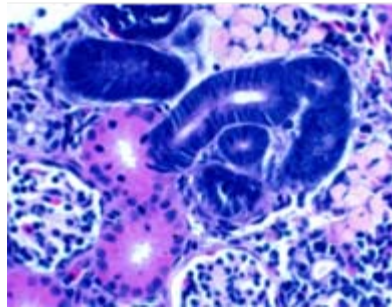


**Practicing  
Veterinarian**

**Aquatic Diagnostic Pathology**



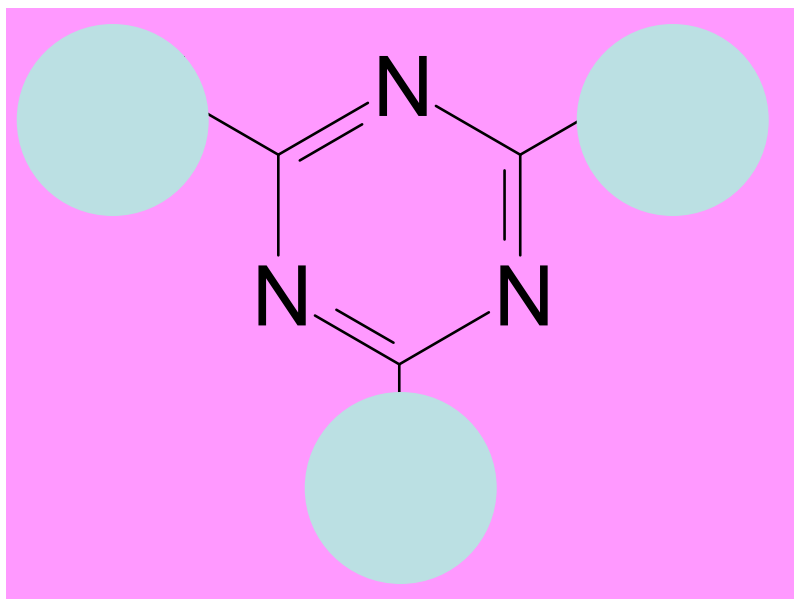
**Kidney  
Research**



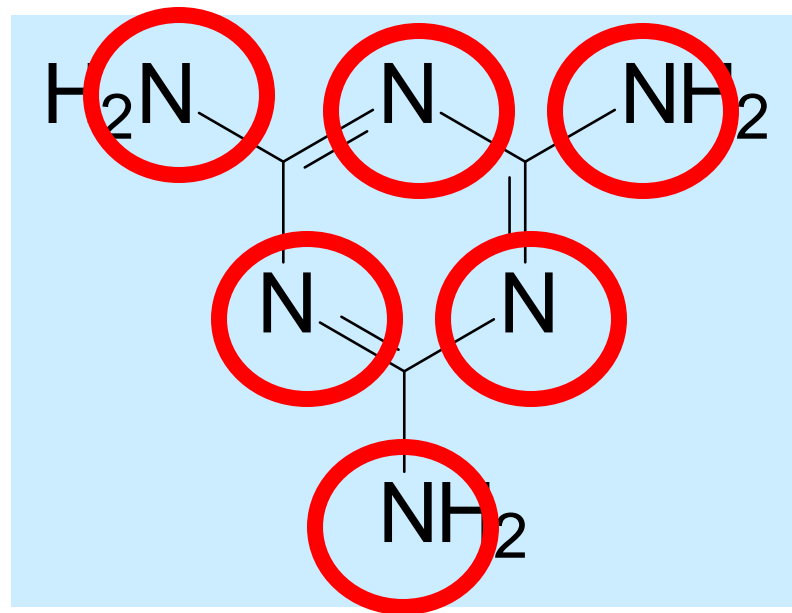
**Center for Veterinary  
Medicine**



# Triazines - Melamine



3 N's



6 N's

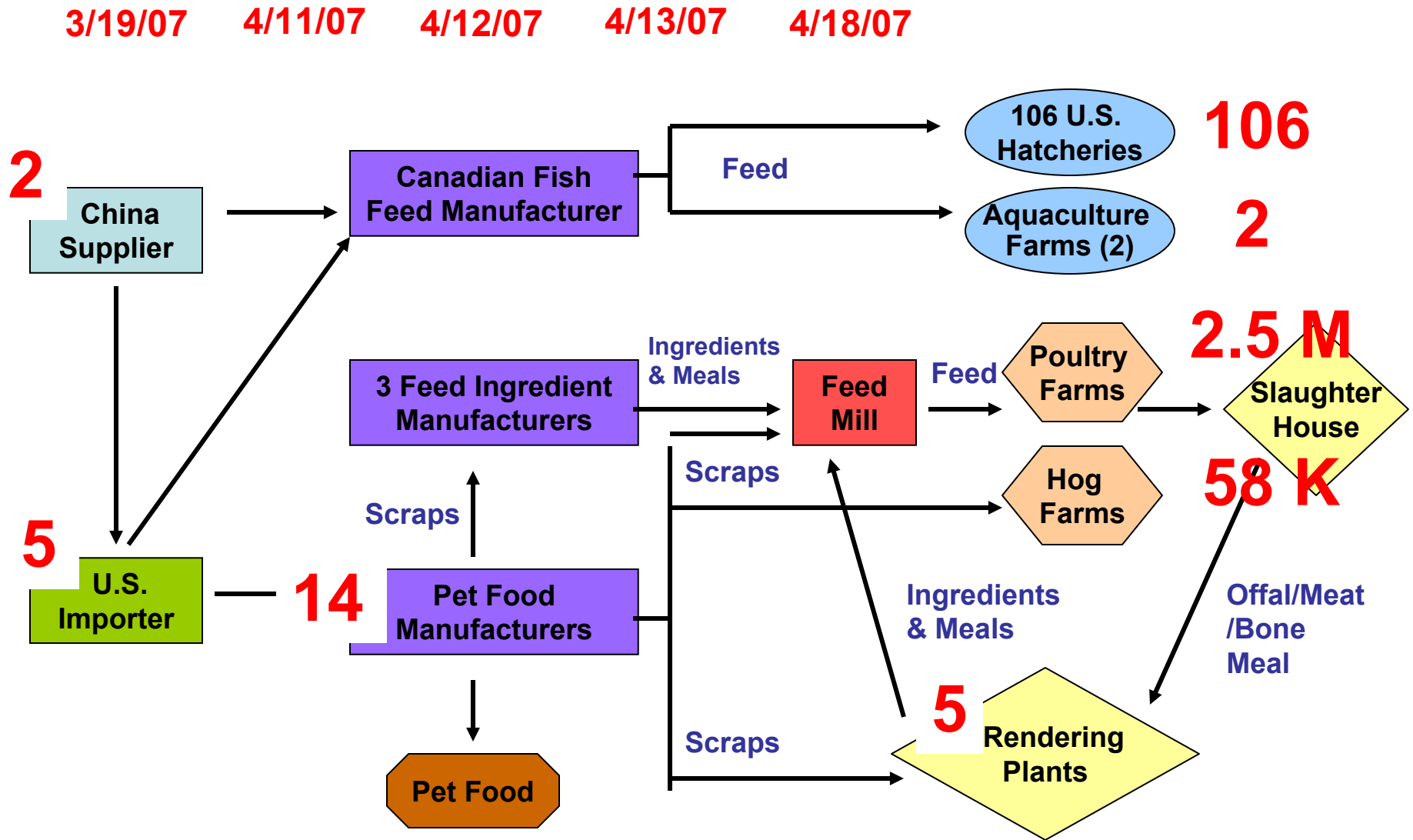
Mar. 15, 2007



- Menu Foods announced recall
- 60 million containers, “cuts and gravy” style food; 100 brands
- Company had received complaints, animals in kidney failure

# Contaminated Pet Food/Animal Feed Incident – 2007

## Sequence of Events



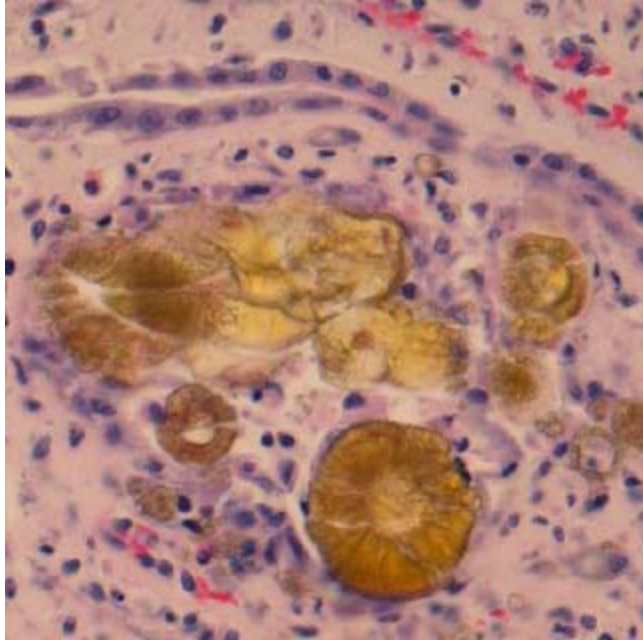
**LARGEST RECALL – 18,700 calls in 11 weeks**

# Vet Pathologists Reported: “Unusual Crystals”

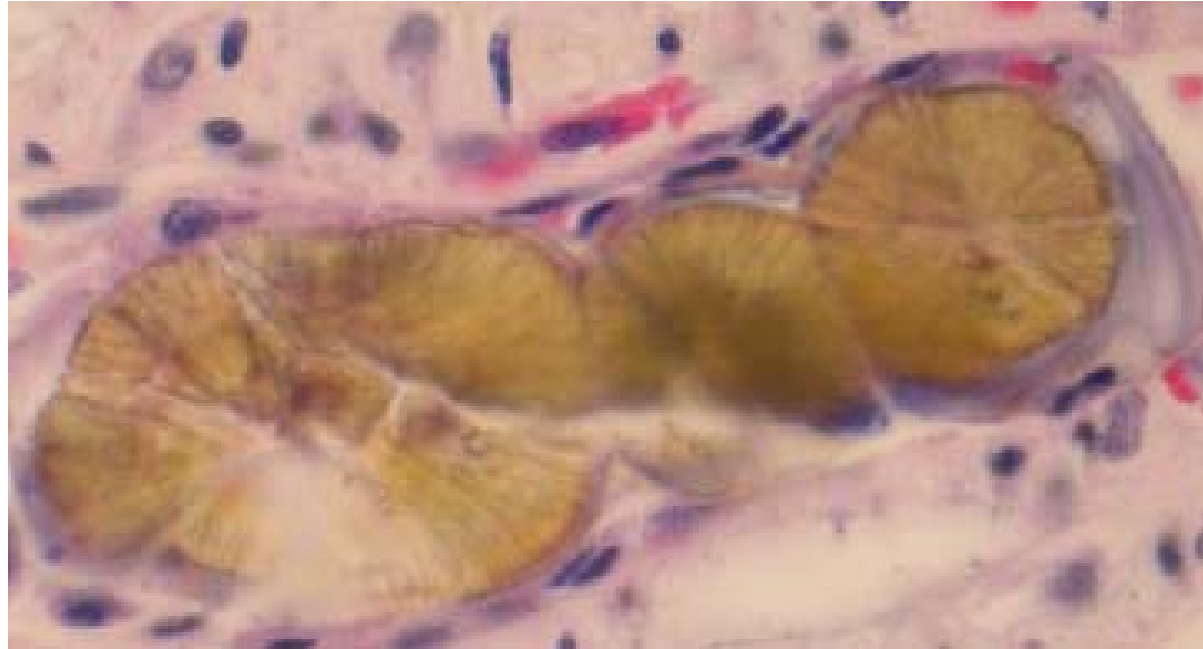
- Pathologists saw **crystals in kidney**  
**but**  
**not enough to cause kidney failure**
- Pathology photos sent to FDA

**Collaborations with American Veterinary Medical Association  
American Association of Veterinary Laboratory Diagnosticians  
were key components to solving the mystery**

# Crystal Morphology



Michigan State University- Apr 3, 2007



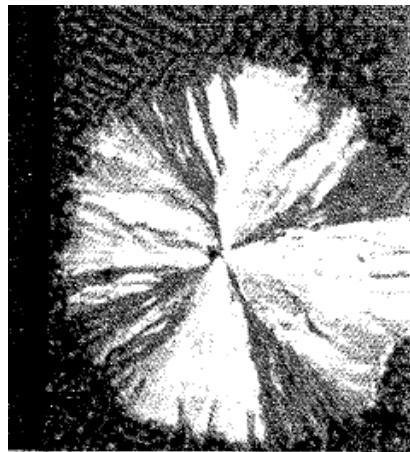
Needle like crystals arranged in a radial sphere

These crystals looked familiar to me

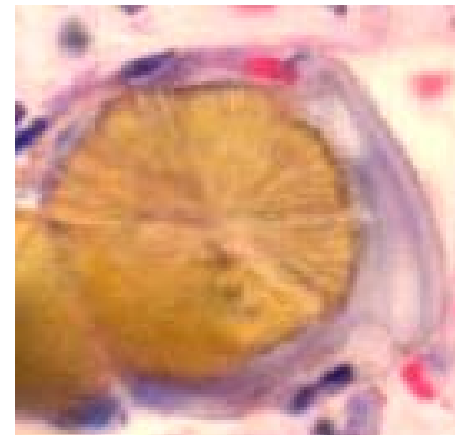


Received April 3, 2007

# Human Gout – Uric acid crystals



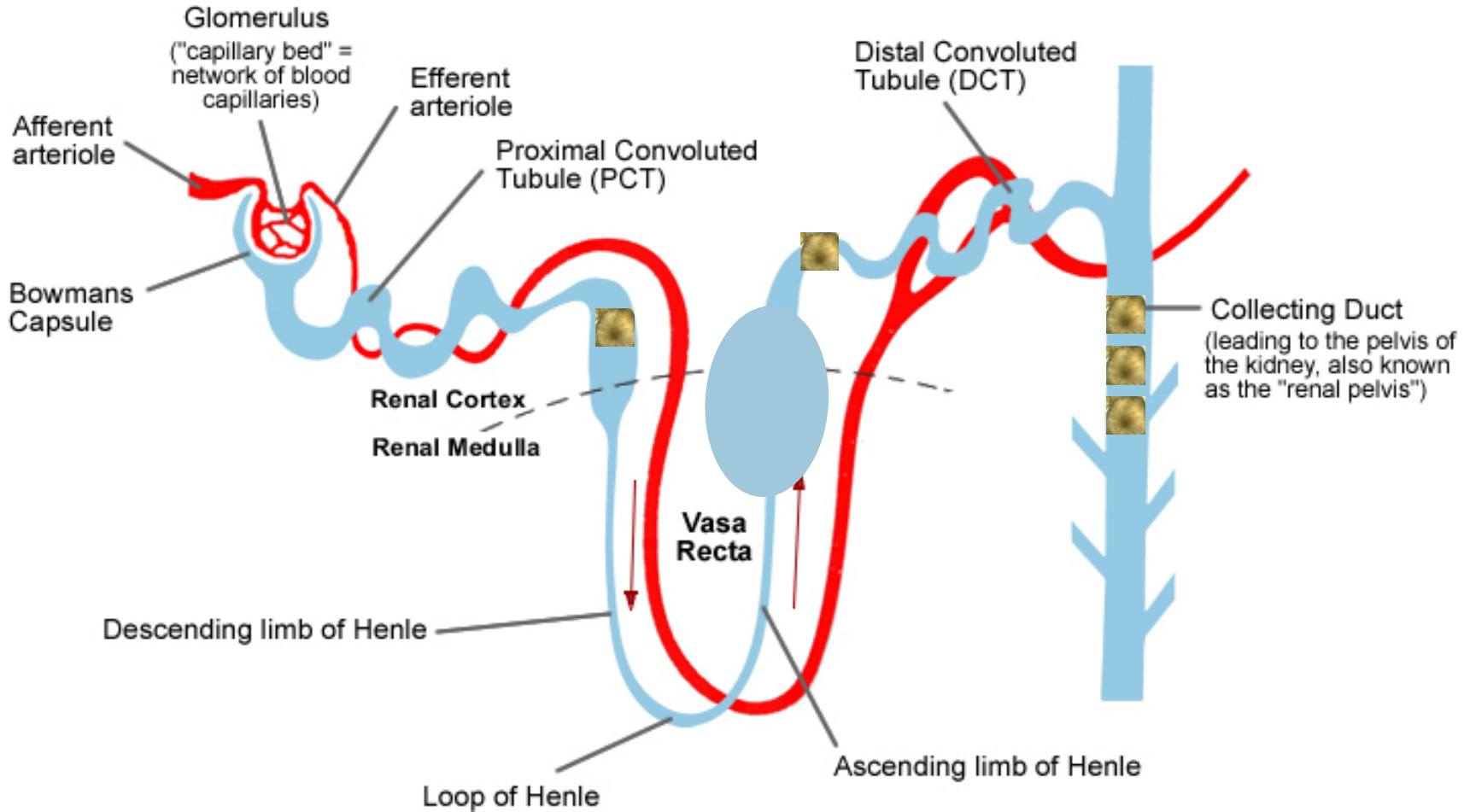
Fiechtner et al. JAMA 1981 245:1533-6



Uric acid crystals dissolve in Formaldehyde, the routine fixative



# Uric acid nephropathy



[http://www.ivy-rose.co.uk/Topics/Urinary/Kidney\\_Nephron\\_clvyRose.jpg](http://www.ivy-rose.co.uk/Topics/Urinary/Kidney_Nephron_clvyRose.jpg)

Crystals obstruct tubules – vascular compromise

Locations vary depending on species

# Massive literature search on melamine

# 2 year rat melamine cancer study

Bladder stones: **Melamine:Uric acid** – 1:1

**Microcrystals** in renal pelvis

Ogasawara, et al (1995)

Urinary bladder carcinogenesis induced by melamine in F344 male rats:

Correlation between carcinogenicity and urolith formation.

*Carcinogenesis*, 16, 2773–2777.



# Hypothesis



Could **a combination** of melamine with uric acid or cyanuric acid be toxic?

Is the pathogenesis similar to **Acute uric acid nephropathy**?



Submitted April 6, 2007



# April 20, 2007 – CYANURIC ACID

Another Triazine - high nitrogen compound was found in pet food

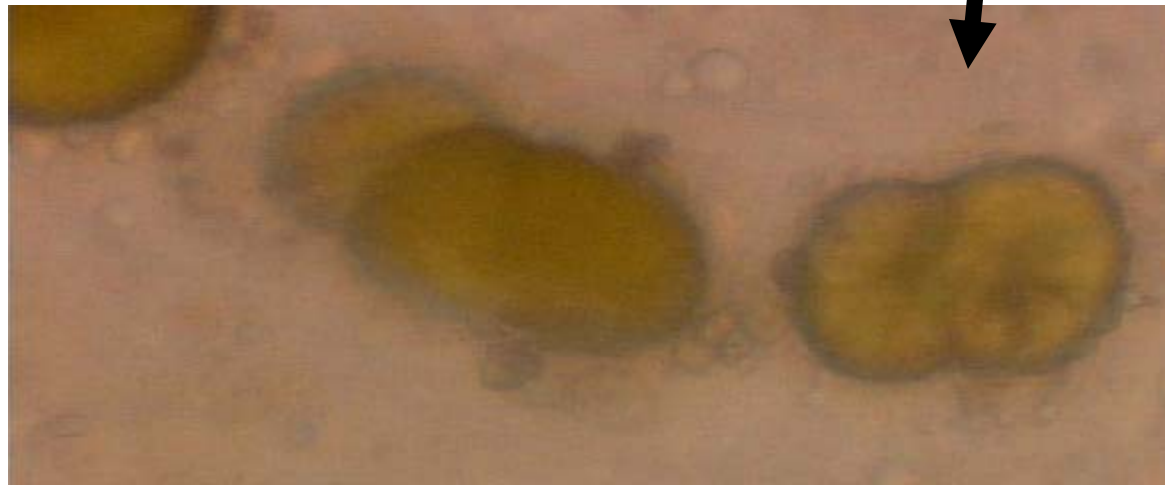
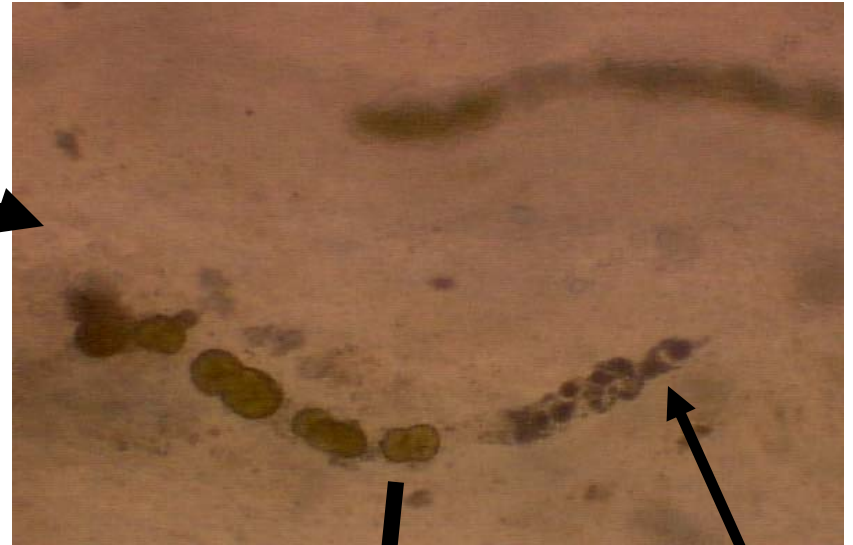


# Test the Hypothesis

## Wet mounts



Received April 13, 2007

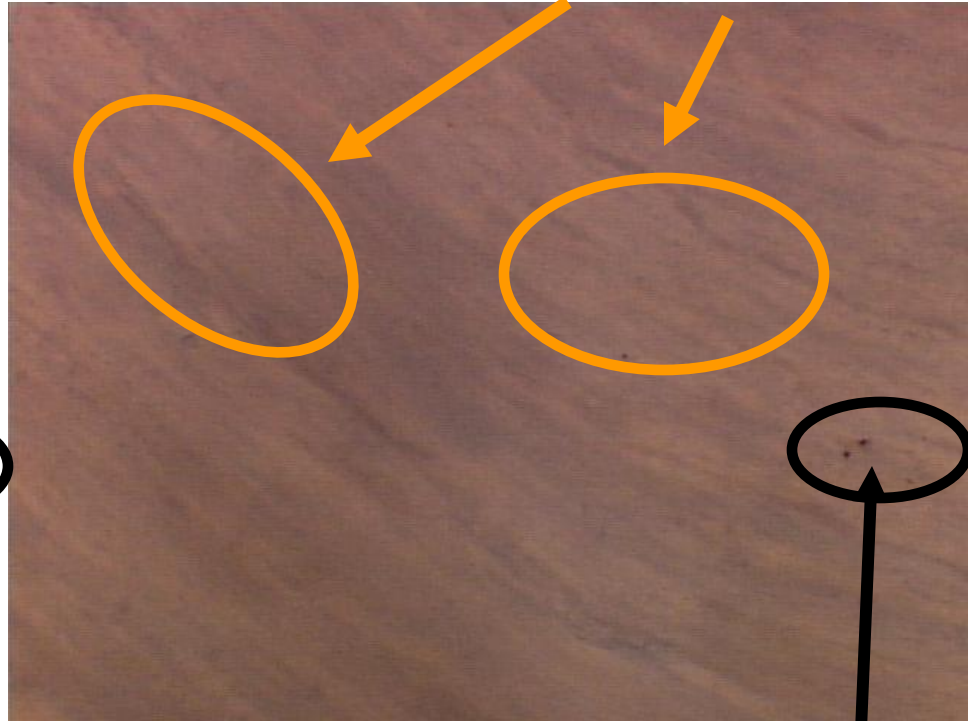


Debris  
caught in  
tubule  
upstream

# Response to Formalin

Crystals

60 hours later  
no crystals



Kidney unfixed  
Friday PM

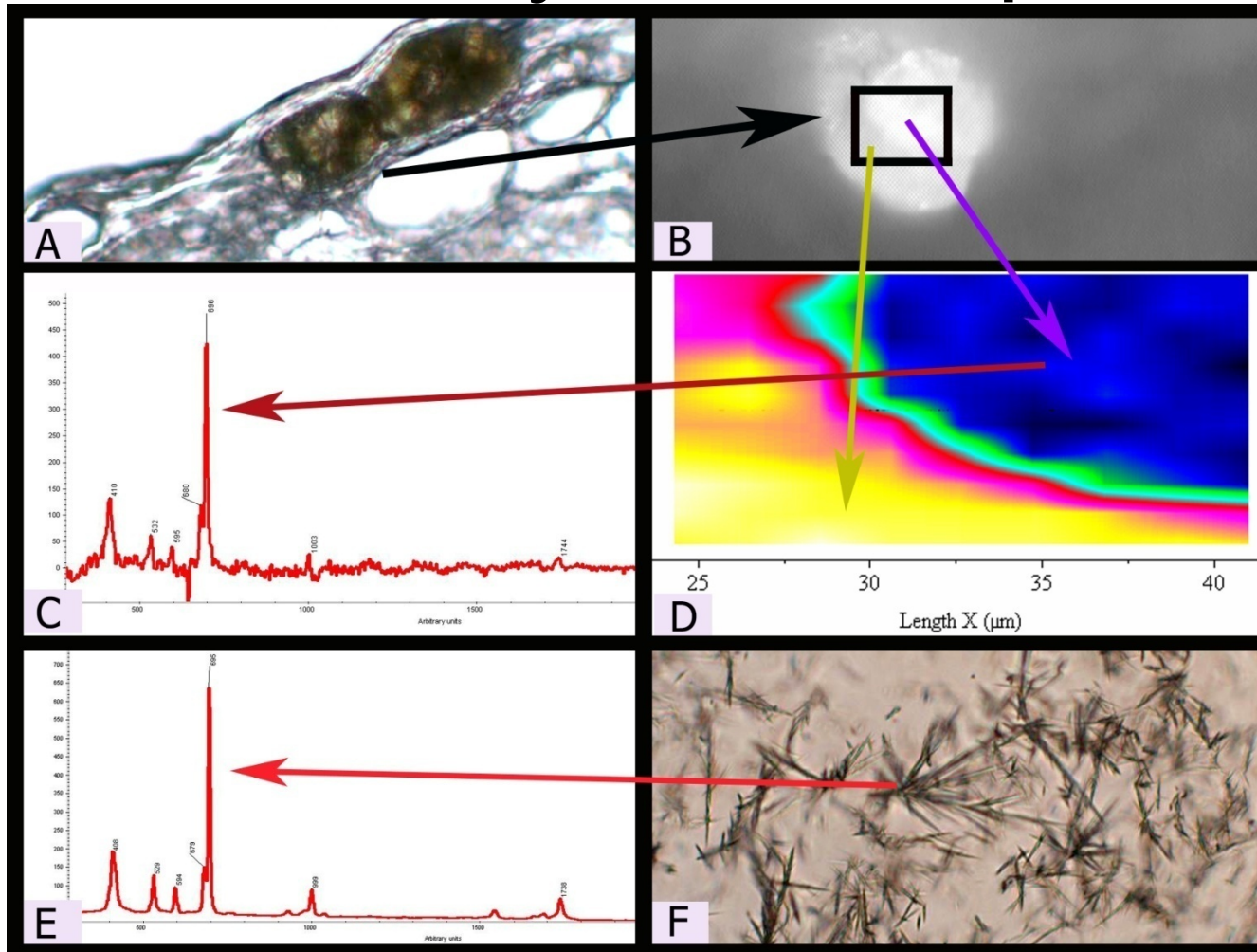
Formalin fixed  
Monday AM

Dirt  
on slide

Dirt  
on slide

Same field – photo taken unfixed, then flooded with formalin, left on microscope over weekend. Crystals not visible on Monday (same field)

# Cat crystals consistent with Melamine:Cyanurate spectrum



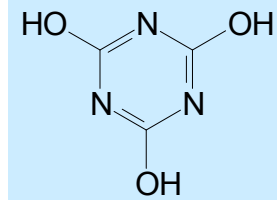


Low Toxicity

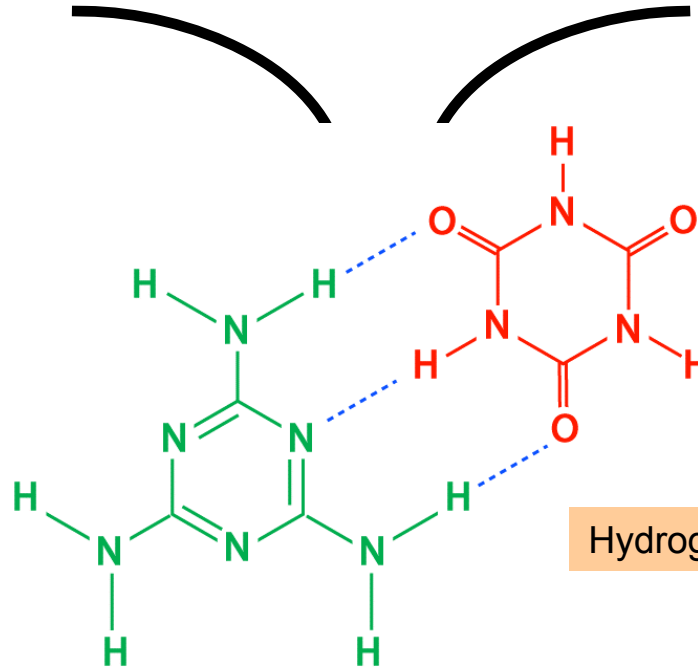


Melamine

Low Toxicity



Cyanuric Acid



Hydrogen bonding- Melamine-cyanurate

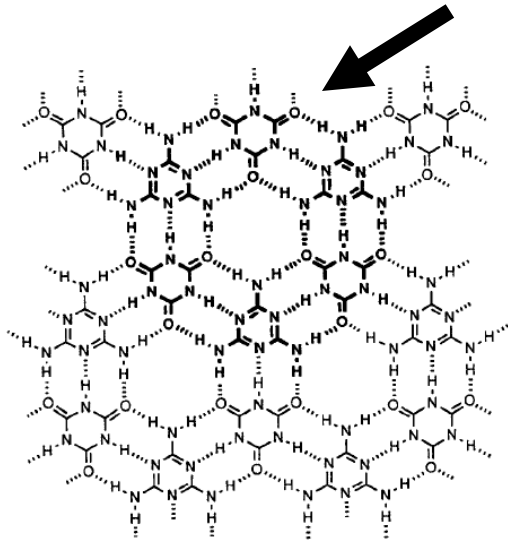
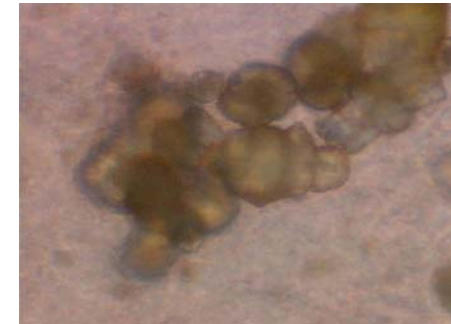
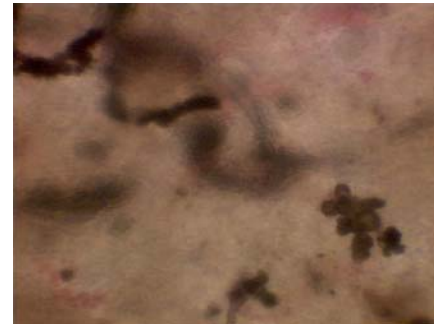


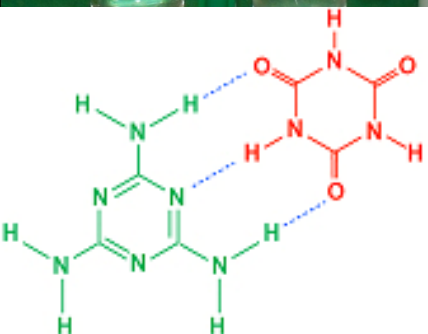
Fig. 6 Cyanuric acid-melamine lattice<sup>12</sup> (cyclic hexamer shown in bold).

Crystal Lattice Structure

Renal crystals



# Why does the combination cause crystals?



# FDA studies 2007 - 2008

- Because livestock feeds had also been contaminated FDA developed methods to detect melamine in feeds and animal tissues
- Conducted Residue depletion studies



# Sept 11, 2008

## News -Melamine In Infant Formula in China

- Melamine in formula as high as 5000 ppm (Sanlu)
- Primary contaminant – MELAMINE –pure (very very little cya)



# What was happening?

- Melamine was being added to watered down milk by dairy farmers  
(**arrests with melamine in possession**)
- Melamine was being added to watered down milk by producers/distributers.  
(**arrests with melamine in possession**)



# Sept 11, 2008

## News -Melamine In Formula

- Children on formula a long time
- Bloody urine
- Sandy urine
- Stones – urinary obstruction
- Renal Failure (Obstruction)
- Formula contained **MELAMINE**



[http://www.latimes.com/news/printersection/section/lat-mik\\_kraavyncz0080917/042550,0,44/1277.photo](http://www.latimes.com/news/printersection/section/lat-mik_kraavyncz0080917/042550,0,44/1277.photo)



300,000 infants  
diagnosed

# 8 mo female 0.15 cm<sup>2</sup> sand-like calculus

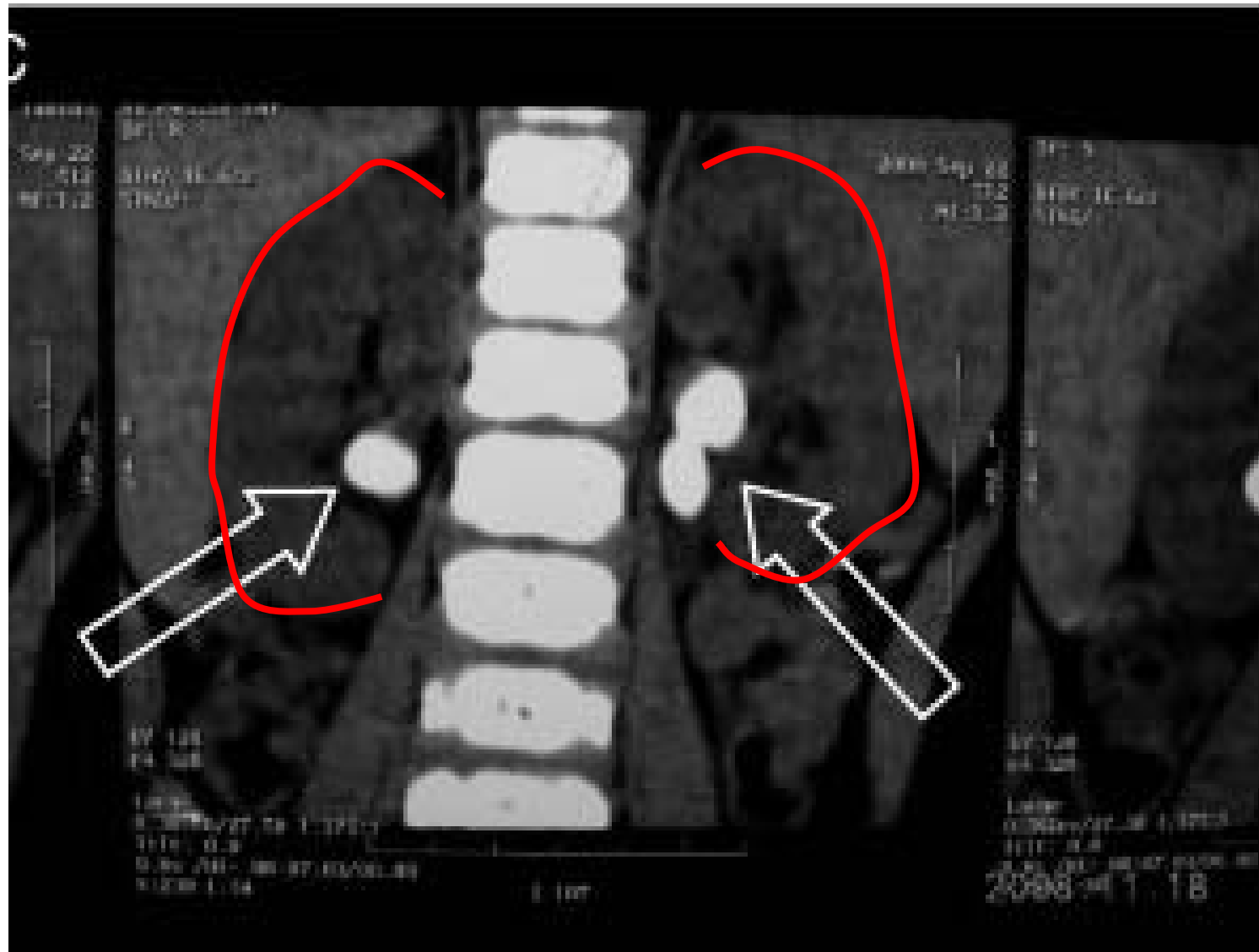


# 10 mo male 0.6-0.4 cm<sup>2</sup> stone-like calculus



Sun et al 2010 Eur J. Pediatr





Wet et al. Journal of Urology

Grases F et al. Urology. 2009  
Melamine Urinary Bladder Stone.  
11 mo infant girl born Nov 2007

# STONES

Melamine-Uric Acid

VS

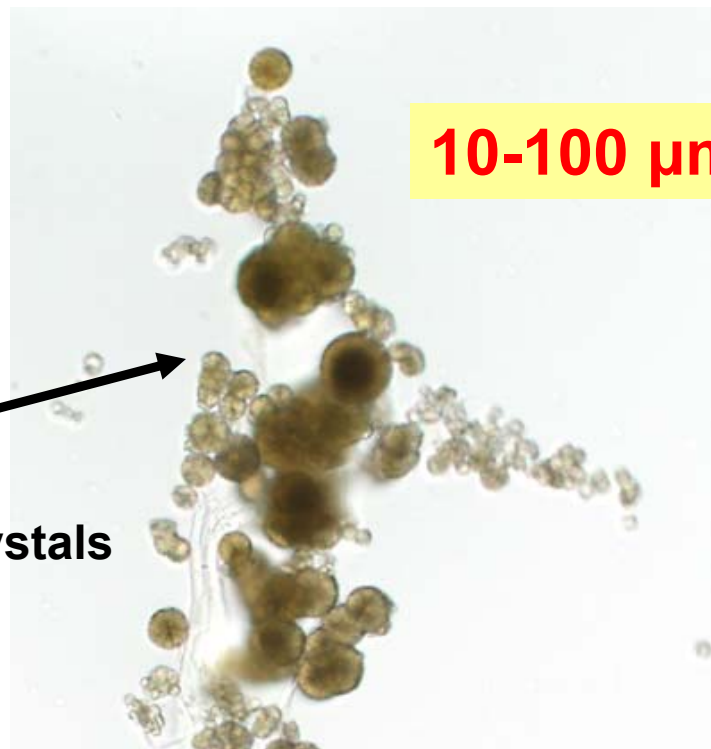
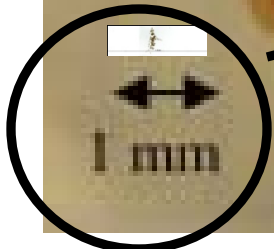
# CRYSTALS

Melamine-Cyanurate

0.7 x 1.2 cm stone

10-100  $\mu\text{m}$

>50 crystals



# MELAMINE EVENTS

2007 – Pet food

Dogs and Cats

SCRAP- Melamine plus  
Cyanuric acid

Kidney Failure-Crystals  
Death

100s – 1000s

2008 – Infant Formula

Babies

PURE Melamine  
(no Cyanuric acid)

Kidney Stones  
No signs, Pain, Death (6)

300,000

# Many milk products were affected worldwide

DAILY NEWS | Money

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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 a Haven store, days after the



AP

el check on the



White rabbit candy



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

# Zoo animals with kidney stones



<http://www.msnbc.msn.com/id/26886627/>



<http://gorilladoctors.wildlifedirect.org/2008/06/29/ndakasis-fight-to-survive-revisited-part-2-one-year-ago/>



<http://educationfirst.com/Portals/42866/6-baby-orangutan-in-sunrise.jpg>

## Zoo animals also victims of tainted milk crisis

All were fed milk powder made by company at the heart of China scandal

msnbc.com news services  
updated 11:34 a.m. ET, Thurs., Sept. 25, 2008



An officer prepares to destroy unqualified milk powder which was confiscated, in Shanghai November 14, 2008.

REUTERS/Stringer

# China Milk Recall 2008 Unearths Another 170 Tons of Melamine Milk Powder in 2010



Published February 10, 2010 by:

**Sylvia Cochran**

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## Milk Problems in China Packed for Resale

In 2008, melamine tainted powdered milk and infant formula led to the death of another 860 babies and two executions of guilty parties. Now more po

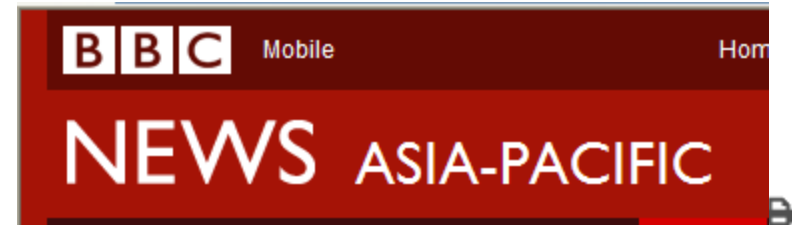
# China

# July 2010

# 64 Tons

# Feb 2010

# 170 Tons



9 July 2010 Last updated at 05:20 ET

## China dairy products found tainted with melamine

**Chinese food safety officials have seized 64 tonnes of raw dairy materials contaminated with the toxic industrial chemical melamine.**

The Chinese state news agency, Xinhua, reported that the quality watchdog in Qinghai province took the material from a dairy plant there.

Test samples showed the milk powder carried up to 500 times the maximum allowed level of the chemical.



Six babies died and 300,000 were ill

# Importance of truly getting rid of contaminated products



[http://en.wikipedia.org/wiki/Image:Melamine\\_biscuits.jpg](http://en.wikipedia.org/wiki/Image:Melamine_biscuits.jpg)



**FDA**



## Questions?

## Further Info.

- Reimschuessel et al. **Evaluation of the renal effects of experimental feeding of melamine and cyanuric acid to fish and pigs.** *Am. J. Vet. Res.*69:1217-1228. 2008.
- Andersen et al. **Determination and confirmation of melamine residues in catfish, trout, tilapia, salmon, and shrimp by LC-MS-MS.** *J Agri Food Chemistry.* 56:4340–4347. 2008.
- Karbiwnyk et al. **Determination of cyanuric acid residues in catfish, trout, tilapia, salmon and shrimp by liquid chromatography-tandem mass spectrometry.** *Analytica Chimica Acta* 637: 101–111. 2008.
- Dobson et al. **Identification and characterization of toxicity of contaminants in pet food leading to an outbreak of renal toxicity in cats and dogs.** *Toxicological Sciences* 106:251-262. 2008.
- Heller et al. **Simultaneous determination and confirmation of melamine and cyanuric acid in animal feed.** *Rapid Comm in Mass Spectrometry* 22::3624-32. 2008.
- Reimschuessel et al. **Residue depletion of melamine and cyanuric acid in catfish rainbow trout following oral administration** *Journal of Veterinary Pharmacology and Therapeutics.* 2009 33, 172–182, 2010.
- Reimschuessel et al. **Renal crystal formation after combined or sequential oral administration of melamine and cyanuric acid.** *Food and Chemical Toxicology,* 48:2898–2906, 2010
- Karbiwnyk et al.. **Bioaccumulation of cyanuric acid in edible tissues of shrimp following experimental feeding.** *Food Additives & Contaminants: Part A* pub on line at: <http://dx.doi.org/10.1080/19440049.2010.517221> 2010
- Jacob et al. **Dose-response assessment of nephrotoxicity from a seven-day combined-exposure to melamine and cyanuric acid in F344 rats.** *Toxicological Sciences* 2010 *IN PRESS*

# Questions?

If you would like to send a question to the CVM Home Page write us directly at:

***AskCVM@fda.hhs.gov***