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Melamine:
A lesson in preventing what you don't expect

GUIRR meeting

February 4, 2009

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Melamine

- **Nitrogen-rich organic compound with multiple uses:**
  - **Agricultural: herbicides, pesticides, fungicides**
  - **Sanitizing agent for food processing equipment**
  - **Plastic resins, Melaware cups and dishes, and coatings**
  - **Adhesives**
  - **Paper and paperboard agents**
  - **Flame retardant fibers**

Melamine is now notorious

- **2008 – more than 300,000 Chinese infants with kidney stones attributable to adulterated milk in baby formula**
- **2007 – dogs and cats in US, Canada, South Africa sickened by adulterated pet food**
- **In both instances, melamine probably was used to boost the apparent protein content.**

2004 - Renal failure in dogs

- Increasing incidence of an unusual presentation of canine renal failure in several Asian countries
  - no evidence of increase in renal failure in cats
- Mars veterinary investigation demonstrated strong correlation with feeding PEDIGREE (dry) manufactured in Thailand
- Mold contamination found in two silos at factory in Thailand
- All dry foods made in Pak Chong withdrawn from markets
  - including cat foods as a precautionary measure
- Outbreak linked to melamine and cyanuric acid (Brown CA *et al* 2007, 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.)

Recent studies with *solus* triazines

Species	Diet triazine content ppm	Intake mg/kgBWT/d	Outcome	Reference
Cat	M = 10,000 CA = 10,000	M = 181 (11d) CA = 243 (3d)	No evidence of renal failure	Puschner 2007
Rat	Oral gavage	AMD=100 (1d) AMN=100 (1d)	No evidence of toxicity	Dobson 2008

Puschner B, Poppena RH, Lowenstine LJ *et al*. Assessment of melamine and cyanuric acid toxicity in cats. *J Vet Diagn Invest* 2007;19:616-624.
Dobson RLM, Motlagh S, Quijano M *et al*. Identification and characterization of toxicity of contaminants in pet food leading to an outbreak of renal toxicity in cats and dogs. *Tox Sci* (Advanced Access) Aug 2008.

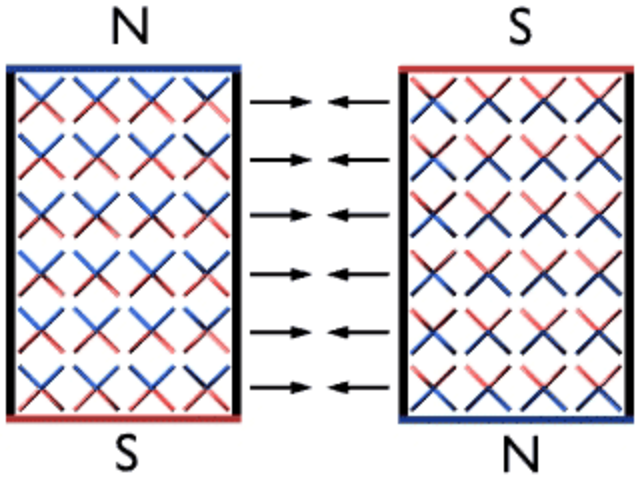
Conclusion #1

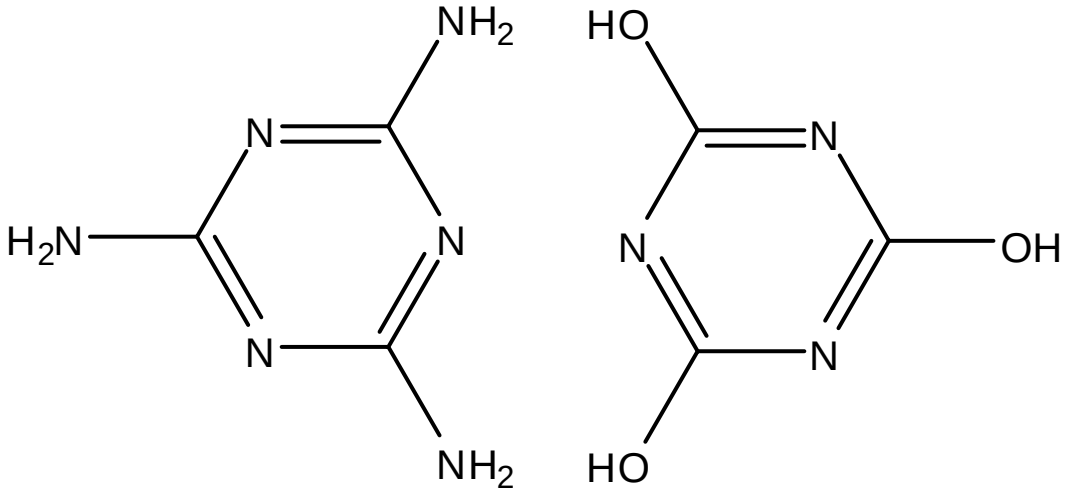
- Pure melamine has relatively low toxicity.

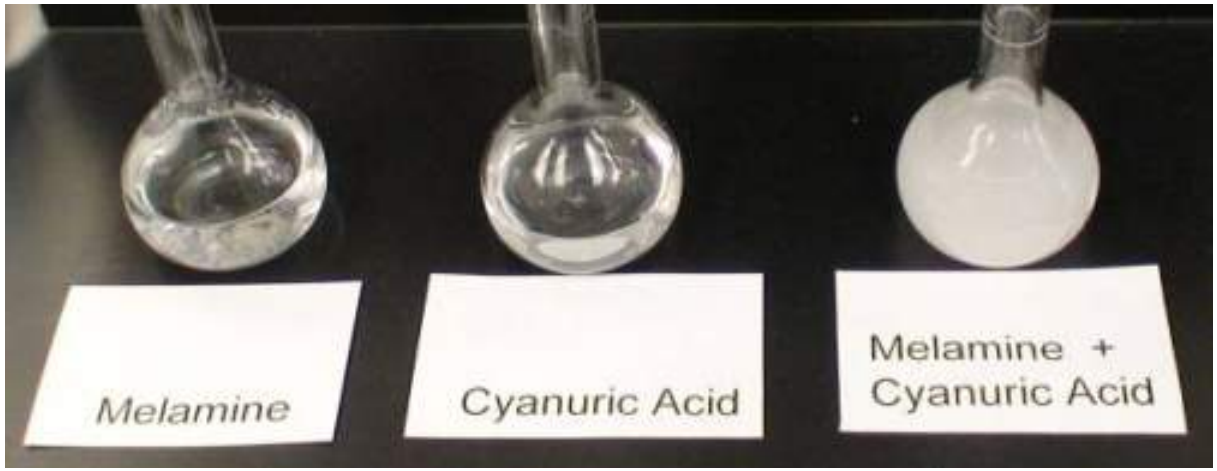
If melamine has low toxicity…

- Something else must be present to have caused the formation of melamine-containing crystals, stones, and the renal toxicity.

FDA investigation in 2007 found ….







Studies with mixed triazines

Species	Diet triazine content ppm	Intake mg/kgBWT/d	Outcome	Reference
Cat	M = 2000 CA = 2000 M:CA = 1:1	M & CA = 32	ARF in <48 hr	Puschner 2007
Rat	M:CA = 1:1 M:CA = 10:1 Oral gavage	M & CA = 400 M = 400 & CA / AML / AMD = 40	ARF in <96 hr	Dobson 2008
Pig	M = 3209 AML = 949 CA = 1126 M:CA ~ 3:1	Not reported	High mortality in 1-2 months Renal failure	Nilubol 2008

Nilubol D, Pattanaseth T, Boonsri K, Leepipatpiboon N. Case report: evidence of melamine toxicity causing renal failure in pigs. *Proc Int Pig Vet Soc Conf* 2008, 256.

Conclusion #2

- Mixtures of triazines can induce renal failure
  - melamine and cyanuric acid appear most important
  - role of ammelide & ammeline less clear
    - low solubility important in nephrolith formation?

Could companies have anticipated and prevented these crises?

YES & No….

- 2004 and 2007 - Pet food issues most likely not
  - practice of “protein boosting” is not new
- 2008 - Milk issue
  - Learnings from 2007 pet poisonings not applied to human foods
  - Materials priced on protein content should have been considered “high risk”
  - Importance of understanding risk throughout the entire pipeline cannot be underestimated

MARS responses

- 2004 – product recall, close and sanitized factory, research to understand problem's cause
- 2007 – suspend imports of Chinese plant proteins, implement melamine testing within quality management program
- 2008 – for Chinese manufactured products: test milk, other raw materials, finished product for melamine; global risk assessment, outreach to Oak Ridge National Laboratory

The food industry's two dilemmas

- How do you protect against adulteration that you don't expect?
  - Melamine may be one of several adulterants used to boost the apparent quality of a raw material and that have passed largely undetected.
- How will regulators deal with these issues?
  - Melamine has multiple uses in food production and processing and, therefore, may be present in many foods at low, but detectable levels. Plus, the chemical analysis is difficult and false positives are likely.

What should government, universities, indust do to prevent future problems?

- Better intelligence about agricultural practices
- Risk assessments should include potential for “protein boosting” and linked to specifications
    - Traditional protein determination methods not adequate, need to apply alternate means (i.e. amino acid profiling)
    - Need to explore the development of rapid & reliable “front gate” testing technologies based on risks
    - Better understanding of raw material composition and diagnostics (fingerprinting)
- Melamine testing programs should be validated and laboratories accredited (up to 53% of laboratories evaluated do not provide statistically valid results for melamine, FAPAS July/August ‘08)
- Need to understand the difference between economic adulteration and background “noise” to focus proper corrective actions (from pesticides, packaging, dyes, test error, etc.)
- Supplier relations and total pipeline understanding are crucial

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Unresolved Issue: Government-University-Industry research

- "Front-gate" testing technologies to identify chemical contaminants, adulterants and pathogens
  - Research talent and capacity exist in national labs, universities
  - FDA lacks research funds, FSIS lacks research authority
  - ARS and CSREES fund most food safety research
  - Not a priority for NIH, NSF
  - Food industry has applied "band-aids", not mounted long-term research program