Clinical Biomarkers used to Diagnose and Treat Acute Poisoning in Animals

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Purpose

"…examine the clinical and physiologic measurements and observations used to diagnose and treat poisoning due to acute chemical poisoning in animals."

"…describe the types of clinical and physiologic information derived from animal studies that could improve the diagnosis and treatment of acute systemic chemical exposures (e.g. melamine)…"

Overview

- Animal Poison Control cases
- Clinical measurements
- Physiologic measurements
- Information needed
- Extrapolation
- Mechanism/pathology
- Pet Food Recall

ASPCA Animal Poison Control Center
2007 Animal Exposures

- 136,500 new records
- 94,435 patient groups
- 69,584 dogs
- 11,933 cats
- 16% serious illness
- 1% death
- Data management

ASPCA Animal Poison Control Center 2007 Most Common Substances

- 89,076 pharmaceuticals
- 39,974 pesticides
- 11,200 foods
- 9,594 biologicals
- 7,267 cleaning products
- 7,090 other chemicals

Clinical Measurements

- Hematology
- Coagulation profile
- Serum electrolytes
- Blood gas
- Renal, liver function
- Cardiac, respiratory function
- Blood cholinesterase
- Blood lead, iron, etc.
- Specific agents and metabolites

Physiologic Measurements

- General
  - Activity level, appetite
  - Body condition
- Integument
  - Wounds
  - Alopecia, pruritus
- Gastrointestinal
  - Vomit, diarrhea
- Neurologic
  - Depression
  - Tremors, seizures
- Cardiovascular
- Respiratory

Clinical and Physiologic Information Needed From Acute Animal Studies

- Species, sex, age
- Route of exposure
- Delivery system/carrier
- Mechanism of action
- Metabolic pathways
- Clinical sign chronology
- Organ systems affected
- Organ system pathology
- Outcome

The Challenge: Extrapolation

- Absorption
  - Monogastric Vs. Ruminant
- Distribution
  - Lean canine breeds
- Metabolism/Excretion
  - Carnivore Vs. Omnivore/Herbivore
  - Specific pathway differences
    - Dogs poor acetylators
    - Cats limited glucuronidation

Mechanisms: Liver

- Free radical production
  - Acetaminophen, iron, carbon tetrachloride
- Disruption of calcium homeostasis
  - Acetaminophen, quinines, cadmium
- Mitochondrial injury
  - Ethanol
- Cytoskeletal disruption
  - Microcystin (blue-green algae)
  - Amanitin (hepatotoxic mushrooms)
- Cholestasis
  - Sporodesmin (mycotoxin), sapogenic cmpds (eg *Tribulus terrestris*)
- Immune-mediated (suspected)
  - NSAID hepatopathy, sulfonamides, phenytoin, halothane (ie many idiosyncratic drug reactions)

ASPCA

Histopathology: Liver

- *Cycas sp:* centrilobular/midzonal coagulative necrosis
- Zinc phosphide: centrilobular necrosis
- Acetaminophen: centrilobular necrosis
- Xylitol: diffuse to massive necrosis
- Metaldehyde: congestion, degeneration
- Carbon tetrachloride: centrilobular necrosis
- Aflatoxin: biliary hyperplasia, hepatocelluar swelling, lipidosis and vacuolation
- *Aminita sp*: centrilobular necrosis
- Microcystin: centrilobular to massive necrosis

Mechanisms: Kidney

- Crystalluric tubular damage
  - E glycol, sulfonamides, oxalates
  - Melamine/cyanuric acid
- Ischemic tubular damage
  - NSAIDs, salicylates, amphotericin B
- Direct tubular damage
  - Heavy metals, *Amaranthus,* oak
- Renal mineralization
  - Vitamin D and analogues
- Glomerular damage
  - Snake venom, mercury

Histopathology: Kidney

- Ethylene glycol: proximal tubular necrosis
- Melamine/cyanuric acid: distal tubular necrosis
- Calcipotriene: generalized mineralization
- Aminoglycosides: proximal tubule
- Grapes/raisins: proximal tubular degeneration
- Ochratoxin: proximal tubular necrosis
- NSAID: collecting duct/loop of Henle/papillary necrosis

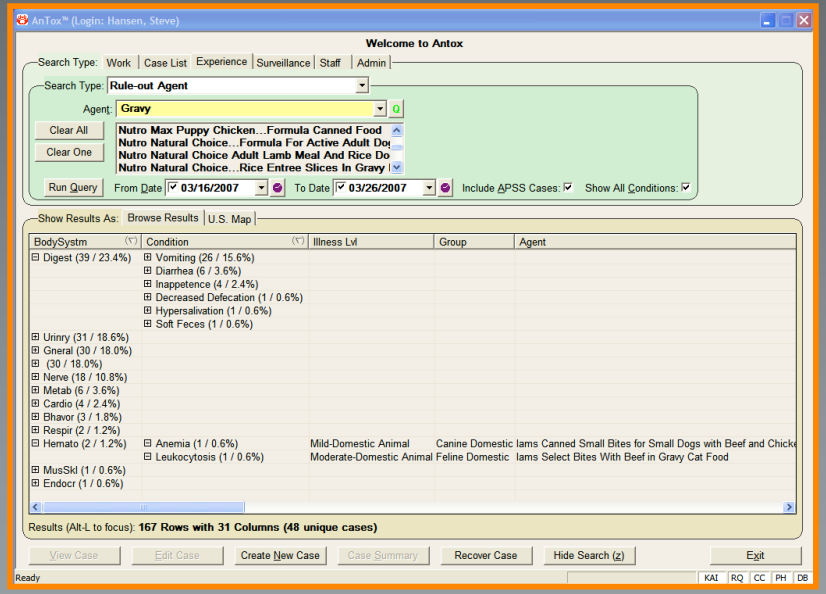
Mechanisms: Nervous System

- Neurotransmission alterations
  - Serotonin (SSRIs, MAOIs)
  - Glycine (strychnine, tetanus)
  - GABA (avermectins, benzodiazepines)
  - Norepinephrine (albuterol, yohimbine, TCAs)
- Alteration of Ion Channels
  - Sodium (saxitoxin, tetrodotoxin, pyrethroids)
  - Potassium (4-aminopyridine, quinidine, bee venom)
  - Chloride (benzodiazepines, barbiturates, KBr)
- Interference w/ neuronal respiration/energy production
  - 5-fluorouracil
- Uncoupling of Oxidative Phosphorylation
  - Bromethalin, salicylic acid

Pet Food Recall and Clinical Data

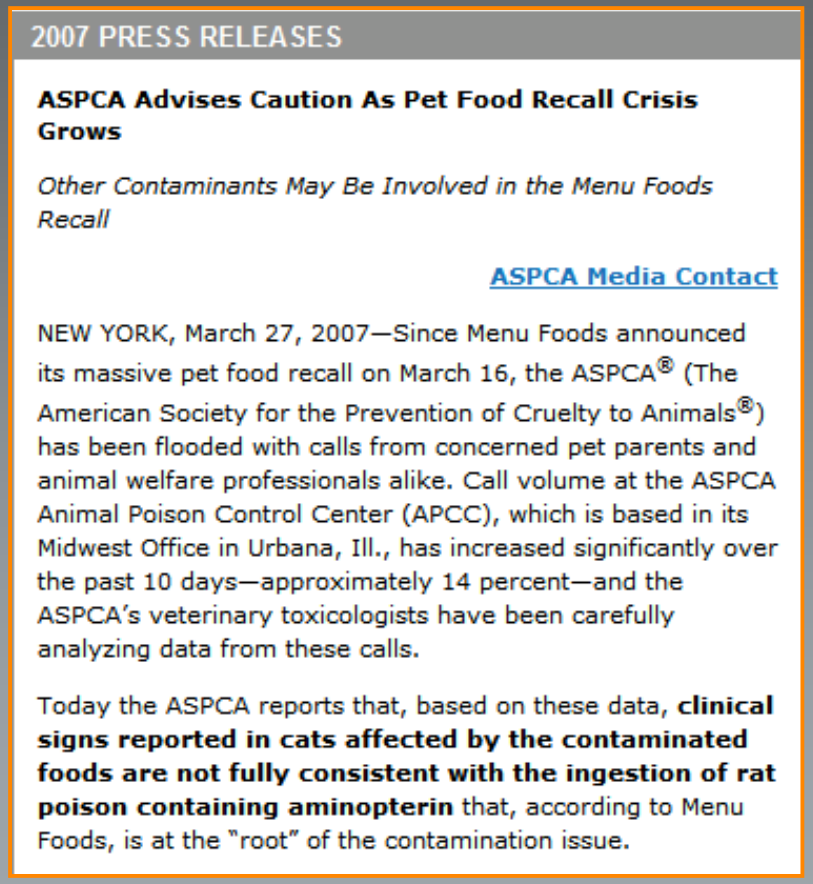
- Cases Mar. 16-26, 2007
- Cats and dogs
- All pet foods

Is aminopterin consistent?



Mar 27, 2007 Press Release

- Aminopterin inconsistent
  - Poison case data
  - Clinical experience
  - Published literature
  - Vet Diagnostic Labs
  - Industry research



2007 PRESS RELEASES

ASPCA Advises Caution As Pet Food Recall Crisis Grows

Other Contaminants May Be Involved in the Menu Foods Recall

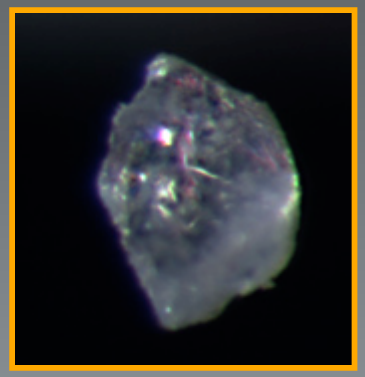
ASPCA Media Contact

NEW YORK, March 27, 2007—Since Menu Foods announced its massive pet food recall on March 16, the ASPCA® (The American Society for the Prevention of Cruelty to Animals®) has been flooded with calls from concerned pet parents and animal welfare professionals alike. Call volume at the ASPCA Animal Poison Control Center (APCC), which is based in its Midwest Office in Urbana, Ill., has increased significantly over the past 10 days—approximately 14 percent—and the ASPCA's veterinary toxicologists have been carefully analyzing data from these calls.

Today the ASPCA reports that, based on these data, **clinical signs reported in cats affected by the contaminated foods are not fully consistent with the ingestion of rat poison containing aminopterin** that, according to Menu Foods, is at the "root" of the contamination issue.

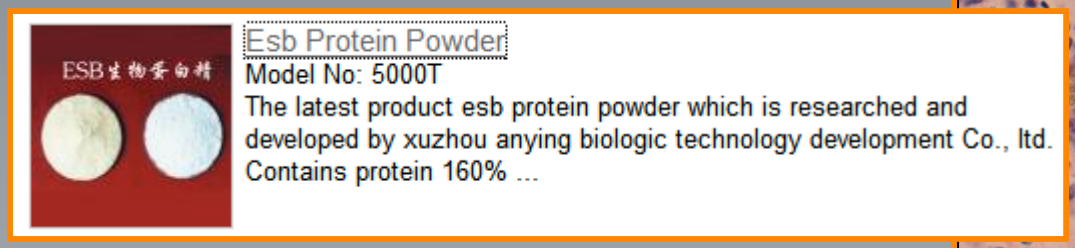
FDA Investigation

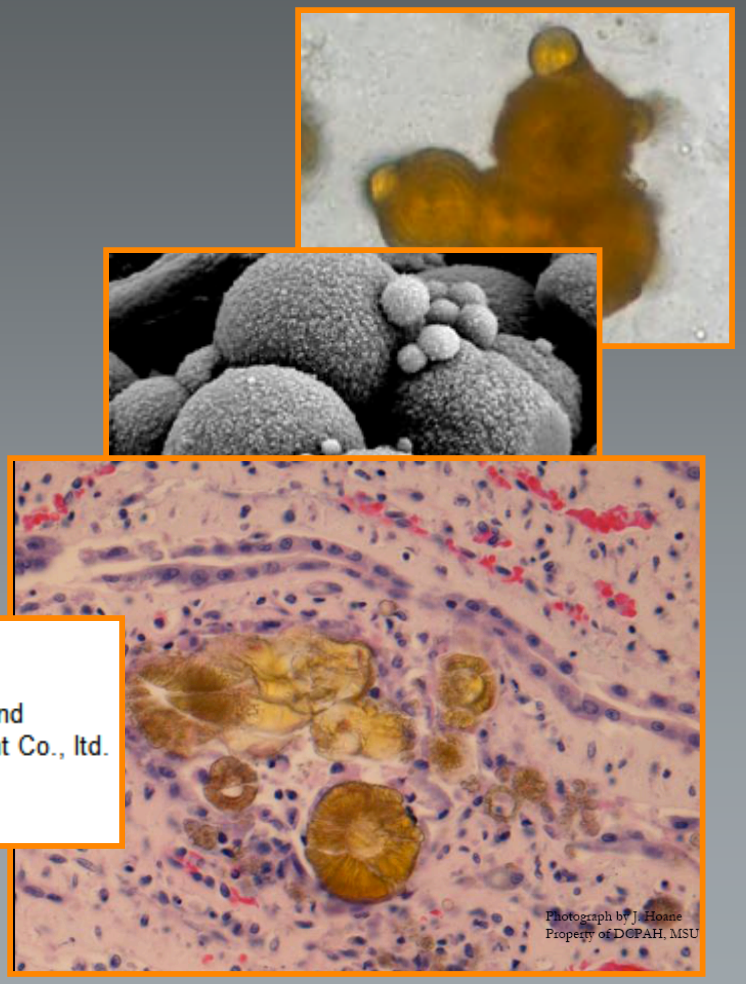
- Mobilized 400 employees
- Foreign particles isolated
- Could not confirm aminopterin
- GC MS detects melamine > 0.001%

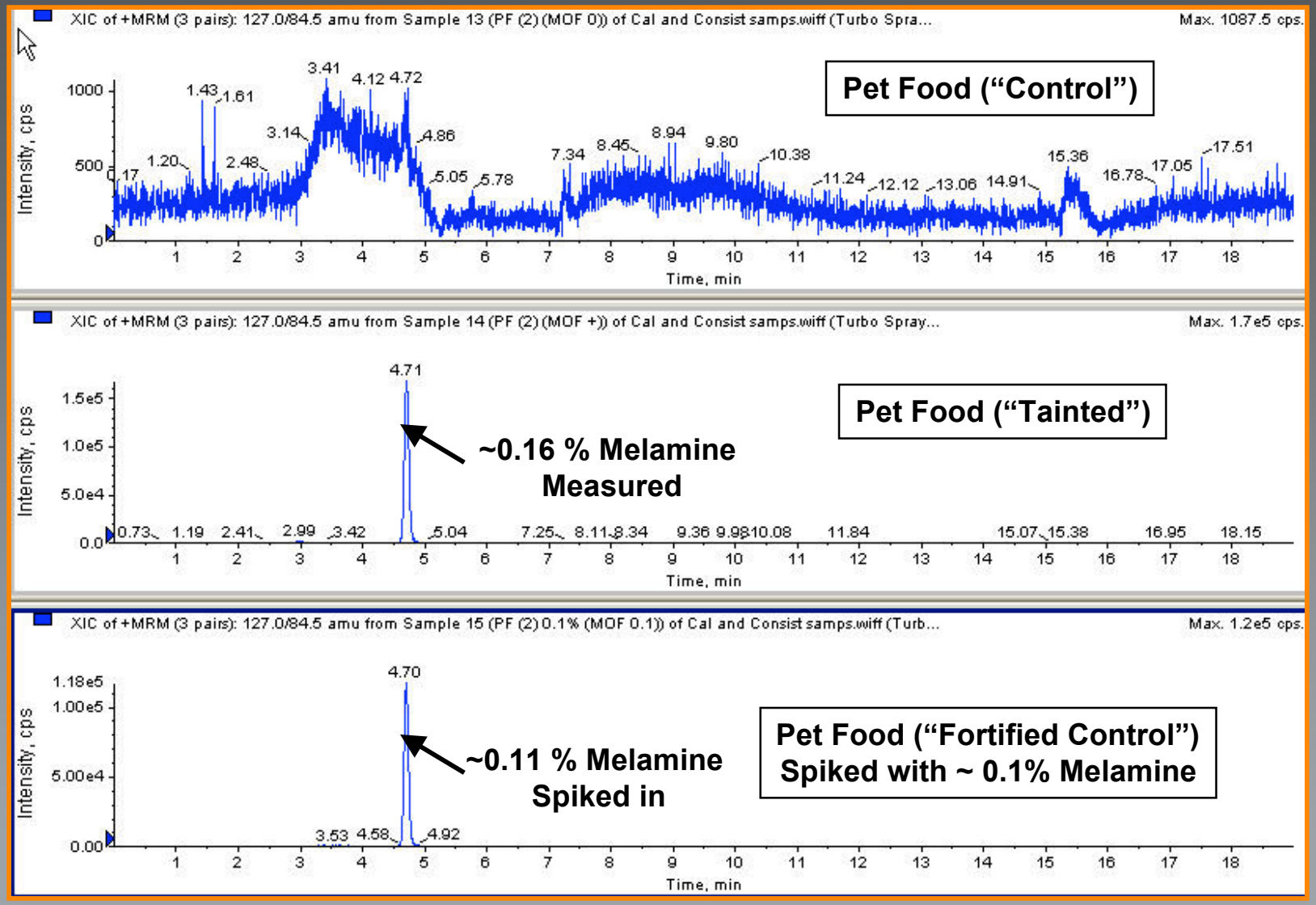


Mar 30, 2007

- FDA announces melamine
  - Moderately toxic
  - Crystals in urine
- Connection not clear

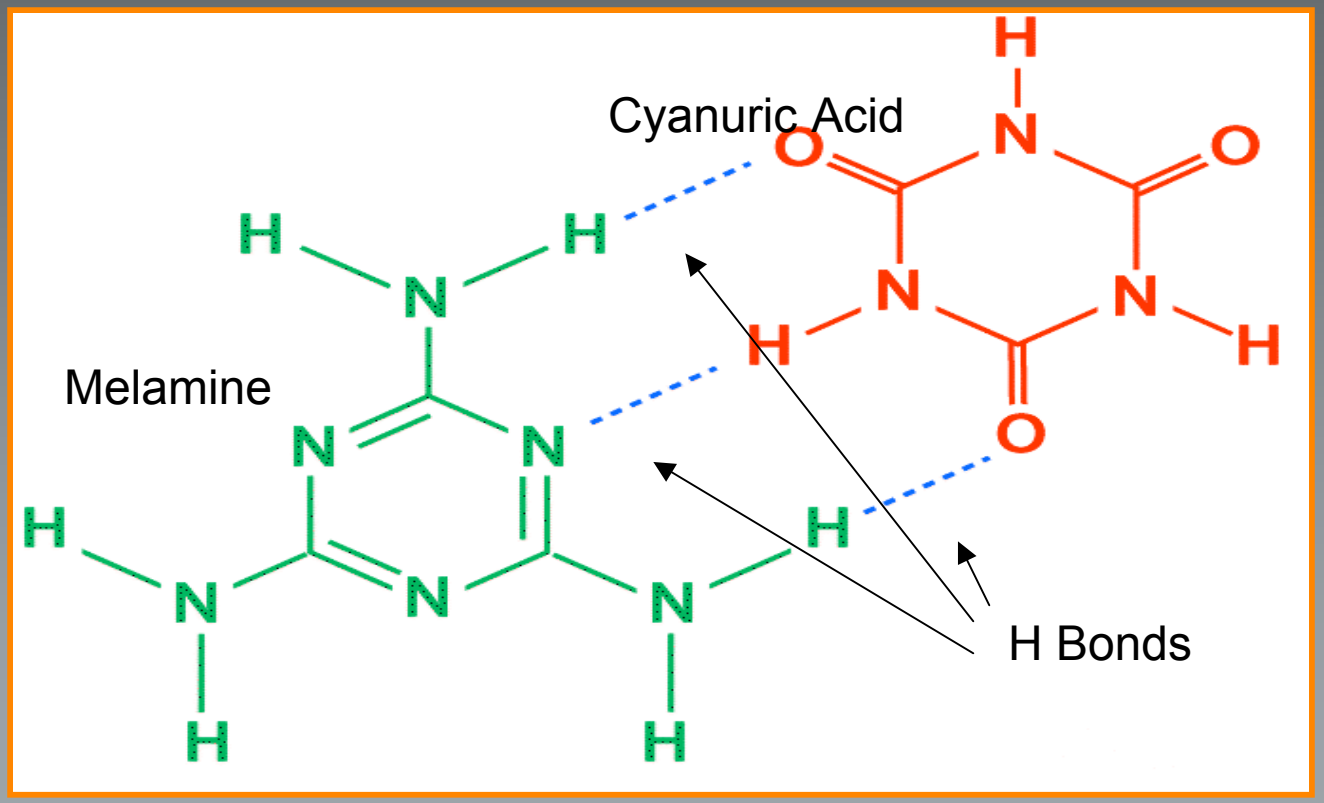






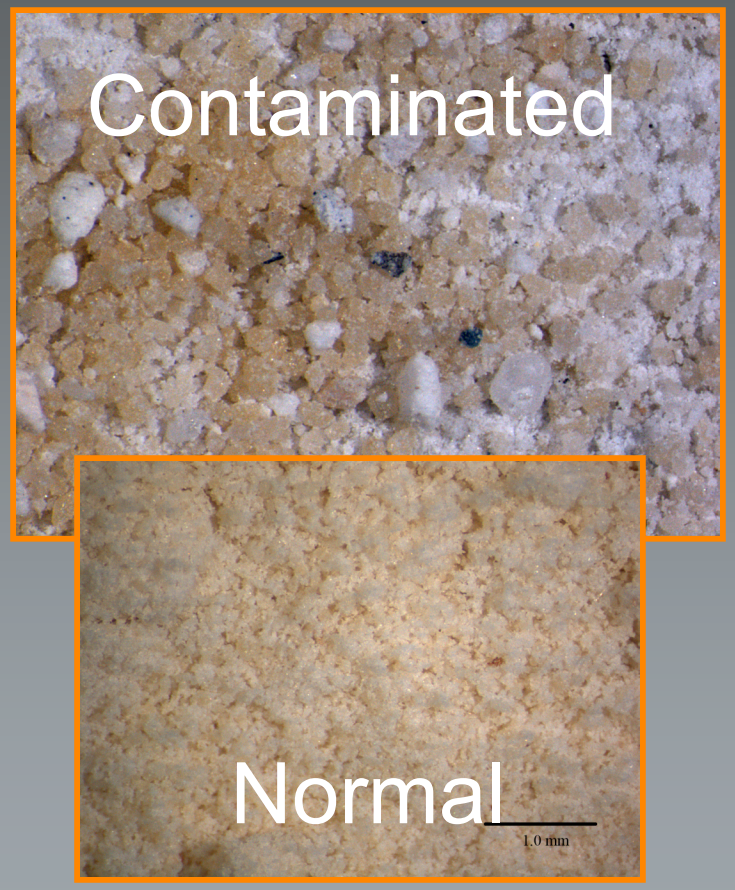
HPLC(HILIC)/MS/MS (SRM = m/z 127 – to – 85)

Melamine Cyanurate



Melamine Fraud

- Added to boost N
- Increase protein equivalent
- Increase $ value
- Melamine low tox
- Cyanuric acid low tox
- Together recrystalize
- Blocks kidney tubules
- Renal failure



Chinese Connection

- Binzhou Futian Biology Technology
- Mislabeled wheat flour
- “I don’t even know what melamine is.”
- Company closed April 25
- Head of China’s food and drug administration executed July 10

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China detains manager at heart of U.S. pet food recall

POSTED: 1120 GMT (1920 HKT), May 9, 2007

STORY HIGHLIGHTS

- Chinese company sold wheat flour containing melamine to pet food distributors
- "I don't even know what this melamine is," detained manager says
- FDA has confirmed deaths of 17 cats and dogs related to pet food recall

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China food safety head executed

The former head of China's State Food and Drug Administration, Zheng Xiaoyu, has been executed for corruption, the state-run Xinhua news agency reports.

He was convicted of taking 6.5m yuan ($850,000; £425,400) in bribes and of dereliction of duty at a trial in May.

Zheng Xiaoyu headed the food and drug agency for seven years

The bribes were linked to sub-standard medicines, blamed for several deaths.

China has been criticised over a number of recent cases involving tainted goods, and correspondents say Zheng had become a symbol of the crisis.

Zheng had appealed against his sentence, arguing that it was "too severe" and saying he had confessed his crimes and co-operated with police.

But his appeal, heard in mid-June, was rejected shortly afterwards.

VIDEO AND AUDIO NEWS

Reaction to the execution of Zheng Xiaoyu

WATCH

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Would better acute data have helped?

J. S. Afr. vet. med. Ass. 37 (3) 1966

MELAMINE CRYSTALLURIA IN SHEEP

R. Clark, Onderstepoort.

Summary

Melamine was found capable of producing fatal uraemia due to crystalluria in sheep even when given in relatively small amounts (10g/day). For this reason it is not considered a safe non-protein nitrogen supplement.

Introduction

The value of melamine as a non-protein nitrogen supplement in rations for sheep has been tested by van der Merwe[1] and MacKenzie[2]. Both authors found the nitrogen could be utilized by the ruminal flora but MacKenzie reported five deaths among sheep which had been receiving melamine, but he had no way of establishing the cause of death.

Van der Merwe reported that a
with 67 g melamine had shown "stres
day and died on the 6th day" while a
50 g had shown "stress on the 6th d
on the 7th day". Autopsy of the secor
shown "inflammation and severe deg
the liver, kidneys, bladder and lungs.
were in the worst state and the blad
of blood". The cause of death was n
was therefore decided to investigate
toxic effects of melamine.

Methods

Merino wethers were used throughou
Experiments 1 to 4 carried permar
fistulae which were used for dosing th
the removal of ruminal contents for pH
tions and the recording of ruminal mo
in the case of Experiments 1 to 3 the
sheep were housed in metabolism cage
faeces bags. Twenty-four hour urine
collected.

Blood and urine examinations were
by standard methods as used in this

Results

Experiment 1.

A sheep weighing 46 kg was given
mine in a single dose.

The blood urea level rose progressively as shown in Table 1.

On the tenth day after dosing the animal stood with its back arched and showed complete anore-

MELAMINE AS A DIETARY NITROGEN SOURCE FOR RUMINANTS

G. L. Newton and P. R. Utley

University of Georgia College of Agriculture
Coastal Plain Station, Tifton 31794

mine may not be hydrolized in the rumen at a rate sufficient to promote maximum ruminal protein synthesis and incompletely hydrolized fractions may be absorbed and voided in the urine. These observations would tend to indicate

and 49 of the trial. On day 53 the steer receiving the urea diet had to be removed from the trial due to an injury. After the remaining two steers had been fed their respective diets for 88 days they were sampled for ruminal ammonia, fatted

Clues to cat deaths found in UCD study

Researchers show what they had suspected after pet food recalls: Two chemicals, eaten together, kill felines.

By Carrie Peyton Dahlberg - cpeytondahlberg@sacbee.com

Published 12:00 am PST Wednesday, November 14, 2007
Story appeared in METRO section, Page B1

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Further clarifying the role that a pair of chemicals played in the deaths that prompted massive pet food recalls earlier this year, UC Davis researchers have shown that cats died only when fed two chemicals in combination.

communications

Hydrogen-bonded networks

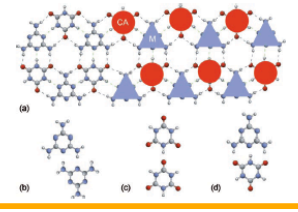
DOI: 10.1002/smll.200600407

Cyanuric Acid and Melamine on Au(111): Structure and Energetics of Hydrogen-Bonded Networks**

Wei Xu, Mingdong Dong, Henkjan Gersen, Eva Rauls, Socorro Vázquez-Campos, Mercedes Crego-Calama, David N. Reinhoudt, Ivan Stensgaard, Erik Lægsgaard, Trolle R. Linderoth, and Flemming Besenbacher**

Supramolecular chemistry based on noncovalent interactions is a powerful synthetic tool for the preparation of complex molecular architectures.[1,2] In particular, hydrogen bonds are considered to be useful for controlling molecular self-assembly due to the reversibility, specificity, directionality, and cooperative strength of this class of interactions.[3,4] In recent years, a number of studies have characterized hydrogen-bonded structures formed by molecules adsorbed on solid surfaces under vacuum conditions.[5–7] Besides fundamental interest, these studies are driven by the technological relevance of molecular surface structures from perspectives such as surface coatings, biochemical sensors, organic electronics, and heterogeneous catalysis. Most studies so far have involved only homomolecular interactions, and very systems with sufficiently high intermolecular binding strengths have to be identified.[11,12]

An extensively studied heteromolecular H-bonding motif results from the interaction between diaminopyridine and diimide moieties, exhibiting three complementary NH···O and NH···N hydrogen bonds.[13–15] This classic H-bonding interaction has been exploited in the solution phase,[14,15] in the solid state,[5] and more recently at interfaces.[8,9,16–18] A prototypical molecular system exhibiting this complementary interaction is the cyanuric acid/melamine (CA/M) system. The basic structure formed from these compounds both in solution, in bulk, and on surfaces is a symmetric two-dimensional (2D) array consisting of cyclic hexamers of 3 M and 3 CA molecules (see Figure 1a), which



Environmental Health Perspectives
Vol. 69, pp. 287-292, 1986

dies on
ed Derivatives

bee,** Takeshi Inoue,†
s,* Michel W.
o Cascieri§

nts. In the presence of water, these
uate the safety of exposure to these
ew summarizes the results of acute
ute, subchronic, reproduction, me-
e are also summarized. Results from
swimming pools.

pport the registration of these materials
A.

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urates

icity

and trichloroisocyanurates are considered
slightly toxic when administered as single
rats. The LD_{50} values range from 600 to
These materials are practically nontoxic
d as a single dose to rabbit skin, since the
is consistently greater than 5000 mg/kg
unpublished observations).
d isocyanurates are generally corrosive
d to the rabbit eye and are severely irri-
rrosive to rabbit skin when applied under
ditions for 24 hr according to procedures
the Federal Hazardous Substances Act
wever, when tested in the 4-hr Department
tation (DOT) test, these materials are not
rabbit skin (Monsanto, unpublished obser-
vations).

companies of The Industry *ad hoc* Committee on Isocyanurates. All of the latter studies have been submitted to the U.S. Environmental Protection Agency

*Monsanto Company, 800 N. Lindbergh Blvd., St. Louis, MO 63167.
**Olin Corporation, 91 Shelton Ave., New Haven, CT 06511.
†Nissan Chemical Ind., Ltd., 200 Park Ave., New York, NY 10017.
‡Shikoku Chemicals Corp., 301 N. Rampart #C, Orange, CA 92668.
††ICI Americas, Inc., Wilmington, DE 19897.
§FMC Corporation, U.S. Highway 1, Box 8, Princeton, NJ 08540.

Subchronic Toxicity

Several inhalation studies have been conducted with rats exposed to chlorinated isocyanurate dust. In an early study that provided little information on experimental details, the LC_{50} of trichloroisocyanurate dust was reported to be 25 mg/m^3 (*1*). As part of this investigation, 1.88 mg/m^3 of the trichloroisocyanurate dust,