Melamine and Analogues in Food

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• Toxicology of Melamine and Analogues

• Sources of Melamine and Analogues in Food
Melamine and Analogues

Melamine

Ammeline

Ammelide

Cyanuric acid
Toxicology of Melamine and Analogues

• Melamine Toxicity (given alone): LD$_{50}$ = >3 gm/kg-bw
• 13-wk study = NOAEL 63 mg/kg-bw/day in rats; used for TDI calculation
• This study: better measurement of microcrystal formation in urine
• TDI = maximum daily intake for lifetime without appreciable toxicity
• 2007 RA: 100-fold safety factor = TDI = 0.63 mg/kg-bw/day
• 2008 RA: 1000-fold safety factor = TDI = 0.063 mg/kg-bw/day
Toxicology of Melamine and Analogues

- NTP reported on bioassay results in rats: NOAEL = 126 mg/kg-bw/day (1983)
- Higher dose (263 mg/kg-bw/day) produced bladder stones and tumors
- Most authorities consider the tumors secondary to the chronic irritation and hyperplasia of the bladder epithelium
- Lower doses without stones do not produce bladder tumors
Toxicology of Melamine and Analogues

Other toxicities:

- Time to eliminate one-half dose = 2-4 hours
- Genotoxicity: well-accepted tests were negative
- Overall, non-genotoxic and non-mutagenic
Toxicology of Melamine and Analogues

Developmental & Reproductive Toxicity:

• Developmental toxicity:
  NOAEL = 1,060 mg/kg-bw/day

• Maternal Toxicity:
  NOAEL = 400 mg/kg-bw/day

• No effect on reproductive organs: high dose
Toxicology of Melamine and Analogues

Toxicity of Cyanuric Acid (given alone):

- Time to eliminate one-half dose = 2 hrs
- Acute toxicity $LD_{50} = >3,000\ mg/kg$-bw
- Kidney toxicity = 5,400 mg/kg-bw/day
- Long term: NOAEL = 154 mg/kg-bw/day (NaCYA, WHO)

Reproductive & Developmental:

- Rabbits: 500 mg/kg-bw/day
- Rats: 5000 mg/kg-bw/day
Toxicology of Melamine and Analogues

Toxicity of Melamine and Cyanuric Acid (CYA) given at same time:

• Cats from 2007 exposure died from acute renal failure
• Microscopic exam of kidneys showed massive infiltration and obstruction of tubules, collecting ducts
• Some cats recovered but returned later with chronic renal insufficiency or failure
Toxicology of Melamine and Analogue

Cats: short term study (Puschner)

- 32, 121, 181 mg/kg-bw/day (each at this dose, melamine and cyanuric acid)
- All groups developed: depression, vomiting, anorexia
- Renal impairment at 36 hours: abnormal clinical chemistries, kidney edema, tubular dilatation
- 32 mg/kg-bw/day is still an toxic effect dose
Toxicology of Melamine and Analogues

Melamine cyanurate has been shown in:

- Mice, cats, pigs (400 mg/kg-bw) and fish (20 mg/kg-bw) kidneys
- Non-toxic combined dose without crystals must be determined in mammals (5 mg each/kg-bw in rats?)
- Studies are being conducted at FDA Center for Veterinary Medicine and National Center for Toxicological Research
Product-specific Import Alert and Advise to Consumers
If MC is present as 2.5 mg/kg concentration (excluding infant formula), U.S. per capita MC intake from milk-derived food ingredients:

• Total per capita ingredient intake: 17 g/p/d
• Total per capita MC intake: 42.5 µg/p/d
• Total intake of MC (adult only): 1.1 % of TDI/10
  (TDI: Tolerable daily intake = 0.63 mg/kg-bw/day)
Melamine (MC) and Analogues in Food from Regulated Uses

Uses of Melamine (MC) and Analogues

• Plastics, resins, sanitizers, pesticides, binding agent, colorant, flame retardant, fertilizer, etc.

• Not approved for direct addition to food
Melamine (MC) and Analogues in Food from Regulated Uses

- Food Contact Materials
- Melamine-Formaldehyde Resins (MFR)
Melamine (MC) and Analogues in Food from Regulated Uses

Food Contact Materials:

Use as a component of Adhesive (21 CFR 175. 105) as an indirect food Additive.
Melamine (MC) and Analogues in Food from Regulated Uses

Melamine-Formaldehyde Resins (MFR)

- Tableware
- Laminates
- Glue
- Molding compounds
- Coating
- Adhesive
- Paper/paperboard
MFR Tableware

Monkey Melamine 12-pc. Dinnerware Set
$14.99
List price: $19.99
You Save: $5.00 (25%)

Availability:
Usually ships in 24 hours
This item is available online, but is not available in stores.
Melamine (MC) and Analogues in Food from Regulated Uses

MFR are thermoset resins. MC is part of the resin and only the residue of MC would be available for migration.
Melamine (MC) and Analogues in Food from Regulated Uses

Migration of MC from MFR Tableware

- No migration detected into water
- Small amount into 3% acetic acid (70 °C, 2 hrs)
- Continuing life time migration (Heat, acid)
- Under specific migration limit (EU,SML: 30 mg/kg)
Melamine (MC) and Analogues in Food from Regulated Uses

• For the use of MFR as coating, it is practically used on the exteriors of cans, rarely used for interior (food contact side) in the U.S.

• The exposure from the uses of MFR in molded articles and filters would be minimal due to repeated-use application
Melamine (MC) and Analogues in Food from Regulated Uses

Estimated Level of MC in Food from the Uses

• Adhesive: < 7 ppb

• Component in tableware, paper/paperboard, packaging etc.: 3.4 ppb

• Total: < 15 ppb
Melamine (MC) and Analogues in Food from Regulated Uses

Cyanuric Acid (CYA) and Derivatives

- As components in sanitizing solutions 21 CFR 178.1010) on food-processing equipments and utensils, and on other food-contact articles within defined conditions as described in CFR.

- The cumulative exposure to CYA from the use is estimated at 81 ppb.
Melamine (MC) and Analogues in Food from Regulated Uses

Cyanuric Acid (CYA) and Derivatives - 2

- FDA permits the presence of CYA (≤30%) as a byproduct in feed-grade biuret. Biuret is an approved additive for ruminant feed products to provide non-protein nitrogen with specific labeling. (21 CFR 573.220)

- Label must state the maximum percentage of equivalent crude protein from non-protein nitrogen
Melamine (MC) and Analogues in Food from Regulated Uses

Trichloromelamine (TCM)

- TCM is regulated as sanitizing solutions (21 CFR 178.1010) on food-processing equipments and utensils, and on other food-contact articles within defined conditions in CFR. TCM may not be used as a sanitizer in dairy or milk production operation in the United States.
Trichloromelamine (TCM) - 2

• TCM decomposes to MC. The exposure to TMC from regulated use as sanitizing solution has been estimated at 0.27 ppm. This estimate is supported by EPA (0.28 ppm).

• Conservative assumption: all sanitizers are TCM, then exposure to melamine from TCM: 0.14 ppm
Cyromazine (CY)

CY, a pesticide, could metabolize to melamine. (40 CFR 180.414) However, EPA has proposed to drop MC as a component of the CY tolerances in 2000 because EPA concluded that only the parent residue, cyromazine, should be a residue of concern.
Summary

In the food, MC/CYA may potentially come from

• Adhesives used in food contact materials
• MFR used in tableware, packaging, paper/paperboard, molding/filter, etc.
• Sanitizing solutions used on food processing equipment, utensils, containers (not for milk)
• The dietary exposure to MC from regulated uses are conservatively estimated.
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