Sources and pathways of human exposure to melamine and its derivatives

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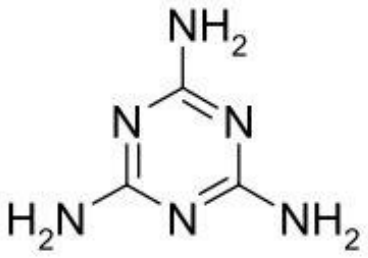
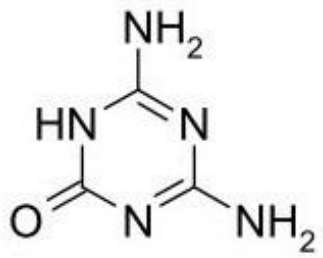
Melamine and its derivatives

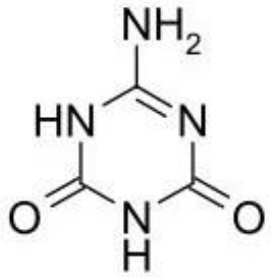
Triazine skeleton, high N content (67%)



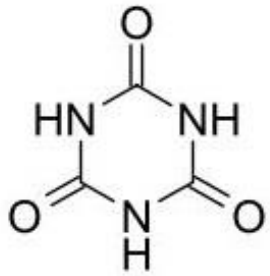
Melamine



Ammeline



Ammelide



Cyanuric acid

Pet food contamination in North America in 2007 resulted in >39,000 cats and dogs developed acute renal failure; >8,500 deaths

Toxic milk powder scandal in China in 2008: 294,000 cases of urinary stones, which resulted in ~50,000 hospitalizations for renal failure and at least six deaths

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Uses of melamine and its derivatives

Melamine

1.2 million tons/year (2007)

Melamine-formaldehyde resin (laminates, formica, dry-erase whiteboards, adhesives, textiles, cleaning materials, kitchenware)**: Hard, scratch/impact/heat resistant, dishwasher safe,**

Flame retardant (PUF, paints, apparel)

Textiles (wrinkle/stain resistance)

Fertilizer

Cyanuric acid

175,000 tons/year (2016)

Disinfectants and bleaches

Chlorine stabilizer in swimming pools

NPN additives in animal feed

Flame retardant

Hair conditioner

https://melamine.cefic.org/index.php/melamine/applications

Biomonitoring of melamine

Environmental Pollution 238 (2018) 248–254

Melamine and its derivatives in dog and cat urine: An exposure assessment study☆

Rajendiran Karthikraj [a], Rasya Bollapragada [a], Kurunthachalam Kannan [a, b, c, *]

Environment International 123 (2019) 375–381

Inter-day and inter-individual variability in urinary concentrations of melamine and cyanuric acid

Hongkai Zhu[a], Kurunthachalam Kannan[a,b,*]

Median urinary concentrations (ng/mL); n=30/30 for cats and dogs; n=19/213 samples for humans: Detection frequency: >99% for MEL and CYA in humans

	Humans	Dogs	Cats
Melamine	1.6	7.4	15
CYA	8.7	29	74
Ammeline	0.37	0.5	<1
Ammelide	0.75	6.4	4.8

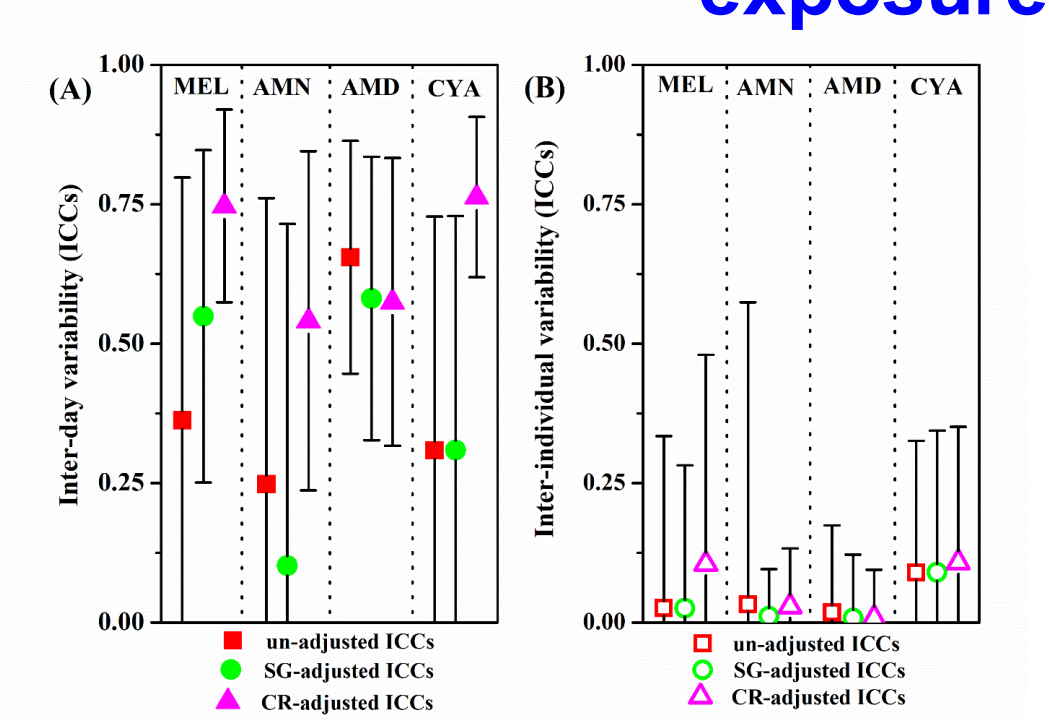
CYA > MEL

Total Conc Range (ng/mL)

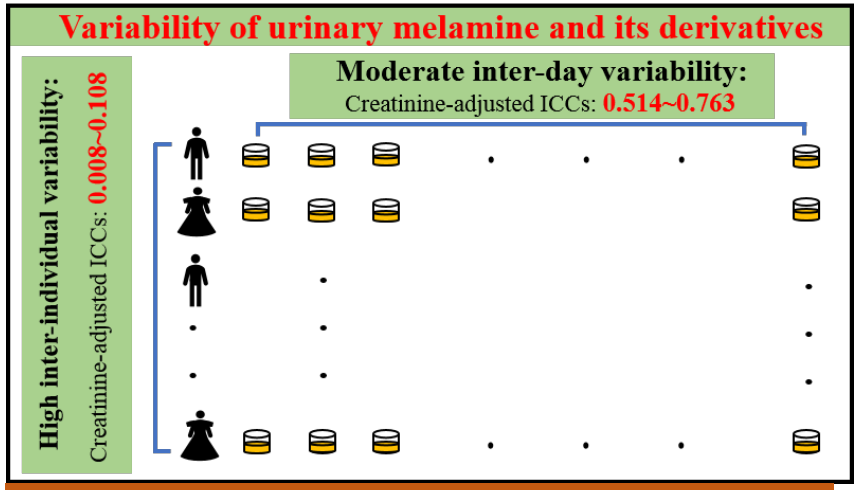
Humans : 3.5-190; > in children
Dogs : 13-510
Cats : 5.8-760

Tentative melamine reference: 63 ug/g Cr; our values 0-25 ug/g Cr (approx. 31.5 ng/mL and our values nd-57 ng/mL)

Inter and intra-individual variations in melamine exposure



Intraclass correlation coefficients (ICCs) for inter-day and inter-individual variabilities in un-adjusted, specific gravity (SG)-adjusted, and creatinine (CR)-adjusted melamine and its derivatives' concentrations in human urine.

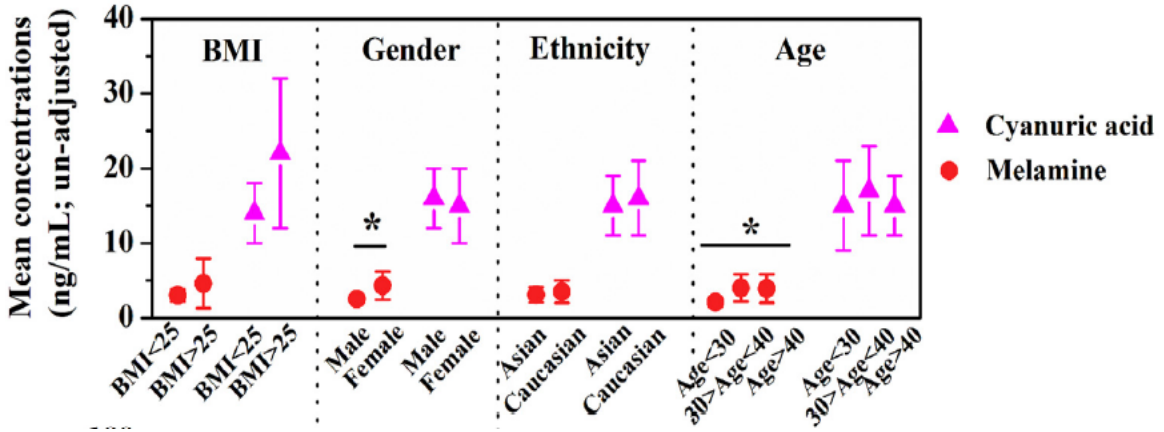


19 individuals, 45 con. days, 213 urine
ICC >0.75 excellent, 0.6-0.74 good, 0.4-0.59 fair, <0.4 poor

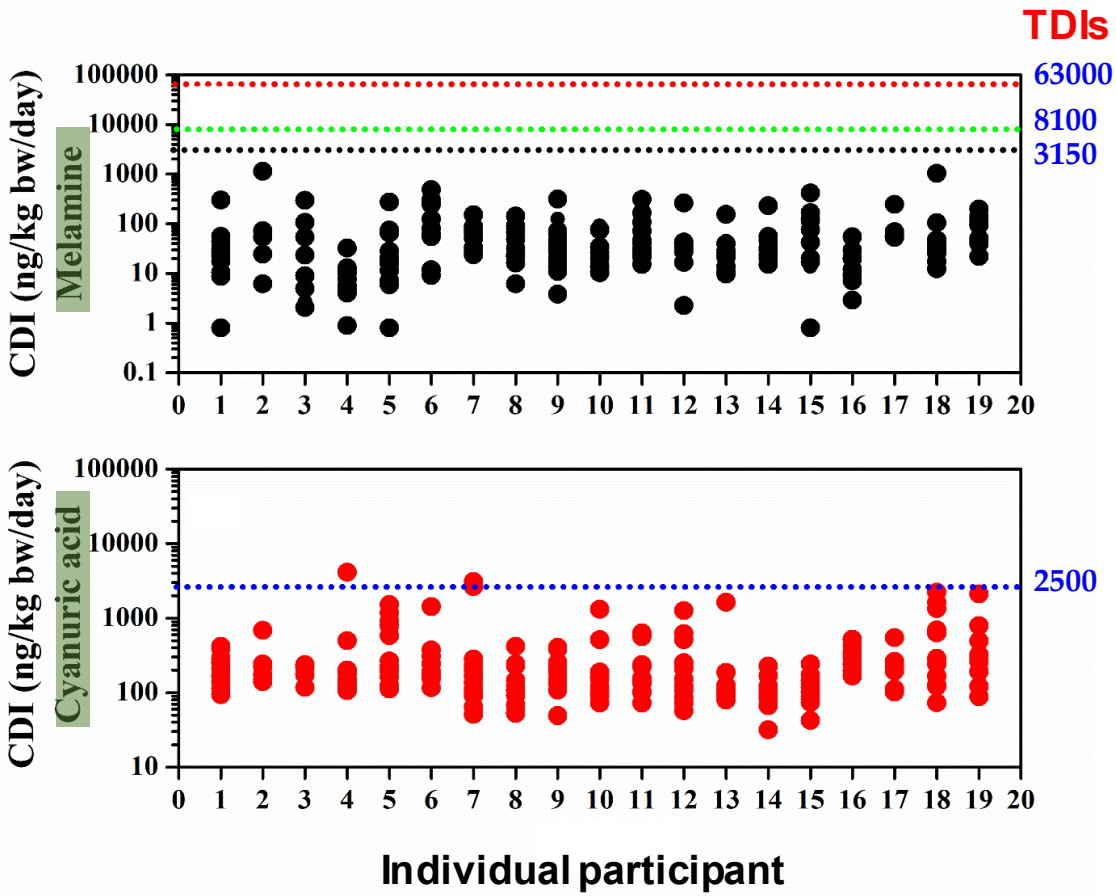
Creatinine normalization improves predictability of urinary melamine concentrations ICC=0.51-0.76

Determinants of melamine exposure

- A weak but significant correlation existed between melamine and cyanuric acid in urine
- Gender, ethnicity and BMI were not significant predictors of urinary concentrations – age at times showed significance: but our sample size is small
- Urinary concentrations of MEL were not correlated with creatinine



Cumulative daily intake of melamine



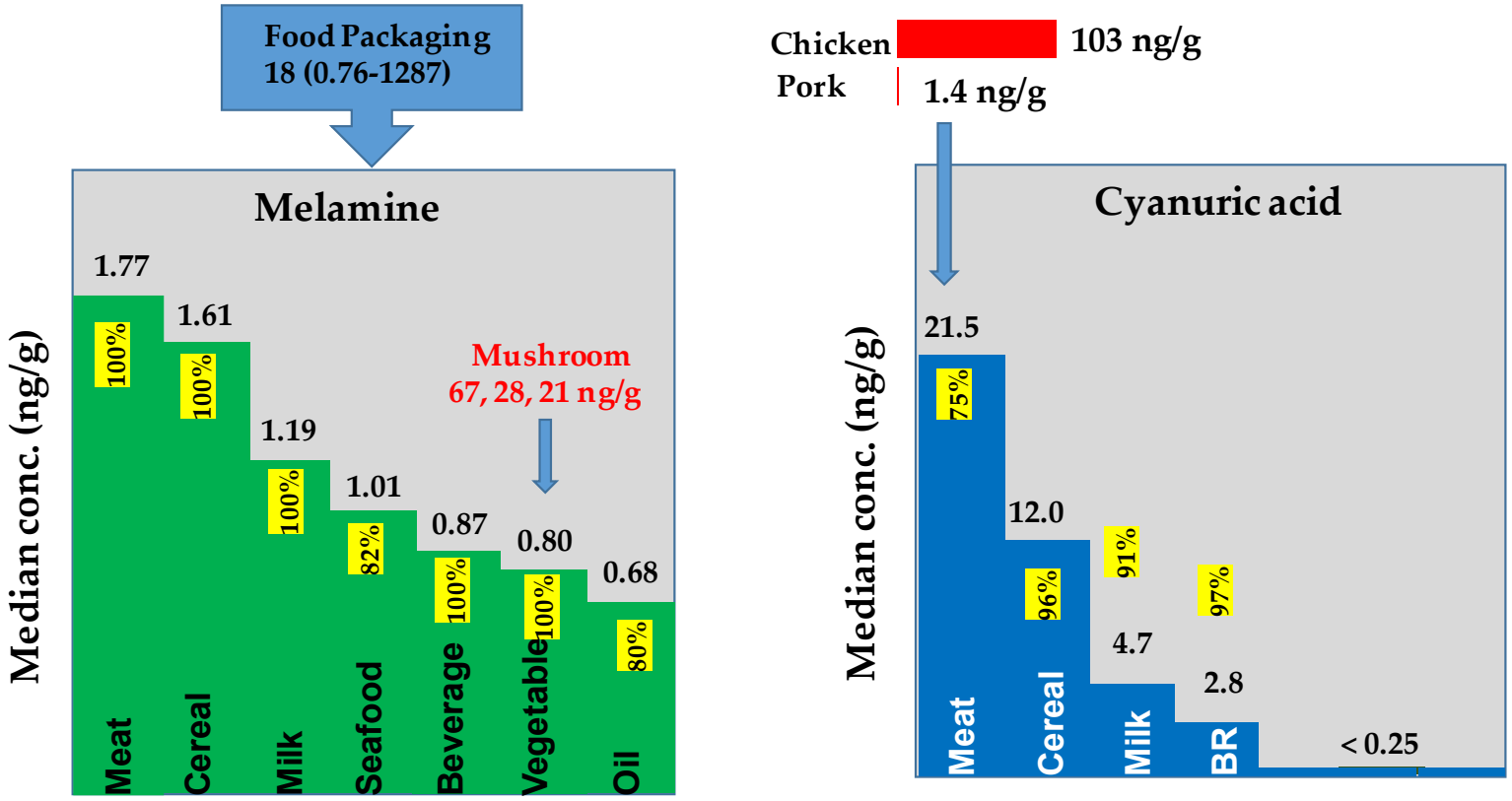
CDI adults (ng/kg bw/d)
MEL: 0.8-1130 (mean: 66)
CYA: 32-4130 (mean: 315)

Daily intake is 10-100 times lower than the TDI

Melamine and cyanuric acid in foodstuffs from the United States and their implications for human exposure

Hongkai Zhu[a], Kurunthachalam Kannan[a,b,c,*]

Environment International 130 (2019) 104950



DIET

121 foodstuffs, 24 packaging, 12 animal feed

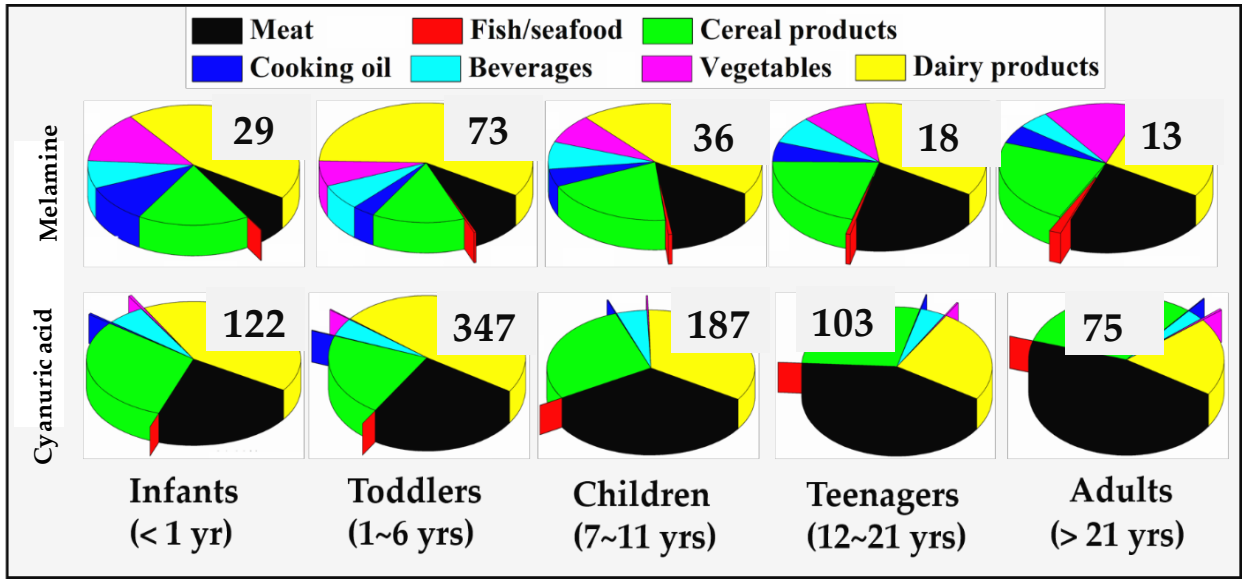
Albany, NY, in 2018

Sum median conc: 23.6 ng/g in meat to 2.2 ng/g in veggies. Highest 305 ng/g in chicken

Animal feed: 57 ng/g

Packaging: 36 ng/g; max 1570 ng/g (pasta)

Dietary intake of melamine/cyanuric acid



Dietary intake of MEL: 13-73 ng/kg bw/d
Dietary intake of CYA: 75-347 ng/kg bw/d

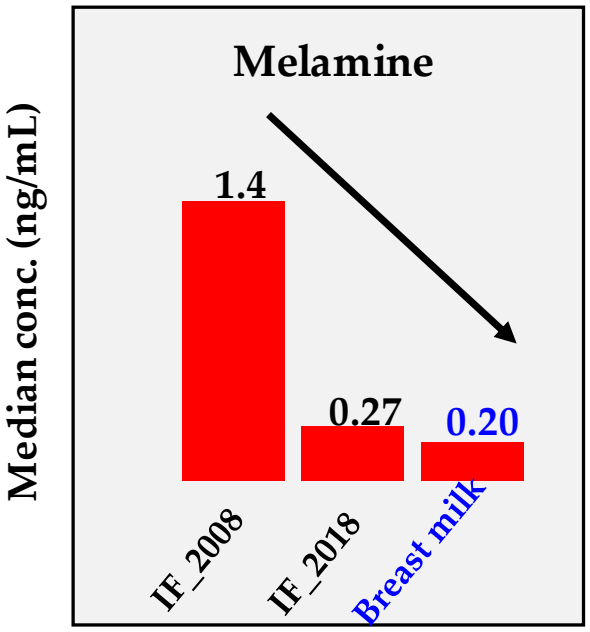
Dairy, Meat, and Cereal products: > 80%

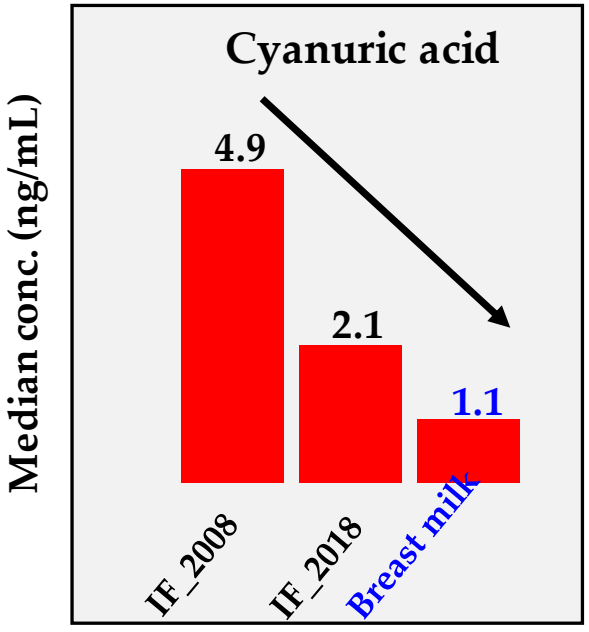
- CYA > MEL
- Toddlers > children > infants > teenagers > adults
- EFSA 2010: 1070 ng/kg bw/d for MEL
- 1680 ng/kg bw/d for CYA
- DIET explains ~20-25% of exposure

Occurrence of Melamine and Its Derivatives in Breast Milk from the United States and Its Implications for Exposure in Infants

Hongkai Zhu† and Kurunthachalam Kannan*,†,‡

Environ. Sci. Technol. 2019, 53, 7859–7865





>94% samples contained MEL and CYA; highest conc 7.14 ng/mL.
Breast milk levels are 2-5-fold lower than those in infant formula (2.7 ng/mL) and cow milk (7.9 ng/mL)

Melamine/cyanuric acid in infant formula (IF) and breast milk

100 breast milk (NCS specimen bank) 2009-2012

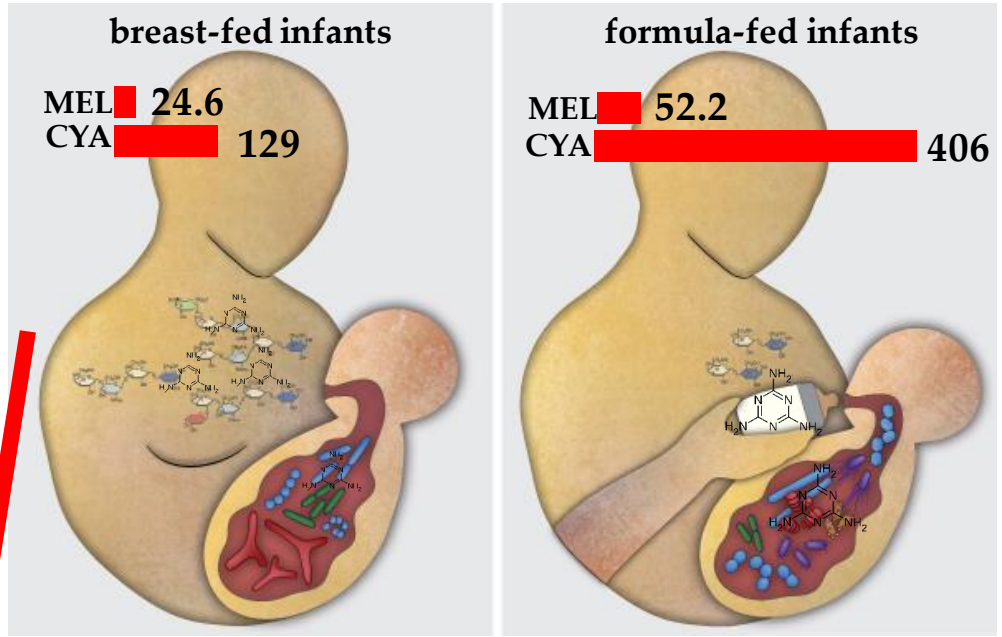
Infant formula: 2008 and 2018

Continuing Occurrence of Melamine and Its Derivatives in Infant Formula and Dairy Products from the United States: Implications for Environmental Sources

Hongkai Zhu[†,‡] and Kurunthachalam Kannan[*,†,‡]

Environ. Sci. Technol. Lett. 2018, 5, 641–648

Breast-fed or Formula-fed?



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Median Intake through breast feeding
MEL: 17-31 ng/kg bw/d
CYA: 89-161 ng/kg bw/d

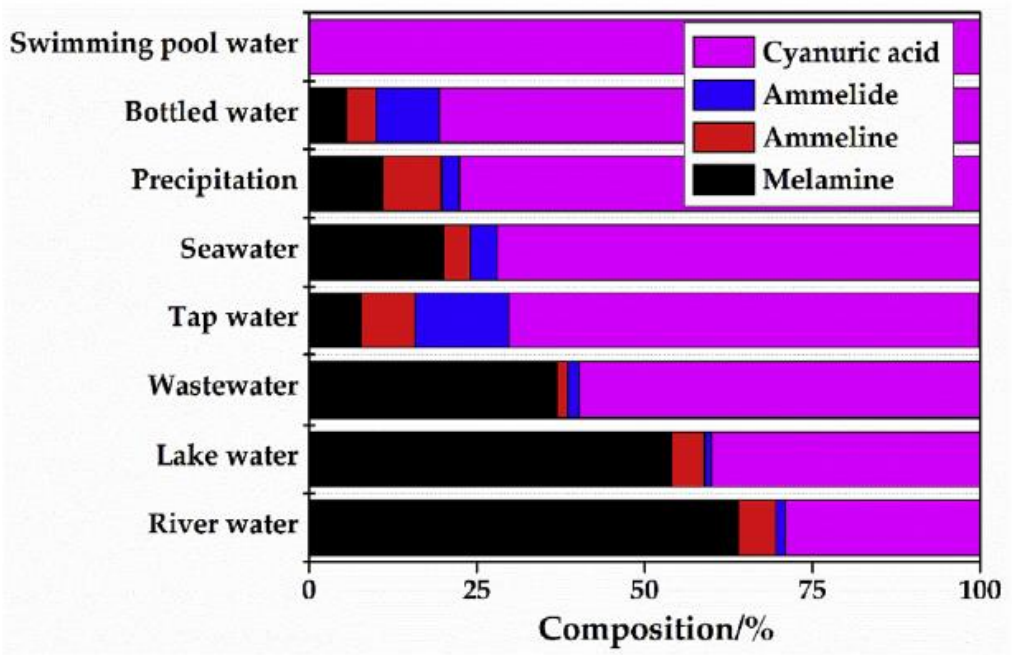
Median Intake through formula feeding
MEL: 28-67 ng/kg bw/d
CYA: 219-523 ng/kg bw/d

10-100 times below TDI

Occurrence and distribution of melamine and its derivatives in surface water, drinking water, precipitation, wastewater, and swimming pool water☆

Hongkai Zhu [a], Kurunthachalam Kannan [a, b, *]

Environmental Pollution 258 (2020) 113743



Median conc (ng/L)

Swimming pool water	15000000
Bottled water	98
Precipitation	739
Seawater	186
Tap water	512
Wastewater	1240
Lake water	347
River water	370

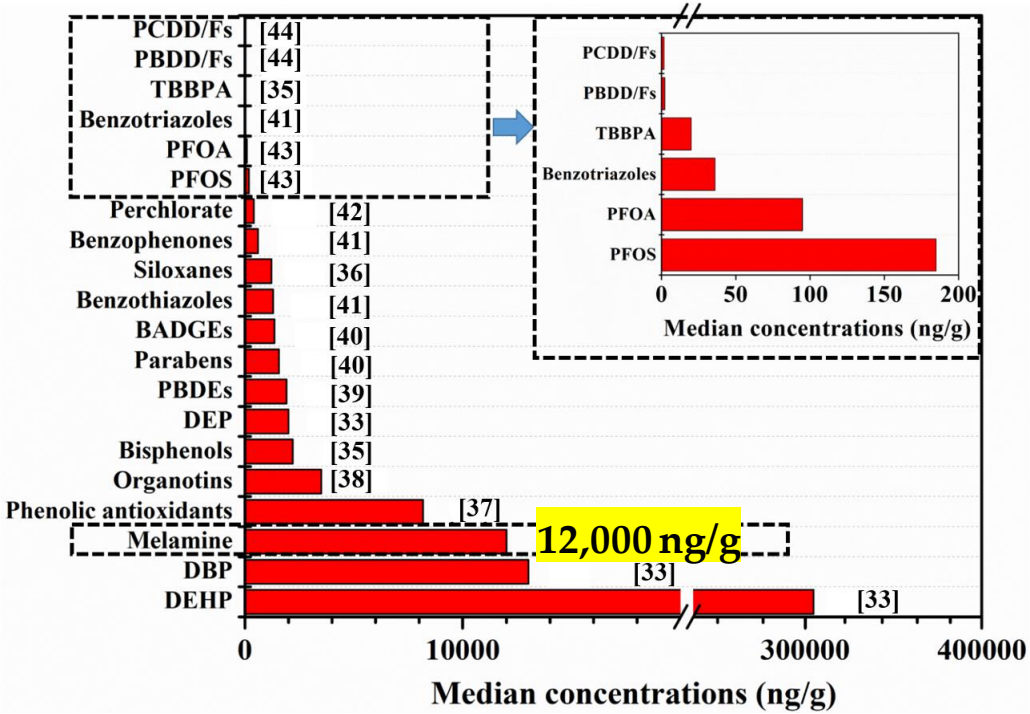
MEL concentrations were significantly correlated with ATRAZINE concentrations in surface waters.

Daily intake of MEL and CYA through drinking water: 0.18-0.79 and 2.9-13 ng/kg bw/d.

Distribution Profiles of Melamine and Its Derivatives in Indoor Dust from 12 Countries and the Implications for Human Exposure

Hongkai Zhu[†] and Kurunthachalam Kannan[*,†,‡]

Environ. Sci. Technol. 2018, 52, 12801−12808



Median concentrations of melamine and other chemicals measured in indoor dust collected from Albany, New York, United States

Dust ingestion as a source of exposure

MEL > CYA in dust

MEL: 9.38−80.0 ng/kg-bw/d
CYA: 2.27−19.3 ng/kg-bw/d

Not a trivial source!

Toddlers 10 times > adults

Determination of melamine and its derivatives in textiles and infant clothing purchased in the United States

Hongkai Zhu [a], Kurunthachalam Kannan [a,c,b,*]

Science of the Total Environment 710 (2020) 136396

- **77 samples, Albany, NY in 2016.**
- **Raw textiles and infant clothing (ng/g)**

  MEL: 1.2 – 81,800 (median: 53)
  CYA: 3.2-17,800 (44)
  Ammeline: <1.2-25,700 (3.4): Ammelide: <0.5-550 (4.4)
- **13/77 had conc > 10,000 ng/g**
- **MEL > CYA**
- **Cotton fabrics/clothes > synthetic fabrics/socks (crease-resistance)**
- **Washing removed 76-90%**
- **Dermal exposure : <1-2 ng/kg bw/d**

Melamine/cyanurate exposure doses (ng/kg bw/d)

Exposure route	Melamine					Cyanuric acid				
	Infants	Toddlers	Children	Teenagers	Adults	Infants	Toddlers	Children	Teenagers	Adults
Drinking tap water	0.79	0.40	0.25	0.18	0.25	13	6.6	4.1	2.9	4.1
Drinking bottled water	0.21	0.11	0.07	0.05	0.07	2.3	1.2	0.73	0.52	0.73
Swimming activity	n.a.	n.a.	4.7	2.7	1.3	n.a.	n.a.	573,000	332,000	156,000
Indoor dust ingestion	34	80	19	9.4	7.5	8.3	19	4.5	2.3	1.8
Dietary intake[a]	29	73	36	18	13	122	347	187	103	75
Breast milk ingestion	25	n.a.	n.a.	n.a.	n.a.	129	n.a.	n.a.	n.a.	n.a.
Infant formula ingestion	52	n.a.	n.a.	n.a.	n.a.	406	n.a.	n.a.	n.a.	n.a.

CDI adults (ng/kg bw/d)
MEL: 0.8-1130 (mean: 66)
CYA: 32-4130 (mean: 315)

Infants/toddlers >> Adults

Summary

- Widespread exposure of humans to melamine and cyanuric acid; urinary concentrations approximately 10 times below the reference value.
- Dairy, meat and cereals are the major sources of dietary exposure and diet is the major source for adults; clothing, paper packaging contain significant levels of melamine.
- Infants and toddlers are more highly exposed than adults and exposure doses are in general 10-100 times below the reference values.
- Gender, ethnicity and BMI are not predictors of exposure.
- Swimming activity can significantly increase exposure to cyanuric acid
- Diet, dust, drinking water account for only for about 30% of the total exposures; there exists other unknown sources.

Thank you

NYU Langone Health

Table 1 | Changes in TDI over time for melamine and related compounds in human food

Date of publication	Organization	TDI (mg/kg body weight)	Compound
June 2003	WHO[61]	1.5	Cyanuric acid
May 2007	FDA and other US organizations[60]*	0.63	Melamine and related compounds (ammeline, ammelide, cyanuric acid)
September 2008	European Food Safety Authority[64]	0.5	Melamine
October 2008	FDA[68]	0.063	Melamine and related compounds (ammeline, ammelide, cyanuric acid)
November 2008	Health Canada[65]	0.35	Melamine
December 2008	WHO[63] and Health Canada[65]	0.2	Melamine

*Food Safety and Inspection Service of the Department of Agriculture, Centers for Disease Control, Department of Homeland Security, Environmental Protection Agency. Abbreviation: TDI, tolerable daily intake (the amount of a substance that healthy individuals can be exposed to on a daily basis throughout their lifetime without incurring any substantial health risk).

Dalal, R. P. & Goldfarb, D. S. *Nat. Rev. Nephrol.* **7**, 267–274 (2011); published online 22 March 2011; doi:10.1038/nrneph.2011.24