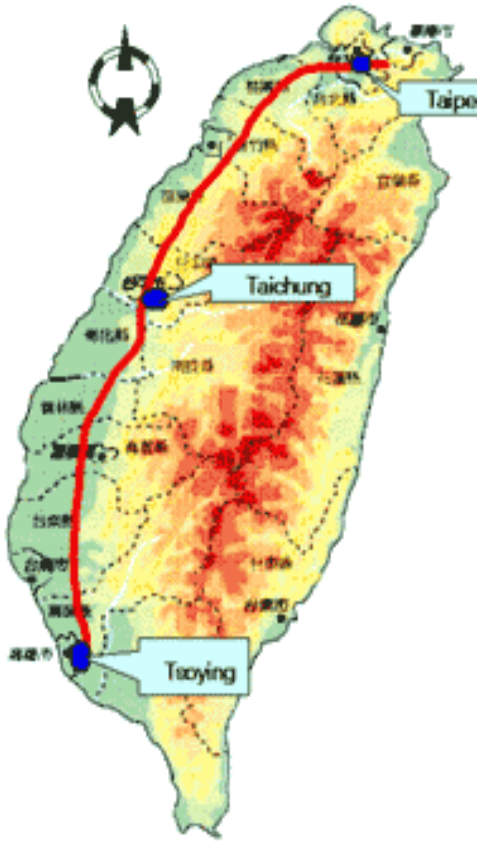


Environmental Melamine Exposure & Renal Diseases

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Taiwan

Taipei



Kaohsiung



Kaohsiung Medical University & Affiliated Hospitals





• Until December 2008, the Chinese Ministry of Health reported that more than 294,000 children were affected, over 51,900 were hospitalized, and at least 6 died by melamine-tainted formula event.

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Page last updated at 11:07 GMT, Wednesday, 17 September 2008 12:07 UK

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Chinese baby milk toll escalates

More than 6,200 babies have fallen ill after drinking formula milk made from contaminated powder, Chinese Health Minister Chen Zhu has said.

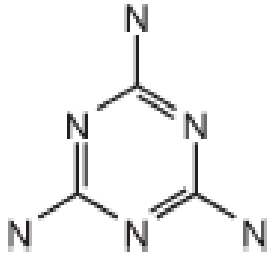
The figure is five times higher than previously announced.

Mr Chen said a third baby had

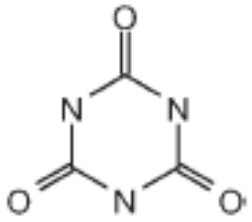


The 2008 Melamine-tainted Baby Formula Food Scandal:

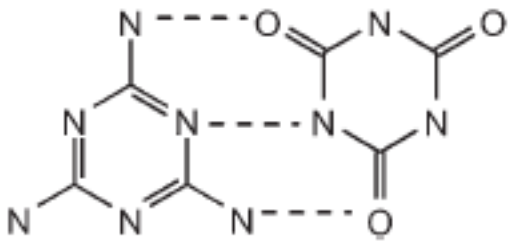
1) **High dose**
2) **Mainly affected in baby and children**



Melamine

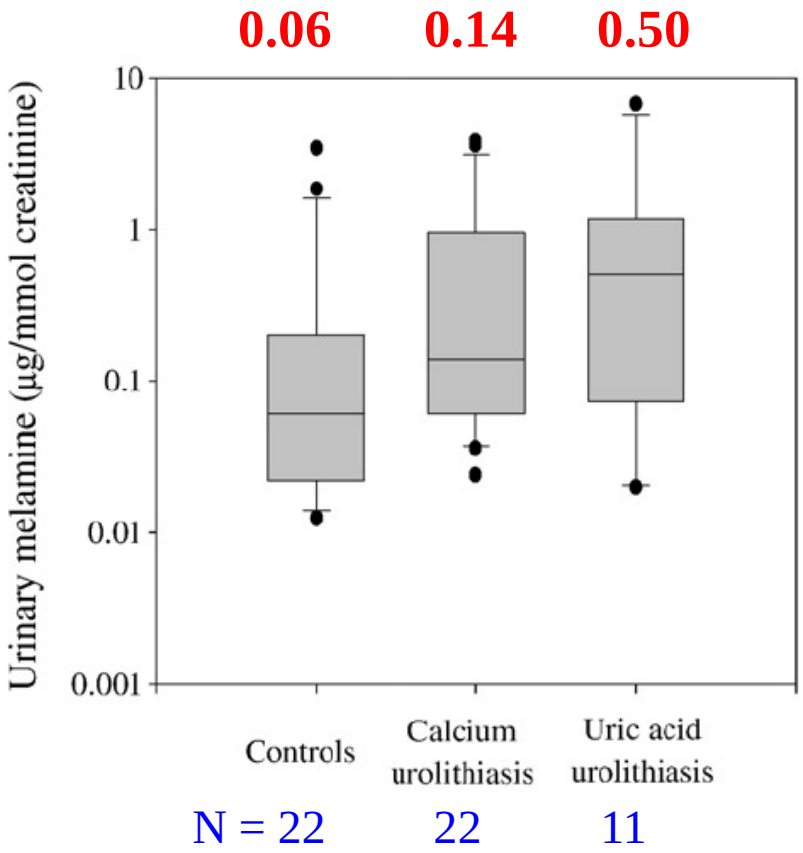


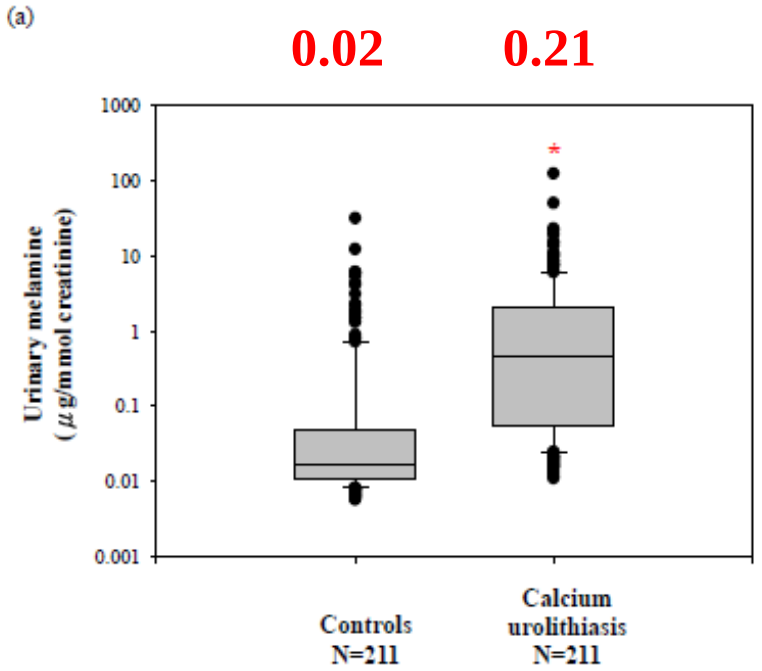
Cyanuric acid

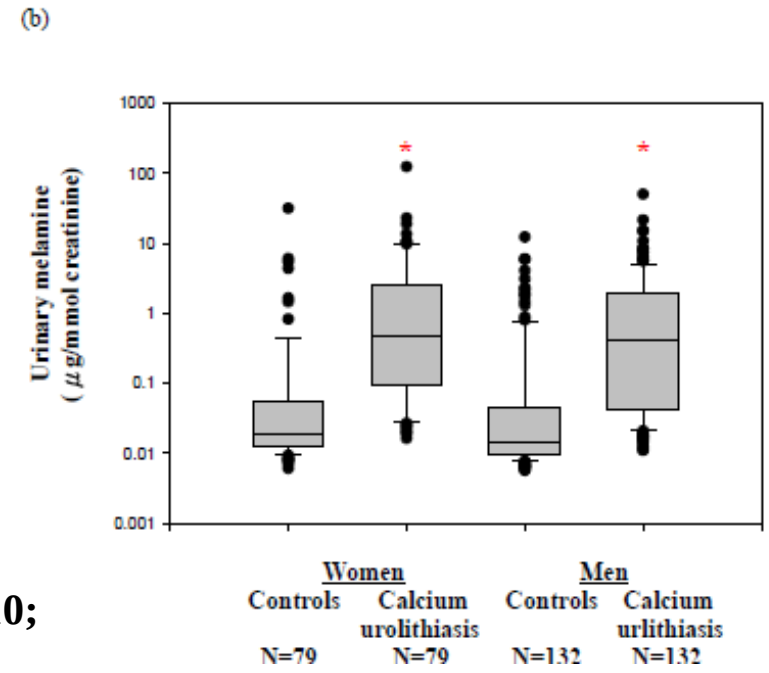


Melamine cyanurate

Melamine (low-dose) ??? Adult urolithiasis







Wu et al., Clin Chim Acta 2010;
Liu et al., Kidney Int 2011

Melamine toxicity: one more culprit in calcium kidney lithiasis

Fernando J. García López[1] and C. Quereda[2]

An outbreak of uric acid and melamine kidney stones and obstructive acute renal failure in children appeared recently in China due to the ingestion of melamine-tainted formula. Liu and colleagues show that calcium urolithiasis is also strongly associated with urine melamine in adults in Taiwan. Although its effect measure is still uncertain, such an association is likely to be causal. These findings prompt further research into the source of exposure, impact in other settings, and changes over time.

Kidney International (2011) **80,** 694–696. doi:10.1038/ki.2011.174

Where is the possible source of melamine exposure in adult?

Journal of Hazardous Materials 188 (2011) 350–356

Contents lists available at ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

High melamine migration in daily-use melamine-made tableware

Chao-Yi Chien[a], Chia-Fang Wu[a], Chia-Chu Liu[b,c,d], Bai-Hsiun Chen[e], Shu-Pin Huang[b,f], Yii-Her Chou[b,f], Ai-Wen Chang[b], Hei-Hwa Lee[e], Chih-Hong Pan[g], Wen-Jeng Wu[b,d,f], Jung-Tsung Shen[d], Mei-Yu Chang[d], Chun-Hsiung Huang[b,f], Jentaie Shiea[h], Tusty-Jiuan Hsieh[i], Ming-Tsang Wu[a,c,j,k,*]



MEL-3



MEL-4

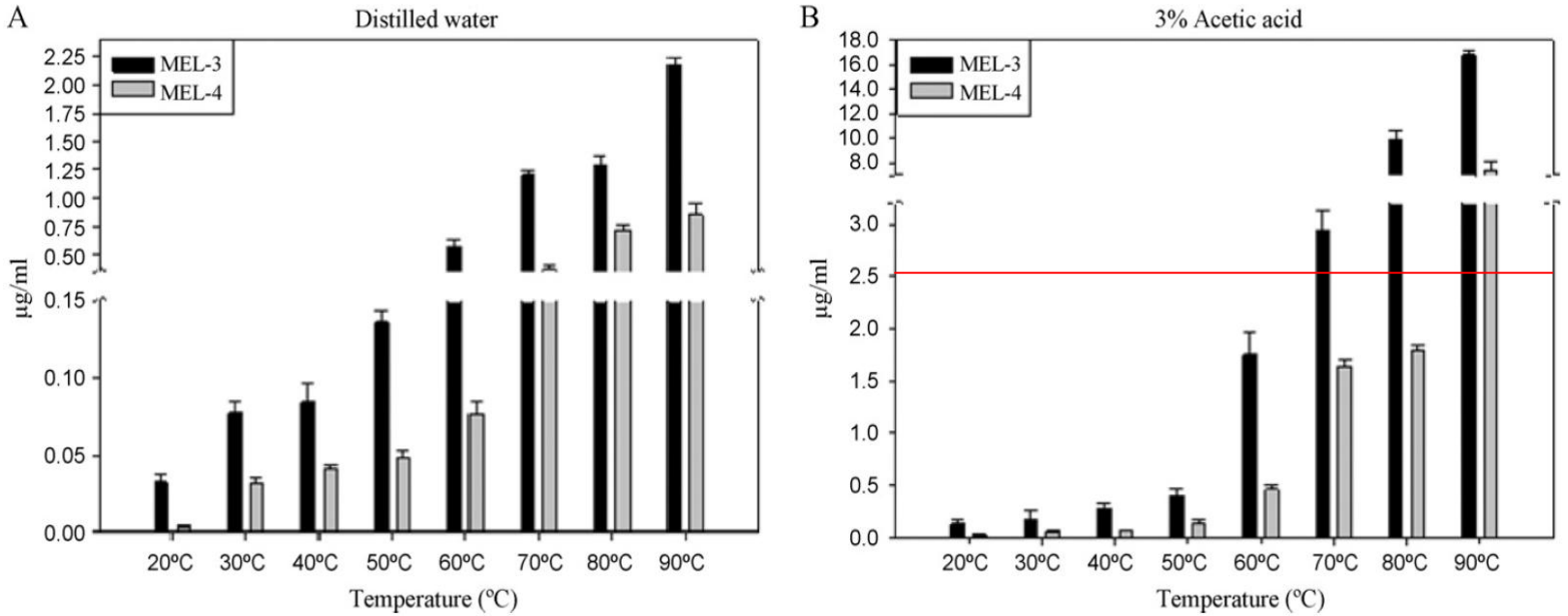


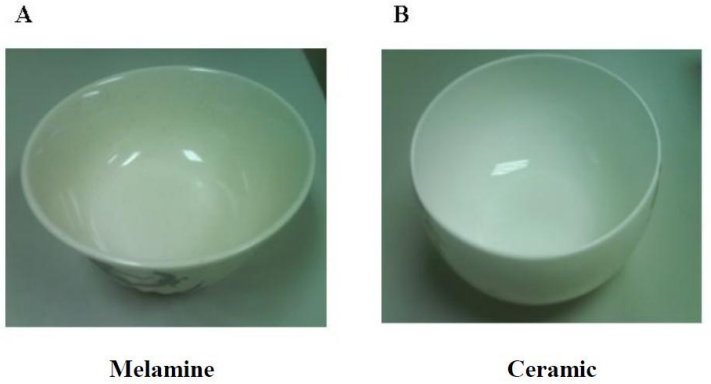
Fig. 2. Comparison of melamine migration levels in melamine-made tableware samples with the cheapest price (MEL-3) *vs.* the most expensive one (MEL-4) in 20 ml simulant (distilled water or 3% acetic acid) at the designated temperature for 30 min (mean ± SD, $n = 8$ repeated experiments, all p-values < 0.05 in distilled water and all p-values < 0.001 in 3% acetic acid).

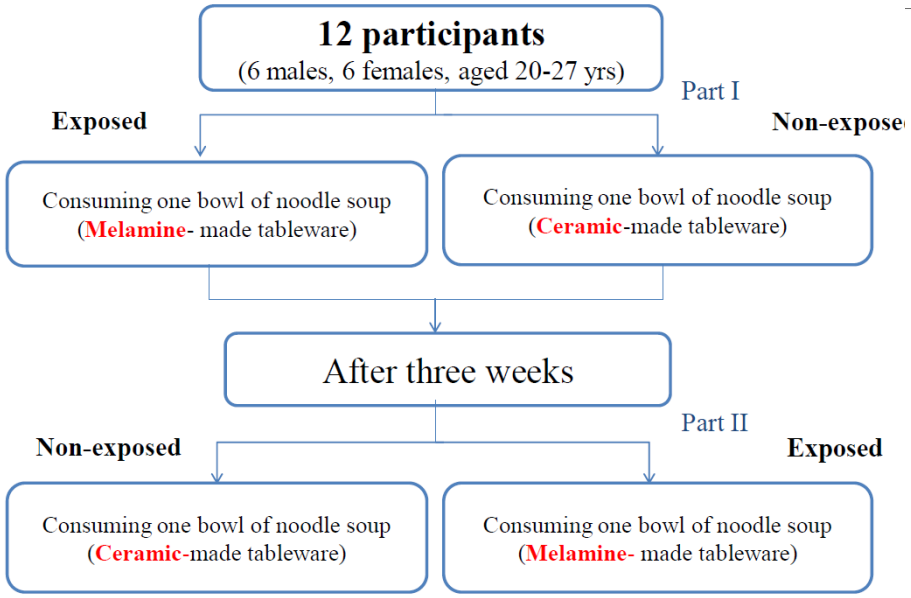
RESEARCH LETTER

Wu et al., JAMA Int Med 2013

ONLINE FIRST

A Crossover Study of Noodle Soup Consumption in Melamine Bowls and Total Melamine Excretion in Urine





•**Research findings reported by 'Time'**



What possible mechanism to form kidney stone by melamine in adult?

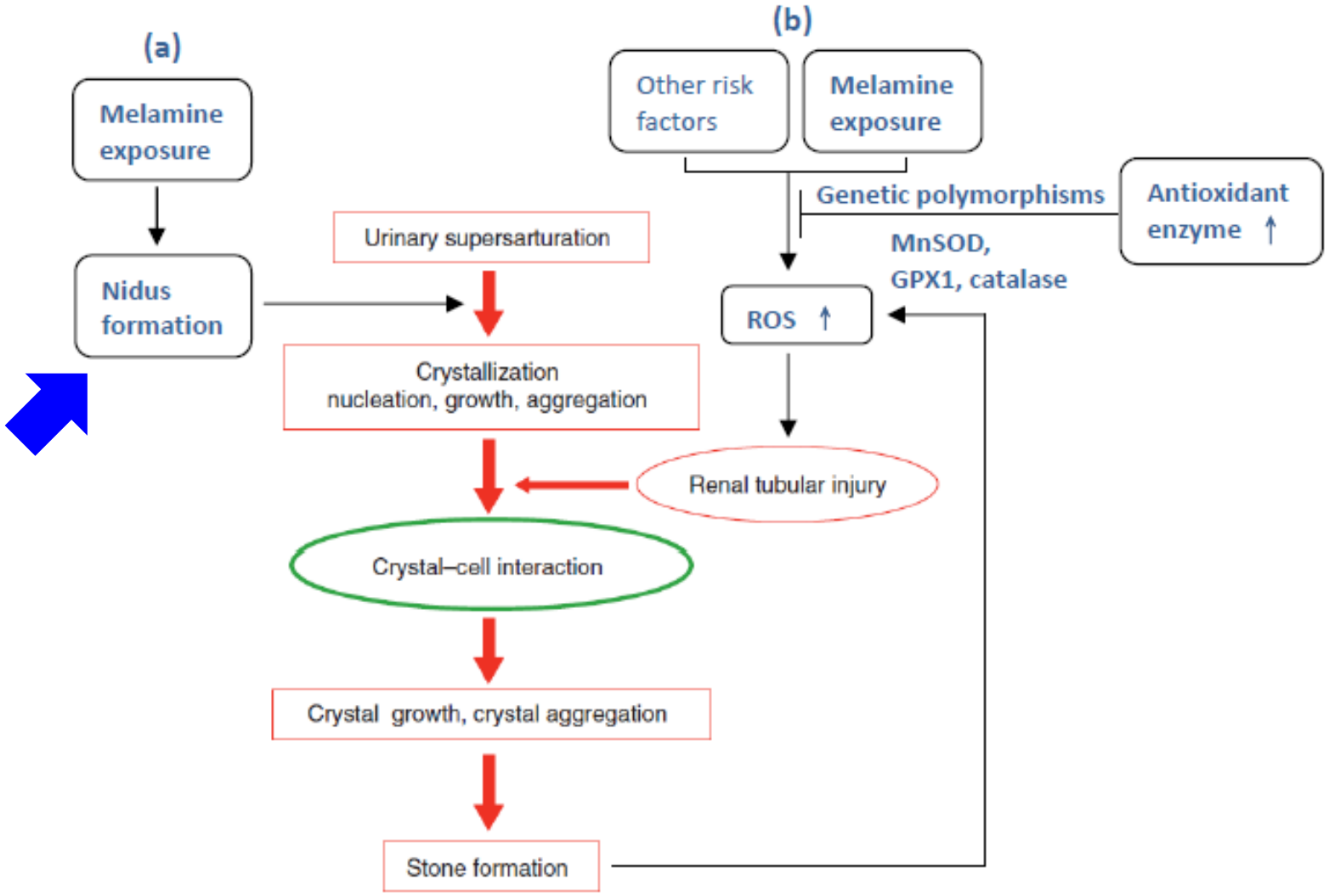
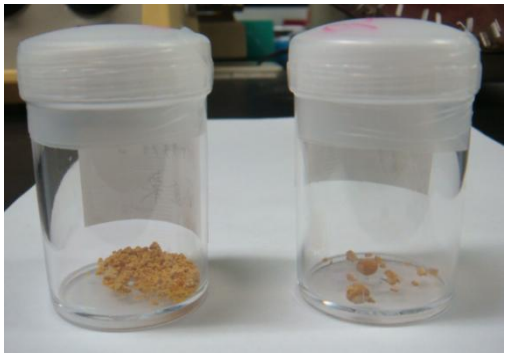


Figure 1. Proposed mechanisms of relationship between melamine exposure and renal urolithiasis (modified from the review article of Tsujihata, 2008).

Progress

- To identify and characterize of melamine cyanurate in stone specimens collected from urolithiasis patients with high urinary melamine levels by **MALDI-TOF**.

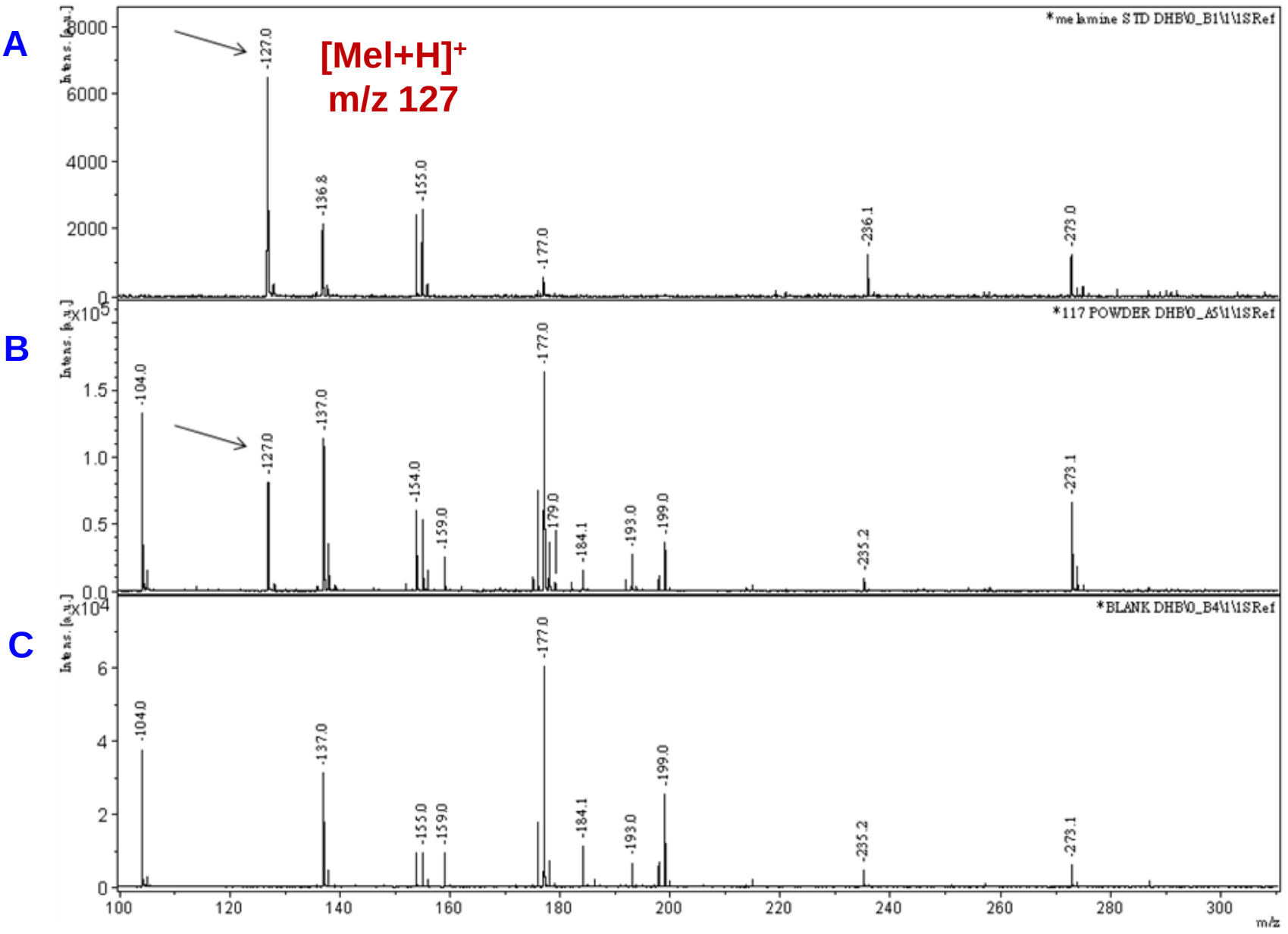


*Ultrasonically extract melamine/cyanuric acid in organic solvent

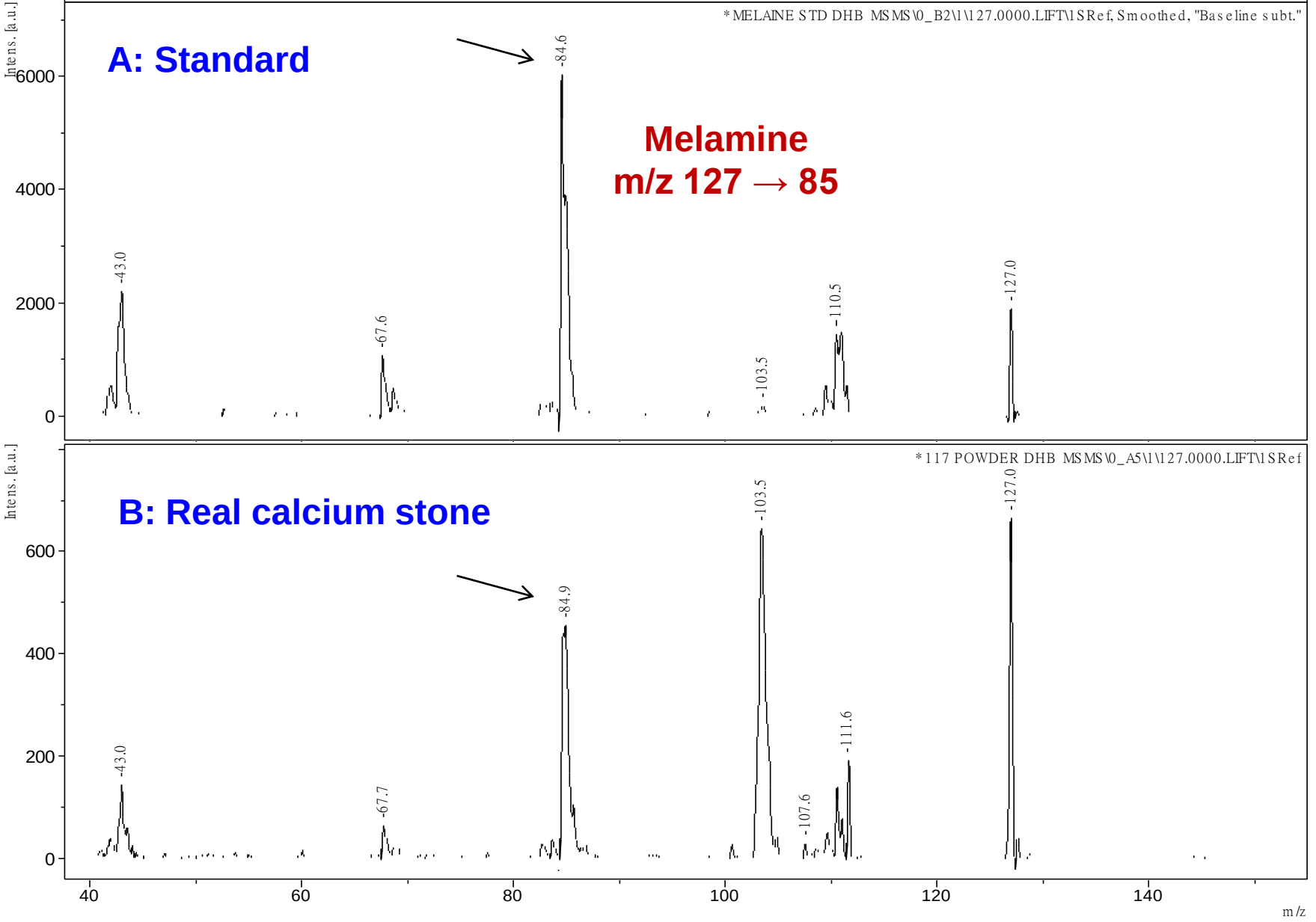
*Mix the concentrated solution with MALDI matrix solution (CHCA/DHB)



Autoflex III
MALDI-TOF MS



A: Standard of melamine cyanurate B: Real calcium stone C: Blank



Liu et al., Clin Chim Acta, 2012

Demographics and clinical characteristics among 42 calcium urolithiasis patients with the absence of typical melamine spectra by Fourier transform infrared spectrophotometer.

Variables	MALDI Positive	MALDI Negative	P values[a]
N	12	30	
Median (IQR) or N (%)			
Age (y)	50.0 (40.5–57.5)	53.0 (44.0–65.0)	NS
Age at first onset (years)	37.5 (29.5–50.5)	47.5 (39.0–64.0)	NS
BMI (kg/m^2)	26.2 (22.6–28.6)	24.5 (22.3–25.5)	NS
Gender			NS
Male	9 (75.0)	13 (43.3)	
Female	3 (25.0)	17 (56.7)	
Years of education			NS
≤9	7 (58.3)	16 (53.3)	
>9	5 (41.7)	14 (46.7)	
Fluid intake (l/day)			NS
> 2	2 (16.7)	2 (6.7)	
1–2	9 (75.0)	16 (53.3)	
< 1	1 (8.3)	12 (40.0)	
Personal habits			
Current smokers	5 (41.7)	10 (33.3)	NS
Current betel quid	1 (8.3)	4 (13.3)	NS
Current drinkers	1 (8.3)	5 (16.7)	NS
Laboratory data			
eGFR	62.7 (52.7–69.5)	68.0 (53.1–82.8)	NS
eCCr	67.6 (54.8–82.0)	68.3 (50.4–85.0)	NS
eGFR < 60 ml/min/ 1.73 m^2,	5 (41.7)	12 (40.0)	NS
Serum, mg/dl			
Uric acid	7.10 (6.64–8.11)	6.60 (5.70–7.50)	NS
Calcium	8.80 (8.55–9.25)	8.80 (8.30–9.00)	NS
Phosphate	4.10 (3.81–4.74)	4.28 (3.80–5.15)	NS
Creatinine	1.29 (1.13–1.38)	1.02 (0.83–1.28)	0.022
Urine, g/g Cr			
Uric acid	0.42 (0.36–0.51)	0.52 (0.41–0.63)	NS
Calcium	0.08 (0.05–0.12)	0.13 (0.09–0.22)	0.011
Phosphate	0.30 (0.20–0.57)	0.46 (0.26–0.64)	NS
Creatinine, mg/dl	103.15 (52.25–133.80)	74.35 (35.60–98.70)	NS
Urinary melamine (ng/ml)	6.03 (1.94–9.23)	1.11 (0.20–3.82)	0.019
Urinary melamine (μg/mmol Cr)	0.71 (0.34–1.28)	0.22 (0.09–0.45)	0.048

12/42 = 28.6%

Wu et al., Clin Chim Acta, 2014

Besides nidus formation, what other possible mechanism to cause rneal damage by melamine in adult?

TOXICOLOGICAL SCIENCES **130(1)**, 17–32 (2012)
doi:10.1093/toxsci/kfs231
Advance Access publication August 21, 2012

Melamine Induces Human Renal Proximal Tubular Cell Injury via Transforming Growth Factor-β and Oxidative Stress

Tusty-Jiuan Hsieh,* Pei-Chen Hsieh,† Yi-Hong Tsai,‡ Chia-Fang Wu,† Chia-Chu Liu,§ Ming-Yen Lin,† and Ming-Tsang Wu†¶‖[1]

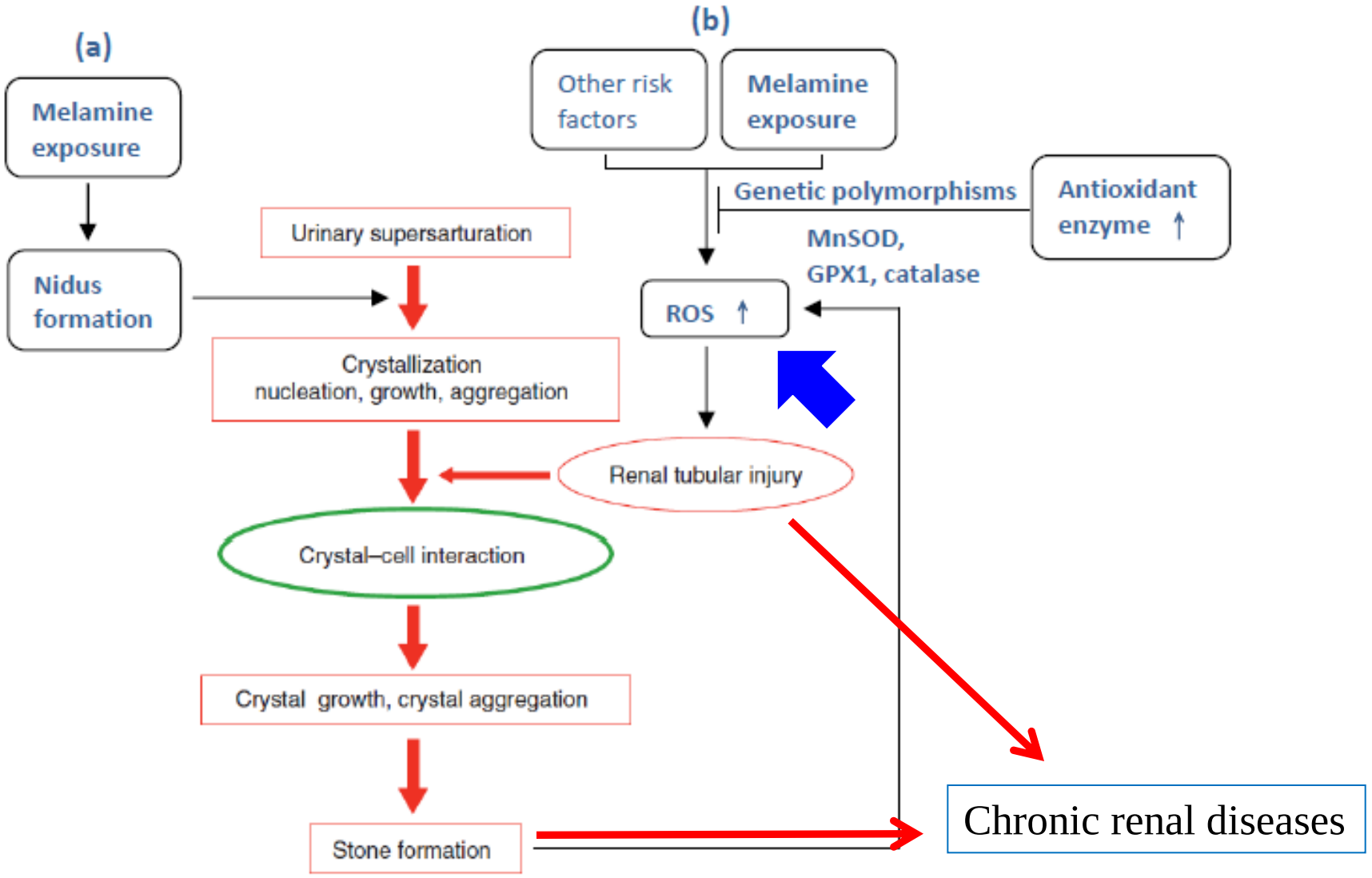


Figure 1. Proposed mechanisms of relationship between melamine exposure and renal urolithiasis (modified from the review article of Tsujihata, 2008).



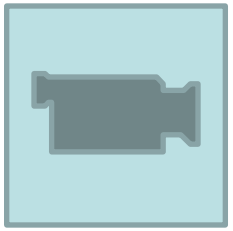


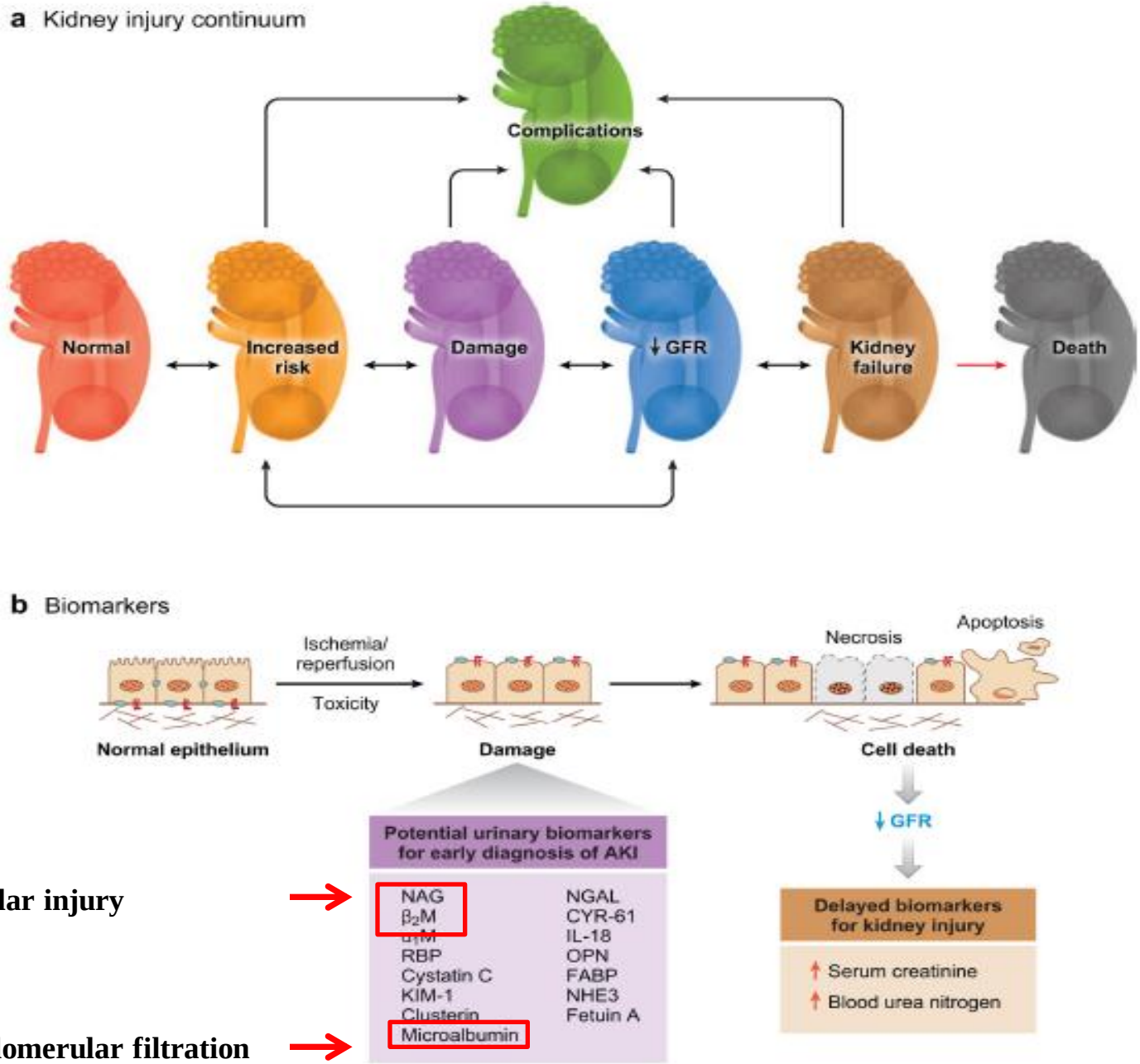




Melamine tableware manufacturing workers

Video





Rental tubular injury

Increased glomerular filtration

Vaidya et al. Annu Rev Pharmacol Toxicol, 2008.

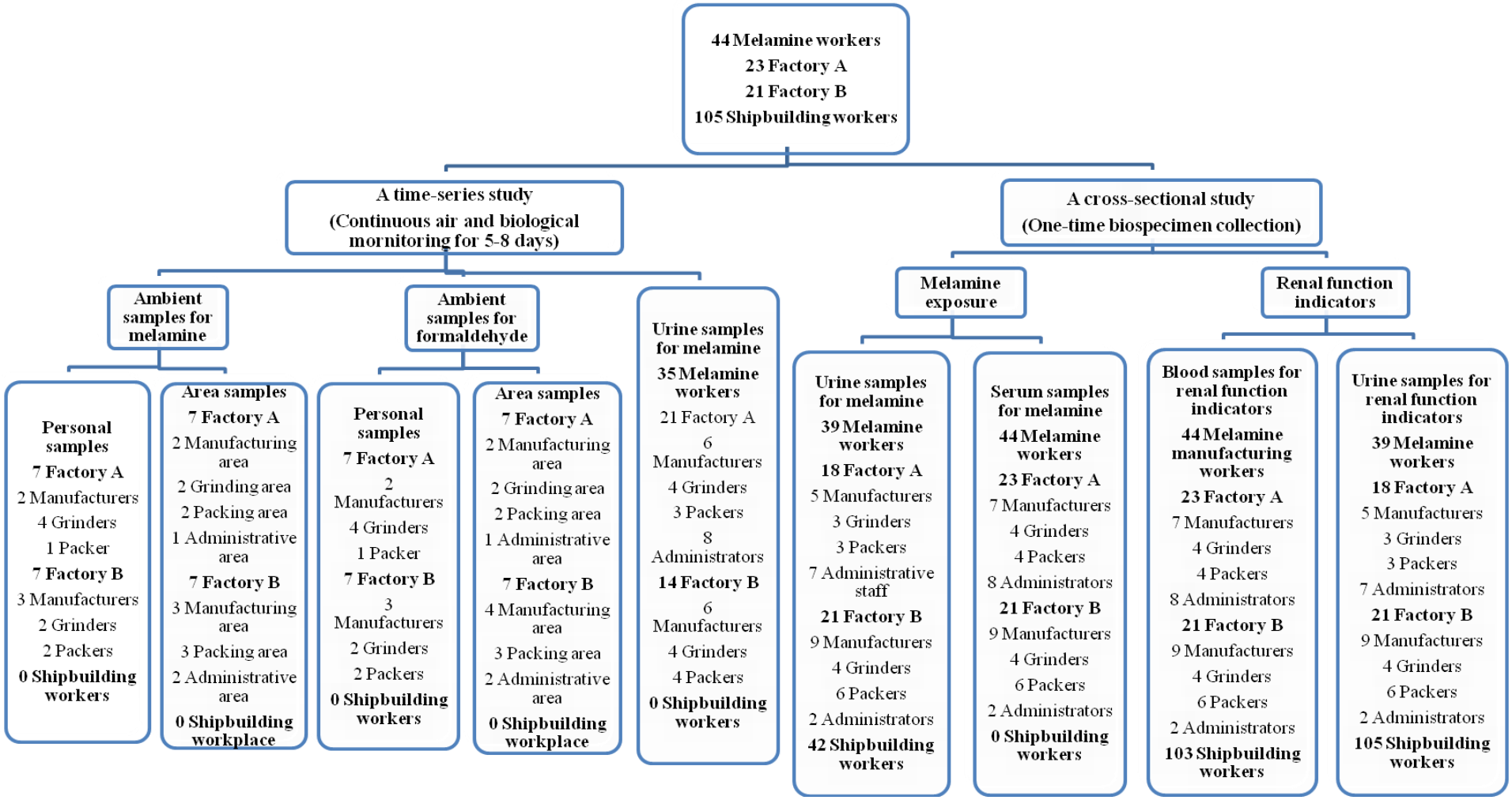
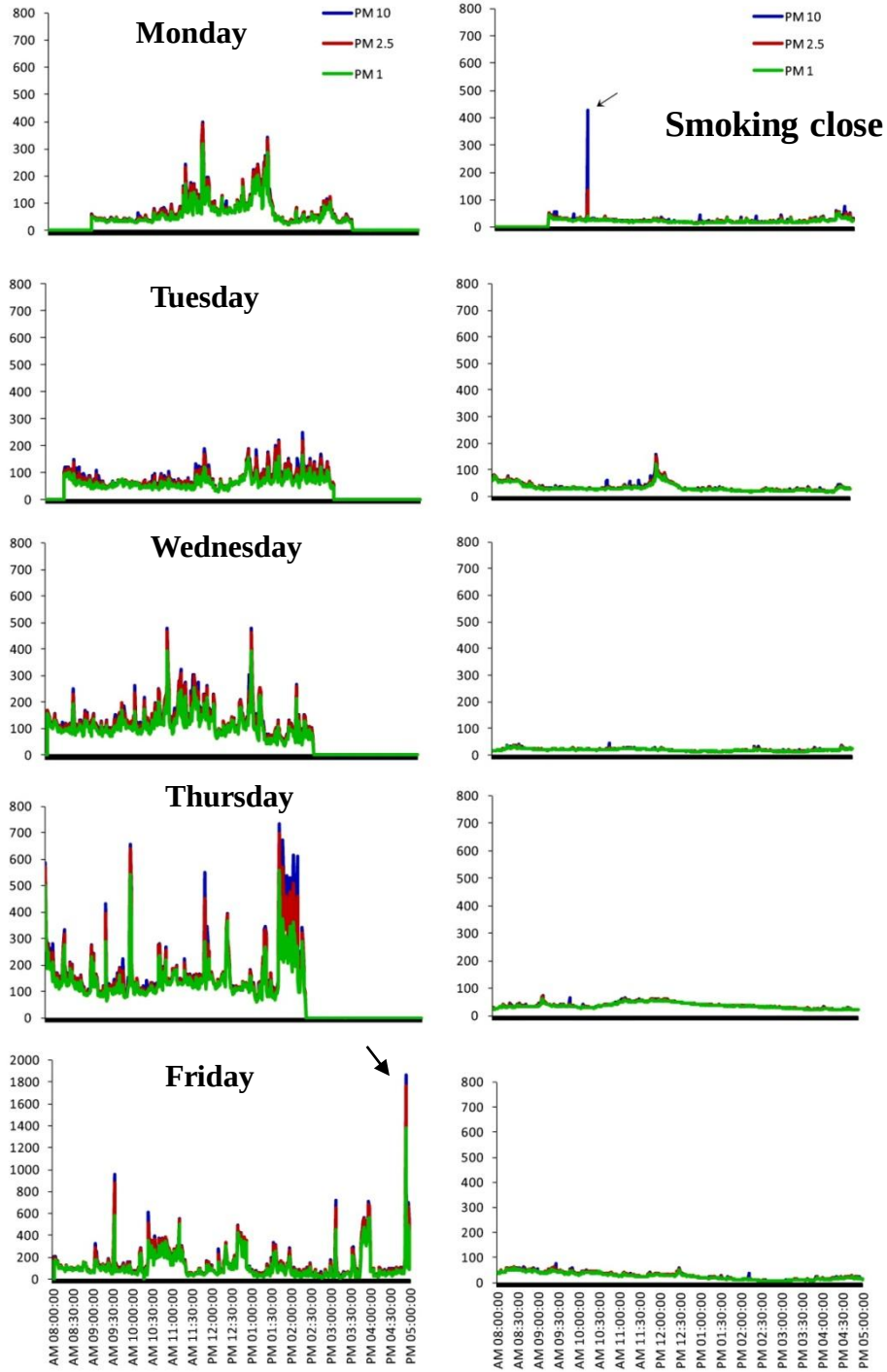


Figure 1. Flowchart of study



Smoking close to area dust monitor

The ambient distribution of different dust particle sizes in a real-time status (one measurement every one minute) by portable laser aerosol spectrometers and dust monitors.



The highest ambient concentrations of PM 10 μm (1861.8 μg/m^3), PM 2.5 μm (1761.1 μg/m^3) and PM 1.0 μm (1384.1 μg/m^3)

Supplemental Table 5. Daily averaged ambient concentrations of different dust particle sizes (particulate matter (PM) 10, 2.5, and 1.0 μm) by portable laser aerosol spectrometers and dust monitors in one melamine manufacturing company (Factory A) during work.

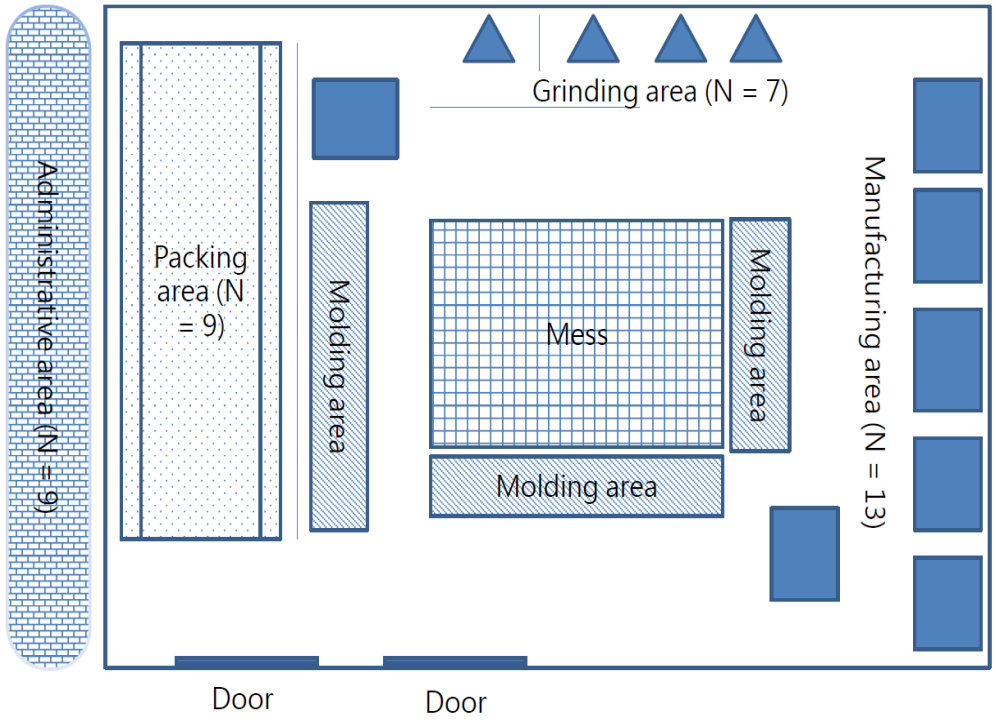
Dust size ($\mu g/m^3$)	Manufacturing area					Administrative area					p-value
	N	≤ 100	>100-≤ 200	> 200	Mean±SD (Min, Median, Max)	N	≤ 100	>100-≤ 200	> 200	Mean±SD (Min, Median, Max)	
Monday											
PM 10	381	300	67	14	75.5±53.5 (23.9, 55.6, 398.5)	476	475	0	1	25.7±20.1 (12.9, 23.2, 426.6)	< 0.0001
PM 2.5		304	63	14	73.9±52.2 (23.8, 54.4, 391.3)		475	0	1	24.4±8.7 (12.9, 22.6, 134.9)	< 0.0001
PM 1.0		324	50	7	65.1 ± 44.0 (20.5, 47.4, 320.5)		476	0	0	22.5±5.9 (12.6, 21.5, 51.5)	< 0.0001
Tuesday											
PM 10	389	303	83	3	81.0±32.7 (31.6, 72.4, 248.7)	569	566	3	0	35.5±16.6 (18.4, 30.2, 156.7)	< 0.0001
PM 2.5		316	71	2	77.4±30.0 (31.6, 70.6, 217.1)		566	3	0	34.8±15.6 (18.4, 29.9, 150.5)	< 0.0001
PM 1.0		359	30	0	65.5±22.1 (30.9, 61.1, 164.8)		567	2	0	32.5±13.9 (17.5, 28.4, 122.2)	< 0.0001
Wednesday											
PM 10	386	110	237	39	132.8±60.1 (39.7, 118.6, 479.2)	576	576	0	0	20.2±5.0 (12.6, 19.9, 67.5)	< 0.0001
PM 2.5		119	228	39	128.7±57.0 (39.1, 116.0, 466.4)		576	0	0	19.9±4.4 (12.6, 19.8, 36.9)	<0.0001
PM 1.0		176	190	20	112.4±47.1 (34.5, 103.6, 394.8)		576	0	0	19.0±4.0 (12.0, 19.1, 32.2)	< 0.0001
Thursday											
PM 10	389	41	258	90	180.5±112.7 (62.5, 138.4, 732.2)	570	570	0	0	36.6±10.9 (12.0, 35.4, 73.9)	< 0.0001
PM 2.5		51	251	87	172.6±100.6 (62.2, 134.4, 695.5)		570	0	0	36.3±10.7 (12.0, 35.2, 70.4)	< 0.0001
PM 1.0		92	226	71	149.7±75.8 (59.1, 126.3, 556.7)		570	0	0	34.9±10.3 (11.8, 33.8, 59.6)	< 0.0001
Friday											
PM 10	541	303	132	106	136.7±146.8 (15.8, 91.7, 1861.8)	574	574	0	0	28.6±14.7 (6.8, 27.2, 75.3)	< 0.0001
PM 2.5		312	128	101	131.9±140.2 (14.5, 88.4, 1761.1)		574	0	0	28.2±14.4 (6.8, 26.9, 63.0)	< 0.0001
PM 1.0		348	111	82	112.6±114.6 (11.5, 77.4, 1384.1)		574	0	0	26.2±13.3 (6.5, 25.7, 58.5)	< 0.0001
Five days											
PM 10	2086	1057	777	252	121.1±102.2 (15.8, 98.3, 1861.8)	2765	2761	3	1	29.6±15.6 (6.8, 26.4, 426.6)	< 0.0001
PM 2.5		1102	741	243	116.7±95.9 (14.5, 95.4, 1761.1)		2761	3	1	29.0±13.2 (6.8, 26.2, 150.5)	< 0.0001
PM 1.0		1299	607	180	100.6±77.4 (11.5, 84.4, 1384.1)		2763	2	0	27.3±12.0 (6.5, 24.7, 122.2)	< 0.0001

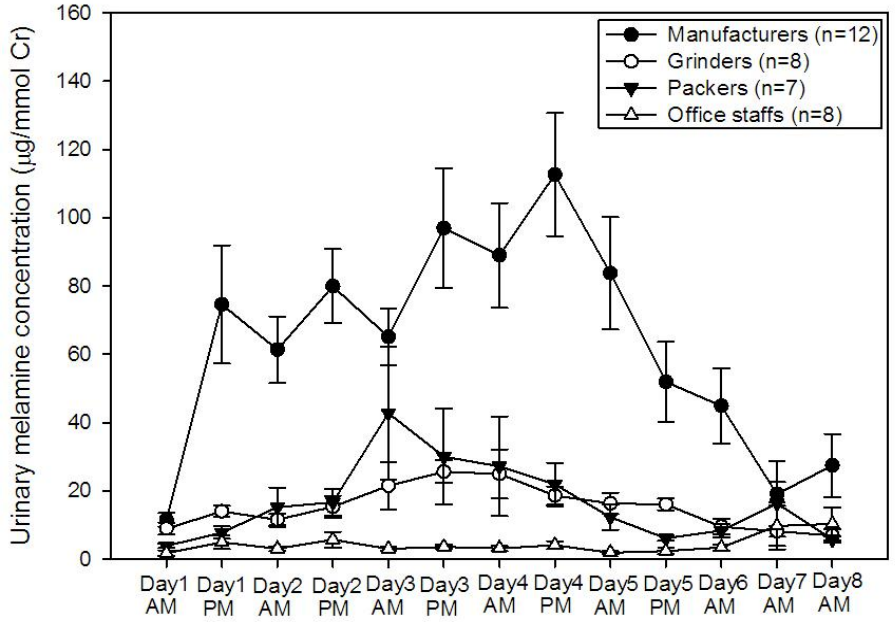
Abbreviation: SD = Standard deviation.

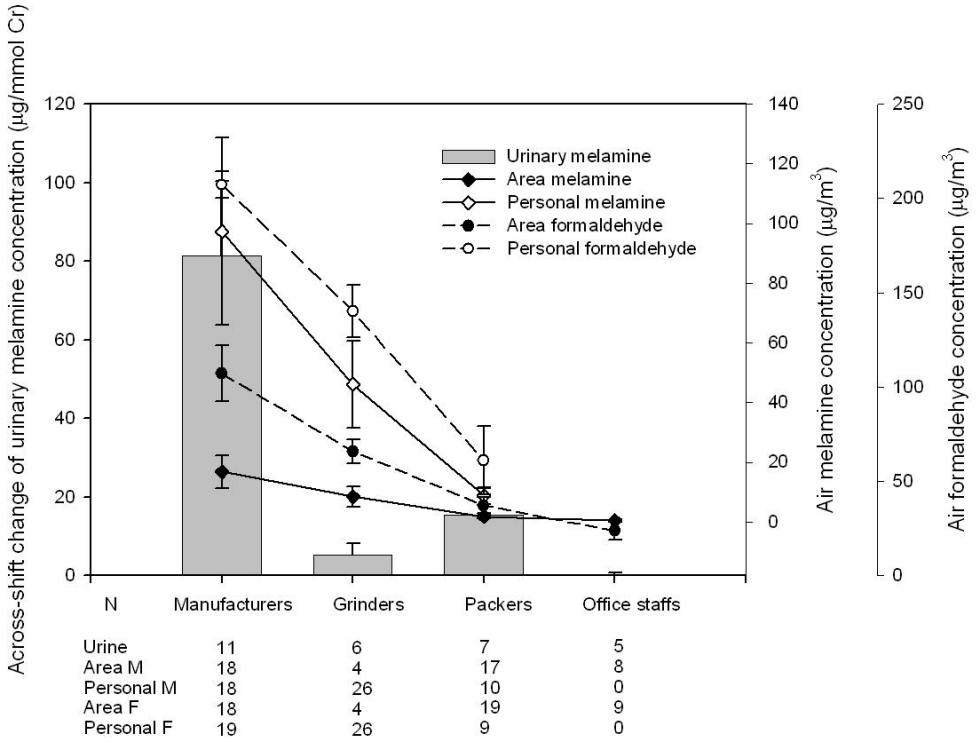
2012 EPA
Indoor air quality
24 hrs
PM10 < 75
PM2.5 < 35
$\mu g/m^3$

Study Area

- 44 melamine workers
  - 16 manufacturers, 8 grinders, 10 packers, and 10 office staffs
- Another 105 office workers from one shipbuilding company.




Urinary melamine concentration (μg/mmol Cr)
Manufacturers (n=12)
Grinders (n=8)
Packers (n=7)
Office staffs (n=8)
0
20
40
60
80
100
120
140
160
Day1 AM
Day1 PM
Day2 AM
Day2 PM
Day3 AM
Day3 PM
Day4 AM
Day4 PM
Day5 AM
Day5 PM
Day6 AM
Day7 AM
Day8 AM


Across-shift change of urinary melamine concentration (μg/mmol Cr)
Air melamine concentration (μg/m3)
Air formaldehyde concentration (μg/m3)
Urinary melamine
Area melamine
Personal melamine
Area formaldehyde
Personal formaldehyde
0
20
40
60
80
100
120
140
150
200
250
N
Manufacturers
Grinders
Packers
Office staffs
Urine 11 6 7 5
Area M 18 4 17 8
Personal M 18 26 10 0
Area F 18 4 19 9
Personal F 19 26 9 0

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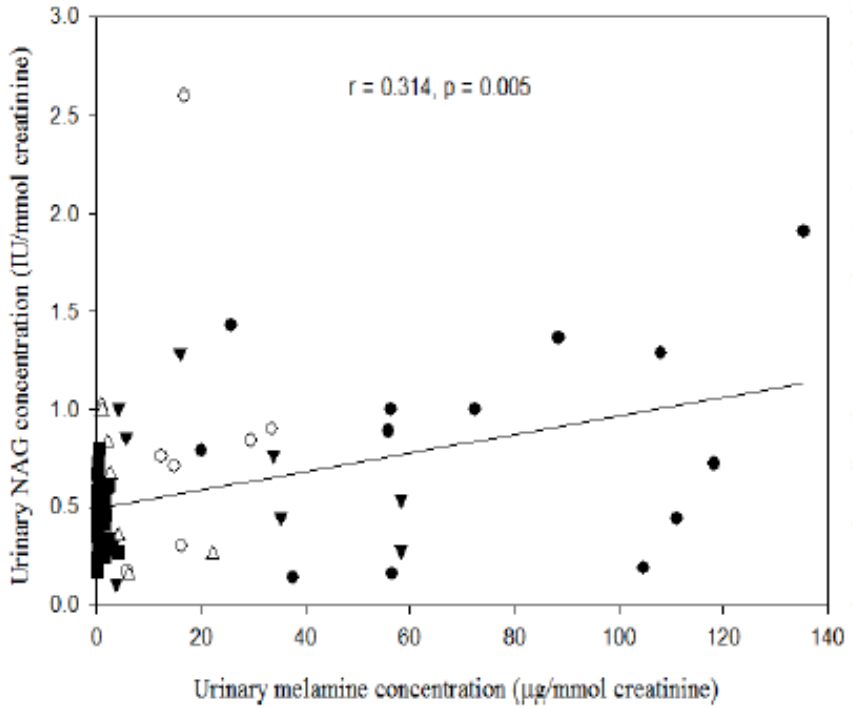
J Am Soc Nephrol, 2016

Ambient Melamine Exposure and Urinary Biomarkers of Early Renal Injury

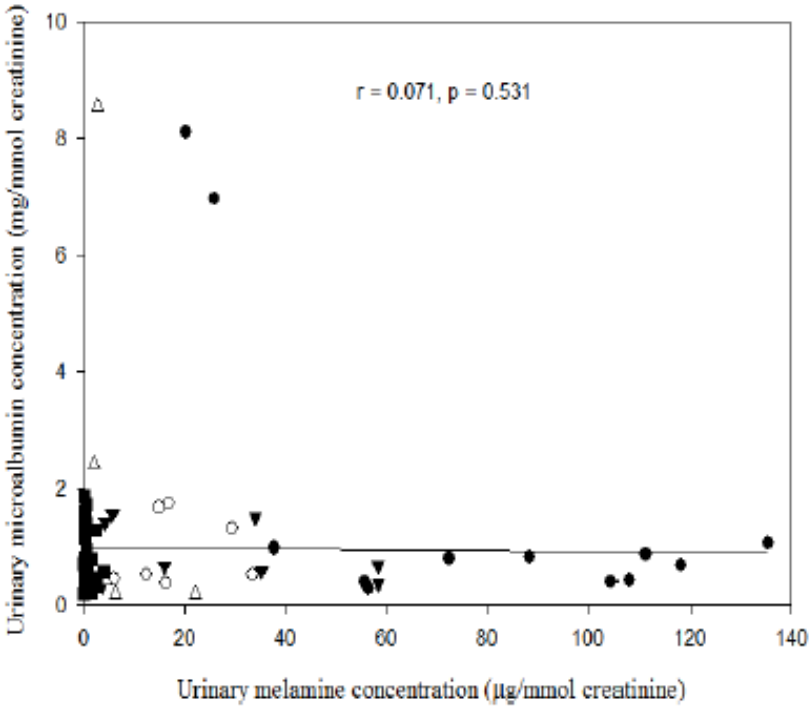
Chia-Fang Wu,* Chiung-Yu Peng,* Chia-Chu Liu,†‡§ Wen-Yi Lin,*‖¶ Chih-Hong Pan,** Ching-Mei Cheng,*†† Hui-Min Hsieh,* Tusty-Jiuan Hsieh,‡‡ Bai-Hsiun Chen,§§‖‖ and

N = 80

b)



c)



Ever use melamine tableware prior to 3 days

Yes: 20.98 ± 35.89, No: 8.69 ± 12.44 ng/ml

Table 2. Melamine markers and renal function indicators by work sites.

Variables	Melamine tableware manufacturing				Shipbuilding	*p*-value[a,c] (Overall)	*p*-value[b,d] (Manufacturers *vs.* controls)
	Manufacturers	Grinders	Packers	Office staff	Controls		
	N=16	N=8	N=10	N=10	N=105		
	Mean ± SD (Median, IQR)						
Exposure markers					N = 42		
Melamine (ng/mL)	917.6 ± 516.4	188.0 ± 107.4	292.6 ± 363.6	109.8 ± 214.7	8.1 ± 9.1	< 0.001	< 0.001
	(943.0, 438.0-1251.8)	(206.3, 64.7-291.6)	(252.6, 42.4-390.3)	(18.2, 12.6-101.3)	(4.3, 1.6-11.2)[g]		
Melamine (μg/mmol Cr)[f]	84.4 ± 47.4	18.4 ± 9.7	24.2 ± 23.0	4.6 ± 6.8	0.7 ± 0.9	< 0.001	< 0.001
	(80.5, 51.3-112.9)	(16.2, 12.3-29.5)	(15.9, 3.9-46.7)	(1.9, 1.0-5.2)	(0.3, 0.1-1.0)[g]		
	7.2 ± 4.6	2.4 ± 0.3	3.6 ± 2.2	1.7 ± 0.4	-		
	(6.7, 4.0-9.6)	(2.4, 2.0--)	(2.4, 2.2--)	(1.6, 1.5--)	-		
Nephrolithiasis markers							
Microalbumin (mg/mmol)	14.8 ± 49.2	1.0 ± 0.6	0.8 ± 0.5	1.5 ± 2.7	1.9 ± 6.8	0.486	0.248
	(0.8, 0.4-2.5)	(0.5, 0.5-1.7)	(0.7, 0.4-1.5)	(0.4, 0.3-1.5)	(0.6, 0.4-0.9)		
NAG (IU/mmol)	1.8 ± 3.5	0.9 ± 0.8	0.6 ± 0.4	0.6 ± 0.3	0.4 ± 0.2	0.002	0.002
	(0.9, 0.4-1.4)	(0.8, 0.3-0.9)	(0.5, 0.3-0.9)	(0.6, 0.3-0.9)	(0.4, 0.3-0.5)		
β-2-microglobulin, N(%)							
Normal	10 (62.5)	6 (75.0)	9 (90.0)	9 (90.0)	101 (96.2)	0.006	0.007
Abnormal > MDL (0.206 mg/L)	4 (25.0)	1 (12.5)	0	0	4 (3.8)		
Missing	2 (12.0)	1 (12.5)	1 (10.0)	1 (10.0)	0		

Conclusion

1. Melamine exposure increases the risk of adult urolithiasis, probably through nidus formation

2. Melamine tableware: one main source of melamine exposure in daily life

3. Melamine causes early renal tubular injury, possibly through oxidative stress


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Thank you for your attention