

Melamine and Kidney Diseases

Ming-Tsang Wu, MD, ScD, MOH
Kaohsiung Medical University,
Kaohsiung, TAIWAN

- 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.

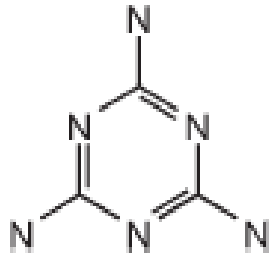
Mr Chen said a third baby had



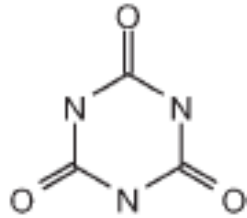
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The 2008 Melamine-tainted Baby Formula Food Scandal:

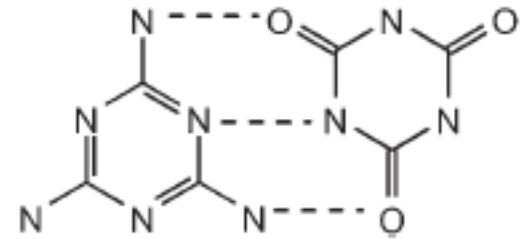
- 1) High dose
- 2) Mainly affected in baby and children



Melamine



Cyanuric acid



Melamine cyanurate

Melamine (low-dose) ??? Adult urolithiasis



Contents lists available at ScienceDirect

Clinica Chimica Acta

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

Urinary melamine and adult urolithiasis in Taiwan

Chia-Fang Wu^{a,1}, Chia-Chu Liu^{b,c,1}, Bai-Hsiun Chen^d, Shu-Pin Huang^{b,c}, Hei-Hwa Lee^d,
Yii-Her Chou^b, Wen-Jeng Wu^b, Ming-Tsang Wu^{a,e,f,*}

<http://www.kidney-international.org>

original article

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Low exposure to melamine increases the risk of urolithiasis in adults

Chia-Chu Liu^{1,2,3,4,14}, Chia-Fang Wu^{5,14}, Bai-Hsiun Chen⁶, Shu-Pin Huang^{1,2}, William Goggins⁷,
Hei-Hwa Lee⁶, Yii-Her Chou^{1,2}, Wen-Jeng Wu^{1,2,8}, Chun-Hsiung Huang^{1,2}, Jentaie Shiea⁹,
Chien-Hung Lee¹⁰, Kuen-Yuh Wu¹¹ and Ming-Tsang Wu^{3,5,12,13}

Melamine toxicity: one more culprit in calcium kidney lithiasis

Fernando J. García López¹ and C. Quereda²

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?**

A



Melamine

B



Ceramic



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Journal of Hazardous Materials

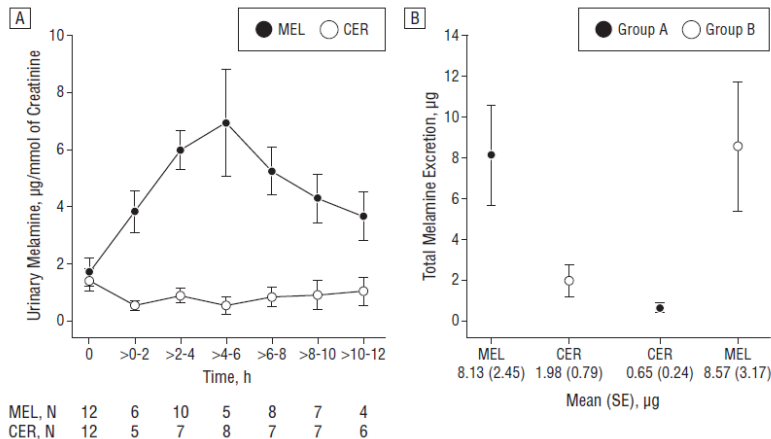
journal homepage: www.elsevier.com/locate/jhazmat

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 Hsiehⁱ, Ming-Tsang Wu^{a,c,j,k,*}

ONLINE FIRST

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



Wu et al. JAMA Intern Med. 2013;173(4):317-9.

•Research findings reported by ‘Time’

TIME Health & Family

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PUBLIC HEALTH

Hot Soups Can Cause Chemical to Leach from Melamine Bowls

By Alexandra Sifferlin | Jan. 22, 2013 | 0

Melamine doesn't break, which makes it a great option for tableware, but a study shows it can taint food when heated.

Melamine is widely used in fertilizers and to make plastic resins, and under normal circumstances, is generally a stable compound. In the U.S., melamine is approved by the Food and Drug Administration (FDA) for manufacturing cooking utensils, plastic and paper products. According to the FDA, it may also be used in food-product packaging but is not approved as an additive in human food or animal feeds. Consistent low-dose exposure to the chemical has been linked to kidney stones in children and adults. In 2008, a

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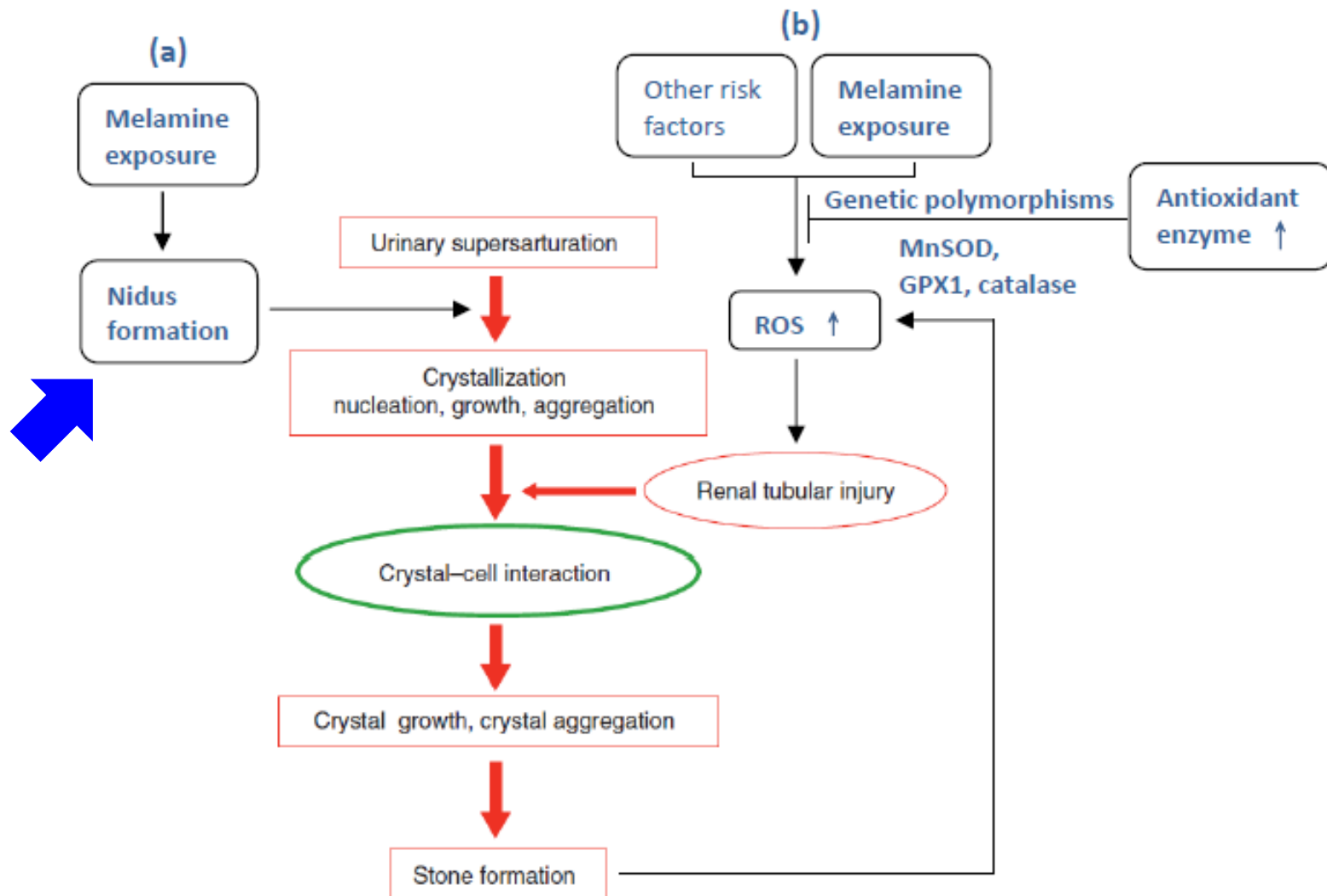
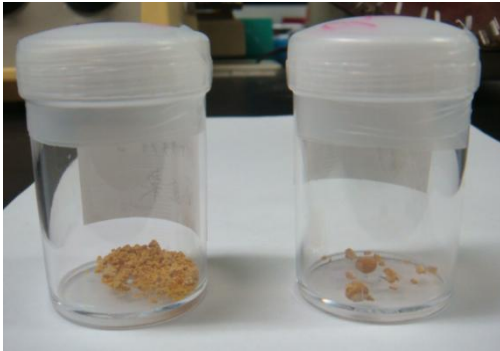


Figure 1. Proposed mechanisms of relationship between melamine exposure and renal urolithiasis (modified from the review article of Tsujihata, 2008).

Progress

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

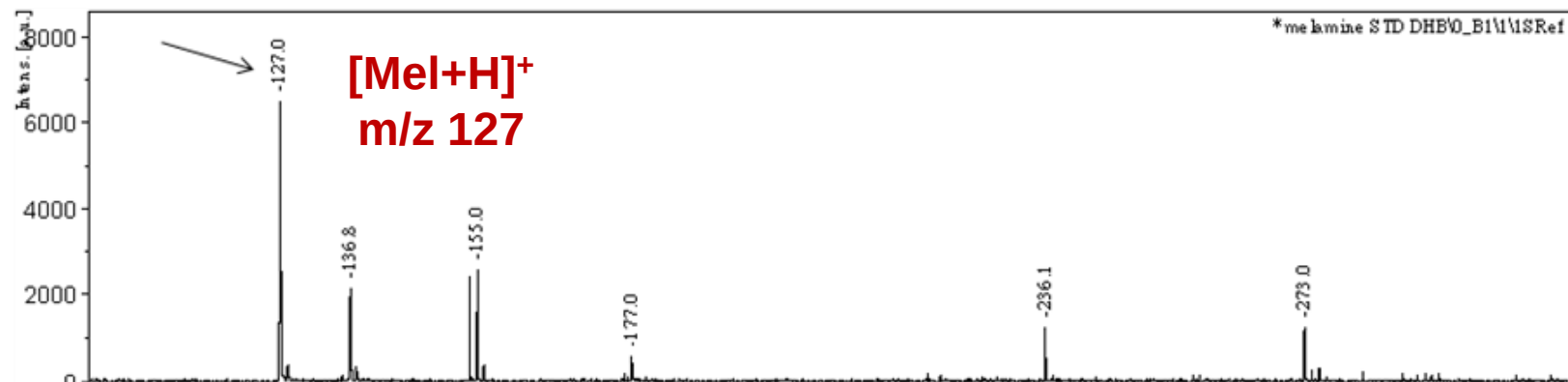
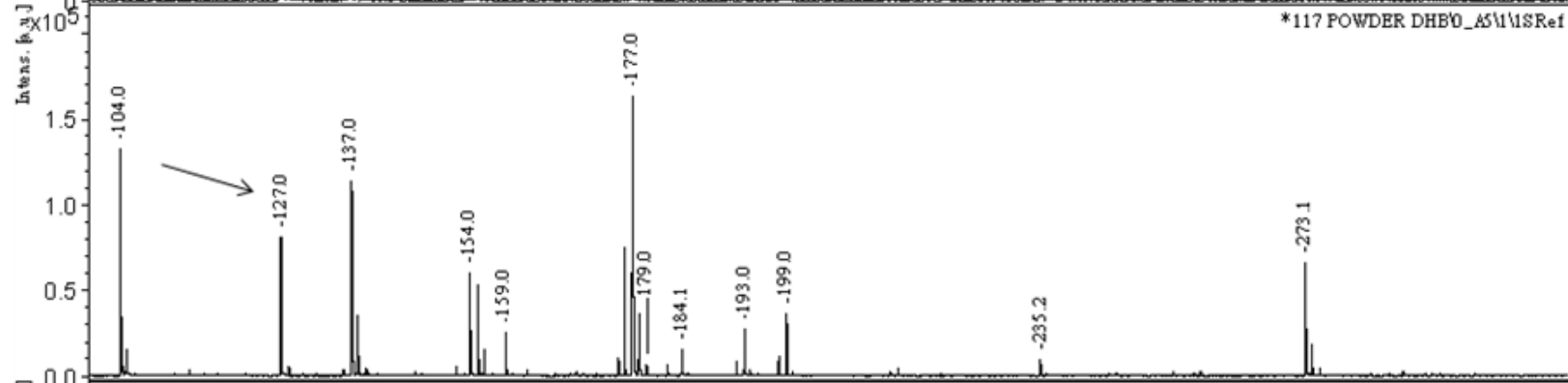
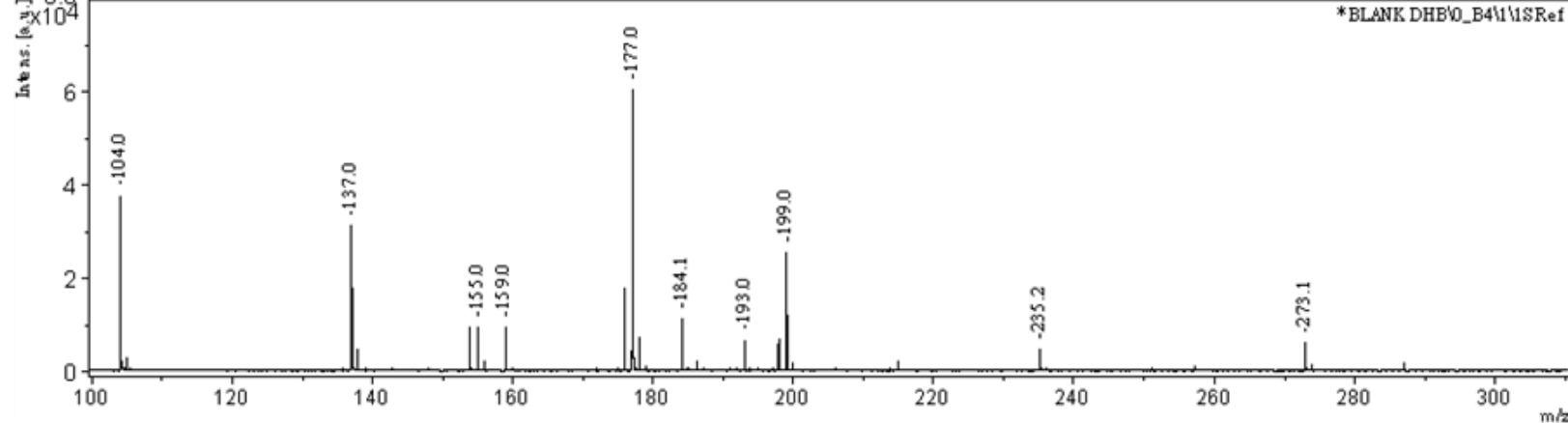


*Ultrasonically extract
melamine/cyanuric acid in
organic solvent

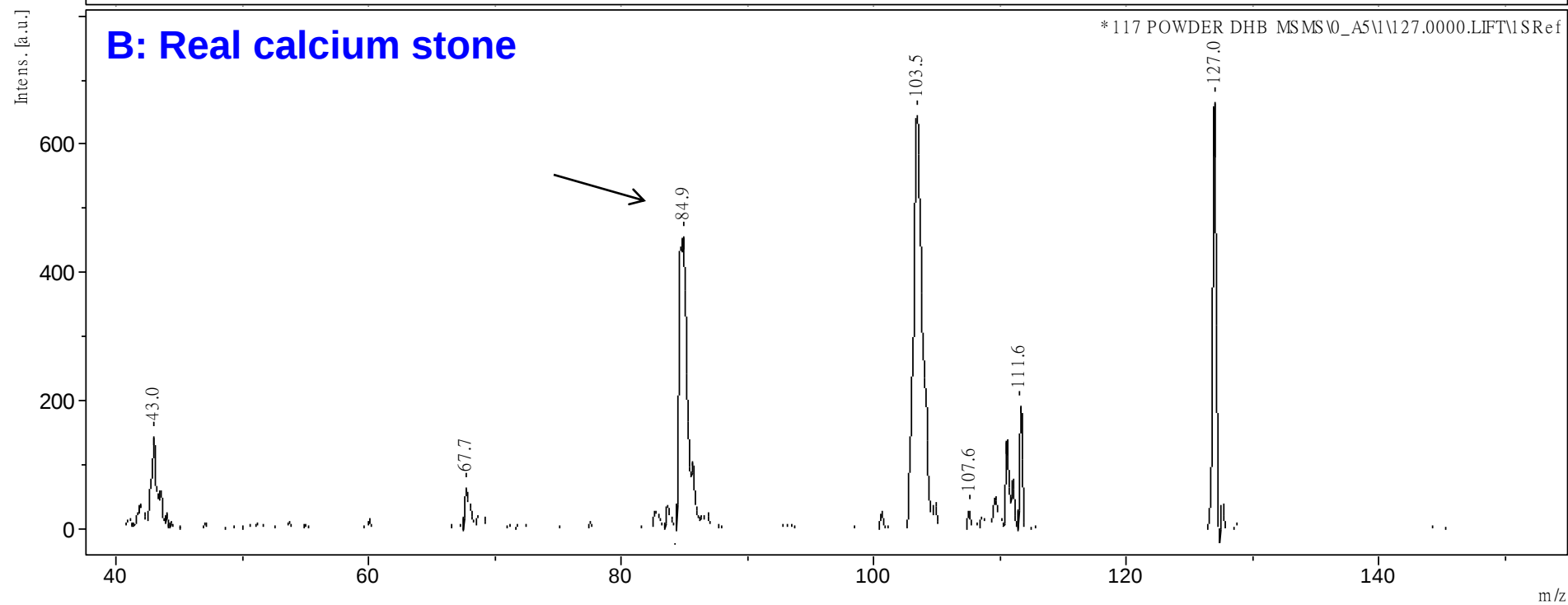
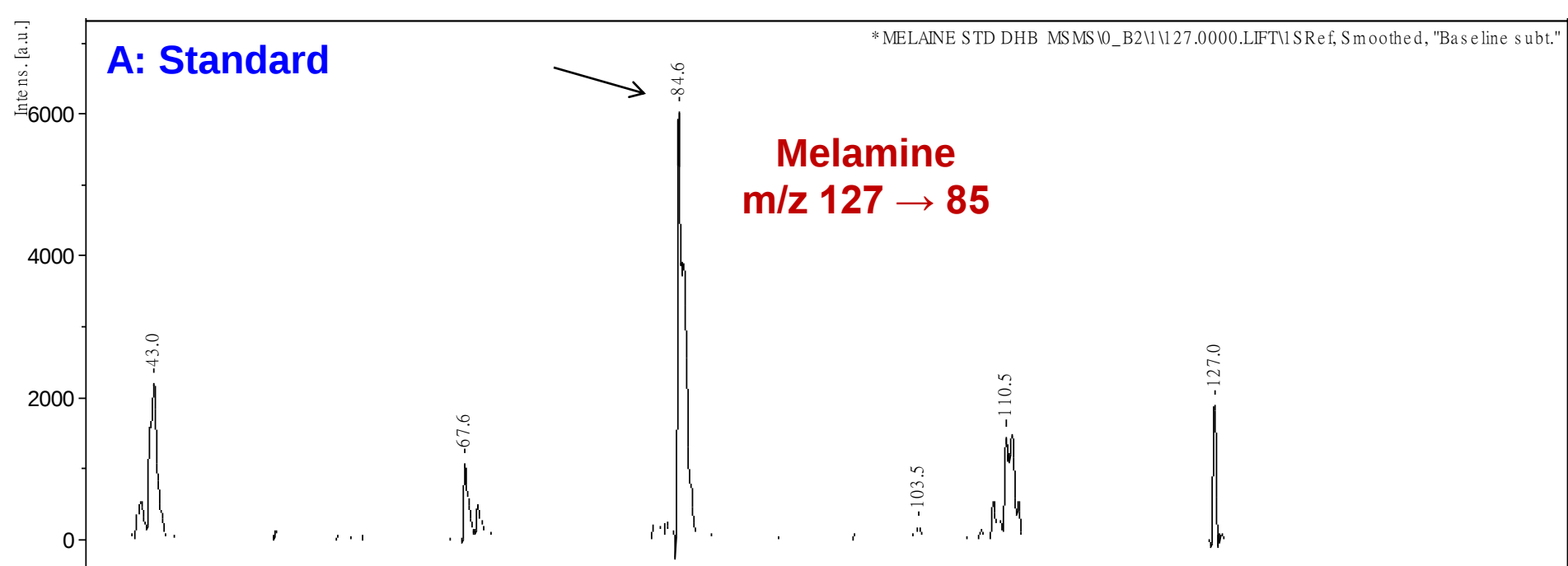
*Mix the concentrated
solution with MALDI matrix
solution (CHCA/DHB)



Autoflex III
MALDI-TOF MS

A**B****C**

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

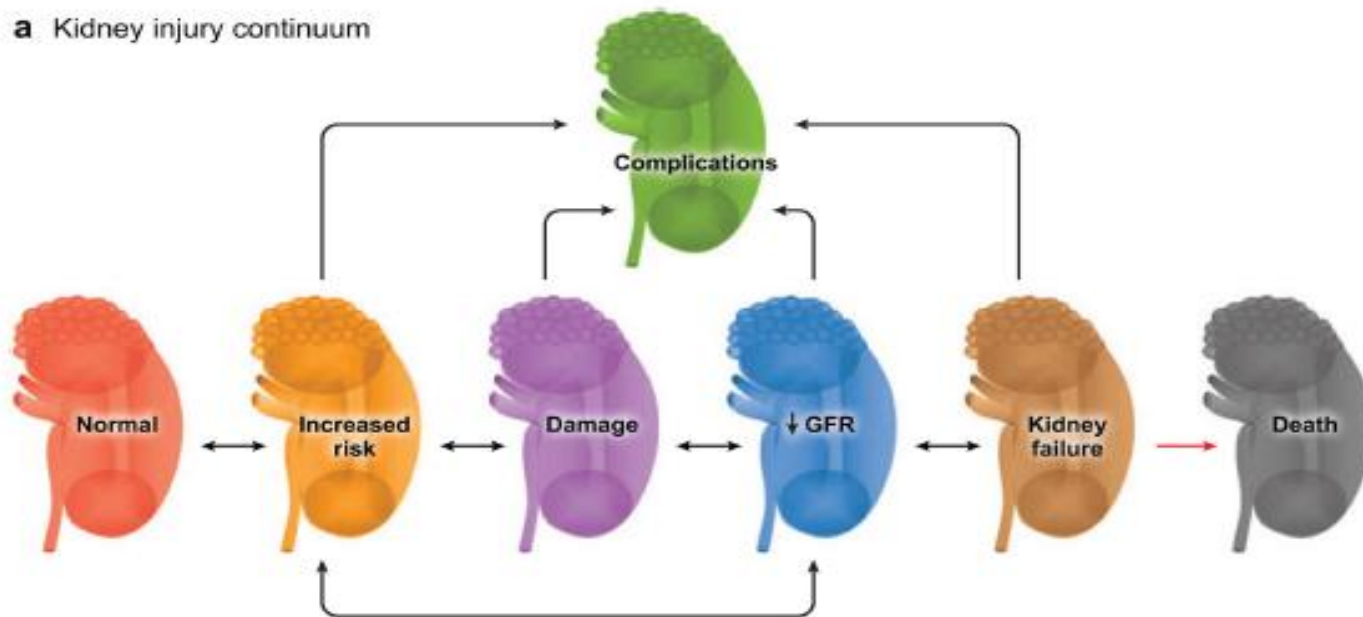


Aims

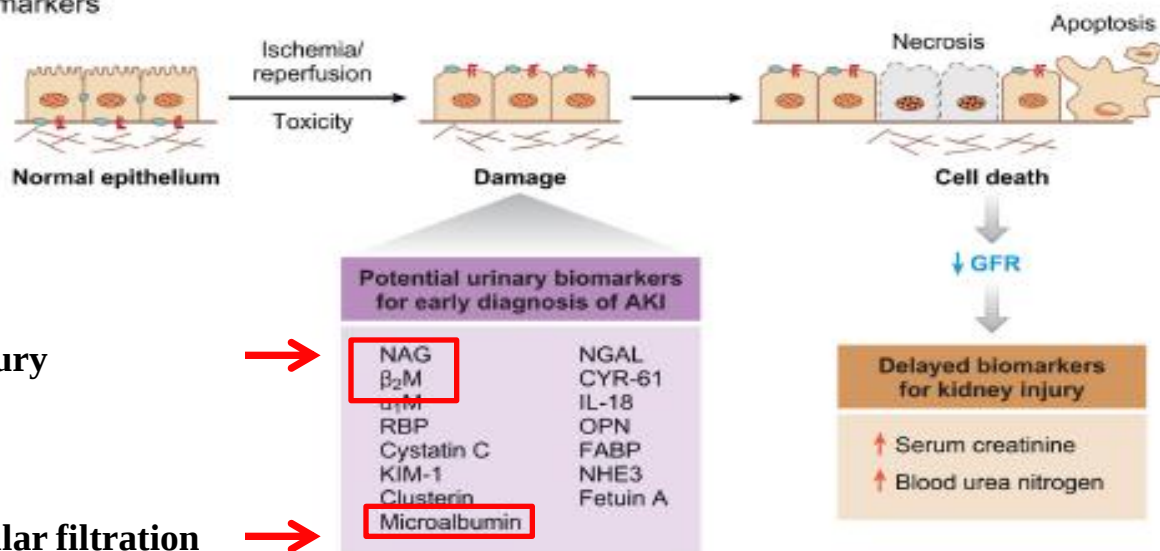
1. Melamine exposure and renal injury in adults
 - Melamine workers

2. Behavioral intervention and decreased melamine exposure from environment
 - University students

a Kidney injury continuum



b Biomarkers



Renal tubular injury

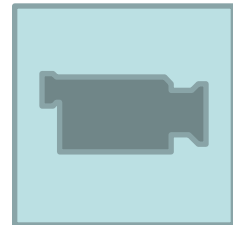


Increased glomerular filtration



Melamine workers

Video



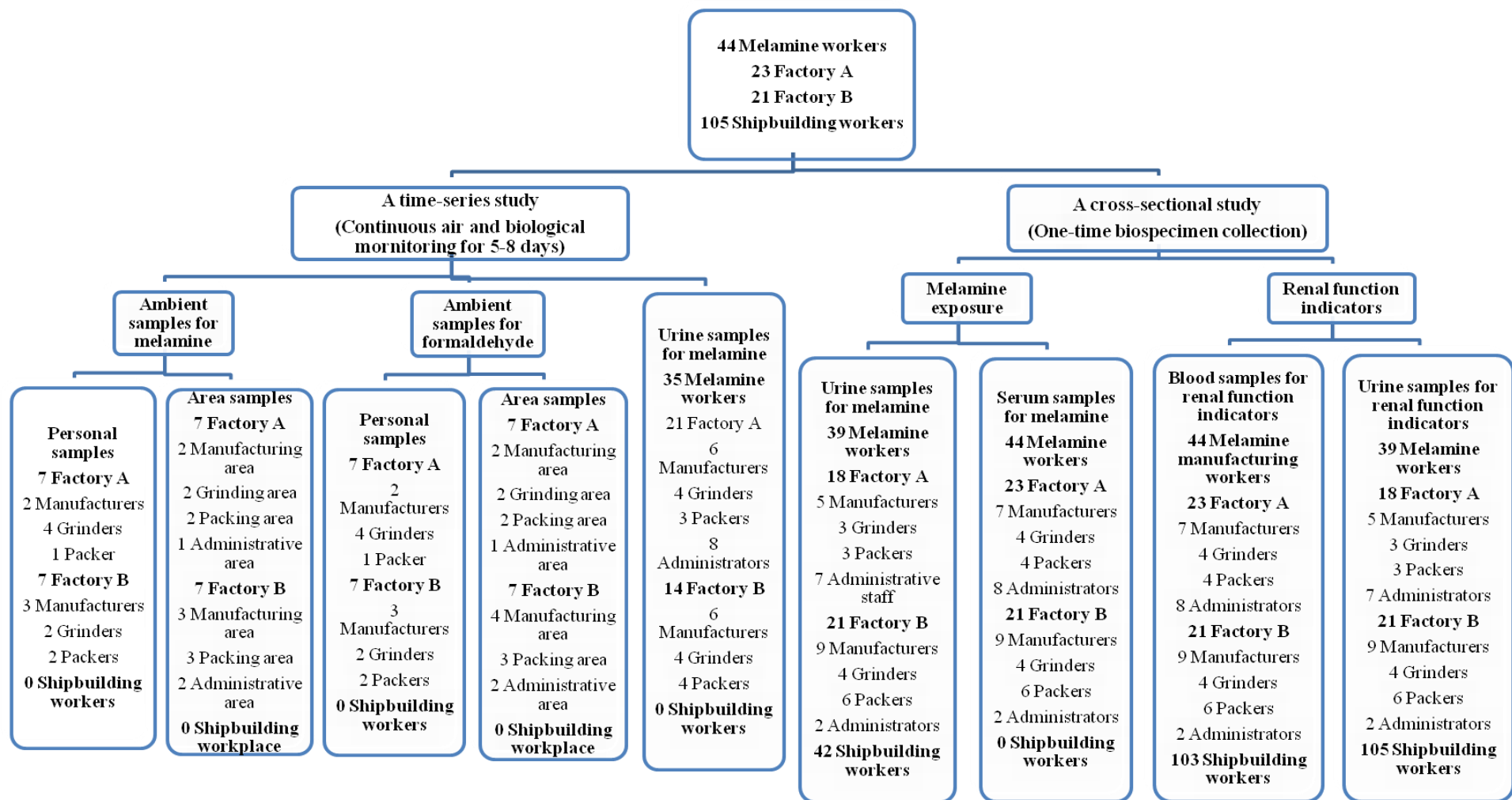
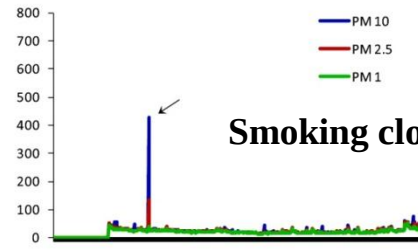
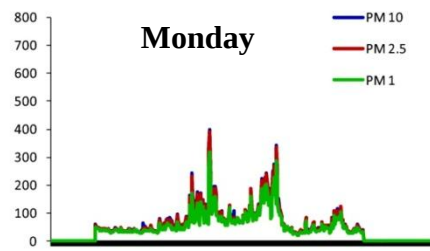
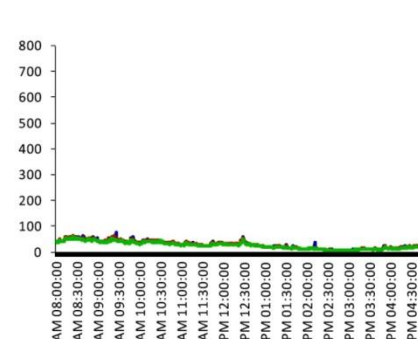
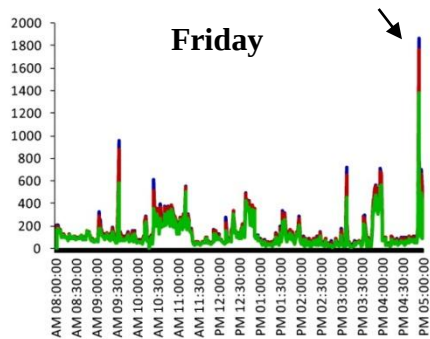
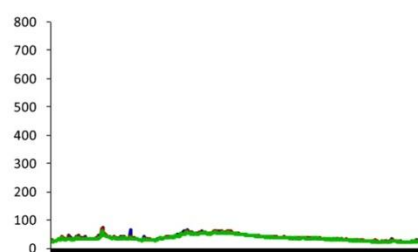
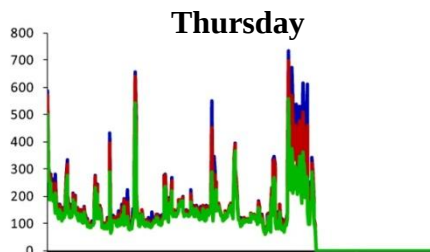
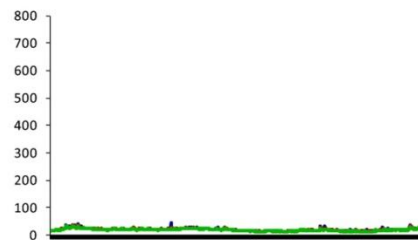
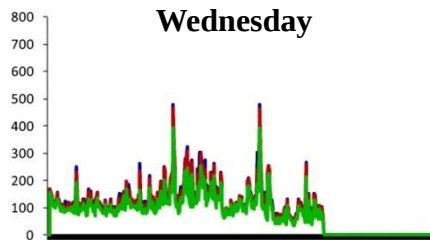
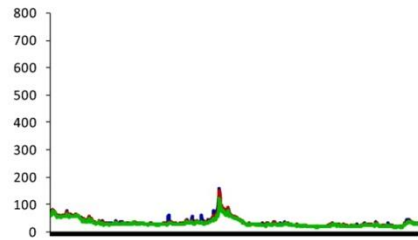
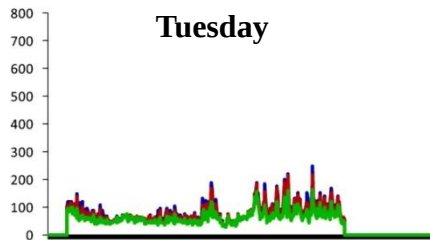


Figure 1. Flowchart of study



Smoking close to area dust monitor

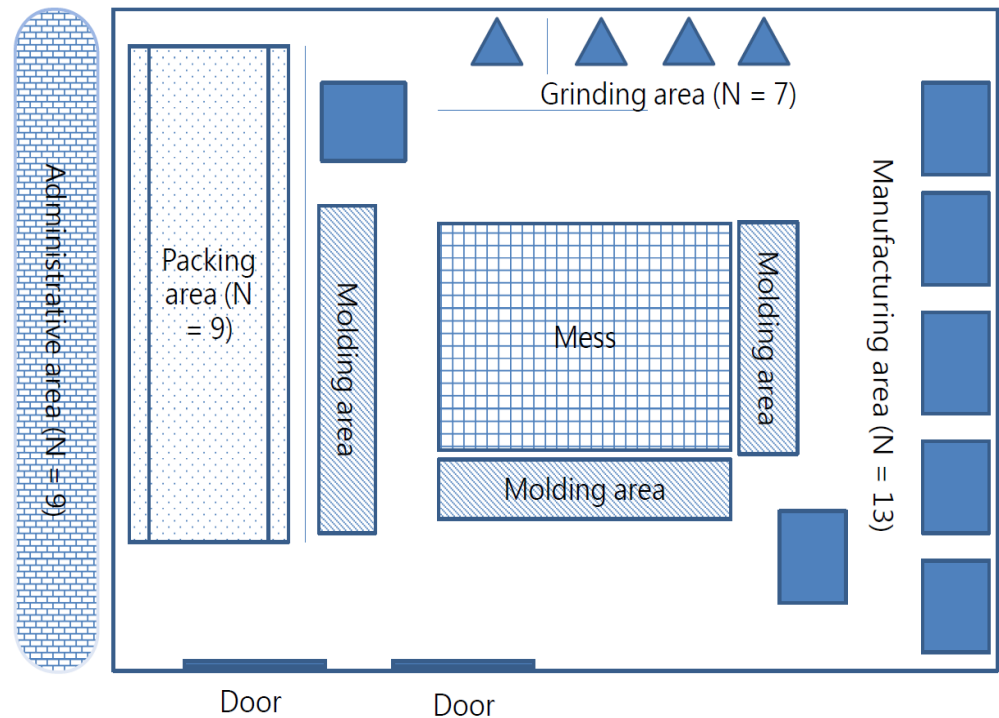
The ambient distribution of different dust particle sizes in a real-time status (one measurement every one minute) by portable laser aerosol spectrometers and dust monitors.

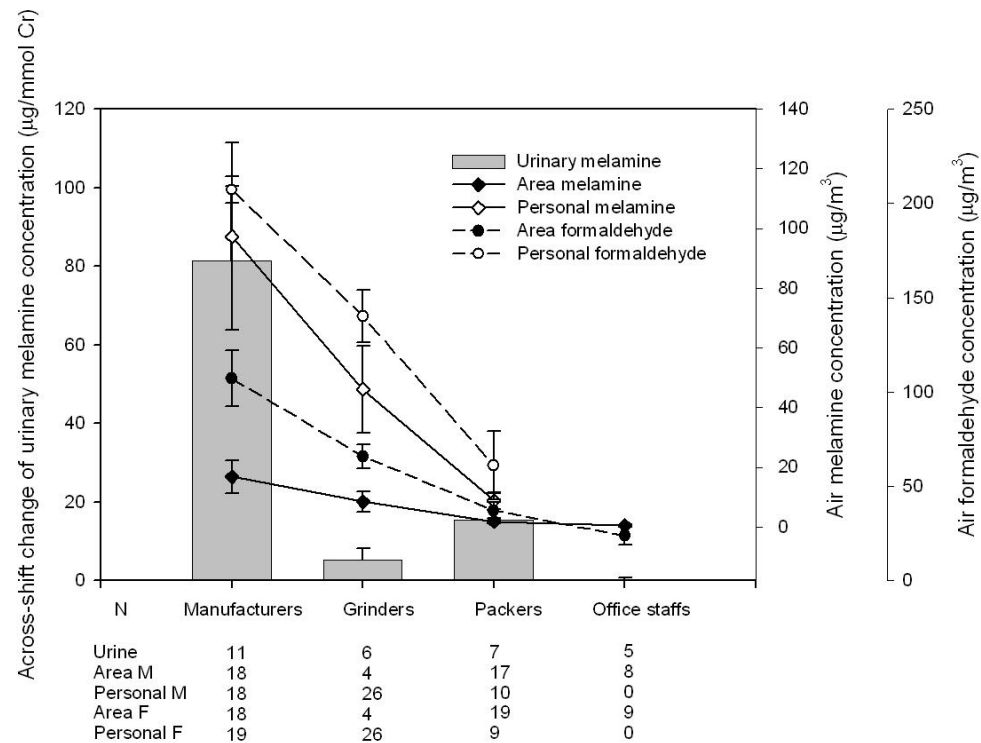
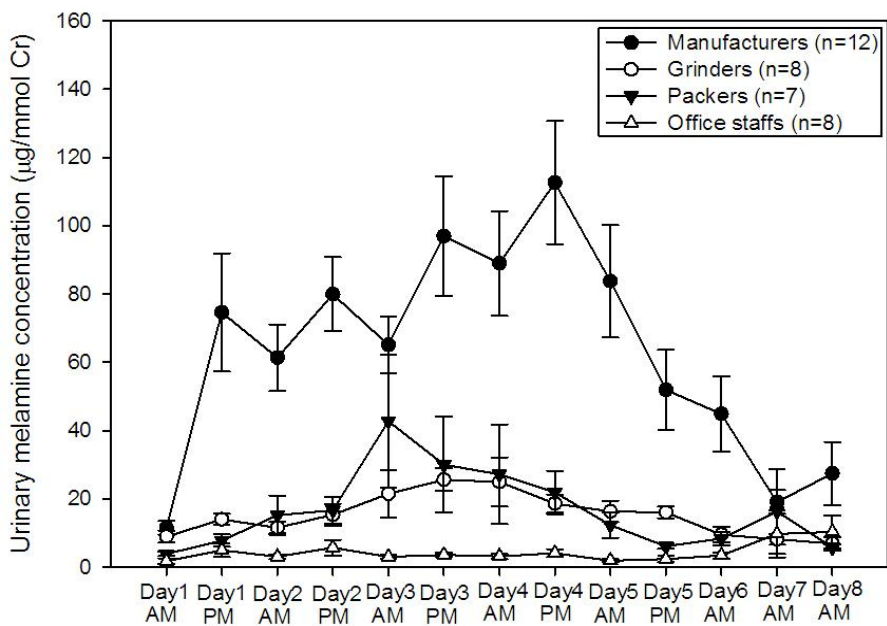


The highest ambient concentrations of PM 10 μm (1861.8 $\mu\text{g}/\text{m}^3$), PM 2.5 μm (1761.1 $\mu\text{g}/\text{m}^3$) and PM 1.0 μm (1384.1 $\mu\text{g}/\text{m}^3$)

Study Area

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

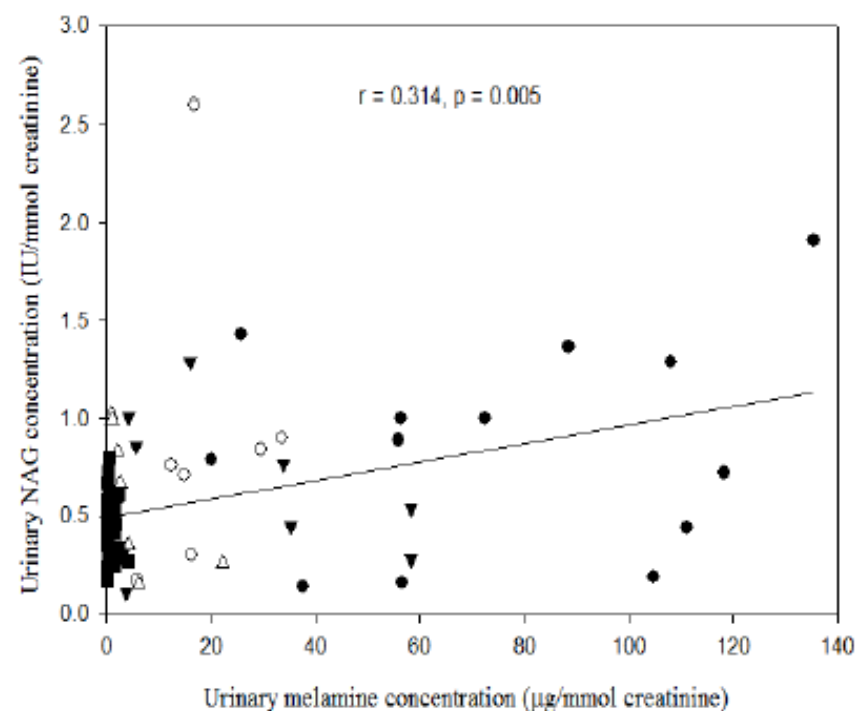




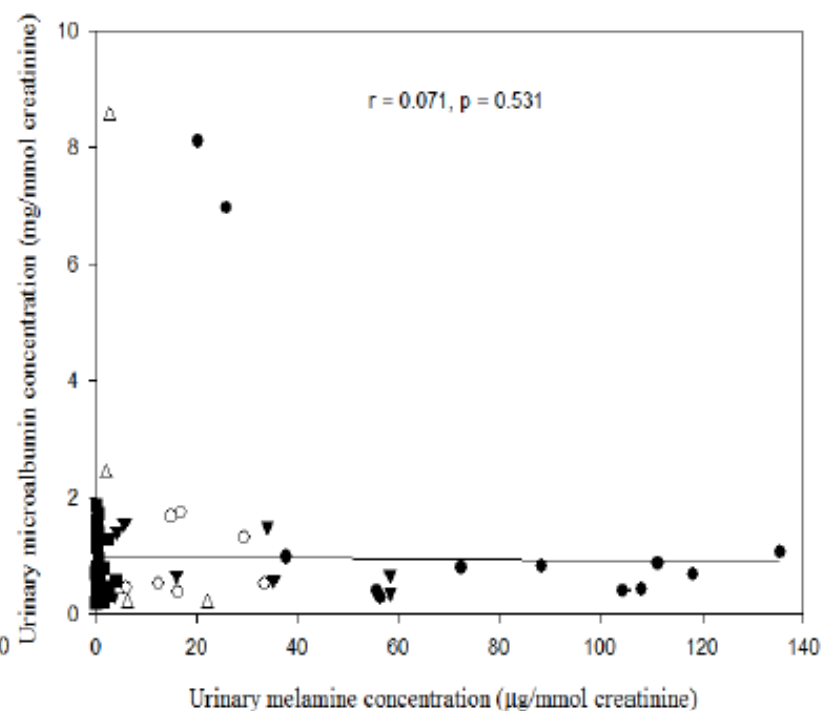
Ambient Melamine Exposure and Urinary Biomarkers of Early Renal Injury

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

b)



c)



N = 80

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	<i>p</i> -value ^{a,c} (Overall)	<i>p</i> -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 (943.0, 438.0-1251.8)	188.0 ± 107.4 (206.3, 64.7-291.6)	292.6 ± 363.6 (252.6, 42.4-390.3)	109.8 ± 214.7 (18.2, 12.6-101.3)	8.1 ± 9.1 (4.3, 1.6-11.2) ^g	< 0.001	< 0.001
Melamine (µg/mmol Cr) ^f	84.4 ± 47.4 (80.5, 51.3-112.9)	18.4 ± 9.7 (16.2, 12.3-29.5)	24.2 ± 23.0 (15.9, 3.9-46.7)	4.6 ± 6.8 (1.9, 1.0-5.2)	0.7 ± 0.9 (0.3, 0.1-1.0) ^g	< 0.001	< 0.001
	7.2 ± 4.6 (6.7, 4.0-9.6)	2.4 ± 0.3 (2.4, 2.0--)	3.6 ± 2.2 (2.4, 2.2--)	1.7 ± 0.4 (1.6, 1.5--)	- -		
Nephrolithiasis markers							
Microalbumin (mg/mmol)	14.8 ± 49.2 (0.8, 0.4-2.5)	1.0 ± 0.6 (0.5, 0.5-1.7)	0.8 ± 0.5 (0.7, 0.4-1.5)	1.5 ± 2.7 (0.4, 0.3-1.5)	1.9 ± 6.8 (0.6, 0.4-0.9)	0.486	0.248
NAG (IU/mmol)	1.8 ± 3.5 (0.9, 0.4-1.4)	0.9 ± 0.8 (0.8, 0.3-0.9)	0.6 ± 0.4 (0.5, 0.3-0.9)	0.6 ± 0.3 (0.6, 0.3-0.9)	0.4 ± 0.2 (0.4, 0.3-0.5)	0.002	0.002
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	1 (12.5)	0	0	4 (3.8)		
Missing	(0.206 mg/L)	1 (12.5)	1 (10.0)	1 (10.0)	0		

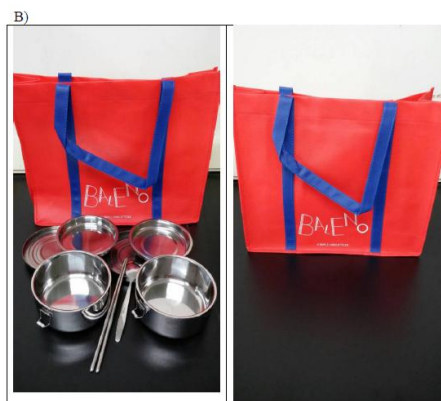
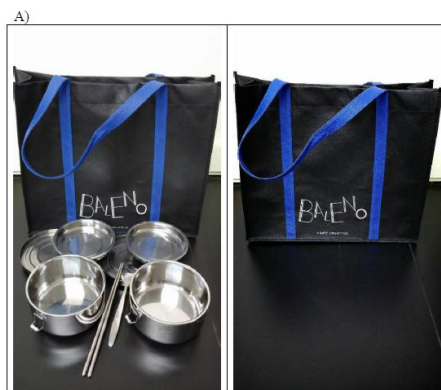
Aims

1. Melamine exposure and renal injury in adults
 - Melamine workers

2. Behavioral intervention and decreased melamine exposure from environment
 - University students

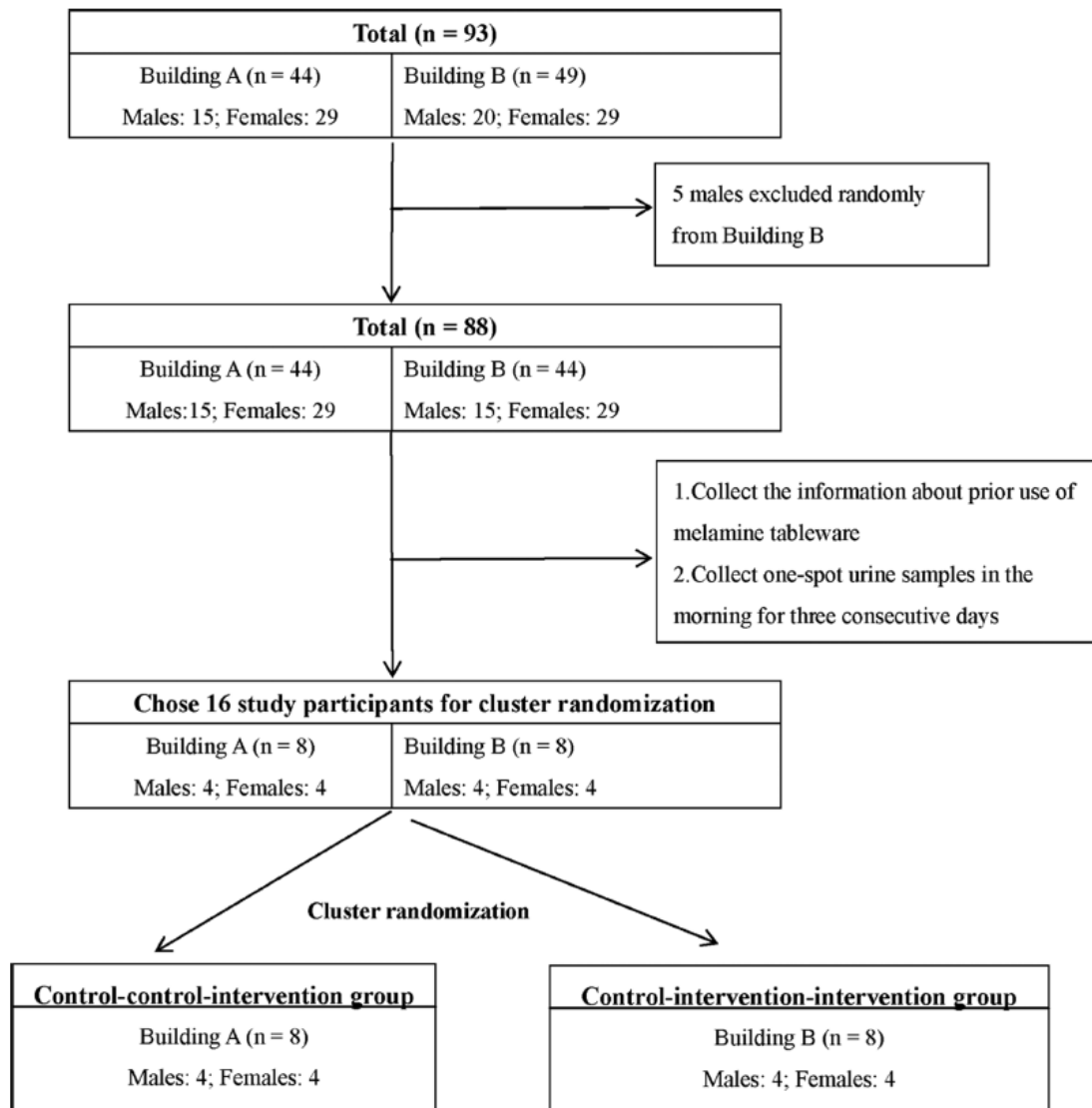
1 Behavioral Intervention and Decreased Daily Melamine Exposure 2 from Melamine Tableware

3 Ming-Tsang Wu,^{*,†,||,‡,§,#} Chia-Fang Wu,[†] and Bai-Hsiun Chen^{‡,§,⊥}



Aim: To examine whether behavior intervention can decrease total urinary melamine excretion.

The primary hypothesis: the continuous use of stainless steel meals boxes to contain and consume high-temperature soups or foods could decrease total melamine excretion in the urine.



Two steps:

1. An observational study

2. A stepped-wedge cluster randomized controlled trial design

88 university students from two academic buildings

Inclusion criteria:

- 1) Aged between 18-30 years;
- 2) Healthy students without cancer or chronic diseases such as hepatic or renal diseases, including renal stones

Exclusion criteria:

- 1) Positive family history of renal stones;
- 2) body weight less than 40 kg.

Urine samples:

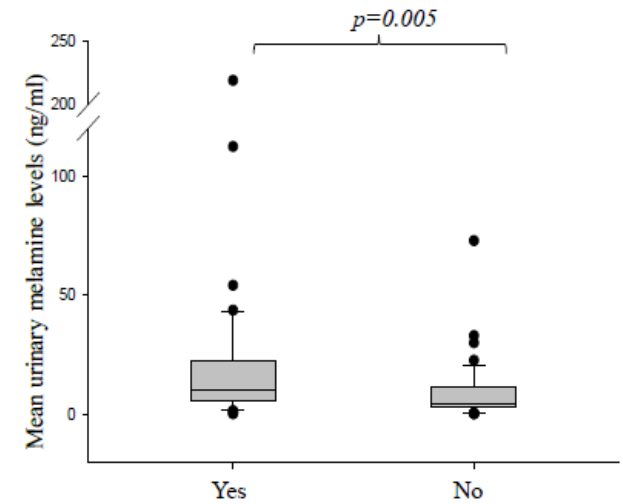
Collected one-spot wake-up urine specimens for three consecutive mornings

Questionnaire:

Have you ever consumed hot soup or hot water by using melamine tableware containers in the past three days?

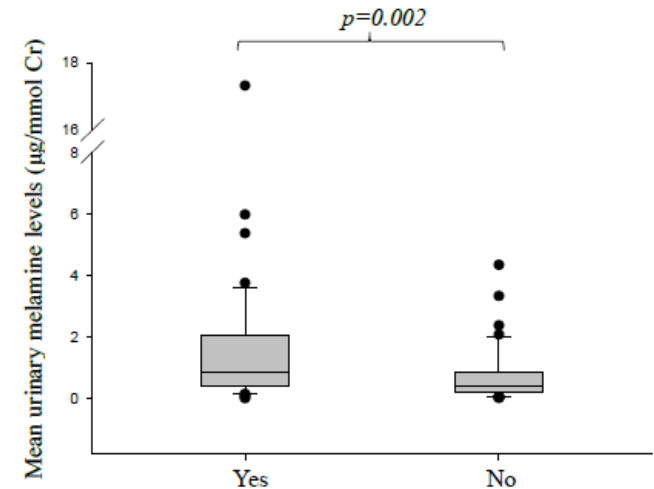
If, yes, “ever use” of melamine tableware

A)



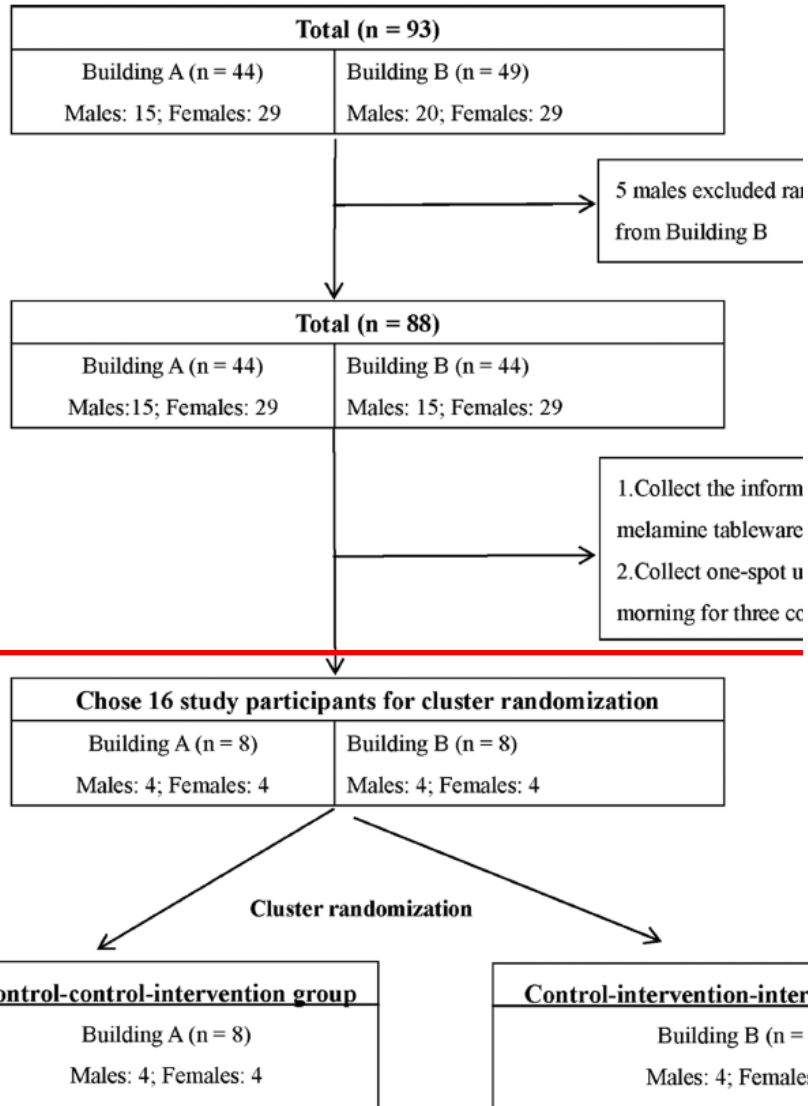
	Use of melamine tableware	
Averaged melamine levels	20.98 ± 35.89	8.69 ± 12.44
Mean ± SD (median, range)	(9.97, 5.77 to 22.34)	(4.29, 2.77 to 11.46)

B)



	Use of melamine tableware	
Averaged melamine levels	1.65 ± 2.73	0.75 ± 0.90
Mean ± SD (median, range)	(0.84, 0.39 to 2.04)	(0.39, 0.22 to 0.88)

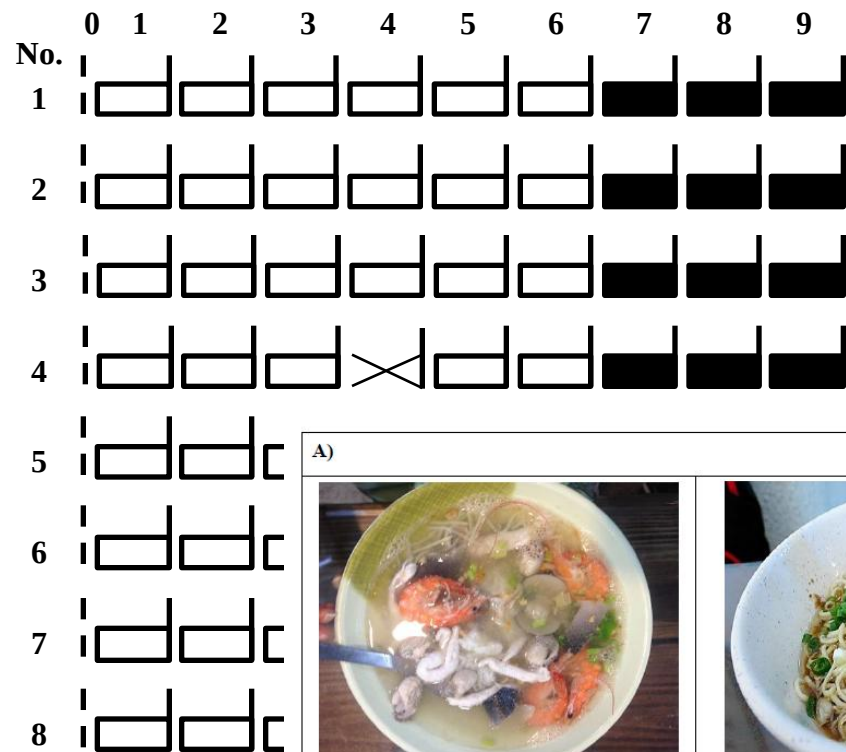
Table 1. Demographic Characteristics and Baseline-Averaged 3 Day Urinary Melamine Levels in 16 Student Participants



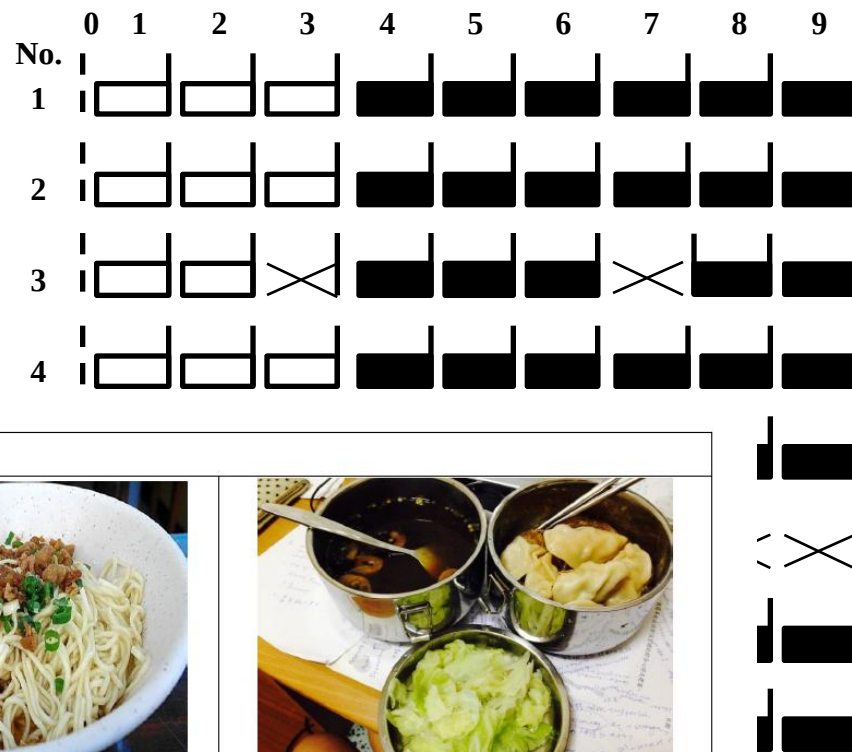
	control–control– intervention group (Building A)	control–intervention– intervention group (Building B)
N	8	8
sex		
male	4	4
female	4	4
	mean ± SD (median, range)	
age (years)	20.9 ± 1.7 (20.0, 20.0 to 25.0)	21.6 ± 1.7 (21.0, 20.0 to 25.0)
body height (cm)	166.5 ± 10.2 (164.0, 153.0 to 181.0)	166.8 ± 7.6 (165.0, 157.0 to 178.0)
body weight (kg)	57.4 ± 10.9 (55.0, 44.0 to 75.0)	60.3 ± 10.8 (56.5, 52.0 to 85.0)
BMI (kg/cm ²)	20.6 ± 2.3 (19.9, 18.2 to 25.6)	21.9 ± 5.1 (20.6, 18.0 to 34.0)
melamine (ng/mL) ¹	19.4 ± 12.7 (13.1, 6.3 to 41.3)	29.1 ± 35.2 (18.8, 0.2 to 112.3)
melamine (μg/mmol Cr) ¹	1.4 ± 0.8 (1.3, 0.5 to 2.6)	2.0 ± 1.8 (1.8, 0.01 to 6.0)

Abbreviations: BMI, body mass index; Cr, creatinine; SD, standard deviation. ¹Averaged melamine levels of three one-spot urinary specimens from the observational study.

Control-control-intervention group (Building A)



Control-intervention-intervention group (Building B)



A)



Control



Control



Intervention

B)



Control

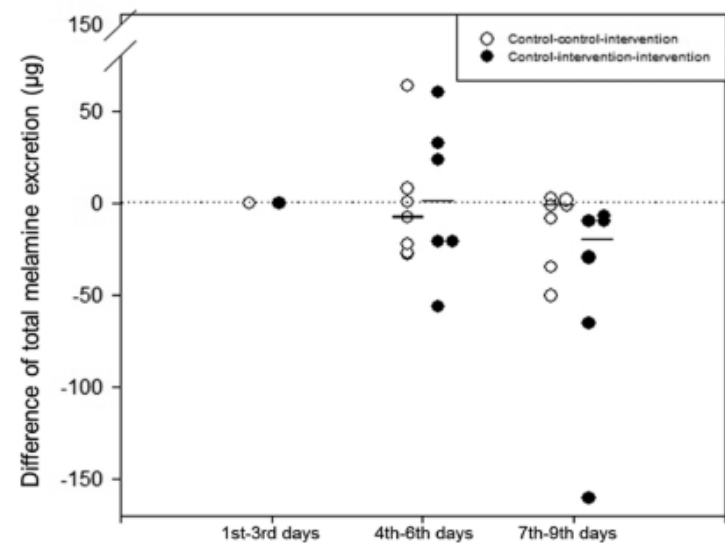


Intervention



Intervention

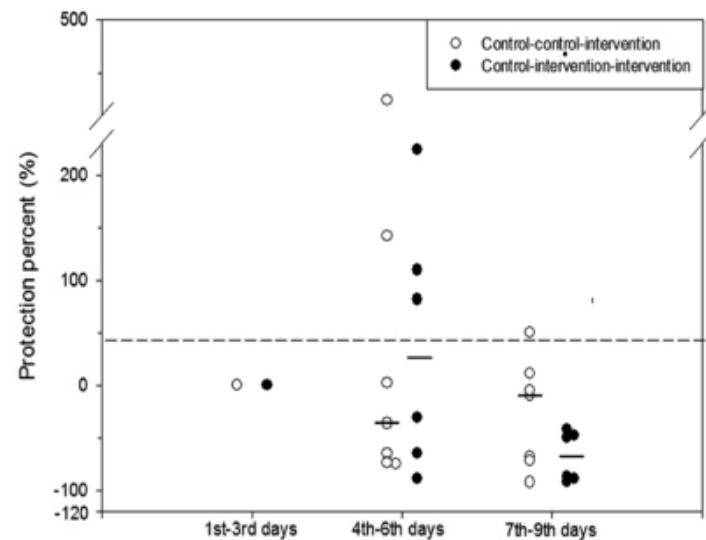
A)



Median (range, µg)

Control-control-intervention (n=7)	Baseline	-7.9 (-28.2 to 63.9)	-1.5 (-50.5 to 2.7)
Control-intervention-intervention (n=6)	Baseline	1.1 (-56.4 to 60.3)	-19.9 (-160.6 to -7.2)*

B)



Median (range, %)

Control-control-intervention (n=7)	Baseline	-36.1 (-74.5 to 424.2)	-9.8 (-92.1 to 49.9)
Control-intervention-intervention (n=6)	Baseline	25.5 (-88.5 to 224.1)	-68.4 (-91.8 to -41.8)*

The melamine levels in their urine decreased after using the containers by 41 to 92 percent.

FOR IMMEDIATE RELEASE

ACS News Service Weekly PressPac: August 05, 2015

A simple tableware switch could reduce exposure to a potentially harmful substance

"Behavioral Intervention and Decreased Daily Melamine Exposure from Melamine Tableware"

Environmental Science & Technology

In households with kids — or grown-up klutzes — a durable set of melamine plates and bowls is a must. But studies suggest that heat and acid can cause melamine from dinnerware to seep into food and potentially cause harmful health effects. Now scientists show that substituting stainless steel containers for melamine ones when serving hot food could reduce the amount of the substance in people's bodies. Their report appears in ACS' journal *Environmental Science & Technology*.



Heat and acid can cause melamine, a potentially harmful substance, to leach into food from dinnerware made out of the plastic material.

Credit: Ivto1/iStock/Thinkstock

PressPac: <http://www.acs.org/content/acs/en/pressroom/presspacs/2015/acs-presspac-august-5-2015/a-simple-tableware-switch-could-reduce-exposure-to-a-potentially-harmful-substance.html> (American Chemical Society)



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Chronic Exposure To Melamine Through Tableware

A simple switch from melamine-containing tableware to stainless steel ones can help reduce environmental exposure to melamine.

[Asian Scientist Newsroom](#) | August 21, 2015 | [In the Lab](#)



AsianScientist (Aug. 21, 2015) - A team of researchers from Kaohsiung Medical University have found that replacing melamine tableware with steel versions can reduce melamine exposure. Their work has been published in *Environmental Science and Technology*.

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國家環境毒物研究中心
National Environmental Health Research Center



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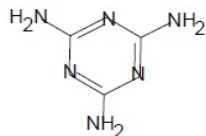
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環境毒物
知多少

三聚氰胺
Melamine



1. 什麼是三聚氰胺(1,3,5-Triazine-2,4,6-triamine, melamine) ?

三聚氰胺最主要的用途是做為三聚氰胺-甲醛樹脂的原料，具有良好的阻燃效果及耐熱、耐水、硬度高的特性，最主要的應用範圍包括以下四大類：(1) 裝飾傢俱用面板；(2) 黏著劑；(3) 熱固性塗料；以及(4) 美耐皿餐具。

2. 我們如何暴露到三聚氰胺？

三聚氰胺主要經由食物暴露，來源可分為以下四大類：

(1) 蓄意添加於奶粉、食物中的污染：如2008年中國大陸爆發的毒奶事件。

(2) 美耐皿餐具遇熱的溶出：若美耐皿餐具製造過程中聚合不完全，高溫或盛裝酸性食品時會產生三聚氰胺單體溶出之情形；此外若使用到劣質的美耐皿餐具(尿素-甲醛樹脂)溶出之情形會更嚴重。民眾日常生活中主要的暴露來源為美耐皿餐具的使用，除了蓄意添加於食品中的污染，其他的暴露來源大致低於美耐皿餐具的使用。研究顯示美耐皿餐具遇熱以及遇酸會釋出三聚氰胺，溫度愈高、其釋出愈多。微波亦不適用美耐皿餐具。根據高雄醫學大學環境醫學研究中心(高醫大環醫中心)的研究團隊研究，自願者在食用美耐皿餐具後，尿液中三聚氰胺濃度確實在短時間內急遽上升且在食用後第6個小時達到最高，之後隨時間增加而濃度開始下降。進一步將同一位自願者分別食用美耐皿餐具及陶瓷餐具所盛裝的熱湯，研究結果證實食用美耐皿餐具者體內三聚氰胺濃度變化顯著的高於食用陶瓷餐具者達8倍，更加說明使用美耐皿餐具確實會增加尿液中排出三聚氰胺濃度。

<http://nehrc.nhri.org.tw/toxic/news.php?cat=news&id=224>

Acknowledgement

Supported by

1. Taiwan National Health Research Institutes (NHRI-EX98-9708PI & NHRI-EX102-10209PI)
2. Taiwan National Science Council (NSC 101-2314-B-037-037-MY3),
3. Kaohsiung Medical University Hospital (KMUH100-0R55 and KMUH101-1I04).

Thank you for your attention