ระดับความปลอดภัยและการประเมินความเสี่ยงของการเคลื่อนย้ายสารเมลามีนจากวัสดุสัมผัสอาหาร
Safety level and risk assessment of melamine migration from food contact materials

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บทคัดย่อ
การตกค้างของสารเมลามีนจากวัสดุสัมผัสอาหารสามารถปนเปื้อนในอาหารได้ สหภาพยุโรปจึงได้ออกกฎระเบียบหมายเลข 1282/2011 เพื่อคุ้มครองสุขภาพของผู้บริโภค ว่าด้วยเรื่องเกณฑ์กำหนดของการไมเกรชันของสารเมลามีนหรือ Specific migration limit (SML) ที่ 2.5 มิลลิกรัมต่อกิโลกรัม ดังนั้น งานวิจัยนี้ศึกษาการไมเกรชันของสารเมลามีนจากวัสดุสัมผัสอาหาร ซึ่งเก็บจากท้องตลาดของประเทศไทยใน 4 ภาคดังนี้ ภาคกลาง ภาคตะวันออกเฉียงเหนือ ภาคเหนือและภาคใต้ โดยใช้กรดอะซิติก ความเข้มข้นร้อยละ 3 โดยน้ำหนักต่อปริมาตรและเทคนิคไฮเพอร์ฟอร์แมนลิควิดโครมาโทกราฟี (HPLC) ด้วยวิธีการสกัดดำเนินการที่ 70 องศาเซลเซียสเป็นเวลา 2 ชั่วโมง การทดสอบปริมาณเมลามีนในตัวอย่างเพื่อประเมินการรับสัมผัสจากการบริโภค พบว่า ค่าเฉลี่ยปริมาณเมลามีนของวัสดุสัมผัสอาหารทุกชนิด คือ 13.5 มิลลิกรัมต่อกิโลกรัม โดยผลการทดสอบได้นำมาประเมินความเสี่ยงของการรับสัมผัสของสารเมลามีน พบว่าอาหารหลายชนิดมีความเสี่ยงสูง เช่น ข้าว นมสด เครื่องดื่มและน้ำดื่ม โดยขึ้นอยู่กับชนิดของอาหาร อายุ การบริโภค และบรรจุภัณฑ์ที่นำมาใช้อีกด้วย ความเสี่ยงสูงที่สุดพบในนมสดสำหรับอายุ 0-3 ปี และน้ำดื่มสำหรับอายุมากกว่า 3 ปี ที่เปอร์เซ็นไทล์ 97.5 เฉพาะผู้บริโภค ดังนั้น ชนิดอาหารที่มีการบริโภคสูงต้องคำนึงถึงว่าอาจมีความเสี่ยงสูงเช่นกัน และควรหลีกเลี่ยงการใช้งานที่ไม่เหมาะสมกับบรรจุภัณฑ์เมลามีนเพื่อป้องกันอันตรายต่อสุขภาพ

Abstract
The residuals of melamine from food contact materials (FCMs) can contaminate into foods. To protect consumer health, the European Union has issued Commission Regulation (EU) No 1282/2011 about specific migration limit (SML) of melamine at 2.5 mg/kg. Therefore, this research was to study the migration of melamine from FCMs which were collected from local markets in 4 regions including Central, Northeast, North and South by using 3% (w/v) acetic acid and high performance - liquid chromatography (HPLC). The extraction method was performed at 70 ^{O}C for 2 hours. The amounts of melamine in samples were tested to estimate dietary exposure. The average of melamine content was found at 13.5 mg kg^{-1} for all types of FCMs. This result had been evaluated for the exposure assessment of melamine and found that various kinds of foods such as rice, fresh milk, beverage and water have high risk depending on food type, age, intake and food packaging used. The highest risk was found in fresh milk for aged 0-3 years and drinking water for aged more than 3 years at 97.5 percentile and eater only. Therefore, the food types with high consumption may have been concerned high risk and avoid misuse of melamine containers in order to prevent a health hazard.

คำสำคัญ: การประเมินความเสี่ยง เมลามีน ไมเกรชัน วัสดุสัมผัสอาหาร
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1. Introduction

Melamine or the chemical name as 1,3,5-triazine-2,4,6-triamine is used in the plastic industry to produce melamine wares which is very popular due to its beautiful material, light weight, durable and low price. The melamine wares are produced from the reaction of formaldehyde and melamine resin. Therefore, the release of formaldehyde and melamine is important to consumer health. During the past decade, most of people are focused on the harmfulness of formaldehyde [1-3]. However, melamine is also dangerous when reacts with cyanuric acid and forms melamine cyanurate known as melamine-cyanuric acid adduct or melamine-cyanuric acid complex. This substance is an insoluble crystal which can clog the kidney tube and cause of kidney stones and bladder cancer. The death was reported from acute renal failure [4-5]. The World Health Organization (WHO) has established a tolerable daily intake (TDI) of 0.20 mg kg^{-1} b.w. (Body weight) day^{-1} [6]. The United States and European Union has issued the TDIs at a higher limits of 0.63 mg kg^{-1} b.w. day^{-1} by the US FDA for food and food ingredients and 0.50 mg kg^{-1} b.w. day^{-1} by the EU for food contact materials [7-8]. The Commission Regulation (EU) No 1282/2011 on 28 November 2011 was disclosed with lower a specific migration limit (SML) of melamine of 2.5 mg kg^{-1} [9].The melamine contamination in FCMs may receive less concern; hence to solve this issue, the risk assessment of melamine could contribute significant level for consumer protection in Thailand. Nowadays, Thailand has not issued the regulation of melamine migration in the FCMs, until 2019 the compulsory standards no. TIS 2921-2562 has been issued by the Thai Industrial Standards Institute (TISI)in safety requirement only [10]. The analytical methods are also a crucial step to provide precise requirement of regulations and standards. Due to small and polar compound of melamine, high performance liquid chromatography (HPLC) was considered suitable for melamine determination in FCMs and foods [11-14]. Many literatures were reported the developing methods of melamine measurement by using various techniques i.e. liquid chromatography - tandem mass spectrometry (LC-MS/MS). The LC-MS/MS could provide a good identification and low detection limit.Recently, the European Committee for Standardization (CEN) has performed interlaboratory validation of LC-MS/MS method for melamine and cyanuric acid in animal feed [15]. Either FCMs or foods have been concerned in the safety of melamine [16-17].The LC-MS/MS was useful to study melamine metabolites e.g. ammelide, ammeline and cyanuric acid [18]. Other techniques such as Fourier transform infrared (FT-IR), FT-Raman, and near-infrared (NIR) spectroscopy were adopted to evaluate the melamine contamination in gelatin [19]. Although there are many techniques applied to determine the melamine concentration, the HPLC gains more advantages such as low detection level and matrix effect. Additionally the HPLC technique with food simulant has been published by British Standards Institution according to standard number: DD CEN/TS 13130-27:2005. To obtain the reliable results, the standard method was used to evaluate the quantity of melamine in FCMs. Since the food safety is important issue for consumer protection, the risk assessment is one tool to evaluate the harm to human health including safety monitoring and standard setup. Normally, the researches of risk assessment were focused on contamination levels in food. Therefore, the risk assessment of FCM was still limited and ignored in the points of source of food contamination. Moreover, the distribution of melamine was found in hen tissue such as kidney, breast muscle, liver and thigh muscle. The melamine aggregation in liver and kidney tissues exhibited a biotransformation of melamine into cyanuric acid. Although the cyanuric acid was eliminated through urine, the lower eggshell strength, lower corpuscular hemoglobin and higher red blood cell presented with intake melamine in laying hen [20].In dairy cows, melamine levels were also found in milk and kidney tissue with fed melamine [21]. Therefore, the dietary intake of contaminated food may cause the health effect. The aim of this research was to conduct risk assessment of melamine in foods as the result of FCM migration. It is assumed that free/residual melamine in FCMs was fully transferred into foods and drinks. The melamine exposure was estimated and the percentage of risk was obtained with different kinds of foods.

2. Experimental methods

2.1 Samples and sampling sites

The various Samples of FCMs were collected from local markets in 4 regions of Thailand: Central, Northeastern, Northern and Southern. The Central regions included six provinces as following: Bangkok, Pathum Thani, Nakhon Sawan, Sing Buri, Saraburi and Lop Buri provinces, while the four provinces of Northeastern were Nong Khai, Mukdahan, Ubon Ratchathani and Nakhon Ratchasima.Chiang Rai and Phitsanulok represented Northern and a province represented Southern was Songkhla. The different types of FCMs were analyzed. They were dish, bowl, cup, spoon and ladle with different shape, size and color as shown in Figure 1. The 89 of FCM samples were collected during January 2013 to September 2019.

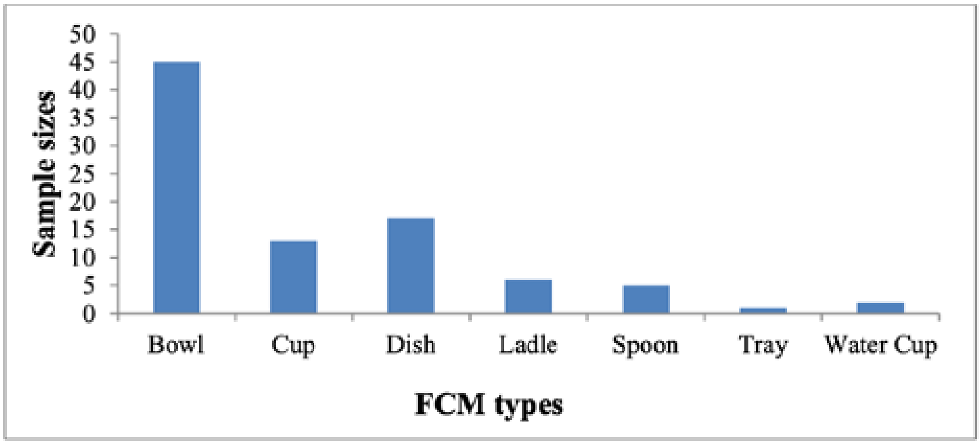

Figure 1. A number of samples sampling from local markets in Thailand

2.2 Reagents and chemicals

All solvents and chemicals were purchased from Merck with analytical grade i.e.glacial acetic acid, sodium dihydrogen phosphate monohydrate, sodium hydroxide. Except for acetonitrile was supplied by Merck with liquid chromatography grade. Ultrapure deionized water with the quality of 18.2 MΩ•cm was applied as dilution and solvent preparation. Standard solution was prepared from melamine, purity > 99 %.

2.3 Instruments and materials

All experiments were performed by using high performance liquid chromatograph (HPLC) with an automatic injector and photodiode array detector (PDA). The chromatographic device was Alliance e2695 and 2998 detector (Waters Corporation, Massachusetts, United States).The stainless steel column was Spherisorb NH_2 (250 mm x 4.6 mm i.d.) with a Spherisorb NH_2 guard column (10 mm x 4.6 mm i.d.) and all packings were 5 µm particle size.The extract condition was operated by thermostatically controlled oven (Binder Inc., Tuttlingen, Germany) after food simulant was pretreated in water bath (GFL Gesellschaft für Labortechnik mbH, Burgwedel, Germany). Balance (Mettler-Toledo LLC, Columbus, Ohio, United States) and micropipette (Rainin, Mettler-Toledo LLC) were utilized for standard and sample preparation including syringe filters PTFE (Agilent Technologies Inc., Santa Clara, California, United States). A pH-meter (Orion, Thermo Scientific, Mansfield, Texas, United States)was applied to control the pH range of mobile phase. All glasswares were class A in Pyrex brand (Tewksbury, Massachusetts, United States).

2.4 Sample preparation

The test specimens were prepared as described in EN 13130-1. In summary, the sample was cleaned with water; otherwise, the article was wiped with a lint-free cloth or brushed with a soft brush to remove dust. The 3% (w v^{-1}) acetic acid was used as food simulant and then the sample was warmed to 70 ^{O}C using water bath.Then, the test sample was filled with enough volume of 3% (w v^{-1}) acetic acid at 70 ^{O}C and placed in the oven for 2 hours. The volume of food simulant was filled the full capacity of test article which was below 0.5 cm of the top. For ladle and spoon, the samples were immersed in the warmed food simulant at 70 ^{O}C for 2 hours with the surface area ratio of

100 cm^2 to food simulant 1 dm^3. In case of repeat used article, the experiment was performed three times with the food simulant and kept the third time for analysis.

2.5 HPLC measurements

The measurement was a modified and validated method of DD CEN/TS 13130-27:2005. This HPLC was equipped with the Spherisorb NH_2 and guard column which temperature was set at 25 ^{O}C. The mobile phase was performed with acetonitrile and 5 mM phosphate buffer at pH 6.5 (75: 25). The isocratic elution was run at a flow rate of 1 mL min^{-1}. The injection volume was 20 μL. The photodiode array detector was set at 230 nm.

2.6 Method performances

The validation parameters were investigated such as linearity, range, relative standard deviation (RSD) and recovery at 3 concentration levels. Their details were published in the Department of Science Service: Bulletin of Applied Sciences [22]. The method validation was complied with EUR 24105 EN: 2009.All experiments provided linearity with correlation coefficient (r) of greater than 0.995. The excellent accuracy and precision were obtained in range of %recovery of 83.1 to 107.9 and %RSD of less than 10, respectively. The limit of detection (LOD) and limit of quantitation (LOQ) were 0.20 and 0.50 mg kg^{-1}, respectively. To accomplish the reliable results, the FAPAS sample was performed by PT program: Aqueous acetic acid 3% (w/v) test materials. Furthermore the LC-MS/MS technique was compared for the melamine measurement and provided non-significant differences at $p > 0.05$, two tailed t-test.

2.7 Internal quality controls

All samples were performed with triplicate and the relative standard deviation was also obtained in acceptable range as calculating by the Horwitz Equation.The spiked samples were also performed per 10 samples and recoveries were calculated.The recovery acceptance ranged from 80-110% (EUR 24105 EN - 1st ed. 2009). The standard check was injected at least per 10 samples to check the performance of HPLC instrument.

2.8 Statistical analysis

All statistical calculations for these experiments were completed by using Microsoft excel version 2010.

2.9 Types of plastic

Analysis of plastic types was carried out by using Fourier transform infrared spectroscopy (FT-IR) with Tensor 27 model by Bruker Biospin AG, Thailand. The sample was scratched on the contact side by silicon carbide sandpaper or carborundum paper and determined at wavelengths: 4,000 - 400 cm^{-1}. The spectrum of sample was compared to that of standard and interpreted the types of FCMs.

3. Results and discussion

3.1 Migration from FCMs

The migration of melamine wares were performed with various kinds of food contact materials such as dishes, bowls, cups, ladles, spoons, tray and water cup. The total of FCMs were 89 samples from 12 provinces and kept during the period of January 2013 to September 2019 which some provinces have limited sample availability due to the sampling with different shape, size, and color. The details of sampling sites and melamine migrations were shown in Table 1.All samples were manufactured in Thailand and imported from other countries, for examples, China, Vietnam and non-identification.

Table 1. Survey of melamine migration using food simulant (3% (w v^{-1}) acetic acid)

Regions	Provinces	Sample sizes	Average of Melamine Migration (mg kg^{-1} food simulant ± SD)	Melamine Migration (mg kg^{-1} food simulant)	
				Max.	Min.
Central	Bangkok	39	4.98 ± 5.06	15.3	not detected
	Pathum Thani	1	26.9 ± 6.27	-	-
	Nakhon Sawan	9	12.9 ± 9.23	23.4	not detected
	Sing Buri	2	136.1±138.5	266.0	6.10
	Saraburi	2	235.2 ± 92.9	455.8	14.5
	Lop Buri	1	8.80 ± 2.62	-	-
Northeastern	Nong Khai	9	10.1 ± 3.32	13.8	3.20
	Mukdahan	10	8.51 ± 12.1	31.2	not detected
	Ubon Ratchathani	4	18.8 ± 7.55	18.8	not detected
	Nakhon Ratchasima	5	2.60 ± 1.37	4.30	1.00
Northern	Chiang Rai	3	10.0 ± 6.01	16.6	4.80
	Phitsanulok	1	not detected	-	-
Southern	Songkhla	3	2.57 ± 2.56	5.50	0.80

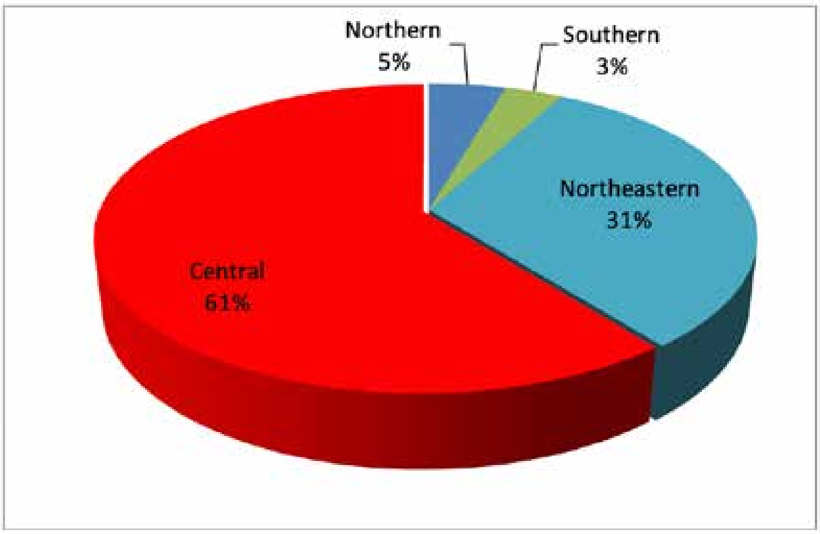

Figure 2. Sampling proportion

Figure 2 displayed the proportion of sampling sites which was related to regions. The predominant migration came from the central area which was found the highest content in Saraburi province and the lowest in Bangkok. Most samples of Bangkok were not detected from 34 of 39 samples (87%). In the Northeastern, the bowl sampling from Mukdahan provided highest concentration comparing to other provinces in this region.The ladles and spoons had provided the trend of the higher melamine content because the cut edge of test article would release the contaminant during extraction time. Each sample was varied melamine contents with large SD which was not depending on the source of sampling site and manufacturing. Even frontier areas which had high volume of sample transfer from other countries were not significant higher amount of melamine i.e.Ubon Ratchathani and Chiang Rai. The 47 samples out of 89 were complied with the specific migration limit of 2.5 mg kg^{-1} as stated by the Commission Regulation (EU) No 1282/2011.

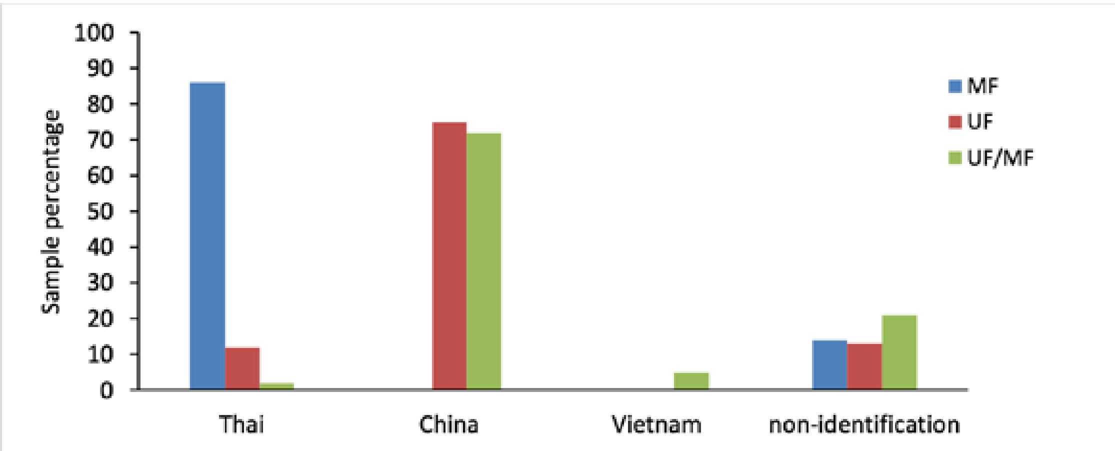

Figure 3. The sample ratio with manufacturing materials and sources

Figure 3 represented the manufacturing of materials and sources. The majority of samples were produced by melamine-formaldehyde (MF). The other materials were urea-formaldehyde (UF) and UF/MF. The UF/MF was composed of two materials: urea-formaldehyde and coating with melamine-formaldehyde.Generally, the type of melamine-formaldehyde (MF) was applied as the contact area to food due to safety issue. However, the plastic type did not provide the relationship with migration amount of melamine as shown in Figure 4. The ladles provided the highest melamine migration as previous mentioned in the range of 266.0 to 455.8 mg kg^{-1}.

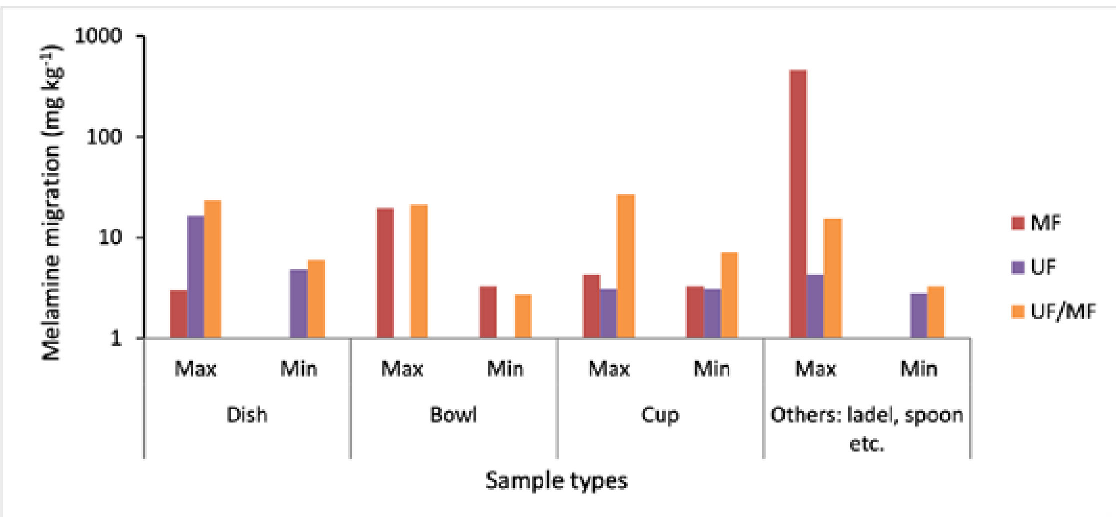

Figure 4. Melamine migrations related to sample types and materials

In another plastic type: UF melamine may be added as additive to make the material properties as similar to MF; hence, UF types were also detected in table wares at 16.6 mg kg^{-1} food simulant. In this study, the average of melamine migration was 13.5 mg kg^{-1} food simulant for all sampling regions in Thailand since the non-detectable (ND) and non-quantifiable (NQ) results of all samples were assumed to be LOD/2 for the ND and NQ proportion at ≤60% [23].

3.2 Food contamination

This study was focused on the effect of melamine migration from FCMs; therefore, the melamine contamination in food was assumed to be 100%. This assumption was the worst case scenario from FCM migration. Thus, the average amount of melamine was 13.5 mg kg^{-1} in food. This value was applied to calculate dietary exposure for all food categories.

3.3 Dietary intake and exposure

The database consumption of the National Bureau of Agricultural Commodity and Food Standards [24] was applied to estimate risk assessment using the entire data of consumption gathered during 2013-2015. The exposure assessment was calculated with the equation:

$$Exp = \frac{Conc\ (mg\ kg^{-1}) \times FC\ (kg\ person^{-1}\ day^{-1})}{BW\ (kg)} \qquad (1)$$

Where Exp is dietary exposure (mg kg^{-1} $person^{-1}$ day^{-1}); Conc is amount of contamination in food (mg kg^{-1}); FC is food consumption (kg $person^{-1}$ day^{-1}) and BW is body weight (kg).

3.4 Risk assessment

The risk assessment was performed by using tolerable daily intake (TDI): 0.20 mg kg^{-1} b.w. day^{-1} (6) as following

$$\%Risk = \frac{Exposure}{TDI} \times 100 \qquad (2)$$

The criteria of risk interpretation were considered by:

%Risk < 100 (or exposure < TDI): safety for consumption.

%Risk > 100 (or exposure > TDI): risk for consumption.

The food categories had been estimated on the risk assessment (Table 2 and 3) depending on the database consumption. The estimation based on two groups: age of 0-3 years and more than 3 years old.

Table 2. Food categories and risk estimation for age of 0-3 years

Food categories	Details	Foods with highest risk	Foods with high risk (%Risk > 100)			
			per capita		eater only	
			Average	percentile at 97.5	Average	percentile at 97.5
Cereal and product	- rice, powder and product (steamed white rice, brown rice, sticky rice, rice congee, mush, thai rice noodle, yellow noodle, macaroni and vermicelli) - bakery and snack (steamed bun and bread)	steamed white rice	-	steamed white rice, rice congee, mush	-	steamed white rice, rice congee, mush
Milk and product	modified milk, milk powder, fresh milk, sweet fresh milk and fermented milk	fresh milk	-	modified milk, milk powder, fresh milk, sweet fresh milk	fresh milk	all types
Ice cream	milk, coconut	ice cream with milk	-	-	-	
Drink and beverage	soft drink, juice, soy milk, green tea, instant coffee and energy drink	soy milk	-	soft drink, soy milk	soy milk	juice, soft drink, soy milk
Seasoning	fish sauce, soy sauce, pickled fish, ketchup	Ketchup	-	-	-	-
Regular water	drinking water	drinking water	drinking water	drinking water	drinking water	drinking water

Note: The "-" displayed none high risk foods or %risk < 100.

Table 3. Food categories and risk estimation for more than 3 years old

Food categories	Details	Foods with highest risk	Foods with high risk (%Risk > 100)			
			per capita		eater only	
			Average	percentile at 97.5	Average	percentile at 97.5
Cereal and product	- rice, corn, powder and product (steamed white rice, brown rice, sticky rice, rice congee, mush, Thai rice noodle, yellow noodle, macaroni, spaghetti, vermicelli, white bread and whole wheat bread) - bakery and snack (steamed bun, sweet bun, salted egg bun, donut, cake, éclair, crepes and deep-fried dough stick) - fast food (burger, hot dog, sandwich, french-fry, pizza and mashed potato)	steamed white rice	steamed white rice	steamed white rice, brown rice, sticky rice	steamed white rice, brown rice, sticky rice, rice congee, mush, Thai rice noodle	steamed white rice, brown rice, sticky rice, rice congee, mush, Thai rice noodle, yellow noodle, macaroni, spaghetti, crepes, burger, pizza
Fish and product	canned food (such as mackerel and sardine), canned tuna and canned fish with chili	canned food (mackerel and sardine	-	-	-	-
Milk and product	fresh milk, sweet fresh milk, condensed milk, fermented milk and yogurt	fresh milk	-	resh milk, fermented milk	fresh milk, fermented milk	fresh milk, sweet fresh milk, fermented milk and yogurt
Ice cream	milk and coconut ice cream	coconut ice cream	-	-	-	-
Drink and beverage	cocoa 3 in 1, cereal drink, soft drink, juice, soy milk, green tea, tea, instant coffee, electrolyte drink and energy drink	soft drink (cola)	-	soy milk, soft drink, green tea, coffee, electrolyte drink	-	soy milk, soft drink, green tea, coffee, electrolyte drink
Thai dessert	- deep fried banana, fried taro and fried potato - fruit in syrup (such as banana, pumpkin, taro and potato)	fried potato	-	-	-	-
Seasoning	fish sauce, soy sauce, pickled fish, ketchup, chicken sauce and vinegar	pickled fish	-	-	-	-

Food categories	Details	Foods with highest risk	Foods with high risk (%Risk > 100)			
			per capita		eater only	
			Average	percentile at 97.5	Average	percentile at 97.5
Curry paste	Da Daeng chili paste and crispy catfish chili paste	Da Daeng chili paste	-	-	-	-
Regular water	drinking water	drinking water	drinking water	drinking water	drinking water	drinking water

Note: The "-" displayed none high risk foods or %risk < 100.

For aged 0-3 years, there were the limitation of food types for consumption and among the all categories fresh milk provided the highest risk at 97.5 percentile for eater only. Only ice cream and seasoning were safe to the health risk in all groups of populations. Due to the high risk of drinking water, it has to concern with contact to melamine tableware especially low quality of FCMs. Moreover the cereals, milks, drinks and beverages were provided high risk for more than 3 years of age at 97.5 percentile for both per capita and eater only.

When investigating by eater only for 0-3 years old, almost all of foods and drinks have to beware to release melamine from FCMs due to their sensitive illness. Furthermore, there are limited kinds of foods and drinks including the large consumption of milks and waters in the infants aged 0-3 years; the FCMs for them are required to be clean and safe. In case of serious situation had been occurred from the intentional addition of melamine into milk powder [25] which would be one of serious issues to manage and control. Normally, FCMs is ignored to beware; this risk would reveal a health hazard which should be managed and avoided in the usage of improper FCMs.

The highest risk of each food category was plotted as shown in Figure 5 and 6. Figure 5 showed the risk assessment of foods and drinks in each category and the higher risk was obtained by using average and percentile at 97.5 consumption for eater only. The risk percentages of whole population were represented in Figure 6for more than 3 years which was separated into per capita and eater only. All foods and drinks were estimated on the contact use of melamine FCMs. Therefore the more contact time was applied; the more migration of melamine was detected in food.

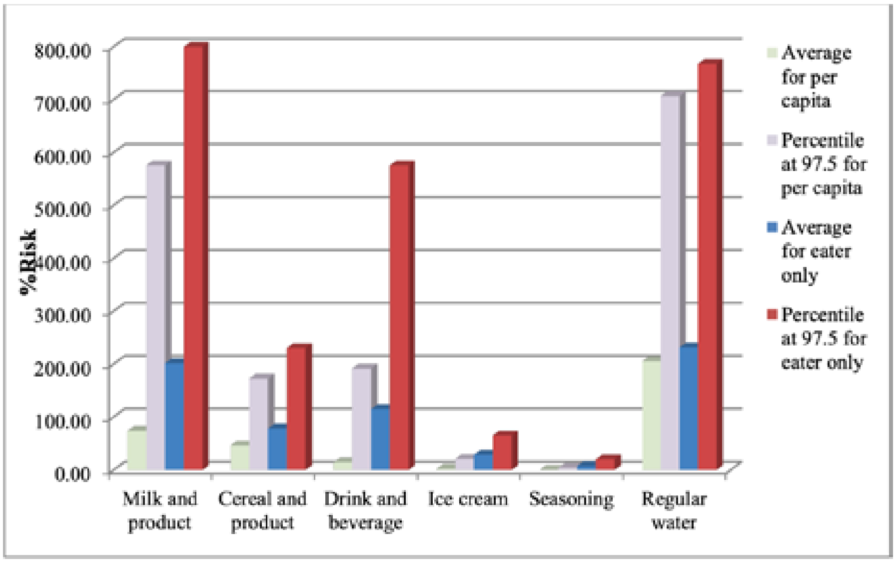

Figure 5. The estimated risk of foods and drinks for aged 0-3 years from the assumption of melamine contaminant in FCMs

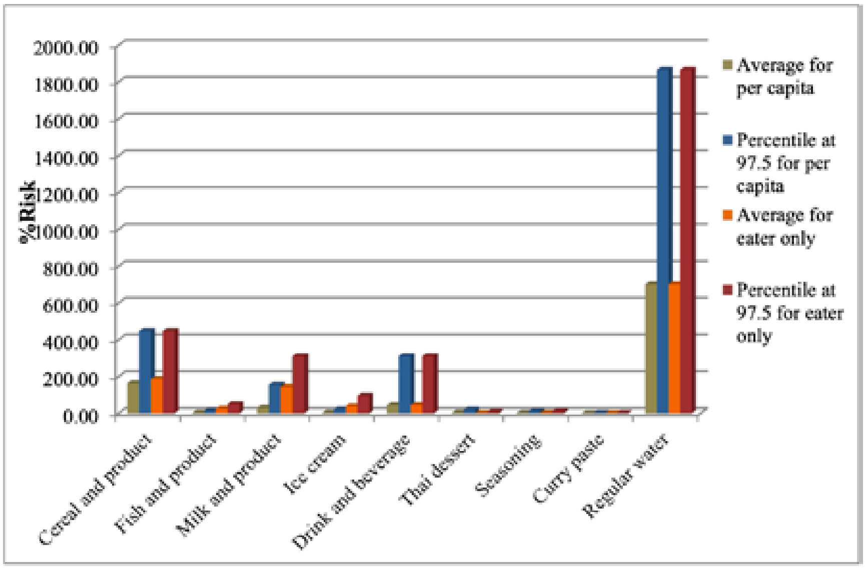

Figure 6. The risk assessment of foods and drinks for aged more than 3 years when the application of melamine wares.

Although various food types provided relatively high risk, generally the melamine compound represents low toxicity. When it presents with cyanuric acid, the melamine cyanurate complex will form and give highly insoluble property. The urinary tract would irritate and obstruct, therefore, kidney function has degenerated and occurred renal failure [26]. Therefore, the awareness is required by manufacturer and consumer for health care protection.

4. Conclusion

The highest melamine migration of 455.8 mg kg^{-1} was found in ladle sample collected from Saraburi province. The average of melamine content was 13.5 mg kg^{-1} for all types of FCMs. The risk assessment was found relatively high risk in various kinds of food due to large amount of consumption. For aged 0-3 years, the highest risk was found in fresh milk at 97.5 percentile and eater only, while ice cream and seasoning were safe for consumption.For more than 3 years old, the regular water obtained the highest risk at 97.5 percentile and eater only as well as cereals, milks, drinks and beverages. Therefore, the FCM applications are required to beware for the quality selection and manufacturer.The low quality of kitchenware is the one source of melamine contamination and the consumer should follow instruction manual strictly for the use of FCMs. The food types with high consumption have been concerned high risk and avoid the food contact with melamine containers in order to prevent a health hazard.

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