



Review

Melamine and Cyanuric Acid in Milk and Their Quantities, Analytical Methods and Exposure Risk: A Systematic Review and Meta-analysis



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ARTICLE INFO

Keywords:

Cyanuric acid
Melamine
Meta-analysis
Milk contamination

ABSTRACT

Melamine, as a toxic compound, needs to be controlled in food, especially in dairy products. In this systematic study, quantities of melamine and cyanuric acid in various types of milk were investigated. A comprehensive database search was performed using the keywords pasteurized milk, milk, sterilized milk, melamine, and cyanuric acid without time limitation. A total of 24 articles related to melamine and cyanuric acid were thoroughly reviewed. The overall mean concentration of melamine in milk was estimated by meta-analysis to be 11.3 µg/L. Publication bias was not addressed in the associated assays; however, it was addressed as highly heterogeneous between studies. Subgroup analysis was carried out, and the milk type was a cause of heterogeneity. This systematic review investigated a range of melamine in milk products and discussed different analytical methods.

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Both intentional and unintentional contamination of food can harm human health. Regulatory organizations try to reduce the contamination of food by setting standards and continuously monitoring products. Milk and milk-based products are among the products used by babies and the elderly. These products can be contaminated with various chemicals. Melamine (C₃H₆N₆) (MA) is one of the compounds that

does not occur naturally in foods. In general, the use of this substance in foods, especially in milk, is well known as a fraud. Melamine is frequently combined with cyanuric acid. Cyanuric acid is an impurity that occurs naturally in melamine. When these substances enter the bloodstream, melamine, and cyanurate accumulate and react with the microtubules of the kidneys, forming large numbers of yellow,

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<https://doi.org/10.1016/j.jfp.2025.100454>

Received 14 August 2024; Accepted 9 January 2025

Available online xxxx

0362-028X/© 2025 The Author(s). Published by Elsevier Inc. on behalf of International Association for Food Protection.

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spherical crystals that damage the kidney cells and their ducts. As melamine is not metabolized and has a short half-life, its combination with cyanuric acid may lead to crystallization and formation of kidney or bladder stones and urinary tract obstruction in humans (Melekoğlu et al., 2020; Rajpoot et al., 2021). Therefore, there are pains in the abdomen and damages to the kidney cells (Melekoğlu et al., 2020). In China, this led to urolithiasis and acute kidney injury in exposed infants (Guo et al., 2020). The adulteration of dairy products with melamine causes serious damages to the country's economy in addition to health damages (Singh & Gandhi, 2015).

Several methods based on liquid chromatography (LC) and gas chromatography (GC), as well as novel methods, have been developed for the identification of melamine in milk. Barreto et al. (2021) proposed a rapid method using emission-excitation matrix fluorescence spectroscopy (EEM) and second-order calibration methods (PARAFAC and U-PLS/RBL) for the detection and quantification of melamine in milk (Barreto et al., 2021). The proposed method used an acetic acid clean-up step, resulting in a rapid, inexpensive, and environmentally friendly method in line with green chemistry principles. The two methods, PARAFAC and U-PLS/RBL, were able to detect more than 120.6 and 146.5 mg/kg melamine in milk, respectively, which was sufficient for adulteration above 2% by volume.

Mechanism of melamine-induced toxicity. The most sensitive body organs to melamine are the kidneys. After ingestion, almost 90% of melamine is excreted in the urine (Wu et al., 2021). Based on the results, crystal nephropathy in humans exposed to melamine and cyanuric acid was identical to uric acid nephropathy (Kim et al., 2023). Simultaneous ingestion of these two triazines precipitates melamine-cyanurate crystals in the renal tubules (Fig. 1).

These stones can block different parts of the duct. This eventually leads to abdominal discomfort and kidney cell damage (Brown et al., 2007). Long-term intake of melamine can cause urinary tract infections, nephritis, kidney failure, and the formation of bladder and kidney stones, which can progress to bladder carcinoma (Borts, 2019). Oxidative stress and inflammation may be responsible for the mechanism of melamine toxicity. These complications may occur through the activation of NF- κ B/cox-2 and NOX/ROS pathways (Rai et al., 2022). Oxidative stress is caused by an imbalance between the generation of reactive oxygen species (ROS) and antioxidant power (Ahmed et al., 2021; Sadighara et al., 2016). Urinary levels of the two biomarkers of oxidative stress, 8-oxo-2'-deoxyguanosine (8-OHdG) and malondialdehyde (MDA), were higher in workers who produced melamine

dishes and hence were exposed to melamine (Liu et al., 2020). Recent studies have shown that melamine causes infertility in exposed female mice (Rajpoot et al., 2021). In addition, melamine has been detected in the amniotic fluid, confirming the transfer of melamine from the mammalian mothers to their fetuses (Wu et al., 2020). Therefore, the aim of this systematic study was to investigate the amount of melamine and cyanuric acid in different types of milk. Furthermore, different analytical methods for the evaluation of these compounds in foods were discussed. Different methods of sample preparation were also reviewed. A meta analysis was performed for the overall estimation of melamine in foods. For health risks, the hazard quotient (HQ) is usually calculated (Zhu & Kannan, 2018). If the HQ for a contaminant in a food is calculated to be less than one, consumption of that food will be without adverse health effects for that contaminant (Nag & Cummins, 2022). In studies, the potential health risk for melamine in food is also calculated with HQ (Shi et al., 2020; Zhu & Kannan, 2018). Therefore, the calculated HQ values of the studies were summarized. Furthermore, possible causes of heterogeneity between the studies were investigated using meta-regression.

Methods

All stages of this systematic review were carried out according to the PRISMA checklist. To reduce potential bias, the review was conducted with the involvement of two team members, who performed each step of the process. In case of disagreement, the corresponding author reported.

Search strategy. Databases were searched on 15 May 2023. All potential articles in the databases were carefully selected without temporal restrictions. A comprehensive search was performed using PubMed, Science Direct, and Scopus databases. The selection of the targeted keywords included ("pasteurized milk" OR milk OR "sterilized milk") AND (melamine OR cyanuric acid).

Inclusion and exclusion criteria. Table 1 shows the inclusion and exclusion criteria of the study. Inclusion criteria for this systematic review were primary articles that used reliable laboratory techniques to quantify the amount of melamine and cyanuric acid in milk. The full text of the selected articles was assessed using a checklist. This checklist was formulated using quintuplet of key points. Inclusion criteria for the present study were articles with a score of three or more. Furthermore, studies without a clearly defined sample size were excluded from the meta-analysis.

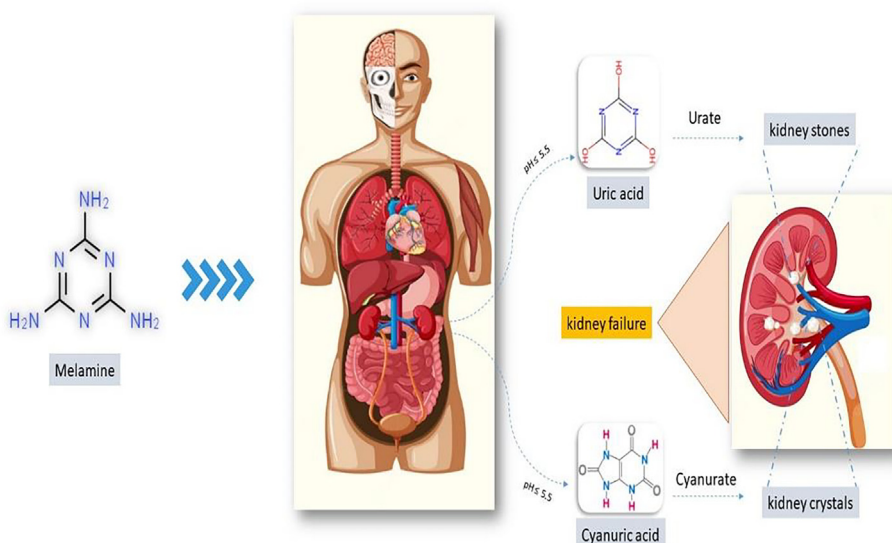


Figure 1. Relationship of kidney stones with increased concentration of melamine in foods.

Table 1
Inclusion and exclusion criteria of this study

Inclusion criteria	Exclusion criteria
Assessing quantity of melamine in milk	Animal study
Assessing quantity of cyanuric acid in milk	<i>In vitro</i> study
	Clinical trial
	Method develop
	Protein analysis study
	Other pollutants, including pesticides
	Not available and non-English articles
	Lack of sample size

Data extraction. Table 2 shows all the data extracted from the articles. The table includes sample type, sample size, analytical method, melamine and cyanuric acid content, hazard quotient (HQ), countries, and references. At all stages of data extraction, disagreements were checked with the corresponding author.

Table 2
Major data extracted from the published articles (melamine)

Sample type	Analytical method	Sample size	Quantity (mean \pm SD)	HQ	Country	Author/year
Raw milk	N-methylmesoporphyrin IX (NMM)/G-quadruplex	3	51.3 \pm 0.6 μ g m/L	–	China	Wang et al., 2020
Whole milk	Spectrophotometry	3	75.8 \pm 7.10 μ g/L	–	Türkiye	Altunay et al., 2017
Semi-skimmed milk	Spectrophotometry	3	55.1 \pm 8.10 μ g/L	–		
Liquid milk (toned milk)	HPLC-UV	5	2.87 \pm 0.02 μ g m/L	–	India	Anirudhan et al., 2017
Raw milk	Novel pincer zinc complex	3	3 \pm 0.06 mol/L	–	China	Bao et al., 2021
Whole UHT	Sequential injection chromatography	3	2.64 \pm 0.18 m/L	–	Brazil	Batista et al., 2014
Whole UHT	HPLC	3	2.77 \pm 0.26 m/L	–		
Whole UHT	Sequential injection chromatography	3	4.30 \pm 0.13 m/L	–		
Whole UHT	HPLC	3	4.22 \pm 0.44 m/L	–		
Pasteurized skimmed	Sequential injection chromatography	3	1.81 \pm 0.11 m/L	–		
Pasteurized skimmed	HPLC	3	1.90 \pm 0.01 m/L	–		
Pasteurized skimmed	Sequential injection chromatography	3	3.54 \pm 0.14 m/L	–		
Pasteurized skimmed	HPLC	3	3.67 \pm 0.03 m/L	–		
Semi-skimmed UHT	Sequential injection chromatography	3	2.12 \pm 0.10 m/L	–		
Semi-skimmed UHT	HPLC	3	2.04 \pm 0.39 m/L	–		
Semi-skimmed UHT	Sequential injection chromatography	3	3.60 \pm 0.17 m/L	–		
Semi-skimmed UHT	HPLC	3	3.42 \pm 0.20 m/L	–		
Pasteurized skimmed	Sequential injection chromatography	3	2.09 \pm 0.22 m/L	–		
Pasteurized skimmed	HPLC	3	1.95 \pm 0.01 m/L	–		
Pasteurized skimmed	Sequential injection chromatography	3	3.03 \pm 0.12 m/L	–		
Pasteurized skimmed	HPLC	3	3.14 \pm 0.10 m/L	–		
Raw milk	UPLC-MS	5	9.11 \pm 1.66 mg/kg	–	United States	Baynes et al., 2010
Liquid milk	Gold nanoparticles-based LSPR via optical fibers	9	0.30 \pm 1.28 μ M	–	China,	Chang et al., 2017
Liquid milk	Silver nanoparticles functionalized with sulfanilic acid	2	15.7 \pm 1.6 M	–	China	Song et al., 2015
Liquid milk	FASI-CE-C ⁴ D	3	0.0076 μ g/mL	–	China	Ji et al., 2014
Liquid milk	HPLC-MS	3	0.0080 μ g/mL	–		
Liquid milk	LC-MS/MS	15	1.054 \pm 0.245 μ g/ml	–	Iran	Hassani et al., 2013
Liquid milk (1.5% fat)	Ion-pair-based HF-LPME combined with HPLC	3	0.08 mg/kg	–	China	Gao and Jönsson 2012
UHT milk	HPLC	50	0.00 μ g/kg	–	Türkiye	Filazi et al., 2012
Pasteurized milk	HPLC	50	0.00 μ g/kg	–		
Raw Milk	Immunogold chromatographic assay (IGCA)	5	0.00 μ g/mL	–	China	Li et al., 2011
Fresh milk	GC-MS/MS	1	0.28 mg/kg	–	China	Hong et al., 2009
Raw milk	HPLC	3	0.10 mg/kg	–	Iran	Abdolmohammad-Zadeh et al., 2020a
Milk	HPLC	15	0.23 \pm 0.09 mg/kg	–	Iran	Poorjafari et al., 2015
Milk	HPLC	23	0.22 mg/kg	THQ \leq 1	Iran	Alizadeh et al., 2023
Milk and dairy	HPLC-MS/MS	34	0.48–3.66 ng/g		United States	Zhu and Kannan 2019
Milk	HPLC-MS/MS	42	7.9 ng/g	3.1 \times 10 ⁻⁴ (adult) 0.011 (children)	United States	Zhu and Kannan 2018

Meta-analysis of data. Meta-analysis was performed using Comprehensive Meta-analysis (CMA) v3.3.070 software. Heterogeneity was assessed using I^2 and Q test methods. The Egger test was used to assess the presence of publication bias. Meta-regression analysis was also performed to investigate factors contributing to the heterogeneity.

Results

Search processes. Number of the articles linked to the research objectives was 1357. Title and abstract of the articles were carefully reviewed and assessed. Articles that did not meet the predetermined inclusion criteria were excluded from the study. Then, a comprehensive analysis was carried out on all the selected articles, and quality assessment of the articles was carried out. Quality assessment of the article was carried out by two authors. Then, 24 articles were selected for inclusion in the study. The current study was carried out on an established framework of the PRISMA checklist. Fig. 2 shows a diagram of the search strategy.

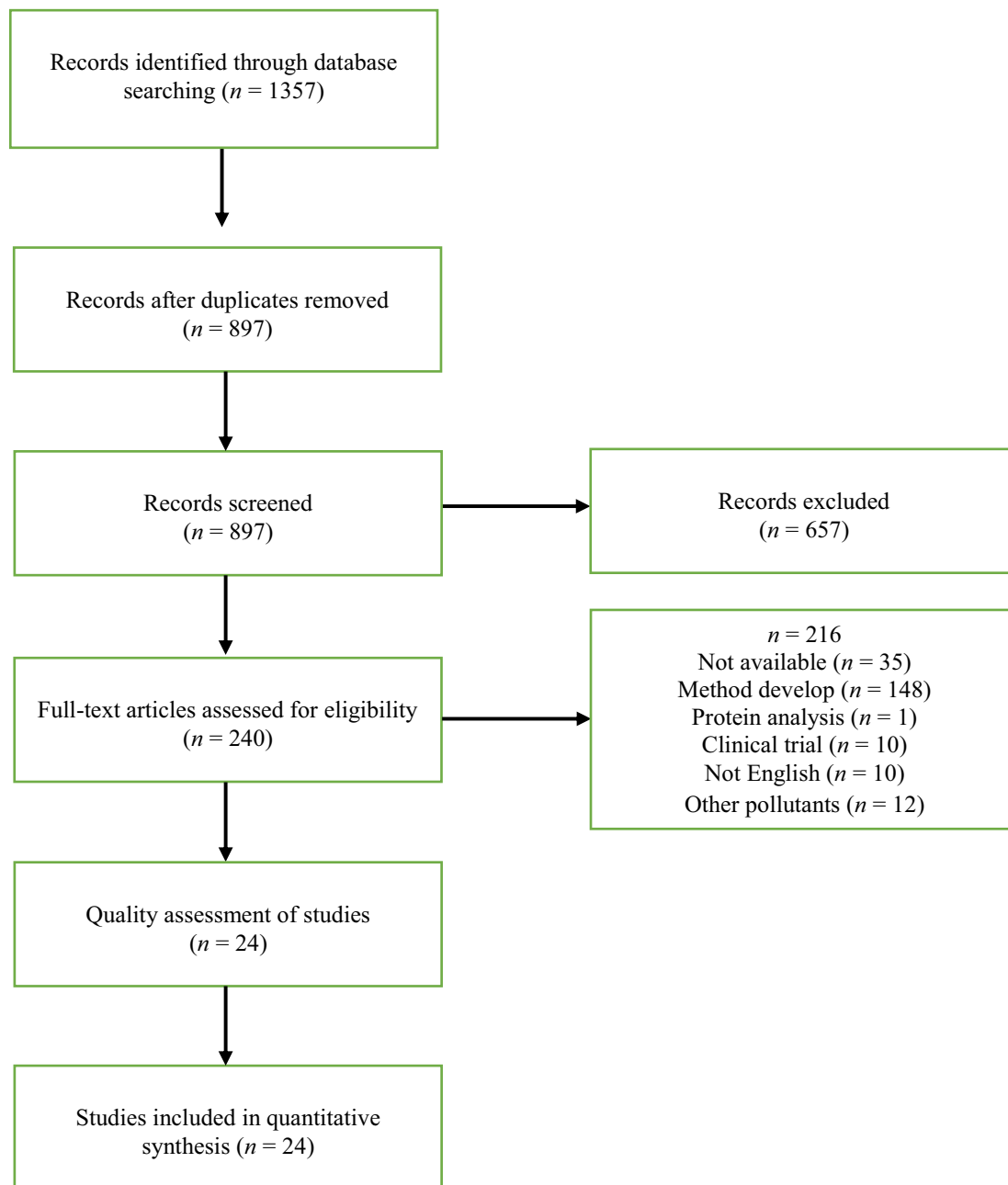


Figure 2. Search process diagram of this study.

Meta-analysis. Meta-analysis of the extracted data for melamine was performed using CMA software. The overall mean concentration of melamine in milk was calculated to be $11.3 \pm 0.53 \mu\text{g/L}$ using the random effect model for melamine in milk. The I-squared test was used to assess heterogeneity. Its value was calculated as 99.98, indicating high heterogeneity. Begg's test and funnel chart (Fig. 3) were performed for publication bias. The p value of the Begg test was 0.5.

Descriptive results of the screened articles. A selection of 24 articles was included in the systematic review. Tables 2 and 3 show the relevant data from the articles, including sample type, sample size, analytical method, melamine and cyanuric acid content, hazard quotient (HQ), countries, and references. Melamine ranged from ND to $75.8 \mu\text{g/mL}$ in different countries. Most of the studies were carried out in China, possibly because of the 2008 melamine in baby foods.

Discussion

Milk containing melamine and cyanuric acid poses potential health risks for all age groups, especially for children. Studies on this topic began in 2009, which indicated the possibility of milk contamination with melamine after the 2008 crisis in China (Table 2). Melamine enters milk in several ways. Due to the widespread use of melamine, contamination of water and soil is common. Therefore, there is a possibility of melamine entering the food chain. Melamine may migrate from packaging to food. In some cases, animal feed supplements may be contaminated with melamine. Melamine is also a by-product of cyromazine. This compound is used in veterinary medicine (Melough et al., 2020). Based on European Union (EU) regulations, the permissible limit for melamine is 2.5 mg/kg for dairy products (EFSA Panel on Contaminants in the Food Chain (CONTAM) & EFSA

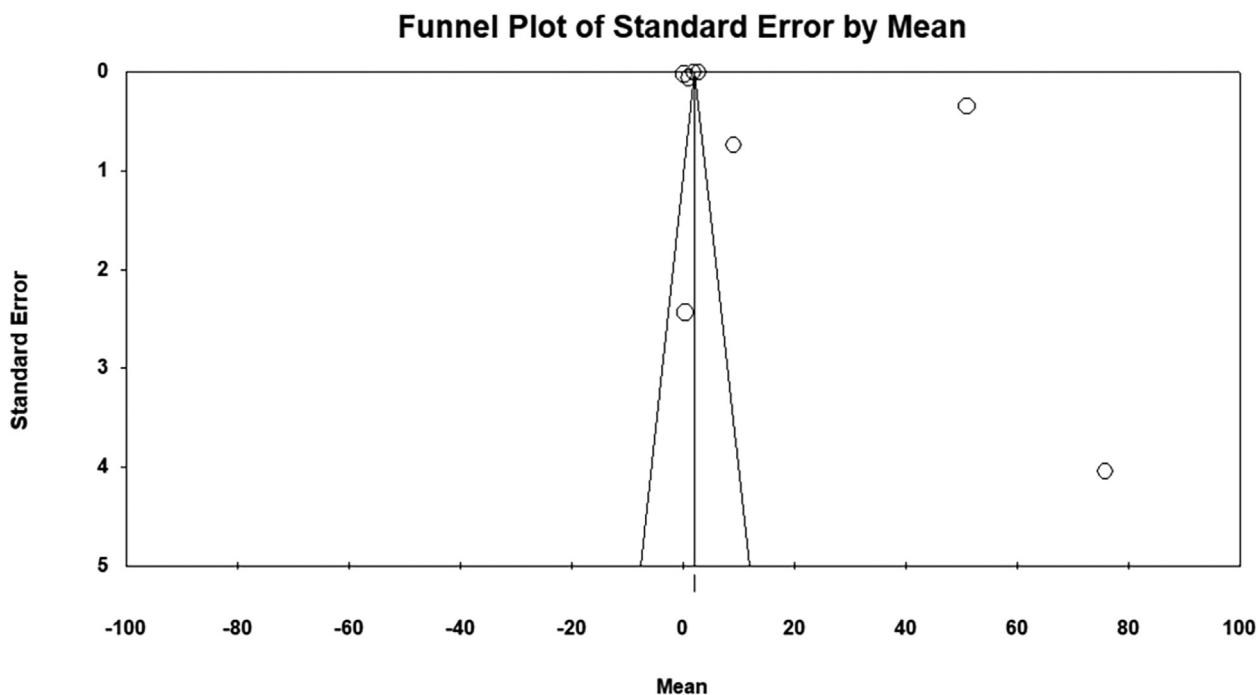


Figure 3. The funnel plot.

Table 3

Major data extracted from the published articles (cyanuric acid)

Sample type	Analytical method	Sample size	Quantity (mean \pm SD)	HQ	Country	Author/year
Fresh milk	GC-MS/MS	6	1.64 \pm 2.1 mg/kg	–	China	Miao et al., 2009
Milk	Differential Pulse Polarography	5	3.95 \pm 5.06 μ M	–	Turkey	Yilmaz and Yazar 2010
UHT milk	Micellar electrokinetic chromatography	5	0.08 \pm 0.12 μ g/mL	–	Thailand	Vachirapatama and Maitresorasun 2013
Milk and dairy	HPLC-MS/MS	34	Range: < 0.06–52.7) ng/g	5.03×10^{-5}	United States	Zhu and Kannan 2019

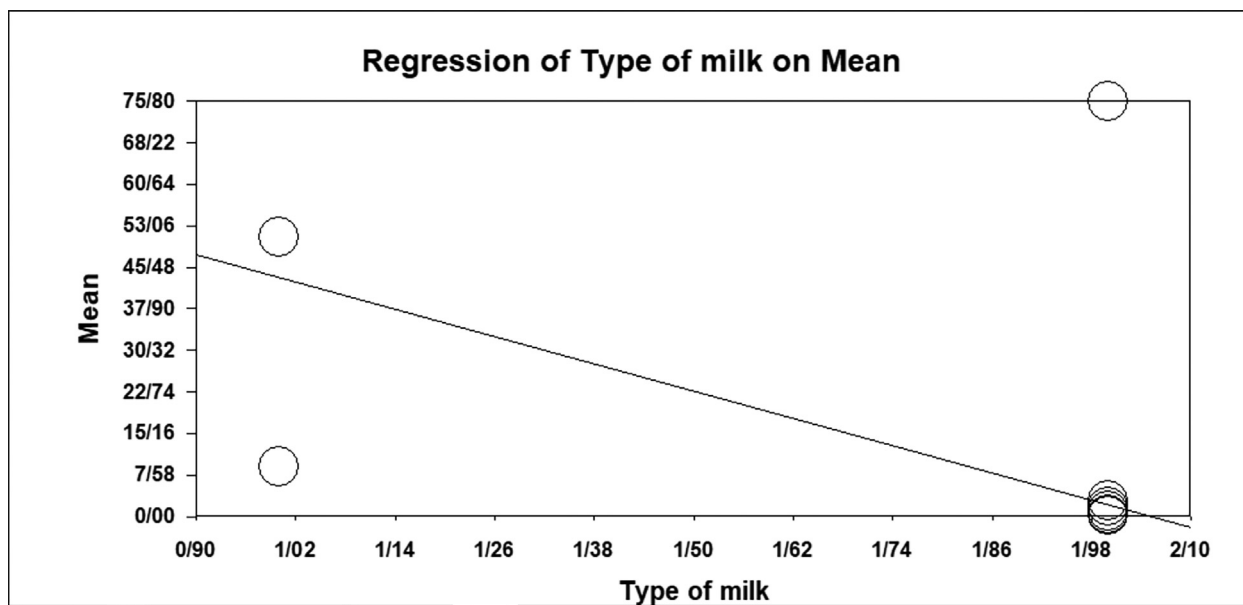


Figure 4. The meta-regression plot based on the type of milk.

Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2010). Based on the data collected in this study, the amount of melamine detected in all studies was less than the permissible limit.

For potential risk, the HQ calculated in the studies was taken into account. The HQ is the ratio of the estimated daily intake (EDI) to the tolerable daily intake (TDI). The TDI for melamine is estimated to be 63 μ g/kg bw/day. The mean daily intake of melamine and its

three derivatives, including cyanuric acid, ammeline, and ammelide, for the US population was calculated to be approximately 0.687 µg/kg bw/day for children through infant formula consumption and 0.032 µg/kg bw/day for adults through dairy consumption (Zhu & Kannan, 2019). In this study, the calculated HQ for adults and children was determined to be 5.0×10^{-4} and 0.011, respectively (Zhu & Kannan, 2018). Furthermore, in two recent studies conducted in Iran, the HQ for milk was also calculated to be less than one for adults (Abedini et al., 2023; Ghanati et al., 2023). However, the calculated HQ for melamine was greater than one for some brands tested for children in the study by Abedini et al. (2023).

The reported amounts are in different ranges (Table 2). A subgroup analysis based on the type of milk (raw or pasteurized) was performed to find the reasons for this heterogeneity. The *p* value was 0. Therefore, the type of milk contained effects. Meta-regression was also performed. Figure 4 shows the results of the meta-regression based on the type of milk. Based on the test, the *p* value was also 0, so the type of milk could be related to the effect size. After analyzing and reviewing the data extracted in this systematic review, it was shown that the amount of melamine in raw milk was higher than in processed milk. Contamination of raw milk is either directly caused by the milking animal itself or it may be contaminated indirectly during milking, collection, storage, and transport (Motarjemi et al., 2014). Raw milk may come into contact with melamine containers and equipment during milking, transport, and storage.

Studies have shown that different methods have been used to assess melamine and cyanuric acid in different types of milk (Tables 2 and 3). Currently, the available methods for measuring melamine include gas-chromatography-mass spectrometry (GC-MS), liquid chromatography-tandem mass spectrophotometry (LC-MS/MS), ultrasound-assisted extractive electrospray ionization mass spectrometry (EESI-MS), enzyme-linked immunosorbent assay (ELISA), surface-enhanced Raman spectroscopy (SER), and high-performance liquid chromatography (HPLC) (Liu et al., 2018). Based on the data, most of the methods used to assess melamine were based on liquid chromatography. For samples with low levels of melamine, HPLC-based methods have a favorable analytical capability. Furthermore, spectrophotometry may be used to evaluate melamine in food products in a realistic, accurate, and cost-effective manner (Öztürk & Demir, 2021). Therefore, HPLC-MS/MS method is usually the best method to determine the amount of melamine in food (Hieu-Tran, 2021).

Due to the small and polar structure of the molecule, methods such as liquid chromatography coupled to mass spectrometry (LC-MS) or tandem mass spectrometry (TMS or MS/MS) are the best analytical approaches for the assessment of melamine. However, these methods have disadvantages such as time consumption and the need for preparation, equipment, and specialists (Li et al., 2020). Technically, GC-MS is a practical and sensitive method for the evaluation of melamine in dairy products. The detection limit of this method is less than ng/g (Tzing & Ding 2010). A disadvantage of this method is the need for derivatization (Nascimento et al., 2017). Extraction techniques are an important factor in increasing the efficiency of analytical methods. In cases where the amount of analysis is small, the matrix effect should be minimized (Altunay et al., 2020). Based on the specific identification of melamine, several techniques for sample extraction, cleaning, and enrichment have been established (Ritota and Manzi 2018).

The use of solid-phase extraction (SPE) technique can increase selectivity and purification speed. Efficiency of HPLC with SPE has been verified well (Table 2). Another method of sample preparation is microextraction. This fast and accurate method is one of the green chemistry methods (Altunay et al., 2020). Another optimal method for the extraction of melamine from milk samples is the use of deep eutectic solvents (DES). The DESs have high thermal stability. Furthermore, if DES is combined with paramagnetic materials, it increases efficiency of the analyte extraction from the matrix (Elik et al., 2023). In addition, methods based on magnetic solid-phase extraction

(MSPE) have been verified with good efficiency (Abdolmohammad-Zadeh et al., 2020b; Liao et al., 2021a). In this method, the target analyte is effectively extracted from the matrix (Liao et al., 2021b).

The use of novel methods such as artificial intelligence and machine learning may be useful approaches. Key information should be collected on feed, housing, and medications used by dairy animals (Liu et al., 2022). In addition, important information on transportation and important processes that are carried out in the factory on milk-based products should be collected. Integrating these two sets of information can provide important approaches to more rapidly assess melamine and cyanuric acid and predict which types of milk may be more susceptible to adulteration and contamination (Kutyauripo et al., 2023). Accurate assessment of the composition of each type of milk with different proportions of proteins and fats is one of the factors contributing to the increased accuracy of artificial intelligence (AI)-based methods (Marialuisa et al., 2023). In addition, the use of artificial noses and modern photographic methods can significantly increase the accuracy and speed of melamine analysis in milk (Neethirajan 2023).

Conclusion

Due to the importance of melamine presence in dairy products, this systematic study was carried out to investigate the amount of melamine in dairy products, analytical methods, and sample preparation. The mean total melamine in milk was estimated. The estimated value was lower than that of the limits set by the competent authorities. The risk assessment or HQ was partially carried out in studies, all of which were less than one that revealed safety of the consumed products. The most frequently used analytical method was based on LC. The best preparation methods were based on microextraction and SPE columns. Melamine is usually detected at low levels in food, making its separation in food matrices difficult. Therefore, the development of fast, low-cost environmental friendly methods is strongly recommended.

CRedit authorship contribution statement

Amirhossein Abedini: Writing – original draft. **Zahra Hadian:** Investigation. **Mahdie Kamalabadi:** Writing – original draft. **Mahla Salimi:** Methodology. **Paliz Koohy-Kamaly:** Investigation. **Burhan Basaran:** Methodology. **Parisa Sadighara:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

This study was carried out with support from National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences (project no. 43005549).

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