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Theoretical study of food contamination mechanisms by melamine and hazard of melamine for health

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ABSTRACT

Purpose: The purpose of this investigation is to theoretical study of food contamination mechanisms by melamine and hazard of melamine for health. This purpose is justified as follows. A high percentage of nitrogen has caused the abuse of this chemical, because this amount of nitrogen brings about the properties of decomposition of protein molecules into this material, as a result of the increase in melamine in foods. The primary issues discussed are related to o introduce melamine and its sources to the potential of exposure to melamine and to address the risks of this hazardous material and enhance the safety of food products.

Design/methodology/approach: The investigation was carried out using analytical analysis. Melamine accumulates in the body of humans and has different effects. The presence of melamine at a very low level is also dangerous for children, and the food safety incidents that occurred in 2008 were due to the presence of melamine in children's infant formula in China, has raised concerns about food security around the world.

Findings: As a result analytical research we have this conclusion. Melamine is a chemical compound that is widely used in industry and especially in the production of packaging materials. Reducing the risk to human health can be achieved through the combined use of three factors: using proper control programs to prevent melamine from getting into food, preventing the migration of melamine in food and using no melamine detergents.

Research limitations/implications: The investigation was carried out on the basis of open sources of information on the chemical properties of melamine, its presence in household and other materials and its ability to interact with organic media.

Practical implications: The results of this study can be recommended to the Ministry of Health and the Ministry of Industry for the development of control programs to prevent melamine from getting into food.

Originality/value: The main problem of food pollution by melamine is that this substance is contained in most packaging materials. And a study of the mechanisms the migration of melamine in food and a generalization of the results on the methods for determining melamine in food will help solve the problem of unhealthy food.

Keywords: Melamine, Contamination, Food products, Toxicity, Exposure

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CLEANER PRODUCTION AND BIOTECHNOLOGY

1. Introduction

Melamine (1, 3, 5-triazine-2, 4, 6-triamine) is widely used in products. Yellow, ink and ink pigments are used and can be used with formaldehyde to produce durable resins, glues, cleansers and polymerization flame retardants. Cyanuric acid, a modest product of melamine production and degradation, is used to extract chlorine in swimming pools. Protein in foods is estimated based on nitrogen content. Because melamine is 67 % nitrogen with a molecular weight, it is added to food (both humans and animals) to increase the estimated protein content [1]. Figure 1 shows the structure of melamine and cyanuric acid.

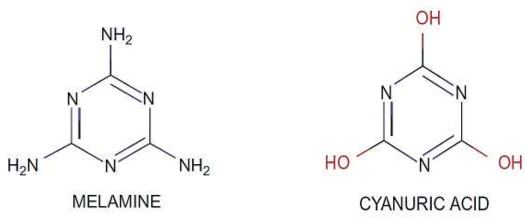

Fig. 1. Structural formulas of melamine and cyanuric acid [1]

Melamine is a typical organic compound that is often used in combination with formaldehyde in the production of plastics, including whiteboard, kitchenware and commercial filters [2]. Melamine is also used as fertilizer, because it contains 667 grams of nitrogen in kilograms [3].

2. Materials and methods of investigations

The investigation was carried out using analytical analysis. Melamine accumulates in the body of humans and has different effects. The presence of melamine at a very low level is also dangerous for children, and the food safety incidents that occurred in 2008 were due to the presence of melamine in children's infant formula in China, has raised concerns about food security around the world.

2.1. Melamine as a component of food products

Human beings can enjoy a wide variety of melamine substances. For example, a mess contains typically some melamine-related products. Melamine may migrate in a small amount of these foods to foods and beverages used in this cutlery [4]. In the work [5] have shown that factors affecting the degree of melamine migration, such as temperature, acidity and frequent use of melamine plastics, are strongly affected [5]. Melamine contamination in food may also be caused by cyromazine metabolites, which is an insecticide [6], which is widely used in herbal products to control the moulting process. In addition, due to the high concentration of nitrogen and low prices, melamine has been added to foods, especially milk products, since 2007. As a result, thousands of humans and animals consume contaminated foods that lead to various diseases [4,7,8].

Melamine is not an organic product and has not been approved for directly adding to food. However, melamine is used as part of some foods [2]. Melamine industrial chemicals were used in 2007 and 2008 to enhance the apparent protein content of livestock feed and fresh water, respectively [9]. Melamine contamination has been reported in food products of animal origin, such as milk and milk powder [10,11], dairy products, meat and meat products, eggs, fish and fishery products, etc., main food such as wheat gluten, rice protein concentrate and beverages [11]. Soybean products are widely used in animal feed industries as protein-rich foods and are known to be melamine [12]. Melamine has been used as a filler for protein-rich diet by unusual manufacturers [13].

Melamine contamination sources are divided into "baseline" levels that refer to food levels that are not caused by deception or abuse and cheating, and to levels of food intake resulting from the deliberate and illegal addition of melamine to food or feed. Such a diagnosis is useful for practical purposes, but it is obvious that clear distinction is not always possible. For example, a low level of melamine in foods can be counterfeit from the transfer of animal feed. Melamine baseline concentrations in the environment and food chain are due to the widespread use of melamine-containing substances. Baseline levels are generally expected to be less than 1 mg/kg and this is not considered a health concern. Melamine concentrations in excess of the baseline levels in food and animal feeds lead to abuse or cheating. High levels of melamine detected in many products related to the 2008 incident are a clear indication of fraud. Data show that the presence of melamine in animal tissue (including fish), milk and eggs occurs in transmission from the feed to tissue, milk and eggs.

Figure 2 illustrates four major ways of deliberately polluting melamine: a) liquid milk at milk collection stations used later in the production of dried infant formula, liquid milk and powdered milk production, and the production of milk-containing foods; b) animal feed that lead to contamination of milk, eggs and meat; c) non-dairy cream and protein powder that result in the contamination of immediate non-dairy beverages; and d) ammonium bicarbonate used to produce various types of processed food [14].

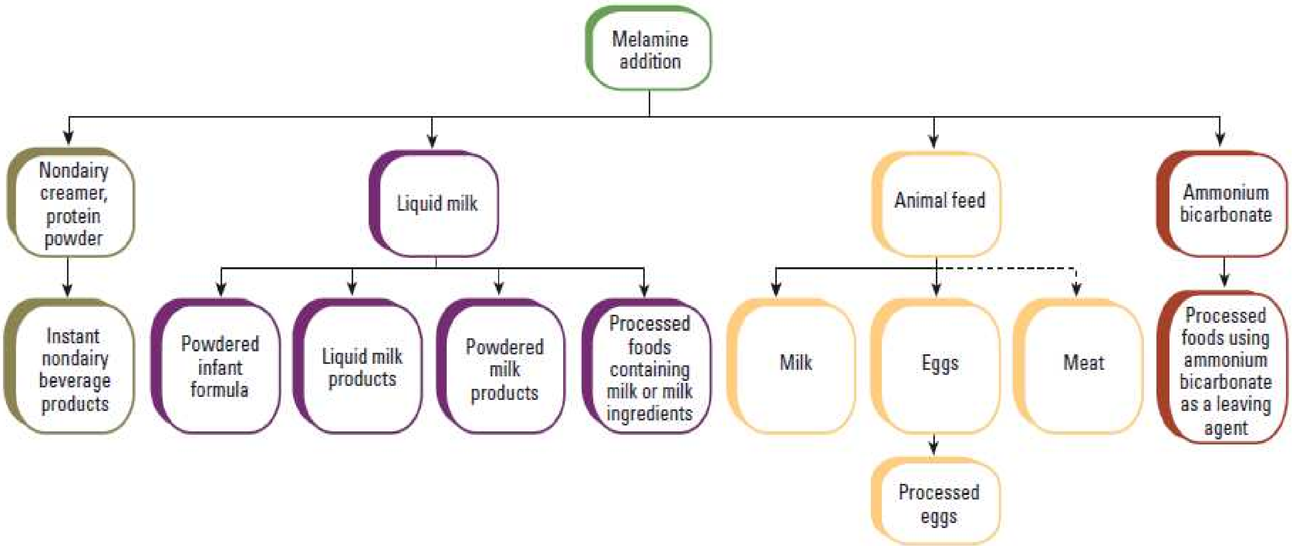

Fig. 2. Flow chart of the melamine-contamination chain from adulteration

Dairy products are essential components of a healthy diet for all age groups due to their high nutritional value [6]. The amount of protein in milk is important for the production of many products, with a significant impact on its sensory and rheological properties, and is therefore used in many industries as the owner of quality. Since nitrogen-rich compounds can imitate a high protein concentration, standard methods can not differentiate nitrogen from protein and non-protein, resulting in widespread use of these compounds for cheating on milk-based products [6]. Melamine has recently been found in livestock and animal foods, where it has probably been added to obtain a misconception of high protein content [15]. The reason is the gentle addition to the milk to make it in the protein in order to achieve a reasonable price for milk [15,16]. Pure melamine was added to milk products, including infant formula, and caused warts in infants and children. Melamine and cyanuric acid in the kidneys make up crystals, producing kidney failure in cats and dogs. Melamine is also associated with uric acid, which caused kidney stones to be found in children in 2008. Biomarker studies indicate that physiological disorders caused by melamine and cyanuric acid affect the metabolism of amino acids and energy and cause apoptosis in the tubular renal epithelium in vitro [1].

Milk protein contains several biologically active peptides, with antimicrobial activity, the source of the essential amino acid, calcium, zinc, copper and phosphate. In addition, milk proteins facilitate the absorption of many nutrients [6]. Milk is one of the common goals for cheating.

Usually, the counterfeit milk is produced by adding water, milk cheese, caustic sodium, salt, sucrose, urea, and many other contaminants [6]. Melamine is not approved by the food industry and is commonly used for a variety of applications such as lamination, coating and plastics [6]. However, melamine has recently been added to produce protein (such as dairy products and animal feed) due to cheating to increase apparent protein measurements [17]. Adding 1 gram of melamine to 1 liter of milk improperly increases protein content by 0.4% [18]. In addition, milk is used as an ingredient in many products that leads to the detection of contaminants in food from a wide range of industries, including the production of breast milk, milk products, candy, protein powder, chocolate yogurt, Biscuits, snacks and cookies [6,19]. The remaining melamine in milk products by illegal cheating has been a source of serious concern because of its adverse effects on infant health [20]. Melamine intake at higher levels of immunity can lead to kidney failure and infant death [6]. Infants are more affected by infected dairy products because of their dependence on milk as a regular supply [6]. Some studies on melamine in various foods are shown in Table 1.

Table 1.
Some studies on melamine in food products

Products	Sample	Country	Method	Results	Refrence
Dairy	poultry meat hen eggs ultrafiltration cheese dairy cream	Iran	HPLC	* The average amount of melamine in samples of poultry meat, hen eggs, ultrafiltration cheese, the dairy cream was reported, 1.31, 1.41, 1.29 and 1.30 (mg/kg), respectively. * Results were within International Standards (FDA), confirming low health risks for these four products.	[11]
	milk powder	Uruguay	HPLC	*The mean melamine contamination was 0.028 mg/kg. * levels of melamine do not constitute a health risk for consumers.	[21]
	milk yogurt infant formula coffee mate cheese	Iran	HPLC	* Amounts of melamine (µg/g) range: 0.20-0.26 for milk, 0.57-0.99 for yogurt, 0.35-3.40 for infant formula, 0.09-1.23 for the coffee mate and 0.30-2.50 for cheese *the mean values of melamine in products were evaluated as 0.24, 0.76, 1.38, 0.56 and 1.16, respectively. * Comparison of test results with the standards set by the European Union and the US Food and Drug Administration for dairy products contaminated with melamine showed that levels determined by tests had higher health risks than the regulations allowed. * The amount of melamine in dairy products exhibited concentrations: milk<yogurt <coffee mate <cheese <infant formula.	[22]
	powder milk liquid milk	Iran	LC-MS/MS	* Amounts of melamine range: 1.50-30.32 µg/g for powder milk and 0.11-1.48 µg/mL for liquid milk. * all samples were contaminated with melamine * No cyanuric acid was detected in samples, which decreases the risk of melamine toxicity for consumers	[23]
	dairy products	China	HILIC	*HILIC method with amino column was reported for determination of melamine. * HILIC method was satisfactorily applied to determination of melamine in liquid and solid dairy products.	[17]
	powdered milk	Kingdom Saudi Arabia	HPLC	* HPLC method is simple, sensitive and robust and allows for analysis of large number of samples, without degradation in column performance. * this proposed method has the potential to be a useful tool for the routine melamine monitoring in real-time.	[15]

Products	Sample	Country	Method	Results	Refrence
	dairy products (UHT milk, pasteurized milk, fruit yogurt, milk powder, powdred infant formula, soft cheese	Turkey	HPLC	*Melamine was not found in infant formulas and pasteurized UHT milk, whereas 2% of cheese, 8% of milk powder, and 44% of yogurt samples contained melamine at the 121, 694 ± 146, and 294 ± 98 μg/kg levels, respectively. *These findings were below the limits set by the Codex Alimentarius Commission and European Union legislation.	[24]
Infant formula	infant formula	Iran	ELISA	*The infant formula is not considered a health hazard from the melamine contamination	[25]
	infant formula	USA	HPLC–UV	The method provides recoveries of 97.2-101.2% in the concentration range of 5-40 gmL-^{1}, intra- and inter-day variation in <1.0% R.S.D. The limit of detection (LOD) and limit of quantification (LOQ) values are 0.1 gmL-1 and 0.2 gmL-1, respectively	[26]
	Infant formula powder	India	NIR/FTIR	NIR and FTIR methods enable rapid detection of 1 ppm melamine in infant formula powder.	[27]
Meat	Catfish, trout, tilapia,salmon shrimp	USA	LC–MS/MS	MEL residues were found in edible tissues from all of the fish with concentrations ranging from 0.011 to 210 mg/kg (ppm)	[28]
Cereals	Rice protein concentrate feeds	Spain	HPLC–DAD	the proposed method was successfully applied to the analysis of other rice protein concentrates and several animal feed samples.	[29]
	Cereal flours	USA	HPLC–UV	Matrix-matching compensates for analyte losses during sample preparation, and for matrix effects. The method was successfully applied to wheat, corn, and rice flours, and is expected to be applicable (with some modifications) to soy flour as well. The method allows for the detection of melamine, ammeline, and ammelide at approximately 5 mgg_1, and cyanuric acid at approximately 90 mgg_1 in wheat flour.	[30]

2.2. Toxicology of melamine

By 2007, it was believed that melamine was relatively toxic to animal. Oral melamine LD50 in male rats is 3200 mg/kg, in female rats of 3800 mg/kg and in male mice 3300 mg/kg and in female mice is 7000 mg/kg. Long-term prescription of melamine to laboratory rodents at concentrations between 0.225% up to 0.9% of the diet causes kidney stones [1]. The combination of melamine and cyanuric acid is considerably more toxic than when each animal is given alone [1]. Melamine has a low acute oral toxicity, but chronic consumption of high concentrations can cause kidney damage, even death, especially in infants and children [13]. Melamine and its related compounds, such as ammeline and ammelide, can accumulate in the human body complexes when fed through hydrogen bonds [6].

Long-term exposure to melamine reduces fertility and fetus toxicity in animal. In chronic exposure to melamine in dogs, they were fed by feeding them with 3 % melamine in terms of weight in food for 1 year, changes in urine specific weight, melamine crystalluria, and proteinuria with microscopic hematuria. The most commonly reported chronic renal toxicity is the formation of stones. The main effect of melamine toxicity on rats and mice are urinary bladder hyperplasia, formation of calculi and inflammatory reactions. Melamine at 800 mg/kg causes significant renal toxicity, as kidney weight gain and kidney pathology symptoms have been proven [26].

2.3. The mechanism of the effect of melanin on human health

Cats and dogs had infected food and had evidence of kidney failure. Although previous animal studies have shown that both melamine and cyanuric acid, when given separately, are relatively non-toxic, if present, cause the formation of crystals in the kidney tubes [1]. Melamine and Cyanuric acid crystallize and form a molecular network structure at pH = 5.8. The crystals are formed in diastolic kidney tubes containing 70 % cyanuric acid and 30 % melamine based on infrared spectra. Intravenous blockage leading to an increase in intravenous pressure is likely to contribute to pathology [1]. After consuming an infected formula for 3 to 6 months, children with kidney stones, which can lead to obstruction and secondary kidney changes [1].

Compared to adults, human babies repel 5 to 8 times more uric acid, but they are more likely to be hypersensitive to melamine poisoning. Urine pH 5.5 is associated with the formation of urate crystals and low pH and can help to form melamine/urate stones [1]. There are no studies on toxicity in humans due to edible consumption of melamine. LD_{50}, the mortality rate of a specific compound that causes the death of 50% of tested animals, is 3.1 g/kg of body weight for melamine in rats [6]. It is recognized that the main aspect of the toxic effects associated with melamine-induced renal function is due to its rapid removal in the kidney [31]. Unfortunately, melamine can lead to the formation of insoluble cyanyrate melons in the kidneys, which causes kidney failure, kidney stones, and urinary problems [11,32].

The combination of melamine and cyanuric acid forms insoluble crystals in the kidneys [33]. All children with the disease were exposed to milk for about 3 to 6 months before the onset of the disease [6]. With the best evidence available in human studies and animal studies, we highlight several points about melamine poisoning: high doses of melamine cause urinary stones, crystalluria, and acute renal failure in humans and animals. The formation of stone is likely to increase with smaller body size, higher doses of melamine, and lower levels of fluid intake; studies in animals show that men are more affected than women; the toxicity of melamine, despite other impurities associated with melamine synthesis, in particular cyanuric acid, it is further enhanced. Tubal damage may occur with blockage of the crystals and chronic inflammation of the kidney; if melamine is present at high doses or in combination with cyanuric acid, toxicity may not be limited to the formation of stones in animal studies [18]. Melamine with cyanuric acid is believed to be the cause of death from kidney stones due to the formation of an insoluble melamine-cyanurate compound. The consequences for the youngest, the babies and the small children are fatal [15]. Figure 3 induces kidney tubular/glomerular damage in mammals that leads to renal failure after exposure to melamine through the formation of stones by the formation of urate or crystal by the cyanurate and the experimental method for its diagnosis (Serum/urine biomarkers (BUN, KIM-1), renal gene expression, pathology) [34].

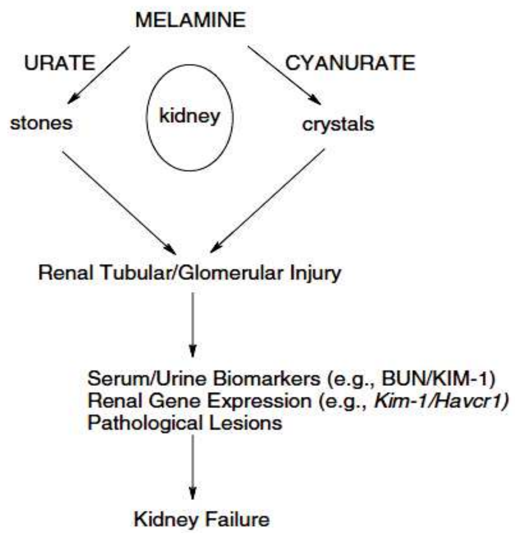

Fig. 3. Induction of tubal/glomerular damage in mammals [34]

2.4. Analysis of methods for the detection and measurement of melamine in food products

There are many techniques to measure the total protein in the diet, including Kjeldahl, Dumas, modified Lassaigne and infrared methods. However, some methods are not able to produce protein accuracy in the tested sample [6]. The protein content of the milk is non-specific as a cumulative parameter by detecting nitrogen compounds by Kjehldahl, such that the addition of melamine is not detected. Therefore, the determination of melamine and other low-nitrogenous compounds (ammeline, ammelide and cyanuric acid) are important for the importance of food safety [15]. To diagnose melamine using various analytical techniques due to demand, several methods are developed such as: chromatography [35-39], enzyme-linked immunosorbent assay [40], solid phase extraction [8], colorimetry [41], high performance liquid chromatography/mass spectroscopy [42], surface enhanced Raman spectroscopy [43], ultraviolet spectroscopy (UV) [44], and ion pair chromatography [45].

Methods of identification and determination of melamine were widely studied. Initially, as a derivative of triazine herbicide, melamine was detected by GC and HPLC. HPLC methods for determining the melamine extracted from the cup made of melamine resin and in beverages, migrate from the container. Currently, melamine detection methods include HPLC or HPLCeMS and GCeMS. However, the time-consuming separation method is usually necessary to isolate melamine GC. Hence, HPLC and related techniques (sometimes associated with MS detection) are commonly used to determine melamine in different types of specimens. Most of these HPLC methods include reverse-phase liquid chromatography (RP-HPLC) and sometimes ion-exchange chromatography (HPIC). Recent approaches to hydrophilic interaction liquid chromatography (HILIC) have attracted much attention [17].

HPLC is very important to determine the amount of melamine in milk products, some foods, animal feed to monitor food contamination, and studies on melamine have been considered in recent years [25].

Common methods to determine melamine in food products including: Capillary electrophoresis (CE) [46,47], High-performance liquid chromatography (HPLC) [46,47], Liquid chromatography-mass spectrometry (LC-MS), Liquid chromatography-triple-quadrupole tandem mass spectrometry (LC-MS2), Gas chromatography-mass spectrometry (GC-MS) [20,46,48], Matrix-assisted laser desorption/ionization-mass spectrometry (MALDI-MS), Nuclear magnetic resonance spectroscopy (NMR spectroscopy) and vibrational spectroscopy techniques (e.g., surface-enhanced Raman spectrometry (SERS), and near-infrared spectrum((NIR) [46, 49] and midinfrared spectroscopy (MIR) which are the most important methods have been published.

Infrared spectroscopy (IR) can be used correctly to determine the level of protein in milk and other foods. IR is based on the emission of electromagnetic energy, which is subjected to minor variations with a matrix that absorbs some of this energy, which shows a certain chemical composition [6]. The IR results derived from the data components of the various techniques are derived, including: near-infrared spectroscopy (14,000 to 4000 cm^{-1}) (NIR), mid-infrared spectroscopy (4000 to 400 cm^{-1}) (MIR) and far infrared spectroscopy (400 to 50 cm^{-1}). Important that MIR and NIR are used to detect food contaminants. IR spectroscopy has become an attractive alternative to traditional analytical methods, because it requires the preparation of low samples and less use of hazardous solvents. Additionally, a high degree of sensitivity and specificity can act as a fingerprint technique [6]. Given the specificity of this technique, many researchers have reported using IR spectroscopy and chemical analysis to detect and measure melamine in milk [6]. Efforts have been made to analyze for melamine quickly, including using: Raman spectrometry, immunoassay and aptamer-based bioassay [20].

Raman spectroscopy also suitable for similar studies. Raman signals are generated by the random dissonance of light from a sample and deformation in the frequency or wavelength of the scattered light. The techniques of Raman include: dispersive Raman spectroscopy, Fourier transform (FT) Raman spectroscopy, surface-enhanced Raman spectroscopy (SERS), and spatially offset Raman spectroscopy (SORS). The spectra provided by these methods can provide a fingerprint of a particular substance, which helps analyze this compound in several types of specimens and provides a basis for structural analysis and qualitative analysis [6]. In addition, Raman spectroscopy offers more important advantages than IR spectroscopy. In particular, because Raman spectroscopy does not interfere with the spectrum, it is a promising analytical tool in food production and quality control [6]. A number of researchers have identified Melamine using Raman spectroscopy [6,10,20,50] reported that SERS is a precise, simple, fast, cost effective, and sensitive method for detecting melamine in liquid milk. SERS can be a quick and sensitive tool for detecting melamine in complex compounds [6]. Raman spectroscopy is capable of detecting and measuring melamine in foods, including dairy products [6]. A portable Raman spectrometer is available for melamine, but its LOD (100 μg/L) is much higher than laboratory methods [20]. The use of immunoassay [e.g., an enzyme-linked immune-sorbent assay (ELISA)] has been reported to determine melamine [2,20,46,47,51,52]. ELISA is a sensitive method for the determination of melamine in various matrices. The disadvantages of this approach are that the analysis is only semi-quantitative and sometimes leads to false positive results.

ELISA requires a specific antibody against analite, which requires considerable work. However, in practice, this method is used for unique advantages (for example, high sensitivity, simple sample preparation, high speed and high power) [46]. Compared to these common methods, electrochemical methods have many advantages such as simple pre-treatment, low cost, portability, rapid analysis, and very sensitive flow measurement [53].

Aptamers are DNA sequences or RNAs that can be selectively linked to the target molecule. Compared to an antibody in an immunoassay, aptamers have shown low-cost benefits, chemical synthesis and high stability [20]. Different aptamer biosensors are designed for various applications [54,55].

Sensor technology has been widely used recently due to sensitivity, speed, simplicity and cost. Sensors are also for analysis of melamine and its analogues, including Molecularly Imprinted Polymer-based sensors (MIP-based) and Nanoparticle-based sensors (NP-based sensors) are designed. MIP-based measurement technology is a useful platform for detecting melamine and its analogues, and can be used for rapid monitoring on samples [46,47].

Visual Detection based on the following. Nanoparticles (NPs) can combine with hydrogen bonding with melamine molecules whose signals are obtained by unprotected eyes or by instruments such as spectrometry, voltammetry or colorimetry [20]. Unmodified gold nanoparticles produce a colored signal output [56]. A simple and rapid method for detecting melamine is based on the discoloration created by label-free gold nanoparticles (Au NPs) [53].

3. Results of investigation and discussion of them

3.1. The compliance of food products with the allowed melamine content of international food regulations

Melamine intake of more than 1 mg/kg/day in children and 3 mg/kg/day in adults is toxic because it produces complex compounds in the kidneys followed by inflammation of the urinary system or urolithiasis [6]. The US Food and Drug Administration concluded that the level of melamine and its analogues of less than 2.5 ppm in foods and melamine levels, or one of its analogues, is less than 1.0 ppm in the infant formula, does not cause concern about general health [19]. The maximum permitted levels for melamine in food products are set by the Food and Drug Administration (FDA), the European Community and other countries. Standard limits of 1 ppm for melamine in breast milk and 2.5 ppm in other milk products have been introduced by many countries [53]. Maximum residue level (MRL) for melamine, set by many countries and WHO, is 1 mg for 1 kg for milk formula and 2.5 mg for 1 kg for other milk and food based on milk or other foods [57]. The tolerable daily intake (TDI) of melanin in humans may be 0.63 mg/kg body weight per day [11]. The tolerable daily intake (TDI) for melamine, as determined by the WHO, is 0.2 mg/kg body w/day day, while the maximum residue limit (MRL) varies across regions of the world; For example, 0.5 mg/kg and 1.0 mg/kg for infant formula is in Japan and the United States, respectively [32]. Improving quality assurance processes and monitoring with melamine detection methods regarding contamination sources, the level of melamine in food products should also be carefully monitored [11]. Improving quality assurance processes and monitoring with reliable, cost-effective, and efficient methods are critical to preventing potential risks to consumer health [6]. Control of all types of foods is important to prevent melamine contamination [2].

3.2. Using proper control programs to prevent melamine entering the food

Given the adverse effects of melamine on human health, especially in newborns, it appears that serious control programs are in place to prevent the introduction of melamine in milk and dairy products. It is very effective in controlling the level of melamine in Good Manufacturing Practice (GMP) milk and good quality control programs [58].

3.3. Preventing the migration of melamine to food

The use of melamine-formaldehyde resins in the production of molded plastics and as coatings in contact with food is approved by the U.S. Food and Drug Administration (FDA) as long as the yield of chloroform-soluble does not exceed 0.5 mg/in² of food contact surface [59].

3.4. The lack of melamine containing detergents

The use of some disinfectants for food equipment such as trichlorolamine and purification of drinking water like sodium dichloroisocyanurate, is common in some factories. Therefore, attention to prevention and non-exposure to these compounds are also necessary [60].

4. Conclusions

As a result analytical research we have:

1. Melamine is a chemical compound that is widely used in industry and especially in the production of packaging materials.
2. Reducing the risk to human health can be achieved through the combined use of three factors: using proper control programs to prevent melamine from getting into food, preventing the migration of melamine in food and using no melamine detergents.

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Additional information

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