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Invited Review

Analytical chemistry, toxicology, epidemiology and health impact assessment of melamine in infant formula: Recent progress and developments

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ABSTRACT

This review summarizes the most recent scientific literature and regulations regarding analytical chemistry, toxicology, epidemiology, exposure, and risk assessment of melamine in infant formula. For analyses, enzyme-linked immunosorbent assay, high-performance liquid chromatography, capillary electrophoresis, gas chromatography coupled with mass spectrometry and liquid chromatography coupled with tandem mass spectrometry have commonly been used. Organization of proficiency test programs provided good evidence to facilitate granting laboratories accreditation and to ascertain the measurement reliability of melamine methods. Metabolic studies demonstrated that melamine is predominantly restricted to blood or extracellular fluid and is not extensively distributed to organs and tissues. Studies of human renal histopathology and clinical diagnoses indicated that melamine-related obstructive nephropathy derives from melamine precipitation in the lower urinary tract, with stones that are thought to be melamine–uric acid complexes. Epidemiologic studies showed that the occurrence of melamine-related urolithiasis is related to both the concentration of melamine in ingested milk products and the duration of ingestion. Long-term follow-up cohort studies should be continued to further investigate the epidemic and chronic hazard of melamine-induced nephrotoxicity. The World Health Organization set a tolerable daily intake of 0.2 mg/kg bw/day to be applied to "the whole population including infants". Other authorities and research institutes have set/proposed lower values.

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1. Introduction

Melamine (2,4,6-triamino-1,3,5-triazine), an organic compound that is commercially synthesized from urea, is produced in large amounts mainly for use in the synthesis of melamine–formaldehyde resins for the manufacture of laminates, plastics, coatings, commercial filters, glues or adhesives, dishware and kitchenware. The analogs (cyanuric acid, ammeline and ammelide) of melamine can also be produced as impurities during the manufacturing process for melamine (Fig. 1). In addition, the bacterial metabolism of melamine if the melamine is not completely metabolized to ammonia and carbon dioxide may contribute to the production of these analogs (WHO, 2008a).

Surprisingly, such a commercial chemical for industrial use had illegally been blended with dairy products to give the illusion of an increase the protein content, causing the melamine scandal in infant formula in 2008 (Wu et al., 2009; Chen, 2009a; Xin and Stone, 2008). In the beginning, 16 infants from Gansu Province were diagnosed with kidney stones. An increasing number of nephrolith symptoms in infants caused concern among pediatricians in Gansu, Hebei, Beijing and other cities/provinces in China (Chen, 2009b; Wu et al., 2009). Then, the survey results indicated that all of the kidney stone cases were found to have consumed powdered formula manufactured by a Chinese dairy products company (Sanlu Group, Shijiazhuang, China) (MOH, 2009). Further investigation conducted by China State Administration of Quality Supervision, Inspection and Quarantine found that 22 of 109 brands of commercially available formula powder had detectable levels of melamine. The melamine levels in samples from the Sanlu Group reached an astounding 2563 mg/kg, while levels ranged from 0.09 mg/kg to 619 mg/kg in formula powder samples from other companies (GAQSIQ, 2008).

Such an unusual epidemic attracted quick responses from Chinese national and regional governments and was followed by a comprehensive survey to identify the source and cause. Based on the report released by the Ministry of Health (MOH) in China, 294,000 infants and young children had been diagnosed to have urinary tract stones by the end of November 2008. Although most of the patients had no symptoms and signs, acute renal failure occurred in a small proportion of patients. More than 50,000 infants were hospitalized, and six deaths were confirmed (MOH, 2009). Following the melamine crisis, many countries have introduced control criteria to set up maximum limits for melamine in infant formula and other foods. The Chinese government promulgated an interim control limit for melamine at 1 mg/kg for infant formula and at 2.5 mg/kg for other milk products in October 2008, and this interim limit became official for all foodstuffs in April 2011.

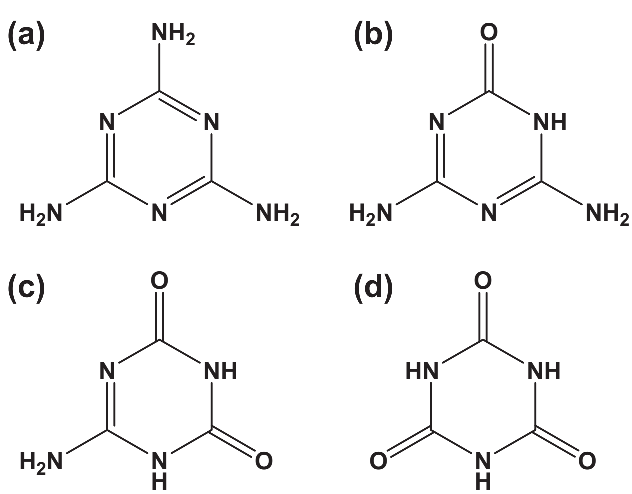

Fig. 1. Chemical structures of (A) melamine, (B) ammeline, (C) ammelide, and (D) cyanuric acid.

The health concern for Chinese infants who suffered from the melamine hazard was then advanced in an international level. In September 2008, the World Health Organization (WHO) reported on the toxicity, preliminary risk assessment and guidance on levels of melamine and its analog cyanuric acid in food. In collaboration with the Food and Agriculture Organization (FAO) supported by Health Canada, WHO conducted an expert meeting to review toxicological aspects of melamine and cyanuric acid in December 2008 (WHO, 2008b). The Codex Alimentarius Committee (CAC) has promulgated the maximum limits of 1 mg/kg in powdered infant formula and 2.5 mg/kg in food (other than infant formula) and feed in 2010, and 0.15 mg/kg for melamine in liquid infant formula finally adopted in 2012. Previously in 2007, there was a large incident of renal failure in cats and dogs in the United States, which was associated with the ingestion of pet food contaminated with melamine and cyanuric acid. Similarly, current melamine crisis of infant formula evoked a health alarm and a series of related research. This review summarizes analysis, toxicology, risk assessment and health guidance aspects of melamine and its analogs and reports recent progress made to date.

2. Analytical chemistry of melamine and its analogs

2.1. National monitoring and surveillance

The adulteration of milk and milk products with melamine contaminant in China has promoted analytical method validations and sample investigations worldwide. Various government administrations, university institutes and inspection agencies focused on the determination of melamine and related analogs in milk, milk-ingredients and compound products containing milk-derived ingredients using different methods (Pei et al., 2011). Most cases concerned Chinese dairy products and other mixed foods containing dairy ingredients manufactured or sourced from China. The measurement of baseline levels of melamine in these types of products for imported and domestically produced items was also conducted. However, in many cases analyses for cyanuric acid, ammeline and ammelide were not conducted. Generally, surveillance and monitoring data that were submitted to the WHO by various countries for the 2008 expert consultation, as well as information available on the web pages of international scientific bodies, indicated that the majority of samples analyzed were