Expert meeting to review toxicological aspects of melamine and cyanuric acid

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Executive Summary

According to a report from the Chinese Ministry of Health, 294 000 infants had been affected by melamine-contaminated infant formula by the end of November 2008. More than 50 000 infants have been hospitalized, and six deaths have been confirmed. Because of the large potential health impact, the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) convened an Expert Meeting.

Melamine produces crystals in urine when its concentration exceeds a threshold. Exposure below this threshold will generally not result in adverse health effects. Many of the affected infants in the Chinese incident had stones, or calculi, in the kidney, ureter or bladder. These calculi were composed of uric acid (a normal waste product in human urine) and melamine.

Melamine is an industrially synthesized chemical used for a wide variety of applications, such as laminates, coatings and plastics. Commercially produced melamine may contain structural analogues, such as cyanuric acid, ammelide and ammeline.

Humans are exposed to melamine and its analogues from a number of different sources, including food and environmental sources. Sources range from breakdown of the pesticide cyromazine, which is approved for use in many countries, to migration from approved food packaging material to the adulteration of specific foods. A specific source of exposure for which very few data exist is carry-over from the (mostly non-approved) presence of melamine in animal feed or feed ingredients. Data have shown carry-over from feed to products of animal origin (e.g. milk, eggs, meat), including fish.

Methods are available for the screening and quantification of melamine in food and feed. Selective methods are able to detect very low concentrations of melamine and its analogues in such products.

For this report, the sources of melamine have been divided into “baseline” levels, which refer to levels in food that do not result from adulteration or misuse, and “adulteration” levels, which refer to levels in food that result from the intentional addition of melamine to food or the unapproved use or misuse of melamine or substances that can degrade to form melamine.

Adulteration occurs, in part, because commonly used methods for protein analysis cannot distinguish between nitrogen from protein and non-protein sources. This results in incorrectly high protein measurements for products containing non-protein nitrogen sources like melamine and provides an economic incentive for their (illegal) addition. New, simple, specific, rapid and cost-effective methods for protein quantification should be developed to discourage adulteration.

The baseline exposure has been estimated from (limited) data on concentration levels in different food groups and food consumption data based on the WHO regional diets and other national data. However, industry data on baseline occurrence have generally not been published and have not been made available to FAO and WHO, although such data exist for a number of industrial food products. The very limited availability of data seriously hampered the ability of the Expert Meeting to estimate exposure. The food and feed industries should be encouraged to share data, and FAO and WHO should set up better systems for confidential data sharing.

Because of insufficient human data, it was necessary to rely on toxicological studies in laboratory animals to characterize the human health risk related to melamine in food.

Based on dose–response assessment of subchronic rat studies, modelling of the incidence of bladder stones and application of a safety factor of 200 to account for extrapolation from rats to humans, variation within humans and uncertainties associated with the data, a tolerable daily intake (TDI) of 0.2 mg/kg body weight for melamine was established. The TDI is applicable to the whole population including infants.

This TDI is applicable to exposure to melamine alone. Although data were inadequate to develop TDIs for compounds that are structurally related to melamine, such as ammeline and ammelide, a TDI of 1.5 mg/kg body weight for cyanuric acid has previously been derived by WHO, suggesting that these analogues would be no more toxic than melamine. Available data indicate that simultaneous exposure to melamine and cyanuric acid is more toxic than exposures to each compound individually. Data are not adequate to allow the calculation of a health-based guidance value for this co-exposure.

The dietary exposure based on the consumption of melamine-adulterated infant formula in China at the median levels of melamine reported in the most contaminated brand was estimated to range from 8.6 to 23.4 mg/kg body weight per day, based on data provided by the Chinese Center for Disease Control and Prevention. This is about 40–120 times the TDI of 0.2 mg/kg body weight, explaining the dramatic health outcome in Chinese infants. Conservative estimates of potential exposure of adults to melamine from foods containing adulterated milk products were 0.8–3.5 times the TDI. Estimates of exposure to baseline levels of melamine from all sources (up to 13 μg/kg body weight per day) were well below the TDI.

Many countries have introduced limits for melamine in infant formula and other foods. Limits for melamine in powdered infant formula (1 mg/kg) and in other foods (2.5 mg/kg) would provide a sufficient margin of safety for dietary exposure relative to the TDI.

The Expert Meeting provided a range of recommendations for further information and new studies to better understand the risk to human health posed by melamine and its analogues.