codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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Agenda Item 5 **CX/CF 10/4/5**
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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON CONTAMINANTS IN FOODS

4th Session
Izmir, Turkey, 26 – 30 April 2010

PROPOSED DRAFT MAXIMUM LEVELS FOR MELAMINE IN FOOD AND FEED (N13-2009)

Codex Members and Observers wishing to submit comments at Step 3 on the above matter, including possible implications for their economic interests, should do so in conformity with the *Uniform Procedure for the Elaboration of Codex Standards and Related Texts* (Codex Alimentarius Commission Procedural Manual) before **12 April 2010**. Comments should be directed:

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BACKGROUND

1. The Codex Committee on Contaminants in Foods (CCCF) at its Third Session held in March 2009 agreed to initiate new work on the establishment of maximum levels (MLs) for melamine in food and feed, and to the establishment of an electronic working group (e-WG), led by Canada and open to all members. This new work proposal was approved at the 32nd session of the Codex Alimentarius Commission (CAC). A number of Codex members and observers expressed an interest in participating in the e-WG following distribution of the invitation.

2. The purpose of the current document is to provide background information on the sources of melamine in food and feed, and to present proposed draft MLs for melamine in food and feed (**paragraph 75**). These MLs are to apply to levels of melamine resulting from its non-intentional and unavoidable presence in food or feed from approved uses of melamine and from the use of substances which can subsequently give rise to melamine (e.g. cyromazine, trichloromelamine) and not to the deliberate addition of melamine to food or feed (occurring as part of fraudulent activities). Melamine in food and feeds resulting from deliberate addition is not to be tolerated at any level. These MLs aim to promote consistency in national and international risk management

practices and protect public health without introducing unnecessary impediments to international trade.

REQUEST FOR COMMENTS

3. Comments are requested on the proposed draft maximum levels for melamine in food and feed as presented in paragraph 75 together with the other recommendations and conclusions of the Working Group (paras 74 – 82).

INTRODUCTION

4. Melamine ($C_3H_6N_6$; 1,3,5-triazine-2,4,6-triamine) is a synthetically produced chemical used in the manufacture of a variety of products including electrical equipment, adhesives, laminates, permanent-press fabrics, flame-retardants, textile finishes, tarnish inhibitors, coatings and papers, and fertilizer urea mixtures. It is primarily utilized in the synthesis of melamine formaldehyde resins for the manufacture of laminates, plastics, coatings (including can coatings), commercial filters, adhesives, and dishware/kitchenware.

5. Melamine has been reported to migrate into test solutions and food samples from melamine-formaldehyde plastic ware (5,39,47,48). Residues of melamine may also be present in the environment and in food from the degradation of other industrially used compounds such as trichloromelamine (used in sanitizing solutions for food-processing equipment and food-contact articles) and triazine-based pesticides/herbicides (e.g. cyromazine) (45,51,61). Melamine may also enter the food chain indirectly as a result of carryover from animal feeds into products of animal origin (e.g. milk, eggs, meat and fish) (3,13,41,62,67). Animal feed may contain melamine as a result of its presence in the environment and from the approved direct addition of precursor compounds such as cyromazine. Trace amounts of melamine may be found in food as a result of these permitted uses.

6. The deliberate, direct addition of melamine to food is not permitted. However, throughout 2008, high levels of melamine were detected in a wide variety of foods originating in China. Foods included infant formula; other liquid and powdered milk products (e.g., milk-based candies, instant powdered coffee products, biscuits, chocolates, milk-based drinks, and cakes); and a variety of non-milk-based products (ammonium bicarbonate, animal feed and feed ingredients, egg powders and fresh eggs, and non-dairy creamers). Consumption of melamine-contaminated infant formula by infants led to severe health effects in a number of Chinese infants and young children, among which there were six deaths (67).

7. Earlier, in 2007, a pet food incident in North America and elsewhere resulted in observations of acute renal failure and kidney stones in thousands of cats and dogs that were associated with the consumption of pet food containing melamine “scrap”-adulterated wheat gluten and/or rice protein concentrate (6,10,15,67). Exposure to melamine “scrap” through adulterated pet food ingredients was also the cause of numerous pet deaths. In this incident, the melamine “scrap” was a combination of melamine and related triazines, namely, cyanuric acid, ammelide and ammeline. Cyanuric acid was the most abundant triazine found in combination with melamine in that incident (15).

8. Melamine had been added in an attempt to artificially increase the apparent protein content. Melamine is high in nitrogen (66.64% by mass) which is often used as an indicator of protein content based on the Kjeldahl and/or Dumas analytical methods. These currently used methods for protein analysis cannot distinguish between nitrogen from protein sources and nitrogen from non-protein sources.

9. This discussion paper, in support of the need to establish MLs for melamine, will attempt to address and consider both the Risk Analysis Principles applied by the CCCF in the Codex

Procedural Manual (11), and the Principles for establishing MLs in foods and feeds as contained in the preamble to the Codex General Standard for Contaminants and Toxins in Food (12). However, it is noted that the circumstances surrounding melamine are slightly different from that of "typical" contaminants, as defined by the Codex Alimentarius, in that health effects were seen as a result of deliberate adulteration (i.e., the direct addition of melamine to food, feed or their ingredients).. While the JECFA has not undertaken an assessment for melamine or related analogues, a scientific evaluation was conducted in December 2008 by scientists attending the World Health Organization (WHO) Expert Meeting held in collaboration with the Food and Agriculture Organization (FAO) (http://www.who.int/foodsafety/fs_management/infosan_events/en/index.html). The outcomes of the WHO Expert Meeting, as well as more recent published and unpublished information, will help to inform the current discussion paper on melamine.

10. The WHO Expert Meeting reviewed and evaluated current knowledge on the chemistry of melamine alone and in combination with related analogues (cyanuric acid, ammeline, ammelide); analytical methodologies; melamine occurrence; the toxicity of melamine alone and in combination with its analogues; and the estimated dietary exposure from different sources. Knowledge gaps were identified in order to guide further research efforts and guidance developed on assessing risks associated with its presence in food and feed.

11. Prior to, and subsequent to, the 2008 WHO Expert Meeting several governments developed MLs for melamine in food products and some, also in feed (Appendix 1). However, the need for international consensus has been identified to promote consistency in risk management practices related to the presence of melamine in food and feed. MLs are also required in part to support governments in their efforts to discriminate between the occurrence of melamine as a result of its unavoidable presence in food and feed, and that resulting from deliberate adulteration, as well as to prevent potential trade barriers from being put in place as a result of the acceptable presence of melamine in foods and feed. Melamine, when present in food and feed above baseline levels, can be considered to present a significant risk to public health and represents a known or expected problem in international trade, two of the criteria for establishing MLs in accordance with the Codex General Standard for Contaminants and Toxins in Food and Feed (12).

12. This discussion document is not intended to consider MLs for melamine-related chemicals (e.g. cyanuric acid, ammelide and ammeline), but recognizes that these chemicals, alone or in combination with melamine, present a more unique toxicological concern compared to melamine alone.

PHYSICAL-CHEMICAL PROPERTIES

13. Melamine (Chemical Abstract Service [CAS] No. 108-78-1) is a nitrogen-rich heterocyclic triazine compound, which can be produced from different starting materials: urea, cyanamide, dicyandiamide, or hydrogen cyanide. It is a white crystalline solid at room temperature and is partially soluble in water. The purity of melamine products is highly dependent upon the manufacturing process and level of purification employed (60,67). Both high and low purity melamine is available. Impurities and by-products of melamine synthesis and degradation include various oxytriazine (eg. ammeline) and heptazine species, as well as polycondensates (melem, melam and melon) (60).

14. Triazine compounds are able to form self-assembling, supramolecular complexes through hydrogen bonds and aromatic ring stacking (60). By way of the sp^2 hybridized nitrogen atoms of the triazine ring structure, melamine contains three pairs of unshared electrons that act as hydrogen bond acceptors. The melamine structure also includes three primary amines capable of providing a pair of hydrogen bond donors. These features are complementary to similar

donor/acceptor group characteristics found in other triazine compounds such as cyanuric acid, where the sp^3 hydribized nitrogen atoms within the triazine ring act as donors and the six pairs of unshared electrons from the carbonyl oxygen atoms act as hydrogen bond acceptors.

15. Biomolecules with a similar cyclic imide structure as the one in cyanuric acid (e.g. uracil and uric acid), have the potential to form complexes with melamine due to complementary hydrogen bond acceptor/donor features. Competitive hydrogen bonding with low molecular weight and water soluble compounds is generally insufficient to overcome intermolecular forces in the melamine-cyanuric acid complex. However, the hydrogen bond network may be prevented by compounds that covalently bond to the donor/acceptor functions. The self-assembly and aggregation of melamine and its mixture with uric/cyanuric acid have been investigated by utilizing scanning tunnelling microscopy (STM) and atomic force microscopy (AFM) (68).

16. The effects of pH on the stability and solubility of the melamine-uric acid complex have been studied (as reviewed in 67). In comparison to results at neutral pH, the melamine urate network was found to be increasingly stronger as conditions became more acidic. However at a pH of 7, the melamine-cyanuric acid complex was found to be 29-fold stronger than the melamine-uric acid complex. The solubility of the melamine cyanurate complex was minimal at a pH of 5.0, where co-existence of the melamine free base and the non-ionized cyanuric acid were favoured. Solubility increased significantly as the pH dropped to 3.5, but only increased slightly as the pH rose to 7.5.

17. Characteristic distinctions between laboratory melamine-cyanuric acid crystals formed in the presence of serum or urine, and those produced in water or aqueous buffer solutions, imply that biomolecules such as proteins or protein fragments may be involved in the formation of calculi potentially associated with renal effects.

TOXICOLOGICAL AND EPIDEMIOLOGICAL EVALUATION

Toxicity, Absorption, distribution, metabolism and excretion

18. The toxicological and health aspects of melamine and cyanuric acid have recently been assessed through an Expert Consultation held by WHO, in collaboration with FAO (67).Both melamine and cyanuric acid are extensively absorbed following oral exposures and rapidly excreted, essentially unchanged, mainly through the urine. As such, neither is considered to be acutely toxic. A recent kinetic study in non-human primates administered a single dose of 1.4 mg/kg body weight melamine suggested a plasma half life (t1/2) of 4.4 hours (46). Limited toxicological information is available for melamine analogues such as ammelide or ammeline or the melamine:cyanurate complex.

19. Available data from pets, livestock, fish and pigs does indicate that simultaneous oral exposure to melamine and a combination of triazines, especially cyanuric acid, is more toxic to the renal system than exposure to each compound individually (67). Crystal formation occurs when a critical concentration/threshold is reached in the excretory organ, which is dependent on the solubility of the melamine-cyanuric acid complex. Incidence of crystal formation in kidneys and renal tubules of test animals exposed to co-administered melamine and cyanuric acid occurred at a higher rate than in test animals exposed to either melamine or cyanuric acid only. The toxicity of melamine and cyanuric acid is considered to be mediated by the formation of crystals in the urine resulting in tissue damage, blockage of the kidney tubules and then renal failure (15,31,53,54) and is thought to be similar to acute uric acid nephropathy in humans (6,10,40,54,55,67). It should be noted that similar clinical, histological and toxicological findings to those reported in cats and dogs from the 2007 pet food incident, were found in the renal system of affected piglets, where fixed kidney tissues contained high concentrations of ammeline, followed by ammelide, melamine and cyanuric acid (26).

20. Main toxic effects observed in experimental animals following longer term exposure to melamine include calculus formation, bladder hyperplasia and kidney inflammation. Neither melamine nor cyanuric acid is considered to be genotoxic, teratogenic (developmental) or a reproductive toxicant (67). While urinary bladder carcinomas were observed in male rats following chronic exposure to melamine, tumour findings correlated with calculus formation and irritation/hyperplasia. A recent review of the histopathological changes induced in rat kidney following oral exposure to melmaine revealed cortical and medullary tubular effects, with features consistent with what was termed as '*retrograde nephropathy' (30)*. More specific details regarding the toxicology of melamine and cyanuric acid can be found in the WHO Expert Consultation Report, "Toxicological and Health Aspects of Melamine and Cyanuric Acid".

Clinical and epidemiological data from humans

21. The Chinese Ministry of Health reported that up to December 1, 2008, over 22 million examinations were performed on infants who were potentially exposed to melamine from adulterated infant formula (67). By December 1st,2008, the Chinese Ministry of Health reported that six deaths, 51,000 hospitalizations and 294,000 cases of urinary tract abnormalities (urinary problems, possible renal tube blockages and possible kidney stones) had been associated with the consumption of melamine contaminated milk and milk products (27,67). The melamine used as an adulterant in this 2008 incident was found to be relatively pure (ie. primarily melamine alone or with very low levels of cyanuric acid).

22. Clinical signs and symptoms of renal impairment in infants included: crying (in some cases, while urinating), vomiting, fever, haematuria, dysuria, oliguria, anuria, high blood pressure, oedema and pain in the kidney area (29,65,67). However, most children with stones or calculi did not show clinical signs (i.e., usually only the most severe cases presented with signs), with detection by ultrasonography being the sole indicator of the condition. It has been hypothesized that a proteinaceous matrix is not present in a melamine-containing stone and therefore, it does not react with the urinary epithelium and consequently produce urinary findings (16,43). Because many children with identified calculi were asymptomatic, it is likely that there may have been many more cases that were not brought to the attention of medical authorities (27). As well, it is likely that microscopic changes, individual crystals, crystal aggregates and smaller stones (< 1mm) would not be identified and consequently found by ultrasound, due to its resolution limits. It is important to note that the adverse effects seen in experimental animals, and probably in humans, as well, are due to a local mechanical obstruction rather than a systematic toxic effect (27,43).

23. Stones were radiolucent and X-ray films failed to show their presence (31,67). The melamine stones in humans were characterized as usually occurring bilaterally with multiple soft and small stones, often less than 1 cm in size (31,42). The presence of sand-like material was found in the urine of some affected infants (67).

24. Melamine induces the formation of crystals in the urine when its concentration exceeds a precipitation threshold. Chinese infants affected by exposure to contaminated formulas had stones or calculi in the kidney, ureter or bladder. The calculi were composed of uric acid and melamine (ratios on a molar basis ranged from 1.2:1 – 2.1:1 in 15 analysed calculi); cyanuric acid was not detected in the calculi (28,67). Both melamine and urine metabolic factors, promoting the formation of calculi, are important in determining the risk of formation of melamine related stones (42). The cyclic imide structure of uric acid allows for hydrogen bonding with melamine leading to the formation of larger complexes that eventually precipitate into crystals. The molecular structure of a melamine and uric acid co-crystalization with water upon sonication was predicted (2). Humans and non-human primates have serum uric acid concentrations ten to twenty times higher than other mammals because they lack the uric acid oxidase enzyme (21,66).

Children may be even more susceptible to the adverse effects of melamine in food because: they eat more food relative to their body mass, their kidneys are under development, they have differences in absorption compared to adults, they feed more frequently, and nutritional factors such as inadequate protein intake in their diet may differ from adults (29,67). In addition, normal uric acid levels in urine and serum of infants are higher than those of older children and adults (as reported in 67), which may increase their chances of developing uric acid-melamine precipitates. As well, lower levels of solutes (citrate, phosphate, etc.), which could potentially compete for binding, may suggest that infants are more susceptible to melamine (16).

25. One case study reported that of 589 children who were equally likely to have symptoms, 8.5% had stones, 19% were suspected of having stones and 72.5% had no stones (29). Many children had small calculi or stones that were not detectable using standard methods. This suggests that there may be more asymptomatic cases and therefore undiagnosed children with renal crystals or stones as a result of consuming melamine-contaminated products (27).

26. A clinical study on 2085 children from the Gansu Province in China identified stones in 348 cases (17%); 216 were males and 132 were females. These results mirror those from toxicology studies in rats showing that males had a higher incidence of stone formation than females. Case studies in China also show that infant age may be a factor in the rate of stone development as higher proportions of stone occurrence was observed in neonates and infants less than 6 months of age and gradually decreased in infants up to > 30 months (67). Elsewhere, it was suggested that age, sex and the use of formula alone or in combination with breast milk, were not significantly associated with the presence of stones; however, preterm birth was (29). The risk of stone formation also appears to be determined by the amount of melamine consumed, as well as the duration of exposure (43,44,67,69). However, elsewhere it has been suggested that the size of the melamine-induced stones are dependent on the melamine content of the infant formula, but not on the duration of exposure (29,35). Lam and colleagues (42) found a significant correlation between renal stone size, using ultrasonography, and urinary melamine levels in children suffering from urolithiasis with a confirmed history of consuming melamine-contaminated milk products in China.

27. An 8-month old infant girl consuming Sanlu formula for 15 days (breastfed prior to the consumption of formula) was found to have multiple stones in both kidneys and the ureter, where it attaches to the bladder (67). Information on the concentration of melamine in the consumed infant formula was unavailable.

28. Accurate dose-response information could not be generated, based on clinical and epidemiological data from study cases of patients in China, because, in many cases, the exact amount of melamine intake (concentration in formula and amount consumed) could not be determined. Many children were exposed to different brands of infant formula containing different concentrations of melamine, for various amounts of time. There was large variation in melamine concentrations within the same brands and between different brands, and the exact melamine concentrations were not determined for all cases. Conservative estimates of melamine exposure by children exposed to adulterated infant formula range from 8.6-23.4 mg/kg bw/day or 40-120 times greater than the TDI suggested by WHO (40,67).

29. There is a lack of information on the long-term health effects of melamine in humans. Consequently, the need for large scale epidemiological investigations to follow-up with the affected infant cohorts has been suggested (29,43,67).

Dose-response and derivation of the WHO TDI

30. Based on insufficient dose-response details available for humans, the WHO Expert consultation considered bladder calculi formation and the incidence of bladder stones from

experimental animal studies as the most relevant toxicological endpoints to derive a health-based guidance value. A Tolerable Daily Intake (TDI) for melamine of 0.2 mg/kg body weight per day was developed. More details on the dose response characterization and risk assessment can be found at (http://whqlibdoc.who.int/publications/2009/9789241597951_eng.pdf). A TDI of 1.5 mg/kg body weight for cyanuric acid has previously been derived by the WHO (67).

Toxicological findings published after the WHO Expert Meeting Report

31. Recently, it has been suggested that the WHO TDI developed for melamine may not be sufficiently protective of human health (36,44). Utilizing the same experimental data set as WHO, but a more conservative risk level and a higher uncertainty factor, an estimated TDI of 0.00809 mg/kg bw/day was proposed (36). However, by comparing urinary concentrations of melamine and cyanuric acid over a range of doses, including those estimated by infants who had consumed contaminated formula, and the limits of solubility for the melamine:cyanuric acid complex, it has been proposed that the presence of 1 ppm each of melamine and cyanuric acid in infant formula is unlikely to represent a significant health concern (16).

32. There is also a recent report indicating an increased incidence of nephrolithiasis in young children who had consumed contaminated formula and were assigned to the lowest melamine exposure category (>0-0.2 mg/kg bw/day). Based on epidemiological data collected during the recent melamine infant formula adulteration incident it has been suggested that the TDI should be lower than 0.1 mg/kg bw per day for young children (44). However, it should be noted that the 95% confidence interval for the odds ratio of developing nephrolithiasis in the dose group with an estimated melamine intake of >0-0.1 mg/kg bw/day included unity (0.8-2.6). The difficulties in obtaining accurate melamine exposures for infants who consumed adulterated infant formula were noted previously (para. 26) and considered by the WHO Expert Meeting (67).

METHODS OF ANALYSIS

33. Analytical methods have been developed for both screening and quantitation of melamine and its analogues (cyanuric acid, ammelide, ammeline) in food and feed (67). Current methods range from sensitive liquid chromatographic-tandem mass spectrometric techniques to less sensitive immunoselective assays, such as ELISA. Impediments in analysis may include contamination, matrix effect, and analyte instability. The impact of these obstacles generally depends on the method used, the food matrices involved and the analyte examined (58).

34. Methods for melamine analysis have been developed to study the fate of the pesticide cyromazine, of which melamine is a potential degradation product, and to evaluate melamine-formaldehyde resins used in the manufacture of plastics coming into contact with food. Following the pet food incident in 2007, a number of methods were developed to analyze melamine in pet food and related ingredients (58). More recently, methods used for the analysis of foods for human consumption have been developed or adapted from some methods initially used for animal feeds (58), including a method that can quantitatively determine melamine and cyanuric acid simultaneously in milk and milk-based infant formula (14). As a result, existing methods include less specific rapid screening methods, highly selective quantitative methods, and even methods for multi-residue analysis (melamine, cyanuric acid, ammelide, ammeline, cyromazine) (58).

35. Selective techniques for melamine analysis generally utilize either high performance liquid chromatography (HPLC) or gas chromatography (GC) with a selective detection technique. These detection systems include, in order of most selective to least selective, tandem mass spectrometry (MS/MS), single stage mass spectrometry (MS), diode array detection (DAD), and ultraviolet absorption (UV). The latter two detection systems used in combination with HPLC require more intensive method validation. HPLC-MS/MS and GC-MS/MS techniques are the

most reliable and sensitive methods available for analyzing low levels of melamine and related compounds in food and feed (67). Further information can be found in reference 58.

36. The method chosen for the analysis of melamine and related compounds must be suitable for its intended purpose (e.g., rapid check of suspected items versus need to determine baseline levels). The required sensitivity and selectivity will in turn dictate which method should be used. However, the choice of method may also be driven by available instrumentation. All analytical methods should undergo thorough validation and proficiency testing.

OCCURRENCE OF MELAMINE IN FOOD AND FEED

37. Melamine in food or feed can be found at what can be considered "baseline" levels, which refer to levels occurring indirectly from the approved uses of melamine or melamine-precursors, or it can be found at "adulteration" levels, which refer to levels that result from the intentional, illegal addition of melamine or melamine–precursors directly to food and/or feed (including the misuse of melamine or substances that degrade to form melamine). A clear distinction between baseline and adulteration levels is not always possible. As an example, low levels of melamine could occur in foods of animal origin as a result of carryover from animals consuming adulterated animal feed, or in processed food products containing a small amount of adulterated milk powder. Generally, baseline levels are expected to be below 1 mg/kg (34,67). However, baseline levels may also vary from one country to another depending on the permitted/accepted uses of melamine, its analogues, and any precursors that degrade into melamine. For example, baseline levels in food may be higher in countries that permit the use of cyromazine as a veterinary drug in animals and/or as a pesticide on crops.

Baseline levels of melamine in food

38. Based on studies conducted under controlled conditions, using food or food-simulates, as well as harsh conditions for sample preparation (high temperatures and acidic substances), baseline levels of melamine in food as a result of migration from melamine-containing tableware are expected to generally be below 1 mg/kg (67).

39. Trichloromelamine, which decomposes to melamine, is a U.S. FDA cleared disinfectant for use on food packaging materials, except milk containers (21 C.F.R §178.1010(b)(10)), and is the subject of an exemption from a tolerance permitting residues of trichloromelamine when used on food processing equipment and utensils, except for dairy applications (40 C.F.R. § 180.940). The U.S. FDA estimates a melamine concentration of 0.14 mg/kg in food based on the assumption that all disinfectants contain trichloromelamine.

40. Melamine has been found to be a metabolite of triazine-based pesticides, such as cyromazine, occurring in crop plants, poultry, ruminants and other animals. Cyromazine can be used as an insecticide, pesticide or veterinary drug. Melamine residues on the edible part of vegetables where cyromazine was applied are generally expected to be below 1 mg/kg (67). Such melamine levels were found in tomato fruit, lettuce head, celery stem/leaf, potato and bean plants treated with cyromazine (34,67). However, the extent of melamines' presence, resulting from the degradation of cyromazine or other triazine-based compounds, will depend on the application rate of these compounds, the extent of their use, as well as the MRLs for the pesticides or veterinary drugs in each country. It has been reported that melamine residues are approximately 10% of cyromazine residues for most plant crops in which cyromazine is applied as a pesticide, with the exception of edible offal and mushrooms, where melamine residues were of a similar magnitude to those of cyromazine (22,61). Melamine and other triazine-based compounds may be used as nitrogen sources in urea-based fertilizer mixtures. The occurrence of melamine in crop foods as a result of its use in fertilizers is unknown.

41. Melamine may enter the environment from other legitimate widespread uses of melamine or melamine-precursor compounds, such as the manufacture of laminates, flame retardants, etc., as well as from the industrial production and disposal of melamine and substances that degrade to form melamine, leading to the possibility of melamine being present in water effluents. However, data on the melamine content of water is limited.

42. Datasets from health authorities around the world were submitted for consideration at the WHO Expert Meeting (67). A wide variety of foods were sampled to identify not only adulteration but measure melamine from possible carryover from animal feed, as well as, in some cases, baseline levels. The melamine levels in submitted data sets could not be easily distinguished as resulting from baseline contamination or intentional adulteration, since a large number of samples were targeted as a result of potential adulteration. However, the data indicated that the majority of food samples analysed were provided according to a limit of reporting of 1 mg/kg, rather than at a limit of detection, and that the majority of samples were below this reporting limit (67).

43. A Health Canada survey was conducted to determine the baseline levels of melamine in infant formula using LC-MS/MS with a limit of detection of 0.004 mg/kg (32,59). Melamine was detected in 60 of the 80 infant formulas tested, and the concentrations of the products "as purchased" ranged from 0.0043 to 0.346 mg/kg. Estimated melamine concentrations in the products "as consumed", when accounting for reconstitution factors in concentrated and powdered formulas, ranged from 0.00053 to 0.0689 mg/kg.

44. The highly sensitive method was then used to survey melamine levels in other products containing milk and milk- or soy-derived ingredients and composite foods containing milk ingredients available in Asian markets (n=246). In this survey, melamine concentrations ranged from 0.00435 to 0.282 mg/kg, with only 14% of individual food items and 11% of Total Diet Study dairy-composite samples containing quantifiable levels of melamine (56). This dataset was used by the WHO Expert Meeting to estimate the baseline dietary exposure to melamine from foods other than infant formula. A further survey of a variety of egg-containing, soy-based, vegetable or fish products were analyzed (57). Melamine was quantified in 98 of the 378 samples analyzed. Concentrations of melamine in egg-containing items ranged from 0.00507-0.247 mg/kg; in soy-based meat substitutes, from 0.00408-0.0479 mg/kg; in fish and shrimp products, from 0.00409-1.10 mg/kg; and in vegetable products, items ranged from 0.00464-0.688 mg/kg. Melamine was detected more frequently in fish, shrimp and vegetable products. Most Total Diet Study shrimp composites collected after 2001 were found to contain melamine.

Transfer of melamine from animal feed and feed ingredients into animal-derived food

45. Baseline occurrence of melamine and cyanuric acid in animal feed may be the result of approved uses in pesticides, fertilizers, veterinary drugs, and feed additives. The potential carryover from animal feed to animal derived foods has been demonstrated, with data showing the presence of melamine in milk, eggs, and animal/fish tissue as reviewed in the WHO Expert Meeting Report (67). Melamine concentrations ranging from 10 – 170 ng/g have been detected in the muscle of cattle which were administered cyromazine (17). Melamine was also reported in the milk of goats dosed with C14-cyromazine (Simoneux and Marco 1984, and Tortora 1991 as reported in 58). In a study investigating residues of cyromazine and melamine in chicken, egg, beef, mutton, and pork, one beef sample contained detectable levels of cyromazine, while melamine was not detected in any sample (LOD 0.02 mg/kg) (9). Combined melamine and cyromazine levels up to 0.25 mg/kg have also been estimated in chicken meat and eggs from hens fed up to 5 mg/kg cyromazine.

46. More recent reports (1) have suggested that some milk products in South Africa, and possibly other areas, may have been contaminated with melamine as a result of carryover from

animal feed made using melamine-adulterated raw materials from old stocks dating back to the 2007 pet food incident. Consequently, it has been suggested that melamine-adulterated cattle feed may have been the source of low ppm levels of melamine in some milk-containing food products, where there was no direct indication of adulteration of the source milk ingredients with melamine (13,52). Subsequent studies where melamine-contaminated feed was intentionally fed to dairy cows have confirmed the transmission of melamine to milk (13). Residual levels of melamine and cyanuric acid were also found in fish and shellfish tissue according to studies where fish and shellfish were dosed with high amounts of melamine and cyanuric acid either via intragastric tubing or through oral capsules (4,41).

47. In Japanese feeding studies where Holstein cows were provided feeds containing melamine at concentrations of 50 or 100mg/kg for 28 days, concentrations of melamine in the muscle, fat, liver and kidney reached concentrations of 0.46-0.69 mg/kg, 0.25-0.63 mg/kg, 0.58-1.0 mg/kg, and 2.3-3.4 mg/kg, respectively (49). Melamine concentrations in milk peaked at 0.9 mg/kg and 2 mg/kg in low and high dose groups, respectively, within 2-days of initial ingestion. Concentrations of melamine in milk dropped to or below 0.1 mg/kg, seven days after melamine was removed from the diet. Similarly, melamine was found to transfer into the muscle, kidney and liver samples of layer hens. Melamine concentrations in eggs reached a plateau of 0.7 mg and 1.6 mg/kg, respectively, in low (30 mg/kg) and high (60 mg/kg) dose groups, within 12 days after initial ingestion of melamine. Melamine concentrations in eggs dropped to or below 0.04 mg/kg after 7 or 14 days of melamine being removed from the diet (49). Melamine concentrations in the muscle of rainbow trout and prawn fed melamine-contaminated feed correlated strongly with melamine concentrations in the feed. In all cases, melamine concentrations in the muscle dropped after the cessation of melamine contaminated feed (50).

Melamine in feed and feed ingredients

48. As mentioned previously, baseline occurrence of melamine in animal feed may be a result of the legitimate use of pesticides, fertilizers, veterinary drugs, and/or feed additives. However, there is a very limited amount of available data on melamine levels in animal feeds or their raw materials, which prevents any kind of distinction between baseline and adulterated levels in feeds to be made. Guanidino acetic acid (GAA), an authorized feed additive for chickens, can contain up to 15mg/kg melamine and up to 25 mg/kg of melamine and structurally related compounds (cyanuric acid, ammeline, ammelide) as an impurity. GAA can be incorporated into animal feed at a level up to 600mg/kg feed. Under these circumstances, the use of GAA would result in a very low concentration of melamine in animal feed (~0.009 mg MEL/kg feed) (20). Similarly, it has been suggested that the use of urea as a feed additive (non-protein nitrogen source), could result in low levels of melamine being present in feed, as levels of melamine up to 50 mg/kg and of cyanuric acid up to 200 mg/kg have been found as impurities in urea.

49. In 2007, after the pet food incident, authorities learned that melamine-contaminated pet food resulting from the use of the adulterated pet food ingredients (wheat gluten and rice protein concentrate), had been used in the manufacture of some animal feeds (62). It has been suggested that the adulteration of animal feed with melamine has been common practice (4,67), and that contamination of feed may have occurred as early as the 1980's (7) and as early as 2003 in pig feed (26). Further information can be found in the WHO Expert Meeting Report (67) and elsewhere (34,37). It was also reported that finished feed samples of 85 independent Chinese cattle feed suppliers, obtained from farms, were analyzed for melamine; 30% of the samples contained between 5 and 100 mg/kg, 10% contained more than 100 mg/kg (maximum level: 700 mg/kg), and melamine was not detected below the detection limit of 5 mg/kg in the remaining 60% (52).

DIETARY EXPOSURE

50. The WHO Expert Meeting estimated melamine dietary exposure for scenarios using baseline and adulterated concentrations in food (67). Estimated dietary exposures in infants from melamine-adulterated infant formula in China at the median levels reported in the most contaminated brand ranged from 8.6 to 23.4 mg/kg body weight per day (40). The dramatic health outcome in Chinese infants may be explained by this estimated level of exposure which is approximately 40-120 times the TDI of 0.2 mg/kg body weight. However, Chinese researchers emphasized that the infant formula samples collected were not necessarily representative of the infant formula consumed, that concentrations in the adulterated Sanlu formula varied and that these products may not have necessarily been consumed all of the time. Dietary exposure from other foods containing adulterated levels of melamine was also estimated. Using a highly conservative approach, the Expert Meeting estimated a dietary exposure of 0.16 to 0.7 mg/kg body weight per day for adults from the consumption of melamine adulterated products.

51. The WHO Expert Meeting also estimated baseline dietary exposures to melamine utilizing the limited data on baseline levels of melamine in different foods, and food consumption data or very conservative exposure estimates (e.g., based on uses of trichloromelamine). The food consumption data utilized included: the 13 GEMS/Food consumption cluster diets (see Appendix 2) for estimates of melamine exposure resulting from the use of cyromazine; the Concise European Consumption Database for melamine exposures resulting from baseline levels of melamine found in processed foods; and other national data for melamine exposures resulting from the consumption of infant formula containing baseline levels of melamine (Table 1). Estimated exposures from baseline levels of melamine from each source, including a maximum estimate of 13 µg/kg body weight per day from the migration of melamine in tableware, were well below the TDI. Available data was insufficient to estimate melamine exposure from migration from melamine-formaldehyde resins (e.g., coating of food cans). Additional data on melamine carryover from animal feed to animal derived foods were also not available to the Expert Meeting for assessment. Other potential sources of baseline exposure not considered due to lack of data include those from the legitimate use of melamine or cyromazine and/or cyanuric acid in fertilizers, veterinary drugs, or feed additives, all of which may result in low level residues in food. It should be noted that baseline exposure will be different for each country depending on approved uses of melamine and substances which can subsequently give rise to melamine (e.g. cyromazine, trichloromelamine) in their respective countries.

52. Table 1. Estimated baseline exposure to melamine from the WHO Expert Meeting (reproduced from reference (67))

Source	Estimated daily exposure (µg/kg body weight)	Comment
Infant formula	0.54 – 1.6	Mean exposure
Other foods	0.03 – 0.12	Adults, mean exposure
Disinfection in food processing (trichloromelamine)	7	Adults, very conservative estimate
Migration from melamine-containing plastics	13	Adults, conservative estimate
Migration from melamine-containing adhesives	< 0.35	Adults, conservative estimate
Residues arising from cyromazine use as pesticide* (agricultural trial data; STMR, supervised trial median residue)	0.04 – 0.27	Adults, conservative estimate

*Melamine concentrations were assumed to be 10% cyromazine levels for crops other than mushrooms and mammalian offal, where concentration assumed to be equal to cyromazine

RISK MANAGEMENT

Risk Management Strategies in various countries

53. Forty-seven countries, not including those countries who did not report their findings to the International Food Safety Authorities Network (INFOSAN) or those who did not perform analyses, were reported to have received melamine contaminated products or products containing melamine adulterated ingredient(s) originating from China by direct or indirect distribution (27). An estimated 68 countries had banned or recalled foods, feeds or their ingredients in response to the 2008 incident in China because they were suspected of containing melamine. Responses to the discovery of melamine-contaminated foods ranged from no action to the complete ban of imported milk and milk-based products, or other products, from China (27,38). Many regulatory authorities issued preliminary health risk assessments and guidance on melamine levels in food, implemented interim regulatory measures by setting limits for melamine in foods and feed, and/or implemented control measures such as random testing of all imported Chinese products or testing of implicated products.

54. A list of some countries who established limits or threshold levels for further risk assessment and appropriate risk management actions for melamine in food are found in Appendix 1. In general, the limits or threshold levels of 1 mg/kg and 2.5 mg/kg of melamine in food have been considered suitable by many countries for distinguishing between the unavoidable background presence of melamine and unacceptable adulteration (67). The most common melamine limits set by different countries were 1 mg/kg for infant formula and 2.5 mg/kg for other milk and milk-based foods or all other foods. The WHO Expert Meeting noted that these limits provide a sufficient margin of safety from any dietary exposure to melamine which could pose a health risk (67). Proposed MLs in this document are based, in part, on those that have already been established by many countries.

55. In its risk assessment of October 2008, the U.S. Food and Drug Administration (FDA) used a worst case scenario in which half of a person's total daily food intake (typically estimated at 3 kg composed of 1.5 kg liquid and 1.5 kg solid foods) was contaminated with melamine (63).

With this conservative approach, the U.S. FDA deemed a 2.5 mg/kg melamine level in foods other than infant formula as an appropriate safety limit. Later, a level of 1 mg/kg was established by the U.S. FDA for melamine or one of its analogues when present alone in infant formula (64).

56. Food Standards Australia New Zealand (FSANZ) undertook a preliminary dietary risk assessment using a melamine TDI of 0.63 mg/kg body weight per day which was derived as part of the U.S. FDA's risk assessment for melamine from the 2007 pet food incident (24). They concluded that maximum melamine levels of 1 mg/kg in infant formula (powdered) and 2.5 mg/kg in dairy-based foods and foods containing dairy-based ingredients are considered appropriate as threshold levels for further action. FSANZ also indicated that a level of melamine above 2.5 mg/kg is indicative of adulteration. The levels established by FSANZ are threshold levels for further action. When levels above this threshold level were detected, the risk posed by the particular product was estimated based on the level of melamine detected and the likely consumption patterns for that particular food, and appropriate risk management action was taken.

57. In Canada, interim standards of 1 mg/kg melamine in infant formula and sole source nutrition products, and 2.5 mg/kg in other food products containing milk or milk-derived ingredients, were established based on a toxicological reference dose of 0.35 mg/kg body weight per day and conservative intake estimations (33). Following the results of the WHO Expert Meeting, Health Canada lowered its ML for melamine in infant formula and sole source nutrition products to 0.5 mg/kg, due to the various forms in which infant formulas are present on the market (ready-to-eat, concentrated and powdered).

58. The European Commission implemented a maximum level of 2.5 mg/kg melamine in composite products containing milk, milk products, soya or soya products and ammonium bicarbonate, originating from China (18,19). The Commission stated that based on available occurrence data, the level of 2.5 mg/kg melamine is appropriate to distinguish between unavoidable background levels of melamine and unacceptable adulterated levels.

Proposed Codex Maximum Levels

59. **Infant formula – proposed 1 mg/kg maximum level**: Infant formula may often constitute a sole source of nourishment for infants. For this reason, it is proposed that a maximum level specific to infant formula be established. Based on the limited data on baseline levels, melamine exposures among infants of various ages/weights were estimated using a theoretical melamine concentration of 1 mg/kg in infant formula whether ready-to-consume (i.e., liquid milk or soy formula) or powder (Table 2), and high infant formula consumption rates adapted from reference 23. The highest estimated melamine intake from the consumption of powdered infant formula containing a maximum of 1 mg/kg melamine is 0.0286 mg/kg body weight, which is roughly 14% of the WHO TDI. A level of 1 mg/kg melamine in ready-to-consume infant formula may lead to an exposure that approaches the WHO TDI of 0.2 mg/kg body weight. For this reason, additional consideration for high consumers of infant formula may need to be given in countries that have ready-to-consume (i.e., liquid milk or soy) infant formulas available on the market. It is recommended that for countries where ready-to-consume infant formula is available, consideration be given to establishing a lower ML for melamine, such as 0.5 mg/kg, in such ready-to-consume formulae.

60. It has been suggested that in order for powdered infant formula to meet the 1 mg/kg proposed ML for melamine, raw milk used in the manufacture of this powdered formula must not contain melamine at concentrations greater than approximately 0.1 mg/L (Nestlé 2008, unpublished comments to the melamine e-WG). Therefore, raw food materials used to make dehydrated or concentrated products must have lower levels of melamine to ensure that the final product, if analysed as sold, is compliant with the proposed MLs. Preliminary information provided by Nestlé suggests that cows fed melamine-containing feed at a level of 5 mg/kg, may

approach the minimum level of melamine that raw milk may contain if it is used to make powdered infant formula (52).

61. Table 2. Estimated melamine intakes from infant formulas (powdered and ready-to-consume) based on a theoretical melamine concentration of 1 mg/kg (infant formula intake figures adapted from *Table 6. Infant group definitions presented as options in the risk assessment model* of reference (23)).

Infant group	Weight (g)	Daily intake infant formula (ml/kg bw)		Melamine intakes (mg/kg bw/day)	
		Ready	Powder[(a)]	Ready	Powder[(a)]
Extremely low birth weight (Birth weight < 1000 g)	800	150	21.4	0.15	0.0214
Very low birth weight (Birth weight < 1500 g)	1250	200	28.6	0.2	0.0286
Low birth weight (Birth weight < 2500 g)	2000	200	28.6	0.2	0.0286
Premature neonate (Prior to 37 completed weeks)	2250	150	21.4	0.15	0.0214
Term non-low-birth weight neonate (0 to 28 days of age)	3600	150	21.4	0.15	0.0214
Young infant (29 days to 6 months of age)	5000	150	21.4	0.15	0.0214
Older infant (6 to 12 months of age)	9000	55[(b)]	7.9[(b)]	0.055	0.0079

(a) Powder infant formula assumes a 7-fold reconstitution factor.

(b) Value assumes that formula is not the sole source of nutrition for older infants.

62. **Foods (other than infant formula) and animal feed – proposed 2.5 mg/kg maximum level**: Assuming a theoretical melamine concentration of 2.5 mg/kg in all foods, melamine intakes were estimated for the general population using the 13 GEMS/Food consumption cluster diets (25) and a 60 kg body weight (Table 3). The highest percent contribution of estimated melamine intake, assuming a concentration of 2.5 mg/kg in all foods, to the WHO TDI is approximately 47%. As such, a maximum level of 2.5 mg/kg melamine in foods (other than infant formula) would be adequate to protect human health; particularly as the general adult population is less susceptible on a body weight basis in comparison to infants who were taken into account in the establishment of the TDI. Based on the occurrence data available at this time, the 2.5 mg/kg limit would also be considered an appropriate guideline to distinguish between baseline and adulterated melamine levels.

63. A maximum level of 2.5 mg/kg in animal feed is also proposed in light of the increasing evidence of transmission of melamine from feed to animal-derived foods. In the absence of additional melamine contamination sources, the 2.5 mg/kg limit in feed would ensure that the same limit is met in animal-derived foods even under the conservative assumption that transmission from feed to animal food is 100%. Studies looking at the transfer of melamine from adulterated animal feed into the milk of cows consuming this feed, suggests that melamine levels must be controlled in feed in order to ensure that finished milk-containing products meet the proposed MLs (13,49,50,52). Empirical data on residue levels of melamine in feed from the use of cyromazine pesticides/insecticides are not available. However, there is no evidence to suggest that melamine residue levels in feed from such use will exceed the 2.5 mg/kg limit based on residue levels found on crops after repeated uses of cyromazine-based pesticides. However, as mentioned previously, the extent of melamines' presence, resulting from the degradation of cyromazine or other triazine-based compounds, will depend on the application rate of these compounds, the extent of their use, as well as the MRLs for the pesticides or veterinary drugs in each country.

64. Table 3. Estimated total food intake (g/person/day), melamine intake (mg/kg bw/day) assuming 2.5 mg/kg in all foods, and percent contribution of estimated melamine intakes to the

WHO TDI of 0.2 mg/kg bw/day for the general, global population using the 13 GEMS/Food consumption cluster diets and assuming a 60 kg body weight

GEMS/Food consumption cluster diet	A	B	C	D	E	F	G	H	I	J	K	L	M
Total diet (g/person/day)	1626.6	2774.2	1765.2	1828.8	1929.5	1666.3	1519.9	1805.7	1402.4	1419.8	1990.2	1683.0	2263.1
Estimated melamine intake (mg/kg bw/day)	0.068	0.116	0.074	0.076	0.080	0.069	0.063	0.075	0.058	0.059	0.083	0.070	0.094
Percent contribution of estimated melamine intake to TDI of 0.2 mg/kg bw	33.9	57.8	36.8	38.1	40.2	34.7	31.7	37.6	29.2	29.6	41.5	35.1	47.1

Notes: See Appendix 2 for full list of countries comprising each GEMS/Food consumption cluster diet.

65. Although it is possible that when using the same food consumption rates, children of a lesser body weight could exceed the TDI, the conservative nature of the estimated melamine exposures would still ensure an adequate margin of safety for these age groups. The 13 GEMS/Food consumption cluster diets are considered an overestimate since they are based on Food Balance Sheets (FBS). Because waste at the household or individual level is not taken into account, FBS data tend to slightly overestimate consumption. Based on national surveys, average food consumption estimates from FBS are approximately 15% higher than actual average food consumption in the worst cases (e.g., certain fruits and other highly perishable items).

66. Melamine intake estimates from Table 3 assume that all foods contain melamine at the hypothetical level of 2.5 mg/kg. In actuality, adulteration incidences have focused primarily on protein-containing foods (e.g., the recent incident in China was associated with contaminated fluid milk and infant formula manufactured from contaminated milk, or other high protein ingredients), with the exception of ammonium bicarbonate.

67. The proposed ML for melamine in foods other than infant formula would be applied across all food items including raw materials, ingredients and finished foods. As such, melamine levels will be even lower in composite/finished foods where the maximum level has already been enforced on the raw material or ingredients.

68. Some food items may only contain melamine as a result of carryover from feed and therefore levels of melamine that may be present in foods of animal origin (e.g., meats, eggs, etc.) as a result of carryover will be significantly less than the proposed 2.5 mg/kg limit, if the maximum level was also being enforced for feed and feed ingredients.

69. The limited data available on baseline melamine levels in foods, such as that from the Health Canada surveys used by the WHO Expert Meeting in their assessment, suggest that baseline levels are below these proposed MLs. However, the data remains insufficient to set MLs on the basis of typical baseline levels from accepted melamine and related compound uses. Consideration can be given to reducing the MLs at a later date when more information on baseline melamine levels in foods become available. The currently proposed MLs are based on safety (having taken into consideration the WHO TDI for melamine of 0.2 mg/kg bw/day), rather than on an extensive data set of baseline levels of melamine resulting from accepted uses of

melamine and compounds that degrade to form melamine. The proposed MLs are expected to adequately protect consumers as baseline levels appear to be readily achievable through Good Agricultural Practice (GAP), Good Manufacturing Practice (GMP) and Good Veterinary Practice (GVP), which preclude intentional adulteration. However, each country may need to examine their approved uses of melamine and substances which can subsequently give rise to melamine (e.g., cyromazine, feed additives) and use levels of these substances, in order to ensure that baseline levels are indeed below the proposed MLs.

TRADE CONSIDERATIONS

70. National measures regarding food contamination should avoid the creation of unnecessary barriers to international trade in food or feed commodities. The problem of fraudulent use of melamine quickly reached an international scale, demonstrating the complexities associated with the global trade of food, feed, and their ingredients. Health protection measures required the assistance and coordinated efforts of governments and organizations from around the world to deal with the large number of potentially contaminated products, including composite products made from ingredients originating from different countries.

71. The proposed MLs for melamine are not expected to create barriers to trade. Their intent is to exclude fraudulent manufacturing practices. Although limited, the available data suggests that baseline melamine levels in foods fall below the proposed MLs. Countries that do not have limits in place should be cognisant of the risk that they may be inappropriately targeted as a market for products that cannot meet standards in countries with MLs. These limits are intended to provide a science-based risk management option for developed and developing countries and to facilitate a harmonized approach to mitigating risks posed by melamine. Similar MLs have been adopted by several regulatory authorities around the world. The expected cost of control and enforcement is not considered to outweigh the benefits. However, it is recognized that cost will vary among countries, and will need to be considered in each respective country.

TECHNOLOGICAL CONSIDERATIONS/TECHNOLOGICAL POSSIBILITIES

72. Incidences involving melamine-contaminated food or feed products have originated as a result of the attempt to falsify apparent protein content for economic gain. Current quantitative methods for total/crude protein analysis (Kjeldahl/Dumas) are based on the detection of nitrogen content, but cannot distinguish between nitrogen from protein and non-protein sources. Quantitative methods that are more discriminating with regard to the presence of true protein content (so as not to include non-protein compounds in the total/crude protein) in food and feed should be developed to help prevent adulteration. Qualitative spectroscopic techniques for assessing the authenticity of food and feed ingredients such as infrared spectroscopy also have the potential to help detect the presence of melamine and other unexpected non-protein compounds, but reliable methods using this technology are not yet available.

73. Melamine is only one of many low molecular weight compounds with high nitrogen content. In the current absence of analytical methods capable of distinguishing between protein and non-protein nitrogen sources, the risk of possible contamination using other compounds similar to melamine remains.

CONCLUSIONS AND RECOMMENDATIONS

74. Given the potential for widespread distribution of adulterated products around the world and the absence of quantitative protein analysis methods capable of distinguishing nitrogen from protein and non-protein sources as well as qualitative authentication methods for protein-based food and feed samples, maximum limits are required to support governments in their efforts to discriminate between occurrence of melamine as a result of its unavoidable presence in food and

feed, from that of deliberate adulteration practices which are not to be tolerated at any level. Maximum limits appear to be the most appropriate approach to reduce health risks from the intentional addition of melamine, and in consideration of maximum or threshold limits that have already been established in some countries.

75. It is recommended that the CCCF consider maximum melamine levels of **1 mg/kg in infant formula (powdered)** and **2.5 mg/kg in foods (other than infant formula) and animal feed**. It is recommended that for countries where ready-to-consume (i.e., liquid milk or soy) infant formula is available, consideration could be given to establishing a lower maximum level for melamine at 0.5 mg/kg in such ready-to-consume infant formula. The possibility of carryover of melamine from feeds to animal-derived foods supports the need for a limit on feeds. It should be noted that each country may need to examine their approved uses of melamine and substances which can subsequently give rise to melamine (e.g. cyromazine, feed additives), as well as the use levels of these substances, in order to ensure that baseline levels are indeed below the proposed MLs.

76. The limited data available on baseline levels of melamine in foods suggests that baseline levels are below the proposed MLs. However, the data remains insufficient to set MLs on the basis of typical baseline levels from accepted melamine uses and the use of substances that can subsequently give rise to melamine. Based on theoretical dietary intake estimates and the WHO TDI for melamine, these proposed MLs are expected to provide a sufficient margin of safety. However, consideration can be given to revisiting the toxicological database at a later date if or when new toxicological findings become available, and to revising the MLs when more information on baseline levels of melamine in foods and feed become available.

77. MLs are also required in part to support governments in their efforts to discriminate between the occurrence of melamine as a result of its unavoidable presence in food and feed, and that resulting from deliberate adulteration, as well as to prevent potential trade barriers from being put in place as a result of the acceptable presence of melamine in foods and feed. International limits for melamine in food and feed will facilitate harmonized practices for both developed and developing countries, and contribute to the safety of the food supply without unfairly impeding potential trade.

78. Findings of melamine in a large number of foods support the need for MLs on all foods. However, it is recognized that based on factors and regulatory provisions specific to each country, verification of compliance may be better placed and more cost effective on raw commodities or ingredients rather than on finished end products.

79. The adoption of MLs may require the development and thorough validation of analytical methods to verify product compliance. Product compliance determinations would be facilitated by a mobile, rapid and simple method that can be used outside of the laboratory. While validated methods are available in a number of countries, the CCCF may wish to request that the Codex Committee on Methods of Analysis and Sampling (CCMAS) be consulted with regards to the development of such validated detection methods in consideration of the availability and suitability of analytical methods to support the implementation of the proposed MLs in the wide variety of food and feed matrices that would be involved.

80. Further, the CCCF may also wish to request that the Codex Committee on Methods of Analysis and Sampling (CCMAS) consider the development of new quantitative protein methods with higher discrimination power against the presence of non-protein nitrogen sources, and complimentary qualitative authentication techniques capable of detecting the presence of unexpected non-protein compounds in food and feed samples.

81. The CCCF may also wish to request that the Codex Committee on Pesticide Residues (CCPR) and the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) aid in the determination and collection of information on potential baseline melamine residues resulting from permitted uses of triazine compounds, such as cyromazine in food crops and as a veterinary drug.

82. Additional research is needed to generate data which would permit the estimation of no effect levels or benchmark doses for mixtures of melamine and melamine analogs. Based on such findings, TDIs for the entire class of compounds (melamine and melamine analogs) could be estimated that would permit development of thresholds for total exposure to melamine and melamine analogs which presumably share a common mode of action.

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Appendix 1[1] - Maximum or threshold levels for melamine in various countries around the world; either established in the countries respective legislation, or developed as part of a risk management framework for further risk assessment and appropriate risk management action(as of September, 2009)

Country	Regulatory authorities	Maximum level
Australia	Food Standards Australia New Zealand (FSANZ)	• 1.0 mg/kg melamine in infant formula • 2.5 mg/kg melamine in dairy-based foods and foods containing dairy-based ingredients
Canada	Health Canada, Canadian Food Inspection agency	• 0.5 mg/kg interim maximum level applies to infant formula and sole source nutrition products, including meal replacements • 2.5 mg/kg maximum level applies to foods containing milk and milk-derived ingredients
China	Ministry of Health	• 1.0 mg/kg in infant formula • 2.5 mg/kg in other dairy products including milk and milk powder, and in food containing more than 15% milk
European Union	European Commission	• Prohibition to import products containing milk or milk products, soy or soy products, intended for particular nutritional use of infants and young children • 2.5 mg/kg level applies to food and feed products containing milk or milk products and was extended to include soya and soya products imported from China, and ammonium bicarbonate • Radom checks may be completed on other food and feed products with high protein contents originating or consigned from China
Hong Kong	Hong Kong Government	• 1.0 mg/kg in milk and food intended to be consumed by children under the age of 36 months, pregnant and lactating women • 2.5 mg/kg in other foods (considered standards of the US and EU in setting the limits)
Japan	Ministry of Health, Labour and Welfare	• 0.5 mg/kg in infant formula and other foods for infants • 2.5 mg/kg for all other foodstuffs
Malaysia	Ministry of Health Malaysia	• 1.0 mg/kg in baby food products • 2.5 mg/kg in adult food products
New Zealand	New Zealand Food Safety Authority (NZFSA)	• 1.0 mg/kg in infant formula • 2.5 mg/kg in dairy-based foods and foods containing dairy-based ingredients • 5 mg/kg in ingredients used in the manufacture of foods
Nigeria	The National Agency for Food and Drug Administration and Control	• Adopted levels used by China
Republic of Korea	Korea Food and Drug Administration	• Not detected in foods for special dietary uses (infant formula, follow-up formula, cereal based food for infants and young children, other foods for infants and young children, foods for special medical purpose) and formulated milk products (formulated milk powder, formulated milk, the formulated milk for a growth period, the formulated milk powder for a growth period, other formulated milk powder, other formulated milk) • 2.5 mg/kg in other foods and food additives
South Africa	Department of Health	• 1.0 mg/kg in foodstuffs intended for children under 36 months of age and foodstuffs for special dietary uses • 2.5 mg/kg for all other foodstuffs

[1] **Established limits or threshold limits for further risk assessment and appropriate risk management actions.**

Switzerland	Federal Office of Public Health	• Adopted levels used in the European Union
Thailand	Thai Food and Drug Administration; Thai Department of Livestock Development (DLD)	• 1.0 mg/kg melamine or melamine analogs in modified milk for infants, modified milk of follow-up formula for infants and children, whole milk powder, partly skimmed milk powder, skimmed milk powder, filled whole milk powder, and filled partly skimmed milk powder • 2.5 mg/kg melamine or melamine analogues in milk containing food products, all other food products (other than milk and milk containing products), and in feed
United Arab Emirates	Government of UAE	• Established import requirements for dairy products. Any food product containing >15 % dairy content to be accompanied by certificate stating presence of melamine does not exceed 2.5 ppm unless exporting country has banned imports of Chinese dairy products
United States	U.S. Food and Drug Administration (U.S. FDA)	• 1.0 mg/kg in infant formula • 2.5 mg/kg in foods other than infant formula
Vietnam	Vietnamese Ministry of Agriculture and Rural Development (MARD); Ministry of Health (MOH)	• 1.0 mg/kg in food for children under 36 months of age • 2.5 mg/kg for all other food and animal and aquaculture feed (established in part through consideration of other countries ML''s)

[1] **Established limits or threshold limits for further risk assessment and appropriate risk management actions.**

Appendix 2 - Countries comprising each GEMS/Food Consumption Cluster.

A = Angola, Burundi, Cameroon, Central African Republic, Comoros, Côte d'Ivoire, Djibouti, Eritrea, Ethiopia, Gabon, Guinea, Guinea Bissau, Liberia, Mauritius, Rwanda, Sao Tome & Principe, Seychelles, Sierra Leone, Somalia, Uganda, Yemen

B = Cyprus, Greece, Israel, Italy, Lebanon, Portugal, Spain, Turkey, United Arab Emirates

C = Algeria, Egypt, Iraq, Jordan, Kuwait, Libya Arab Jamahiriya, Morocco, Saudi Arabia, Syrian Arab Republic, Tunisia

D = Albania, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Bulgaria, Georgia, Islamic Republic of Iran, Kazakhstan, Kyrgyzstan, Republic of Moldova, Romania, Russian Federation, Serbia and Montenegro, Tajikistan, The former Yugoslav Republic of Macedonia, Turkmenistan, Ukraine, Uzbekistan

E = Austria, Belgium, Croatia, Czech Republic, Denmark, France, Germany, Hungary, Ireland, Luxembourg, Malta, Netherlands, Poland, Slovakia, Slovenia, Switzerland, United Kingdom

F = Estonia, Finland, Iceland, Latvia, Lithuania, Norway, Sweden

G = Afghanistan, Bangladesh, Cambodia, China, India, Indonesia, Laos, Malaysia, Mongolia, Myanmar, Nepal, Pakistan, Sri Lanka, Thailand, Viet Nam

H = Bolivia, El Salvador, Guatemala, Haiti, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Saint Kitts & Nevis, St. Vincent & Grenadine

I = Benin, Botswana, Cape Verde, Ghana, Kenya, Lesotho, Malawi, Mozambique, Namibia, South Africa, Swaziland, Togo, United Republic of Tanzania, Zambia, Zimbabwe

J = Burkina Faso, Chad, Democratic Republic of Congo, Republic of Congo, Gambia, Mali, Mauritania, Niger, Nigeria, Senegal, Sudan

K = Antigua & Barbuda, Bahamas, Barbados, Belize, Brazil, Colombia, Costa Rica, Cuba, Dominica, Dominican Republic, Ecuador, Grenada, Guyana, Jamaica, Saint Lucia, Suriname, Trinidad and Tobago, Venezuela

L = Brunei Darussalam, Fiji, Japan, Kiribati, Democratic People's Republic of Korea, Republic of Korea, Madagascar, Maldives, Papua New Guinea, Philippines, Solomon Islands, Vanuatu

M = Argentina, Australia, Canada, Chile, New Zealand, United Sates, Uruguay