Please note that this statement, published on 4 July 2007 replaces the earlier version which contained errors in the sections “occurrence data in feed and food” on page 3, as well as “toxicity data in domestic animals” on page 9.

Parma, 7 June 2007

EFSA´S PROVISIONAL STATEMENT ON A REQUEST FROM THE EUROPEAN COMMISSION RELATED TO MELAMINE AND STRUCTURALLY RELATED COMPOUNDS SUCH AS CYANURIC ACID IN PROTEIN-RICH INGREDIENTS USED FOR FEED AND FOOD

Question N° EFSA-Q-2007-093

BACKGROUND AS SENT BY THE EUROPEAN COMMISSION ON MAY 8TH 2007

Following reports of sickness and death of pet animals (cats and dogs) in the United States (US), an investigation was undertaken by the US authorities to trace the source of these animal health problems. It was found that wheat gluten used for the production of pet food was at the origin of the animal health problems. Recall of pet food in which the wheat gluten was used was initiated in the US from mid-March onwards.

Following investigations, the addition of melamine, an industrial chemical found in plastics, to wheat gluten imported from China, was found to be the cause of the animal health incidents. Later, melamine and cyanuric acid, a compound structurally related to melamine, was found in rice protein concentrate imported from China. Melamine has also been found in South Africa in corn gluten originating from China. Melamine is used in e.g. plastics, glues, etc. As the protein concentration is measured by analysis of the total nitrogen content, the addition of melamine ($C_3H_6N_6$) is to enhance the apparent protein content of wheat gluten and other protein sources.

In the US, besides pet food also pig feed and poultry feed has been found contaminated to a limited extent.

Although melamine and cyanuric acid have only been found in wheat gluten, rice protein concentrate and corn gluten used in animal feed, it can not be excluded that melamine and structurally related compounds have been added to other protein sources intended to be used for feed or food.

Therefore, in line with the actions taken by the US authorities, and although there is no evidence that contaminated wheat gluten or rice protein concentrate or any other protein source originating from China have been imported into the EU, Member States have been asked by the Commission to control consignments of wheat gluten, corn gluten, corn meal, soy protein, rice bran and rice protein concentrate originating from third countries and in particular from China, for the presence of melamine and structurally related compounds (such as cyanuric acid, ammeline and ammelide) and to report the results of the control (both favourable and unfavourable) to the Commission through the RASFF. Besides their use in feed, mainly pet food, these ingredients can also be used in bread, pastas, pizza dough, baby food, foods for gluten allergic people, etc.

TERMS OF REFERENCE

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Commission has asked the European Food Safety Authority to provide urgently a scientific opinion on the risks to animal and human health related to the presence of melamine and structurally related compounds (such as cyanuric acid, ammeline and ammelide) in protein-rich ingredients used for feed and food.

Interpretation of the terms of reference

Considering the urgency of the request for advice, the lack of exposure data of (pet) animals and humans, and the requested short response time, it was decided to produce at this point in time an EFSA Statement rather than an opinion of the Scientific Panel on contaminants in the food chain (CONTAM). The chair and the vice-chairs of the CONTAM Panel have been involved in the drafting of this EFSA Statement.

INTRODUCTION

This statement is based on extensive literature searches performed using the web pages of international scientific bodies such as the WHO, IPCS, IARC, the web pages of the U.S. Environmental Protection Agency and the U.S. Food and Drug Administration (FDA), and search engines such as Pubmed from NCBI (1966 to 4 June 2007).

Melamine (2,4,6-triamino-1,3,5-triazine, CAS number 108-78-1) is a chemical intermediate used in the manufacture of amino resins and plastics. Its use has a long standing history since it has been commercially available from the late 1930s onwards (IARC, 1999) in a range of products i.e. in combination with formaldehyde to produce melamine resin as durable thermosetting plastics, and melamine foam, a polymeric cleaning product. Other end products include countertops, fabrics, glues and flame retardants. It is also a major component of pigment yellow 150 (colorant for inks and plastics), fertilizers, and derivatives of arsenical drugs for the treatment of African sleeping sickness (trypanosomiasis). Melamine is also a minor metabolite of cyromazine, an approved insecticide used on a broad range of vegetable crops (FAO, 2006).

Melamine is degraded by hydrolysis by three successive deamination reactions to ammeline (4,6-diamino-2-hydroxy-1,3,5-triazine), ammelide (6-amino-2,4-dihydroxy-l,3,5-triazine) and cyanuric acid (s-triazine-2,4,6-triol, in equilibrium with the trione form depending on pH). Cyanurate is the anion of cyanuric acid and can thus form salts with cations, eg. sodium to form sodium cyanurate. Depending on the pH either cyanurate or cyanuric acid dominates.

LEGISLATION

In Europe, melamine is approved for use as a monomer and as an additive in plastics with a specific migration limit of 30 mg/kg food (Commission Directive EC No 2002/72 related to materials and articles intended to come into contact with foodstuffs from 6 August 2002)[1] .

ANALYTICAL METHODS

Melamine and its analogues (ammeline, ammelide, cyanuric acid) can be determined by gas chromatography (GC) after trimethylsilylation (Stoks and Swharts, 1979) or high-performance liquid chromatography (HPLC) (Beilstein *et al*., 1981; Sugita *et al*., 1990).

For the determination of melamine in food such as lard, potato proteins, food-simulants and beverages only few methods have been reported such as spectrophotometry (Hirt *et al*., 1955), liquid chromatography (Bisaz and Kummer, 1983; Inoue *et al*., 1985; Ishiwata *et al*., 1987; CEN, 2005) as well as GC (Isiwata *et al*., 1986). The U.S. FDA (2007b) used GC-MS (gas chromatography-mass spectrometry) after trimethylsilylation for the determination of melamine and its analogues in wheat gluten and pet food matrices. This method has also been recommended by the European Commission to be used by its Member States to analyse consignments of wheat gluten, corn gluten, corn meal, soy protein, rice bran and rice protein concentrate originating from third countries, in particular from China.

OCCURRENCE DATA IN FEED AND FOOD

The presently available data for melamine and its analogues in feed and food are scarce since these compounds have not been routinely monitored.

Melamine has been detected using liquid chromatography in beverages at levels of 0.54, 0.72, 1.42 and 2.2 mg/kg in coffee, orange juice, fermented milk and lemon juice respectively, with a limit of detection 0.05 mg/L. These levels originate from migration of melamine from the cup, made of melamine-formaldehyde resin, into the beverage under experimental hot and acidic conditions (95°C for 30 mn) (Ishiwata *et al*., 1987).

The pesticide cyromazine is partially metabolised to melamine and maximum levels of 0.25 mg/kg of combined cyromazine and melamine (expressed as melamine equivalents) have been estimated in chicken meat and eggs for layer hens fed a maximum level of 5

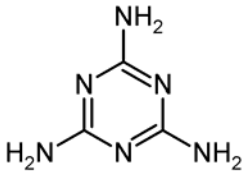
[1] OJ L 220, 15.08.2002, p.18-58

mg/kg of cyromazine (Meek *et al.*, 2003). When drinking water is treated with sodium dichloroisocyanurate for disinfection purposes (rapidly dechlorinated to cyanurate), exposure has been estimated to be 0.06 mg/kg b.w. per day in adults, 0.19 mg/kg b.w. per day for children and 0.28 mg/kg b.w. per day for a bottle fed infant (FAO/WHO, 2004).

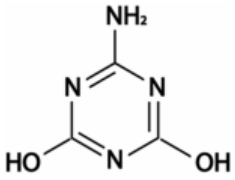
Recent data reported by the U.S. FDA showed melamine in wheat gluten and rice protein concentrate imported from China at levels in the range of 0.2 to 8 % (i.e. 2 to 80 g/kg). Melamine, cyanuric acid, ammelide and ammeline have also been determined in pet food scraps (n=57), bakery meal (n=27), swine (n=17) poultry (n=21) and fish (n=7) feed samples as well as in animal tissues (US-FDA, 2007a). A lot of samples tested were negative for melamine with concentrations below the limit of detection (LOD) (50 to 100 µg/kg). Results for the positive samples are reported below. Different pet food scraps samples ranged for melamine, cyanuric acid, ammelide and ammeline from 9.4 to 1,952 mg/kg, 6.6 to 2,180 mg/kg, 6.0 to 10.8 mg/kg and 3.0 to 43.3 mg/kg, respectively, were given. In bakery meal samples the concentrations were much lower with values ranging from 10.6 to 59.6 mg/kg, 1.8 to 146.3 mg/kg, 1.2 to 24.9 mg/kg, and 20.1 mg/kg for melamine, cyanuric acid, ammeline and ammelide, respectively. In swine feed samples the concentrations for melamine, cyanuric acid, ammeline and ammelide ranged from 30 to 120 mg/kg, 6.6 to 22.5 mg/kg, 5.6 to 10.8 mg/kg and 33.6 to 43.2 mg/kg, respectively. In poultry feed samples the samples were negative for melamine and ammeline and positive for cyanuric acid, (2.11 to 2.63 mg/kg) and ammelide (13.9 mg/kg). Concentrations of melamine in fish feed samples ranged between 53 and 400 mg/kg (US-FDA, 2007a). The concentrations of melamine in swine and poultry tissues were below the LOD. Base on these data the U.S. FDA conducted an interim melamine and analogues safety/risk assessment and concluded that the consumption of pork, chicken, domestic fish, and eggs from animals inadvertently fed animal feed contaminated with melamine and its analogues it is very unlikely to pose a human health risk.

TOXICOKINETICS: ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION

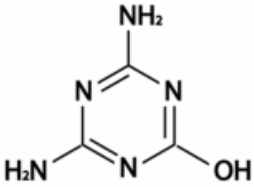
Melamine is degraded by hydrolysis by three successive deamination reactions to ammeline, ammelide and cyanuric acid in mammals and bacteria (Mast *et al.*, 1983, Shelton *et al.*, 1997). The respective chemical structure is presented in figure 1.



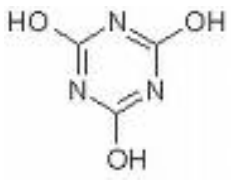
Melamine



Ammelide



Ammeline



Cyanuric acid

Figure 1. Chemical structure of melamine and its analogues

Melamine

The metabolism, excretion and disposition of melamine was assessed after oral administration of a single dose of 0.025 mCi (0.38 mg) [^{14}C] melamine to adult male Fischer 344 rats. Overall, 90 % of the administered dose was excreted within the first 24 hours into urine and negligible radioactivity appeared in the exhaled air and the faeces. Virtually no residual radioactivity was observed in tissues examined after 24 hours. Only slight differences in levels of radioactivity between blood, liver or plasma were observed, suggesting that melamine is distributed in the body water. Radioactivity levels were much higher in the kidney and the bladder compared to plasma. The authors concluded that bladder levels were highest, probably due to either back diffusion from urine or a contamination of the bladder tissue with urine. However, these hypotheses are questionable since reabsorption of the compound can also happen and would be dependent of the pH of the organ and the urine itself since melamine is a basic compound (for further details please see toxicity in domestic animals).

The elimination half-life derived from plasma data was 2.7 hours and was similar to the urinary-excretion half-life of 3.0 hours. Renal clearance of melamine was 2.5 ml/min. This rapid clearance from the body shows that melamine and its analogues do not accumulate in mammalian tissues. Biological oxidation of 2,4-diamino-6-substituted pyrimidines have been studied using hepatic microsomes from various mammalian species. With the 6-hydroxy-, 6-amino-, and unsubstituted 2,4-diaminopyrimidines and melamine, no N-oxidative metabolites were detected (El Ghomari and Gorrod, 1987). The results indicate that melamine is hydrolysed and excreted thereafter without further metabolism (Mast *et al.*, 1983).

Cyanuric acid, ammeline and ammelide

Cyanurate is rapidly absorbed following oral ingestion by rats, dogs and human volunteers and eliminated unchanged into the urine (Allen *et al.*, 1982, Hammond *et al.*, 1986). Absorption and excretion of cyanuric acid has been studied in long-distance swimmers exposed by swimming in pools disinfected with chlorinated isocyanurates, and in two volunteers given an unspecified solution of cyanuric acid orally. More than 98 % of the administered dose was recovered unchanged in urine after 24 hours. The half-life of excretion was about 3 hours (Allen *et al.*, 1982).

There is no data on the toxicokinetics of ammeline or ammelide in animals or humans.

The insecticide cyromazine is metabolised to melamine but only to a minor extent. Toxicokinetic studies in rats given ^{14}C-labelled cyromazine as single or repeated oral doses showed that it is rapidly and nearly completely absorbed from the gut, distributed to all organs and tissues and excreted rapidly into the urine (97 % of the dose after 24 hours). It is incompletely metabolized via methylation, hydroxylation or N-dealkylation and the parent compound represents 71 – 72 % of the radiolabel; melamine reprsents only 7 %, the remaining 20 % are hydroxycyromazine. methylcyromazine and unidentified metabolites. In monkeys (*Macaca fasicicula*), radiolabelled cyromazine excretion was also rapid and extensive, representing 95 % of urinary radioactivity, the remaining 5 % radioactivity was attributed to melamine (FAO, 2006). These data show that melamine exposure of humans through residues in meat as a consequence of cyromazine treatment of animals would be low.

TOXICITY DATA

Melamine

The acute toxicity of melamine in rodents is low (oral LD_{50} 3100 - 3300 mg/kg b.w.). In rabbits, the dermal LD_{50} was 1000 mg/kg. Melamine does not cause eye irritation in rabbits nor is it a sensitizer in guinea pigs and humans. After repeated dietary administration of high doses to rats and mice, the main toxic effects are calculi formation, inflammatory reactions and hyperplasia in the urinary bladder, especially in males (IARC, 1999; FAO, 2006). In the male rat, the only treatment related effect in a 90 day study was an increased incidence of urinary bladder stones at dietary concentrations of 1,500 mg/kg and higher (equivalent to 150 mg/kg b.w.) while no bladder stones were seen in female rats at dietary concentrations up to 12,000 mg/kg (NTP 1983). To perform the recent melamine risk assessment the U.S. FDA used a NOAEL of 63 mg/kg/b.w. per day from a 13 weeks oral rat study (OECD, 2002; US-FDA, 2007a). The lowest calculated NOAELs for oral reproductive and developmental toxicity in rats are 400 mg/kg b.w. per day (maternal) and 1060 mg/kg b.w. per day (fetal), respectively (OECD, 2002; US-FDA, 2007a).

Melamine (>95 % pure) was given to groups of 50 male rats and 50 mice of each sex for 103 weeks via diets containing 2,250 or 4,500 mg/kg melamine. Groups of 50 female rats were fed diets containing 4,500 or 9,000 mg/kg melamine. Transitional-cell carcinomas were found in the urinary bladder of male rats (controls, 0/45; low dose, 0/50; high-dose,

8/49 (16 %)). These tumors were not observed in female rats. Seven of the eight high-dose male rats with the transitional-cell carcinomas also had bladder stones (NTP, 1983). Although bladder tumors related to calculi formation are not considered to be species-specific, they are related to the administration of high doses (IARC, 1999; Meek, 2003).

The recent IARC assessment for the carcinogenicity of melamine concluded that melamine is not classifiable as to its carcinogenicity to humans (Group 3) (IARC , 1999).

In conclusion, melamine is not genotoxic, carcinogenic or teratogenic. The Scientific Committee of Food (SCF) derived a TDI of 0.5 mg/kg b.w. per day for food contact materials but no details were given for its derivation (EC, 1986). The recent U.S. FDA assessment supports this TDI since a NOAEL of 63 mg/kg b.w. per day was used to derive a TDI of 0.63 mg/kg b.w. per day using an uncertainty factor of 100 (US-FDA, 2007a).

Cyanuric acid, ammeline and ammelide

Data on the toxicity of cyanuric acid are scarce (Canelli, 1974; Hammond *et al.,* 1986; US-EPA, 2007). Cyanuric acid has a very low acute toxicity in rats (LD_{50} >5000 mg/kg b.w.).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has assessed sodium dichloroisocyanurate which is rapidly and completely dechlorinated to cyanurate when dissolved in water (FAO/WHO, 2004). In mice receiving drinking-water containing sodium cyanurate at a concentration of up to 5375 mg/L (the limit of solubility at pH 7.0; equivalent to 0, 252, 522 or 1500 mg/kg b.w. per day), for 13 weeks, the only compound-related change reported was the occurrence of bladder calculi in two males in the group given the highest dose. The NOAEL was 1792 mg/L (equivalent to 522 mg/kg b.w. per day) (FAO/WHO, 2004).

Rats were given drinking-water containing sodium cyanurate at a concentration of 896, 1792 or 5375 mg/L, equivalent to 72, 145 or 495 mg/kg b.w. per day, for 13 weeks. A number of male rats in the group given a dose of 495 mg/kg b.w. per day (weeks 6 and 8, 1/4; week 10, 2/4; week 13, 4/20) and one male from the group given a dose of 145 mg/kg b.w. per day at week 13 had epithelial hyperplasia of the bladder. No treatment-related effects were observed in the kidney or in any other tissue (FAO/WHO, 2004)).

Rats were given drinking-water containing sodium cyanurate at a concentration of 400, 1200, 2400 or 5375 mg/L, equivalent to 0, 26, 77, 154 or 371 mg/kg b.w. per day, for a period of 2 years. There was no substance-related increase in tumour incidence. Lesions of the urinary tract and heart were reported in males at the high dose, occuring mostly in the first 12 months of the study. Urinary lesions, consisting of hyperplasia, bleeding and inflammation of the urinary bladder epithelium, inflamed ureters and renal tubular nephrosis were probably related to calculi formation. Acute myocarditis, necrosis and vascular mineralization were secondary to the uraemia caused by the urinary tract lesions. The NOAEL was 2400 mg/L (equivalent to 154 mg/kg b.w. per day) (FAO/WHO, 2004).

In a similar 2-year study in which mice received a dose of sodium cyanurate equivalent to 30, 110, 340 or 1523 mg/kg b.w. per day, survival was similar in all groups and there were no treatment-related changes in the incidence of tumours or other histopathological lesions (FAO/WHO, 2004).

There were no signs of toxicity in adult animals and no effects reported in the offspring of groups of Charles River COB and CD rats given sodium cyanurate at doses of 0, 200, 1000 or 5000 mg/kg b.w. per day, by gavage, on days 6–15 of gestation.

Three generations of Charles River CD rats were given drinking-water containing sodium cyanurate at an estimated dose of 26, 77 or 100 mg/kg b.w. per day, with control groups receiving untreated drinking-water or sodium hippurate. There were no treatment-related effects on reproductive parameters. Sodium cyanurate was not genotoxic in four different tests (FAO/WHO, 2004).

In conclusion, sodium cyanurate did not induce any genotoxic, carcinogenic or teratogenic effect. The NOAEL for sodium cyanurate derived from the 2-year study in rats was 154 mg/kg b.w. per day. Consequently, a TDI of 1.5 mg/kg b.w. per day can be established by applying an uncertainty factor of 100 to this NOAEL.

There are no data on the toxicity of ammeline or ammelide in animals or humans in the public domain.

Toxicity data for domestic animals

In an oral toxicity study in dogs fed 1200 mg melamine/kg b.w. per day for one year, crystalluria was reported after 60 to 90 days and persisted throughout the study period but no other effects were observed (OECD, 2002; US-FDA, 2007a). A 4-week oral study was also performed in female dogs applying a lower dose of 126 mg/kg. In this case no toxicity was reported at the clinical, pathological or histological level (Lipschitz and Stokey, 1945; OECD, 2002). A report of melamine toxicity is available in merino sheep. At doses of 100, 50, 25 g/animal per day, the sheeps died within 7 to 11 days, increases in urea blood levels were observed and crystals in the kidney and nephrosis of the kidney tubules were found post mortem. No further details on dose-response levels were given in the study. Three sheep's were given 10 g/animal per day of melamine; two of them died after 16 and 31 days after loss of appetite and development of uremia. Three days before death levels of urea and creatinine in blood were rising sharply. At post mortem observation, crystals in the kidneys and severe oedema of the lungs were observed. Melamine was fed to sheep (7g/sheep per day) by mixing it into maize meal and all animals survived for 6 weeks. No excessively high values for urea in blood were observed. No effect on pH or motility of rumen and no hepatotoxicity were found (Clark, 1966).

The recent incidence of death of pet animals (cats and dogs) in the U.S. has been linked to acute renal failure and investigations are still ongoing to elucidate if the combination of melamine and cyanuric acid may be responsible for the observed toxicity.

In the absence of other diseases, the specific sensitivity of these two animal species is likely to be explained by melamine and cyanuric acid kinetics parameters rather than being attributable to non-recognized species-specific toxicological effects. One of the relevant aspects is the amount of either melamine or cyanuric acid reaching the urine.

Dependent of the pH in urine, melamine will form insoluble complexes with cyanuric acid. This could lead to crystallization and subsequent tissue injury. The weak acid cyanuric acid is likely to be ionised in an alkaline environment. As urine contains a number of monovalent and divalent ions, the formation of insoluble salts can easily occur, again resulting in crystal formation and subsequent tissue injury. These mechanisms are described for a large variety of compounds and medicinal products, explaining the differences in species sensitivity and renal and urinary tract injury. It should be noted that cats and dogs physiologically have an acid urine, rats and pigs as omnivorous species have a neutral urinary pH, and herbivorous species, like sheep, cattle and horses, have an alkaline urine.

CONCLUSIONS

The Scientific Committee of Food (SCF) derived a tolerable daily intake (TDI) of 0.5 mg/kg body weight (b.w.) per day for melamine for food contact materials but no details were given for its derivation. Recently the U.S. Food and Drug Administration (FDA) derived a TDI of 0.63 mg/kg b.w. per day which is in line with the TDI derived by the SCF. For melamine a specific migration limit of 30 mg/kg food was agreed by the SCF assuming a maximum consumption of 1 kg food containing the substance for a 60 kg person.

Based on the NOAEL for sodium cyanurate derived from the 2-year study in rats of 154 mg/kg b.w. per day, a TDI of 1.5 mg/kg b.w. per day can be proposed using an uncertainty factor of 100.

There is a lack of toxicity data for ammeline and ammelide. Because of the structural similarities to melamine these compounds have been assumed to be of equal potency.

In conclusion, EFSA provisionally recommends to apply a TDI of 0.5 mg/kg b.w. per day for the total of melamine and its analogues (ammeline, ammelide, cyanuric acid). Because of a lack of toxicity data in domestic animals, EFSA provisionally recommends to apply this tolerable intake level as established for humans also to domestic animals.

A source of uncertainty is the combined toxicity of melamine and cyanuric acid and their possible synergistic effects in relation to the recently observed toxicity linked to the acute renal failure and death of pet animals (cats and dogs) in the U.S. This mechanism is currently under investigation.

Ocurrence data on melamine and its analogues in food and feed from Europe are needed to perform a comprehensive risk assessment.

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