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Melamine-contamination event, China, September 2008

Description of the event

More than 54 000 infants and young children have sought treatment for urinary problems, possible renal tube blockages and possible kidney stones related to the melamine contamination of infant formula and related dairy products. Three deaths among infants have been confirmed, more than 14 000 infants have been hospitalized and a little less than 13 000 remain so. Kidney stones in infants are very rare.

While the exact onset date of illness resulting from contamination and the beginning of the contamination itself remain unknown, a manufacturer (Sanlu) received a complaint of illness in March 2008.

Chinese media reported at the beginning of September that Sanlu brand infant formula produced by Hebei-based Sanlu Group was contaminated with melamine. Sanlu's powdered infant formula is widely consumed by infants across China because the product is relatively affordable compared to others.

Following inspections conducted by China's national inspection agency, at least 22 dairy manufacturers across the country were found to have melamine in some of their products.

Two companies, Guangdong Yashili and Qingdao Suokang, exported their products to Bangladesh, Burundi, Myanmar, Gabon and Yemen. While contamination in those exported products remains unconfirmed, a recall has been ordered from China.

Other countries, however, have also reported finding melamine in dairy products manufactured in China.

So far, contamination has also been found in liquid milk, frozen yogurt dessert and in coffee drink. All these products were most probably manufactured using ingredients made from melamine contaminated milk.

In 2007, melamine was found in pet feed manufactured in China and exported to the United States of America, and caused the death of a large number of dogs and cats due to kidney failure.

Melamine contamination

Presentation of melamine

Melamine is a chemical compound that has a number of industrial uses, including the production of laminates, glues, dinnerware, adhesives, molding compounds, coatings and flame retardants. Melamine is a name used both for the chemical and for the plastic made from it. In this event, all references are to the chemical. There are no approved direct food uses for melamine, nor are there any recommendations in the Codex Alimentarius. Melamine is illegally added to inflate the apparent protein content of food products. Because it is high in nitrogen, the addition of melamine to a food artificially increases the apparent protein content as measured with standard tests.

Source of the contamination

In this event, contamination appears to have happened as fraudulent contamination in primary production. Chinese government officials have pinpointed milk collecting stations as the sites where the melamine was added. According to Sanlu, contaminated milk was used in the manufacture of powdered infant formula processed before 6 August 2008 and the tainted milk powder has also been used in the manufacture of a number of other products.

Contamination levels

There are a total of 175 infant formula manufacturers across China, of which 66 have halted production and the remaining 109 manufacturers have undergone inspection due to the current events of melamine contamination. The inspections' results presented by the Administration of Quality Supervision, Inspection and Quarantine (AQSIQ) show evidence of the presence of melamine. Out of 491 batches tested, 69 of them, produced by 22 companies, tested positive for Melamine.

According to the State Council of China, the levels found in the batches ranged between 0.09 mg/kg and 619 mg/kg. Batches from the company Shijiangzhuang Sanlu Co. contained the highest levels, up to 2563 mg/kg.

Toxicology of melamine

Based on the previous incidents of melamine contaminated pet food and the development of kidney stones and subsequent acute kidney failure in cats and dogs, it appears that melamine and its structural analogues, such as cyanuric acid, may act together to form crystals. This crystal formation occurs at very high-dose levels and is a threshold and concentration dependent phenomenon, which would not be relevant at low levels of exposure (US FDA/CFSAN Interim Melamine and Analogues safety/risk assessment http://www.cfsan.fda.gov/~dms/melamra.html).

Exposure

Consumer exposure to melamine is considered to be low, but may occur through the extraction of melamine from compression moulds by acidic foods, such as lemon or orange juice or curdled milk, at high temperature. Taking into account these sources the estimated oral uptake of melamine is around 0.007 mg melamine/kg/day (OECD 1998).

Toxicity of melamine

Melamine is not metabolized and is rapidly eliminated in the urine. No human data could be found on the oral toxicity of melamine but there are data from animal studies. These show the compound to have a low acute toxicity, with an oral LD_{50} in the rat of 3161 mg/kg body weight. In animal feeding studies, high doses of melamine have an effect on the urinary bladder, in particular causing inflammation, the formation of bladder stones and crystals in the urine. Analysis of the bladder stones has shown that these are a mixture of melamine, protein, uric acid and phosphate. Animal studies have generally not shown any renal toxicity or the formation of kidney stones.

Carcinogenicity

The International Agency for Research on Cancer (IARC) has concluded that there is sufficient evidence in experimental animals for the carcinogenicity of melamine under conditions in which it produces bladder stones. There is inadequate evidence for carcinogenicity in humans.

Role of melamine in the formation of kidney stones

Animal data have not shown that melamine alone causes renal failure or the formation of kidney stones. Evidence from an earlier outbreak of acute renal failure in cats and dogs associated with contaminated pet food suggests that a combination of melamine and cyanuric acid does cause renal toxicity. Both of these compounds were found in the pet food together with other triazine compounds. Subsequent experimental studies in animals have shown that when they are fed a mixture of melamine and cyanuric acid this causes the formation of crystals in the tubules of the kidneys,

eventually blocking them and causing renal damage and renal failure. The source of the cyanuric acid in the pet food was unknown but it may have been present as a contaminant of the melamine that had been illegally added to wheat gluten used in formulating the petfood. In the current event in China, the presence of cyanuric acid has not yet been confirmed.

Health-based Guidance Values

Following the petfood incident in 2007 described above, several authorities have preformed preliminary risk assessments.

The US FDA has published an interim safety/risk assessment on melamine and structural analogues and has established for melamine a tolerable daily intake TDI of 0.63 mg per kg of body weight per day.

The European Food Safety Authority has published a provisional statement and recommended to apply a TDI of 0.5 mg per kg of body weight per day as tolerable intake value for melamine.

Epidemiology and treatment

Suggested surveillance case definition

Identification of possible cases related to the consumption of melamine-contaminated products from China

Member States should be aware of the possible distribution of the contaminated products either through formal or informal channels, because of the large quantities involved and the seriousness of the public health consequences of this event. The period of production of contaminated product is uncertain and the incriminated raw material and products may have been exported as infant formula or other milk containing products to other Member States. Therefore WHO is suggesting this surveillance case definition to Member States to increase their awareness of signs that their population may be affected.

Clinical description

The following symptoms have been observed in infants affected by the melamine-contaminated infant formula in China:

- Unexplained crying in infants, especially when urinating, possible vomiting
- Macroscopic or microscopic haematuria
- Acute obstructive renal failure: oliguria or anuria
- Stones discharged while passing urine. For example, a baby boy with urethral obstruction with stones normally has dysuria
- High blood pressure, edema, painful when knocked on kidney area

WHO experts believe an additional symptom may be unexplained fever arising from urinary tract infections/bacteraemia secondary to urine stasis resulting from obstruction.

Surveillance case definition

A case is defined as an infant with kidney stones or other kidney problems (e.g. anuria, renal failure) having consumed powdered infant formula produced in China before 6 August 2008, and where other potential causes of kidney stones have been excluded by differential diagnosis.

Treatment

The World Health Organization has agreed to circulate the information contained herein regarding the treatment plan that is being implemented in China by the Ministry of Health. The information below does not reflect the rules, regulations, policies and guidelines of the World Health Organization.

The following regimen has been issued by the Ministry of Health, China.

Clinical manifestations

1. Unexplained crying, especially when urinating, possible vomiting
2. Macroscopic or microscopic haematuria
3. Acute obstructive renal failure: oliguria or anuria
4. Stones discharged while passing urine. For example, a baby boy with urethral obstruction with stones normally has dysuria
5. High blood pressure, edema, painful when knocked on kidney area

Key diagnostic criteria

1. Been fed with melamine-contaminated infant milk formula
2. Having one or more of the above clinical manifestations
3. Laboratory test results: routine urine tests with macroscopic or microscopic haematuria; blood biochemistry; liver and kidney function tests; urine calcium/creatinine ratio (usually normal); urinary red blood cell morphology shows normal morphology of red blood cells (not glomerular haematuria); parathyroid hormone test (usually normal).
4. Imaging examination: preferably ultrasound B exam of urinary system. If necessary, abdominal CT scan and intravenous urography (not to be used in case of anuria or renal failure). Kidney radionuclide scans can be used where available to evaluate renal function.
5. Ultrasound examination features:
    - **General features:** bilateral renal enlargement; increased echo on solid tissue; normal parenchyma thickness; slight pyelectasia and calicectasis; blunt renal calyx. If the obstruction locates in the ureter, then the ureter above the obstruction point dilates. Some cases have edema with perinephric fat and soft tissue around the ureter. As the disease develops, the renal pelvis and ureter wall may have secondary edema. A few cases have ascites.
    - **Stone features:** most stones affect the collecting system and ureters on both sides. Ureteral stones are mostly at pelviureteral junction, the part where the ureter passes across iliac artery, and ureter-bladder junction. Stones stay collectively, covering massive areas. Lighter echo in the background. Most stones are different from the calcium oxalate stones. Urinary tract is mostly completely obstructed by the stones.

Differential diagnosis

1. Haematuria differentiation: need to rule out glomerular haematuria.
2. Stone differentiation: the stones are normally radiolucent and have a negative image on urinary tract x-ray. This feature differentiates the stones from those of radiopaque stones of calcium oxalate and calcium phosphate.
3. Differentiation of acute renal failure: need to rule out pre-renal and renal failure.

Clinical treatment

1. Immediately stop using melamine-contaminated infant formula milk powder.
2. Medical treatment: use infusion and urine alkalinization to dispel the stones. Correct the water, electrolyte and acid-base imbalance. Closely monitor routine urine tests, blood biochemistry, renal functions, ultrasound findings (with particular attention to the renal pelvis, ureter expansion, and the change of the stones in shape and location). If the stones are loose and sand-like, they are very likely to be passed out with urine.
3. Treatment of complicated acute renal failure: priority should be given to the treatment of life-threatening complications such as hyperkalemia. Measures include the administration of sodium bicarbonate and

insulin. If possible, blood dialysis and peritoneal dialysis can be used early. Surgical measures can be taken to remove the obstruction if necessary.

4. Surgical treatment: if medical treatment is not effective, and hydrocele and kidney damage present, or blood dialysis and peritoneal dialysis are not available in case of renal failure, surgical methods can be considered to remove the obstruction. Stones can be removed by different methods including cystoscope retrograde intubation into the ureter, percutaneous kidney drainage, surgical removal and percutaneous kidney stone removal. Extracorporeal shock wave lithotripter (ESWL) is greatly limited in its application, because the stones are loose and mainly composed of urate, and the patients are infants.

Follow-up

Once the urinary obstruction is relieved, and the general condition and renal function and urination are back to normal, the children can be discharged.

Key issues to follow-up

Urine routine tests; ultrasound of urinary system; renal function tests; IVP (intravenous pyelogram) if necessary.

Actions taken by INFOSAN

INFOSAN is working directly with Ministry of Health (MoH), China in collaboration with the WHO Country Office in China. Through the INFOSAN Emergency surveillance system, WHO has learned of the contamination of infant formula with melamine and requested further information about the event on the 11 September 2008. MoH confirmed on 12 September 2008 that incriminated products from the Sanlu Company had not been exported and provided WHO with a description of the development of the event. Through further interaction between INFOSAN and MoH the issue of potential other use of the contaminated milk powder as well as parallel (illegal) distribution of contaminated milk powder was raised. An INFOSAN alert was subsequently distributed to the entire network on the 16 September 2008 alerting members of the event and of the possibility of contaminated products finding their way to other markets.

INFOSAN has several times during the past week, kept the entire network informed of developments in relation to this event as well as additional information on other products being found contaminated, information about the toxicity of the melamine and other information to help Member States better understand and assess the potential risks associated with melamine contaminated products.

The Chinese authorities, in their on-going investigation, discovered that 2 producers found to have products contaminated with melamine had exports going to five countries, INFOSAN informed these five countries of the situation.