TOXICOPATHOLOGIC EFFECT OF MELAMINE IN ANIMALS

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ABSTRACT

Nephrolithiasis and acute kidney injury outbreaks in pet animals During 2007-2008, animals and humans from many nations were Linked with melamine and cyanuric acid toxicity. Melamine and cyanuric acid since then, The pathogenic process includes melamine and melamine precipitation, and Cyanuric acid forms crystals in the distal renal tubules, which, in turn, Inflicting kidney damage. Melamine and co-exposure Also, cyanuric acid has been reported to worsen renal toxicity. Alone, with melamine or cyanuric acid. Besides nephrotoxicity, Recent animal experiments have shown the potential for endocrine and neurotoxic impact. Melamine. pet-food and human-food safety accidents occurred worldwide causing infants, cats, dogs, and pigs to suffer diseases and deaths. Veterinary testing laboratories helped classify melamine and melamine analogs as pollutants in affected foods in dogs and cats.

INTRODUCTION

An industrial chemicals associated with triazine used in the manufacture of plastics, flame retardants and other products in the spring of 2007 have been found to be contaminated with melamine (MEL) ,Insoluble melamine cyanurate (MEL-CYA) was formed in the kidney by cyanuric acid (CYA) which caused renal failure in hundreds of U.S. cats and dogs consuming adulterate food (1).

MEL was also found in human-generated animal feed, including poultry, dogs and fish. As these animals were fed MEL contaminated feed, the control of these edible MEL animals tissue that can access the food supply of human beings MEL residues is important (2, 3). Examined MEL and CYA traces from cats and dogs affected in kidney tissue and urine by contamination of pet food, It is possibly due to the high concentrations found in kidneys and urine of infected animals. The procedure for measuring residues of MEL in pig muscle using the LC-MS / MS detection limit (LOD) of 1.7 µg/kg Filigenzi et al. has been validated (1). In our field, the Filigenzi method for the determination of MEL in the catfish muscles has been successfully adapted (4). Other methods for controlling CYA, fish and shrimp residues and MEL and CYA (1) in fish and pork tissues were also being established. this approach has been validated for several fish and shrimp species in this study and used in the examination of muscle samples from MEL, CYA, intentionally fed catfish, truffle, tilapia and salmon. Finally, a selection of more than 100 market fish also was included in this survey (3).

Biochemical aspects

Melamine In animals is consumed easily and reaches the highest plasma levels within 1 h of a single oral dosage (5). His plasma half-life is approximately 2.7. The removal of melamine is unaltered, the half-life in the pig is around 4 hours, with a clearing of 0.11 l/h per kilogram and a distribution volume of 0.61 l/kg (6). There is little information available on other animals. Melamine was detected in dogs' urine during the 2007 animal feed episode (7). In a case study, melamine has been found to be excreted in cows' milk exposed to high protein concentrates tainted by melamine (3). In rats with half-life of approximately 1-2,5 h, cyanuric acid will be rapidly absorbed and disposed in the urine, depending on the given dose. Cyanuric acid can be present in feces when administered at large doses (500 mg/kg. The half life of dogs is 1.5-2 h, and the removal takes place even through the kidneys. In the urine or feces no cyanuric acid metabolites were identified (8). In humans, the absorption of cyanuric acid and excretion was examined in the long-distance swimmers subjected to swimming in disinfected, chlorinated isocyanurate pools and in.More than 98% of the dose was recovered in the urine after 24 hours without improvement.

The half-life of excretion was about 3 hours (9). There was no information available for other structural analogs. Minimal information is available on the absorption of melamine simultaneously administered with cyanuric acid (as separate chemicals and not as the melamine cyanurate complex). Melamine was identified in the urine for pet dogs and cats in the 2007 episode and the kidneys contained melamine-cyanurate cries. Melamine and cyanuric acid in cats dosed with both melamine and cyanuric acid (10). Similarly, traces of muscles and kidneys of orally supplied fish contained both melamine and cyanuric acid, and both compounds were consumed and subsequently excreted. A large number of white precipitate crystals is a truce (11). The absorption and excretion of the melamine-cyanurate complex can vary significantly from the individual absorption and excretion. Preliminary findings for fish indicate that a 28-dose complex absorption of melamine and cyanuric acid is extremely low (12). The destiny of the complex is currently unknown in mammals. The complex can be dissociated in an acidic stomach but no studies research the absorption of the complex ..

Toxicological proof

The preliminary results of recent studies indicate that melamine crystals are easily dissolved by formalin (13). In such tissue, the use of formalin to preserve tissues for histopathology couldn't have been found as all research before 2007 (3).Acute toxicity Of melamine there is low acute toxicity. In male and female rats, the median lethal dose (LD50) was reported at 3161mg/kg of body weight, which is the lowest oral LD 50 in tested rodents (14).

The oral LD50 for (rats and mice) was same. Rodent Toxicity tests In a 14-day survey, melamine has been supplied to 5000, 10 000, 15 000, 20 000 and 30 000 mg/kg dietary concentrations of male and female rats. Until the end of the study, all animals survived. Medium and high doses (15 000 mg/kg diet and above) of male and female rats showed reduction in body weight.. The urinary bladder has a daily dose of 34 mice and hard crystalline materials for all males and some females (15). Sub-chronic toxicity of melamine has been assessed in three 13-week National Toxicology Program (NTP) oral studies in Fischer 344 rats.

The dietary levels of 0, 6000, 9000, 12 000, 15 000, 18 000 mg/kg were used for male and female melamine a 6000 mg/kg diet and a 12 000 mg/kg diet or more in both the sexes, toxicity involved a decreasing weight gain and body weight. A diet of 18 000 mg/kg killed one male rat and 2 males died in a diet of 6000 mg/kg and stones were present in animal urinary bladders .In the (males) 6000 and 12 000 mg/kg diets reported 10% decreased weight gain compared to (females). In all (females) dosed categories, the weight gain was the same as in the control. Feed intake was not affected in either male or female rats category. In 1:10 male rats a diet of 3000 mg/kg was present with transitional bladder epithelium hyperplasia, 3:10 male rats were present on a 6000 mg/kg diet and 9:9 male rats were present on a diet of 12 000 mg/kg. These improvements were seen only in bladder stone male rats. Bladder stones, including a diet of 750 mg/kg, have appeared in all dosing classes. The dose-related calcareous deposits were found in the straight segments of the proximal tubules of female rats (3/10 in a diet of 750 mg/kg, 4/10 in a diet of 1500 mg/kg, 10/10 in a diet of 3000 mg/kg, 8/10 in a diet of 6000 mg/kg, 10/10 in the diet of 12 000 mg per kg (16).

13-week trial, has been carried out to determine the addition of one percent of ammonium chloride in control rats and rats to the 18 000 mg of melamine/kg diet. Ammonium chloride treatment was not affected by the formation of stones (16). Male and female mice were fed melamine in a mouse-sample with dietary concentrations between 6000 and 18 000 mg/kg. The body weight gain decreased in all treatment groups. In mice, bladder stones also occurred in dose-related settings, and incidence is higher among (male) compared to (female). An epithelial ulceration of the bladder was observed and there was a dose associated presence. In 60% of bladder ulcer animals, kidney stones were also seen. epithelial hyperplasia was observed only for males treated at the maximum dosage . Found in a study on the production (0.2, 0.4, 0.7, 1.0, 1.3, 1.6, and 1.9 percent) of melamine stones, which were equal to 2000, 4000, 7000, 10 000, 13 000, 16 000 and 19 000 mg in diets (16, 17).

Other species there's only one dog study publicly available, and thus the detail is incredibly brief. Dogs were fed with melamine at 1200 mg/kg weight per day for 1 year. Crystalluria continued throughout the whole study. One of those dogs formed a

large bladder stone with proof of chronic cystitis (18). In the study with sheep receiving melamine, melamine induced crystal urea and mortality were reported (19). Melamine-fed sheep have experienced weight loss and mortality, but the cause of death has been unknown. In both of these trials, the use of data in the risk evaluation of melamine in ruminants was prevented by severe constraints of experimental designs.

Experiments with long-term toxicity and carcinogenicity Rats were given 0,4500, or 9000 mg/kg in female diet, and 0,2250, or 4500 mg/kg in male diet for 2 years in an NTP carcinogenicity study.

On the other hand, pancreatic islet cell carcinomas were observed in males and endometrial current polyps in females with the statistically important negative trend (16). Mice were fed 2250 or 4500 mg/kg of melamine in a concomitant mouse sample. A reduced rate of survival was found in high-dose males. Stones (calculi) and acute and chronic inflammatory changes in the urinary bladder were observed in treated males. These changes were also observed in high-dose women, but with a slightly lower incidence rate. No neoplasms were present in female bladders (16). Melamine and Cyanuric Acid Toxicological and health Aspects 36 Male rats had 3 or 1% or 3%, 1 or 0.3% (purity, >99 percent; equal to 30 000, 10 000 or 3 000 mg/kg) of melamine in their diet over a 36-week recovery period, followed by 4-week recovery. Besides the calculus, both carcinoma and papillomas were detected in urinary bladders and ureters.

The effects on melamine-induced calculus of sodium chloride and the proliferation of kidney injuries have been assessed in rats. In addition to 10% to 5% of common salt in the diet or 10% of common sodium chloride (100 000 or 50 000 mg/kg in the diet) alone, or 10% sodium chloride alone for 36 weeks, the feeds were fed 3 to 1% melamines in the diet and were fed for 4 weeks. The clinical symptoms of 3% dosed animals included a decreased consumption of food with a lower weight loss, an increase in urine volume and lower osmolality. At the top of the sample were measurements and analyzes showed that the composition was equimolar to melamine and acid. The findings showed that common salt suppresses the development of calculus and hyperplasia of papilla within the kidney. In sedimentary urine,

microcrystals were observed. Ischemic changes were recorded during histopathology in focal fibrosis, inflammation and renal tubular regeneration.

Geneotoxicity Several abstracts say that in chromatid in *vitro or in vivo*, melamine was not mutagenic in a bacterial mutagenicity test in the Chinese hamster ovary cells *Salmonella typhimurium* (20). The Melnick study (21) has shown no evidence of adverse effects on reproductive organs in the 13-week toxicity or the carcinogenicity studies mentioned above, Teratogenic melamine is not in a rodent. The NOAEL amount is approximately 1060 mg/kg body weight per day.

Acute toxicity Cyanuric acid has poor acute oral toxicity. The lowest oral LD50s reported for rats have weight 7700 mg/kg, and for mice 3400 mg/kg body weight (22). Short-term tests of sodium cyanide in mice with levels to 5375 mg/l (equivalent to 1500 mg/kg body weight p) in 13-week studies.

In a related rat sample, 1⁄28 males in the 1792 mg / l (145 mg / kg body weight a day) and 7/28 males in the maximum dose category (495 mg/ Kg body weight a day) were observed with epithelial bladder hyperplasia (15). In an early study, 0.8% to 8% sodium cyanure (equal to 8,000 and 80,000 mg/kg) in diet have been treated orally during 20 weeks.

A number of early experiments in ruminants have been performed, but due to flaws in the studies and their documentation these are not further considered.

Long term experimental toxicity and carcinogenicity In a 2-year trial, rats were given body weight at a dose of 0, 26, 77, 154 or371 mg/kg (0,400, 1200, 2400 and 5375 mg/l), drinking water by control groups, containing sodium hip urate equal to or untreated drinking water content. The highest dose category demonstrated significantly lower survival (9).

In (male rat) who died and obtained in the first year of the studies, multiple urinary tract lesions were reported as secondary to pain and obstruction of the urinary tract (halculi and hyperplasia, bleeding and bladder epithelia inflammation, dilated and inflamed ureters and renal nephrosis tubular) and cardiac lesions (acute myocarditis, necrotic and vascular mineralis) No bladder measurement was found in (female rat) in the first year. In some high-dose males who died earlier, inflammatory heart injuries were evident. No treatment related effects of toxicologically significant

body weight 154 mg/kg, called NOAEL, have been observed in this study (15). In the same two-year study, mice obtained doses equal to 0, 30 and 110; 340 and 1523 mg/kg of the body weight per day of sodium cyanurate (0, 400 and 1200; 2400 melamine and cyanuric acid (38 and 5 375 mg/L);

Cyanuric acid has been found to be non-genotoxic in successful in-*vitro* and in-*viv*o research batteries (15). Cat and dog animals which developed renal crysstals causing renal failures are apparent in multiple case reported in 2007, in which melamine plus cyanuric acid and other structural analogs are the effects of mixed triazin exposure, particularly melamine and cyanuric Acid (17). Thousands of pigs died after melamine-containing diets at 3026 mg/kg, 958 mg/kg ammeline, and 69 031 mg/kg cyanuric acid (16). Melamine & cyanuric acid co-administered oral caused much more harm to the renal than melamine or cyanuric acid alone. Cats receiving 32 or 121 mg/kg body weight of both melamine and cyanuric acid for 2 days showed acute renal failure with urinary crystals and kidney (elevated blood urea nitrogen and creatinine).However, no changes were found with equal doses of melamine or cyanuric acid in individually treated cats for longer periods (23). Melamine as well as cyanuric acid were given to pigs orally (a total of 400 mg/kg body weight had both high nitrogen and creatinine in serum blood urea and formed kidney crystals; no clinical changes or crystals were found in pig, treated with the same dose of melamine or cyanuric acid separately; for 3 days, the mixture melamine and cyanuric acid were given as an oral dose of fish (400 mg/kg body weight). The excretion of certain chemicals is slower in fish than in mammals. It is not possible to grasp the importance of this knowledge for mammals. For the melamine-cyanuric acid mixture administered together in rats, the acute threshold dose is 5 mg/kg body weight per day for 3 day (24).

Preliminary findings for a small number of fish indicate a dosage of 2.5 mg/kg of fish in a 4-day threshold, but that when given for 14 days, the fish are able to grow crystal-high (25). Crystalluria and renal failure evolved and died with different concentrations of melamines, sheep given ammelin or ammelide Long-term melamine, cyanuric acid or analogs co-administrated toxicity, carcinogenicity or genotoxicity have not been reported (26). The toxicity of the melamine-cyanurate complex is not adequately demonstrated. In a study on the acute verbal toxicity of melamine cyanurates in rats and mice, LD50s to b were found. Renal failure induced

by crystal has been described and referred to as 'acute uric acid nephropathy' Renal insufficiency caused by the development of intrarenal uric acid crystals in humans and animals (27). The precipitation of crystals in kidneys is correlated with an acidic urinary-pH of less than 5.5. (These crystals block urine flow in the tubules, contributing to uric acid nephropathy). However, the authors have not given a predictable threshold of uric acid precipitation for uric acid. Serum levels of uric acid are of 80 and 185 mg/dl Toxicological and Health As a predictive threshold for uric acid precipitation (28-30).

The local macrophage and T-cell infiltration granulomate inflammation involves persistent changes in human kidneys (31). Similar alterations have been observed in laboratory rats and mouse models, including intratubular uric and inflammatory infiltrates with the associated necrotic debris, Crystal-induced nephropathy appears to be similar to the nephropathy of uric acid in animals which are exposed to melamine and cyanuric acid because it is a mechanical blockage which leads to renal rather than to a device (32).

A diagnostic problem is created by the detection of non-experimental nephropathy crystal. Because of the method resolution limitations, it is likely that no ultrasound is recognized or found on individual crystals, crystal aggregates or smaller stones. Certain changes are microscopic. Ultrasound reveals only significant changes in the anatomy of the kidney, changes in total medullary density or more than 1 mm of stones. Early changes in the kidneys, including diffuse deposits of calcareous calories, such as in the analysis of NTP (15) in female rats are required by additional methods (32) .

Dose-response considerations In the case of Fischer 344 male rats following exposure to dietary melamine for 13 weeks, a lower oral dose of general toxic effects recorded was 63 mg/kg body weight per day after the use of the dietary melamine for 13 weeks Dose-response considerations (15). The combined review of data in the two independent studies showed a clear response to both the toxicological and health aspects of the development and the occurrence of bladder epithelial hyperplasia. Similar effects have been found in female rats, but at a lower rate of incidence.

Although calcareous deposits showed a high level of melamine in the kidneys of the female rats following subchronic exposure, this was not consistent (only found in one

study). Compared to the previous chronic melamine exposures (2250 or 4500 mg/kg diet), the development of bladder stone occurred less rapidly in both sexes, but in chronic kidney inflammation and nephropathy a dose-dependent rise in female rats (15) .

In the sub-chronic rats the least dose was 750 mg/kg in the diet and resulted in 1/22 compared to 2/10 male rats with bladder stones. The dose-response trend in these data is nevertheless significant ($P < 0.01$), and the second-lowest dose used in male rats is significant ($P < 0.01$) in comparison with combined controls. The Heck & Tyl research in 1985, which showed that after shorter exposure, there was a threshold or NOAEL (0.2% in diet or 2000 mg/kg diet). Modeling with dose responses was chosen as an alternative to traditional NOAEL to capture the overall trend in the dose-response system fully. No major differences between control or presence of melamine crystalluria were found in subchronic animal testing and urinalysis. No bload stones were found in weaning rats (28 days old) at 0,2 percent (2000 mg/kg) for dose comparisons for 4 weeks (34) described above. This is a dosage of about 200 mg/kg bodyweight per day, given the normal dietary factor is 10 (Annex 5).

The BMDL10 estimates for cystolith production for this study are approximately 384 mg/kg of weight a day (0.384 percent of diet). This is 10 times higher than the average daily dose of 35 mg/kg of body weight in subchronic rats. This suggests BMDL10 is a conservative value of 35 mg/kg body weight per day (3٤).

التأثير السمي المرضي للميلامين في الحيوانات

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الخلاصة

حدث وباء ادى لاصابة العديد من البشر والحيوانات في حصى المجاري البولية واذى الكلية الحاد خلال عام ٢٠٠٧ و٢٠٠٨.بسبب الميلامين وحامض السيانويوريك عام ٢٠٠٧ و٢٠٠٨ في واظهرت الدراسات ان الميلامين والسيانويوريك منذ ذلك الحين بانها السبب في ترسب اشكال بلورية في في الانابيب الكلوية

القاصية والتي ادت الى تحطيم الكلي . فيما بعد تبين ان الميلامين لوحده او مع وحامض السيانويوريك بانه السبب في السمية الكلوية، بجانب السمية الكلوية سجل في الحيوانات المختبرية حالات من الاصابة بامراض الغدد الصم فضلا عن السمية العصبية . وجود الميلامين في اغذية البشر وطعام الكلاب والقطط و الخنازير في كل انحاء العالم ادى الى حالات موت عديدة في هذه الحيوانات وخاصة الرضع منها. الفحوصات المختبرية البيطرية ساهمت في تصنيف الميلامين ونظائره كملوث غذائي للكلاب والقطط.

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