

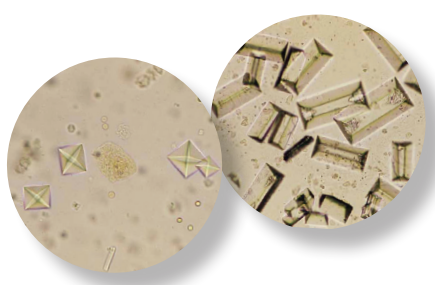
CRYSTALLISATION INHIBITORS ARE DIFFERENT ORGANIC AND INORGANIC SUBSTANCES THAT STABILIZE URINE AND ALLOW SUPERSATURATED URINE TO BE STABLE WITHOUT PRECIPITATION. IT HAS BEEN SHOWN THAT INHIBITORS ACT ON KINETICS, INTERFERING WITH ENUCLEATION, GROWTH AND AGGREGATION OF CRYSTALS.

Various inhibitors have been reported, including:

- **Citrate** is one of the strongest inhibitors of the formation and aggregation of crystals containing calcium. It forms soluble complexes with calcium (calcium chelator) and therefore reduces the supersaturation with respect to calcium oxalate in urine. Citrate also inhibits growth of hydroxyapatite crystals and calcium oxalate and the aggregation of monohydrate calcium oxalate crystals.
- **Phytate or inositol hexaphosphate** has demonstrated its capacity to inhibit the growth of calcium stones in vitro as well as reducing the level of free ionised calcium in the urine
- **Glycosaminoglycans (GAGs)** are macromolecules that can retain a large amount of water. They can be found on the surface of cells in the urinary tract, creating a water barrier that protects from the adhesion of bacteria and crystals. GAGs also act as calcium chelators.

» 4.2 CRYSTALLISATION CATALYSTS

Urine contains some compounds (organic matter, protein, etc.) that may act as crystallisation catalysts. These compounds can react with urine crystalloids, increasing the precipitation of the same urine which is not particularly concentrated.



» OTHERS: ANTIOXIDANTS AND OMEGA-3 FATTY ACIDS

Antioxidants are also recommended for dietary treatment of kidney stones. Since the deposition of calcium oxalate crystals in urinary tract cells causes oxidative stress, it has been proposed that an increased intake of EPA and DHA may reduce the risk of kidney stones by reducing inflammation.

To assess the risk of struvite and oxalate crystal precipitation in the urine of a patient, there is the possibility of analysing the urine's ability to dissolve an added quantity of calcium oxalate or struvite. URINE PRECIPITATION RISK (UPR) is the method described by Lulich et al (2004), to assess the effects of various diets on the cat urine characteristics.

URINE PRECIPITATION RISK, UPR, IS THE METHOD USED BY AFFINITY FOR DEVELOPING ITS NEW PRODUCT, ADVANCE VETERINARY DIETS URINARY FELINE.

THE UPR METHOD IS MORE COMPLETE THAN THE EXCLUSIVE VALUATION OF RELATIVE SATURATION. (RSS)

FELINE IDIOPATHIC CYSTITIS

Feline idiopathic cystitis (FIC) is the leading cause of FLUTD. The diagnosis is generally performed by exclusion of other lower urinary tract disorders. The clinical findings seem to prove the hypothesis that stress is a factor in the development of FIC in cats.

BEHAVIOUR MANAGEMENT

It has been shown that multimodal environmental modification (MEMO) gives good results for relieving FIC symptoms. This involves arrangement of litter, food and drink; environmental enrichment (toys, scratching place, places to climb, exploration opportunities); having a quiet place to rest, provision of environments with different characteristics (more or less heat, places to hide, private space) and increased social interactions.

The effect of the use of pheromones on the stress reduction in cats can justify its use in the treatment of cats with FIC.

DIETARY TREATMENT OF FIC

A scientific study showed that the FIC recurrence after 12 months was reduced when cats are fed a wet diet low in pH (compared to a dry diet low in pH).

Glycosaminoglycans (GAG) are normal components of the mucosa of the urinary bladder and urinary tract and are excreted in urine. Oral treatments to replenish GAGs have been used successfully in people with interstitial cystitis syndrome, a very similar syndrome to FIC.

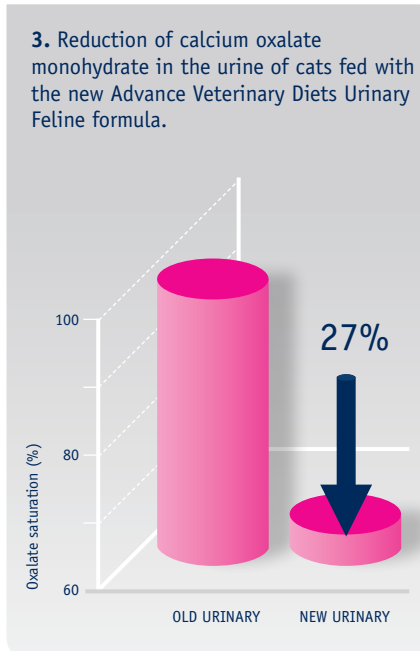
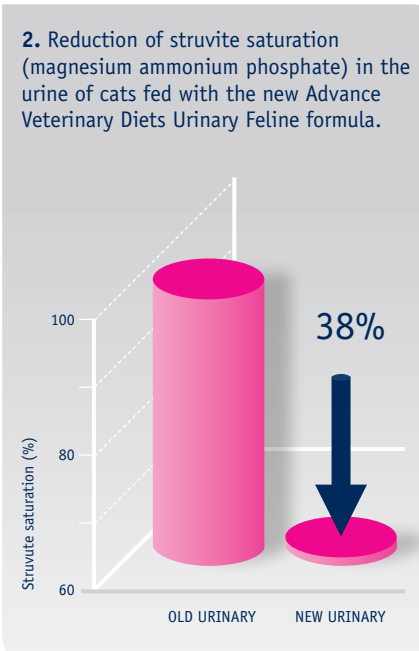
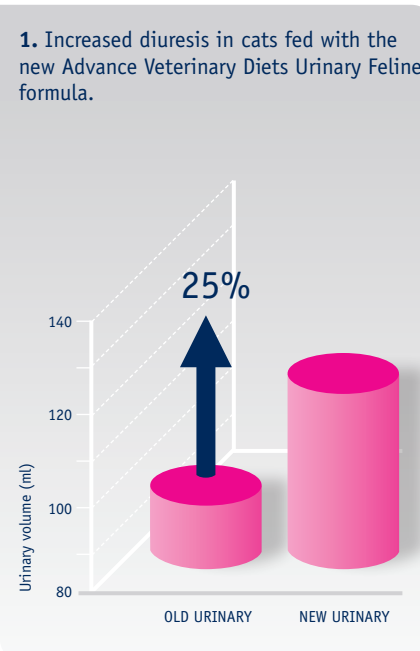
Enrichment of the diet with exogenous GAGs can allow them to repair the defects of urinary mucosa, thus reducing its permeability and decreasing the feeling of pain.

RESULTS OF DIETARY TREATMENT ON THE AMOUNT AND CHARACTERISTICS OF URINE IN CATS FED THE NEW FORMULA ADVANCE VETERINARY DIETS FELINE URINARY

MATERIALS AND METHODS

The same neutered cats were always used. They were fed with the New / Previous ADVANCE Veterinary Diet during the 15-20 days prior to the 24-hour urine sampling to record: urine volume, density and pH. An aliquot of urine from each cat was sent to the lab of the chemical separation technique group (GTS) of the Autonomous University of Barcelona (UAB) to analyse P, Ca, Mg, Na, K, S, uric acid, creatinine, citrate, oxalate, pyrophosphate, phytates, fluorides, chlorides, sulphates, ammonium and glycosaminoglycans.

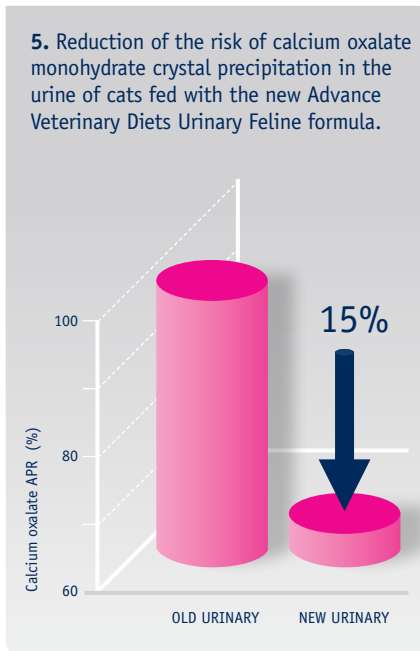
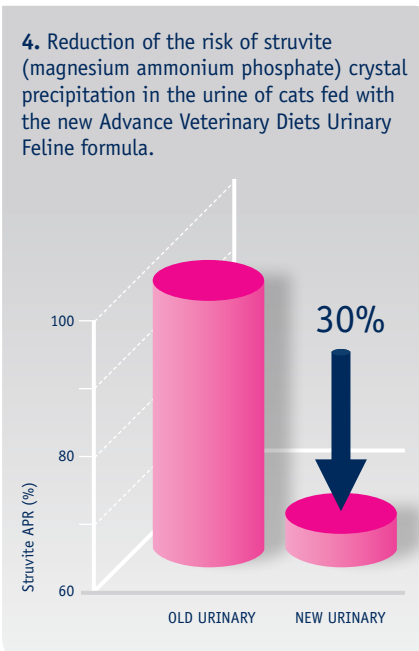
The concentrations of the various compounds were entered into the EQUIL software (Florida, 1998) to calculate the saturation of each compound of interest (struvite and calcium oxalate monohydrate) in those urines.



ASSESSMENT OF CRYSTAL URINE PRECIPITATION RISK (UPR) OR ACTIVITY PRODUCT RATIO (APR)

To assess the risk of oxalate and struvite precipitation in different urines, we used the method described by Lulich et al (2004), which comprises adding calcium oxalate or struvite crystals in the urine and to assessing whether these crystals are dissolved or precipitated.

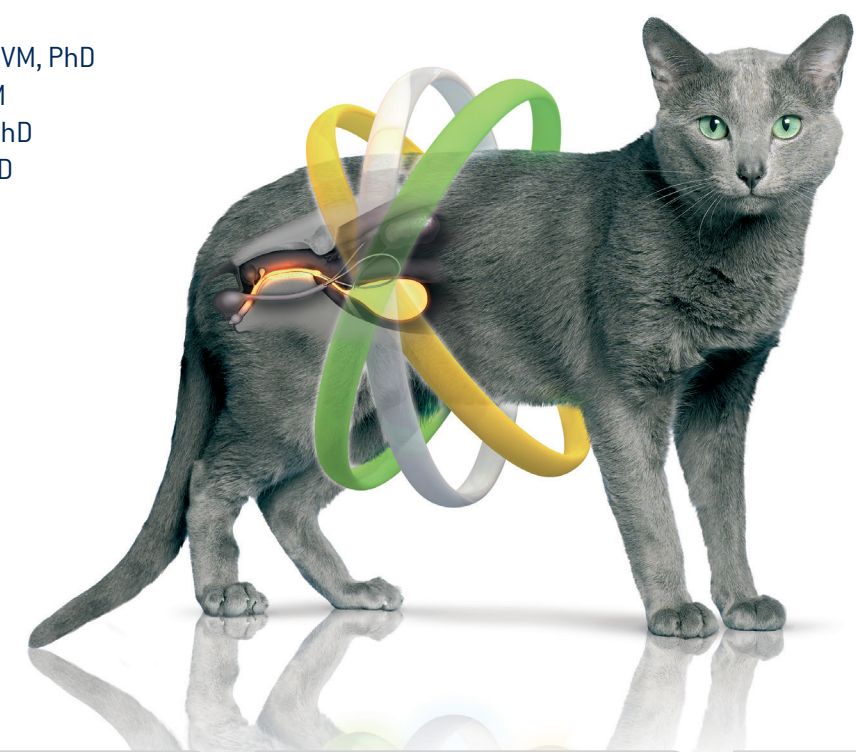
The APR is calculated by dividing the saturation values of urine before and after incubation with the added crystals.



Gerber et al. 2005. *J. Small Anim Pract.* Dec;46(12):571-7 // Lulich et al. 2004. *J. Am. Anim. Hosp. Assoc.* May-Jun 40 (3):185-91 // Osborne et al. 2009. *Vet Clin North Am Small Anim Pract.* 2009 Jan; 39(1):183-97 // Pieras Ayala. 2004. *Tesis Doctoral, Laboratorio Investigación Litiasis Renal. UIB*

Feline lower urinary tract disease (FLUTD) and dietary treatment

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INTRODUCTION

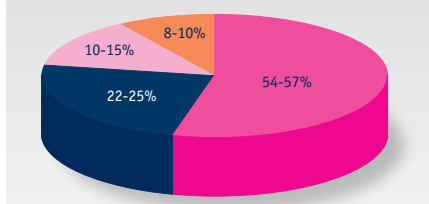
Feline Low Urinary Tract Disease (FLUTD), also known as feline urologic syndrome (FUS), comprises several diseases of various origins but with similar clinical symptoms: bloody urine (hematuria), increased urination frequency (pollakiuria), discomfort and pain during urination (dysuria, strangury) or urinating outside designated places (periuria). It affects approximately 1.26% of the feline population. The recurrence rate is high (30-50%) and even reaches 65% after a period of 6 months in cases of feline idiopathic cystitis (FIC).

FLUTD CAUSES AND RISK FACTORS

FLUTD may be due to a large number of diseases.

ALL STUDIES CONCLUDE THAT IDIOPATHIC CYSTITIS, UROLITHIASIS AND PLUGS ARE THE MOST COMMON CAUSES OF FLUTD AND ACCOUNT FOR OVER 85% OF ALL CASES. (see Figure 1)

Figure 1. Proportion (%) of FLUTD cases in a recent Swiss study (adapted from Gerber et al, 2005).



● Idiopathic ● Uroliths ● Urinary plugs ● Infection

UROLITHS AND PLUGS

TYPE OF MINERAL: STRUVITE, CALCIUM OXALATE AND OTHERS

The crystalline components of urinary calculi include various minerals:

- Struvite (magnesium ammonium phosphate),
- Calcium oxalate (monohydrate (COM) or dihydrate (COD)),
- Others: calcium phosphate, urate, xanthine, cystine, silica, urea.

Or they may also comprise a mix of components.

Uroliths and urinary stones are mineral concretions which can normally be found in different parts of the urinary tract: in the bladder (42%), the urethra (55%) or both. In the case of stones in the lower urinary tract, historically struvite has been the predominant form (>60% struvites, <30% calcium oxalate), although recently the tendency has reversed.

This observation is true in the US, but has also been demonstrated in Canada and Europe.

CURRENTLY, IF WE RELY ON UROLITHS SUBMITTED TO THE TESTING LABORATORY OF THE UNIVERSITIES OF MINNESOTA AND CALIFORNIA WE CAN SAY THAT **CALCIUM OXALATE STONES ARE AS COMMON AS STRUVITE**. ACCORDING TO THE TREND IN THE LAST 3 YEARS, IT APPEARS THAT **STRUVITE STONES ARE ON THE RISE AGAIN**. (see Figure 2)



RISK FACTORS FOR STRUVITE STONES AND CALCIUM OXALATE

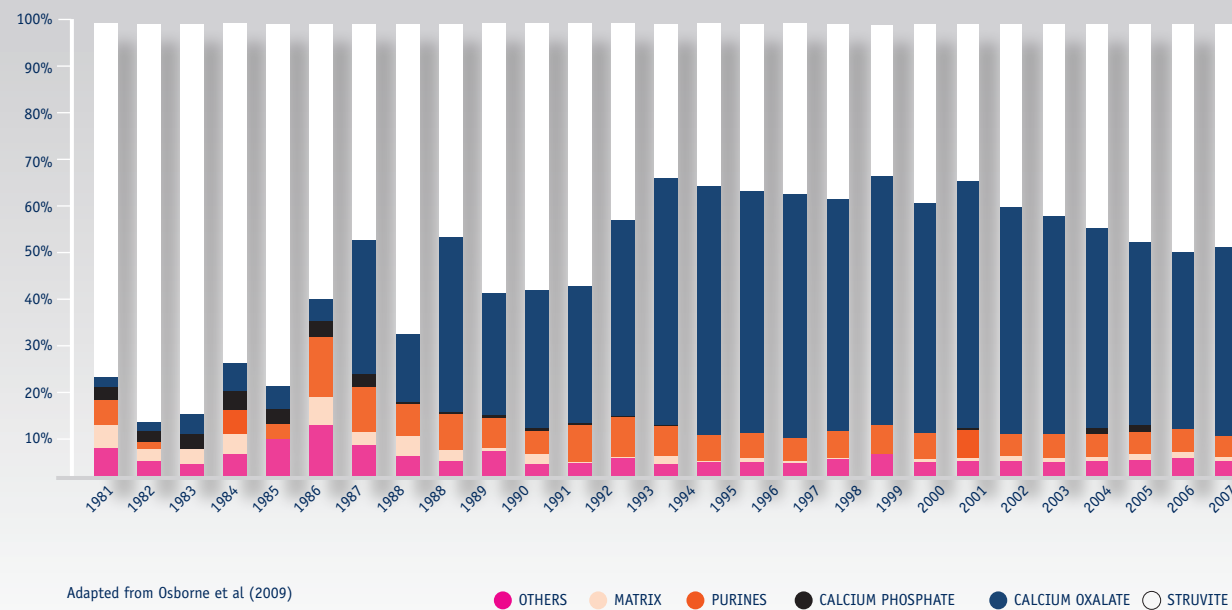
- **SEX** Neutered cats are at greater risk of developing both struvite (x3.5) and calcium oxalate (x7) stones than non-neutered cats. This increased risk could be related to neutered cats' tendency toward being overweight and suffering hormonal changes.
- **AGE** Calcium oxalate and struvite stones in cats may occur at any age. However, cats between 4 and 7 years are at increased risk for struvite stones than younger adult cats (1 to 2 years), while old cats (over 7 years) have an increased risk of developing calcium oxalate stones.

Urethral plugs are diagnosed in between 10% and 21% of cats with FLUTD and contain large amounts of organic matrix (mucoproteins, comprising mucus and inflammatory residues) with varying amounts of minerals.

Urethral plugs are the most common cause of blockages in male cats (60%).

Any crystal may end up trapped in the matrix of a urethral plug, but in most cases (> 80%) they are **struvite crystals**.

Figure 2. Breakdown of feline uroliths sent to the Minnesota Urolith Center from 1981 to 2007.



DIETARY MANAGEMENT OF FELINE UROLITHS AND PLUGS

Some urine features are linked to the risk of developing uroliths:

1. **CONCENTRATION OF FREE LITHOGENIC SUBSTANCES IN URINE.** Chemically evaluated as THE RELATIVE SATURATION (RSS) OF EACH COMPONENT IN URINE.
2. **URINE PH**
3. **THE AMOUNT OF URINE** and the crystal's capacity to remain in the urinary tract, as well as the urine retention time.
4. **INHIBITOR OR CRYSTALLISATION CATALYST CONCENTRATION, GROWTH OF CRYSTALS AND STONE FORMATION.**

» 1. FREE LITHOGENIC SUBSTANCES IN URINE: RELATIVE SATURATION OF URINE FOR EACH COMPONENT CRYSTAL)

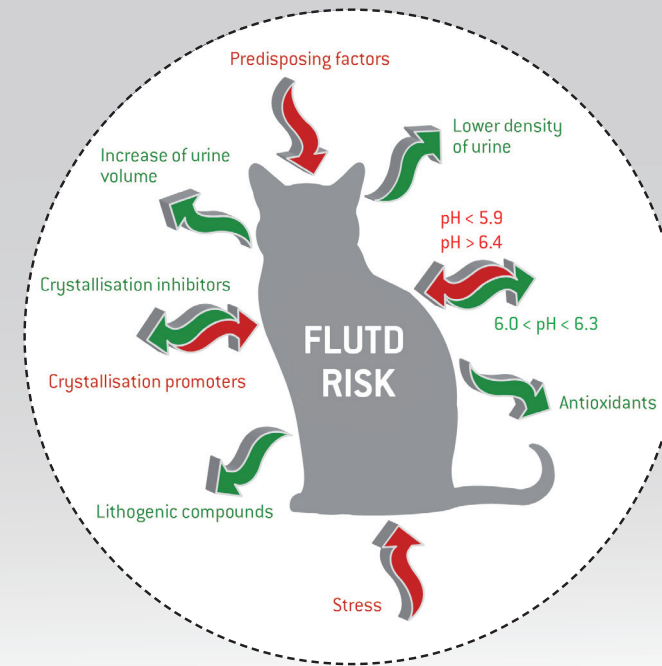
The relative saturation of urine for each crystalline compound is the point at which an addition of the compound will appear as a precipitate. The crystallisation process depends on the chemical compound and the concentration and chemical structure of each compound present in the solution. Depending on the concentration of each substance, the urine may have little saturation or may be supersaturated for that substance, by virtue of its solubility, urine pH, temperature, ionic charge and crystal catalysts.

To determine the relative saturation (RSS) of calcium oxalate and struvite in urine, the concentration of the major ions which interact must be known: phosphorus, magnesium, calcium, oxalate, sodium, potassium, urea, uric acid, etc. The calculations of ion activity of each compound related to the solubility constant are generated by sophisticated computer programs that use databases of equilibrium constants and solubility products (EQUIL, JESS, SUPERSAT, MEDUSA, etc.) (see Figure 4)

» 2. pH

Chemically, struvite is soluble at a urine pH less than or equal to 6.6, but in order

Figure 3. Urolith risk factors: Global Urolith development Risk (GUR).

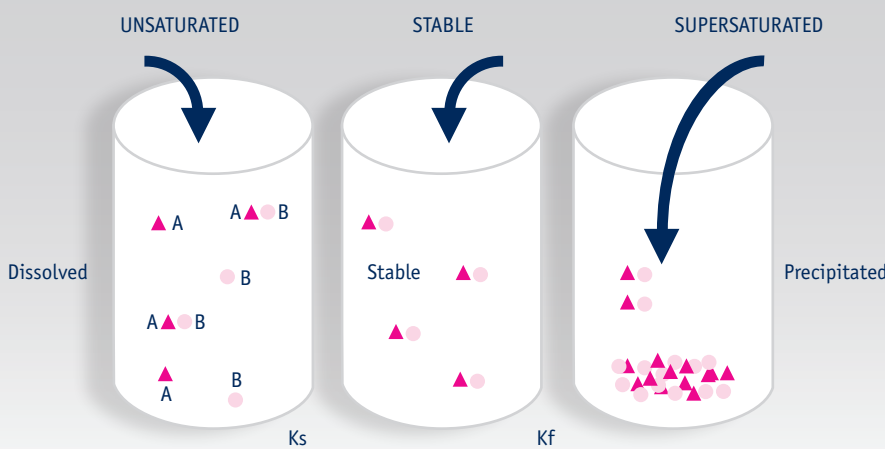


for struvite crystals, already formed, to dissolve, a urine pH below 6.1 is required.

Regarding the precipitation of calcium oxalate in cat urine, some authors have stated that lower lithogenic concentrations are more important than merely a certain pH level, as long as it is not overly acidic.

THE GOAL OF DIETARY TREATMENT IS TO PRODUCE URINE IN WHICH THERE IS NO PRECIPITATION OF CALCIUM OXALATE OR STRUVITE AND IN WHICH THERE IS A STABLE SOLUTION OF BOTH COMPOUNDS, MINIMIZING THE RISK OF UROLITH FORMATION.

Figure 4. Classification of urine with respect to each compound by virtue of their concentration or saturation. RSS



THUS MODERATELY ACIDIC URINE (PH 6.0-6.3) CAN DISSOLVE AND CONTROL THE GROWTH OF STRUVITE CRYSTALS WITHOUT INCREASING THE RISK OF PRECIPITATION OF CALCIUM OXALATE STONES.

» 3. WATER CONSUMPTION, URINE VOLUME AND DENSITY

Increasing **water intake** in cats is important to increase the volume of urine produced and obtain a low density of the same, because:

- It reduces the concentration of stone-forming minerals in urine;
- The frequency of urination is increased and urine transit time is reduced, with less time for the formation, growth and aggregation of crystals.

There are several ways to increase water consumption: add water to the food (dry or canned), use various water cans or fountains, add another source of liquid (canned tuna, clam juice, low-salt gravy, etc.), change the type of water, feed the animal several times a day, etc.

The evidence shows that more salt in the diet increases water intake and urine volume in cats and other species. However, certain veterinary circles question this practice due to the potential adverse

health effects in cats that a 1.1% level of dietary sodium versus recommended levels of 0.35% in dry diets could provoke.

However, Affinity tests have shown that a moderate increase of sodium along with a moderate increase in potassium may also increase water intake and urine volume in cats.

» 4.1 CRYSTALLIZATION INHIBITORS

URINE CONTAINS COMPOUNDS THAT PROMOTE OR INHIBIT FORMATION OF STONES and modulate the lithogenic risk of normally supersaturated urine.

IT IS THEREFORE POSSIBLE TO INCREASE **WATER INTAKE AND DIURESIS** IN CATS BY REDUCING THE DENSITY OF URINE WITH A FORMULATED DIET CONTAINING HEALTHY LEVELS OF SALT (NaCl).

Figure 5. The formulation of a diet with healthy levels of salt can increase water intake and urine output. Water intake in cats fed with Advance Veterinary Diets Feline Urinary as compared with the old formula.

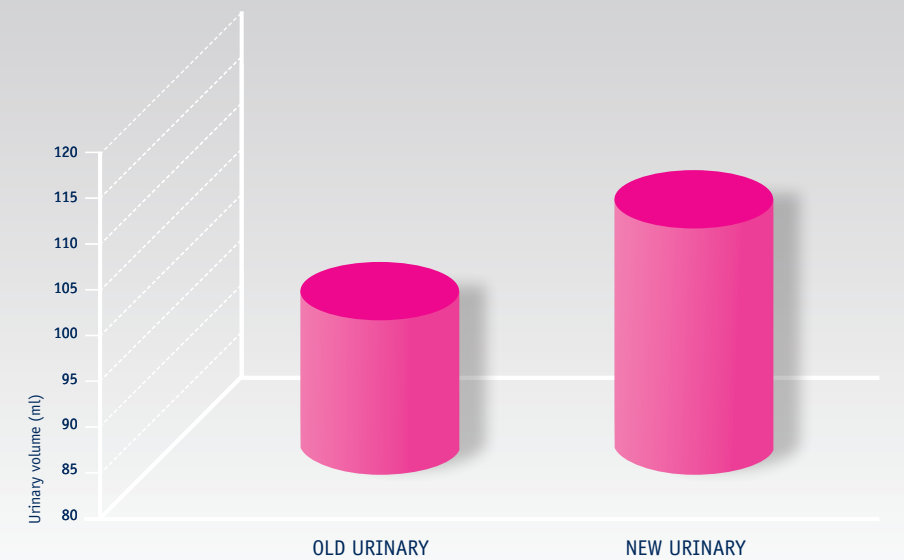
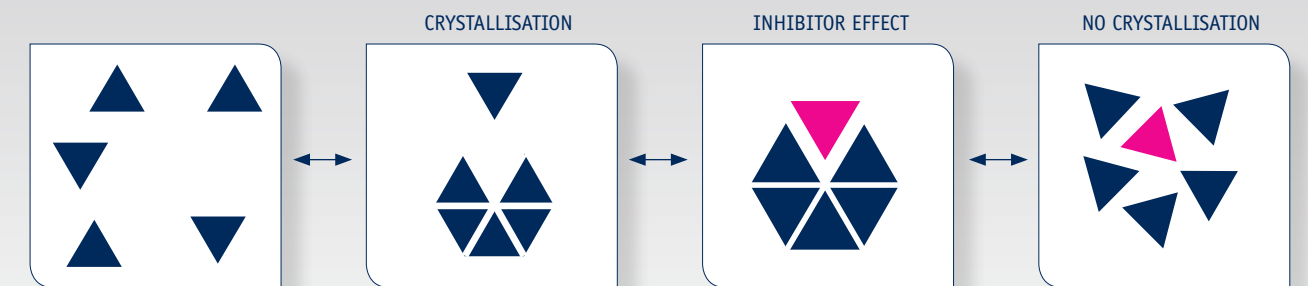


Figure 6. Crystal formation process and inhibitor effects.



From: Pieras Ayala (2004)