

# Clinical Evidence Report

## Managing the most common causes of feline lower urinary tract signs with nutrition

Nutritional management with Hill's® Prescription Diet® c/d® Multicare effectively manages the most common causes of lower urinary tract signs in cats.

- Reduces the rate of recurrent feline idiopathic cystitis (FIC) signs by 89%
- Safely and effectively dissolves struvite uroliths in as early as 7 days (average = 27 days) and reduces risk of recurrence
- Helps manage risk for urethral plugs, which often are associated with FIC and struvite crystalluria
- Significantly lowers the likelihood for calcium oxalate to precipitate in urine

Feline lower urinary tract signs (LUTS) and urethral obstruction are common challenges managed in clinical practice and can have important consequences on the pet-family bond. Inappropriate elimination, a common sign of disorders affecting the lower urinary tract, is a frequent reason for relinquishment of cats to shelters.<sup>1</sup> The most common causes of feline LUTS include FIC, which is responsible for approximately two-thirds of cases, followed by uroliths and urethral plugs.<sup>2</sup> Struvite and calcium oxalate are the most common uroliths in cats and urethral plugs are almost always composed of struvite.<sup>3</sup> Urethral obstruction is very common in male cats with urethral plugs and frequently occurs in cats with FIC.<sup>4-7</sup>

### Feline Idiopathic Cystitis

- Of the available management options for FIC, Hill's Prescription Diet c/d Multicare has the best evidence (published Grade 1 clinical study) for decreasing the rate of recurrent episodes of FIC signs.<sup>8,9</sup>
- Feeding c/d Multicare was associated with an 89% reduction in the rate of recurrent FIC signs compared with cats fed a control food in a 1-year study.<sup>9</sup>
- Cats with FIC that were fed c/d Multicare had a significantly lower ( $P < 0.05$ ) proportion of days with LUTS compared with cats fed a control food.<sup>9</sup>
- Significantly fewer ( $P = 0.02$ ) cats with FIC required analgesics for pain management when fed c/d Multicare (35%) compared with cats fed a control food (86%).<sup>9</sup>

Effects of nutritional management of cats with FIC were evaluated in a controlled, double-blinded 1-year clinical study.<sup>9</sup> Owners chose to feed either moist or dry food exclusively for the duration of the study and cats were assigned to either the test food group (n=11) and were fed c/d® Multicare, or the control group (n=14). The control food was an experimental food designed to mimic the nutrient profile of popular selling grocery brand cat foods. Compared with the test food, the control food contained substantially lower concentrations of omega-3 fatty acids from fish oil and antioxidants. The same protocol for environmental enrichment (including litter box management) was recommended for all cats (test and control food groups) and owners were able to request, and/or veterinarians could prescribe, opioid analgesic medication to manage cats' pain as needed.

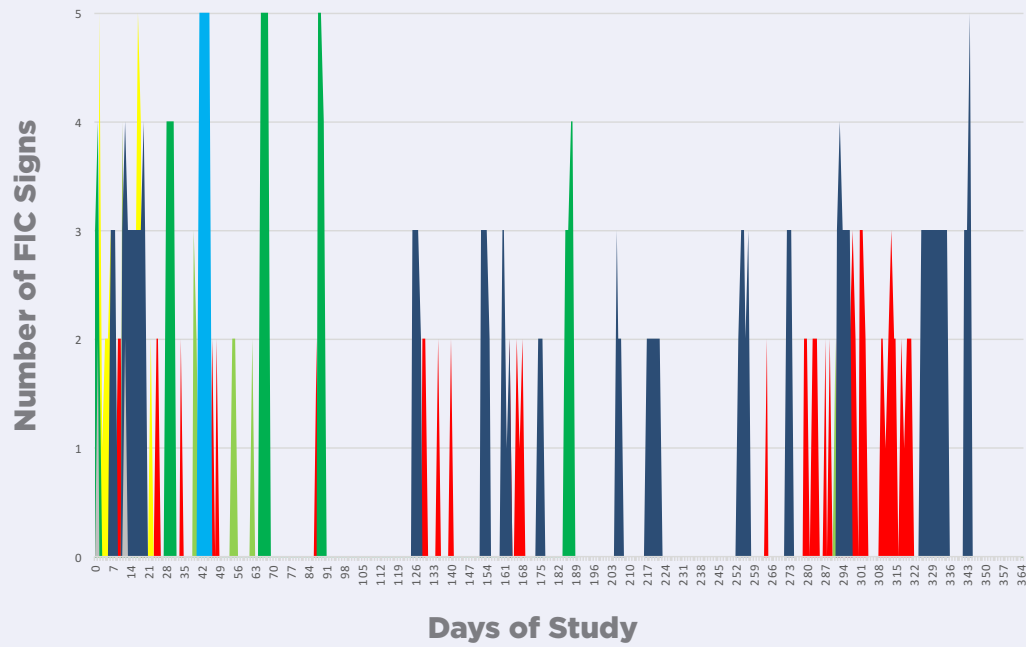
Owners were instructed to monitor for presence of five clinical signs (dysuria, hematuria, periuria, pollakiuria, stranguria) and record their observations daily. The primary endpoint was the number of recurrent episodes in which a cat had multiple ( $\geq 2$  concurrent) LUTS within a day (defined as multiple-sign day). Further, multiple sign days that were contiguous or that were separated by no more than 24 hours with a single sign were considered a single episode. Episodes were considered to have concluded when there were two or more days with 1 or 0 clinical signs. Secondary endpoints were the

number of recurrent episodes of a single LUTS. Mean incidence rate was calculated as the proportion of the number of recurrent episodes of clinical signs out of the total number of days a cat was in the study. There was no statistical difference in recurrence of LUTS between cats eating dry versus moist food, therefore, data from cats in the dry and moist food groups were combined and comparisons were made between nutritional profiles (test food versus control food).

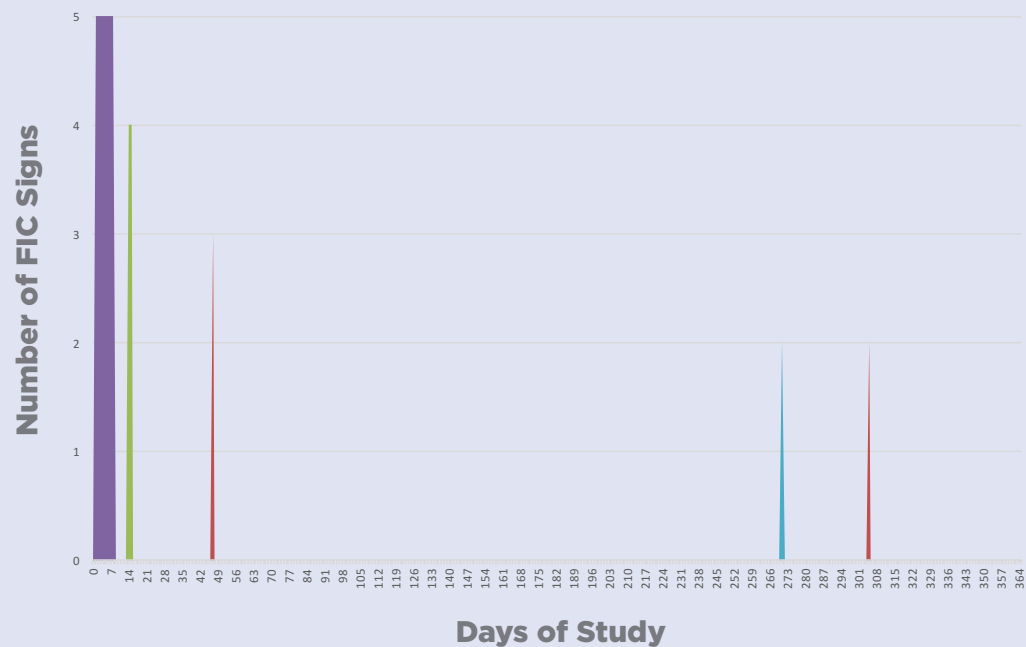
There were no significant differences between groups regarding major stressors reported over the course of the study (e.g., changes in number of people or pets, moving, remodeling, visitors, or pet sitters during owner absences), availability of window perches and scratching posts, increased number of litter boxes, or change in litter box type or location. The overall mean urine specific gravity for cats fed the test food ( $1.052 \pm 0.015$ ) was not significantly different compared with the control food group ( $1.049 \pm 0.015$ ). The median time of study enrollment was 364 days (range, 187 to 400 days) for cats fed test food and 352 days (range, 47 to 370 days) for cats fed control food. The mean  $\pm$  SD time of enrollment for cats fed control food ( $301 \pm 115$  days) was significantly ( $P = 0.03$ ) shorter than that of cats fed test food ( $355 \pm 58$  days); in total, 3,904 cat days were analyzed for the test food group (11 cats) and 4,215 days for the control food group (14 cats).

## Key Findings

- The overall incidence rates for recurrent episodes of multiple-sign days were 1.3 episodes/1,000 cat-days for cats fed test food and 11.2 episodes/1,000 cat-days for cats fed control food, representing an 89% decrease in the rate of recurrent FIC signs in cats eating c/d Multicare (Figure 1).<sup>9</sup>
- Cats with FIC fed c/d Multicare had a significantly lower mean incidence rate for multiple sign days ( $P=0.01$ ) (Figure 1).<sup>9</sup>
- A significantly ( $P = 0.04$ ) lower proportion of cats fed c/d Multicare (18%, 2/11) had stranguria compared with cats fed control food (64%, 9/14).<sup>9</sup>
- Mean incidence rates of individual signs for hematuria ( $P=0.01$ ), dysuria ( $P=0.02$ ), and stranguria ( $P=0.01$ ) were significantly lower in cats fed c/d Multicare compared with control food.<sup>9</sup>
- Opioid analgesics were dispensed during the study to a significantly ( $P = 0.02$ ) greater proportion of cats fed control food (86%, 12/14) than cats fed c/d Multicare (35%, 4/11) (Figure 2).<sup>9</sup>

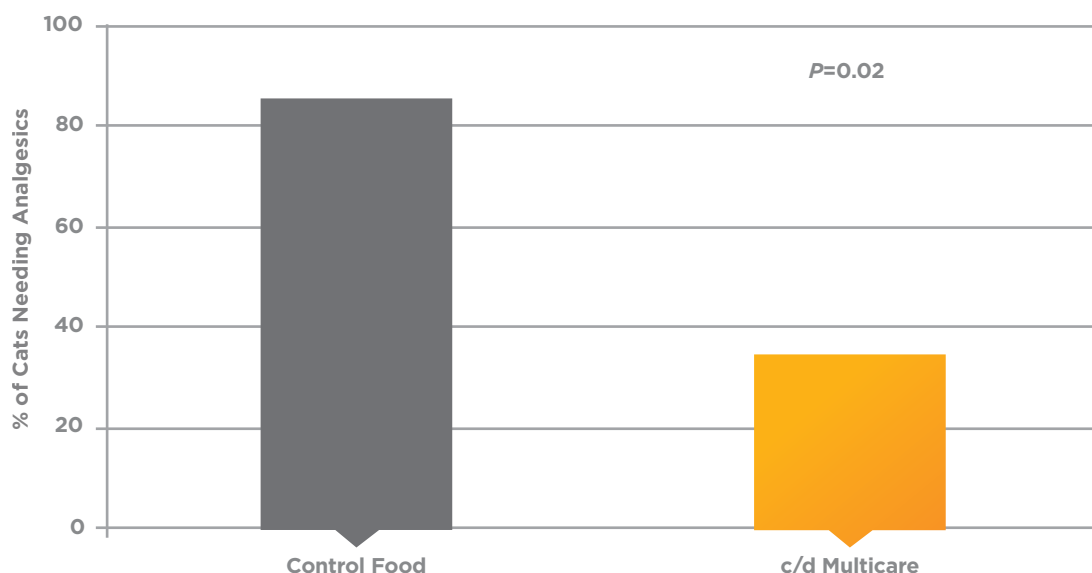


**Figure 1a.** There was a total of 47 episodes of FIC signs in 9 of 14 cats eating the control food for 1 year, representing an overall incident rate (47 episodes/4215 study days) of 11.2 episodes per 1000 study days. The number of FIC signs observed on each day is indicated on the vertical axis and the duration of each episode is shown on the horizontal axis. The episodes for each cat are represented by different colors.



**Figure 1b.** There was a total of 5 episodes of FIC signs in 4 of 11 cats eating c/d® Multicare for 1 year, representing an overall incident rate (5 episodes/3904 study days for 4 cats) of 1.3 episodes per 1000 study days. Cats with FIC fed c/d Multicare had a significantly lower mean incidence rate for multiple sign days compared with the control group (P=0.01).

**Figure 2.** Opioid analgesics were dispensed during the study to a significantly greater proportion of cats fed control food (86%, 12/14) compared with cats fed the test food, Prescription Diet® c/d® Multicare (35%, 4/11).



## Struvite Uroliths and Urethral Plugs

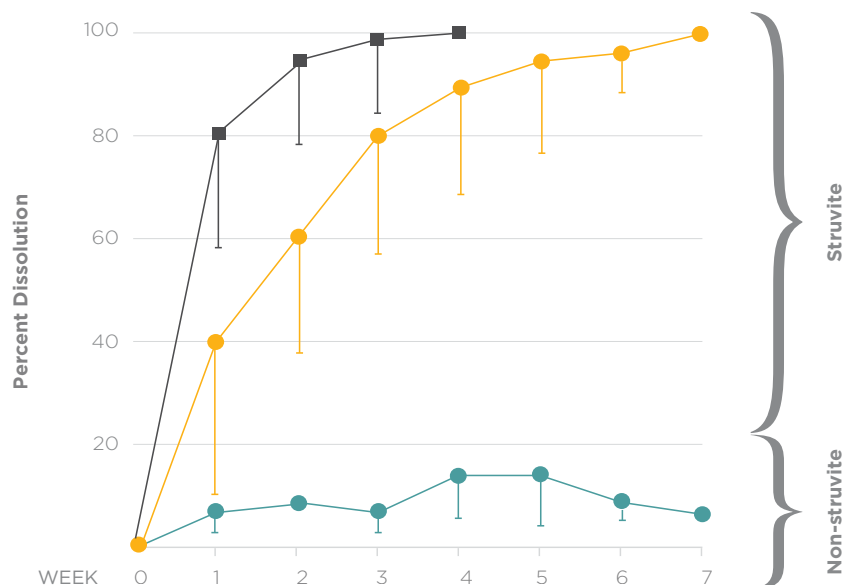
- Nutritional dissolution of feline struvite uroliths is quick, safe, and effective and is now the standard of care for these patients.<sup>10</sup>
- Nutritional management dissolves struvite uroliths in as little as 7 days (mean = 27 days for c/d Multicare).<sup>11</sup>
- Within 2 weeks of feeding c/d Multicare to cats with struvite uroliths, an average 50% reduction in urolith size occurs (Figure 3).<sup>11</sup>
- Long-term feeding of c/d Multicare significantly reduces occurrence of struvite crystalluria and risk for forming struvite uroliths and plugs.<sup>12</sup>

## Struvite Urolith Dissolution

Based on the 2016 ACVIM Consensus Guidelines, nutritional dissolution is now the standard of care for managing cats with struvite uroliths.<sup>10</sup> It is highly effective and avoids risks and complications of anesthesia and surgery including suture-induced urolith recurrence.<sup>10,13</sup> Surgical removal of uroliths is not 100% effective; 14 to 20% of cats and dogs undergoing cystotomy in a veterinary teaching hospital had incomplete urolith removal in three studies.<sup>14-16</sup> Although some believe nutritional dissolution may increase risk for urethral obstruction in male cats, this has not been reported.

In a prospective, multicenter, randomized clinical trial, 37 cats with presumed sterile struvite uroliths were randomly assigned to be

fed either Prescription Diet® s/d® Feline (dry) or c/d® Multicare (dry).<sup>11</sup> Diagnostic evaluation was performed at baseline and weekly until radiographic disappearance of uroliths. A total of 32 cats had complete urolith dissolution and mean time ( $\pm$  SD) to observe a 50% reduction in urolith size was  $0.69 \pm 0.1$  weeks for cats fed s/d Feline and  $1.75 \pm 0.27$  weeks for cats fed c/d Multicare (Figure 3). Mean time for complete urolith dissolution was significantly lower for cats fed s/d Feline ( $13 \pm 2.6$  days; range 6 to 28 days) compared with cats fed c/d Multicare ( $27 \pm 2.6$  days; range of 7 to 52 days) ( $P < 0.002$ ). Adverse events, including urinary tract obstruction, were not observed in any cats during the study.

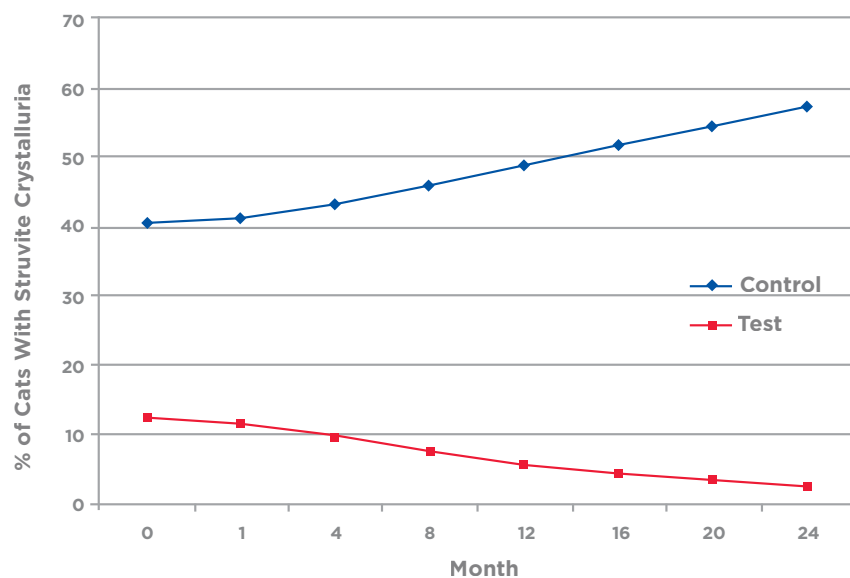


**Figure 3.** Percent urolith dissolution (mean  $\pm$  SD) by week for cats with struvite uroliths that were fed either Hill's® Prescription Diet® s/d® Feline (n=16 [black squares]) or Hill's® Prescription Diet® c/d® Multicare Feline (n=16 [gold circles]) and five cats fed either food that had uroliths composed of ammonium urate (4) or calcium oxalate (1). Note that at 2 weeks, struvite uroliths were (on average) > 50% or more dissolved whereas non-struvite uroliths had minimal change. Evidence of a marked reduction (at least 50% compared with baseline) in urolith size by 2 weeks can be used to support a diagnosis of struvite uroliths, and the decision to continue nutritional dissolution therapy.

### Decreasing Risk for Struvite Urolith & Urethral Plug Recurrence

Therapeutic foods with low magnesium and phosphorus that acidify urine ( $\text{pH} \leq 6.4$ ) are recommended to decrease recurrence of sterile struvite uroliths and urethral plugs in cats.<sup>3,10</sup> Effects of feeding c/d Multicare were evaluated in a 2-year, randomized, controlled, double-blinded clinical study of cats with struvite uroliths.<sup>12</sup> Cats were assigned to receive either test food (n=19), c/d Multicare, or control food (n=18) with a nutritional profile similar to the top five selling grocery food brands. The test food contained decreased magnesium and phosphorus

compared with the control food, and had a target urine pH of 6.2-6.4 (versus 6.6-6.8 for the control food). During the study, four control food cats (22%) and one test food cat (5%) had recurrence of struvite uroliths. The relative risk of forming a urolith was 4.2 times higher when cats were fed control food, and struvite relative supersaturation was 2.97 times higher in control cats ( $P=0.004$ ). There was also a significant month-diet interaction such that struvite crystalluria increased over time in the control food group and declined in cats eating c/d Multicare (**Figure 4**).<sup>12</sup>



**Figure 4.** During the 2-year study the % of cats with struvite crystalluria increased to over 50% in the control food group and decreased to less than 10% in cats eating Prescription Diet c/d Multicare (test group); the difference between groups was significant ( $P=0.0456$ ).

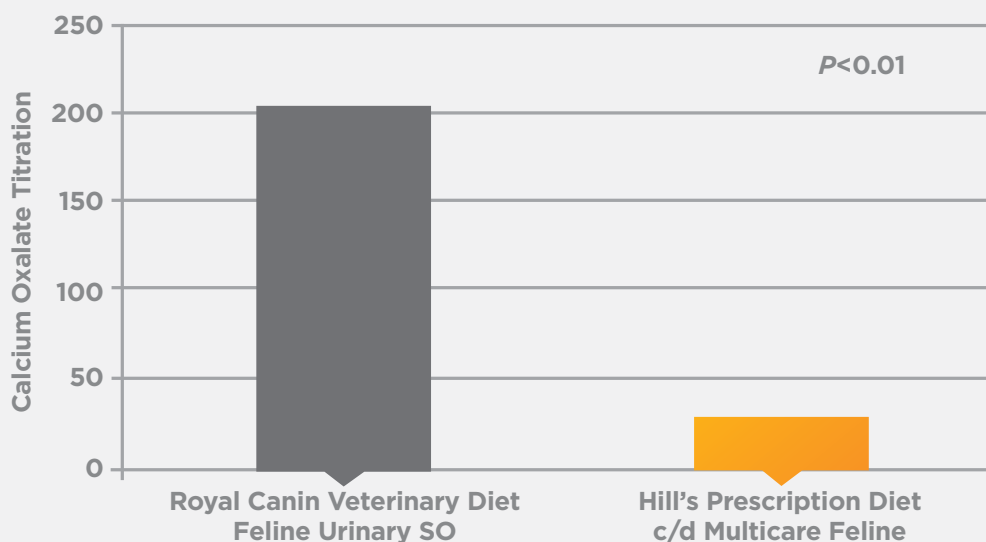
## Calcium Oxalate Uroliths

- The Hill's calcium oxalate titration (COT) test assesses the likelihood that calcium oxalate will precipitate in urine
- Feeding c/d® Multicare significantly lowers the risk of calcium oxalate (CaOx) precipitation in urine (as measured by the Hill's COT test) compared with Royal Canin Veterinary Diet® Feline Urinary SO®\* (Figure 5).<sup>17</sup>
- Cats eating Hill's Prescription Diet c/d Multicare had significantly lower urine calcium and higher urine citrate (a CaOx crystal inhibitor),<sup>17</sup> and significantly decreased urinary calcium excretion per day compared with cats eating Royal Canin Veterinary Diet Feline Urinary SO (Figure 6).<sup>18</sup>

Recently, the Hill's COT test was introduced as a new method for evaluating risk of forming CaOx crystals and uroliths.<sup>19,20</sup> This test measures the propensity for CaOx to precipitate in urine when titrated with an oxalate salt, therefore, it provides an assessment of urine stability and likelihood for CaOx crystals and uroliths to form. In contrast to relative supersaturation (RSS), a major advantage of the Hill's COT test is that it evaluates whole, unaltered urine and results take into consideration effects of various naturally occurring urinary crystal inhibitors (e.g., citrate, glycosaminoglycans) and promoters (e.g., cellular debris).

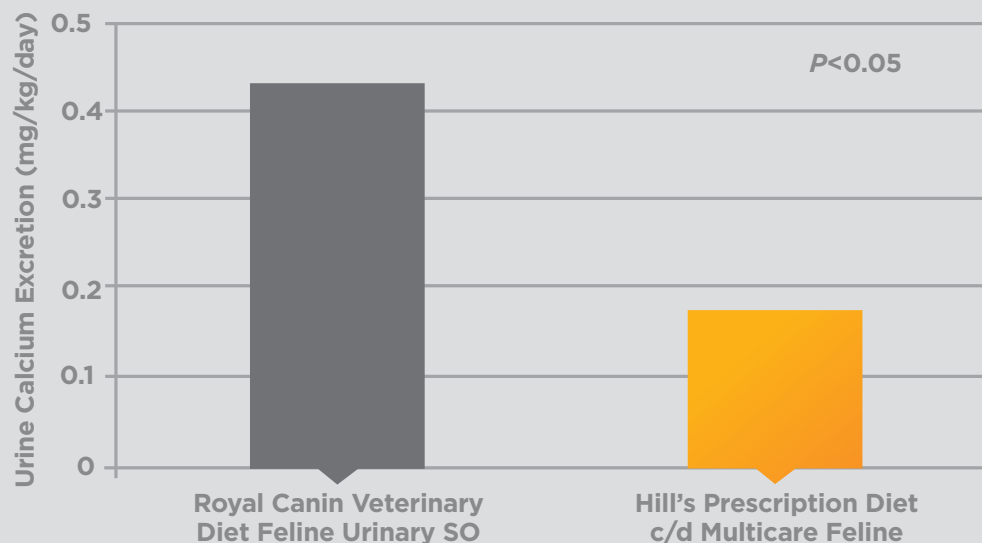
The COT test was used to evaluate effects of feeding dry c/d Multicare Feline and dry Royal Canin Veterinary Diet® Feline Urinary SO® in 12 healthy adult cats.<sup>17</sup> Cats were individually housed and had access to group socialization and natural light on a daily basis and all

activities were approved by the animal care and use committee. Cats were fed each diet for 14 days in monadic feeding studies and on day 11 of feeding, urine from each cat was collected for at least 24 hours and maintained at 37° C. Evaluation included urine sediment examination, measurement of urine chemistries, and determination of COT test results. The calcium oxalate precipitation risk (based on Hill's COT test results) was significantly lower in cats eating c/d Multicare (Figure 5). In addition, cats eating c/d Multicare had significantly lower urine calcium concentrations and significantly higher urinary citrate (a CaOx crystal inhibitor) compared with cats eating Urinary SO. Results were similar to a previously published study where 24-hour urine calcium excretion was significantly lower in cats eating dry c/d Multicare compared with dry Urinary SO (Figure 6).<sup>18</sup>



**Figure 5.** Mean (± SEM) values for calcium oxalate titration (COT) were significantly lower in cats eating Hill's Prescription Diet c/d Multicare (dry) (28 ± 30) compared with Royal Canin Veterinary Diet Feline Urinary SO\* dry (202 ± 33).

**Figure 6.** Urine calcium excretion (mean  $\pm$  SD) was significantly lower in cats eating Prescription Diet c/d Multicare ( $0.18 \pm 0.07$ ) compared with Royal Canin Veterinary Diet® Feline Urinary SO® ( $0.43 \pm 0.22$ ).



## Summary

**Results of clinical studies support that nutritional management with Hill's® Prescription Diet® c/d® Multicare effectively manages the most common causes of lower urinary signs in cats.<sup>9,11,12,17</sup> Consistent feeding of c/d Multicare results in:**

- **Significantly lower rate of recurrent episodes of FIC signs and requests for pain management<sup>9</sup>**
- **Safe, quick, and effective dissolution of struvite uroliths<sup>11</sup>**
- **Significantly decreased occurrence of struvite crystalluria and therefore decreased risk for recurrence of struvite uroliths and urethral plugs<sup>12</sup>**
- **Significantly reduced risk for precipitation of CaOx in urine (based on the Hill's COT test) and urine calcium concentration<sup>17</sup>**

\*Lot 112508, Purchased in the USA November 2016, Royal Canin Veterinary Diet® Feline Urinary SO® Chicken Dry

## References

- <sup>1</sup>Salman MD, et al. Human and animal factors related to relinquishment of dogs and cats in 12 selected animal shelters in the United States. *J Appl Anim Welf Sci.* 1998;1:207-226.
- <sup>2</sup>Forrester SD, et al. Evidence-based management of feline lower urinary tract disease. *Vet Clin North Am Small Anim Pract.* 2007;37(3):533-558.
- <sup>3</sup>Minnesota Urolith Center ([www.urolithcenter.org](http://www.urolithcenter.org)), accessed January 2018.
- <sup>4</sup>Dorsch R, et al. Feline lower urinary tract disease in a German cat population. A retrospective analysis of demographic data, causes and clinical signs. *Tierarztl Prax Ausg K Kleintiere Heimtiere.* 2014;42(4):231-239.
- <sup>5</sup>Gerber B, et al. Evaluation of clinical signs and causes of lower urinary tract disease in European cats. *J Small Anim Pract.* 2005;46(12):571-577.
- <sup>6</sup>Kruger JM, et al. Clinical evaluation of cats with lower urinary tract disease. *J Am Vet Med Assoc.* 1991;199(2):211-216.
- <sup>7</sup>Saevik BK, et al. Causes of lower urinary tract disease in Norwegian cats. *J Feline Med Surg.* 2011;13(6):410-417.
- <sup>8</sup>Forrester SD, et al. Feline idiopathic cystitis. *Vet Clin North Am Small Anim Pract.* 2015;45(4):783-806.
- <sup>9</sup>Kruger JM, et al. Comparison of foods with differing nutritional profiles for long-term management of acute nonobstructive idiopathic cystitis in cats. *J Am Vet Med Assoc.* 2015;247(5):508-517.
- <sup>10</sup>Lulich JP, et al. ACVIM small animal consensus recommendations on the treatment and prevention of uroliths in dogs and cats. *J Vet Intern Med.* 2016;30(5):1564-1574.
- <sup>11</sup>Lulich JP, et al. Efficacy of two commercially available, low-magnesium, urine-acidifying dry foods for the dissolution of struvite uroliths in cats. *J Am Vet Med Assoc.* 2013;243(8):1147-1153.
- <sup>12</sup>Lulich J, et al. A two year-long prospective randomized double-masked study on the effect of nutrition on the recurrence of magnesium ammonium phosphate urolithiasis in stone-forming cats. *J Vet Intern Med.* 2014;28:1081.
- <sup>13</sup>Appel SL, et al. Evaluation of risk factors associated with suture-nidus cystoliths in dogs and cats: 176 cases (1999-2006). *J Am Vet Med Assoc.* 2008;233(12):1889-1895.
- <sup>14</sup>Bevan JM, et al. Comparison of laser lithotripsy and cystotomy for the management of dogs with urolithiasis. *J Am Vet Med Assoc.* 2009;234(10):1286-1294.
- <sup>15</sup>Grant DC, et al. Frequency of incomplete urolith removal, complications, and diagnostic imaging following cystotomy for removal of uroliths from the lower urinary tract in dogs: 128 cases (1994-2006). *J Am Vet Med Assoc.* 2010;236(7):763-766.
- <sup>16</sup>Lulich JP, et al. Incomplete removal of canine and feline urocystoliths by cystotomy (abstr). *J Vet Intern Med.* 1993;7:124.
- <sup>17</sup>Hill's Pet Nutrition, Inc. Data on File, 2017.
- <sup>18</sup>Gluhek T, et al. Evaluation of 3 struvite-oxalate preventative diets in healthy cats. *J Vet Intern Med.* 2012;26:801.
- <sup>19</sup>MacLeay JM, et al. Comparison of relative supersaturation for calcium oxalate to a new method to determine the propensity of urine to precipitate calcium oxalate, the calcium oxalate risk index. *J Vet Intern Med.* 2014;28:1366.
- <sup>20</sup>Davidson SJ, et al. The calcium oxalate risk index: a new method for determining the propensity for formation of calcium oxalate uroliths. *J Vet Intern Med.* 2014;28:1083.





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