

# Serum levels of the uraemic toxin indoxyl sulfate (IS)

in geriatric cats, determined using an LC/MS-MS method (API5500), after giving Renaltec® daily in comparison with a control group

## The special needs of the elderly

In many cats, the filtration performance of the kidneys declines continually in old age. However, the protein requirement of the cat, an obligate carnivore, remains unchanged. This leads to a dilemma: On the one hand, the protein content of the food should be limited in order to reduce nitrogen-containing degradation products. On the other hand, the aging cat – with its increased tendency towards chronic illness – has a particular need for sufficient high-quality protein. The selective binding of degradation products in the intestine and their continual excretion via the faeces appears to be a sensible alternative.

The amino acid tryptophan from the protein in the food is degraded to produce indole, from which the **uraemic toxin indoxyl sulfate (IS)** is synthesised. Although IS is excreted in the urine by cats (and dogs) with kidneys that are functioning well, an excess of indoxyl sulfate causes problems because it cannot be completely eliminated.

**Renaltec®** has been developed as a selective high-performance adsorber which the cat consumes daily in its wet food without problems. In a pilot study, investigations were carried out into the extent to which 500 mg Renaltec® daily over a period of eight weeks causes indole to be bound in the colon and eliminated, and whether – and, if so, to what extent – the serum indoxyl sulfate level then sinks correspondingly.

## Material and methods

### Selection of animals

The aim was to choose cats that, although clinically normal, were at risk of exhibiting reduced kidney filtration performance because of their age. All cats in this study were therefore required to be at least ten years old. At the time of the study, 18 animals were available meeting this age specification. They included animals of both sexes.



### Allocation to the Renaltec® group and the untreated control group

Almost all older animals are accustomed to dry food with simultaneous higher water uptake and some refuse even small amounts of wet food. Because Renaltec® consists of small spheres that are firm and dry, it has to be mixed with a small amount (10 g) of wet food to ensure oral uptake. The wet food refusers had to be allocated to the control group in advance; the remaining animals were allocated randomly to the two groups: Renaltec® group (n=12), control group (n=6).

### Renaltec® group (n=12)



### Control group (n=6)



All cats in the Renaltec® group received the same daily dose of 500 mg Renaltec® given with a 10 g wet food snack. After they had consumed this completely all the cats were given an identical senior cat food ad libitum.

### Blood samples

All 54 blood samples (18 x 3) were taken by veterinary surgeons from a cooperating practice. All blood samples were taken in the morning in a fasting state; the procedure was carried out in the animals' familiar surroundings and was therefore performed quickly and without agitation. Part of each blood sample was sent to IDEXX for assay of parameters relevant to the kidneys. The other part was transferred to EDTA plasma tubes and sent to Ardena Biolanalytical Laboratory (ABL) in the Netherlands for measurement of IS. This occurred on Days 0, 28 and 56.

### Modification and validation of the analytical method of measuring human indoxyl sulfate (IS) for use with cat plasma

ABL had established a published method by which to measure human IS in the laboratory and had modified this method to examine cat plasma. The procedure was as follows:

Qualification	Analysis
500 µg/l–500,000 µg/l	500 µg/l–500,000 µg/l 100 µg/l–500,000 µg/l

The range for the IS values used, on the basis of the small amount of published data on IS in cats, was taken to be 100 µg/l to 500,000 µg/l.

## Results

### Results for serum samples: creatinine, SDMA, P

After none of the animals was clinically abnormal, the serum levels of creatinine, phosphate and SDMA were analysed. Typically, these values change when the filtration performance of the kidneys is reduced. For the reference ranges of the individual parameters we turned to MORITZ A.(2014). This paper reported the normal range of phosphate levels to be 2.1–5.2 mg/dl.

At the beginning of the pilot study the **creatinine level** was elevated in only 1 of 18 animals (248 µmol/l). It was nevertheless surprising that the level of symmetric dimethylarginine (**SDMA**), which is seen as the “early diagnosis parameter”, was also elevated in only 3 of 18 animals in spite of their advanced age. However, in 2 of the 3 animals – all of which were in the Renaltec® group – the SDMA level dropped back into the normal range during the eight-week period. The level also dropped in the third animal.

### Elevated serum levels of P (= inorganic phosphate) in Renaltec® group

Start of study (6 elevated out of 12)



End of study (1 elevated out of 12)

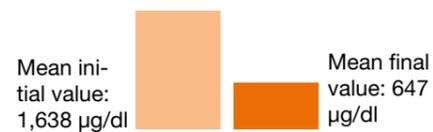


### Results on indoxyl sulfate (IS) in the serum

The serum levels of indoxyl sulfate varied considerably within individuals. This variation was apparent both on Day 0 – the initial value – and on Days 28 and 56. In the Renaltec® group the highest value on Day 0 was 6,180 µg/dl. By Day 56 it had fallen to 346 µg/dl. The lowest initial value on Day 0 was 382 µg/dl. This fell to 100 µg/dl on Day 56.

In the untreated control group the highest initial value on Day 0 was 763 µg/dl. By Day 56 this had increased to 1,410 µg/dl. The lowest initial value was 45 µg/dl. On Day 56 this was found to be practically unchanged at 50 µg/dl. When the baseline levels on Day 0 are compared with the levels on Day 56, the mean levels in the Renaltec® group showed a significant drop of > 60% (p = 0.0058). In the untreated group there was no significant difference over the 56 day period (p = 0.5670).

### Renaltec® group (n = 6)



Mean reduction of > 60% (p = 0.0058)

### Control group (n = 12)



No difference (p = 0.5670)

The comparison between the two groups – Renaltec® and untreated – is striking: with a **descriptive value of p = 0.0619** it shows a clear trend towards significant reduction of indoxyl sulfate.

### Results for body weight

The cats differed not only in age (11–16 years) but also in body weight. Over the 56 day period their weights ranged between 2.5 and 7.7 kg. The average body weight remained unchanged over the course of the study.

## Discussion

The results show that **Renaltec®** given with the food was very well accepted and tolerated by the relevant group throughout the 56 day period.

The different absolute levels of **indoxyl sulfate (IS)** can be explained by the differences in amount of food taken daily, body weight, age and assumed GFR. After eight weeks the average serum levels of indoxyl sulfate (IS) were reduced by more than 60% compared to the initial level.

It is to be assumed that the permanent binding and excretion of indole resulting from the selective binding to Renaltec® in the colon, and the reduction in serum IS that results from this, leads to **lasting relief of the kidneys** from this harmful uraemic toxin. This study was able to demonstrate a clear reduction in the serum IS level in cats that were old but clinically normal and thus relatively healthy.

In case of a reduction in kidney filtration a highly selective adsorber such as Renaltec®, when given with any form of cat food, serves to bind and eliminate the precursors of harmful metabolites of some proteins. The use of this adsorber via the food strengthens the remaining nephrons and can be an elegant way to relieve cats' kidneys helpfully at an early stage, thus potentially maintaining a high quality of life for a long time.

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