

# COSEQUIN<sup>®</sup>



Research and Clinical Studies



QUALITY BY DESIGN · PRODUCTS FOR LIFE®

# COSEQUIN®

*The science is in every bottle.*



Cosequin is manufactured by Nutramax Laboratories, Inc. in a state-of-the-art facility. Following manufacturing standards practiced by the pharmaceutical industry, Nutramax Laboratories, Inc. produces the finest quality joint health supplements available.

*All Cosequin products contain:*

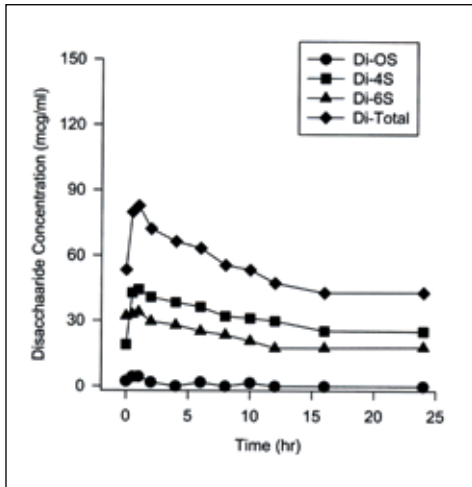
- TRH122® Low Molecular Weight Chondroitin Sulfate 95%—exclusive to Nutramax Laboratories, Inc.—the only chondroitin sulfate used in published studies that has been shown to be absorbable in dogs and horses and has been shown to accumulate with continued administration.
- FCHG49® Glucosamine HCl—the only salt used in published veterinary clinical studies—glucosamine hydrochloride provides more glucosamine per gram than any other glucosamine salt.
- Manganese Ascorbate—a co-factor in the synthesis of glycosaminoglycans and collagen in the cartilage matrix.

***Studies featured in this publication have been assigned a reference code number. Please specify this number when requesting studies.***

Cosequin® contains TRH122® Sodium Chondroitin Sulfate and FCHG49® Glucosamine HCl, Nutramax Laboratories® exclusive veterinary researched specifications and the only combination of these ingredients shown effective, safe, and bioavailable in published, controlled U.S. veterinary studies.

## Veterinary Trials—Small Animal

NL 320

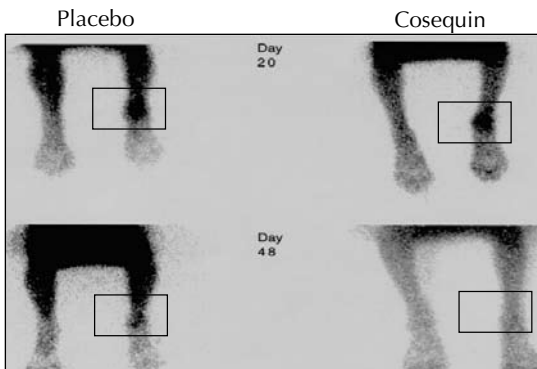


Plasma  $\Delta$ Di-OS,  $\Delta$ Di-4S and  $\Delta$ Di-6S and total disaccharide concentration vs. time profile for day 7 after daily 1200 mg p.o. CS administration.

Adebowale A, Du J, Liang Z, et al. The bioavailability and pharmacokinetics of glucosamine hydrochloride and low molecular weight chondroitin sulfate after single and multiple doses to beagle dogs. *Biopharmaceutics and Drug Disposition* 2002;23(6):217-225.

TRH122<sup>®</sup> low molecular weight (LMW) chondroitin sulfate and FCHG49<sup>®</sup> glucosamine hydrochloride were administered to dogs either intravenously or orally. Compounds were given as a single administration to measure bioavailability and were also given for 7 consecutive days to measure steady state pharmacokinetics. Glucosamine hydrochloride was absorbed quickly (about 1.5 hours) and did not accumulate in the blood with continued administration. LMW chondroitin sulfate was also absorbed quickly (about 2 hours). Unlike glucosamine hydrochloride, TRH122 LMW chondroitin sulfate showed significant accumulation in the serum with steady state administration; bioavailability was estimated at over 200 percent. This phenomenon explains the carry-over effect of TRH122 LMW chondroitin sulfate as used exclusively in Cosequin<sup>®</sup> following discontinuation of oral administration. This also supports administration of lower levels of Cosequin for long-term maintenance.

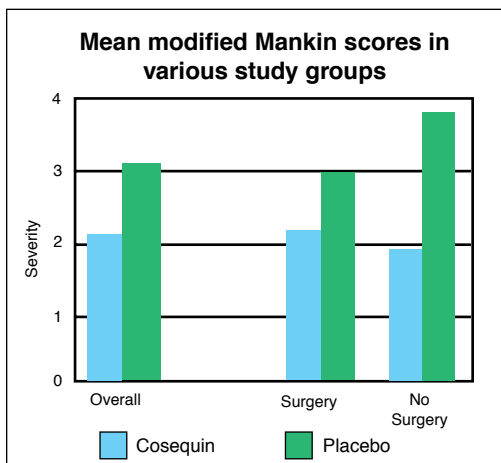
NL 167



Canapp SO Jr., McLaughlin RM Jr., Hoskinson JJ, et al. Scintigraphic evaluation of dogs with acute synovitis after treatment with glucosamine hydrochloride and chondroitin sulfate. *American Journal of Veterinary Research* 1999;60(12):1552-1557.

In a double-blind, placebo-controlled study, dogs were administered Cosequin or placebo prior to their carpal joint being injected with chymopapain to induce a short-term, self-resolving inflammation. The dogs that were pre-administered Cosequin had significantly less inflammation at 48 days. Lameness associated with this short-term synovitis was also significantly less in the Cosequin group. The authors concluded that Cosequin administration prior to joint insult had a protective effect against synovitis and bone remodeling. All dogs were adopted out at the end of the study.

NL 141



Hulse DS, Hart D, Slatter M, et al. The effect of Cosequin in cranial cruciate deficient and reconstructed stifle joints in dogs, in *Proceedings. 25th Annual Conference Veterinary Orthopedic Society* 1998,64.

In a double-blind, placebo-controlled study, dogs that had a ruptured cruciate ligament were surgically corrected with or without Cosequin supplementation during the healing process. The authors concluded that Cosequin had two primary effects in this study: a reduction in the severity of cartilage breakdown in the operated joints, and a return of the repaired joint to a more normal physiologic state.

# Veterinary Trials—Small Animal

NL 102

McNamara PS, Barr SC, Erb HN. Hematologic, hemostatic, and biochemical effects in dogs receiving an oral chondroprotective agent for thirty days. *American Journal of Veterinary Research* 1996;57(9):1390-1394.

Cosequin® was shown safe in dogs administered a high amount for 30 days. All biochemical, hematologic and hemostatic indices stayed within normal limits.

NL 199

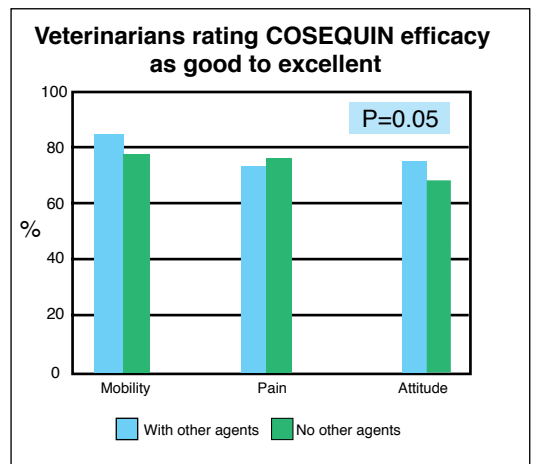
McNamara PS, Barr SC, Erb HN, et al. Hematologic, hemostatic, and biochemical effects in cats receiving an oral chondroprotective agent for thirty days. *Veterinary Therapeutics* 2000;1(2):108-117.

Cosequin was shown safe in cats administered a high amount for 30 days. All biochemical, hematologic and hemostatic indices stayed within normal limits.

NL 172

Anderson MA, Slater MR, Hammad TA. Results of a survey of small-animal practitioners on the perceived clinical efficacy and safety of an oral nutraceutical. *Preventive Veterinary Medicine* 1999;38:65-73.

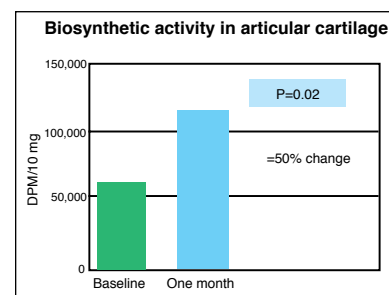
3,080 veterinarians were surveyed and asked to assess the efficacy of Cosequin over the past six months prior to the survey. The veterinarians estimated that over this time period they administered Cosequin for 28,898 problem joints. The most commonly affected joint was the hip followed by the stifle, elbow, shoulder and hock. Forty six percent of the responding veterinarians use Cosequin as the first form of management. Fifty nine percent use Cosequin in combination with agents such as NSAIDs with the majority noting that the other usage was decreased or discontinued over time with Cosequin. Overall, the veterinarians rated Cosequin as good to excellent in reducing pain, improving mobility and improving attitude in over 80 percent of the animals administered Cosequin. Side effects were also recorded with less than 2 percent of the dogs developing a mild GI upset.



NL 181

Lippiello L, Idouraine A, McNamara PS, et al. Cartilage stimulatory and antiproteolytic activity is present in sera of dogs treated with a chondroprotective agent. *Canine Practice* 1999;24(1):18-19.

Serum of healthy dogs was collected before and after Cosequin administration for one month. At 30 days the level of glycosaminoglycans (GAG) in the serum significantly increased by 42 percent. The serum was used to incubate cartilage segments. The GAG biosynthetic rate of the cartilage segments increased significantly by 50 percent. In addition, significant reduction (59 percent) in proteolytic degradation was observed. The authors concluded that Cosequin given orally, over extended periods of time, elevated levels of circulating agents in the serum which stimulate cartilage metabolism while inhibiting cartilage degradation.



## Veterinary Trials—Small Animal

NL 289

Johnson KA, Hulse DA, Hart RC, et al. Effects of an orally administered mixture of chondroitin sulfate, glucosamine hydrochloride and manganese ascorbate on synovial fluid chondroitin sulfate 3B3 and 7D4 epitope in a canine cruciate ligament transection model of osteoarthritis. *Osteoarthritis and Cartilage* 2001;9(1):14-21.

The authors concluded that Cosequin® was associated with altered concentrations of 3B3 and 7D4 epitope in synovial fluid, suggesting that these compounds may act to modulate articular cartilage matrix metabolism in vivo.

NL 345

Lippiello L, Han MS, Henderson T. Protective effect of the chondroprotective agent CosequinDS on bovine articular cartilage exposed in vitro to nonsteroidal antiinflammatory agents. *Veterinary Therapeutics* 2002; 2(3):128-135.

This study tested whether the concurrent use of CosequinDS with etodolac or carprofen, as well as other NSAIDs, could “protect” cartilage against the adverse effects on cartilage from these NSAIDs. CosequinDS was shown to be effective in counteracting the potentially adverse effects on cartilage of etodolac and to enhance the mild cartilage stimulatory effect of carprofen. Further studies using animal models should be completed to confirm these in vitro results. The data do suggest that there is a firm rationale for incorporating CosequinDS as an adjunct with some NSAIDs, in particular etodolac and perhaps carprofen.

NL 363

Sauvé F, Paradis M, Refsal KR, et al. Effects of oral administration of meloxicam, carprofen, and a nutraceutical on thyroid function in dogs with osteoarthritis. *Canadian Veterinary Journal* 2003;44:474-479.

Thyroid function tests (serum total T4, free T4, and TSH levels) were not affected in dogs receiving Cosequin.

## Veterinary Trials—Equine

NL 251

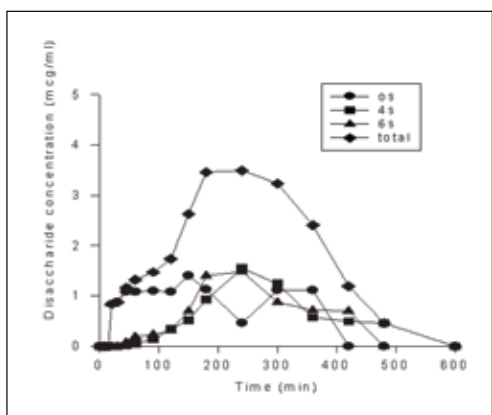
Du J, White N, Eddington ND. The bioavailability and pharmacokinetics of glucosamine hydrochloride and chondroitin sulfate after oral and intravenous single dose administration in the horse. *Biopharmaceutics and Drug Disposition* 2004;25:109-116.

TRH12® low molecular weight (LMW) chondroitin sulfate and FCHG49® glucosamine hydrochloride were administered to horses either intravenously or orally to measure bioavailability. TRH12 LMW chondroitin sulfate was absorbed rapidly in the horse (1.3-2.3 hours), with bioavailability estimated at 22 percent. Oral bioavailability of glucosamine was estimated at 2.5 percent. This study provides the first determination of the bioavailability of low molecular weight chondroitin sulfate and glucosamine in the horse.

Agent	Time (hr.)	Change in Synthetic Activity Relative to Control		
		Before CosequinDS	After CosequinDS	P value*
Etodolac	24	4%	21%	<.04
	144	-22%	51%	<.004
Carprofen (10 <sup>11</sup> g/ml)	144	15%	30%	<.009

\* Significance of difference between before and after values.

Synthetic Activity Measured by 35-Sulfate Incorporation in Cartilage Explants Exposed to NSAID and CosequinDS.



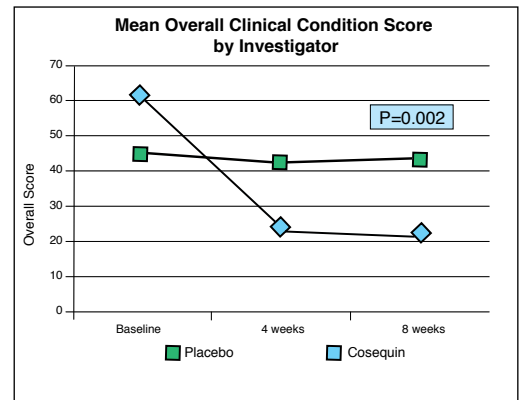
Total and individual disaccharides [ΔDi-OS, ΔDi-4S, ΔDi-6S] after oral (3g) administration with TRH122 CS to horse #5.

# Veterinary Trials—Equine

NL 259

Hanson RR, Brawner WR, Blaik MA, et al. Oral treatment with a nutraceutical (Cosequin®) for ameliorating signs of navicular syndrome in horses. *Veterinary Therapeutics* 2001;2(2):148-159.

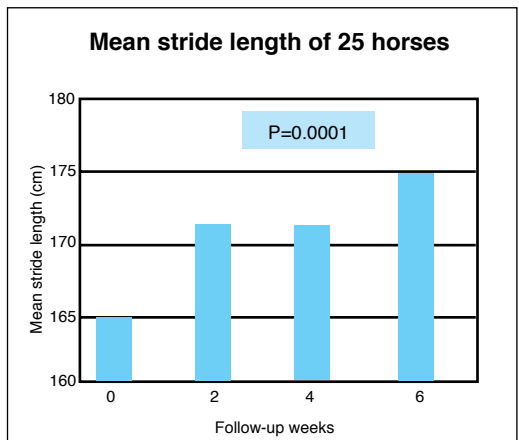
Double-blind, placebo-controlled study of 14 horses between the ages of 5 to 15 with a progressive forelimb lameness present for 3 to 12 months. Horses were administered Cosequin Equine Powder or placebo twice daily for two months. A global clinical score, which included a lameness exam, was performed by a veterinary equine specialist at 0, 28, and 56 days. There was a significant improvement in veterinary score at 56 days in the Cosequin group compared to the placebo group. The authors concluded that Cosequin supplementation was effective in these horses.



NL 127

Hanson RR, Smalley LR, Huff GK, et al. Oral treatment with a glucosamine-chondroitin sulfate compound for degenerative joint disease in horses: 25 cases. *Equine Practice* 1997;19(9):16-22.

Open label trial of 25 performance horses with radiographically confirmed cartilage breakdown of the hock, knee, fetlock joint, or coffin joint. Horses were administered Cosequin Equine Powder for 6 weeks. Every two weeks, lameness grade, flexion test and stride length were measured. In all parameters, there was a rapid, significant improvement in the first two weeks that continued at a slower pace for the remainder of the study. The authors concluded that significant improvement was noted irrespective of the horse's age, joint affected or use of the horse. Some horses returned to competition after the second week of supplementation.



NL 267

Kirker-Head CA, Kirker-Head RP. Safety of an oral chondroprotective agent in horses. *Veterinary Therapeutics* 2001;2(4):345-353.

No clinically significant changes were seen in hematologic, serum biochemical, or synovial values after the oral administration of five scoops Cosequin Equine Powder twice daily (five times the recommended maintenance amount) to six healthy adult horses for 34 days. No adverse effects on physical examination parameters were noted.

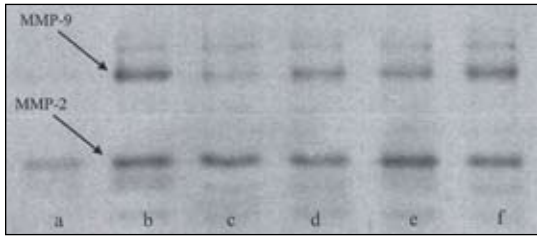
NL 271

DeChant JE, Baxter GM, Frisbie DD, et al. Effects of glucosamine and chondroitin sulphate, alone and in combination, on normal and interleukin-1 conditioned equine articular cartilage explant metabolism. *Equine Veterinary Journal* 2005;37(3):227-231.

In an in vitro study using equine cartilage explants, no adverse effects were seen with glucosamine and chondroitin sulfate, alone or in combination, on cartilage metabolism. The combination of FCHG49® glucosamine hydrochloride and TRH122® low molecular weight chondroitin sulfate lowered IL-1 induced glycosaminoglycan release into the culture media, as opposed to glucosamine alone or lower amounts of chondroitin sulfate alone. It was suggested that more beneficial effects in terms of stimulating cartilage production and protecting from degradation were seen with the combination of glucosamine and chondroitin sulfate versus either compound alone.

## Veterinary Trials—Equine

NL 324



Orth MW, Peters TL, Hawkins JN. Inhibition of articular cartilage degradation by glucosamine-HCl and chondroitin sulphate. *Equine Veterinary Journal Suppl.* 2002;(34):224-229.

In vitro studies were completed using equine cartilage explants. FCHG49<sup>®</sup> glucosamine hydrochloride and TRH122<sup>®</sup> low molecular weight (LMW) chondroitin sulfate were shown to augment each other in inhibiting the degradation induced by lipopolysaccharide, an inflammatory mediator. Expression of matrix metalloproteinase 9 (MMP-9) was decreased by the combination of 1 mg/ml of glucosamine and 0.25 mg/ml of chondroitin sulfate (Lane c). Neither lower amounts of the combination nor glucosamine or chondroitin sulfate alone affected expression of MMP-9 as determined by gelatin zymography. It was concluded that glucosamine and chondroitin sulfate appear to compliment each other in decreasing cartilage degradation.

NL 371

Schlueter AE, Orth MW. Further studies on the ability of glucosamine and chondroitin sulphate to regulate catabolic mediators in vitro. *Equine Veterinary Journal* 2004;36(7):634-636.

The combination of FCHG49 glucosamine hydrochloride and TRH122 LMW chondroitin sulfate when added to lipopolysaccharide-stimulated equine cartilage explants was shown to inhibit the production of the inflammatory mediators nitric oxide and prostaglandin E<sub>2</sub> and to suppress activity of MMP-9, a proteolytic enzyme. This study provided additional evidence that the combination of FCHG49 glucosamine hydrochloride and TRH122 LMW chondroitin sulfate protects against cartilage breakdown in vitro.

NL 384

Orth MW, Chan PS. Pharmacologically relevant concentrations of glucosamine and chondroitin sulfate regulate nitric oxide and prostaglandin E<sub>2</sub> synthesis, in *Workbook*. AAEP Focus on Joints Conference 2004;192-199.

The combination of FCHG49 glucosamine hydrochloride and TRH122 LMW chondroitin sulfate, at levels likely able to be reached in synovial fluid in vivo, decreased the production of nitric oxide and/or prostaglandin E<sub>2</sub> in equine cartilage explants.



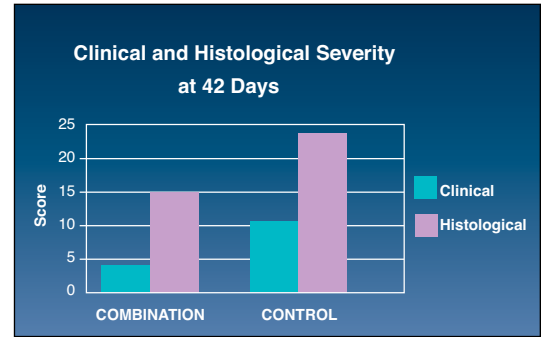
# Additional Studies Evaluating Mechanism of Action Using FCHG49® Glucosamine HCl and TRH122® Low Molecular Weight (LMW) Chondroitin Sulfate

(found exclusively in Nutramax Laboratories, Inc. products)

NL 216

Beren J, Hill SL, Diener-West M, et al. Effect of pre-loading oral glucosamine HCl/chondroitin sulfate/manganese ascorbate combination on experimental arthritis in rats. *Experimental Biology and Medicine* 2001;226:144-151.

The effect of FCHG49 glucosamine hydrochloride and TRH122 LMW chondroitin sulfate was investigated in a rat model of collagen-induced autoimmune cartilage breakdown. Fifty rats were used in the study in two groups, placebo and intervention. A statistically significant reduction in the incidence was found in rats administered the combination of FCHG49 glucosamine hydrochloride, TRH122 LMW chondroitin sulfate, and manganese ascorbate, as found in Cosequin®, (54 percent) as compared to the placebo group (96 percent). The degree of severity, assessed both clinically and histologically, was also significantly less in the intervention group.



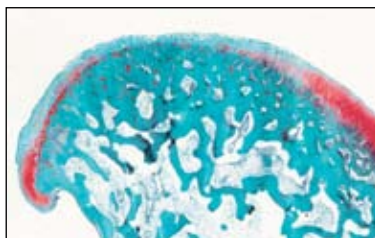
NL 204

Lippiello L, Woodward J, Karpman R, et al. In vivo chondroprotection and metabolic synergy of glucosamine and chondroitin sulfate. *Clinical Orthopaedics and Related Research* 2000;381:229-240.

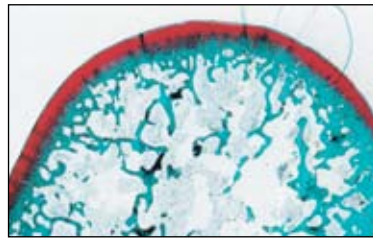
The authors concluded that in-vitro FCHG49 glucosamine hydrochloride and TRH122 LMW chondroitin sulfate together acted synergistically in stimulating chondrocyte proteoglycan synthesis and was superior to administration of glucosamine or chondroitin sulfate alone. In an instability model, no severe cartilage lesions were found in the group administered the combination of FCHG49 glucosamine hydrochloride, TRH122 LMW chondroitin sulfate, and manganese ascorbate, as found in Cosequin, whereas individual agent groups had severe lesions. Only the combination group was significantly different from the placebo.

Group	(N)	Total Grade	P Value	Total Linear Involvement	P Value
Control	(11)	16.6 ± 2.2	---	12.3 ± 1.3	---
Chondroitin SO <sub>4</sub>	(6)	11.0 ± 2.2	NS	7.2 ± 1.2	NS
Glucosamine	(6)	12.2 ± 3.0	NS	8.6 ± 1.0	NS
Manganese Ascorbate	(6)	8.8 ± 1.4	NS	8.8 ± 1.8	NS
Combination of Agents	(11)	4.4 ± 1.0	0.05*	5.1 ± 1.2	0.05*

Values represent the Mean ± SE; NS = Not Significant, \* p < 0.05 by Scheffe Test



Placebo Group

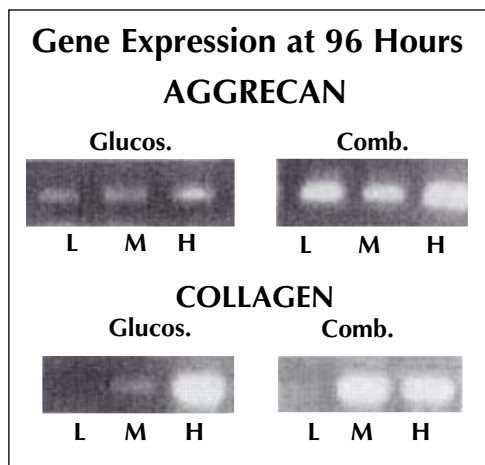


Combination Group

## Additional Studies Evaluating Mechanism of Action Using FCHG49® Glucosamine HCl and TRH122® Low Molecular Weight (LMW) Chondroitin Sulfate

(found exclusively in Nutramax Laboratories, Inc. products)

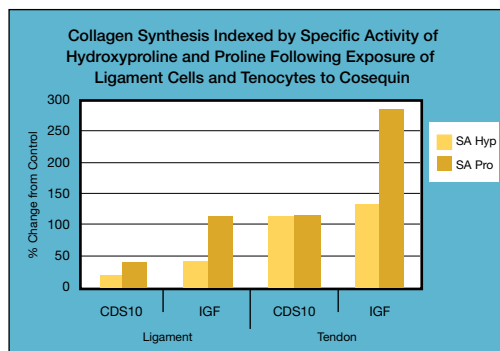
NL 283



O'Grady CP, Marwin SE, Grande DA. Effects of glucosamine hydrochloride, chondroitin sulfate, and manganese-ascorbate on cartilage metabolism, in *Proceedings. AAOS 68th Annual Meeting 2001*; paper #157.

Articular cartilage explants were cultured with FCHG49 glucosamine hydrochloride, TRH122 LMW chondroitin sulfate, manganese ascorbate, and the combination of all three agents or in media alone. The explants cultured in the combination, as found in Cosequin®, compared to controls had greater production of aggrecan (cartilage matrix), the least amount of IL-1 induced aggrecan degradation and had increased expression of the genes coding for both aggrecan and collagen II (see picture at left). The results demonstrated that glucosamine, chondroitin sulfate, and manganese ascorbate may act as signaling molecules for up-regulation of the genes for aggrecan and collagen II, not just as substrates for cartilage production.

NL 411



Lippiello L, Prudhomme A, Kettenacker R. Stimulation of collagen synthesis in bovine chondrocytes, tenocytes and ligament cells by exposure to micro levels of glucosamine HCl and chondroitin sulfate (Cosequin®), in *Proceedings. 32nd Annual Conference Veterinary Orthopedic Society 2005*;56.

In an in vitro study, Cosequin, at very low levels, which can readily be reached with oral administration as per label directions, significantly stimulated collagen synthesis in ligament cells, tenocytes and chondrocytes. This study demonstrated that Cosequin, by enhancing collagen synthesis, can support joint structure and function not only by stimulating cartilage matrix component production but also by helping support ligaments and tendons, the accessory structures, which thereby guards against joint instability.

# Additional Studies Evaluating Mechanism of Action Using FCHG49<sup>®</sup> Glucosamine HCl and TRH122<sup>®</sup> Low Molecular Weight (LMW) Chondroitin Sulfate

(found exclusively in Nutramax Laboratories, Inc. products)

NL 386

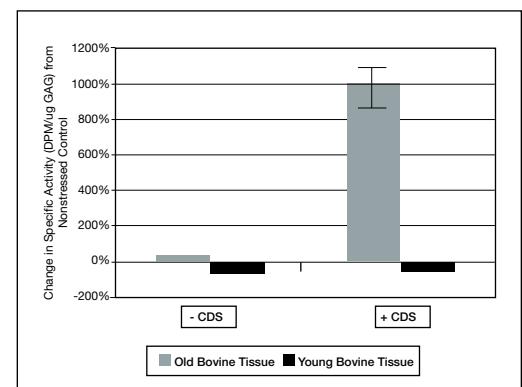
Williams A, Gillis A, McKenzie C, et al. Glycosaminoglycan distribution in cartilage as determined by delayed gadolinium-enhanced MRI of cartilage (cGEMRIC): potential clinical applications. *American Journal of Roentgenology* 2004;182:167-172.

In this pilot study examining the usefulness of delayed gadolinium-enhanced magnetic resonance imaging (MRI) in monitoring the glycosaminoglycan (GAG) content of articular cartilage, effects on GAG content in knee articular cartilage were noted in ten patients administered the combination of FCHG49 glucosamine hydrochloride, TRH122 LMW chondroitin sulfate, and manganese ascorbate, as found in Cosequin<sup>®</sup>. Four of these patients who were very active and had high GAG content initially had no change in GAG content, which indicated that there was no adverse effect from taking the combination. In two other patients, who were recovering from arthroscopic surgery and initially had low GAG content, GAG content increased. Researchers concluded that the combination appeared to support cartilage GAG content in the knee in these patients.

NL 356

Lippiello L. Glucosamine and chondroitin sulfate: biological response modifiers of chondrocytes under simulated conditions of joint stress. *Osteoarthritis and Cartilage* 2003;11(5):335-342.

In an in vitro study evaluating the effects of FCHG49 glucosamine hydrochloride, TRH122 LMW chondroitin sulfate, and manganese ascorbate, as found in Cosequin, on aged and young cartilage under simulated conditions of in vivo joint stress, cartilage from aged animals and cartilage that was stressed were more responsive than were young tissue and non-stressed tissue. The study demonstrated that the exclusive ingredients in Cosequin may act as a Biological Response Modifier (a compound that increases a tissue's own protective mechanisms under adverse conditions) under conditions of joint stress.



Effect of preconditioning cartilage from young and aged bovine joints with glcN plus CS on metabolic response to static pressure. Data expressed as percent change ( $\pm$ S.E.M.) in specific activity of GAG (cpm/mg GAG) of 10 replicates. Young tissue inhibited by -65% with no change after CDS conditioning. Aged tissue uptake stimulated by 40% without conditioning and 1000% after conditioning.

# Additional Studies Evaluating Mechanism of Action Using FCHG49<sup>®</sup> Glucosamine HCl and TRH122<sup>®</sup> Low Molecular Weight (LMW) Chondroitin Sulfate

(found exclusively in Nutramax Laboratories, Inc. products)

## NL 416

Guastella DB, Cook JL, Kuroki K, et al. Evaluation of chondroprotective nutraceuticals in an in vitro osteoarthritis model, in *Proceedings*. 32nd Annual Conference Veterinary Orthopedic Society 2005;5.

Articular cartilage and synovium explants were cultured with FCHG49 glucosamine hydrochloride and IL-1 $\beta$ , TRH122 LMW chondroitin sulfate and IL-1 $\beta$ , or the combination of both compounds along with IL-1 $\beta$ . Either compound alone or IL-1 $\beta$  was added to control cultures. The results showed that in general, FCHG49 glucosamine hydrochloride and TRH122 LMW chondroitin sulfate in combination counteracted the inhibition of expression of cartilage matrix components and of proteinase inhibitors induced by IL-1 $\beta$ . Each agent alone also inhibited the increase in proteinases and inflammatory mediators induced by IL-1 $\beta$ . It was suggested that FCHG49 glucosamine hydrochloride and TRH122 LMW chondroitin sulfate may help protect against cartilage breakdown by inhibiting the effects of IL-1 $\beta$ .

## NL 390

Ray LM, Guo D, Homandberg GA. Mixtures of glucosamine and chondroitin sulfate reverse fibronectin fragment mediated damage to cartilage more effectively than either agent alone. *Osteoarthritis and Cartilage* 2004;12(Suppl B):P328.

In cartilage explants to which fibronectin fragments (fragments that cause loss of cartilage matrix proteoglycans) and physiological levels of a combination of FCHG49 glucosamine hydrochloride and TRH122 LMW chondroitin sulfate were added, significantly less proteoglycan loss occurred. When the combination was added after the depletion of proteoglycan had occurred, the tissue proteoglycan level was restored back to normal. The combination also appeared to increase proteoglycan levels in normal cartilage. Researchers suggested that a synergistic effect may be present between the agents. They proposed that the noted effects were due to stimulation of proteoglycan production.

# Additional Studies Evaluating Mechanism of Action Using FCHG49® Glucosamine HCl and TRH122® Low Molecular Weight (LMW) Chondroitin Sulfate

(found exclusively in Nutramax Laboratories, Inc. products)

NL 392

Chan PS, Caron JP, Orth MW. Glucosamine and chondroitin sulfate regulate IL-1 induced gene expression. *Osteoarthritis and Cartilage* 2004;12(Suppl B):P326.

In this in vitro study using cartilage explants, FCHG49 glucosamine hydrochloride and TRH122 LMW chondroitin sulfate in combination decreased IL-1-induced expression of the genes encoding for several matrix metalloproteinases and aggrecanases implicated in cartilage breakdown. The study provided additional evidence that these agents protect against cartilage breakdown in vitro and may do so via inhibiting gene expression of various proteolytic enzymes.

NL 418

Chan PS, Caron JP, Rosa GJM, Orth MW. Glucosamine and chondroitin sulfate regulate gene expression and synthesis of nitric oxide and prostaglandin E<sub>2</sub> in articular cartilage explants. *Osteoarthritis and Cartilage* 2005;13(5):387-394.

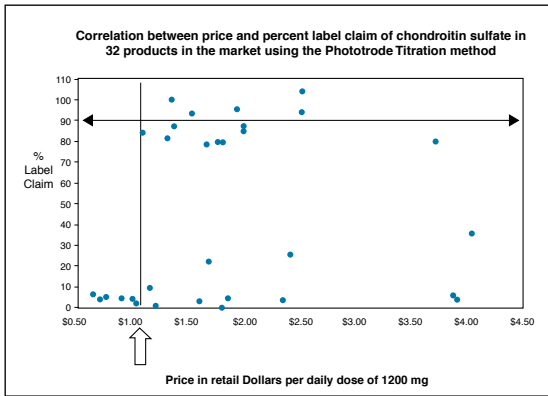
FCHG49 glucosamine hydrochloride with TRH122 LMW chondroitin sulfate at levels that can be reached in the blood inhibited IL-1-induced expression of the genes encoding for nitric oxide (NO) and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and thereby decreased production of NO and PGE<sub>2</sub>. The study provided additional evidence that these agents protect against cartilage breakdown in vitro and may do so via inhibiting gene expression of NO and PGE<sub>2</sub>, which are both implicated in the process.

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FCHG49® glucosamine hydrochloride and TRH122® LMW chondroitin sulfate have been evaluated in numerous human trials. For information on these trials, please request our *Cosamin®DS Clinical and Experimental Studies* booklet.

# 84% OF OTHER BRANDS DON'T MEET LABEL CLAIM

NL 326



Adebowale A, Cox D, Liang Z, et al. Analysis of glucosamine and chondroitin sulfate content in marketed products and the Caco-2 permeability of chondroitin sulfate raw materials. *Journal of the American Nutraceutical Association* 2000;3(1):37-44.

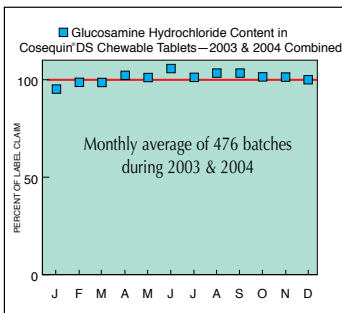
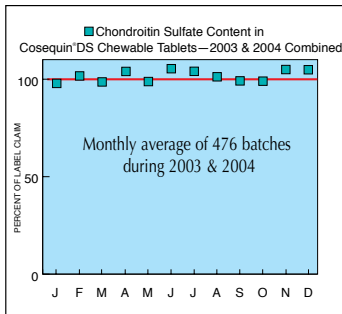
Contents of glucosamine and chondroitin sulfate marketed products were analyzed. Eighty four percent of all tested products did not meet label claim with contents ranging from 0 percent to 115 percent of the label claim. It was shown using an absorption model that some grades of chondroitin sulfate are not absorbed, whereas the low molecular weight form exclusive to Cosequin® had the best absorption profile.

## Use the Researched Product

NL 376

Verges J, Castaneda-Hernandez G. On the bioavailability of oral chondroitin sulfate formulations: proposed criteria for bioequivalence studies, in *Proceedings*. West Pharmacology Society 2004;47:50-53.

The authors note that the chondroitin sulfate (which is used in Cosequin) should be used as the reference standard when evaluating other chondroitin sulfate products. They suggest that other products have not been shown to be bioequivalent.



## The Cosequin Proof of Quality

Raw materials and finished product are tested with validated analytical methods to ensure batch-to-batch consistency.

## ADVICE FROM THE FDA FOR CONSUMERS ABOUT NUTRITIONAL SUPPLEMENTS

Contact the manufacturer for more information about the specific product that you are purchasing. If you cannot tell whether the product you are purchasing meets the same standards as those used in the research studies you read about, check with the manufacturer or distributor. Ask to speak to someone who can address your questions, some of which may include:

- 1 What information does the firm have to substantiate the claims made for the product? Be aware that sometimes firms supply so-called “proof” of their claims by citing undocumented reports from satisfied consumers, or “internal” graphs and charts that could be mistaken for evidence-based research.
- 2 Does the firm have information to share about tests it has conducted on the safety or efficacy of the ingredients in the product?
- 3 Does the firm have a quality control system in place to determine if the product actually contains what is stated on the label and is free of contaminants?
- 4 Has the firm received any adverse events reports from consumers using their products?

**From the FDA website, <http://vm.cfsan.fda.gov/~dms/ds-savvy.html>**

*Please ask us about 1-4 above—we have information, research, an extensive quality control system, and a suspected adverse event reports system in place.*

*The science is in every bottle.*

*Cosequin® is analyzed using validated assay methods  
and is documented in scientific publications to meet label claims.\**

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# COSEQUIN®

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## VETERINARY REVIEW ARTICLES REFERENCING COSEQUIN

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U.S. Patent No. 5,587,363

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▼ Sources: Surveys conducted in October 2001 and March 2004 of small animal veterinarians who recommended oral joint health supplements. Surveys conducted in the Fall of 2002 and March 2004 of equine veterinarians who recommended oral joint health supplements.