08/604 - final

VKM Report 2008: 25

Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

Opinion of the Panel on Animal Feed of the Norwegian Scientific Committee for Food Safety

Adopted 02 June 2008

Assessment of glucosamine and chondroitin in feed

ISBN: 978-82-8082-247-5

CONTRIBUTORS

Persons working for VKM, either as appointed members of the Committee or as *ad hoc* experts, do this by virtue of their scientific expertise, not as representatives for their employers. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

Assessed by

Panel on Animal Feed: Marit Aursand (chair), Heidi Amlund, Aksel Bernhoft, Gro-Ingunn Hemre, Bjørn M. Jensen, Trond Møretrø, Live L. Nesse, Birger Svihus, Ole Torrissen.

Scientific coordinator from the secretariat: Tron Øystein Gifstad

Acknowledgements

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) wishes to acknowledge Aksel Bernhoft (main author) and Birger Svihus for their valuable contribution to this opinion.

SUMMARY

Glucosamine and chondroitine sulphate are endogenous substances in human and animal cartilage, and may be exogenously administered to cure or prevent clinical arthritis. The veterinary products are mainly used in dogs, cats and horses. In Norway, remedies (tablets and powders) for such purposes are prescriptional medicines. The Norwegian Food Safety Authority (Mattilsynet) has asked the Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet,VKM) for a risk assessment regarding allowing glucosamine and chondroitin and analogue substances below an established limit in feed, at which the substances do not have a pharmacological effect, but are of nutritional value.
The Norwegian Food Safety Authority requested that the following aspects should be addressed in particular:

1. An assessment of the risk for classification of products containing glucosamine, chondroitin and analogue substances as complementary feed to horse, dog and cat.
2. An assessment of the concentration of the same substances in feed where there can not be expected any pharmacological effects.

The request has been answered by VKM Scientific Panel on Animal Feed (Panel 6).

The recommended doses are mainly based on results from clinical trials with single intake levels. *In vivo* data on dose-response relationship are lacking. In addition, the substances are available via supplements in some feed products to reduce or prevent joint diseases, and they may also occurring naturally in common complete feed products for carnivores. The concentrations of the substances in the feeds are however, usually not specified. However, neither in EU´s list of feedingstuffs for particular nutritional purposes (Commission directive 2008/38/EC) or in the Norwegian Forskrift om fôrvarer av 7. november 2002, are included particular feedingstuffs to prevent joint diseases. Glucosamine and chondroitine sulphate at the ranges of dosages commonly ingested are regarded as safe and produce no recognisable pattern of adverse effects.

As the substances are endogenously produced and reasonably contribute in a self repair process of the joints, and extra exogenous supplement may increase the curative effect up to a certain dosage level, there is probably no biological threshold for a curative effect of these substances. Setting a threshold dose between pharmacological and non-pharmacological dose would be arbitrary and is not recommended. A distinction between the use of glucosamine

and chondroitin sulphate added in feed products where the purpose is treatment of joint diseases and the use of the substances as prescriptional remedies seems impossible. It may be reasonable to distinguish between this medical use from the use for nutritional purposes when these substances are parts of natural raw materials in feed.

SAMMENDRAG

Glukosamin og kondroitinsulfat er endogent produserte stoffer som finnes i bruskvev hos mennesker og dyr. Stoffene kan også tilføres som behandling eller forebyggelse av leddbetennelse. I veterinærmedisinen benyttes slike preparater hovedsakelig til hund, katt og hest. I Norge er preparater med gluokosamin og kondroitinsulfat (tabletter og pulvere) reseptpliktige. Mattilsynet har bedt Vitenskapskomiteen for mattrygghet (VKM) om å risikovurdere om man kan tillate innhold av glukosaminer, chondroitin og tilsvarende stoffer under en viss grense i fôrvarer, der stoffene ikke har farmakologisk effekt, men har næringsverdi. Mattilsynet ønsket spesielt følgende aspekter belyst:

1. Vurdere risikoen ved å fastsette en grenseverdi for innhold av glukosaminer, chondroitin og tilsvarende stoffer i fôrvarer, der fôrvarer med innhold under grensen kan klassifiseres som tilskuddsfôr til hest, hund og katt.
2. Vurdere på hvilket nivå innhold av glukosaminer, chondroitin og tilsvarende stoffer i fôrvarer er så lavt at det ikke har farmakologisk effekt.

Oppdraget er besvart av VKMs faggruppe for fôr til terrestriske og akvatiske dyr (Faggruppe 6).

Anbefalte doser er i all hovedsak basert på resultater fra kliniske utprøvninger/forsøk der en har benyttet kun ett doseringsnivå. Det mangler *in vivo*-data på dose-respons forhold. Glukosamin og kondroitinsulfat er også tilsatt i en del fôrprodukter for å redusere eller forebygge leddlidelse. Konsentrasjonene av stoffene i fôret er vanligvis ikke angitt. For øvrig er glukosamin og kondroitinsulfat naturlig til stede i vanlig fullfôr til kjøttetere (hund og katt). Diettfôr for å hindre leddlidelse er imidlertid ikke med på EUs liste over fôr for spesielle ernæringsformål (Commission directive 2008/38/EC) eller i den norske Forskrift om fôrvarer av 7. november 2002. Glukosamin og kondroitinsulfat ved de dosene som vanligvis inntas, regnes som trygge og det er ingen gjenkjennelig bivirkningsprofil.

Da stoffene produseres i kroppen og bidrar i normalt vedlikehold av leddene, og inntak ved ekstra behov kan øke den helbredende effekten opp til et visst nivå, er det sannsynligvis ingen biologisk terskel for en helbredende effekt av disse stoffene. Å sette en terskeldose mellom farmakologisk og ikke-farmakologisk ville være vilkårlig og kan ikke anbefales. Det synes umulig å skille mellom bruken av gluksoamin og kondroitinsulfat tilsatt i fôrprodukter der formålet er å helbrede leddproblemer og bruken av stoffene i medisinske preparater. Det kan være mer naturlig å skille mellom bruk med medisinsk hensikt på den ene siden og på den annen side bruk som næringsstoff hvor disse forbindelsene finnes som naturlige ingredienser i fôrråvarer.

BACKGROUND

Glucosamine is an aminomonsaccharide and is the principal component of O-linked and N-linked glycosaminoglycans, forming the matrix of all connective tissues, including cartilage. The raw material for glucosamine supplements has historically been derived form extraction of chitin, a component of shellfish. Recent technological advances have led to a more efficient means of production of a vegetarian source by fermentation (Hathcock and Shao, 2007). Chondroitin is a glycosaminoglycan with a polymerised disaccharide base. It is found in the proteoglycans of articular cartilage. As a dietary supplement, chondroitin is usually derived from bovine trachea, although other sources such as ovine or porcine trachea and shark skeleton are also used (Hathcock and Shao, 2007).

There are several remedies for human use as well as veterinary remedies (tablets and powders) and complementary feeds available on the market containing glucosamine, or glucosamine and chondroitin to reduce symptomes concerning arthrosis. The veterinary products are mainly for dogs, cats, and horses. Raw materials containing glucosamine and chondroitin are also supplements in complete diet feed products to reduce joint diseases. The concentrations of the substances, are however, usually not specified. Furthermore, some producers of animal feed emphasize the content of these compounds in their common complete feed products. In fact, complete feed products for dogs and cats (carnivores) have a certain but unspecified content of glucosamine and chondroitin as the substances are natural components in the raw materials.

In Norway, these substances are principally classified as prescriptional medicines, both for animals and humans. However, within the EU they are considered as “borderline” products and do not have a common classification. Several countries have national regulations for these substances; some classify glucosamine and chondroitin for animal use as medicines, whilst other countries classify them as feedingstuffs for particular nutritional purposes or even as common feedingstuffs. However, particular feedingstuffs against joint diseases are not included on EU´s list of feedingstuffs for particular nutritional purposes (Commission directive 2008/38/EC) or in the Norwegian Forskrift om fôrvarer av 7. november 2002. That common carnivorous feeds by nature contain some glucosamine and chondoitin, or elevated concentrations of these substances by supplementation for nutritional or clinical purposes may interfere with the classification as prescriptional medicine. These problems are elucidated in the present opinion.

TERMS OF REFERENCE

The Norwegian Food Safety Authority commissions the Norwegian Scientific Committee for Food Safety (VKM) for a risk assessment regarding allowing glucosamine and chondroitin and analogue substances below an established limit in feed, at which the substances do not have a pharmacological effect, but are of nutritional value. The content with respect to the limit will determine whether products with these substances should be classified as prescriptional remedies or feedingstuffs.

The Norwegian Food Safety Authority requests that the following aspects will be addressed in particular:

1 An assessment of the risk for classification of products containing glucosamine, chondroitin and analogue substances as complementary feed to horse, dog and cat.
2 An assessment of the concentration of the same substances in feed where there can not be expected any pharmacological effects.

ASSESSMENT

The panel has the opinion that the term “glucosamine, chondroitin and analogue substances” is inaccurate, and will prefer to use the term “glucosamine and chondroitin”. However, conclusions on glucosamine and chondroitin may be of principal relevance for other analogue substances.

Chemistry and pharmacokinetics

Glucosamine is produced in the animal and human body by the addition of an amino group to glucose. This molecule is subsequently acetylated, and sulphate may then be added at 4- or 6-position and constructs glycosaminoglycans (Deal and Moskowitz, 1999). Chondroitin sulphate is a specific glycosaminoglycan.

In commercial production of glucosamine and chondroitin, an enzymatic depolymerization appears to be common (Sim et al., 2007). Glucosamine based on shellfish can be extracted from purified shells (chitin) by the use of hydrochloric acid (Mojarrad et al., 2007), and chondroitin can be extracted from trachea by the use of the enzyme papain (Lagocka et al., 1997). Thus, commercial products used as supplements will in many cases be different from products found naturally in feed components, e.g. meat and bone meal or shrimp shells. Digestibility values for intact cartilage and of shellfish shells has not been found in literature, but both these substances appears to be digested to some extent even when in native form, since acid hydrolysis will to some extent depolymerize the mucopolysaccharide (Mojarrad et al., 2007).

Both endogenous and exogenously administered glucosamine may be involved in the synthesis of components of cartilage and synovial fluid. The sulphate moiety plays an important role in the synthesis of proteoglycans, because the constituent glycosaminoglycans are highly sulphated.

The main form of glucosamine in ingestable products is as sulphate, but other forms as hydrochloride, N-acetyl or chlorhydrate salt or as a dextrorotatory isomer may also be available. Following oral administration of glucosamine sulphate in humans and dogs, at least 90 % is absorbed (Deal and Moskowitz, 1999). Approximately 20-30 % subsequently appears in the urine, and up to 70 % appears as exhaled CO2, with approximately 8-12 % retained in

the tissues. The other forms of glucosamine, though less studied, may have different kinetics and reduced therapeutic effect. Chondroitin sulphate is a larger molecule which is much less absorbed. Deal and Moskowitz (1999) indicate less than 10 % absorption.

Pharmacologcal effect and dosage level

Glucosamine and chondroitin sulphate are popular substances intended to support joint health in man and animals. A large body of human and animal reseach suggests that oral intake of these ingredients either alone or in combination, reduces joint pain and improves mobility. Long time treatment may also modify the progession of osteoarthritis (Matheson and Perry, 2003; Hathcock and Shao, 2007). Both glucosamine and chondroitin sulphate have a beneficial role in cartilage metabolic responses and anti-inflammatory effects (Deal and Moskowitz 1999). Glucosamine has been characterised as a slow-acting drug and the effect may elicite after 2-4 weeks. Most studies concern glucosamine as the main substance. Chondroitin sulphate is an additional compound in several studies, and contribute together with glucosamine is to slow the process of osteoarthritis.

The recommended human dose of glucosamine in Norway is 1200 mg/day for adults (Legemiddelverket, 2005). General human doses recommended in international reviews on glucosamine and chondroitin sulphate are 1500 mg/day for glucosamine, and it may be combined with chondroitin sulphate at 1200 mg/day (Deal and Moskowitz 1999; Matheson and Perry, 2003). Hathcock and Shao (2007) indicate safe upper supplement levels of 2000 mg/day of glucosamine and 1200 mg/day of chondroitin sulphate.

The used dosage level of glucosamine related to body weight in animals is quite similar the human dosage, and chondroitine sulphate is included at a certain level. As an example, the recommended doses of a veterinary remedy which contains glucosamine- and chondroitin sulphate are as follows: For adult horses (500-600 kg) with arthritis, a dose of 10.000 mg glucosamine sulphate and 2.000 mg chondroitin sulphate per day is recommended. The recommended dose for miniature dogs (<5 kg) and cats with arthritis is relatively high, 400 mg glucosamine sulphate and 80 mg chondroitin sulphate per day. For larger dogs weighing 20-40, the recommended daily dose is 1000 mg glucosamine sulphate and 200 mg chondroitin sulphate. For dogs above 50 kg is the recommended daily dose 1400 mg glukosamine

sulphate and 280 mg chondroitin sulphate. After clinical improvement or for preventive use, lower maintainance doses (50 %) are recommended for the animals.

The recommended doses of glucosamine and chondroitin sulphate are mainly based on results from clinical trials. Most of the data relate to single intake levels, and no systematic study of the dose-response relationship has been conducted (Hathcock and Shao, 2007). In addition, there are *in vitro* data on mechanisms of actions. There are data on dose-response relationship among these *in vitro* results, but they are of little value in trying to establish a non-pharmacological-effect level *in vivo*. That the substances are also endogenously produced is a complicating factor where the purpose is to find a threshold between non-pharmacological and pharmacological effect.

It is reasonable to maintain that the endogenous production of glucosamine and chondroitin contributes in a self repair process, which may succeed or not in conditions of arthritis. The inflamed joint may need additional help of exogenous supplement of these substances together with the normal endogenous processes for maintainance and regeneration of the joints. Thus, the exogenous supplement of glucosamine and chondroitin sulphate may imply an additional level of curative substances. This effect may increase with dose up to a certain level, which by experience has been set as the recommended observed safe level. There is probably no biological threshold for a curative effect of these substances. Any dose might improve the condition in a continuous matter. A threshold dose between pharmacological and non-pharmacological dose would be arbitrary.

Adverse effects

In general, the evidence suggests that glucosamine and chondroitin sulphate at the ranges of dosages commonly ingested are safe and produce no recognisable pattern of adverse effects (Hathcock and Shao, 2007). Patients with shellfish allergy may not use glucosamine from shellfish. Systematic evaluation of the reseach designs and data do not provide a basis for risk assessment and the usual safe upper level of intake derived from it. Thus, the highest levels used in clinical trials have been observed safe, and these levels have been identified as observed safe intake levels (Hathcock and Shao, 2007). The LD_{50} for glukosamin hydrochloride is greater that 5000 mg/kg, and the NOAELs in rats and dogs are 2700 and 2150 mg/kg body weight, respectively (Anderson et al., 2005).

There does not seem to be a principal toxicological risk for classification of products containing glucosamine and chondroitin as complementary feed. However, a distinction between their use as prescriptional medicine in tablets or powders and their use in feed supplied with the substances to cure joint diseases seems impossible. Thus, the difference between regarding glucosamine and chondroitin sulphate as prescriptional medicine or as substances in complementary/complete feed may lay in the purpose for its use. If the substances are used to cure arthritis, it is reasonably medical use. If the substances occur in the product as parts from the raw material used as feedingstuff, they are feed nutrients.

If the raw material for the substances comes from animal sources, the risk of using the products for herbivorous spieces (horses or others) has to be considered.

CONCLUSIONS

• Glucosamine and chondroitine sulphate are enodenous substances in human and animal cartilage, and may be exogenously administered to cure clinical arthritis. The veterinary products are mainly used in dogs, cats and horses. In Norway, remedies (tablets or powders) containing glucosamine and chondroitin sulphate against the joint disease are prescriptional medicines. In addition, the substances are available via supplements in some feed products to reduce or prevent joint diseases, and they are also occurring naturally in common complete feed products for carnivores.

• Glucosamine and chondroitin sulphate at the ranges of dosages commonly ingested are regarded as safe and produce no recognisable pattern of adverse effects. Thus, principally, there does not seem to be a toxicological risk for classification of products containing glucosamine and chondroitin as complementary feed.

• The recommended doses are mainly based on results from clinical trials with single intake levels. *In vivo* data on dose-response relationship are lacking. However, as the substances are endogenously produced and reasonably contribute in a self repair process of the joints, and extra exogenous supplement may increase the curative effect up to a certain dosage level, there is probably no biological threshold for a curative effect of these substances. Thus, a

threshold dose between pharmacological and non-pharmacological dose would be arbitrary and is not recommended.

- A distinction between the use of glucosamine and chondroitin sulphate added in feed products where the purpose is treatment of joint diseases and the use of these substances as prescriptional remedies seems impossible. Is is reasonable to distinct this medical use from the use for nutritional purposes when these substances are parts of natural raw materials in feed.

REFERENCES

Anderson, J.W., Nicolosi, R.J., Borzelleca, J.F. 2005. Glucosamine effects in humans: a review of effects on glucose metabolism, side effects, safety considerations and efficacy. Food Chem. Toxicol., 43: 187-201.

Commission directive 2008/38/EC of 5 March 2008 establishing a list of intended uses of animal feedingstuffs for particular nutritional purposes.

Deal, C.L., Moskowitz, R.W. 1999. Nutraceuticals as therapeutic agents in osteoarthritis. The role of glucosamine, chondroitine sulphate, and collagen hydrolysate. Rheumatic Dis. Clin. North Am., 25(2): 379-395.

Hathcock, J.H., Shao, A. 2007. Risk assessment for glucosamine and chondroitin sulfate. Reg. Toxicol. Pharmacol., 47: 78–83.

Lagocka, J., Sadowska, M., Synowlecki, J. 1997. Separation and characteristics of different mucoplysaccharides from bovine trachea cartilage. Food Chem., 60: 533-536.

Landbruksdepartementet, Fiskeridepartementet. 2002. Forskrift om fôrvarer av 7. november 2002.

Legemiddelverket. 2005. Glukosamin. Nytt om legemidler, 2: 12-14.

Matheson, A.J., Perry, C.M. 2003. Glucosamine. A review of its use in the management of osteoarthritis. Drugs Aging, 20(14): 1041-1060.

Mojarrad, J.S., Nemati, M. Valizadeh, H., Ansarin, M., Bourbour, S. 2007. Preparation of glucosamine from exoskeleton of shrimp and predicting production yield by response surface methodology. J. Agric. Food Chem., 55: 2246-2250

Sim, J.S., Im, A.R., Cho, S.M., Jang, H.J. 2007. Evaluation of chondroitin sulfate in shark cartilage powder as a dietary supplement: Raw materials and finished products. Food Chem., 101: 532–539.