Risk assessment for glucosamine and chondroitin sulfate

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Abstract

Glucosamine and chondroitin sulfate are two popular dietary ingredients present in dietary supplements intended to support joint health. A large body of human and animal research suggests that oral intakes of these ingredients, either alone or in combination, reduces joint pain and improves mobility in persons with osteoarthritis. The increased awareness and use of these ingredients in dietary supplements warrant a comprehensive review of their safety. Systematic evaluation of the research designs and data do not provide a basis for risk assessment and the usual safe upper level of intake (UL) derived from it unless the newer methods described as the observed safe level (OSL) or highest observed intake (HOI) are utilized. The OSL risk assessment method indicates that the evidence strongly supports safety at intakes up to 2000 mg/d for glucosamine, and 1200 mg/d for chondroitin sulfate, and these levels are identified as the respective OSL. These values represent the highest levels tested in human clinical trials. The complete absence of adverse effects at these levels supports a confident conclusion of their long-term safety.

Keywords: Glucosamine; Chondroitin sulfate; Upper level of intake (UL); Observed safe level (OSL)

1. Introduction

Glucosamine is an aminomonosaccharide and it is the principal component of O-linked and N-linked glycosaminoglycans, which form the matrix of all connective tissues, including cartilage (Harris et al., 2005). The evidence that orally administered glucosamine compounds may be effective in ameliorating pain due to osteoarthritis has been accumulating for 30–40 years (Deal and Moskowitz, 1999). Dietary supplements in the United States may contain glucosamine hydrochloride, glucosamine sulfate, or N-acetyl-glucosamine. The raw material for glucosamine supplements has historically been derived from extraction of chitin, a component of shellfish (shrimp, crab, and lobster). Recent technological advances have led to a more efficient means of production of a vegetarian source by fermentation (Almada, 2003). Numerous clinical trials have investigated the efficacy of oral glucosamine compounds, often in combination with chondroitin sulfate, in individuals with osteoarthritis. Long-term (3 year) clinical trials (Reginster et al., 2001; Pavelka et al., 2002), clinical trials of various durations (Drovanti et al., 1980; Pujalte et al., 1980; Muller-Fassbender et al., 1994; Noack et al., 1994; McAlindon et al., 2004; Clegg et al., 2006) and meta-analyses (McAlindon et al., 2000; Richy et al., 2003; Zerkak and Dougados, 2004); (Poolsup et al., 2005; Towheed et al., 2005) support the efficacy and safety of oral glucosamine in osteoarthritis. In general, the evidence suggests that glucosamine, at the range of dosages commonly consumed, is not toxic and produces no recognizable pattern of adverse effects. Most of the data relate to a single intake level, namely 1500 mg/d, although this is sometimes divided into three or more individual doses. While most published studies have been on the sulfate form, a few have used the hydrochloride form. One 12-week clinical trial involved a daily dose of 2000 mg of glucosamine hydrochloride (Braham et al., 2003).

Chondroitin sulfate is a glycosaminoglycan with a polymerized disaccharide base linked to a sulfate group, and is...
found in the proteoglycans of articular cartilage (Harris et al., 2005). As a dietary supplement, chondroitin sulfate is usually derived from bovine trachea, although other sources such as ovine or porcine trachea and shark skeletons (shark cartilage) are also used in some dietary supplements (Nagib, 2003). The concept that orally administered chondroitin sulfate, along with glucosamine, might slow the process of osteoarthritis has also been recognized for decades. Numerous clinical trials have investigated the efficacy of oral chondroitin sulfate and/or glucosamine in individuals with osteoarthritis. Meta-analysis tends to support the assertion of efficacy (Rovetta and Monteforte, 1996; Bourgeois et al., 1998; McAlindon et al., 2000; Richy et al., 2003). In general, the evidence suggests that chondroitin sulfate, at the range of dosages commonly consumed (usually 1200 mg/d), is not toxic and produces no recognizable pattern of adverse effects. Most of the data relate to single intake levels, and no systematic study of the dose–response relationship has been conducted.

The increase in both public awareness and usage of these ingredients in dietary supplements warrants a comprehensive review of their safety. Most upper safe levels of nutrients and related substances are based on widely applicable risk assessment models used by the US Food and Nutrition Board (FNB) in its Dietary Reference Intakes documents in 1997 and after (Food and Nutrition Board, Institute of Medicine, 1997, 1998a, b, 2000, 2001). The FNB method and reviews are a formalization and extension of the quantitative methods widely used earlier in risk assessment of other substances, and by the food and dietary supplement industries. Because of the systematic, comprehensive and authoritative character of the FNB risk assessment method for nutrients, this approach has gathered widespread support and adoption by others such as the European Community Scientific Committee on Food (SCF) (European Commission, 2001), the United Kingdom Expert Group on Vitamins and Minerals (EVM) (Food Standards Agency, 2003) and more recently by the Food and Agriculture Organization/World Health Organization project report A Model for Establishing Upper Levels of Intake for Nutrients and Related Substances (FAO/WHO, 2006) with some slight modifications. All these reports reflect the concepts and procedures established much earlier for the risk assessment of non-carcinogenic chemicals (National Research Council, 1983).

2. Methods

The safety evaluation method applied to orally administered glucosamine or chondroitin sulfate is that of the Council for Responsible Nutrition (CRN) Vitamin and Mineral Safety, 2nd ed. (Hathcock, 2004), which contains the basic features of the FNB method and also the observed safe level (OSL) modification recently adopted as a highest observed intake (HOI) in the FAO/WHO report.

Overall, this risk analysis was derived from the human clinical trial database through the following major steps:

1. Derive a safe upper level of intake (UL) if the data are appropriate:
   (a) Search for data that identify a hazard related to excessive intake.
   (b) Assess the dose–response relationship for the identified hazard.
   (c) Consider uncertainty and assign an uncertainty factor (UF).
   (d) Derive a UL from the no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL), and the UL = NOAEL/UF.

2. If no data establish adverse effects in humans, the above procedure cannot be used. In these circumstances, the highest intake level with sufficient evidence of safety is identified as a value named the OSL by CRN and the HOI by FAO/WHO. Uncertainty is considered in selection of the OSL value and the selection is made with sufficient conservatism to justify assignment of UF = 1.0.

We applied the first procedure to the glucosamine and chondroitin sulfate human trial data and found no basis for a NOAEL or LOAEL, and thus could not derive a classical UL. Consequently, we applied the OSL procedure to the clinical trial data, with the results described in the sections below.

Due to the nature of the raw material sources for these two ingredients, there is little, if any dietary contribution, and therefore the OSL value identified from the trials does not require correction for dietary intakes, and the OSL can be identified as a safe upper level for supplements (ULS).

3. Scientific evidence related to safety—glucosamine

3.1. Human studies

Publications on the clinical trials of glucosamine for effectiveness in osteoarthritis also contained much useful information relating to safety. None of the clinical trials have found significant patterns of adverse effects related to glucosamine consumption (Deal and Moskowitz, 1999; Reginster et al., 2001; Pavelka et al., 2002; Richy et al., 2003; Zerkak and Dougdos, 2004; Clegg et al., 2006). In the clinical trials of three duration, substantial numbers of several different adverse health events occurred in both the placebo and the treatment groups, but none of the small differences in adverse event frequency approached statistical significance (Reginster et al., 2001; Pavelka et al., 2002). The conclusions from these studies are further supported by the absence of significant adverse effects in other clinical trials (Drovanti et al., 1980; Pujalte et al., 1980; Muller-Fasbender et al., 1994; Noack et al., 1994; Braham et al., 2003; McAlindon et al., 2004; Clegg et al., 2006). Human clinical trial data have shown no cause for concern about the safety of oral glucosamine at current and plausible intakes (Matheson and Perry, 2003; Bruyere et al., 2004).

Speculation over a causal relationship between glucosamine intake and diabetes has led to the investigation of the possible effects on insulin function and glucose metabolism, but not always with an appropriate experimental protocol. Infused glucosamine can increase the hexosamine pathway flux, suggesting a potential adverse effect of this supplement on glucose homeostasis (Monauni et al., 2000). The hexosamine pathway activation leads to deterioration of pancreatic β-cell function, thereby posing the possibility that glucosamine could enhance the risk of diabetes (Kaneto et al., 2001; Yoshikawa et al., 2002).

Concerns about a possible adverse effect of glucosamine on glucose homeostasis or diabetes have prompted direct
evaluation of these endpoints in clinical trials. One clinical trial administered a daily dose of 1500 mg glucosamine hydrochloride for 90 days and found no effects on hemoglobin A1c concentrations in diabetic subjects (Scroggie et al., 2003), and another found no effects of 1500 mg/d of glucosamine sulfate on blood glucose or serum insulin in normal volunteers after 12 weeks (Tannis et al., 2004). Thorough review of the evidence on this relation of glucosamine to glucose metabolism and function reveals no adverse effects (Anderson et al., 2005). Thus, concerns about a possible diabetogenic effect of glucosamine that arose from biochemical studies have been investigated in clinical trials, and the human data directly demonstrate that this effect does not occur in normal or diabetic subjects who consume 1500 mg/d of glucosamine for up to 12 weeks. Because of the small size of the clinical trials involved, the possibility of an effect in sensitive individuals cannot be entirely excluded.

The highest glucosamine dosage utilized in a double-blind, placebo-controlled, randomized clinical trial was 2000 mg of glucosamine hydrochloride/d for 12 weeks in subjects with osteoarthritis of the knee (Braham et al., 2003). Subjects (24 assigned to glucosamine and 22 to placebo) were monitored for the side effects of nausea/vomiting, gastrointestinal upset/cramps, headache, bloating, dry mouth, and tenderness in the knee. The total side effects reported were similar, with 11 among the 24 subjects in the glucosamine group and 10 among the 22 placebo controls, with no significant differences in any category.

The NIH-sponsored glucosamine/chondroitin arthritis intervention trial (GAIT) involved more than 1500 osteoarthritis patients who ingested 1500 mg/d glucosamine hydrochloride, 1200 mg/d chondroitin sulfate, the combination of the two, 200 mg/d of the prescription pain medication Celebrex™, or placebo for 24 weeks (Clegg et al., 2006). Adverse effects were closely monitored throughout the study period. A total of 634 patients were exposed to glucosamine hydrochloride. Results showed no significant difference in the incidence of adverse effects between any of the treatment arms.

The glucosamine fraction of total weight is higher with the hydrochloride than with the sulfate; the bioavailability of both forms exceeds 90%, with glucosamine hydrochloride approaching 100% (Deal and Moskowitz, 1999; Matheson and Perry, 2003; Institute of Medicine, 2005; Anderson et al., 2005). With these chemical differences and bioavailability similarities, the safety conclusions reached for hydrochloride can be appropriately and confidently extrapolated to the sulfate.

3.2. Animal and in vitro studies

The large number of animal and in vitro studies addressing the safety as well as the metabolism and metabolic effects of glucosamine have been reviewed in detail (Anderson et al., 2005). The LD50 of glucosamine hydrochloride is greater than 5000 mg/kg, and the NOAEL is 2700 mg/kg in rats and 2149 mg/kg in dogs (Anderson et al., 2005). Assuming a 60 kg adult body weight, the 1500 mg daily dose in humans amounts to 25 mg/kg, and the 2000 mg dose equals 33 mg/kg. Thus, extrapolation of the extensive data obtained from the animal and in vitro toxicology studies suggests that adverse effects are unlikely in humans.

4. Human NOAEL or OSL (HOI)—glucosamine

4.1. NOAEL or LOAEL

None of the clinical trials found adverse effect related to glucosamine administration in any form, and therefore there is, by definition, no basis for identifying a LOAEL. In the absence of a LOAEL, a NOAEL is not usually set. Without either of these two values the establishment of a UL is not appropriate (Food and Nutrition Board, Institute of Medicine, 1998b).

4.2. OSL

The glucosamine dosage that was utilized in most clinical trials seems to be 1500 mg/d. The one clinical trial that used 2000 mg of glucosamine hydrochloride found no adverse effects. There are ample data to identify 1500 mg of glucosamine sulfate as the OSL. The absence of adverse effects in clinical trial at 2000 mg of glucosamine hydrochloride, together with the huge margins of safety indicated by animal studies and the direct evidence against a diabetogenic effect in humans is sufficient grounds for setting the OSL at 2000 mg of glucosamine hydrochloride. Further, the differences in glucosamine content and bioavailability allow this OSL to be applied to glucosamine sulfate as well.

In one placebo-controlled, double-blind randomized clinical trial of glucosamine hydrochloride (1500 mg) in combination with chondroitin sulfate (1200 mg) two subjects in the active group experienced allergic responses, compared with none in the placebo group (Nguyen et al., 2001). The combined treatment prevents attribution of the effect to a specific ingredient, but allergic responses related to glucosamine of shell fish origin have been reported previously (Anderson et al., 2005). In the US, supplement products containing glucosamine from this source are required carry an allergy warning statement (US Food and Drug Administration, 2004). Glucosamine derived from plant sources would not need such warnings.

Identification of 2000 mg/d as the OSL for oral consumption of glucosamine (either the hydrochloride or the sulfate) carries little uncertainty, due to the confidence gained from substantial safety in animal and in vitro tests.

The subjects in the clinical trials would have been consuming little-to-no glucosamine in their diet, and therefore the quantities of glucosamine added in clinical trials discussed were supplemental amounts well above the very small quantities potentially consumed in foods. Therefore,
no correction is required for glucosamine in the food supply and this risk assessment represents a direct approach to the safe upper level for supplements (ULS). No correction is needed for the glucosamine in the food supply. The OSL for glucosamine set at 2000 mg is also identified as the ULS. Allergic warnings are appropriate and required only for products including glucosamine of shell fish origin.

NOAEL and LOAEL: No toxicological basis.
OSL: 2000 mg glucosamine compound (hydrochloride or sulfate).
ULS: 2000 mg/d.

5. Scientific evidence related to safety—chondroitin sulfate

5.1. Human studies

Several clinical trials have involved the oral administration of chondroitin sulfate (Rovetta and Monteforte, 1996; Bourgeois et al., 1998; Mazieres et al., 2001; Verbruggen et al., 2002; Rovetta et al., 2004; Uebelhart et al., 2004; Clegg et al., 2006). The age, health conditions, dosage, duration, and monitoring and evaluation methods have differed greatly. For confidence in the results, those studies with stronger designs carry more weight regarding a conclusion of safety at that dosage. In a risk assessment, the studies with strong designs and involving higher dosages deserve greater weight in identifying the highest dosage that can be confidently concluded to carry no identifiable risk of adverse effects.

The highest oral chondroitin sulfate dosage administered in published clinical trials is 1200 mg/d (Bourgeois et al., 1998; Verbruggen et al., 2002; Clegg et al., 2006). Other trials have utilized dosages of 1000 mg (Mazieres et al., 2001) and 800 mg (Rovetta and Monteforte, 1996; Rovetta et al., 2004; Uebelhart et al., 2004). The number of subjects in the trials varied from 12 to 635, and the clinical monitoring capable of detecting adverse effects ranged from sparse to extensive (e.g., self-reports of possible adverse effect to clinical evaluation combined with extensive hematological and clinical chemistry indices). None of these clinical trials found any significant adverse effects.

The clinical trial by Verbruggen and coworkers (Verbruggen et al., 2002) is especially convincing regarding the safety of oral chondroitin sulfate. It involved 165 subjects treated for 3 years with an oral dose of 1200 mg/d. The monitoring included examination by three physicians. The adverse events were closely monitored throughout the study period. A total of 635 patients were exposed to chondroitin sulfate. Results showed no significant difference in the incidence of adverse effects between any of the treatment arms. None of the clinical trials found any adverse effects on clinical chemistry (blood and urine) or hematological measurements resulting from oral chondroitin sulfate.

The clinical trial evidence has been the subject of four published meta-analyses (Leeb et al., 2000; McAlindon et al., 2000; Edelist and Evans, 2001; Richy et al., 2003) and one review/commentary (McAlindon, 2001). These publications focused primarily on the benefits of oral chondroitin sulfate in limiting the progression of osteoarthritis, but they also have relevance to the safety of this ingredient. The meta-analyses support the safety of oral chondroitin sulfate at 1200 mg/d, the highest intake systematically studied.

5.2. Human NOAEL

The absence of adverse effects at any of the dosages used in the clinical trials does not support identification of a LOAEL or NOAEL. The evidence indicates no adverse effect of 1200 mg/d of oral chondroitin sulfate, but does not suggest at what dosage adverse effects might occur. Therefore there is, by definition, no basis for identifying a LOAEL. In the absence of a LOAEL, a NOAEL is not usually set. Without either of these two values the establishment of a UL is not appropriate.

6. Human NOAEL or OSL (HOI)—Chondroitin sulfate

6.1. OSL

The highest chondroitin sulfate dosage that has been utilized in clinical trials is 1200 mg/d. There are sufficient data at this level to identify it as the OSL. The nearly complete absence of any adverse effects of chondroitin sulfate within the range of the clinical trials reviewed (800–1200 mg/d) suggest that the highest level, 1200 mg/d, is not a true NOAEL and that any LOAEL is likely to be much higher. The single case of gastritis among hundreds of subjects treated suggests that this one case is not causally related to chondroitin sulfate, or that the individual had a very unusual sensitivity, and should not influence the outcome of the risk assessment. Identification of 1200 mg/d as the OSL for oral consumption of chondroitin sulfate up to three years by adults carries little uncertainty—there are no known adverse effects to be avoided. Due to the relatively low consumption of chondroitin sulfate in the diet, this risk assessment represents a direct approach to the ULS. Therefore, the OSL of 1200 mg is identified as the ULS.
6.2. Animal studies

Because the human clinical trial data are judged sufficient to support identification of an OSL value, the data from animal experiments were not reviewed.

NOAEL and LOAEL: no toxicological basis
OSL: 1200 mg chondroitin sulfate
ULS: 1200 mg/d

7. Conclusions

Glucosamine and chondroitin sulfate are two dietary ingredients whose use continues to increase among Americans in the form of dietary supplements. While a substantial body of evidence exists supporting the beneficial effects of these on joint health, official documentation of their safety using risk assessment has not, to our knowledge, yet been published. The present review of the available published human clinical trial data involving glucosamine and chondroitin sulfate, along with several published meta-analyses, provide for a high level of confidence in the safety of these ingredients. The absence of a well-defined critical effect for either ingredient precludes the selection of a NOAEL or LOAEL, and therefore required use of the observed safe level (OSL) or highest observed intake (HOI) approach established by FAO/WHO to conduct this risk assessment. Evidence from well-designed randomized, controlled human clinical trials indicates that the ULS for is 2000 mg/d for glucosamine and 1200 mg/d for chondroitin sulfate.

References


