SUMMARY OF DATA FOR CHEMICAL SELECTION

Chondroitin Sulfate
9007-28-7
9082-07-9

BASIS OF NOMINATION TO THE CSWG

Chondroitin sulfate is brought to the attention of the Chemical Selection Working Group because it is widely used in dietary supplement that would be consumed over a period of many years to maximize potential beneficial effects. No chronic toxicity studies to support the safety of such long-term use were found in the available literature.

Used with glucosamine, chondroitin sulfate alleviates pain and inflammation from osteoarthritis and reportedly has a beneficial effect on degenerated joints. Thus dietary supplements containing glucosamine and chondroitin sulfate have a potential market of tens of millions of Americans who suffer from osteoarthritis, athletes and dancers who may have joint overuse, and aging baby boomers interested in maintaining their joints.

Chondroitin sulfate is a glycosaminoglycan that functions as a component of proteoglycans. Proteoglycans are found throughout the human body, forming the intricate extracellular matrix. Glycosaminoglycans have also interactive roles in cell-cell recognition and cell growth.

Virtually no information on the potential toxicity of chondroitin sulfate was found in the available literature. This chemical has been described as a teratogen in the older literature; this possible effect needs to be examined using modern approaches.

SELECTION STATUS

ACTION BY CSWG: June 20, 2002

Studies requested:

- Carcinogenicity – chondroitin sulfate alone
- Carcinogenicity – chondroitin sulfate in combination with glucosamine

Priority: High

Rationale Remarks:

- CSWG will consider additional special mechanistic studies at a later date
- Widespread consumer exposure from use in dietary supplements
- Used in dietary supplements to affect chronic conditions, e.g., osteoarthritis, suggesting long-term consumer exposure
- No information whatsoever on the possible adverse or toxic effects from long term (multiyear) exposures

CHEMICAL IDENTIFICATION

CAS Registry Number: 9007-28-7
9082-07-9 (sodium salt)

Chemical Abstracts Service Name: Chondroitin sulfate (9CI)

Synonyms: 9007-28-7: chondroitin sulfuric acid, chondroitin polysulfate, chonsurid, chondroitin sulphate (ChemID, 2002)

9082-07-9: chondroitin hydrogen sulfate, sodium salt; chondron; chondroitin polysulfate sodium; sodium chondroitin sulfate (ChemID, 2002)

Components: Specific chondroitin sulfates are listed in Table 1

Table 1. Components of Chondroitin Sulfate Mixtures

Component	Synonyms	CAS No.	Reference
Chondroitin sulfate A	Chondroitin sulfuric acid A Chondroitin 4-sulfuric acid Chondroitin 4-sulfate Turkadon Translagen	24967-93-9	ChemID, 2002
Chondroitin sulfate A, sodium salt	Chondroitin 4-sulfate sodium salt	39455-18-0	Sigma-Aldrich, 2001a
Chondroitin sulfate C	Chondroitin 6-sulfate	25322-46-7	ChemID, 2002
Chondroitin sulfate C, sodium salt		12678-07-8	Sigma-Aldrich, 2001a
Chondroitin sulfate D		50814-15-8	ChemID, 2002
Chondroitin sulfate E			Ueoka *et al.*, 2000
Chondroitin sulfate G		96639-00-8	CAS, 1987
Chondroitin sulfate H		34410-22-5	CAS, 1987

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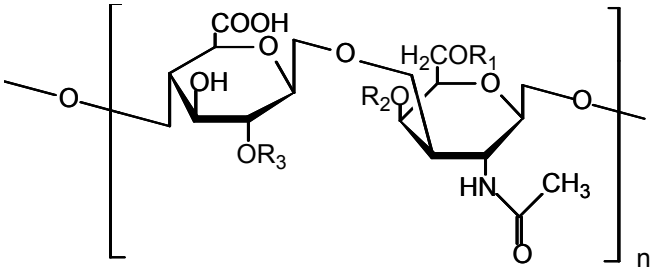
Component	Synonyms	CAS No.	Reference
Chondroitin sulfate K			Kinoshita *et al.*, 1997
Chondroitin sulfate trisaccharide	N-Acetylgalactosamine 6-sulfate-glucuronic acid-N-acetylgalactosamine 6-sulfate	71901-46-7	ChemID, 2002

Structural Class: Glycosaminoglycan; mucopolysaccharide

Structure and Molecular Weight:



Chondroitin sulfate A	R_1: H	R_2: SO_3H	R_3: H
Chondroitin sulfate C	R_1: SO_3H	R_2: H	R_3:

Mol. wt.: 10,000 - 100,000 Da

Chemical and Physical Properties: These properties are listed in Table 2.

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Table 2. Chemical and Physical Properties of Chondroitin Sulfates

Chemical	Description	Solubility
Chondroitin sulfate	High viscosity mucopolysaccharide (Budavari, 1996)	
Chondroitin sulfate, sodium salt	Slightly hazy, faintly yellow (Sigma-Aldrich, 2001a)	Soluble in water (100 mg/ml) (Sigma-Aldrich, 2001a)
Chondroitin sulfate C, sodium salt	Clear, colorless (Sigma-Aldrich, 2001a)	Soluble in water (10 mg/ml) (Sigma-Aldrich, 2001a)

Technical Products and Impurities: Chondroitin sulfate [CAS No. 9007-28-7] is a mixture of derivatives of chondroitin which have a sulfate moiety esterified to the galactosamine moiety of chondroitin. The sodium salt of chondroitin sulfate, which is the commercially available form, has a different Chemical Abstracts Services number [CAS No. 9082-07-9]. Chondroitin sulfate and sodium chondroitin sulfate are unspecified mixtures; the major components are two isomers, chondroitin sulfate A and C (ChemID, 2002; Sigma-Aldrich, 2001a).

The following chondroitin sulfate salts are available from Sigma-Aldrich (Sigma-Aldrich, 2001a):

- Chondroitin sulfate, sodium salt [CAS No. 9082-07-9] from bovine trachea
- A mixture of chondroitin sulfate A, sodium salt [CAS No. 39455-18-0] (~70%) and chondroitin sulfate C, sodium salt [CAS No.12678-07-8] (~30%) from bovine trachea
- Chondroitin sulfate C, sodium salt [CAS No.12678-07-8] with less than 10% of chondroitin sulfate A, sodium salt [CAS No. 39455-18-0] from shark cartilage

Naturally occurring chondroitin sulfate, which is widely distributed in animal tissues, has a molecular weight of 50,000 to 100,000 Da. Most dietary supplements contain chondroitin

sulfate with a lower molecular weight, ~16,900 Da. The low molecular weight form has a potentially superior absorption rate to that of high molecular weight chondroitin sulfate (Adebowale *et al.*, 2000; Biobérica, 2002).

In a test conducted by Consumers Union, 15 of 19 dietary supplements containing chondroitin sulfate or chondroitin sulfate/glucosamine combinations contained at least 90% of the labeled amount of chondroitin sulfate (Consumers Union of US, Inc., 2002). Another study conducted at the University of Maryland found that 26 of 32 products contained less than 90% of the chondroitin sulfate stated on the label with 17 products containing less than 40% of label claim (Adebowale *et al.*, 2000).

EXPOSURE INFORMATION

Production and Producers:

Manufacturing Process: Chondroitin sulfate is produced from enzymatic digestion of bovine and marine animal tissues, specifically bovine nasal septum and trachea, and shark cartilage (CTPP, 2002; Klinkenborg, 2001; Roy,1998). Detailed information on the manufacturing process used to produce chondroitin sulfate was not found in the available literature.

Producers and Importers: Eight US producers or distributors of chondroitin sulfate, two US producers or distributors of chondroitin sulfate A, one US producer or distributor of chondroitin sulfate C, and five US producers or distributors of chondroitin sulfate A, sodium salt, are listed by Chemical Sources International (2001).

According to recent issues of chemical directories, chondroitin sulfate is manufactured and/or distributed by AIDP, Inc.; ATZ Chemical Inc.; Aceto Corp.; Aerchem, Inc.; AF Nutraceutical Group, Inc.; Amax Nutritional, Inc.; American Ingredients, Inc.;

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American Laboratories, Inc.; American Mercantile Corp.; Anmar International Ltd.; Ashland Distribution Co.; Austin Chemical Co., Inc.; Barrington Chemical Corp.; Belmont Chemicals Inc.; Biosynergy Nutriceuticals; Botanicals International, Inc.; Charles Bowman & Co.; Buckton Scott Nutrition, Inc.; Buckton Scott USA, Inc.; CPB International, Inc.; Carbomer, Inc.; Celsus Laboratories, Inc.; Compound Solutions, Inc.; Diosynth Inc.; Eby Sales International, Inc.; Fabrichem, Inc.; The Graymor Chemical Co., Inc.; R.W. Greeff & Co., L.L.C.; Helm New York, Inc.; Irma Corp.; Kaltron/Pettibone; Marcor Development Corp.; Maypro Industries, Inc.; Morse Chemicals, Inc.; National Biochemicals; Pharmline, Inc.; RIA International LLC; Ronas Chemicals Ind. Ltd.; Sattva Chemical Div., Pechiney World Trade (USA), Inc.; Paul Schueller International Inc.; Spectrum Chemical MFG Corp., Stauber Performance Ingredients, Inc.; Stryka Botanics Co., Inc.; F.H. Taussig, Inc.; Tomen (America) Inc.; WESTCO Fine Ingredients, Inc.; Wilke International, Inc.; Xenos BioResources, Inc. (Block, 2001; Hunter, 2001; Tilton, 2001).

Production/Import/Export Level: Chondroitin sulfate is listed in the EPA Toxic Substances Control Act (TSCA) Inventory (ChemID, 2002).

Over an 18-month period between September 28, 2000 and March 25, 2002, the Piers Imports database listed 162 entries for chondroitin sulfate. Based on a 3-month subset of the PIERS data, the volume of chondroitin sulfate exported is approximately16% of imports (Dialog Information Services, 2002).

Use Pattern: The market for glucosamine/chondroitin sulfate supplements is large. In the one-year period between July 1998 and May 1999, retail sales in the US were estimated at more than $500,000,000 (Adebowale *et al.*, 2000).

Low molecular weight chondroitin sulfate (MW ~16,900), used alone or in combination with glucosamine and/or dimethyl sulfone, is marketed primarily for pain and inflammation relief in osteoarthritis and related autoimmune diseases that affect the joints. More than 40 million Americans have been reported to suffer from osteoarthritis (Adebowale *et al.*, 2000; Good 4 All, 2000).

Several animal studies and clinical trials in humans have shown that orally administered chondroitin sulfate improved mobility, joint effusion, and swelling (Bali *et al.*, 2001; Deal & Moskowitz, 1999; Johnson & Mokler, 2001; Kelly, 1998; McAlindon *et al*., 2000). These beneficial effects are supported by *in vivo* anti-inflammatory properties shown in animal models and *in vitro* regulation of chondrocyte metabolism, such as stimulation of proteoglycan and collagen synthesis, and inhibition of the production of cytokines involved in cartilage degradation (Bali *et al.*, 2001). These claims have also led to the marketing of chondroitin sulfate/glucosamine/dimethyl sulfone combinations to all persons concerned with joint stability and improved mobility, not just to those with osteoarthritis.

However, McAlindon and coworkers (2000) conducted a meta-analysis of human clinical trials that tested glucosamine or chondroitin for knee or hip osteoarthritis treatment. Studies were identified from a search of MEDLINE (1966-June1999) and the Cochrane Controlled Trials Register. Studies selected for inclusion had to be double-blinded, randomized, placebo-controlled trials of 4 or more weeks duration. Although the authors found some degree of efficacy, they also noted that quality issues and likely publication bias suggest that reports of these benefits are exaggerated.

In addition to its use as a dietary supplement, chondroitin sulfate is a minor component

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of gelatin. Thus, chondroitin sulfate is found in almost all gelatin-derived products (food, cosmetics, pharmaceuticals, industrial and photographic material. A spin-off of Knox gelatin, Knox NutraJoint® is advertised as a dietary supplement to rebuild cartilage and increase flexibility (Good 4 All, 2000; Knox NutraJoint, 2001; RxList, 2001; Supralife, 1998).

According to the International Nomenclature of Cosmetic Ingredients (INCI), chondroitin sulfate is used as an antistatic and hair conditioning agent. It is also an ingredient in creams and moisturizers (CTPP, 2001; Herbalicious.com, 2002; INCI, 2000).

Chondroitin sulfate is a component of VISCOAT® viscoelastic solution (4% chondroitin sulfate and 3% sodium hyaluronate). VISCOAT® is used as a surgical aid in anterior segment procedures including cataract extraction and intraocular lens implantation (Alcon Canada, 2002).

Chondroitin sulfate is a component of Integra® Dermal Regeneration Template, an FDA-approved skin substitute consting of a "dermal" layer (bovine collagen and chondroitin sulfate) and an "epidermal" silicone layer. Its primary use is for the treatment of burns (Integra LifeSciences, 2001; Phillips, 1998).

Chondroitin sulfate has also been promoted for treating or preventing atherosclerosis. The supplement's potential benefits for this condition are less clear than for osteoarthritis (Albertini *et al.*, 1999; AbdelFattah & Hammad, 2001; Johnson & Mokler, 2001).

There were 1,477 patents using chondroitin sulfate on file with the US Patent and Trademark Office (USPTO) as of November 2001.

Human Exposure: The principal source of human exposure to chondroitin sulfate occurs from its use as a dietary supplement. A dose of 1,200 mg/day of chondroitin sulfate has been used in clinical trials (Adebowale *et al.*, 2000). However, for a short-term healing phase the recommended dose appears to be 1,200-1,800 mg/day, with a maintenance dose of 600-750 mg/day, to improve clinical signs of osteoarthritis (ClicNature.com, 2002; Nutrimart, 2002; Sport Dietary Supplements, 2002).

Dermal exposure to small amounts of chondroitin sulfate would occur as a result of its use as a cosmetic ingredient (CTPP, 2001; Herbalicious.com, 2002; INCI, 2000).

Environmental Occurrence: As described in the section on metabolism, chondroitin sulfate is one of the glycosaminoglycan (GAG) chains of proteoglycans (PG). Proteoglycans are present on cell surfaces and in the extracellular matrix of almost all animal tissues. No information on any other environmental occurrence of chondroitin sulfate was identified in the available literature.

Regulatory Status: No standards or guidelines have been set by the National Institute for Occupational Safety and Health (NIOSH) or the Occupational Safety and Health Administration (OSHA) for occupational exposure to or workplace allowable levels of chondroitin sulfate. Chondroitin sulfate was not on the American Conference of Governmental Industrial Hygienists (ACGIH) list of compounds for which recommendations for a threshold limit value (TLV) or biological exposure index (BEI) are made.

Since 1994, dietary supplements have been regulated under the Dietary Supplement Health and Education Act (DSHEA). The DSHEA requires no proof of safety for dietary supplements on the market prior to October 15, 1994. Labeling requirements for dietary supplements allow warnings and dosage recommendation as well as substantiated "structure or function" claims. All claims must prominently note that they have not been evaluated by the FDA, and they must bear the statement "This product is not intended to diagnose, treat, cure, or prevent any disease" (FDA, 1995).

Chondroitin sulfate is not an approved drug in the US.

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EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the exposure of chondroitin sulfate and cancer risk in humans were identified in the available literature.

A number of clinical trials have shown that chondroitin sulfate is well tolerated; the only side effect following oral administration was nausea (Kelly, 1998; Leffler *et al*., 1999).

In a clinical trial of limited duration (8 weeks), patients with chronic knee or low back pain were given 1,500 mg/day of glucosamine hydrochloride, 1,200 mg/day of chondroitin sulfate and 228 mg/day of manganese ascorbate. The treatment was well tolerated and no significant differences were found in vital signs, occult blood testing, and hematologic parameters between the treated and placebo groups (Leffler *et al*., 1999).

The National Center for Complementary and Alternative Medicine (NCCAM) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) are conducting a multicenter study to investigate the efficacy of Pfanstiehl Laboratories glucosamine hydrochloride and/or Bioibérica, S.A. chondroitin sulfate for treating knee pain associated with osteoarthritis. The study will be a 24 week clinical trial with a total of 1,588 individuals. In addition, one-half of the patients will receive blinded treatment for eighteen more months (NIH News Release, 2000).

Animal Data: No 2-year carcinogenicity studies of chondroitin sulfate in animals were identified in the available literature.

The LD_{50} values for chondroitin sulfate, sodium salt are given in Table 3.

Table 3. Acute Toxicity Values for Chondroitin Sulfate, Sodium Salt

Species	Route of administration	LD_{50} (mg/kg)
rat	oral	>10,000
rat	intraperitoneal (ip)	2,900
rat	subcutaneous (sc)	3,700
rat	intravenous (iv)	>3,125
mouse	oral	>10,000
mouse	ip	9,800
mouse	sc	>10,000
mouse	iv	4,980

Source: Sigma-Aldrich (2001b)

Short-Term Tests: Sodium chondroitin sulfate was not mutagenic in *Salmonella typhimurium* strains TA92, TA94, TA98, TA100, TA1535 and TA1537 at concentrations up to 5 mg/plate. Mutagenicity was not enhanced by rat liver S-9. It did not induce chromosomal aberrations (CA) in a Chinese hamster fibroblast cell line at concentrations up to 3 mg/ml (Ishidate *et al.*, 1984).

Metabolism: *Exogenous Chondroitin Sulfate:* Several studies have dealt with the absorption of glycosaminoglycans, including chondroitin sulfate, following oral administration in animals and humans, and the data reported are extremely contrasting (Baici *et al.*, 1992).

Baici and coworkers (1992) reported that oral consumption of 2 g of chondroitin

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sulfate (64% chondroitin sulfate A and 32% chondroitin sulfate C) by 18 subjects did not produce measurable changes in the total serum concentration of glycosaminoglycans, suggesting that chondroitin sulfate is not absorbed. The possibility that low molecular weight, desulfated oligomers and monomers may be produced and absorbed could not be ruled out.

Baici and coworkers described the results of studies conducted by Palmieri and coworkers, Conte and coworkers, Dohlman, Andermann and Dietz, and others. As detailed below, Palmeieri's group reported that more than 70% of the radioactivity administered orally to rats and dogs is absorbed. Conte and coworkers reported that the absolute bioavailability of the glycosaminoglycan was13.2% of the administered dose of chondroitin sulfate. Dohlman administered $^{35}SO_4$-chondroitin sulfate orally to rats and demonstrated that only a small portion of the radioactivity was absorbed. The remaining radioactivity was excreted in the feces. When $^{35}SO_4$-chondroitin sulfate was administered orally to rats pretreated with antibiotics to depress the bacterial flora, almost all the radioactivity was found in the feces. Dohlman concluded that sulfatases present in the intestinal bacterial flora were responsible for sulfate splitting from the chondroitin sulfate chain, and that no intact chondroitin sulfate can be absorbed through the intestinal wall. Findings of Anderson and Dietz that chondroitin sulfate was not absorbed when administered to rabbits were confirmed by other studies in rats and mice (Baici *et al.*, 1992).

Palmieri and coworkers (1990) dosed Wistar rats and dogs orally with 16 mg/kg bw of a mixture of tritiated chondroitin sulfate A and C (MW 14,000 Da). More than 70% of the radioactivity was absorbed. Radioactivity was found in tissues, and urine was the main route of excretion. However, the known lability of tritium coupled with the use of

a chromatographic gel size that could not distinguish compounds in the molecular weight range of concern raise doubts that the measured radioactivity can be equated to chondroitin sulfate.

Other studies support that chondroitin sulfate is absorbed in the intestinal tract, however. In general, oral administration of 2 or 3 g of chondroitin sulfate to humans produced an increase in the concentration of chondroitin sulfates in the blood after 3-6 hours. These studies were summarized in a review article by Bali and coworkers (2001).

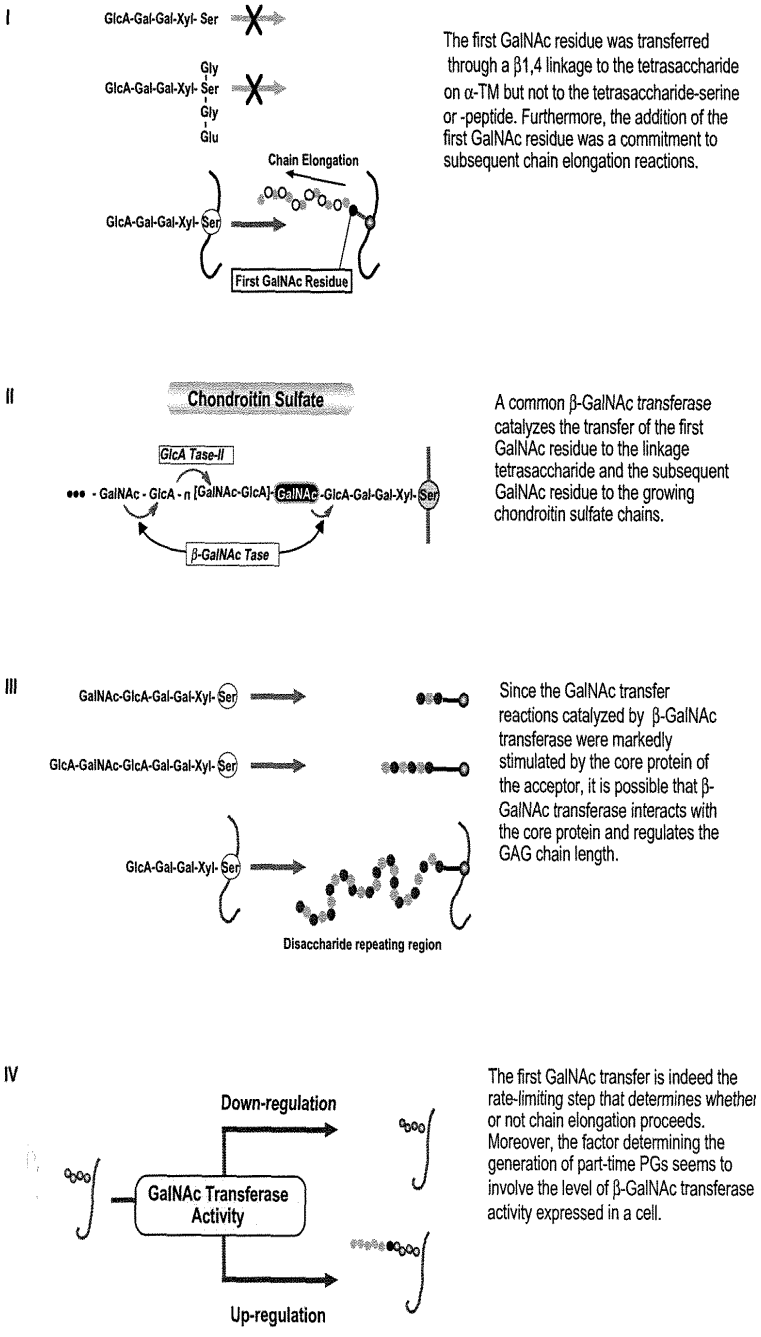
Endogenous Chondroitin Sulfate: Chondroitin sulfate is present in normal human plasma, accounting for 77-80% of the total serum glycosaminoglycan content. The major site of metabolism for circulating chondroitin sulfate is the liver, where it may partly degrade to oligosaccharides and inorganic sulfate. Some of the glycosaminoglycans are incorporated into cells, where they are catabolized to low molecular weight products. Inorganic sulfate and intact chondroitin sulfate are excreted in the urine (Baici *et al.*, 1992).

Chondroitin 4-sulfate and chondroitin 6-sulfate are the most abundant mucopolysaccharides in the body and occur both in skeletal and soft connective tissue. The sulfation pattern of chondroitin disaccharides from normal human cartilage varies with age, topography of the joint surface, and the zone of cartilage examined. As cartilage ages and thins, the chondroitin 6-sulfate form predominates. In cancellous or compact bones, chondroitin 4-sulfate is the usual form (Bali et al., 2001; Budavari, 1996).

Chondroitin sulfate chains occur in animal tissues usually as proteoglycans, in which the polysaccharide chains are covalently attached to a core protein. The total molecular weight of a proteoglycan monomer is 1.5-2.5 x 10^6 (Bali *et al*., 2001; Nadanaka *et al.*, 1998).

Chondroitin sulfate biosynthesis is initiated by the addition of xylose to serine residues in the core protein (i.e., thrombomodulin, ∀-TM), followed by sequential addition of two galactose (Gal) residues and one glucuronic acid (GlcA) residue (Fig. 1). Chondroitin polymerization then takes place by alternating acetylgalactosamine (Ga1NAc) and GlcA, forming the repeating disaccharide region. Finally, sulfotransferases transfer sulfate residues to the different positions of the repeating unit (Nadanaka, 1999).

Fig. 1. Biosynthesis of chondroitin sulfate



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Other Biological Effects:

Tumor Inhibition: Chondroitin sulfate A showed a synergistic effect with mitomycin C in combination therapy of sarcoma 180 ascites tumor implanted in dd mice, approximately doubling the 60-day survival rate in mice implanted with 1 x 10^6 tumor cells (Mikami *et al.*, 1980).

Teratogenicity: Sc injections of 20 mg of chondroitin sulfate to pregnant ddN mice on days 9-11 of gestation produced non-statistically significant increases in malformations, such as cleft palate and flexed or curled tail, and significant growth inhibition in the fetuses (Kamei, 1961).

A follow-up study showed that chondroitin sulfate administered to ddN mice in the same manner along with im injections of cortisone (2.5 mg/day) or vitamin A (5,000 I.U./day) produced a synergistic teratogenic and growth inhibitory effect in both instances. When given in combination with exposure to noise (100 Phon, 6 h/day), chondroitin sulfate did not show any cooperative teratogenic effect (Ishii *et al*.,1962).

Effects on Cell Regulation:

1. Two chondroitin sulfate mixtures (MW 16,800 Da) predominantly composed of either chondroitin sulfate A (68.3%) or chondroitin sulfate C (63.1%) increased the rate of proliferation of a fibroblast-like human malignant mesothelioma cell line, SATV-FCS, in a dose-dependent manner. Similar effects were not observed in an epithelial-like human malignant mesothelioma cell line SATV-AB (Syrokou *et al.*, 1999).
2. Chondroitin sulfate A or C inhibited the growth of cultured Tawa sarcoma cells during fast growth and accelerated it during slow growth (Nagasawa *et al.*, 1993).
3. Two chondroitin sulfate A and C mixtures significantly increased the growth of the monoblastic leukemia cell line, U-937. The molecular weights of these mixtures were

17,200 and 26,950 Da. In contrast, a mixture of chondroitin sulfate A (32.6%), chondroitin sulfate C (35.2%), and desulfated chondroitin sulfate D (19.1%) had no effects on the rate of proliferation of U-937 cells (Volpi *et al.*, 1993).

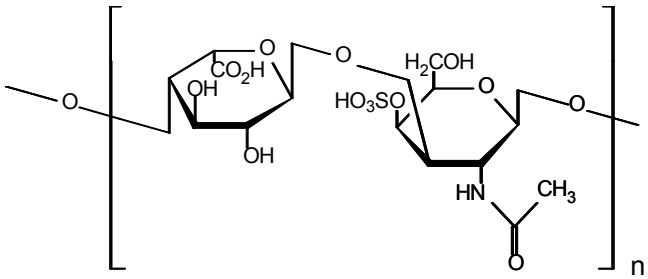
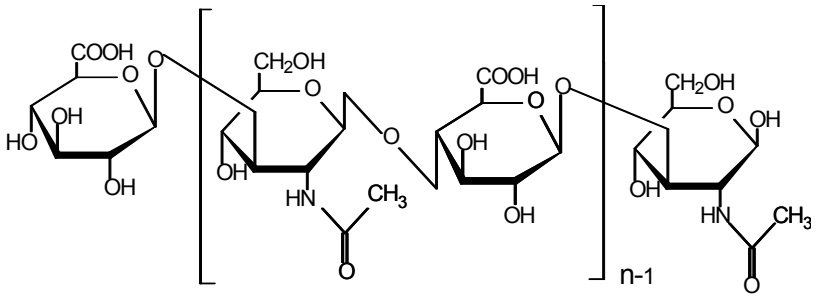
4. Chondroitin sulfate increased RNA synthesis in cultured chondrocytes, which correlated with increased synthesis of proteoglycans and collagens (Johnson & Mokler, 2001).
5. Chondroitin sulfate injected ip to Balb C mice led to accumulation of hyalin deposits in liver, spleen, and lymph nodes (Kozlowski & Hrabowska, 1970).

Anticoagulant Effects: Because of the heparinoid structure of chondroitin sulfate, several studies have been conducted to determine its potential anti-coagulant effect. It appears that chondroitin sulfate possesses a mild, if any, anticoagulant effect that is significantly lower than that of heparin (AbdelFattah & Hammad, 2001).

Structure-Activity Relationships:

Four gangliosaminoglycans structurally related to chondroitin sulfates were selected for review. These chemicals were dermatan sulfate, hyaluronic acid, heparan sulfate, and heparin. No carcinogenic or genotoxic information was found for any of these compounds in a search of the National Library of Medicine TOXNET databases, including TOXLINE. No information on any of these chemicals was located in the 1999 CD-Rom version of the *Public Health Service, Survey of Compounds Which Have Been Tested for Carcinogenic Activity (PHS 171).*

Table 4. Pharmacological and Toxicological Information on Four Structurally Related Glycosaminoglycans

Compound	Pharmacological/ Toxicological Effects
Dermatan sulfate [CAS No. 24967-94-0] 	Anticoagulant (ChemID, 2002)
Hyaluronic acid [CAS No. 9004-61-9] 	Not teratogenic in rats and rabbits (Wada *et al.*, 1991) Adjuvant (ChemID, 2002)

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Compound	Pharmacological/ Toxicological Effects
Heparin and **heparan sulfate** have heterogenous structures and consist of a disaccharide repeat of glucosamine (acetyl glucosamine or N-sulfoglucosamine) and a hexuronic acid (glucuronic or iduronic acid). Ester (O)-sulfation occurs predominantly at C-2 of the iduronic acid and C-6 of the glucosamine residues (Turnbull *et al.*, 1999; Vivès *et al*., 1999)	
Heparin [CAS No.9005-49-6] N-sulfation extensive, enriched in iduronic acid residues and O-sulfate groups (Vivès *et al*., 1999)	Anticoagulant and antithrombotic agent (Vivès *et al*., 1999)
Heparan sulfate [CAS No. 9050-30-0] Highly sulfated regions alternate with unmodified regions of glucuronic acid -N-acetylglucosamine repeats (Vivès *et al*., 1999)	Anticoagulant and antithrombotic agent (Vivès *et al*., 1999)

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