



MULTIPLE INGREDIENT JOINT HEALTH PRODUCTS

This monograph is intended to serve as a guide to industry for the preparation of Product Licence Applications (PLAs) for natural health product (NHP) market authorization. The monograph is not intended to be a comprehensive review of the medicinal ingredients.

Notes

- ▶ Text in parentheses is additional optional information which can be included on the PLA and product label at the applicant's discretion.
- ▶ The solidus (/) indicates that the terms or statements are synonymous. Either term or statement may be selected by the applicant.

Date

June 13, 2014

Proper name(s), Common name(s), and Source material(s)

Table 1 Proper names, common names and source materials of joint health ingredients

Proper name ¹	Common name ²	Source material ³
<i>Boswellia serrata</i> Roxb. ex Colebr. (Burseraceae)	<ul style="list-style-type: none"> • Boswellia • Indian frankincense • Indian olibanum; 	<ul style="list-style-type: none"> • Stem bark oleogum resin • Trunk bark oleogum resin
Fruit bromelain	<ul style="list-style-type: none"> • Fruit bromelain • Juice bromelain • Pineapple fruit bromelain 	<i>Ananas comosus</i> var. <i>comosus</i> (fruit or stem)
Stem bromelain	<ul style="list-style-type: none"> • Stem bromelain • Bromelain • Pineapple stem bromelain 	
Chondroitin sulfate	Chondroitin sulfate	Chondroitin sulfate sodium obtained from one or more of the following: <ul style="list-style-type: none"> • Bovine (Bovidae) – cartilage⁴ • Porcine (Suidae) – cartilage⁴ • Avian (Phasianidae) – cartilage⁴
(1E,6E)-1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione	Curcumin	<i>Curcuma longa</i> rhizome
<i>Harpagophytum procumbens</i> (Burch.) DC. ex Meisn. (Pedaliaceae)	Devil's claw	Secondary root tuber
Fish oil	Fish oil	<ul style="list-style-type: none"> • Engraulidae – whole⁵ • Carangidae – whole⁵ • Clupeidae – whole⁵

Proper name ¹	Common name ²	Source material ³
		<ul style="list-style-type: none"> • Osmeridae – whole⁵ • Scrombridae – whole⁵ • Ammodytidae – whole⁵ • Salmonidae – whole⁵
Glucosamine hydrochloride	Glucosamine hydrochloride	<ul style="list-style-type: none"> • Shrimp (<i>Penaeidae</i>) – exoskeleton⁶ • Krill (<i>Euphausiidae</i>) – exoskeleton⁶ • Prawn (<i>Penaeoidea</i> and/or <i>Sergestoidea</i>) – exoskeleton⁶ • Crab (<i>Cancridae</i>) – exoskeleton⁶ • Lobster (<i>Nephropidae</i>) – exoskeleton⁶ • <i>Aspergillus</i> sp. (<i>Trichocomaceae</i>) – fermented⁸ • <i>Monascus</i> sp. (<i>Elaphomycetaceae</i>) – fermented⁸ • <i>Rhizopus</i> sp. (<i>Mucoraceae</i>) – fermented⁸
Glucosamine sulfate	Glucosamine sulfate	<ul style="list-style-type: none"> • Shrimp (<i>Penaeidae</i>) – exoskeleton^{6,7} • Krill (<i>Euphausiidae</i>) – exoskeleton^{6,7} • Prawn (<i>Penaeoidea</i> and/or <i>Sergestoidea</i>) – exoskeleton^{6,7} • Crab (<i>Cancridae</i>) – exoskeleton^{6,7} • Lobster (<i>Nephropidae</i>) – exoskeleton^{6,7}
Hyaluronic acid	Hyaluronic acid	<ul style="list-style-type: none"> • Hyaluronic acid/Sodium hyaluronate obtained from <i>Gallus gallus comb</i> 9 • Sodium hyaluronate obtained from the extracellular capsule of <i>Streptococcus, Lancefield Groups A and C</i> 9
Hydrolyzed collagen	Hydrolyzed collagen; Collagen hydrolysate	<ul style="list-style-type: none"> • Porcine skin • Porcine bones • Fish skin • Fish bones • Bovine skin/hide split • <i>Gallus gallus cartilage</i>
<ul style="list-style-type: none"> • Methylsulfonylmethane • Dimethyl sulfone • Sulfonylbismethane 	Methylsulfonylmethane (MSM)	Methylsulfonylmethane (MSM)
<i>Curcuma longa</i> L. (Zingiberaceae)	Turmeric	Rhizome
<i>Salix alba</i> L.	White willow	Bark
Vitamin A; Vitamin C; Vitamin D; Vitamin K; Boron; Calcium; Magnesium; Manganese; Beta-carotene	NHPD Multi-Vitamin/Mineral Supplements monograph	



- ¹ At least one of the following references was consulted per proper name: ChemIDPlus 2012; Martindale 2012; Merck 2012; Ph.Eur. 2012; USP 35; USDA 2011; USDA 2009; ICIDH 2008; Kralovec and Barrow 2008; Towheed and Anastassiades 2007; O’Neil et al. 2006; IUBMB 1992.
- ² At least one of the following references was consulted per common name: BP 2012; ChemIDPlus 2012; Martindale 2012; Merck 2012; Ph.Eur. 2012; USP 35; USDA 2009; Goel et al. 2008; ICIDH 2008; Kralovec and Barrow 2008; Towheed and Anastassiades 2007; O’Neil et al. 2006; Boon and Smith 2004; McGuffin et al. 2000; Moskowitz 2000; IUBMB 1992; Deodhar et al. 1980.
- ³ At least one of the following references was consulted per source material: Martindale 2012; Merck 2012; Ph.Eur. 2012; Schauss et al. 2012; USP 35; EP 2011; ITIS 2011; USDA 2011; Khan and Abourashed 2010; Evans 2009; Sato and Iwaso 2008; Yoshida et al. 2009; Froese and Pauly. 2008; Goel et al. 2008; Kalman et al. 2008; Kralovec and Barrow 2008; NIH 2008; Schrieber and Gareis 2007; Dahiya et al 2006; O’Neil et al. 2006; Chong et al. 2005; PPRC 2005; Boon and Smith 2004; Wichtl 2004; Baziwane and He 2003; ESCOP 2003; Barnes et al. 2002; Sato et al. 2002; Blumenthal et al. 2000; FCC 7; BHC 1992; Deodhar et al. 1980.
- ⁴ Cartilage must be derived from healthy and domestic animals used for food by humans (USP 35).
- ⁵ Corresponds to oil from the body of one or more of the following species in its natural triglyceride/triacylglycerol form and/or its concentrated esterified form:
 - Anchovy (any species of Engraulidae)
 - Jack or pompano (any species of Carangidae)
 - Herring, shad, sardine or menhaden (any species of Clupeidae)
 - Smelt (any species of Osmeridae)
 - Mackerel, tuna, or bonito (any species of Scombridae)
 - Sand lance (any species of Ammodytidae)
 - Salmonids (any species of Salmonidae)
- ⁶ The specific organisms used as source material(s) must be indicated in the Animal Tissue Form (ATF); simply indicating “crustaceans” is insufficient.
- ⁷ Acceptable salts include potassium chloride and sodium chloride (Kralovec and Barrow 2008). Example of labelling: glucosamine sulfate potassium chloride from shrimp.
- ⁸ References: Sitanggang et al. 2012; Kralovec and Barrow 2008; Chmielowski et al. 2007; Dahiya et al 2006.
- ⁹ The stabilizing salt (i.e. sodium) if present should be indicated.

Route(s) of administration

Oral

Dosage form(s)

- ▶ The acceptable pharmaceutical dosage forms include, but are not limited to capsules, chewables (e.g. gummies, tablets), liquids, powders, strips or tablets.
- ▶ This monograph is not intended to include foods or food-like dosage forms such as bars, chewing gums or beverages.

Use(s) or Purpose(s) Statement(s) to the effect of

Notes

- ▶ It is mandatory for all products to cite at least one use or purpose statement from Table 2.
- ▶ A use or purpose statement is acceptable only if at least one medicinal ingredient associated with that statement is present at a dose at or above the minimum daily dose listed in Table 2.

- ▶ Medicinal ingredients which do not meet the minimum daily dose for a use or purpose statement will be considered as acceptable complementary medicinal ingredients in product formulations.
- ▶ The daily dose for glucosamine hydrochloride in combination with glucosamine sulfate is subject to the following limitations: the sum of the percents of their individual maximum daily doses must not exceed 120%; [(e.g. a product providing a daily dose of 2000 mg glucosamine hydrochloride (100% of the 2000 mg maximum daily dose) + 300 mg glucosamine sulfate (20% of the 1500 mg maximum daily dose) would be acceptable (100%+20%=120%)].

Table 2 Joint health uses or purposes and associated daily doses

Medicinal ingredient	Use or purpose ¹	Daily dose	
		Minimum ²	Maximum ³
Boswellia serrata	Helps to relieve joint pain and swelling associated with osteoarthritis of the knee.	1000 mg extracts standardized to 40% boswellic acid, in 3 divided doses	1000 mg extracts standardized to 40% boswellic acid, in 3 divided doses
Chondroitin sulfate	Helps to relieve (joint) pain associated with osteoarthritis (of the knee)	800 mg	1200 mg
Curcumin	Used in Herbal Medicine to help relieve joint inflammation	400 mg, 3 times per day	400 mg, 3 times per day
Devil's claw	Used in Herbal Medicine to help relieve joint pain associated with osteoarthritis.	600 mg	7500 mg
Fish oil ⁴	In conjunction with conventional therapy, helps to reduce the pain of rheumatoid arthritis.	2800 mg eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) with a EPA:DHA ratio of 0.5-2:1	3000 mg EPA+DHA with a EPA:DHA ratio of 0.5-2:1
Glucosamine hydrochloride	Helps to maintain healthy cartilage/joint health.	1500 mg	2000 mg
Glucosamine sulfate	<ul style="list-style-type: none"> • Helps to relieve joint pain associated with osteoarthritis (of the knee). • Helps to protect against the deterioration of cartilage. • A factor in maintaining healthy cartilage and/or joint health. 	1500 mg	1500 mg
Hyaluronic acid	Helps support joint health	48 mg, from <i>Gallus gallus</i> comb extract	120 mg, from <i>Gallus gallus</i> comb extract

Medicinal ingredient	Use or purpose ¹	Daily dose	
		Minimum ²	Maximum ³
		120 mg, from microbial fermentation	200 mg, from microbial fermentation
Hydrolyzed collagen	Helps to reduce joint pain associated with osteoarthritis	1200 mg	10 000 mg
Methylsulfonylmethane (MSM)	Helps to relieve (joint) pain associated with osteoarthritis (of the knee).	1500 mg	6000 mg, not to exceed 2000 mg per dose
Turmeric	Turmeric is (traditionally) used in Herbal Medicine as an anti-inflammatory to help relieve joint pain.	1000 mg dried rhizome OR extracts standardized to 3-5% curcuminoids	9000 mg dried rhizome OR extracts standardized to 3-5% curcuminoids
White willow	(White willow is traditionally) used in Herbal Medicine for the relief of minor joint pain (due to osteoarthritis)	3000 mg dried bark, in divided doses	9000 mg dried bark, in divided doses, not to exceed 3000 mg per dose
		45 mg total salicin, in divided doses	240 mg total salicin, in divided doses, not to exceed 120 mg salicin per dose or 0.5-1% total salicin (after hydrolysis)

¹ At least two of the following references were consulted per use or purpose: Bruyère et al. 2012; Benito-Ruiz et al. 2009; EMEA 2009; Yoshida et al. 2009; Clark et al. 2008; Winston and Kuhn 2008; Herrero-Beaumont et al. 2007; Mazières et al. 2007; Sontakke et al. 2007; Towheed and Anastassiades 2007; Kim et al. 2006; Mills and Bone 2005; Uebelhart et al. 2004; Usha and Naidu 2004; Braham et al. 2003; ESCOP 2003; Hoffmann 2003; Kimmatkar et al. 2003; Pavelka et al. 2002; Sato et al. 2002; Mazières et al. 2001; Reginster et al. 2001; Thie et al. 2001; Blumenthal et al. 2000; Mills and Bone 2000; Volker et al. 2000; Houpt et al. 1999; Bourgeois et al. 1998; Bucsi and Poor 1998; Uebelhart et al. 1998; Sköldstam et al. 1992; Deodhar et al. 1980.

² At least one of the following references was consulted per minimum dose: Bruyère et al. 2012; Benito-Ruiz et al. 2009; EMEA 2009; WHO 2009; Yoshida et al. 2009; Clark et al. 2008; Kalman et al. 2008; Herrero-Beaumont et al. 2007; Mezieres et al. 2007; Sontakke et al. 2007; Fitzpatrick 2005; Mills and Bone 2005; Boon and Smith 2004; Uebelhart et al. 2004; Usha and Naidu 2004; Wichtl 2004; ESCOP 2003; Hoffmann 2003; Kimmatkar et al. 2003; Williamson 2003; Barnes et al. 2002; Pavelka et al. 2002; Reginster et al. 2001; Mezieres et al. 2001; Blumenthal et al. 2000; Volker et al. 2000; Houpt et al. 1999; Bucsi and Poor 1998; Uebelhart et al. 1998; Deodhar et al. 1980.

³ At least one of the following references was consulted per maximum dose: Bruyère et al. 2012; Benito-Ruiz et al. 2009; EMEA 2009; Sato et al. 2008; WHO 2009; Clark et al. 2008; Herrero-Beaumont et al. 2007; Sontakke et al. 2007; Hathcock and Shao 2006; Kim et al. 2006; Mills and Bone 2005; Boon and Smith 2004; Wichtl 2004; Braham et al. 2003; ESCOP 2003; Kimmatkar et al. 2003; Williamson 2003; Barnes et al. 2002; Pavelka et al. 2002; Sato et al. 2002; Reginster et al. 2001; Blumenthal et al. 2000; Bourgeois et al. 1998; US FDA 1997; BHC 1992; Deodhar et al. 1980.

⁴ The EPA:DHA ratio for fish oil must be between 0.5 and 2:1 (Volker et al. 2000; Sköldstam et al. 1992) and potency must be expressed as the quantity (mg) and/or percent (%) of EPA and DHA (% w/w) relative to the total quantity of fish oil.

Table 3 Uses or purposes related to joint and bone health and associated daily doses

Medicinal ingredient	Use or purpose ¹	Daily dose	
		Minimum ²	Maximum ³
Boron	Helps maintain healthy calcium metabolism	0.7 mg	3.36 mg
Bromelain	Used in herbal medicine to help relieve minor pain, swelling and inflammation (anti-inflammatory)	20 mg ⁴ and 480 000 FCC papain units per day	600 mg, not to exceed 300 mg per single dose ⁴ and 20 000 000 FCC papain units per day, not to exceed 10 000 000 FCC papain units per single dose.
Calcium	<ul style="list-style-type: none"> • Adequate calcium (and vitamin D) (throughout life) as part of a healthy diet, (along with physical activity) may help prevent bone loss/osteoporosis / may reduce the risk of developing osteoporosis (in peri- and postmenopausal women) (in later life). • Helps in the development and maintenance of bones 	65 mg	1500 mg
Vitamin A; Vitamin C; Vitamin D; Vitamin K ⁵ ; Magnesium; Manganese; Beta-carotene ⁶	Helps in the development and maintenance of bones	NHPD Multi-Vitamin/Mineral Supplements monograph	

¹At least two of the following references were consulted per use or purpose: Hunt CD 2012; FDA 2008; Tang et al. 2007; IOM 2006; NAMS 2006; Shils et al. 2006; Devirian and Volpe 2003; Brown and Josse 2002; Walker et al. 2002; Groff and Gropper 2000; NIH 2000; Blumenthal 1998; Hunt et al. 1997; IOM 1997; Nielsen et al. 1987.

²At least one of the following references was consulted per minimum daily dose: Hunt CD 2012; IOM 2006; Walker et al. 2002; Blumenthal 1998.

³At least one of the following references was consulted per maximum daily dose: Hunt CD 2012; IOM 2006; Kerkhoffs et al. 2004; Singer et al. 2001.

⁴Dose unit information must include the quantities of both the enzyme preparation and its enzymatic activity, in FCC PU. Note that:

- One papain unit (PU) is defined as that quantity of enzyme that liberates the equivalent of 1 µg of tyrosine per hour under the conditions of the assay (FCC 8).
- One gelatin digestion unit (GDU) is approximately equivalent to 15 000 FCC papain units (1 GDU ≈ 15 000 FCC PU).

⁵ The recommended use for Vitamin K is “Helps in the maintenance of bones” only.

⁶ The recommended use for Beta-carotene is “Source of vitamin A/Provitamin A to help in the development and maintenance of bones”.

Dose(s)

Subpopulation(s)

Adults (≥ 18 y)

Quantity(ies)

Refer to Tables 2 and 3.

Direction(s) for use

Table 4 Directions for use

Medicinal ingredient	Direction(s) for use
Boron	If product is not a source of Vitamin D and Calcium: Take with vitamin D and calcium (Devirian and Volpe 2003; Zittermann 2003).
Bromelain	Optional: Take with food/meal (NHPD 2012).
Calcium	Take a few hours before or after taking other medications or natural health products (Sweetman 2007, ASHP 2005).
Methylsulfonylmethane (MSM), for products providing ≥ 1500 mg per day	<ul style="list-style-type: none"> • Take with food (Kim et al. 2006). • Avoid taking at bedtime (Kim et al. 2006).

Duration of use

Notes

- ▶ A minimum duration of use statement is required for all products citing use or purpose statements associated with boswellia, chondroitin sulfate, devil’s claw, glucosamine (hydrochloride and sulfate), hydrolyzed collagen or methylsulfonylmethane (MSM).
- ▶ If more than one duration of use statement is indicated for a particular product formulation, only the shortest applicable duration of use statement is required on the PLA and product label. For example, a product citing use or purpose statements for chondroitin sulfate and glucosamine hydrochloride need only include the following duration of use statement on the product label: “Use for a minimum of 1 month to see beneficial effects.”
- ▶ A maximum duration of use statement is required for all products containing bromelain or white willow.

Minimum duration of use

Table 5 Minimum duration of use

Medicinal ingredient	Minimum duration of use ¹
Hydrolyzed collagen	Use for a minimum of 5 months to see beneficial effects.
Chondroitin sulfate	Use for a minimum of 3 months to see beneficial effects.
Devil's claw	Use for a minimum of 2-3 months to see beneficial effects.
Boswellia	Use for a minimum of 2 months to see beneficial effects.
glucosamine hydrochloride	Use for a minimum of 1 month to see beneficial effects.
glucosamine sulfate	
methsulfonylethane (MSM)	

¹ At least one of the following references was consulted per duration of use: Bruyère et al. 2012; Benito-Ruiz et al. 2009; Clark et al. 2008; Bjordal et al. 2007; Mehta et al. 2007; Sontakke et al. 2007; Kim et al. 2006; Usha and Naidu 2004; ESCOP 2003; Kimmatkar et al. 2003; Houpt et al. 1999; Qiu et al. 1998.

Maximum duration of use

Products containing bromelain and/or white willow

For prolonged use, consult a health care practitioner (NHPD 2012; EMEA 2009; Beer and Wegener 2008; Biegert et al. 2004; Chrubasik 2000).

Risk Information Statement(s) to the effect of

Caution(s) and warning(s)

All products

- ▶ If you are pregnant or breastfeeding, consult a health care practitioner prior to use.
- ▶ If symptoms worsen, consult a health care practitioner.

Table 6 Caution(s) and warning(s)

Medicinal ingredient	Caution(s) and warning(s)
Boron	If you have been diagnosed with estrogen-dependant cancer, consult a health care practitioner prior to use (Nielsen et al. 1992).
	If you have a kidney disorder, consult a health care practitioner prior to use (Usuda et al. 1996).
Bromelain	If you have a gastrointestinal lesion/ ulcer, are taking an anticoagulant/ blood thinner, anti-inflammatory or antibiotic, or are having surgery, consult a health care practitioner prior to use (Martindale 2011; Brinker 2010; Blumenthal et al. 2000).
Curcumin	If you are taking antiplatelet medication or blood thinners, consult a health care practitioner prior to use (Mills and Bone 2005; Brinker 2001).
	If you have gallstones or a bile duct obstruction, consult a health care

	practitioner prior to use (ESCOMP 2003; Brinker 2001; McGuffin et al. 1997). If you have stomach ulcers or excess stomach acid, consult a health care practitioner prior to use (Brinker 2001; McGuffin et al. 1997).
Fish oil AND White willow combined	If you have a gastrointestinal lesion/ulcer, are taking blood thinners or are having surgery, consult a health care practitioner prior to use (Block et al. 2012, 2013; Larson et al. 2008).
Hydrolyzed collagen, for doses above 2.8 g per day	If you have liver or kidney disease or if you have been instructed to follow a low protein diet, consult a health care practitioner prior to use (Shils et al. 2006; Goldman and Ausiello 2004).
Manganese	Doses > 5 mg If you have a liver disorder, consult a health care practitioner prior to use (IOM 2006; IOM 2001; Krieger et al. 1995)
Turmeric	If you have gallstones or a bile duct obstruction, consult a health care practitioner prior to use (ESCOMP 2003; Brinker 2001; McGuffin et al. 1997).
	If you have stomach ulcers or excess stomach acid, consult a health care practitioner prior to use (Brinker 2001; McGuffin et al. 1997).
Vitamin K	Doses > 6 µg If you are taking blood thinners, consult a health care practitioner prior to use (ASHP 2005; Franco et al 2004; IOM 2001; Hansten et al 1997)
White willow	If you have asthma or peptic ulcer disease, consult a health care practitioner prior to use (EMEA 2009).
	If you are taking anticoagulants or products containing acetylsalicylic acid (ASA) or other salicylates, consult a health care practitioner prior to use (EMEA 2009).

Contraindication(s)

Products containing white willow

- ▶ If you are pregnant or breastfeeding, do not use this product (Brinker 2010; EMEA 2009; Wichtl 2004; ESCOP 2003; Barnes et al. 2002; Blumenthal et al. 2000).
- ▶ If you are allergic to acetylsalicylic acid (ASA) or other salicylates, do not use this product (Brinker 2010; EMEA 2009; Wichtl 2004, ESCOP 2003; Barnes et al. 2002; Blumenthal et al. 2000).

Known adverse reaction(s)

Products containing boswellia and/or bromelain

Hypersensitivity (e.g. allergy) has been known to occur; in which case, discontinue use (Martindale 2011; Brinker 2010; WHO 2009; Murray and Pizzorno 2006; Blumenthal et al. 2000; Baur and Fruhmann 1979).

Products containing boswellia, bromelain, hydrolyzed collagen, methylsulfonylmethane and/or white willow

Some people may experience mild gastrointestinal disturbances such as diarrhoea, abdominal pain, heartburn, nausea and vomiting; in which case, discontinue use (Martindale 2011; Brinker



2010; EMEA 2009; Sontakke et al. 2007; Brien et al. 2006; Kim et al. 2006; Wichtl 2004; ESCOP 2003; Kimmatkar et al. 2003; Barnes et al. 2002; Blumenthal et al. 2000; McGuffin 2000; Moskowitz 2000).

Products providing > 350 mg magnesium per day

Some people may experience diarrhea (IOM 2006, IOM 1997).

Storage conditions

All products

Store in airtight container, protected from light (Ph.Eur. 2012; USP 35).

Products containing fish oil, except those encapsulated

Refrigerate after opening (Wille and Gonus 1989).

Products containing hydrolyzed collagen

Protect from heat and moisture (Ph.Eur. 2012).

Non-medicinal ingredients

Must be chosen from the current NHPD *Natural Health Products Ingredients Database* and must meet the limitations outlined in that database.

Specifications

- ▶ The finished product specifications must be established in accordance with the requirements described in the NHPD *Quality of Natural Health Products Guide*.
- ▶ The medicinal ingredient must comply with the requirements outlined in the *Natural Health Products Ingredients Database* (NHPID).
- ▶ In order to minimize the risk of Transmissible Spongiform Encephalopathies (TSEs) from products sourced from bovine tissues, product licence applicants must have a veterinary certificate on file and must ensure that the following criteria have been met (Ph.Eur. 2012):
 - i. Source animal is fit for human consumption;
 - ii. Source material can be traced back to the herd or animal;
 - iii. Avoidance of cross-contamination with high-infectivity tissues is ensured during sourcing;
 - iv. Manufacturing procedures that are known to reduce infectivity are implemented (e.g. procedures that are in accordance with those outlined in Chapter 5.02.08 of the



European Pharmacopoeia 2012 ‘Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products’).

- ▶ Peroxide, anisidine, and totox values of fish oil and omega-3 fatty acids derived from fish oil must be in accordance with the methods set out by the Association of Analytical Community (AOAC) and/or Pharmacopoeial analytical methods. These specifications are necessary to ensure the oxidative stability of the fish oil and the omega-3 fatty acids derived from fish oil (HC 2013). Refer to Table 7 below.
- ▶ The dioxins, polychlorinated dibenzo-*para*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs); the dioxin-like polychlorinated biphenyls (dioxin-like PCBs); and the polychlorinated biphenyls (PCBs) are contaminants in oils from marine sources. Testing for these contaminants are required and must be performed using either the analytical method of the European Commission Regulation EU 252/2012 (EU 2012) or the U.S. Environmental Protection Agency’s method 1613B for PCDDs and PCDFs and method 1668A for PCBs (USP 35; US EPA 2010, 2008,1994). Applicants are advised to consult the Council of the European Union document on these contaminants for further information (EU 2011). Refer to Table 8 below.
- ▶ *Bromelain*
 - i. Details of the manufacturing of the enzyme at the raw material stage should include fermentation medium, and the isolation process of the medicinal ingredient.
 - ii. The specifications must include testing for enzymatic activity of the medicinal ingredient at appropriate stages of formulation and manufacturing using the assay outlined in the current Food Chemicals Codex (FCC): PLANT PROTEOLYTIC ACTIVITY.
 - iii. Where published methods are not suitable for use, manufacturers will use due diligence to ensure that the enzymes remain active to the end of the shelf life indicated on the product label.
- ▶ *Hyaluronic acid*
 - i. Information pertaining to the molecular weight of the hyaluronic acid must be available upon request for characterization (e.g. Certificate of Analysis, Technical Data Sheet, Product Information, etc). The molecular weight of hyaluronic acid obtained from *Gallus gallus* comb must be 800 kDa. The molecular weight of sodium hyaluronate from *Streptococcus equi* must be between 30-900 kDa
 - ii. Information regarding Method of preparation must be provided upon request
 - iii. For all products obtained through microbial fermentation, the species of Streptococcus used must be provided upon request and should be substantiated by the evidence. Information regarding manufacturing processes that reduce or eliminate pyrogenic or inflammatory components of the cell wall must be submitted upon request.
 - iv. The content of sulfated glycosaminoglycans, nucleic acids, protein, and microbial contamination derived from this ingredient must be in accordance with the methods set out by the European Pharmacopoeia:
 - Sulfated glycosaminoglycans: maximum 1%, if the ingredient is extracted from *Gallus gallus* comb
 - Nucleic acids: the absorbance of solution at 260 nm is maximum 0.5
 - Protein: maximum 0.3%
 - Microbial contamination: Total Aerobic Microbial Count of 10² CFU/g
- ▶ *Hydrolyzed Collagen*

- i. For the purpose of this monograph, hydrolyzed collagen has no jelling power and is soluble in cold water (Schrieber and Gareis 2007; Moskowitz 2000).
- ii. The average molecular weight of hydrolyzed collagen is approximately 2-6 kDa (Moskowitz 2000; Oesser et al. 1999).

Table 7 Maximum values of oxidative stability parameters for fish oil (HC 2013)

Oxidative stability parameter	Maximum value
Peroxide value (PV)	5 mEq/kg
<i>p</i> -Anisidine value (AV)	20 mEq/kg
Totox value	26 mEq/kg (calculated as (2 x PV) + AV)

Table 8 Acceptable limits of dioxins and dioxin-like polychlorinated biphenyls in oils from marine sources

Dioxin and dioxin-like polychlorinated biphenyl contaminants	Maximum level ¹
Sum of PCDDs + PCDFs	2.0 pg TEQ TEF/g oil
Sum of dioxins and dioxin-like PCBs ²	10.0 pg TEQ TEF/g oil

¹ Expressed in World Health Organization (WHO) toxic equivalents using WHO-toxic equivalent factors (TEFs). Analytical results relating to 17 individual dioxin congeners of toxicological concern are expressed in a single quantifiable unit: 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) toxic equivalent concentration or TEQ (EU 2006).

² The dioxin-like PCBs that can be determined by Method 1668B are the 12 PCBs designated as toxic by WHO: congeners 77, 81, 126, 169, 105, 114, 118, 123, 156, 157, 167, and 189 (EPA 2008; EU 2006).

References cited

Acs N, Banhidy F, Puho E, Czeizel AE. Teratogenic effects of vaginal boric acid treatment during pregnancy. *International journal of gynaecology and obstetrics* 2006;93(1):55-56.

ASHP 2005: American Society of Health-System Pharmacists. *American Hospital Formulary Service (AHFS) Drug Information*. Philadelphia (PA): Lippincott Williams and Wilkins; 2005.

Barnes J, Anderson LA, Philipson JD. *Herbal Medicines: A Guide for Healthcare Professionals*. 2nd edition. London (GB): The Pharmaceutical Press; 2002.

Baur X, Fruhmann G. Allergic reactions, including asthma, to the pineapple protease bromelain following occupational exposure. *Clinical Allergy* 1979;9(5):443-450.

Baziwane D, He Q. Gelatin: The paramount food additive. *Food Reviews International* 2003;19(4):423-435.

Beer A.-M, Wegener T. Willow bark extract (*Salicis cortex*) for gonarthrosis and coxarthrosis-Results of a cohort study with a control group. *Journal of Phytomedicine* 2008;15:907-913.



Benito-Ruiz P, Camacho-Zambrano MM, Carrillo-Arcentales JN, Mestanza-Peralta MA, Vallejo-Flores CA, Vargas-López SV, Villacís-Tamayo RA, Zurita-Gavilanes LA. A randomized controlled trial on the efficacy and safety of a food ingredient, collagen hydrolysate, for improving joint comfort. *International Journal of Food Sciences and Nutrition* 2009;60 Suppl 2:99-113.

Biegert C, Wagner I, Ludtke R, Kotter I, Lohmuller C, Gunaydin I, Taxis K, Heide L. Efficacy and safety of willow bark extract in the treatment of osteoarthritis and rheumatoid arthritis: results of 2 randomized double-blind controlled trials. *Journal of Rheumatology* 2004;31(11): 2121-2130.

BHC 1992: Bradley PR, editor. *British Herbal Compendium: A Handbook of Scientific Information on Widely Used Plant Drugs, Volume 1*. Bournemouth (GB): British Herbal Medicine Association; 1992.

Bjordal JM, Klovning A, Ljunggren AE, Slørdal L. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: A meta-analysis of randomised placebo-controlled trials. *European Journal of Pain* 2007;11(2):125-138.

Block RC, Abdolahi A, Smith B, Meednu N, Thevenet-Morrison K, Cai X, Cui H, Mousa S, Brenna JT and Georas S. Effects of low-dose aspirin and fish oil on platelet function and NF-kappaB in adults with diabetes mellitus. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 2013;89(1):9-18.

Block RC, Kakinami L, Jonovich M, Antonetti I, Lawrence P, Meednu N, Artero PC, Mousa SA, Brenna JT, Georas S. The combination of EPA+DHA and low-dose aspirin ingestion reduces platelet function acutely whereas each alone may not in healthy humans. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 2012;87(4-5):143-151.

Blumenthal M. *The complete german Commission E monographs: Therapeutic guide to herbal medicines*. Boston (MA): American Botanical Council; 1998.

Blumenthal M, Goldberg A, Brinkman J. *Herbal Medicine: Expanded Commission E Monographs*. Boston (MA): Integrative Medicine Communications; 2000.

Boon H, Smith M. *The Complete Natural Medicine Guide to the 50 Most Common Medicinal Herbs*. Toronto (ON): Robert Rose Inc; 2004.

Bourgeois P, Chales G, Dehais J, Delcambre B, Kuntz JL, Rosenberg S. Efficacy and tolerability of chondroitin sulfate 1200 mg/day vs chondroitin sulfate 3 x 400 mg/day vs placebo. *Osteoarthritis Cartilage* 1998;6(Suppl A):25-30.

BP 2012: *British Pharmacopoeia*. London (GB): The Stationary Office on behalf of the Medicines and Healthcare products Regulatory Agency (MHRA); 2012.

BP 2008: British Pharmacopoeia, Volume 1. Londron (GB): British Pharmacopoeia Commission. The Stationary Office; 2008.

Braham R, Dawson B, Goodman C. The effect of glucosamine supplementation on people experiencing regular knee pain. *British Journal of Sports Medicine* 2003;37(1):45-49.

Brien S, Lewith G, Walker AF, Middleton R, Prescott P, Bundy R. Bromelain as an adjunctive treatment for moderate-to-severe osteoarthritis of the knee: a randomized placebo-controlled pilot study. *QJM: An International Journal of Medicine* 2006;99(12): 841-850.

Brinker F. *Herb Contraindications and Drug Interactions*, 3rd edition. Sandy (OR): Eclectic Medical Publications; 2001.

Brinker F. *Final Updates and Additions for Herb Contraindications and Drug Interactions*, 3rd edition. Sandy (OR): Eclectic Medical Publications; 2010. [Accessed 2012 March 28]. Available from: <http://www.eclecticherb.com/emp/updatesHCIDI.html>

Brown JP, Josse RG. Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada. *Canadian Medical Association Journal* 2002;167(S10):S1-S34

Bruyère O, Zegels B, Leonori L, Rabenda V, Janssen A, Bourges C, Reginster JY. Effect of collagen hydrolysate in articular pain: A 6-month randomized, double-blind, placebo controlled study. *Complementary Therapies in Medicine* 2012;20:124-130.

Bucsi L, Poor G. Efficacy and tolerability of oral chondroitin sulfate as a symptomatic slow acting drug for osteoarthritis (SYSADOA) in the treatment of knee osteoarthritis. *Osteoarthritis Cartilage* 1998;6(Suppl A):31-36.

ChemIDplus 2012: ChemIDplus Advanced [Internet]. Bethesda (MD): Specialized Information Services, National Library of Medicine, National Institutes of Health, United States Department of Health & Human Services. [Accessed 2012 March 23]. Available from: <http://chem.sis.nlm.nih.gov/chemidplus>

Chmielowski RA, Wu HS, Wang SS. Scale-up of upstream and downstream operations for the production of glucosamine using microbial fermentation. *Biotechnology Journal* 2007;2(8):996-1006.

Chong BF, Blank LM, Mclaughlin R, Nielsen LK. Microbial hyaluronic acid production. *Appl Microbiol Biotechnol* 2005;66:341-351.

Chrubasik S, Eisenberg E, Balan E, Weinberger T, Luzzati R, Conradt C. Treatment of low back pain exacerbations with willow bark extract: a randomised double-blind study. *The American Journal of Medicine*. 2000;109: 9-14.

Clark KL, Sebastianelli W, Flechsenhar KR, Aukermann DF, Meza F, Millard RL, Deitch JR, Sherbondy PS, Albert A. 24-Week study on the use of collagen hydrolysate as a dietary

supplement in athletes with activity-related joint pain. *Current Medical Research and Opinions* 2008;24(5):1485-1496.

Dahiya N, Tewari R, Hoondal GS. Biotechnological aspects of chitinolytic enzymes: a review. *Applied Microbiology and Biotechnology* 2006;71(6):773-782.

Deodhar SD, Sethi R, Srimal RC. Preliminary studies on antirheumatic activity of curcumin (di-feruloyl methane). *Indian Journal of Medical Research* 1980;71:632-634.

Devirian TA and SL Volpe. The physiological effects of dietary boron. *Critical Reviews in Food Science and Nutrition* 2003;43(2):219-231.

EMA 2009  European Medicines Agency. Community Monograph. London (GB): EMA Committee on Herbal Medicinal Products (HMPC), 14 January 2009. [Accessed 2013-01-09].

EP 2011: *European Pharmacopoeia*, 7th edition. Strasbourg (France): Directorate for the Quality of Medicines and HealthCare of the Council of Europe (EDQM); 2011.

ESCAP 2003: *ESCAP Monographs: The Scientific Foundation for Herbal Medicinal Products*, 2nd edition. Exeter (GB): European Scientific Cooperative on Phytotherapy and Thieme; 2003.

EU 2012: European Commission. Commission Regulation (EU) No 252/2012 of 21 March 2012 laying down the methods of sampling and analysis for the official control of levels of dioxins and dioxin-like PCBs and non-dioxin-like PCBs in certain foodstuffs and repealing Regulation (EC) No 1883/2006. *Official Journal of the European Union* L 84/1 23.3.2012 [Internet]. [Accessed 2012 June 29]. Available from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:084:0001:0022:EN:PDF>

EU 2011: European Commission. Commission Regulation (EU) No 1259/2011 of 2 December 2011 amending Regulation (EC) No 1881/2006 as regards maximum levels for dioxins, dioxin-like PCBs and non dioxin-like PCBs in foodstuffs. *Official Journal of the European Union* L 320/18 3.12.2011 [Internet]. [Accessed 2012 June 29]. Available from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:320:0018:0023:EN:PDF>

Evans W. *Trease and Evans Pharmacognosy*, 16th edition. Edinburgh: Elsevier Saunders; 2009.

FCC 7: *Food Chemical Codex, Seventh Edition*. Rockville (MD): The United States Pharmacopoeial Convention, 2010.

FCC 8: *Food Chemicals Codex, Eighth edition*. Rockville (MD): The United States Pharmacopoeial Convention; 2012.

FDA 2008: United States Food and Drug Administration. Calcium and Osteoporosis, and Calcium, Vitamin D, and Osteoporosis. [online] *Federal Register*, Volume 73, Number 189, September 29, 2008, Final Rules. Docket Number FDA-2004-P-0205 (formerly Docket Number 2004P-0464) Rockville (MD): Department of Health and Human Services, U.S. Food and Drug

Administration. [Accessed 2009 June 23]. Available from:
<http://www.fda.gov/OHRMS/DOCKETS/98fr/E8-22730.pdf>

Fitzpatrick KC. Invitational Consultation on Fatty Acids. Winnipeg (MB): Nutritech Consulting; 2005.

Franco V, Polanczyk CA, Clausell N, Rohde LE. Role of dietary vitamin K intake in chronic oral anticoagulation: prospective evidence from observational and randomized protocols. *The American Journal of Medicine* 2004;166(10):651-6.

Froese R, Pauly D, editors. 2008. FishBase: A Global Information System on Fishes [Internet]. Penang (MY): WorldFish Center. [Accessed 2012 January 11]. Available from:
<http://www.fishbase.org>

Goel A, Kunnumakkara AB, Aggarwal BB. 2008. Curcumin as "Curecumin": From kitchen to clinic. *Biochemical Pharmacology* 75:787-809.

Goldman L, Ausiello D, editors. Cecil Textbook of Medicine, Volume 1, 22nd edition. Philadelphia (PA): Saunders; 2004.

Groff J, Gropper S. Advanced Nutrition and Human Metabolism, 3rd edition. Belmont (CA): Wadsworth/Thomson Learning; 2000.

Hansten PD, Horn JR, editors. Drug Interactions Analysis and Management. Vancouver (WA): Applied Therapeutics Inc.; 1997.

Hathcock JN and Shao A. Risk assessment for glucosamine and chondroitin sulphate. *Regulatory Toxicology and Pharmacology* 2006;47(1):78-83.

Herrero-Beaumont G, Ivorra JAR, Trabado MC, Blanco FJ, Benito P, Martín-Mola E, Paulino J, Marengo JL, Porto A, Laffon A, Araújo D, Figueroa M, Branco J. Glucosamine sulfate in the treatment of knee osteoarthritis symptoms- a randomized, double-blind, placebo-controlled study using acetaminophen as a side comparator. *Arthritis and Rheumatism* 2007;56(2):555-567.

HC 2013: Natural Health Products Directorate. Quality of Natural Health Products Guide. Ottawa (ON): Natural Health Products Directorate, Health Canada; 2013. Available from:
<http://www.hc-sc.gc.ca/dhp-mps/prodnatur/legislation/docs/eq-paq-eng.php>

Hoffmann D. Medical Herbalism: The Science and Practice of Herbal Medicine. Rochester (VT): Healing Arts Press; 2003.

Houpt JB, McMillan R, Wein C, Paget-Dellio SD. Effect of glucosamine hydrochloride in the treatment of pain of osteoarthritis of the knee. *Journal of Rheumatology* 1999;26(11):2423-2430.

Hunt CD. Dietary boron: Progress in establishing essential roles in human physiology. *Journal of Trace Elements in Medicine and Biology*; 2012.

ICIDH 2008: International Cosmetic Ingredient Dictionary and Handbook, Twelfth Edition, Volume 1. Gottschalck TE, Bailey JE, editors. Washington (DC): The Cosmetic, Toiletry, and Fragrance Association; 2008.

IOM 2006: Institute of Medicine. Otten JJ, Pitz Hellwig J, Meyers LD, editors. Institute of Medicine. Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. Washington (DC): National Academies Press; 2006

IOM 1997: Institute of Medicine. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride. Washington (DC) : National Academy Press; 1997.

IOM 2003: Institute of Medicine. Committee on Food Chemicals Codex, Food and Nutrition Board, Institute of Medicine. Food Chemicals Codex, 5th edition. Washington (DC): National Academies Press; 2003.

IOM 2006: Institute of Medicine. Otten JJ, Pitz Hellwig J, Meyers LD, editors. 2006. Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. Washington (DC): National Academies Press.

IOM 2001: Institute of Medicine. Panel on Micronutrients, Subcommittees on Upper Reference Levels of Nutrients and Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington (DC): National Academies Press; 2001.

ITIS 2011: Integrated Taxonomic Information System. Canadian Biodiversity Information Facility [Internet]. 2009. Ottawa (ON): Government of Canada. [Accessed 2012 January 12]. Available from: http://www.cbif.gc.ca/pls/itisca/taxaget?p_ifx=cbif

IUBMB 1992: IUBMB Enzyme Nomenclature [Internet]. London (GB): Queen Mary, University of London. [stem bromelain: CAS 37189-34-7, EC 3.4.22.32 created 1965 as EC 3.4.4.24, transferred 1972 to EC 3.4.22.4, part transferred 1992 to EC 3.4.22.32; Accessed 2012 March 28]. Available from: <http://www.chem.qmul.ac.uk/iubmb/enzyme/EC3/4/22/32.html>

Kalman DS, Heimer M, Valdeon A, Schwartz H, Sheldon E. Effect of a natural extract of chicken combs with a high content of hyaluronic acid (Hyal-Joint) on pain relief and quality of life in subjects with knee osteoarthritis: a pilot randomized double-blind placebo-controlled trial. Nutrition Journal 2008; Jan 21:7:3.

Kerkhoffs GM, Struijs PA, de Wit C, Rahlfs VW, Zwipp H, van Dijk CN. A double blind, randomised, parallel group study on the efficacy and safety of treating acute lateral ankle sprain with oral hydrolytic enzymes. British Journal of Sports Medicine 2004;38;431-435.

Khan I, Abourashed E. Leung's Encyclopedias of Common Natural Ingredients Used in Food, Drugs and Cosmetics, 3rd edition. Hoboken (NJ): John Wiley & Sons, Inc. ; 2010.

Kim LS, Axelrod LJ, Howard P, Buratovich N, Waters RF. Efficacy of methylsulfonylmethane (MSM) in osteoarthritis pain of the knee: a pilot clinical trial. *Osteoarthritis Cartilage* 2006;14(3):286-294.

Kimmatkar N, Thawani V, Hingorani L, Khiyani R. Efficacy and tolerability of *Boswellia serrata* extract in treatment of osteoarthritis of knee--a randomized double blind placebo controlled trial. *Phytomedicine: International Journal of Phytotherapy & Phytopharmacology*. 2003;10:3-5.

Kralovec A, Barrow CJ. Glucosamine Production and Health Benefits. In: Barrow C, Shahidi F, editors. *Marine Nutraceuticals and Functional Foods*. Boca Raton (FL): CRC Press, Taylor and Francis Group; 2008.

Krieger D, Krieger S, Jansen O, Gass P, Theilmann L, Lichtnecker H. Manganese and chronic hepatic encephalopathy. *Lancet* 1995;246(8970):270-4

Kulkarni RR, Patki PS, Jog VP, Gandage SG, Patwardhan B. Treatment of osteoarthritis with a herbomineral formulation: a double-blind, placebo-controlled, cross-over study. *Journal of Ethnopharmacology* 1991;33(1-2):91-95.

Larson MK, Ashmore JH, Harris KA, Vogelaar JL, Pottala JV, Sprehe M, Harris WS. Effects of omega-3 acid ethyl esters and aspirin, alone and in combination, on platelet function in healthy subjects. *Thrombosis and Haemostasis* 2008;100:634-641.

Martindale 2012: Sweetman SC, editor. *Martindale: The Complete Drug Reference*. [Internet]. London (GB): Pharmaceutical Press. 2012. [Accessed 2012 June 29]. Available from: <http://www.medicinescomplete.com>

Mazières B, Combe B, Phan Van A, Tondut J, Grynfeldt M. Chondroitin sulphate in osteoarthritis of the knee: a prospective, double-blind, placebo-controlled multicenter clinical study. *The Journal of Rheumatology* 2001;28(1):173-181.

Mazières B, Hucher M, Zaïm M, Garnero P. Effect of chondroitin sulphate in symptomatic knee osteoarthritis: a multicentre, randomised, double-blind, placebo-controlled study. *Annals of the Rheumatic Diseases* 2007;66(5):639-645.

McGuffin M, Hobbs C, Upton R, Goldberg A, editors. *American Herbal Products Association's Botanical Safety Handbook*. Boca Raton (FL1997.): CRC Press McGuffin M, Kartesz JT, Leung AY, Tucker AO, editors. 2000. *Herbs of Commerce*, 2nd edition. Silver Spring (MD): American Herbal Products Association.



Mehta K, Gala J, Bhasale S, Naik S, Modak M, Thakur H, Deo N, Miller MJ. Comparison of glucosamine sulfate and a polyherbal supplement for the relief of osteoarthritis of the knee: a randomized controlled trial. *BMC Complementary and Alternative Medicine* 2007;31(7):34.

Merck 2012: The Merck Index Version 14.1. [Internet]. Whitehouse Station (NJ): Merck & Co., Inc. Copyright © 2006, 2012 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. [Accessed 2012 June 29]. Available from: <http://www.medicinescomplete.com>

Mills S, Bone K. *Principles and Practice of Phytotherapy*. Toronto (ON): Churchill Livingstone; 2000.

Mills S, Bone K. *The Essential Guide to Herbal Safety*. St. Louis (MO): Elsevier Churchill Livingstone; 2005.

Mills E, Dugoua J, Perri D, Koren G. *Herbal Medicines in Pregnancy and Lactation: An Evidence-Based Approach*. London (GB): Taylor and Francis Medical; 2006.

Moskowitz RW. Role of collagen hydrolysate in bone and joint disease. *Seminars in Arthritis and Rheumatism* 2000;30(2):87-99.

Murray MT, Pizzorno JE. Bromelain. In: Pizzorno JE, Murray MT, editors. *Textbook of Natural Medicine*, Third edition, volume 1. St. Louis (MI): Churchill Livingstone Elsevier; 2006.

Nagaoka I, Nabeshima K, Murakami S, Yamamoto T, Watanabe K, Tomonaga A, Yamaguchi H. Evaluation of the effects of supplementary diet containing chicken comb extract on symptoms and cartilage metabolism in patients with knee osteoarthritis. *Experimental and Therapeutic Medicine* 2010;1:817-827.

NAMS (The North American Menopause Society). Position Statement - The role of calcium in peri- and postmenopausal women: 2006 position statement of The North American Menopause Society. *The Journal of the North American Menopause Society* 2006;13(6):862-877

Nielsen FH, Gallagher SK, Johnson LK, Nielsen EJ. Boron enhances and mimics some effects of estrogen therapy in postmenopausal women. *Journal of Trace Elements in Experimental Medicine* 1992;5:237-246.

Nielsen FH, Hunt CD, Mullen LM, Hunt JR. Effect of dietary boron on mineral, estrogen, and testosterone metabolism in postmenopausal women 1987;1(5):394-397.

NIH 2000: National Institute of Health. Osteoporosis Prevention, Diagnosis, and Therapy. NIH Consensus Statement Online 2000;17(1):1-36. Bethesda (MD): National Institute of Health; March 27-29, 2000. [Accessed 2007-03-21]. Available from: <http://www.consensus.nih.gov/2000/2000Osteoporosis111html.htm>

NIH 2008: National Institutes of Health. The NCBI Entrez Taxonomy Homepage. [Internet]. Bethesda (MD): Specialized Information Services, National Library of Medicine, National

Institutes of Health, US Department of Health & Human Services. [Accessed 2012 January 11]. Available from: <http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=search&db=taxonomy>

Oesser S, Adam M, Babel W, Seifert J. Oral administration of ¹⁴C labeled gelatin hydrolysate leads to an accumulation of radioactivity in cartilage of mice (C57/BL). *Journal of Nutrition* 1999;129(10):1891-5.

O'Neil MJ, Smith A, Heckelman PE, Budavari S, editors. *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*, 14th edition. Whitehouse Station (NJ): Merck & Co., Inc.; 2006.

O'Neil MJ, Heckelman PE, Koch CB, Roman KJ, editors. 2009. *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*, 14th edition. Electronic version [online]. Whitehouse Station (NJ): Merck & Co., Inc. [Accessed 2009 November 27]. Available at: <http://www.medicinescomplete.com/mc/merck/current/monographs.htm>

Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. *Archives of Internal Medicine* 2002;162(18):2113-2123.

Ph.Eur. 2012: *European Pharmacopoeia*, 8th edition. Strasbourg (FR): Directorate for the Quality of Medicines and HealthCare of the Council of Europe (EDQM); 2012.

PPRC 2005: *Pharmacopoeia of the People's Republic of China*, Volume 1, English edition 2005. Beijing (CN): The State Pharmacopoeia Commission of the People's Republic of China.

Qiu GX, Gao SN, Giacovelli G, Rovati L, Stenikar I. Efficacy and safety of glucosamine sulfate versus ibuprofen in patients with knee osteoarthritis. *Arzneimittelforschung* 1998;48(5):460-474.

Reginster JY, Deroisy R, Rovati LC, Lee RL, Lejeune E, Bruyere O, Giacovelli G, Henrotin Y, Dacre JA, Gossett C. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomized, placebo-controlled clinical trial. *The Lancet* 2001;357(9252):251-256.

Sato T, Iwaso H. 2008. An effectiveness study of hyaluronic acid (Hyabest®(J)) in the treatment of osteoarthritis of the knee on the patients in the United States. *Journal of New Remedies & Clinics* 2008;57(2):128-137.

Sato T, Sakamoto W, Odanaka W, Yoshida K, Urishibata O. Clinical effects of dietary hyaluronic acid on dry, rough skin. *Aesthetic Dermatology* 2002;12:109-120.

Schauss AG, Stenehjem J, Park J, Endres JR, Clewell A. Effect of the novel low molecular weight hydrolyzed chicken sternal cartilage extract, BioCell Collagen, on improving osteoarthritis-related symptoms: a randomized, double-blind, placebo-controlled trial. *Journal of Agricultural and Food Chemistry* 2012;60(16):4096-101

Schrieber R, Gareis H. Gelatine Handbook: Theory and Industrial Practice. Weinheim: Wiley-VCH. 2007

Shils ME, Shike M, Ross AC, Caballero B, Cousins RJ, editors. Modern Nutrition in Health and Disease, 10th edition. Philadelphia (PA): Lippincott Williams and Wilkins; 2006.

Singer F, Singer C, Oberleitner H. Phlogenzym versus diclofenac in the treatment of activated osteoarthritis of the knee. A double-blind prospective randomized study. International Journal of Immunotherapy XVII 2001;(2/3/4):135-141.

Sitanggang AB, Wu HS, Wang SS, Ho YC. Effect of pellet size and stimulating factor on the glucosamine production using *Aspergillus* sp. BCRC 31742. Bioresource Technology 2010; 101(10):3595-3601.

Sköldstam L, Börjesson O, Kjällman A, Seiving B, Akesson B. Effect of six months of fish oil supplementation in stable rheumatoid arthritis. A double-blind, controlled study. Scandinavian Journal of Rheumatology 1992;21(4):178-185.

Sontakke S, Thawani V, Pimpalkhute S, Kabra P, Babhulkar S, Hingorani L. Open, randomized, controlled clinical trial of *Boswellia serrata* extract as compared to valdecoxib in osteoarthritis of knee. Indian J Pharmacol 2007;39:27-9

Sterk V, Buchele B, Simmet T. Effect of food intake on the bioavailability of boswellic acids from a herbal preparation in healthy volunteers. Planta Med 2004;70:1155-1160.

Sweetman SC, editor. Martindale: The Complete Drug Reference, 35th edition. London (GB): Pharmaceutical Press; 2007.

Tang BMP, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fracture and bone loss in people aged 50 years and older: a meta-analysis. Lancet 2007;370(9588):657-666.

Tashiro T, Seino S, Sato T, Matsuoka R, Masuda Y, Fukui N. Oral administration of polymer hyaluronic acid alleviates symptoms of knee osteoarthritis: a double-blind, placebo-controlled study over a 12-month period. The Scientific World Journal 2012, Article ID 167928.

Thie NM, Prasad NG, Major PW. Evaluation of glucosamine sulfate compared to ibuprofen for the treatment of temporomandibular joint osteoarthritis: a randomized double blind controlled 3 month clinical trial. The Journal of Rheumatology 2001;28(6):1347-1355.

Towheed, TE, Anastassiades T. Glucosamine therapy for osteoarthritis: An update. The Journal of Rheumatology 2007;34(9):1787-1790.

Uebelhart D, Malaise M, Marcolongo R, de Vathaire F, Piperno M, Mailleux E, Fioravanti A, Matoso L, Vignon E. Intermittent treatment of knee osteoarthritis with oral chondroitin sulphate:



a one-year, randomized, double-blind, multicenter study versus placebo. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2004;12(4):269-276.

Uebelhart D, Thonar EJ, Delmas PD, Chant Raine A, Vignon E. Effects of oral chondroitin sulfate on the progression of knee osteoarthritis: a pilot study. *Osteoarthritis Cartilage* 1998; 6(Suppl A):39-46.

US EPA 2010: United States Environmental Protection Agency. April 2010. Method 1668C: Chlorinated Biphenyl Congeners in Water, Soil, Sediment, Biosolids, and Tissue by HRGC/HRMS [Internet]. Washington (DC): Engineering and Analysis Division, Office of Science and Technology, Office of Water, U.S. Environmental Protection Agency. [Accessed 2012 March 23]. Available from: http://water.epa.gov/scitech/methods/cwa/upload/M1668C_11June10-PCB_Congeners.pdf

US EPA 2008: United States Environmental Protection Agency. November 2008. Method 1668B: Chlorinated Biphenyl Congeners in Water, Soil, Sediment, Biosolids, and Tissue by HRGC/HRMS [Internet]. Washington (DC): Engineering and Analysis Division, Office of Science and Technology, Office of Water, U.S. Environmental Protection Agency. [Accessed 2012 March 23]. Available from: http://water.epa.gov/scitech/methods/cwa/bioindicators/upload/2009_01_07_methods_method_1668.pdf

US EPA 1994: United States Environmental Protection Agency. October 1994. Method 1613, Revision B: Tetra- through Octa-Chlorinated Dioxins and Furans by Isotope Dilution HRGC/HRMS [Internet]. Washington (DC): Engineering and Analysis Division, Office of Water, U.S. Environmental Protection Agency. [Accessed 2012 March 23]. Available from: http://water.epa.gov/scitech/methods/cwa/organics/dioxins/upload/2007_07_10_methods_method_dioxins_1613.pdf

USDA 2007, 2008, 2009, 2011: United States Department of Agriculture, Agricultural Research Service, National Genetic Resources Program. Germplasm Resources Information Network (GRIN) [Internet]. National Germplasm Resources Laboratory, Beltsville (MD). Available from: http://www.ars-grin.gov/cgi-bin/npgs/html/tax_search.pl

US FDA 1997: Food and Drug Administration. 21 CFR 184 Substances Affirmed as Generally Recognized as Safe: Menhaden Oil [Internet]. Washington (DC): Food and Drug Administration, US Department of Health and Human Services; 1997. [Accessed 2012 January 11]. Available from: <http://www.fda.gov/OHRMS/DOCKETS/dockets/95s0316/95s-0316-rpt0354-058-Ref-F-FR-Rules-Regulations-1997-vol273.pdf>

Usha PR, Naidu MUR. Randomised, double-blind, parallel, placebo-controlled study of oral glucosamine, methylsulfonylmethane and their combination in osteoarthritis. *Clinical Drug Investigation* 2004;24(6):353-363.



USP 32: United States Pharmacopeial Convention. United States Pharmacopeia and the National Formulary (USP 32 - NF 27). Rockville (MD): The United States Pharmacopeial Convention; 2009.

USP 34: United States Pharmacopeia and the National Formulary (USP 34 - NF 29). Rockville (MD): The United States Pharmacopeial Convention; 2012.

USP 35: United States Pharmacopeia and the National Formulary (USP 35 - NF 30). Rockville (MD): The United States Pharmacopeial Convention; 2012.

Usuda K, Kono K, Iguchi K, Nishiura K, Miyata K, Shimahara M, Konda T, Hashiguchi N, Senda J. Hemodialysis effect on serum boron level in the patients with long term hemodialysis. *The science of the total environment* 1996;191(3):283-290.

Volker D, Fitzgerald P, Major G, Garg M. Efficacy of fish oil concentrate in the treatment of rheumatoid arthritis. *The Journal of Rheumatology* 2000;27(10):2343-2346.

Walker AF, Bundy R, Hicks SM, Middleton RW. Bromelain reduces mild acute knee pain and improves well-being in a dose-dependent fashion in an open study of otherwise health adults. *Phytomedicine* 2002;9:681-686.

WHO 2009: World Health Organization. WHO monographs on selected medicinal plants, Volume 4. Geneva (CH): World Health Organization; 2009.

Wichtl M, editor. *Herbal Drugs and Phytopharmaceuticals: A Handbook for Practice on a Scientific Basis*, 3rd edition. Stuttgart (DE): Medpharm GmbH Scientific Publishers; 2004.

Wille HJ, Gonus P. Preparation of fish oil for dietary applications. In: Galli C, Simopolous AP, editors. *Dietary ω 3 and ω 6 fatty acids. Biological Effects and Nutritional Essentiality*. New York (NY): Plenum Press; 1989.

Williamson EM. *Potter's Herbal Cyclopaedia: The Authoritative Reference work on Plants with a Known Medical Use*. Saffron Walden (GB): The C.W. Daniel Company Limited; 2003.

Winston D, Kuhn MA. *Winston and Kuhn's Herbal Therapy and Supplements. A Scientific and Traditional Approach*, 2nd edition. Philadelphia (PA): Lippincott Williams and Wilkins; 2008.

Yoshida T, Kanemitsu T, Narabe H, Tobita M. Clinical effect on dry skin by oral administration of food containing microbial fermented hyaluronic acid. *Journal of New Remedies & Clinics* 2009;58(8).

Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? *The British Journal of Nutrition* 2003;89(5):552-72.

References reviewed



- Ackman RG. 1992. The absorption of fish oils and concentrates. *Lipids* 27(11):858-862.
- Adams ME. 1999. Hype about glucosamine. *The Lancet* 354(9176):353-354.
- Addis PB. 1990. Fish oil and your health [Internet]. Duluth (MN): Minnesota Sea Grant Research and Education. [Accessed 2012 January 30]. Available from: <http://www.seagrant.umn.edu/downloads/f9.pdf>
- Ahmed AA, Holub BJ. 1984. Alteration and recovery of bleeding times, platelet aggregation and fatty acid composition of individual phospholipids in platelets of human subjects receiving a supplement of cod liver oil. *Lipids* 19(8):617-624.
- Albert SG, Oiknine RF, Parseghian S, Mooradian AD, Haas MJ, McPherson T. 2007. The effect of glucosamine on Serum HDL cholesterol and apolipoprotein AI levels in people with diabetes. *Diabetes Care* 30(11):2800-2803.
- Allen KG, Harris MA. 2001. The role of n-3 fatty acids in gestation and parturition. *Experimental Biology and Medicine* 226(6):498-506.
- Altman R, Brandt K, Hochberg M, Moskowitz R, Bellamy N, Bloch DA, Buckwalter J, Dougados M, Ehrlich G, Lequesne M, Lohmander S, Murphy WA Jr, Rosario-Jansen T, Schwartz B, Trippel S. 1996. Design and conduct of clinical trials in patients with osteoarthritis: recommendations from a task force of the Osteoarthritis Research Society; Results from a workshop. *Osteoarthritis Cartilage* 4(4):217-243.
- Anderson JW, Nicolosi RJ, Borzelleca JF. 2005. Glucosamine effects in humans: a review of effects on glucose metabolism, side effects, and safety considerations and efficacy. *Food and Chemical Toxicology* 43(2):187-201.
- Angerer P, Kothny W, Störk S, von Schacky C. 2002. Effect of dietary supplementation with omega-3 fatty acids on progression of atherosclerosis in carotid arteries. *Cardiovascular Research* 54(1):183-190.
- Annuzzi G, Rivellesse A, Capaldo B, Di Marino L, Iovine C, Marotta G, Riccardi G. 1991. A controlled study on the effects of n-3 fatty acids on lipid and glucose metabolism in non-insulin-dependent diabetic patients. *Atherosclerosis* 87(1):65-73.
- Appel LJ, Miller ER, Seidler AJ, Whelton PK. 1993. Does supplementation of diet with 'fish oil' reduce blood pressure? *Archives of Internal Medicine* 153(12):1429-1438.
- ASHP 2005: American Society of Health-System Pharmacists. American Hospital Formulary Service (AHFS) Drug Information. Philadelphia (PA): Lippincott Williams and Wilkins; 2005.



- Audimoolam VK, Bhandari S. 2006. Transhepatic venous access as an alternative for Tesio catheter in the case of a patient on haemodialysis with antiphospholipid syndrome. *Nephrology Dialysis Transplantation* 21(7):2031-2033.
- Bairati I, Roy L, Meyer F. 1992. Effects of a fish oil supplement on blood pressure and serum lipids in patients treated for coronary artery disease. *Canadian Journal of Cardiology* 8(1):41-46.
- Balk E, Chung M, Lichtenstein A, Chew P, Kupelnick B, Lawrence A, DeVine D, Lau J. 2004. Effects of Omega-3 Fatty Acids on Cardiovascular Risk Factors and Intermediate Markers of Cardiovascular Disease. Summary, Evidence Report/Technology Assessment No. 93. AHRQ No. 04-E010-1. Rockville (MD): Agency for Healthcare Research and Quality.
- Bana G, Jamard B, Verrouil E, Mazières B. 2006. Chondroitin sulphate in the management of hip and knee osteoarthritis: an overview. *Advances in Pharmacology* 53:507-522.
- Bassleer C, Rovati L, Franchimont P. 1998. Stimulation of proteoglycan production by glucosamine sulfate in chondrocytes isolated from human osteoarthritic articular cartilage in vitro. *Osteoarthritis and Cartilage* 6(6):427-434.
- Bender NK, Kraynak MA, Chiquette E, Linn WD, Clark GM, Bussey HI. 1998. Effects of marine fish oils on the anticoagulation status of patients receiving chronic warfarin therapy. *Journal of Thrombosis and Thrombolysis* 5(3):257-261.
- Berbert AA, Kondo CR, Almendra CL, Matsuo T, Dichi I. 2005. Supplementation of fish oil and olive oil in patients with rheumatoid arthritis. *Nutrition* 21(2):131-136.
- Bijlsma JW, Lafeber FP. 2008. Glucosamine sulfate in osteoarthritis: the jury is still out. *Annals of Internal Medicine* 148(4):315-316.
- Birch EE, Castaneda YS, Wheaton DH, Birch DG, Uauy RD, Hoffman DR. 2005. Visual maturation of term infants fed long-chain polyunsaturated fatty-acid supplemented or control formula for 12 mo. *The American Journal of Clinical Nutrition* 81(4):871-879.
- Birch EE, Garfield S, Hoffman DR, Uauy R, Birch DG. 2000. A randomized controlled trial of early long-chain polyunsaturated fatty acids and mental development in term infants. *Developmental Medicine and Child Neurology* 42(3):174-181.
- Birch EE, Hoffman DR, Castañeda YS, Fawcett SL, Birch DG, Uauy RD. 2002. A randomized controlled trial of long-chain polyunsaturated fatty acid supplementation of formula in term infants after weaning at 6 wk of age. *The American Journal of Clinical Nutrition* 75(3):570-580.
- Bisby FA, Roskov YR, Orrell TM, Nicolson D, Paglinawan LE, Bailly N, Kirk PM, Bourgoin T, van Hertum J, editors. 2008. Species 2000 & ITIS Catalogue of Life: 2008 Annual Checklist. Digital Resource [Internet]. Reading (GB): Species 2000. [Accessed 2012 January 11]. Available from: <http://www.catalogueoflife.org/annual-checklist/2008/>



Blonk MC, Bilo HJ, Nauta JJ, Popp-Snijders C, Mulder C, Donker AJ. 1990. Dose-response effects of fish-oil supplementation in healthy volunteers. *The American Journal of Clinical Nutrition* 52(1):120-127.

Bønnaa KH, Bjerve KS, Nordøy A. 1992. Docosahexaenoic and eicosapentaenoic acids in plasma phospholipids are divergently associated with high density lipoprotein in humans. *Arteriosclerosis and Thrombosis* 12(6):675-681.

Bonnema SJ, Jespersen LT, Marving J, Gregersen G. 1995. Supplementation with olive oil rather than fish oil increases small arterial compliance in diabetic patients. *Diabetes Nutrition and Metabolism* 8(2):81-87.

Boon H. 2000. Chondroitin sulfate. In: Chandler F, editor. *Herbs: Everyday Reference for Health Professionals*. Ottawa (ON): Canadian Pharmacists Association and the Canadian Medical Association.

Boon H. 2000. Glucosamine. In: Chandler F, editor. *Herbs: Everyday Reference for Health Professionals*. Nepean (ON): Canadian Pharmacists Association and Canadian Medical Association.

Brien S, Lewith GT, McGregor G. 2006. Devil's claw (*Harpagophytum procumbens*) as a treatment for osteoarthritis: a review of efficacy and safety. *The Journal of Alternative and Complimentary Medicine* 12(10):981-993.

Brinker F. 2010. Final Updates and Additions for Herb Contraindications and Drug Interactions, 3rd edition. Sandy (OR): Eclectic Medical Publications. [Accessed 2012 January 11]. Available from: <http://www.eclecticherb.com/emp/updatesHCDI.html>

Buckley MS, Goff AD, Knapp WE. 2004. Fish oil interaction with warfarin. *Annals of Pharmacotherapy* 38(1):50-53.

Buckley R, Shewring B, Turner R, Yaqoob P, Minihane AM. 2004. Circulating triacylglycerol and apoE levels in response to EPA and docosahexaenoic acid supplementation in adult human subjects. *British Journal of Nutrition* 92(3):477-483.

Cairns JA, Gill J, Morton B, Roberts R, Gent M, Hirsh J, Holder D, Finnie K, Marquis JF, Naqvi S, Cohen E. 1996. Fish oils and low-molecular-weight heparin for the reduction of restenosis after percutaneous transluminal coronary angioplasty. The EMPAR Study. *Circulation* 94(7):1553-1560.

Calder PC. 2006. n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. *The American Journal of Clinical Nutrition* 83(6):1505S-1519S.

Calder PC. 2004. n-3 fatty acids and cardiovascular disease: evidence explained and mechanisms explored. *Clinical Science* 107(1):1-11.



Calò L, Bianconi L, Colivicchi F, Lamberti F, Loricchio ML, de Ruvo E, Meo A, Pandozi C, Staibano M, Santini M. 2005. N-3 fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial. *Journal of the American College of Cardiology* 45(10):1723-1728.

Cargill Acidulants. 2004. "Proposal for making a "Substantial Equivalence" notification for Non-Shellfish Glucosamine Hydrochloride under regulation (EC) No. 258/97 for the European Parliament and the Council of Jan 27, 1997 concerning novel foods and novel food ingredients" [Internet]. Eddyville (IA). [Accessed 2012 January 11]. Available from: <http://www.food.gov.uk/multimedia/pdfs/glucosamine1.pdf>

Carlson SE. 1996. Arachidonic acid status of human infants: influence of gestational age at birth and diets with very long chain n-3 and n-6 fatty acids. *The Journal of Nutrition* 126(4):1092S-1098S.

Carlson SE, Werkman SH, Peeples JM, Cooke RJ, Tolley EA. 1993. Arachidonic acid status correlates with first year growth in preterm infants. *Proceedings of the National Academy of Sciences* 90(3):1073-1077.

Carroll DN, Roth MT. 2002. Evidence for the cardioprotective effects of omega-3 fatty acids. *The Annals of Pharmacotherapy* 36(12):1950-1956.

Cazzola R, Russo-Volpe S, Miles EA, Rees D, Banerjee T, Roynette CE, Wells SJ, Goua M, Wahle KW, Calder PC, Cestaro B. 2007. Age- and dose-dependent effects of an eicosapentaenoic acid-rich oil on cardiovascular risk factors in healthy male subjects. *Atherosclerosis* 193(1):159-167.

Chantre P, Cappelaere A, Leblan D, Guedon D, Vandermander J, Fournie B. 2007. Efficacy and tolerance of *Harpagophytum procumbens* versus diacerhein in treatment of osteoarthritis. *Phytomedicine* 7(3):177-183.

Chee KM, Gong JX, Rees DM, Meydani M, Ausman L, Johnson J, Siguel EN, Schaefer EJ. 1990. Fatty acid content of marine oil capsules. *Lipids* 25(9):523-528.

Chrubasik S, Chrubasik C, Kunzel O, Black A. 2007. Patient-perceived benefit during one year of treatment with Doloteffin. *Phytomedicine* 14(6):371-376.

Chrubasik S, Conradt C, Black A. 2003. The quality of clinical trials with *Harpagophytum procumbens*. *Phytomedicine* 10(6-7):613-623.

Chrubasik S, Conradt C, Roufogalis BD. 2004. Effectiveness of *Harpagophytum* extracts and clinical efficacy. *Phytotherapy Research* 18(2):187-189.

Chrubasik S, Model A, Black A, Pollak S. 2003. A randomized double-blind pilot study comparing Doloteffin and Vioxx in the treatment of low back pain. *Rheumatology* 42(1):141-148.



Chrubasik JE, Roufogalis BD, Chrubasik S. 2007. Evidence of effectiveness of herbal antiinflammatory drugs in the treatment of painful osteoarthritis and chronic low back pain. *Phytotherapy Research* 21(7):675-683.

Chrubasik S, Thanner J, Kunzel O, Conradt C, Black A, Pollak S. 2002. Comparison of outcome measures during treatment with the proprietary *Harpagophytum* extract Doloteffin in patients with pain in the lower back, knee or hip. *Phytomedicine* 9(3):181-194.

Clegg DO, Reda DJ, Harris CL, Klein MA, O'Dell JR, Hooper MM, Bradley JD, Bingham CO 3rd, Weisman MH, Jackson CG, Lane NE, Cush JJ, Moreland LW, Schumacher HR Jr, Oddis CV, Wolfe F, Molitor JA, Yocum DE, Schnitzer TJ, Furst DE, Sawitzke AD, Shi H, Brandt KD, Moskowitz RW, Williams HJ. 2006. Glucosamine, chondroitin sulphate, and the two in combination for painful knee osteoarthritis. *The New England Journal of Medicine* 354(8):795-808.

Cleland LG, French JK, Betts WH, Murphy GA, Elliot MJ. 1988. Clinical and biochemical effects of dietary fish oil supplements in rheumatoid arthritis. *The Journal of Rheumatology* 15(10):1471-1475.

Commission of the European Communities. Commission Regulation (EC) No 1883/2006 of 19 December 2006 laying down the methods of sampling and analysis for the official control of levels of dioxins and dioxin-like PCBs in certain foodstuffs. *Official Journal of the European Union* L 364/32 20.12.2006 [Internet]. [Accessed 2012 March 23]. Available from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:364:0032:0043:EN:PDF>

Commission of the European Communities. Commission Regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs. *Official Journal of the European Union* L 364/5 20.12.2006 [Internet]. [Accessed 2012 March 23]. Available from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:364:0005:0024:EN:PDF>

Connor WE, DeFrancesco CA, Connor SL. 1993. N-3 fatty acids from fish oil. Effects on plasma lipoproteins and hypertriglyceridemic patients. *Annals of the New York Academy of Sciences* 683:16-34.

Connor WE, Prince MJ, Ullmann D, Riddle M, Hatcher L, Smith FE, Wilson D. 1993. The hypotriglyceridemic effect of fish oil in adult-onset diabetes without adverse glucose control. *Annals of the New York Academy of Science* 683(1):337-340.

Conrozier T. 1998. Les traitements anti-arthrosiques: efficacite et tolerance des chondroitines sulfates (CS 4&6) [Osteoarthritic treatments: efficacy and tolerance of chondroitin sulfates (CS 4&6)]. *Presse Médicale* 27(36):1862-1865 (in French).

Council for Responsible Nutrition. 2006. VOLUNTARY MONOGRAPH for Omega-3 DHA, Omega-3 EPA, Omega-3 DHA & EPA. [Accessed 2012 January 11]. Available at: <http://www.crnusa.org/pdfs/O3FINALMONOGRAPHdoc.pdf>

Cunnane S, Drevon CA, Harris B, Sinclair A, Spector A. 2004. Recommendations for intake of polyunsaturated fatty acids in healthy adults [Internet]. Devon (GB): International Society for the Study of Fatty Acids and Lipids. [Accessed 2012 January 11]. Available from: <http://www.issfal.org/news-links/resources/publications/PUFAIntakeReccomdFinalReport.pdf>

Delafuente JC. 2000. Glucosamine in the treatment of osteoarthritis. *Complementary and Alternative Therapies for Rheumatic Diseases II* 26(1):1-11.

Deutch B, Jørgensen EB, Hansen JC. 2000. Menstrual discomfort in Danish women reduced by dietary supplements of omega-3 PUFA and B₁₂ (fish oil or seal oil capsules). *Nutrition Research* 20(5):621-631.

Dokholyan RS, Albert CM, Appel LJ, Cook NR, Whelton PK, Hennekens CH. 2004. A trial of omega-3 fatty acids for prevention of hypertension. *The American Journal of Cardiology* 93(8):1041-1043.

Dudek A, Raczekiewicz-Papierska A, Tlustochowicz W. 2007. Efficacy of glucosamine sulfate treatment in patients with osteoarthritis. *Polski Merkuriusz Lekarski: Organ Polskiego Towarzystwa Lekarskiego* 22(129):204-207.

Dunstan JA, Mori TA, Barden A, Beilin LJ, Taylor AL, Holt PG, Prescott SL. 2003. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial. *Journal of Allergy and Clinical Immunology* 112(6):1178-1184.

Dunstan JA, Roper J, Mitoulas L, Hartmann PE, Simmer K, Prescott SL. 2004. The effect of supplementation with fish oil during pregnancy on breast milk immunoglobulin A, soluble CD14, cytokine levels, and fatty acid composition. *Clinical and Experimental Allergy* 34(8):1237-1242.

Engeset D, Alsaker E, Lund E, Welch A, Khaw KT, Clavel-Chapelon F, Thiébaud A, Chajès V, Key TJ, Allen NE, Amiano P, Dorronsoro M, Tjønneland A, Stripp C, Peeters PH, van Gils CH, Chirlaque MD, Nagel G, Linseisen J, Ocké MC, Bueno-de-Mesquita HB, Sacerdote C, Tumino R, Ardanaz E, Sánchez MJ, Panico S, Palli D, Trichopoulou A, Kalapothaki V, Benetou V, Quirós JR, Agudo A, Overvad K, Bjerregaard L, Wirfält E, Schulz M, Boeing H, Slimani N, Riboli E. 2006. Fish consumption and breast cancer risk. The European Prospective Investigation into Cancer and Nutrition (EPIC). *International Journal of Cancer* 119(1):175-182.

Engler MM, Engler MB, Malloy MJ, Paul SM, Kulkarni KR, Mietus-Snyder ML. 2005. Effect of docosahexaenoic acid on lipoprotein subclasses in hyperlipidemic children (the EARLY study). *American Journal of Cardiology* 95(7):869-871.



Eritsland J. 2000. Safety considerations of polyunsaturated fatty acids. *The American Journal of Clinical Nutrition* 71(1):197S-201S.

Eritsland J, Arnesen H, Seljeflot I, Høstmark AT. 1995. Long-term metabolic effects of n-3 polyunsaturated fatty acids in patients with coronary artery disease. *The American Journal of Clinical Nutrition* 61(4):831-836.

Eritsland J, Arnesen H, Seljeflot I, Kierulf P. 1995. Long-term effects of n-3 polyunsaturated fatty acids on haemostatic variables and bleeding episodes in patients with coronary artery disease. *Blood Coagulation and Fibrinolysis* 6(1):17-22.

Eritsland J, Seljeflot I, Abdelnoor M, Arnesen H, Torjesen PA. 1994. Long-term effects of n-3 fatty acids on serum lipids and glycemic control. *Scandinavian Journal of Clinical and Laboratory Investigation* 54(4):273-280.

Felson DT. 2006. Glucosamine and chondroitin sulfate in knee osteoarthritis: where now? *Nature Clinical Practice. Rheumatology* 2(7):356-357.

Fetrow CW, Avila JR. 2004. *Professional's Handbook of Complementary and Alternative Medicines*, 3rd edition. Philadelphia (PA): Lippincott Williams and Wilkins.

Fitzpatrick KC. 2005. *Invitational Consultation on Fatty Acids*. Winnipeg (MB): Nutritech Consulting.

Fortin PR, Lew RA, Liang MH, Wright EA, Beckett LA, Chalmers TC, Sperling RI. 1995. Validation of a meta-analysis: the effects of fish oil in rheumatoid arthritis. *The Journal of Clinical Epidemiology* 48(11):1379-1390.

Franzen D, Schannwell M, Oette K, Höpp HW. 1993. A prospective, randomized, and double-blind trial on the effect of fish oil on the incidence of restenosis following PTCA. *Catheterization and Cardiovascular Diagnosis* 28(4):301-310.

Freese R, Mutanen N. 1997. Alpha-linolenic acid and marine long-chain n-3 fatty acids differ only slightly in their effects on hemostatic factors in healthy subjects. *The American Journal of Clinical Nutrition* 66(3):591-598.

Frestedt JL, Walsh M, Kuskowski MA, Zenk JL. 2008. A natural mineral supplement provides relief from knee osteoarthritis symptoms: a randomized controlled pilot trial. *Nutrition Journal* 17(7):9.

Friedberg CE, Janssen MJ, Heine RJ, Grobbee DE. 1998. Fish oil and glycemic control in diabetes. A meta-analysis. *Diabetes Care* 21(4):494-500.

Fulop N, Marchase RB, Chatham JC. 2007. Role of Protein O-linked N-acetyl-glucosamine in mediating cell function and survival in the cardiovascular system. *Cardiovascular Research* 73(2):288-297.



Fux M, Benjamin J, Nemets B. 2004. A placebo-controlled crossover trial of adjunctive EPA in OCD. *Journal of Psychiatric Research* 38(3):323-325.

Gagnier JJ, vanTulder M, Berman B, Bombardier C. 2008. Herbal medicine for low back pain: a Cochrane review. *Spine* 32(1):82-92.

Gapinski JP, VanRuiswyk JV, Heudebert GR, Schectman GS. 1993. Preventing restenosis with fish oils following coronary angioplasty: a meta-analysis. *Archives of Internal Medicine* 153(13):1595-1601.

Geelen A, Brouwer IA, Schouten EG, Maan AC, Katan MB, Zock PL. 2005. Effects of n-3 fatty acids from fish on premature ventricular complexes and heart rate in humans. *The American Journal of Clinical Nutrition* 81(2):416-420.

Geleijnse JM, Giltay EJ, Grobbee DE, Donders AR, Kok FJ. 2002. Blood pressure response to fish oil supplementation: meta-regression analysis of randomized trials. *Journal of Hypertension* 20(8):1493-1499.

Geusens P, Wouters C, Nijs J, Jiang Y, Dequeker J. 1994. Long-term effect of omega-3 fatty acid supplementation in active rheumatoid arthritis: a 12-month, double-blind, controlled study. *Arthritis & Rheumatism* 37(6):824-829.

Goodnight SH, Harris WS, Connor WE. 1981. The effects of dietary omega-3 fatty acids on platelet composition and function in man: a prospective, controlled study. *Blood* 58(5):880-885.

Grant L, McBean DE, Fyfe L, Warnock AM. 2007. A review of the biological and potential actions of *Harpagophytum procumbens*. *Phytotherapy Research* 21(3):199-209.

Gray HC, Hutcheson PS, Slavin RG. 2004. Is glucosamine safe in patients with seafood allergy? *The Journal of Allergy and Clinical Immunology* 114(2):456-460.

Gregory PJ, Sperry M, Friedman Wilson A. 2008. Dietary supplements for osteoarthritis. *American Family Physician* 77(2):177-184.

Grimsgaard S, Bonna KH, Hansen JB, Nordøy A. 1997. Highly purified eicosapentaenoic acid and docosahexaenoic acid in humans have similar triacylglycerol-lowering effects but divergent effects on serum fatty acids. *The American Journal of Clinical Nutrition* 66(3):649-659.

Haag M. 2003. Essential fatty acids and the brain. *Canadian Journal of Psychiatry* 48(3):195-203.

Haglund O, Luostarinen R, Wallin R, Wibell L, Saldeen T. 1991. The effects of fish oil on triglycerides, cholesterol, fibrinogen and malondialdehyde in humans supplemented with vitamin E. *Journal of Nutrition* 121(2):165-169.

Halldorsson TI, Meltzer HM, Thorsdottir I, Knudsen V, Olsen SF. 2007. Is high consumption of fatty fish during pregnancy a risk factor for fetal growth retardation? A study of 44,824 Danish pregnant women. *American Journal of Epidemiology* 166(6):687-696.

Halliwell B, Chirico S. 1993. Lipid peroxidation: its mechanism, measurement, and significance. *The American Journal of Clinical Nutrition* 57(5):715S-725S.

Hamazaki T, Sawazaki S, Nagao Y, Kuwamori T, Yazawa K, Mizushima Y, Kobayashi M. 1998. Docosahexaenoic acid does not affect aggression of normal volunteers under nonstressful conditions. A randomized, placebo-controlled, double-blind study. *Lipids* 33(7):663-667.

Harel Z, Biro FM, Kottenhahn RK, Rosenthal SL. 1996. Supplementation with omega-3 polyunsaturated fatty acids in the management of dysmenorrhea in adolescents. *The American Journal of Obstetrics and Gynecology* 174(4):1335-1338.

Harris WS. 2007. International recommendations for consumption of long-chain omega-3 fatty acids. *Journal of Cardiovascular Medicine* 8(1):S50-S52.

Harrison N, Abhyankar B. 2005. The mechanism of action of omega-3 fatty acids in secondary prevention post-myocardial infarction. *Current Medical Research and Opinion* 21(1):95-100.

Hayes M, Carney B, Slater J, Brück W. 2008. Mining marine shellfish wastes for bioactive molecules: chitin and chitosan-Part A: extraction methods. *Biotechnology Journal* 3(7):871-877.

Health Canada. Canadian Adverse Drug Reaction Monitoring Program (CADRMP) Online Query and Data Extracts [Internet]. Ottawa (ON): Health Canada; 2011. [Accessed 2012 January 11]. Available from: http://hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/mhpd-dpsc/database-basedon_annou-annon-eng.php

Health Canada. MedEffect Canada: Adverse Reaction Reporting [Internet]. Ottawa (ON): Health Canada; 2011. [Accessed 2012 January 11]. Available from: http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index_e.html

Health Canada. Food Rulings Proposal – EPA and DHA: Level of Addition to Foods. Ottawa (ON): Bureau of Nutritional Sciences, Health Canada; 2006.

He K, Song Y, Daviglius ML, Liu K, Van Horn L, Dyer AR, Goldbourt U, Greenland P. 2004. Fish consumption and incidence of stroke: a meta-analysis of cohort studies. *Stroke* 35(7):1538-1542.

Hendler SS, Rorvik D, editors. 2001. *PDR for Nutritional Supplements*, 1st edition. Montvale (NJ): Thomson PDR.

Hjerkinn EM, Seljeflot I, Ellingsen I, Berstad P, Hjermann I, Sandvik L, Arnesen H. 2005. Influence of long-term intervention with dietary counselling, long-chain n-3 fatty acid



supplements, or both on circulating markers of endothelial activation in men with long-standing hyperlipidemia. *The American Journal of Clinical Nutrition* 81(3):583-589.

Hodge L, Salome CM, Hughes JM, Liu-Brennan D, Rimmer J, Allman M, Pang D, Armour C, Woolcock AJ. 1998. Effect of dietary intake of omega-3 and omega-6 fatty acids on severity of asthma in children. *European Respiratory Journal* 11(2):361-365.

Hodge W, Barnes D, Schachter HM, Pan Y, Lowcock EC, Zhang L, Sampson M, Morrison A, Tran K, Miguelez M, Lewin G. 2005. Effects of Omega-3 Fatty Acids on Eye Health. Summary, Evidence Report/Technology Assessment No. 117. AHRQ No. 05-E008-2. Rockville (MD): Agency for Healthcare Research and Quality.

Holguin F, Téllez-Rojo MM, Lazo M, Mannino D, Schwartz J, Hernández M, Romieu I. 2005. Cardiac autonomic changes associated with fish oil vs soy oil supplementation in the elderly. *Chest* 127(4):1102-1107.

Hooper L, Thompson RL, Harrison RA, Summerbell CD, Moore H, Worthington HV, Durrington PN, Ness AR, Capps NE, Davey Smith G, Riemersma RA, Ebrahim SBJ. 2004. Omega 3 fatty acids for prevention and treatment of cardiovascular disease. [Internet]. The Cochrane Library [Accessed 2012 January 11]. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003177.pub2/full>

Hornstra G. 2000. Essential fatty acids in mothers and their neonates. *The American Journal of Clinical Nutrition* 71(5):1262S-1269S.

Horvath K, Noker PE, Somfai-Relle S, Glávits R, Financsek I, Schauss AG. 2002. Toxicity of methylsulfonylmethane in rats. *Food and Chemical Toxicology* 40(10):1459-1462.

Hughes R, Carr A. 2002. A randomized, double-blind, placebo-controlled trial of glucosamine sulphate as an analgesic in osteoarthritis of the knee. *Rheumatology (Oxford, England)* 41(3):279-284.

Iacoviello L, Amore C, De Curtis A, Tacconi MT, de Gaetano G, Cerletti C, Donati MB. 1992. Modulation of fibrinolytic response to venous occlusion in humans by a combination of low-dose aspirin and n-3 polyunsaturated fatty acids. *Arteriosclerosis, Thrombosis and Vascular Biology* 12(10):1191-1197.

iHerb Products List [Internet]. Irwindale (CA): iHerb Inc.; 2007. [Accessed 2012 January 11]. Available from: <http://www.iherb.com/ProductsList.aspx?c=1&cid=1546>

Institute of Medicine (IOM). *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington (DC): National Academies Press; 2002.

Iso H, Rexrode KM, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, Hennekens CH. 2001. Intake of fish and omega-3 fatty acids and risk of stroke in women. *Journal of the American Medical Association* 285(3):304-312.



Jellin JM, editor. 2011. Natural Medicines Comprehensive Database: Fish Oil [Internet]. Stockton (CA): Therapeutic Research Faculty; 1995-2011. [Accessed 2012 January 11]. Available from: <http://www.naturaldatabase.com>

Jimenez SA, Dodge GR. 1997. The effects of glucosamine sulfate on human chondrocyte gene expression. *Osteoarthritis and Cartilage* 5 Suppl A:72.

Johansen O, Brekke M, Seljeflot I, Abdelnoor M, Arnesen H. 1999. N-3 fatty acids do not prevent restenosis after coronary angioplasty: results from the CART study. *Journal of the American College of Cardiology* 33(6):1619-1626.

Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JW, Dieppe P, Gunther K, Hauselmann H, Herrero-Beaumont G, Kaklamanis P, Lohmander S, Leeb B, Lequesne M, Mazieres B, Martin-Mola E, Pavelka K, Pendleton A, Punzi L, Serni U, Swoboda B, Verbruggen G, Zimmerman-Gorska I, Dougados M. 2003. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a task force of the standing committee for international clinical studies including therapeutic trials (ESCISIT). *Annals of the Rheumatic Disease* 62(12):1145-1155.

Kaul U, Sanghvi S, Bahl VK, Dev V, Wasir HS. 1992. Fish oil supplements for prevention of restenosis after coronary angioplasty. *International Journal of Cardiology* 35(1):87-93.

Kelley DS, Siegel D, Vemuri M, Mackey BE. 2007. Docosahexaenoic acid supplementation improves fasting and postprandial lipid profiles in hypertriglyceridemic men. *The American Journal of Clinical Nutrition* 86(2):324-333

Kjeldsen-Kragh J, Lund JA, Riise T, Finnanger B, Haaland K, Finstad R, Mikkelsen K, Førre Ø. 1992. Dietary omega-3 fatty acid supplementation and naproxen treatment in patients with rheumatoid arthritis. *Journal of Rheumatology* 19(10):1531-1536.

Kremer JM, Bigauoette J, Michalek AV, Timchalk MA, Lininger L, Rynes RI, Huyck C, Zieminski J, Bartholomew LE. 1985. Effects of manipulation of dietary fatty acids on clinical manifestations of rheumatoid arthritis. *The Lancet* 1(8422):184-187.

Kremer JM, Lawrence DA, Jubiz W, DiGiacomo R, Rynes R, Bartholomew LE, Sherman M. 1990. Dietary fish oil and olive oil supplementation in patients with rheumatoid arthritis: clinical and immunologic effects. *Arthritis and Rheumatism* 33(6):810-819.

Kremer JM, Lawrence DA, Petrillo GF, Litts LL, Mullaly PM, Rynes RI, Stocker RP, Parhami N, Greenstein NS, Fuchs BR, Mathur A, Robinson DR, Sperling RI, Bigauoette J. 1995. Effects of high-dose fish oil on rheumatoid arthritis after stopping nonsteroidal anti-inflammatory drugs. *Arthritis & Rheumatism* 38(8):1107-1114.

Kris-Etherton PM, Harris WS, Appel LJ. 2002. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* 106(21):2747-2757.



Krokan HE, Bjerve KS, Mork E. 1993. The enteral bioavailability of eicosapentaenoic acid and docosahexaenoic acid is as good from ethyl esters as from glyceryl esters in spite of lower hydrolytic rates by pancreatic lipase in vitro. *Biochimica et Biophysica Acta* 1168(1):59-67.

Lau CS, McLaren M, Belch JJ. 1995. Effects of fish oil on plasma fibrinolysis in patients with mild rheumatoid arthritis. *Clinical and Experimental Rheumatology* 13(1):87-90.

Lau CS, Morley KD, Belch JJ. 1993. Effects of fish oil supplementation on non-steroidal anti-inflammatory drug requirement in patients with mild rheumatoid arthritis – a double-blind placebo controlled study. *British Journal of Rheumatology* 32(11):982-989.

Laudahn D, Walper A. 2001. Efficacy and tolerance of Harpagophytum extract LI 174 in patients with chronic non-radicular back pain. *Phytotherapy Research* 15(7):621-624.

Lauritzen L, Kjaer TM, Fruekilde MB, Michaelsen KF, Frokiaer H. 2005. Fish oil supplementation of lactating mothers affects cytokine production in 2 ½-year-old children. *Lipids* 40(7):669-676.

Lawson LD, Hughes BG. 1988. Absorption of eicosapentaenoic acid and docosahexaenoic acid from fish oil triacylglycerols or fish oil ethyl esters co-ingested with a high-fat meal. *Biochemical and Biophysical Research Communications* 156(2):960-963.

Leaf A, Jorgensen MB, Jacobs AK, Cote G, Schoenfeld DA, Scheer J, Weiner BH, Slack JD, Kellett MA, Raizner AE, Weber PC, Mahrer PR, Rossouw JE. 1994. Do fish oils prevent coronary angioplasty? *Circulation* 90(5):2248-2257.

Leaf A, Kang JX, Xiao YF, Billman GE. 2003. Clinical prevention of sudden cardiac death by n-3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by n-3 fish oils. *Circulation* 107(21):2646-2652.

Leblan D, Chantre P, Fournié B. 2000. Harpagophytum procumbens in the treatment of knee and hip osteoarthritis. Four-month results of a prospective, multicenter, double-blind trial versus diacerhein. *Joint, Bone, Spine* 67(5):462-467.

Leigh-Firbank EC, Minihane AM, Leake DS, Wright JW, Murphy MC, Griffin BA, Williams CM. 2002. Eicosapentaenoic acid and docosahexaenoic acid from fish oils: differential associations with lipid responses. *British Journal of Nutrition* 87(5):435-445.

Lewin GA, Schachter HM, Yuen D, Merchant P, Mamaladze V, Tsertsvadze A, Clifford T, Kourad K, Barnes D, Armour T, Yazdi F, MacNeil J, McGahern C, Senechal H, Fang M, Barrowman N, Sampson M, Morrison A, Elien D, Saint-Martin M, Sambasivan A, Lowcock E, Pan Y, Lemyre B. 2005. Effects of Omega-3 Fatty Acids on Child and Maternal Health. Summary, Evidence Report/Technology Assessment No. 118. AHRQ No. 05-E025-2. Rockville (MD): Agency for Healthcare Research and Quality.

Lin A, Nguy CH, Shic F, Ross BD. 2001. Accumulation of methylsulfonylmethane in the human brain: identification by multinuclear magnetic resonance spectroscopy. *Toxicology Letters* 123(2-3):169-177.

Linday LA, Dolitsky JN, Shindlecker RD. 2004. Nutritional supplements as adjunctive therapy for children with chronic/recurrent sinusitis: pilot research. *International Journal of Pediatric Otorhinolaryngology* 68(6):785-793.

Lorenz R, Spengler U, Fischer S, Duhm J, Weber PC. 1983. Platelet function, thromboxanes formation and blood pressure control during supplementation of the Western diet with cod liver oil. *Circulation* 67(3):504-511.

Luo XM, Fosmire GJ, Leach RM Jr. 2002. Chicken keel cartilage as a source of chondroitin sulfate. *Poultry Science* 81(7):1086-1089.

MacLean CH, Issa AM, Newberry SJ, Mojica WA, Morton SC, Garland RH, Hilton LG, Traina SB, Shekelle PG. 2005. Effects of Omega-3 Fatty Acids on Cognitive Function with Aging, Dementia, and Neurological Diseases. Summary, Evidence Report/Technology Assessment No. 114. AHRQ No. 05-E011-2. Rockville (MD): Agency for Healthcare Research and Quality.

MacLean CH, Mojica WA, Morton SC, Pencharz J, Hasenfeld Garland R, Tu W, Newberry SJ, Jungvig LK, Grossman J, Khanna P, Rhodes S, Shekelle P. 2004. Effects of Omega-3 Fatty Acids on Lipids and Glycemic Control in type II Diabetes and the Metabolic Syndrome and on Inflammatory Bowel Disease, Rheumatoid Arthritis, Renal Disease, Systemic Lupus Erythematosus, and Osteoporosis. Summary, Evidence Report/Technology Assessment No. 89. AHRQ No. 04-E012-2. Rockville (MD): Agency for Healthcare Research and Quality.

MacLean CH, Newberry SJ, Mojica WA, Issa A, Khanna P, Lim YW, Morton SC, Suttorp M, Tu W, Hilton LG, Garland RH, Traina SB, Shekelle PG. 2005. Effects of Omega-3 Fatty Acids on Cancer. Summary, Evidence Report/Technology Assessment No. 113. AHRQ No. 05-E010-2. Rockville (MD): Agency for Healthcare Research and Quality.

Magnuson BA, Appleton J, Ames GB. 2007. Pharmacokinetics and distribution of [³⁵S]Methylsulfonylmethane following oral administration to rats. *Journal of Agriculture and Food Chemistry* 55(3):1033-1038.

Maillard V, Bougnoux P, Ferrari P, Jourdan ML, Pinault M, Lavillonnière M, Body G, Le Floch O, Chajès V. 2002. N-3 and n-6 fatty acids in breast adipose tissue and relative risk of breast cancer in a case-control study in Tours, France. *International Journal of Cancer* 98(1):78-83.

Malavaki CJ, Asimakopoulou AP, Lamari FN, Theocharis AD, Tzanakakis GN, Karamanos NK. 2008. Capillary electrophoresis for the quality control of chondroitin sulfates in raw materials and formulations. *Analytical Biochemistry* 374(1):213-220.



Marangell LB, Martinez JM, Zboyan HA, Chong H, Puryear LJ. 2004. Omega-3 fatty acids for the prevention of postpartum depression: negative data from a preliminary, open-label pilot study. *Depression and Anxiety* 19(1):20-23.

Maresta A, Balduccelli M, Varani E, Marzilli M, Galli C, Heiman F, Lavezzari M, Stragliotto E, De Caterina R; ESPRIT Investigators. 2002. Prevention of postcoronary angioplasty restenosis by omega-3 fatty acids: main results of the esapent for prevention of restenosis Italian study (ESPRIT). *American Heart Journal* 143(6):E5.

Marieb E. 1992. *Human Anatomy and Physiology*, 2nd edition. Redwood City (CA): The Benjamin/Cummings Publishing Company, Inc.

Marshall PD, Poddar S, Tweed EM, Brandes L. 2006. Clinical inquiries: Do glucosamine and chondroitin worsen blood sugar control in diabetes? *The Journal of Family Practice* 55(12):1091-1093.

Martin RE, Carter EP, Flick GJ, Davis LM, editors. 2000. *Marine & Freshwater Products Handbook*. Lancaster (PA): Technomic Publishing Company, Inc.

Marszalek JR, Lodish HF. 2005. Docosaehaenoic acid, fatty acid-interacting protein, and neuronal function: breastmilk and fish are good for you. *Annual Review of Cellular and Developmental Biology* 21:633-657.

Masson E, Lagarde M, Wiernsperger N, El Bawab S. 2006. Hyperglycemia and glucosamine-induced mesangial cell cycle arrest and hypertrophy: Common or independent mechanisms? *IUBMB life* 58(7):381-388.

Masson E, Wiernsperger N, Lagarde M, Bawab SE. 2005. Involvement of gangliosides in glucosamine-induced proliferation decrease of retinal pericytes. *Glycobiology* 15(6):585-591.

Mazières B, Loyau G, Menkès CJ, Valat JP, Dreiser RL, Charlot J, Masounabe-Puyanne A. 1992. Le chondroïtine sulfate dans le traitement de la gonarthrose et de la coxarthrose : résultats à 5 mois, d'une étude prospective multicentrique, contrôlée, en double aveugle, versus placebo [Chondroitin sulfate for the treatment of coxarthrosis and gonarthrosis. A prospective multicenter, placebo controlled, double-blind trial with five months follow-up]. *Revue du Rhumatisme et des Maladies Ostéo-articulaires* 59(7-8):466-472 (in French).

McAlindon T, Formica M, LaValley M, Lehmer M, Kabbara K. 2004. Effectiveness of glucosamine for symptoms of knee osteoarthritis: results from an internet-based randomized double-blind controlled trial. *The American Journal of Medicine* 117(9):643-649.

McGuffin M, Hobbs C, Upton R, Goldberg A, editors. 1997. *American Herbal Products Association's Botanical Safety Handbook*. Boca Raton (FL): CRC Press.



- Mehta K, Gala J, Bhasale S, Naik S, Modak M, Thakur H, Deo N, Miller MJ. 2007. Comparison of glucosamine sulfate and a polyherbal supplement for the relief of osteoarthritis of the knee: a randomized controlled trial. *BMC Complementary and Alternative Medicine* 31(7):34.
- Meydani M, Natiello F, Goldin B, Free N, Woods M, Schaefer E, Blumberg JB, Gorbach SL. 1991. Effect of long-term fish oil supplementation on vitamin E status and lipid peroxidation in women. *Journal of Nutrition* 121(4):484-491.
- Michel BA, Stucki G, Frey D, De Vathaire F, Vignon E, Bruehlmann P, Uebelhart D. 2005. Chondroitins 4 and 6 sulfate in osteoarthritis of the knee: a randomized, controlled trial. *Arthritis and Rheumatism* 52(3):779-786.
- Mickleborough TD, Ionescu AA, Rundell KW. 2004. Omega-3 fatty acids and airway hyperresponsiveness in asthma. *The Journal of Alternative and Complementary Medicine* 10(6):1067-1075.
- Mickleborough TD, Lindley MR, Ionescu AA, Fly AD. 2006. Protective effect of fish oil supplementation on exercise-induced bronchoconstriction in asthma. *Chest* 129(1):39-49.
- Mihrshahi S, Peat JK, Webb K, Oddy W, Marks GB, Mellis CM. 2004. Effect of omega-3 fatty acid concentrations in plasma on symptoms of asthma at 18 months of age. *Pediatric Allergy and Immunology* 15(6):517-522.
- Mills S, Bone K. 2000. *Principles and Practice of Phytotherapy*. Toronto (ON): Churchill Livingstone.
- Montgomery C, Speake BK, Cameron A, Sattar N, Weaver LT. 2003. Maternal docosahexaenoic acid supplementation and fetal accretion. *British Journal of Nutrition* 90(1):135-140.
- Moore CS, Bryant SP, Mishra GD, Krebs JD, Browning LM, Miller GJ, Jebb SA. 2006. Oily fish reduces plasma triacylglycerols: a primary prevention study in overweight men and women. *Nutrition* 22(10):1012-1024.
- Mori TA, Bao DQ, Burke V, Puddey IB, Beilin LJ. 1999. Docosahexaenoic acid but not eicosapentaenoic acid lowers ambulatory blood pressure and heart rate in humans. *Hypertension* 34(2):253-260.
- Mori TA, Burke V, Puddey IB, Watts GF, O'Neal DN, Best JD, Beilin LJ. 2000. Purified eicosapentaenoic and docosahexaenoic acids have differential effects on serum lipids and lipoproteins, LDL particle size, glucose, and insulin in mildly hyperlipidemic men. *The American Journal of Clinical Nutrition* 71(5):1085-1094.
- Morreale P, Manopulo R, Galati M, Boccanera L, Saponati G, Bocchi L. 1996. Comparison of the anti-inflammatory efficacy of chondroitin sulfate and diclofenac sodium in patients with knee osteoarthritis. *The Journal of Rheumatology* 23(8):1385-1391.

Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Wilson RS, Aggarwal N, Schneider J. 2003. Consumption of fish and n-3 fatty acid and risk of incident Alzheimer disease. *Archives of Neurology* 60(7):940-946.

Morris MC, Sacks F, Rosner B. 1993. Regulation of blood pressure: does fish oil lower blood pressure?: a meta-analysis of controlled trials. *Circulation* 8(2):523-533.

Mueller BA, Talbert RL, Tegeler CH, Prihoda TJ. 1991. The bleeding time effects of a single dose of aspirin in subjects receiving omega-3 fatty acid dietary supplementation. *Journal of Clinical Pharmacology* 31(2):185-190.

Muniyappa R, Karne RJ, Hall G, Cranson SK, Bronstein JA, Ver MR, Hortin GL, Quon MJ. 2006. Oral glucosamine for 6 weeks at standard doses does not cause or worsen insulin resistance or endothelial dysfunction in lean or obese subjects. *Diabetes* 55(1):3142-3150.

Murray MT. 1996. *Encyclopedia of Nutritional Supplements: The Essential Guide for Improving your Health Naturally*. Rocklin (CA): Prima Publishing.

Nagakura T, Matsuda S, Shichijyo K, Sugimoto H, Hata K. 2000. Dietary supplementation with fish oil rich in ω -3 polyunsaturated fatty acids in children with bronchial asthma. *European Respiratory Journal* 16(5):861-865.

Nakamura K, Kariyazono H, Komokata T, Hamada N, Sakata R, Yamada K. 2005. Influence of preoperative administration of ω -3 fatty acid-enriched supplement on inflammatory and immune responses in patients undergoing major surgery for cancer. *Nutrition* 21(6):639-645.

Nakamura H, Masuko K, Yudoh K, Kato T, Kamada T, Kawahara T. 2007. Effects of glucosamine administration on patients with rheumatoid arthritis. *Rheumatology International* 27(3):213-218.

Nakamura M, Barberi AJ, Antonetti DA, LaNoue KF, Robinson KA, Buse MG, Gardner TW. 2001. Excessive hexosamines block the neuroprotective effect of insulin and induce apoptosis in retinal neurons. *The Journal of Biological Chemistry* 270(23):43748-43755.

Nelson GJ, Schmidt PS, Bartolini GL, Kelley DS, Kyle D. 1997. The effect of dietary docosahexaenoic acid on platelet function, platelet fatty acid composition, and blood coagulation in humans. *Lipids* 32(11):1129-1136.

Nemets B, Osher Y, Belmaker RH. 2004. Omega-3 fatty acids and augmentation strategies in treating resistant depression. *Essential Psychopharmacology* 6(1):59-64.

Nettleton JA, Katz R. 2005. N-3 long-chain polyunsaturated fatty acids in type 2 diabetes: a review. *Journal of the American Dietetic Association* 105(3):428-440.

Nielsen GL, Faarvang KL, Thomsen BS, Teglbjærg KL, Jensen LT, Hansen TM, Lervang HH, Schmidt EB, Dyerberg J, Ernst E. 1992. The effects of dietary supplementation with n-3



polyunsaturated fatty acids in patients with rheumatoid arthritis: a randomized, double blind trial. *European Journal of Clinical Investigation* 22(10):687-691.

Nilsen DW, Albrektsen G, Landmark K, Moen S, Aarsland T, Woie L. 2001. Effects of a high-dose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. *The American Journal of Clinical Nutrition* 74(1):50-56.

Nordic Naturals. Why Nordic Naturals? [Internet]. Watsonville (CA): Nordic Naturals, Inc.; 2011. [Accessed 2012 January 11]. Available from: http://www.nordicnaturals.com/en/About_Nordic_Naturals/Why_Nordic_Naturals/86/

Noack W, Fischer M, Förster KK, Rovati LC, Setnikar I. 1994. Glucosamine sulfate in osteoarthritis of the knee. *Osteoarthritis and Cartilage* 2(1):51-59.

Ocean Nutrition Canada. Our Products: Dietary Supplements [Internet]. Dartmouth (NS): Ocean Nutrition Canada Limited; 2011. [Accessed 2012 January 11]. Available http://www.ocean-nutrition.com/products/dietary_supplements

O'Connor GT, Malenka DJ, Olmstead EM. 1992. A meta-analysis of randomized trials of fish oil in prevention of restenosis following coronary angioplasty. *American Journal of Preventive Medicine* 8(3):186-192.

Oh R. 2005. Practical applications of fish oil (Ω -3 fatty acids) in primary care. *Journal of the American Board of Family Practitioners* 18(1):28-36.

Olafsdottir AS, Magnusardottir AR, Thorgeirsdottir H, Hauksson A, Skuladottir GV, Steingrimsdottir L. 2005. Relationship between dietary intake of cod liver oil in early pregnancy and birthweight. *BJOG: an International Journal of Obstetrics and Gynaecology* 112(4):424-429.

Olsen SF, Secher NJ. 2002. Low consumption of seafood in early pregnancy as a risk factor for preterm delivery: prospective cohort study. *British Medical Journal* 324(7335):447-450.

Omacor. Prescribing Information [Internet]. Southampton (GB): Solvay Healthcare Ltd, 2011. [Accessed 2011 December 6]. Available from: <http://www.omacor.co.uk/hcp/omacor-pi.html>

Onwude JL, Lilford RJ, Hjartardottir H, Staines A, Tuffnell D. 1995. A randomised double blind placebo controlled trial of fish oil in high risk pregnancy. *British Journal of Obstetrics and Gynaecology* 102(2):95-100.

Ossendza RA, Grandval P, Chinoune F, Rocher F, Chapel F, Bernardini D. 2007. Hépatite aiguë cholestatique à la Glucosamine forte®. *Gastroentérologie Clinique et Biologique* 31(4):449-450.

Ostojic SM, Arsic M, Prodanovic S, Vukovic J, Zlatanovic M. 2007. Glucosamine administration in athletes: effects on recovery of acute knee injury. *Research in Sports Medicine* 15(2):113-124.



Peat JK, Mihrshahi S, Kemp AS, Marks GB, Tovey ER, Webb K, Mellis CM, Leeder SR. 2004. Three-year outcomes of dietary fatty acid modification and house dust mite reduction in the Childhood Asthma Prevention Study. *Journal of Allergy and Clinical Immunology* 114(4):807-813.

Pedersen HS, Mulvad G, Seidelin KN, Malcom GT, Boudreau DA. 1999. N-3 fatty acids as a risk factor for haemorrhagic stroke. *The Lancet* 353(9155):812-813.

Peet M. 2003. Eicosapentaenoic acid in the treatment of schizophrenia and depression: rationale and preliminary double-blind clinical trial results. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 69(6):477-485.

Persiani S, Roda E, Rovati LC, Locatelli M, Giacobelli G, Roda A. 2005. Glucosamine oral bioavailability and plasma pharmacokinetics after increasing doses of crystalline glucosamine sulfate in man. *Osteoarthritis and Cartilage* 13(12):1041-1049.

Picado C, Castillo JA, Schinca N, Pujades M, Ordinas A, Coronas A, Agusti-Vidal A. 1988. Effects of a fish oil enriched diet on aspirin intolerant asthmatic patients: a pilot study. *Thorax* 43(2):93-97.

Pisenti JM, Delany ME, Taylor, Jr. RL, Abbott UK, Abplanalp H, Arthur JA, Bakst MR, Baxter-Jones C, Bitgood JJ, Bradley FA, Cheng KM, Dietert RR, Dodgson JB, Donoghue AM, Emsley AB, Etches RJ, Frahm RR, Gerrits RJ, Goetinck PF, Grunder AA, Harry DE, Lamont SJ, Martin GR, McGuire PE, Moberg GP, Pierro LJ, Qualset CO, Qureshi MA, Shultz FT, Wilson, BW. 1999. Chapter 2: Avian genetic diversity: Domesticated species. In: *Avian Genetic Resources at Risk: An Assessment and Proposal for Conservation of Genetic Stocks in the USA and Canada*. Report No. 20. Davis (CA): University of California Division of Agriculture and Natural Resources, Genetic Resources Conservation Program.

Radack K, Deck C, Huster G. 1990. The comparative effects of n-3 and n-6 polyunsaturated fatty acids on plasma fibrinogen levels: a controlled clinical trial in hypertriglyceridemic subjects. *Journal of the American College of Nutrition* 9(4):352-357.

Raitt MH, Connor WE, Morris C, Kron J, Halperin B, Chugh SS, McClelland J, Cook J, MacMurdy K, Swenson R, Connor SL, Gerhard G, Kraemer DF, Oseran D, Marchant C, Calhoun D, Shnider R, McAnulty J. 2005. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. *The Journal of the American Medical Association* 293(23):2884-2891.

Rashad S, Revell P, Hemingway A, Low F, Rainsford K, Walker F. 1989. Effect of non-steroidal anti-inflammatory drugs on the course of osteoarthritis. *The Lancet* 2(8662):519-522.

Reddy BS. 2004. Omega-3 fatty acids in colorectal cancer prevention. *International Journal of Cancer* 112(1):1-7.

- Reginster JY. 2007. The efficacy of glucosamine sulfate in osteoarthritis: financial and nonfinancial conflict of interest. *Arthritis and Rheumatism* 56(7):2105-2110.
- Reichelt A, Förster KK, Fischer M, Rovati LC, Setnikar I. 1994. Efficacy and safety of intramuscular glucosamine sulfate in osteoarthritis of the knee. A randomised, placebo-controlled, double-blind study. *Arzneimittelforschung* 44(1):75-80.
- Reichenbach S, Sterchi R, Scherer M, Trelle S, Bürgi E, Bürgi U, Dieppe PA, Jüni P. 2007. Meta-analysis: chondroitin for osteoarthritis of the knee or hip. *Annals of Internal Medicine* 146(8):580-590.
- Reis GJ, Silverman DI, Boucher TM, Sipperly ME, Horowitz GL, Sacks FM, Pasternak RC. 1990. Effects of two types of fish oil supplements on serum lipids and plasma phospholipid fatty acids in coronary artery disease. *The American Journal of Cardiology* 15(66):1171-1175.
- Richardson AJ, Montgomery P. 2005. The Oxford-Durham study: a randomized, controlled trial of dietary supplementation with fatty acids in children with developmental coordination disorder. *Pediatrics* 115(5):1360-1366.
- Richy F, Bruyere O, Ethgen O, Cucherat M, Henrotin Y, Reginster JY. 2003. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis. *Archives of Internal Medicine* 163(13):1514-1522.
- Robertson LA, Kim AJ, Werstuck GH. 2006. Mechanisms linking diabetes mellitus to the development of atherosclerosis: a role for endoplasmic reticulum stress and glycogen synthase kinase-3. *Canadian Journal of Physiology and Pharmacology* 84(1):39-48.
- Rose DP, Connolly JM. 1999. Omega-3 fatty acids as cancer chemopreventive agents. *Pharmacology & Therapeutics* 83(3):217-244.
- Rovetta G. 1991. Galactosaminoglycuronoglycan sulfate (matrix) in therapy of tibiofibular osteoarthritis of the knee. *Drugs under Experimental and Clinical Research* 17(1):53-57.
- Rozendaal RM, Koes BW, van Osch GJ, Uitterlinden EJ, Garling EH, Willemsen SP, Ginai AZ, Verhaar JA, Weinans H, Bierma-Zeinstra SM. 2008. Effect of glucosamine sulfate on hip osteoarthritis: a randomized trial. *Annals of Internal Medicine* 148(4):268-277.
- Runkel DR, Cupp MJ. 1999. Glucosamine sulfate use in osteoarthritis. *American journal of health-system pharmacy: American Journal of Health-System Pharmacy* 56(3):267-269.
- Scientific Advisory Committee on Nutrition, Foods Standard Agency, Department of Health. Advice on Fish Consumption: Benefits and Risks [Internet]. London (GB): TSO (The Stationery Office); 2004. [Accessed 2012 January 11]. Available from: www.sacn.gov.uk/pdfs/fics_sacn_advice_fish.pdf

Sagredos AN. 1991. [Fatty Acid Composition of Fish Oil Capsules]. *Fett Wissenschaft Technologie* 93(5):184-191 (in German).

Sanders TA, Hinds A. 1992. The influence of a fish oil high in docosahexaenoic acid on plasma lipoprotein and vitamin E concentrations and haemostatic function in healthy male volunteers. *British Journal of Nutrition* 68(1):163-173.

Sandy JD, Gamett D, Thompson V, Verscharen C. 1998. Chondrocyte-mediated catabolism of aggrecan: aggrecanase-dependent cleavage induced by interleukin-1 or retinoic acid can be inhibited by glucosamine. *The Biochemical Journal* 335(Pt 1):59-66.

Saynor R, Gillott T. 1992. Changes in blood lipids and fibrinogen with a note on safety in a long term study on the effects of n-3 fatty acids in subjects receiving fish oil supplements and followed for seven years. *Lipids* 27(7):533-538.

Schachter HM, Kourad K, Merali Z, Lumb A, Tran K, Miguelez M, Lewin G, Sampson M, Barrowman N, Senechal H, McGahern C, Zhang L, Morrison A, Shlik J, Pan Y, Lowcock EC, Gaboury I, Bradwejn J, Duffy A. 2005. Effects of Omega-3 Fatty Acids on Mental Health. Summary, Evidence Report/Technology Assessment No. 116. AHRQ No. 05-E022-2. Rockville (MD): Agency for Healthcare Research and Quality.

Schmidt EB, Lervang HH, Varming K, Madsen P, Dyerberg J. 1992. Long-term supplementation with n-3 fatty acids, I: effect on blood lipids, haemostasis and blood pressure. *Scandinavian Journal of Clinical and Laboratory Investigation* 52(3):221-228.

Schuster E, Dunn-Coleman N, Frisvad JC, Van Dijck PW. 2002. On the safety of *Aspergillus niger*: a review. *Applied Microbiology and Biotechnology* 59(4-5):426-435.

Schwellenbach LJ, Olson KL, McConnell KJ, Stolcpart RS, Nash JD, Merenich JA. 2006. The triglyceride-lowering effects of a modest dose of docosahexaenoic acid alone versus in combination with low dose eicosapentaenoic acid in patients with coronary artery disease and elevated triglycerides. *Journal of the American College of Nutrition* 25(6):480-485.

Scroggie DA, Albright A, MD Harris. 2003. The effect of glucosamine-chondroitin supplementation on glycosylated haemoglobin levels in patients with type 2 diabetes mellitus: a placebo-controlled, double-blinded, randomized clinical trial. *Archives of Internal Medicine* 163(13):1587-1590.

Shankland WE. 1998. The effects of glucosamine and chondroitin sulphate on osteoarthritis of the TMJ: a preliminary report of 50 patients. *Cranio: The Journal of Craniomandibular Practice* 16(4):230-235.

Silverman DI, Ware JA, Sacks FM, Pasternak RC. 1991. Comparison of the absorption and effect of on platelet function of a single dose of n-3 fatty acids given as fish or fish oil. *The American Journal of Clinical Nutrition* 53(5):1165-1170.

Simopoulos AP. 2007. Omega-3 fatty acids and athletics. *Current Sports Medicine Reports* 6(4):230-236.

Simopoulos AP. 1999. Essential fatty acids in health and chronic disease. *The American Journal of Clinical Nutrition* 70(3):560S-569S.

Simopoulos AP, Leaf A, Salem N. 1999. Workshop on the essentiality of and recommended dietary intakes for omega-6 and omega-3 fatty acids. *Journal of the American College of Nutrition* 18(5):487-489.

Sirtori CR, Crepaldi G, Manzato E, Mancini M, Rivellesse A, Paoletti R, Pazzucconi F, Pamparana F, Stragliotto E. 1998. One-year treatment with ethyl esters of n-3 fatty acids in patients with hypertriglyceridemia and glucose intolerance: reduced triglyceridemia, total cholesterol and increased HDL-C without glycemic alterations. *Atherosclerosis* 137(2):419-427.

Sivojelezova A, Koren G, Einarson A. 2007. Glucosamine use in pregnancy: an evaluation of pregnancy outcome. *Journal of Women's Health* 16(3):345-348.

Sommerfield T, Price J, Hiatt WR. 2007. Omega-3 fatty acids for intermittent claudication . [Internet]. The Cochrane Library. [Accessed 2012 January 11]. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003833.pub3/full>

Stehr SN, Heller AR. 2006. Omega-3 fatty acid effects on biochemical indices following cancer surgery. *Clinica Chimica Acta* 373(1-2):1-8.

Studer M, Briel M, Leimenstoll B, Glass TR, Bucher HC. 2005. Effect of different antilipidemic agents and diets on mortality: a systematic review. *Archives of Internal Medicine* 165(7):725-730.

Su K, Huang S, Chiu C, Shen WW. 2003. Omega-3 fatty acids in major depressive disorder. A preliminary double-blind, placebo-controlled trial. *European Neuropsychopharmacology* 13(4):267-271.

Sundrarjun T, Komindr S, Archararit N, Dahlan W, Puchaiwatananon O, Angtharak S, Udomsuppayakul U, Chuncharunee S. 2004. Effects of n-3 fatty acids on serum interleukin-6, tumour necrosis factor- α , and soluble tumour necrosis factor receptor p55 in active rheumatoid arthritis. *The Journal of International Medical Research* 32(5):443-454.

Svensson M, Schmidt EB, Jørgensen KA, Christensen JH. 2006. N-3 fatty acids as secondary prevention against cardiovascular events in patients who undergo chronic hemodialysis: a randomized, placebo-controlled intervention trial. *Clinical Journal of the American Society of Nephrology* 1(4):780-786.

SzajewskaH, Horvath A, Koletzko B. 2006. Effect of n-3 long-chain polyunsaturated fatty acid supplementation of women with low-risk pregnancies on pregnancy outcomes and growth



measures at birth: a meta-analysis of randomized controlled trials. *The American Journal of Clinical Nutrition* 83(6):1337-1344.

Takemura Y, Sakurai Y, Honjo S, Tokimatsu A, Gibo M, Hara T, Kusakari A, Kugai N. 2002. The relationship between fish intake and the prevalence of asthma: the Tokorozawa Childhood Asthma and Pollinosis Study. *Preventive Medicine* 34(2):221-225.

Takezaki T, Inoue M, Kataoka H, Ikeda S, Yoshida M, Ohashi Y, Tajima K, Tominaga S. 2003. Diet and lung cancer risk from a 14-year population-based prospective study in Japan: with special reference to fish consumption. *Nutrition and Cancer* 45(2):160-167.

Tannis AJ, Barban J, Conquer JA. 2004. Effect of glucosamine supplementation on fasting and non-fasting plasma glucose and serum insulin concentrations in healthy individuals. *Osteoarthritis and Cartilage* 12(6):506-511.

Terry PD, Terry JB, Rohan TE. 2004. Long-chain (n-3) fatty acid intake and risks of cancers of the breast and the prostate: recent epidemiological studies, biological mechanisms, and directions for future research. *The Journal of Nutrition* 134(12):3412S-3420S.

The Arthritis and Glucosamine Information Centre. Glucosamine Side Effects. [Internet]. Raleigh (NC): DTC Health. [Accessed 2012 January 11]. Available from: <http://www.glucosamine-arthritis.org/glucosamine/glucosamine-side-effects.html>

Theobald HE, Goodall AH, Sattar N, Talbot DC, Chowienczyk PJ, Sanders TA. 2007. Low-dose docosahexaenoic acid lowers diastolic blood pressure in middle-aged men and women. *Journal of Nutrition* 137(4):973-978.

Theodoratou E, McNeill G, Cetnarskyj R, Farrington SM, Tenesa A, Barnetson R, Porteous M, Dunlop M, Campbell H. 2007. Dietary fatty acids and colorectal cancer: a case-control study. *American Journal of Epidemiology* 166(2):181-195.

Thies F, Nebe-von-Caron G, Powell JR, Yaqoob P, Newsholme EA, Calder PC. 2001. Dietary supplementation with eicosapentaenoic acid, but not with other long-chain n-3 or n-6 polyunsaturated fatty acids, decreases natural killer cell activity in healthy subjects aged >55 y. *The American Journal of Clinical Nutrition* 73(3):539-548.

Towheed TE, Maxwell L, Anastassiades TP, Shea B, Houpt J, Robinson V, Hochberg MC, Wells G. 2005. Glucosamine therapy for treating osteoarthritis. [Internet]. The Cochrane Library. [Accessed 2011 December 6. Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002946.pub2/full>

Tsekos E, Reuter C, Stehle P, Boeden G. 2004. Perioperative administration of parenteral fish oil supplements in a routine clinical setting improves patient outcome after major abdominal surgery. *Clinical Nutrition* 23(3):325-330.



Tulleken JE, Limburg PC, Muskiet FA, van Rijswijk MH. 1990. Vitamin E status during dietary fish oil supplementation in rheumatoid arthritis. *Arthritis and Rheumatism* 33(9):1416-1419.

Tulleken JE, Limburg PC, van Rijswijk MH. 1988. Fish oil and plasma fibrinogen. *British Medical Journal* 297(6648):615-616.

Uauy R, Hoffman DR, Mena P, Llanos A, Birch EE. 2003. Term infant studies of DHA and ARA supplementation on neurodevelopment: results of randomized controlled trials. *Journal of Pediatrics* 143(4):S17-S25

US Food and Drug Administration. 21 CFR 184 Substances Affirmed as Generally Recognized as Safe: Menhaden Oil [Internet]. Washington (DC): Food and Drug Administration, US Department of Health and Human Services; 2005. [Accessed 2012 January 11]. Available from: <http://www.epa.gov/fedrgstr/EPA-IMPACT/2005/March/Day-23/i5641.htm>

US Food and Drug Administration. Agency Response Letter, Letter Responding to Health Claim Petition dated November 3, 2003 (Martek Petition): Omega-3 Fatty Acids and Reduced Risk of Coronary Heart Disease [online]. Washington (DC): Food and Drug Administration, Center for Food Safety and Applied Nutrition; 2004. [Accessed 2012 January 11]. Available from: <http://www.fda.gov/ohrms/dockets/dockets/04q0072/04q-0072-pdn0001-18-FDA-vol6.pdf>

US Food and Drug Administration. Agency Response Letter, GRAS Notice No. GRN 000105 [online]. Washington (DC): Food and Drug Administration, Center for Food Safety and Applied Nutrition; 2002. [Accessed 2012 January 11]. Available from: <http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASListings/ucm153913.htm>

Valagussa F, Franzosi MG, Geraci E, Mininni N, Nicolosi GL, Santini M, Tavazzi L, Vecchio C. 1999. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *The Lancet* 354(9177):447-455.

Valk EE, Hornstra G. 2000. Relationship between vitamin E requirement and polyunsaturated fatty acid intake in man: a review. *International Journal for Vitamin and Nutrition Research* 70(2):31-42.

Van der Tempel H, Tulleken JE, Limburg PC, Muskiet FA, van Rijswijk MH. 1990. Effects of fish oil supplementation in rheumatoid arthritis. *Annals of the Rheumatic Diseases* 49(2):76-80.

Velzing-Aarts FV, van der Klis FR, van der Dijs FP, van Beusekom CM, Landman H, Capello JJ, Muskiet FA. 2001. Effect of three low-dose fish oil supplements, administered during pregnancy, on neonatal long-chain polyunsaturated fatty acid status at birth. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 65(1):51-57.

Verbruggen G, Goemaere S, Veys E. 1998. Chondroitin sulfate: S/MOAD (structure/disease modifying anti-osteoarthritis drug) in the treatment of finger joint OA. *Osteoarthritis and Cartilage* 6(suppl A):37-38.



Verbruggen G, Goemaere S, Veys E. 2002. Systems to assess the progression of finger joint osteoarthritis and the effects of disease modifying osteoarthritis drugs. *Clinical Rheumatology* 21(3):231-243.

Viad SC, LaValley MP, McAlindon TE, Felson DT. 2007. Glucosamine for pain in osteoarthritis: why do trial results differ? *Arthritis and Rheumatism* 56(7):2267-2277.

Vidgren HM, Ågren JJ, Schwab U, Rissanen T, Hänninen O, Uusitupa MI. 1997. Incorporation of n-3 fatty acids into plasma lipid fractions, and erythrocyte membranes and platelets during dietary supplementation with fish, fish oil, and docosahexaenoic acid-rich oil among healthy young men. *Lipids* 32(7):697-705.

Villacis J, Rice TR, Bucci LR, El-Dahr JM, Wild L, Demerell D, Soteris D, Lehrer SB. 2006. Do shrimp-allergic individuals tolerate shrimp-derived glucosamine? *Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology* 36(11):1457-1461.

Visioli F, Risé P, Barassi MC, Marangoni F, Galli C. 2003. Dietary intake of fish vs. formulations leads to higher plasma concentrations of n-3 fatty acids. *Lipids* 38(4):415-418.

Voigt RG, Llorente AM, Jensen CL, Fraley JK, Berretta MC, Heird WC. 2001. A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. *The Journal of Pediatrics* 139(2):189-196.

Von Schacky C, Fischer S, Weber PC. 1985. Long-term effects of dietary marine ω -3 fatty acids upon plasma and cellular lipids, platelet function, and eicosanoid formation in humans. *Journal of Clinical Investigation* 76(4):1626-1631.

Von Schacky C, Weber PC. 1985. Metabolism and effects on platelet function of the purified eicosapentaenoic and docosahexaenoic acids in humans. *Journal of Clinical Investigation* 76(6):2446-2450.

Wang C, Chung M, Balk E, Kupelnick B, DeVine D, Lawrence A, Lichtenstein A, Lau J. 2004. Effects of Omega-3 Fatty Acids on Cardiovascular Disease. Summary, Evidence Report/Technology Assessment No. 94. AHRQ No. 04-E009-2. Rockville (MD): Agency for Healthcare Research and Quality.

Whelton SP, He J, Whelton PK, Muntner P. 2004. Meta-analysis of observational studies of fish intake and coronary heart disease. *The American Journal of Cardiology* 93(9):1119-1123.

Williams HJ. 2006. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *The New England Journal of Medicine* 354(8):795-808.

Wohl DA, Tien HC, Busby M, Cunningham C, Macintosh B, Napravnik S, Danan E, Donovan K, Hossenipour M, Simpson RJ Jr. 2005. Randomized study of the safety and efficacy of fish oil (omega-3 fatty acid) supplementation with dietary and exercise counselling for the treatment of



antiretroviral therapy-associated hypertriglyceridemia. *Clinical Infectious Diseases* 41(10):1498-1504.

Wong KW. 2005. Clinical efficacy of n-3 fatty acid supplementation in patients with asthma. *Journal of the American Dietetic Association* 105(1):98-105.

Woodman RJ, Mori TA, Burke V, Puddey IB, Barden A, Watts GF, Beilin LJ. 2003. Effects of purified eicosapentaenoic acid and docosahexaenoic acid on platelet, fibrinolytic and vascular function in hypertensive type 2 diabetic patients. *Atherosclerosis* 166(1):85-93.

Woodman RJ, Mori TA, Burke V, Puddey IB, Watts GF, Beilin LJ. 2002. Effects of purified eicosapentaenoic and docosahexaenoic acids on glycemic control, blood pressure, and serum lipids in type 2 diabetic patients with treated hypertension. *The American Journal of Clinical Nutrition* 76(5):1007-1015.

Yu JG, Boies SM, and JM Olefsky. 2003. The effect of oral glucosamine sulphate on insulin sensitivity in human subjects. *Diabetes Care* 26(6):1941-1942.

Yzebe D, Lievre M. 2004. Fish oils in the care of coronary heart disease patients: a meta-analysis of randomized controlled trials. *Fundamental & Clinical Pharmacology* 18(5):581-592.

Zachara NE, Hart GW. 2006. Cell signaling, the essential role of O-GlcNAc! *Biochimica et Biophysica Acta* 1761(5-6):599-617.

Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P. 2008. OARSI recommendations for the management of hip and knee osteoarthritis part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis and Cartilage* 16(2):137-162.