Schottner M, Spiteller G. Lignans interfering with 5alpha-dihydrotestosterone binding to human sex hormone-binding globulin. *J Nat Prod.* 1998;61:119-121.

Thompson LU, Seidl MM, Rickard SE, et al. Antitumorigenic effect of a mammalian lignan precursor from flaxseed. *Nutr Cancer.* 1996;26:159-165.

Selenium

DESCRIPTION

Selenium is an essential trace element in human and animal nutrition. It is involved in the defense against the toxicity of reactive oxygen species, in the regulation of thyroid hormone metabolism and the regulation of the redox state of cells. Recognition of the vital importance of selenium in human and animal nutrition was long impeded by its very real toxic potential and by fears that selenium might be carcinogenic, fears that have now been largely displaced by some evidence suggesting just the opposite–that selenium may provide protection against some cancers.

The amount of selenium in food is a function of the selenium content of the soil. Selenium enters the food chain through incorporation into plant proteins as the amino acids L-selenocysteine and L-selenomethionine. Selenium, like most trace elements and minerals, is not evenly distributed in the world's soil. Because of the uneven global distribution of selenium, disorders of both selenium deficiency and selenium excess are known. China has regions with both the lowest and highest selenium-containing soils in the world.

Marco Polo gave the first account of selenium toxicity, which he observed during his travels in western China in the 13th century. He linked the sloughing off of the hooves of horses to their consumption of certain plants in the regions. The soils of those areas are now known to contain the highest concentrations of selenium in the world. Soils rich in selenium are referred to as being seleniferous, and the condition of chronic selenium toxicity is known as selenosis. In the 1970s, a human cardiomyopathy endemic to certain areas of China was shown to be linked to dietary selenium deficiency. This disorder, known as Keshan disease, is endemic to those areas of China with some of the most selenium-poor soils in the world. Keshan disease is now treated and prevented by selenium supplementation.

Kashin-Beck disease, also known as "big joint disease," is an osteoarthropathy that is found in areas in China where the soil is selenium-poor. It is also linked to dietary selenium deficiency. Kashin-Beck disease is found in Tibet, Siberia and North Korea, also in areas where the soil is selenium-poor and in which dietary selenium-deficiency is endemic.

Selenium is a metalloid element with atomic number 34 and an atomic weight of 78.96 daltons. It belongs to the sulfur group of elements, which also includes oxygen, tellurium and polonium. Its atomic symbol is Se. Selenium was discovered in 1817 by Berzelius who named it after Selene, the Greek goddess of the moon.

The essentiality of selenium for animals was first reported in 1957. It was found that selenium administered to vitamin E-deficient rats prevented liver necrosis. Subsequently, it was found that selenium could prevent a number of disorders of farm animals. Isolated selenium deficiency in humans has not been described. Selenium deficiency appears to cause an illness or disorder in combination with a co-factor. In the case of Keshan disease, the co-factor appears to be the Coxsackievirus. It has been shown that infection of mice on a selenium-deficient diet with a nonvirulent Coxsackievirus selects a stable cardiovirulent strain. In the case of Kashin-Beck osteoarthropathy, the co-factor appears to be iodine deficiency.

Selenium is found in human and animal tissues as L-selenomethionine or L-selenocysteine. L-selenomethionine is incorporated randomly in proteins in place of L-methionine. These proteins are called selenium-containing proteins. Only a small fraction of L-methionine in proteins is present as L-selenomethionine. On the other hand, the incorporation of L-cysteine into proteins known as selenoproteins is not random. That is, in contrast to L-selenomethionine, which randomly substitutes for L-methionine, L-selenocysteine does not randomly substitute for L-cysteine. In fact, L-selenocysteine has its own triplet code and is considered to be the 21st genetically coded amino acid.

The selenoproteins are comprised of four selenium-dependent glutathione peroxidases (GSHPx-1, GSHPx-2, GSHPx-3 and GSHPx-4), three selenium-dependent iodothyronine deiodinases, three thioredoxin reductases, selenoprotein P, selenoprotein W and selenophosphate synthetase. The glutathione peroxidases, and possibly selenoprotein P and selenoprotein W, are antioxidant proteins. The selenium-dependent iodothyronine deiodinases convert thyroxine to triiodothyronine, thus regulating thyroid hormone metabolism. The thioredoxin reductases reduce intramolecular disulfide bonds and regenerate vitamin C from its oxidized state, among other things.

ACTIONS AND PHARMACOLOGY

ACTIONS

Selenium has antioxidant activity. Selenium may also have immunomodulatory, anticarcinogenic and anti-atherogenic activities. It may have activity in detoxification of some metals and other xenobiotics and activity in fertility enhancement in males.

MECHANISM OF ACTION

The antioxidant activity of selenium is mainly accounted for by virtue of its role in the formation and function of the selenium-dependent glutathione peroxidases (GSHPx). Glutathione peroxidases use reducing equivalents from glutathione to detoxify hydroperoxides. There are four different glutathione peroxidases. GSHPx-1 is present in most cells of the body. GSHPx-2 (originally known as GSHPx-GI) is mainly found in the cells of the gastrointestinal tract. GSHPx-3 is an extracellular glutathione peroxidase. GSHPx-4 is a membrane-bound hydroperoxide glutathione peroxidase. GSHPx-4 is also known as phospholipid hydroperoxide or PHGPx. GSHPx-4 can detoxify phospholipid hydroperoxides and, along with d-alpha-tocopherol, helps prevent oxidative damage to membranes. GSHPx-3, the extracellular glutathione peroxidase, eliminates peroxides in the extracellular fluid.

Glutathione peroxidases detoxify hydrogen peroxide and fatty acid-derived hydroperoxides. This is the antioxidant role of these enzymes. However, recent research indicates that reactive oxygen species play important roles in signal transduction processes. Therefore, by affecting the concentrations of reactive oxygen species in cells, the glutathione peroxidases may also be considered to play regulatory roles in signal transduction.

Antioxidant activity of selenium can also be accounted for by its role in the selenium-dependent thioredoxin reductases. These enzymes reduce intramolecular disulfide bonds and regenerate ascorbic acid from dehydroascorbic acid. Thioredoxin reductases can also affect the redox regulation of a variety of factors, including ribonucleotide reductase (the enzyme that converts ribonucleoside diphosphates to deoxyribonucleoside diphosphates), the glucocorticoid receptor and the transcription factors AP-1 and NF-KappaB.

Selenium deficiency appears to depress the effectiveness of various components of the immune system. In humans, selenium deficiency has been associated with depressed IgG and IgM antibody titers. In animal models, selenium deficiency has resulted in depressed neutrophil activity, decreased Candidacidal activity by neutrophils and depressed cellular immunity. Selenium supplementation in humans has resulted in increased natural killer cell activity. The possible immunomodulatory effects of selenium are not well understood. Selenium's antioxidant activity may play some role, perhaps a major one, in these possible effects. It is postulated that selenium's possible effect on boosting cellular immunity may be due to upregulation of the expression of the T-cell high-affinity interleukin (IL)-2 receptor, providing a vehicle for enhanced T-cell responses, as well as prevention of oxidative stress-induced damage to immune cells. Enhanced cellular immunity may explain the possible stimulatory effects of selenium on antibody production.

The possible anticarcinogenic activity of selenium may be accounted, for, in part, by its antioxidant activity as well as its possible immune-enhancing activity. Selenium has been shown to upregulate apoptosis in tumor cells *in vitro* and increase macrophage killing and protect against oxidative DNA damage, again, *in vitro*. Animal studies suggest that selenium may have anti-angiogenic activity. A possible mechanism for selenium's possible anti-angiogenic activity is its inhibitory effect on the expression of vascular endothelial growth factors (VEGFs). This has been observed in some animal studies. Selenium, in cell culture, has also been found to inhibit the gelatinolytic activity of matrix metalloproteinase-2 (MMP-2).

Some epidemiological studies have shown an inverse relationship between coronary heart disease and selenium intake. The possible anti-atherogenic activity of selenium may be accounted for, in part, by its antioxidant activity. Glutathione peroxidase may protect low density lipoprotein (LDL) from oxidation. Oxidized-LDL is thought to be a crucial etiological factor in atherogenesis. Selenium may decrease platelet aggregation. Selenium deficiency results in lipoperoxide accumulation. Lipoperoxides impair prostacyclin synthesis and promote thromboxane synthesis, which can increase platelet aggregation.

Selenium has been demonstrated to antagonize the effects of a number of toxic metals, including cadmium and arsenic. Selenium inhibits the growth stimulatory effect of cadmium on human prostatic epithelium *in vitro*. The mechanism of the possible antagonistic action of selenium against various toxic metals and other xenobiotics is unclear. One possibility is that it forms inactive complexes with these substances.

Selenium may have fertility enhancing effects for males. Phospholipid hydroperoxide glutathione peroxidase (GSHPx-4), in addition to its antioxidant role in sperm, also appears to be responsible for maintaining the structure of sperm, at least in mouse sperm.

PHARMACOKINETICS

There are various forms of supplemental selenium, including high-selenium yeast, L-selenomethionine, sodium selenate and sodium selenite. High-selenium yeast contains L-selenomethionine in proteins. Proteins in high-selenium yeast are enzymatically digested in the small intestine to yield amino acids, oligopeptides and L-selenomethionine. L-selenomethionine is efficiently absorbed from the small intestine via a similar mechanism to that of L-methionine. L-selenomethionine is transported via the portal circulation to the liver where a fraction is extracted by the hepatocytes and the remaining amount is transported by the circulation to the

various tissues of the body. L-selenomethionine enters the L-methionine pool in the hepatocytes and other cells of the body and shares the same metabolic fate of L-methionine until it is metabolized by the transsulfuration pathway. That is, L-selenomethionine participates in the synthesis of proteins and in the formation of seleno-adenosylmethionine (the selenium form of S-adenosylmethionine or SAMe), homoselenocysteine and L-selenocysteine, among other metabolites.

The metabolism of L-selenocysteine is different in several particulars from that of L-cysteine. L-selenocysteine is converted to hydrogen selenide via the enzyme selenocysteine beta-lyase. Hydrogen selenide can be metabolized to selenophosphate via selenophosphate synthetase or it can be methylated. The methylated metabolites are excreted in the urine. Selenophosphate is the precursor of L-selenocysteine in proteins or of selenium nucleosides in transfer RNA. The incorporation of L-selenocysteine in proteins is via seryl-transfer RNA. Selenocysteine synthase converts seryl-transfer RNA to selenocysteyl-transfer RNA. The L-selenocysteine residues found in all of the selenoproteins is derived from selenocysteyl-transfer RNA.

Free L-selenomethione is absorbed, distributed, and metabolized as described above. The inorganic forms of selenium, selenate and selenite, are also efficiently absorbed from the gastrointestinal tract. The fractional absorption of these inorganic forms is greater than 50%. Selenate or selenite is delivered to the liver via the portal circulation. A fraction is extracted by the hepatocytes and the rest is delivered via the systemic circulation to the various cells of the body. Within cells, these inorganic salts are converted to hydrogen selenide, and the further metabolism of hydrogen selenide is as described above.

Selenium homeostasis is achieved via regulation of its excretion by the kidneys. As selenium intake increases, urinary excretion of selenide metabolite increases. At very high intakes of selenium, volatile forms are exhaled. The odor of the exhaled forms of selenium is garlic-like. The excretory metabolites of selenium are mainly methylated metabolites of selenide. The principal urinary metabolites are methyselenol and trimethylselonium. Selenium excreted in the breath is mainly in the form of dimethylselenide.

INDICATIONS AND USAGE

Low dietary intake of selenium is associated with increased risk of some cardiomyopathies, ischemic heart disease and cardiovascular disease generally. Low intakes are also associated with increased incidence of some cancers, including prostate, lung, colorectal, gastric and skin cancers. Selenium supplementation has diminished these risks in some populations. There is the counterclaim that selenium supplementation might increase some cancers in some individuals. High levels of selenium have also recently been associated with increased risk of diabetes and higher mortality overall. Selenium's narrow therapeutic range makes toxicity a distinct possibility in some individuals. Selenium has demonstrated useful immune-enhancing effects in *in vitro*, animal and human studies. It is essential for healthy immune function. It may also have some anti-inflammatory benefits and could be useful in some with rheumatoid arthritis. It has the ability to detoxify some metals and xenobiotics. Selenium appears to play an important role in maintaining the viability of sperm cells, and supplemental selenium may thus be helpful in some infertile men. There is very preliminary evidence that high doses of selenium might promote modest weight gain. Reports that selenium can inhibit graying of hair are anecdotal.

RESEARCH SUMMARY

Epidemiological data indicate that low dietary intake of selenium is associated with increased incidence of several cancers, including lung, colorectal, skin and prostate cancers. There are *in vitro*, animal and human data showing that supplemental selenium can protect against some cancers. Much interest is now focusing on these findings, given gathering evidence that selenium intakes may actually be declining in some parts of the world, including some areas of the United States and the United Kingdom and other European countries.

There was one large cohort study, however, in which no significant selenium/cancer association was observed. Selenium in this study, however, was measured via selenium content in toenails. Some believe that this is not a reliable indicator of selenium status.

Studies to date indicate that diminished selenium status is not, in itself, carcinogenic but, rather, increases susceptibility to malignancy in the presence of carcinogens. Some studies have also shown that low selenium status predicts a poorer outcome in those who have some cancers. Findings however, are not entirely consistent.

In a recent well-controlled, large study conducted between 1983 and 1993, selenium supplementation (200 micrograms daily delivered via high-selenium brewer's yeast tablets) significantly diminished total cancer mortality (by 52% compared with controls). It did not significantly affect the incidence of basal and squamous cell carcinomas of the skin but did significantly reduce the incidence of lung, colorectal and prostate cancers. A total of 1,312 subjects (mostly men), aged 18-80 years, were enrolled in the study. Subjects had a history of basal cell or squamous cell carcinomas. Subjects, enrolled at seven dermatology clinics in the eastern United

States, were treated for a mean of 4.5 years and were followed up for 6.4 years.

Another long-term study, this one conducted in China, employed 200 micrograms of selenium daily over a four-year period. Those thus supplemented had a significantly lower incidence of primary liver cancer than did unsupplemented controls.

Some investigators have suggested that pharmacological doses of selenium, much higher than those used in typical supplements, might be effective in some established cancers. "Selenium compounds," one group has speculated, "that are able to generate a steady stream of methylated metabolites, in particular of the monomethylated species, are likely to have good chemopreventive potential."

Some now believe, however, that high-dose selenium could be dangerous and that in some susceptible individuals any selenium supplementation might be hazardous, increasing, rather than diminishing, cancer risk or progression. And the best available data suggest that dietary intake of selenium in the United States is on the high side, not the low side, as some previously speculated. A Nutritional Prevention of Cancer (NPC) trial, while finding some evidence for cancer prevention among some patients with lower selenium levels, additionally found a possible small increase in total cancer risk among participants with higher levels. A recent editorial in *The Annals of Internal Medicine* noted that "selenium has a narrow therapeutic range and may be toxic." On the positive side, the NPC study found a significant 49% reduction in prostate cancer risk among study subjects receiving a dietary supplement containing carotenoids, selenium and some other nutrients. Some large scale Phase III clinical trials are ongoing to further investigate the use of selenium in prostate and some other cancers. The World Cancer Research Fund and the American Institute for Cancer Research have both concluded that there is limited evidence suggestive of a selenium-protective effect in both prostate cancer and colorectal cancer. This, however, is not the same as saying there is convincing and conclusive evidence, which must still be sought.

In one recent study, serum selenium levels were measured in 13,887 adult participants in the Third National Health and Nutrition Examination Survey (NHANES III). Follow-up was for 12 years. Increasing selenium levels were associated with lower all-cause and cancer mortality up to a certain level. Thereafter, as levels increased higher so did all-cause and cancer mortality. There was no association between selenium levels and cardiovascular mortality in this study. The authors stated that their results should signal the need for caution in selenium supplementation but noted that "additional epidemiological studies are needed to establish the levels of selenium associated with the lowest incidence of adverse health outcomes."

In both the NHANES III and the NPC trials discussed above, data emerged suggesting that selenium is not useful in diabetes and, in fact, may be harmful. High serum selenium levels were associated with a higher incidence of diabetes mellitus in the NHANES III study, and selenium supplementation was found to increase the risk of diabetes incidence in the NPC trial. Participants in the NPC trial received 200 micrograms of selenium daily for 7.7 years or placebo. This was the longest and largest experimental randomized, double-blind selenium trial to date comparing selenium with placebo. In view of these and other negative findings, editorialists writing in *The Annals of Internal Medicine* expressed the view that "until further randomized, controlled trials show that selenium supplementation does not cause diabetes or establish that the potential risk for diabetes is outweighed by yet unproven health benefits, people with diets that provide the Recommended Dietary Allowance for selenium should avoid selenium supplements, except in the context of experimental studies."

Keshan disease is a cardiomyopathy endemic in regions of China where selenium deficiency is prevalent. The Coxsackie viruses are co-factors with selenium deficiencies in this disease. A selenium-deficient environment in heart tissue appears to select for a cardiovirulent mutant of these viruses. *In vitro* animal and human data show that supplemental selenium can protect against this cardiomyopathy. Cardiomyopathies caused by long-term total parenteral nutrition (TPN) can also be prevented with adequate selenium supplementation.

Epidemiological data have demonstrated an inverse relationship between blood selenium levels and incidence of cardiovascular disease. Diminished selenium status has been associated with increased risk of myocardial infarction. Selenium has shown some ability to protect against oxidative damage to blood vessels. This damage is believed to play a role in the formation of atheromatous plaques. Selenium confers further protection by inhibiting peroxidation of some lipids. Still other heart benefits may accrue from selenium's demonstrated ability to inhibit platelet aggregation, modulate prostaglandin synthesis and protect against heavy metals.

Despite the foregoing positive evidence, large controlled prevention trials are still needed before selenium's preventive and therapeutic roles in cardiovascular disease can be properly assessed.

Selenium has been found to be essential for healthy immune function. Some viruses that are normally benign become pathogenic in those who are selenium deficient. This mechanism has been hypothesized by some to account for

new mutant strains of influenza virus in China each year. Selenium has been shown to play important roles in T-cells and natural killer cells among other immune components. Deficiencies in selenium are associated with numerous adverse effects on immune function, including decreased CD4/ CD8 T-lymphocyte ratios and impaired phagocyte function.

Selenium supplementation has been shown to enhance T-cell responses, to stimulate antibody production and to partially reverse age-related cellular immunosuppression. Selenium supplementation has increased responsiveness to interleukin-2 (IL-2) in some studies. Supplementation also protects immune cells from oxidative damage in some instances. In one study, selenium supplementation reduced the incidence of hepatitis-B-induced hepatoma among those with low selenium status. Selenium status is predictive of survival time in some with AIDS, according to another study. Some have suggested that human immunodeficiency virus (HIV) may have been abetted in crossing the species barrier into humans in areas of Africa where selenium deficiency was prevalent. More research is needed and is ongoing with respect to supplemental selenium's role in immune function.

Selenium's anti-inflammatory effects are also related, at least in part, to its effects on immunity. Supplemental selenium can help protect some against Kashin-Beck Disease, a form of arthritis that afflicts many in selenium-deficient areas of China and other parts of Asia. There is some preliminary evidence that selenium, in combination with vitamin E, might alleviate articular pain and morning stiffness in some with arthritis.

In animal experiments, supplemental selenium has protected against some of the adverse effects of UV-radiation. In a mouse study, selenium significantly reduced the incidence of and mortality from non-melanoma skin cancers secondary to UV-exposure.

Selenium plasma levels have been found to be low in some infertile men. Selenium supplementation in these circumstances may improve sperm motility and enhance fertility. In a study of 64 infertile men living in an area of Scotland where low plasma levels of selenium are common, selenium supplementation over a two-year period significantly enhanced sperm motility compared with placebo. Five of the selenium-supplemented men fathered children; none of the men in the placebo group fathered children. There were 64 men in the study, including controls. Selenium appears to both protect sperm from oxidative damage and to help maintain the structural integrity of mature sperm. Follow-up is needed.

There is one report that selenium, in doses five times the recommended daily allowance (RDA) of this mineral, promoted modest weight gain among healthy men, aged 20 to 45. Supplementation continued for four months. The men all consumed the same diet, except for variations in selenium content. The diets were designed to maintain baseline body weight. The five men consuming the diet with high selenium content gained about 1.5 pounds. The six subjects consuming the diet low in selenium (providing about one fifth of the RDA) lost about 1 pound each. More research may be warranted.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Selenium is contraindicated in those who are hypersensitive to any component of a selenium-containing preparation.

PRECAUTIONS

Pregnant women and nursing mothers should avoid selenium intakes greater than RDA amounts (60 and 70 micrograms daily, respectively).

ADVERSE REACTIONS

Intakes of selenium less than 900 micrograms daily (for adults) are unlikely to cause adverse reactions. Prolonged intakes of selenium of doses of 1,000 micrograms (or one milligram) or greater daily may cause adverse reactions.

The most frequently reported adverse reactions of selenosis or chronic selenium toxicity are hair and nail brittleness and loss. Other symptoms include skin rash, garlic-like breath odor, fatigue, irritability and nausea and vomiting. Perhaps the most famous example of selenium toxicity was reported in 1984. About 11 days after starting to take supplemental selenium, a 57-year-old female who was otherwise in good health noted marked hair loss which progressed over a two-month period to almost total alopecia. She also noted white horizontal streaking on one fingernail, as well as tenderness and swelling on the fingertips and purulent discharge from the fingernail beds. All of her fingernails eventually became involved and she lost the entire fingernail of the first digit affected. She also experienced episodes of nausea, vomiting, a sour-milk breath odor, and increase in fatigue. She learned a little over three months later that the selenium tablets she had taken were recalled by the distributor because they, in error, contained over 27 milligrams of selenium per tablet, 182 times higher than labeled. Others who took the same preparation suffered similar symptoms. Hair loss and fingernail changes (horizontal streaking, blackening, loss) were the most common symptoms.

Daily intake of 3.20 to 6.69 milligrams of selenium (average of 4 mg) by Chinese subjects in China produced loss of hair and nails, skin rash, garlic breath, fatigue, irritability and hyperreflexia. The same report described a 62-year-old man who took supplemental selenium in the form of sodium

selenite; after two years he developed thickened, fragile nails and a garlic-like skin odor.

INTERACTIONS

DRUGS

There are no known interactions with drugs in clinical practice.

NUTRITIONAL SUPPLEMENTS

Iodine: Intake of selenium and iodide may have synergistic activity in the treatment of Kashin-Beck disease.

Vitamin C: Concomitant intake of selenium and the selenite form of selenium may decrease the absorption of selenium.

Vitamin E: Intake of vitamin E and selenium may produce synergistic beneficial effects.

OVERDOSAGE

Selenium overdosage has been reported in the literature. (See Adverse reactions).

DOSAGE AND ADMINISTRATION

Available forms of selenium supplements include high-selenium yeast, L-selenomethionine, sodium selenate and sodium selenite. Typical dosage ranges from 50 to 200 micrograms (as elemental selenium) daily. Se-methylseleno-cysteine is a predominant form of selenium found in garlic.

The average daily intake of selenium in the United States is about 100 micrograms.

The Food and Nutrition Board of the Institute of Medicine of the National Academy of Sciences has recommended the following Adequate Intake (AI) and Recommended Dietary Allowance (RDA) for selenium:

Infants	(AI)
0-6 months	15 micrograms/day (2.1 micrograms/kg)
7-12 months	20 micrograms/day (2.2 micrograms/kg)
Children	**(RDA)**
1-3 years	20 micrograms/day
4-8 years	30 micrograms/day
Boys	
9-13	40 micrograms/day
14-18 years	55 micrograms/day
Girls	
9-13 years	40 micrograms/day
14-18 years	55 micrograms/day
Men	
19-30 years	55 micrograms/day
31-50 years	55 micrograms/day
51-70 years	55 micrograms/day
Older than 70 years	55 micrograms/day
Women	
19-30 years	55 micrograms/day
31-50 years	55 micrograms/day
51-70 years	55 micrograms/day
Older than 70 years	55 micrograms/day
Pregnancy	
14-18 years	60 micrograms/day
19-30 years	60 micrograms/day
31-50 years	60 micrograms/day
Lactation	
14-18 years	70 micrograms/day
19-30 years	70 micrograms/day
31-50 years	70 micrograms/day

The Food and Nutrition Board has recommended the following Tolerable Upper Intake Levels (UL) for selenium:

Infants	(UL)
0-6 months	45 micrograms/day
7-12 months	60 micrograms/day
Children	
1-3 years	90 micrograms/day
4-8 years	150 micrograms/day
9-13 years	280 micrograms/day
Adolescents	
14-18 years	400 micrograms/day
Adults	
19 years and older	400 micrograms/day
Pregnancy	
14-18 years	400 micrograms/day
19-50 years	400 micrograms/day
Lactation	
14-18 years	400 micrograms/day
19-50 years	400 micrograms/day

The Lowest-Observed-Adverse-Effects-Level (LOAEL) for adults is about 900 micrograms daily.

The DV (Daily Value) for selenium, which is used for determining percentage of nutrient daily values on nutritional supplement and food labels, is 70 micrograms. The basis for the DV for selenium is the 1989 Estimated Safe and Adequate Daily Dietary Intake (ESADDI).

LITERATURE

Alaejos MS, Romero FJD, Romero CD. Selenium and cancer: some nutritional aspects. *Nutrition.* 2000;16:376-383.

Beck MA, Shi Q, Morris VC, Levander OA. Rapid genomic evolution of a non-virulent Coxsackievirus B3 in selenium-deficient mice results in selection of identical virulent strains. *Nature Med.* 1995;5:433-436.

Berry MJ, Banu L, Larsen PR. Type I iodothyronine deiodinase is a selenocysteine-containing enzyme. *Nature.* 1991;349:438-440.

Bleys J, Navas-Acien A, Guallar E. Selenium and diabetes: more bad news for supplements. *Ann Intern Med.* 2007;147(4):271-272.

Bleys J, Navas-Acien A, Guallar E. Serum selenium levels and all-cause, cancer, and cardiovascular mortality among US adults. *Arch Intern Med.* 2008;168(4):404-410.

Burk RF, ed. *Selenium in Biology and Human Health.* New York, NY: Springer-Verlag; 1994.

Burk RF, Levander OA. Selenium. In: Shils ME, Olson JA, Shike M, Ross AC, eds. *Modern Nutrition in Health and Disease.* Baltimore, MD: Williams and Wilkins; 1999:265-276.

Clark LC, Combs GF Jr, Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. *JAMA.* 1996;276:1957-1963.

Colditz GA. Selenium and cancer prevention. Promising results indicate further trials required (editorial). *JAMA.* 1996;276:1984-1985.

Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, DC: National Academy Press; 2000.

Diwadkar-Navsariwala V, Prins GS, Swanson SM, et al. Selenoprotein deficiency accelerates prostate carcinogenesis in a transgenic model. *Proc Natl Acad Sci USA.* 2006;103(21):8179-8184.

Dworkin BM. Selenium deficiency in HIV infection and the acquried immunodeficiency syndrome (AIDS). *Chem Biol Interact.* 1994;91:181-186.

Fleet JC. Dietary selenium repletion may reduce cancer incidence in people at high risk who live in areas with low soil selenium. *Nutr Rev.* 1997;55:277-279.

Flores-Mateo G, Navas-Acien A, Pastor-Barriuso R, et al. Selenium and coronary heart disease: a meta-analysis. *Am J Clin Nutr.* 2006;84(4):762-773.

Hendler SS. Micronutrition: vitamins, minerals, and trace elements. In: Newcomer VD, Young EM, eds. *Geriatric Dermatology. Clinical Diagnosis and Practical Therapy.* New York and Tokyo: Igaku-Shoin; 1989:365-393.

Huttunen JK. Selenium and cardiovascular diseases-an update. *Biomed Environ Sci.* 1997;10:220-226.

Ip C. Interaction of vitamin C and selenium supplementation in the modification of mammary carcinogenesis in rats. *J Natl Cancer Inst.* 1986;77:299-303.

Ip C. Lessons from basic research in selenium and cancer prevention. *J Nutr.* 1998;128:1845-1854.

Ip C, Thompson HJ, Zhu HJ, et al. In vitro and in vivo studies of methylseleninic acid: evidence that a monomethylated selenium metabolite is critical for cancer chemoprevention. *Cancer Res.* 2000;60:2882-2886.

Ip C, Zhu Z, Thompson HJ, et al. Chemoprevention of mammary cancer with Se-allylselenocysteine and other selenoaminoacids in the rat. *Anticancer Res.* 1999;19(4B):2875-2880.

Jiang C, Jiang W, Ip C, et al. Selenium-induced inhibition of angiogenesis in mammary cancer at chemopreventive levels of intake. *Mol Carcinog.* 1999;26:213-225.

Kardinaal AF, Kok FJ, Kohlmeier L, et al. Association between toenail selenium and risk of acute myocardial infarction in European men. The EURAMIC Study. European Antioxidant Myocardial Infarction and Breast Cancer. *Am J Epidemiol.* 1997;145:373-379.

Klein EA. Selenium and vitamin E cancer prevention trial. *Ann N Y Acad Sci.* 2004;1031:234-241.

Kohrle J. Thyroid hormone deiodinases—a selenoenzyme family acting as gate keepers to thyroid hormone action. *Acta Med Austriaca.* 1996;23:17-30.

Low SC, Berry MJ. Knowing when not to stop: selenocysteine incorporation in eukaryotes. *Trends Biochem Sci.* 1996;21:203-208.

Moreno-Reyes R, Suetens C, Mathieu F, et al. Kashin-Beck osteoarthropathy in rural Tibet in relation to selenium and iodine status. *N Engl J Med.* 1998;339:1112-1120.

Mukhopadhyay-Sardar S, Rana MP, Chatterjee M. Antioxidant associated chemoprevention by selenomethionine in murine tumor model. *Mol Cellul Biochem.* 2000;206:17-25.

Nadiminty N, Gao AC. Mechanisms of selenium chemoprevention and therapy in prostate cancer. *Mol Nutr Food Res.* Epub: 2008 Aug 22.

Navas-Acien A, Bleys J, Guallar E. Selenium intake and cardiovascular risk: what is new? *Curr Opin Lipidol.* 2008;19(1):43-49.

Olmsted L, Schrauzer GN, Flores-Arce M, Dowd J. Selenium supplementation of symptomatic human immunodeficiency virus infected patients. *Biol Trace Elem Res.* 1989;20:59-65.

Olson GE, Winfrey VP, Nagdas SK, et al. Selenoprotein P is required for mouse sperm development. *Biol Reprod.* 2005;73(1):201-211.

Peters U, Takata Y. Selenium and the prevention of prostate and colorectal cancer. *Mol Nutr Food Res.* Epub: 2008 Sep 2.

Rayman MP. Selenium in cancer prevention: a review of the evidence and mechanism of action. *Proc Nutr Soc.* 2005;64(4):527-542.

Reagan-Shaw S, Nihal M, Ahsan H, et al. Combination of vitamin E and selenium causes an induction of apoptosis of human prostate cancer cells by enhancing Bax/Bcl-2 ratio. *Prostate.* 2008;68(15):1624-1634.

Reilly C. Selenium: a new entrant into the functional food arena. *Trends Food Sci Technol.* 1998;9:114-118.

Schrauzer GN. Selenomethionine: a review of its nutritional significance, metabolism and toxicity. *J Nutr.* 2000;130:1653-1656.

Scott R, MacPherson A, Yates RWS, et al. The effect of oral selenium supplementation on human sperm motility. *J Urol.* 1998;82:76-80.

Selenium Intoxication-New York. *Morbidity and Mortality Weekly.* 1984; Report 33, No.12:157-158.

Stranges S, Marshall JR, Natarajan R, et al. Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial. *Ann Intern Med.* 2007;147(4):217-223.

Suadicani P, Hein HO, Gyntelberg F. Serum selenium concentration and risk of ischaemic heart disease in a prospective cohort study of 3,000 males. *Atherosclerosis.* 1992;96:33-42.

Thorpe JF, Jain S, Marczylo TH, et al. A review of phase III clinical trials of prostate cancer chemoprevention. *Ann R Coll Surg Engl.* 2007;89(3):207-211.

Ursini F, Heim S, Kiess M, et al. Dual function of the selenoprotein PHGPx during sperm maturation. *Science.* 1999;285:1393-1396.

Vunta H, Belda BJ, Arner RJ, et al. Selenium attenuates pro-inflammatory gene expression in macrophages. *Mol Nutr Food Res.* Epub: 2008 May 15.

Vunta H, Davis F, Palempalli UD, et al. The anti-inflammatory effects of selenium are mediated through 15-deoxy-Delta12,14-prostaglandin J2 in macrophages. *J Biol Chem.* 2007;282(25):17964-17973.

Yang G, Wang S, Zhou R, Sun S. Endemic selenium intoxication of humans in China. *Am J Clin Nutr.* 1988;37:872-881.

Yu MW, Horng IS, Hsu KH, et al. Plasma selenium levels and risk of hepatocellular carcinoma among men with chronic virus infection. *Am J Epidemiol.* 1999;150:367-374.

Yu SY, Zhu YJ, Li WG. Protective role of selenium against hepatitis B virus and primary liver cancer in Qidong. *Biol Trace Elem Res.* 1997;56:117-124.

Sesame Seed Lignans

DESCRIPTION

Sesame (*Sesamum indicum* L.) has a fascinating history. It is one of the oldest cultivated plants in the world and has been around for about 6,000 years. Sesame seed and its oil have been utilized as an important foodstuff and also for medicinal purposes, including providing energy and mental tranquility and preventing aging. It has also been used as an insecticide, for the preparation of mummies by the ancient Egyptians and as the fundamental body massage oil in Ayurvedic medicine. These days, bodybuilders use lignans from sesame seeds for supposed performance enhancement and weight loss. Recently, there has been a great deal of interest in studying sesame seed lignans for their biological effects and possible health benefits.

Sesame seed is one of the two major dietary sources of plant lignans, the other major source being flaxseed. The major sesame seed lignan is sesamin. Sesame seed contains about 0.4% sesamin in sesame oil or about 4 mg per gram. Sesame seed also contains about half as much of the lignan sesamolin and smaller amounts of sesamol, sesaminol, and the water-soluble lignans, sesaminol diglucoside and sesaminol triglucoside. (The aglycosides are lipid-soluble.) In addition, it contains small amounts of matairesinol, lariciresinol, pinoresinol and syringaresinol.

Sesamin, like all plant lignans, is a phenylpropanoid dimer. However, in contrast with the flaxseed lignan secoisolariciresinol diglucoside (see Flaxseed Lignans) and the spruce lignan 7-hydroxymatairesinol (see Spruce Lignans), which are of the dibenzylbutyrolactone structural type, sesamin is of the tetrahydrofuran, or furofuran structural type. The two major structural types of lignans in the plant kingdom are the dibenzylbutyrolactone and the tetrahydrofuran, or furofuran types. Sesamin and all of the sesame seed lignans are also classified as phytoestrogens.

The chemical names for sesamin are: 5,5′-(Tetrahydro-1*H*,3*H*-furo[3,4-*c*]furan-1,4-diyl)bis-1,3-benzodioxole; tetrahydro-1,4-bis[3,4-(methylenedioxy)phenyl]-1*H*,3*H*-furo[3,4-*c*]furan, and 2,6-bis(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane.

The molecular formula is $C_{20}H_{18}O_6$ and the molecular weight is 354.35. The CAS Registry Number for sesamin is 606-80-7. The sesamin preparation obtained as a by-product of the refining of edible sesame oil consists of a 1:1 ratio of sesamin and its epimer episesamin. Pure sesamin is available.

The chemical structures that follow are described within this monograph.