Targeting Trace Mineral Bioavailability:
The Case of Selenium

presented by

SABINSA CORPORATION

Authors:

Muhammed Majeed, Ph.D. & Lakshmi Prakash, Ph.D.

info@sabinsa.com www.seleniumselect.com www.sabinsa.com

Targeting Trace Mineral Bioavailability: The Case of Selenium

Why is selenium so important? As a "trace" mineral selenium (Se) is a vital micronutrient, with multiple roles in the growth and functioning of living cells in higher animals and humans. Selenium forms about 14 mg of the proximate composition of the average human. Adequate selenium nutrition is essential to maintain the body's antioxidant defense systems and to efficiently utilize energy. Selenium is involved in immune mechanisms, ubiquinone (coenzyme Q10) synthesis, mitochondrial ATP biosynthesis (energy cycle), and in several metabolic processes. Selenium is also required for normal pancreatic function, which is necessary for the digestion and absorption of lipids including Vitamin E. Once believed to be a carcinogen, selenium was recognized as an essential trace nutrient over forty years ago, and has been extensively researched for its health benefits since the 1990s. Selenium is present as selenomethionine in wheat and other cereals, which therefore represents the major food form of selenium. If ingested in this form, selenium is readily incorporated into selenoproteins in animals and humans.

SELENIUM SOURCES

Selenium is unevenly distributed in the earth's crust. The primary nutritional source is the soil from which it is absorbed by plants and enters the food chain. Selenium content of forage crops depends upon its availability from the soil. Dietary sources of selenium include unrefined grains, organ meats such as kidney and liver, fish, and nuts (brazil nuts are particularly rich in selenium). Geographical variations in the selenium status of populations therefore exist, necessitating selenium supplementation. However, all types of supplemental selenium are not created equal.

The recommended levels for selenium supplementation in humans are 50-200 mcg/day. The recommended daily dietary allowance for selenium is 55 mcg. This recommendation also suggests that intake of selenium from all sources should not exceed 400 mcg. At supranutritional dietary levels, selenium can prevent the development of many types of cancer. At higher concentrations, selenium compounds can be either cytotoxic or possibly carcinogenic. Selenomethionine is a safe form of supplemental selenium (Schrauzer, 2003). Furthermore, organic selenium compounds such as L-Selenomethionine have been clinically proven to be more bioavailable than inorganic selenium supplements such as sodium selenite. (Burk, et al; 2006).

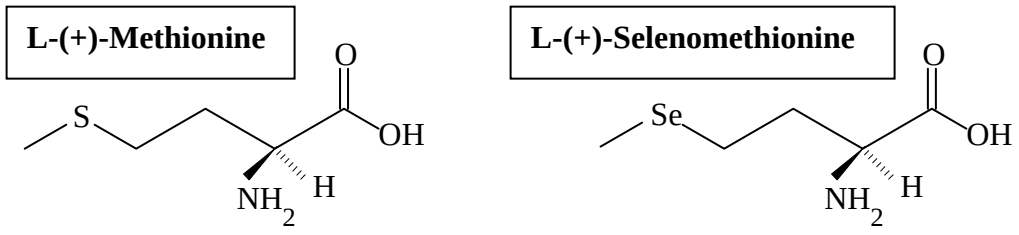
OCCURRENCE AND FUNCTION OF SELENIUM IN THE HUMAN BODY

At the molecular level selenium is an essential component of the active sites of the enzymes glutathione peroxidase, iodothyronine 5'-deiodinase and mammalian thioredoxin reductase, and is also present in several other mammalian selenoproteins (Cronin, 2000). Selenium is also essential to the normal functioning of the thyroid gland and the immune system, particularly cellular immunity. Selenium is also involved in the formation of sperm and the normal functioning of the pancreas and the prostate gland. These functionalities suggest the potential role of selenium as an antioxidant, and "anti-aging" micronutrient. In recent years, laboratory experiments, clinical trials and epidemiological data suggest the potential healthful role of selenium in the prevention of a number of chronic conditions including cancer, inflammatory diseases, cardiovascular disease, neurological diseases, viral infections and immune deficiency, including AIDS (Rayman, 2000, Letavayová et al., 2006).

CHEMISTRY OF SELENOMETHIONINE

Selenomethionine is chemically 2-amino-4-(methylseleno)-butanoic acid, a "selenoamino acid" wherein the sulfur atom in the molecular structure of methionine is replaced with selenium. The dextrorotatory form L(+)-Selenomethionine is the major storage form of selenium in plants. The D(-) forms of amino acids are not well utilized by humans (Lewis, 1995) and DL-methionine is unique among amino acids in that it is the only one listed under "Food Additives permitted for direct addition to foods for human consumption" with the restriction "not for infant foods" (21CFR 172.320). By analogy, this could be true for D(-) and therefore DL-Selenomethionine as well.

To perform its biological functions, the selenoamino acid molecule must fit correctly into the three dimensional structure of proteins (www.seleniumselect.com). Only the natural L(+)-form would meet this requirement in higher animals and plants.

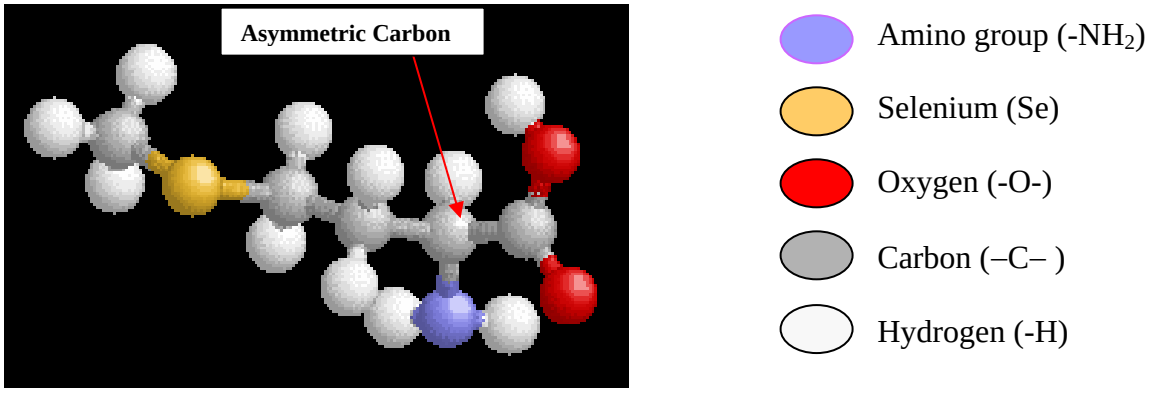


The Chemical Structures Methionine and Selenomethionine

L(+) SELENOMETHIONINE VS OTHER SELENIUM SOURCES

"Chelates" and "organically bound" forms of selenium release inorganic selenium into the body, which is not ideal. L-(+)-Selenomethionine is the preferred form of selenium supplementation due to its inherent safety and its scientific recognition as a bioavailable form of selenium. L-(+)-Selenomethionine is unique in that it is a single chemical entity containing molecularly integrated selenium in place of sulfur in the molecule of the essential amino acid, methionine. L-(+)-Selenomethionine is directly incorporated into the body proteins by metabolic pathways similar to those for methionine. Furthermore, because it's in the L (+) chiral configuration, L-(+)-Selenomethionine is safer and more bioavailable than other "dry blended" selenium and methionine products. It should be noted that amino acids in living cells are usually present in the L-(+) form. High selenium yeast, for example contains the major amount of its selenium content in the form of L(+)-Selenomethionine.

Inorganic selenium salts and chelated forms of selenium (chelates, aspartates) are broken down into elemental selenium. It is important to note that elemental selenium is not bioavailable and may have toxic effects at levels only four to five times the amount normally ingested in the human diet ((Schrauzer, 1998). It is reported that the replacement of methionine by selenomethionine in the protein structure does not induce any functional changes in the protein molecule. In fact, selenium in the protein structure protects the DNA from oxidation more efficiently than the original sulfur in methionine (Burke et al., 1992).



Molecular model of L-(+)-Selenomethionine

The carbon-selenium bond is more easily broken during photochemical reactions as compared to the carbon-sulfur bond. Thus L-(+)-Selenomethionine preferentially "accepts" the energy from light. Therefore topical or orally administered L-(+)-Selenomethionine offers greater protection to the skin against damage by ultraviolet light (Burke et al., 1992). It is reported that selenium levels in the red blood cells of subjects treated with selenomethionine (in the form of selenium yeast) increased by 100% after 16 weeks supplementation. Neither selenite nor selenate supplementation produced significant increases under the same conditions (Alfthan, et al.; 1991).

L-(+)-Selenomethionine is the preferred form of selenium supplementation for humans. The inorganic forms are reported to induce the formation of free radicals and enhance lipofuscin production (Whiting, 1981; Csallany, et al.; 1984). D- and DL forms are not effectively utilized by humans.

Many clinical and animal studies validate the superior beneficial effects of L(+)-Selenomethionine. Selenomethionine was found to be four times as effective as selenite in preventing the characteristic pancreatic degeneration caused by selenium deficiency in chicks (Cantor, et al.; 1995). In a clinical study in China, selenium levels in both the blood plasma and erythrocytes of human volunteers increased at a significantly faster rate when they were given selenomethionine as compared to the levels with inorganic compounds (Xia, et al.; 1992). Organic selenium, as selenium yeast (selenomethionine) was found to be much more effective than inorganic selenium compounds in increasing the selenium concentration of cow's milk. Sodium selenite and sodium selenate had only a marginal effect on milk selenium concentration (Proceedings, STDA; 1998). L-(+)-Selenomethionine is more efficiently absorbed into the muscle protein than inorganic selenium (Lyons and Jacques; 1996).

CLINICAL RESEARCH

A large number of research papers are published on selenium annually. Cancer prevention, antiviral defense, immune-system enhancement, arthritis, and coronary disease are some of the areas that have been explored. Of the studies conducted on the therapeutic benefits of selenium, Clark et al. serves as a landmark study. This 10-year study established selenium as an anticarcinogen in humans. Although selenium supplementation did not significantly affect the incidence of basal cell or squamous cell skin cancer, the focus of the study, it did significantly reduce total cancer mortality, total cancer incidence, and incidences of lung, colorectal, and prostate cancers in the selenium-treated group.

Because selenium's effects on these cancers were not the original focus of the study, critics argue that this study does not confirm selenium's beneficial effects on cancer. Thus, this study generated interest in funding follow-up research on selenium in chronic disease prevention.

A landmark study funded by the National Cancer Institute (NCI) and coordinated by the Southwest Oncology Group (SWOG), is known as SELECT (Selenium and Vitamin E Cancer Prevention Trial). It is a 12-year study conducted with 34,000 men from the United States, Canada and Puerto Rico, to determine the role of selenium and vitamin E in the prevention of prostate cancer. The IND number for this study is #58,212. The exclusive form of selenium chosen and used by NCI for this study is L(+)-Selenomethionine, Sabinsa's SeleniumSeLECT ®. Sabinsa is contracted to supply capsules of Selenium SeLECT ® as well as the placebo for the trial. A subgroup of 10,000 subjects from the trial are also being assessed for the role of selenium and vitamin E in preventing Alzheimer's disease (PREADVISE).

The mechanism of anticarcinogenic action of selenomethionine is as yet unclear. Several hypotheses have been proposed, including the antioxidant effects of selenium mediated through glutathione peroxidase, modification of carcinogen metabolism, effects on the immune system and endocrine functions, production of cytotoxic metabolites, inhibition of protein synthesis and enzymes that catalyze cell proliferation, as well as induction of apoptosis. Recent in vitro studies suggest that selenomethionine protects cellular DNA from damage (Seo, et al.; 2002). Interestingly, selenomethionine was found to inhibit the growth of tumor cell lines in vitro, at 1000 fold lower concentrations than those required to inhibit the growth of normal cells (Redman, et al.; 1998).

HEALTH BENEFITS

- **Chemopreventive Support**

Several research reports indicate the inverse relationship between higher blood levels of selenium and mortality from cancer including lung, colorectal, prostate and skin cancer (reviewed in Cronin, 2000; Rayman, 2000). Laboratory studies indicate the potentially beneficial role of selenium in the management of mammary cancer and colon cancer (Ip et al., 2000; Baines, et al.; 2002). Esophageal squamous cell carcinoma remains a leading cause of cancer death worldwide. A randomized, controlled trial of selenomethionine 200 mcg daily and/or celecoxib 200 mg twice daily,

found selenomethionine to have a protective effect against this form of cancer (Limburg, et al.; 2005). Other clinical studies with reference to cancer prevention have been discussed elsewhere in this paper.

▪ Cardiovascular Health

Selenium is one of the antioxidants that may help to inhibit LDL oxidation (Ozer et al.; 1995). Risk for cardimyopathies, ischemic heart disease and cardiovascular disease is increased with a low dietary intake of selenium (Neve, 1996). Keshan disease is a type of cardiomyopathy endemic in regions of China where selenium deficiency is prevalent. An enlarged heart and poor heart functions are characteristic of this condition. This occurs when selenium intake is less than 16 microgram/day, which is significantly lower than the current RDA.

Additionally, there is an increased risk of myocardial infarction, congestive heart failure, striated muscle degeneration, myositis, etc. with selenium deficiency. Selenium has a protective action by its antioxidant effects on blood vessels via glutathione enzymes, thereby preventing formation of plaques, inhibiting peroxidation of lipids, inhibiting platelet aggregation, modulate prostaglandin synthesis and affording protection against heavy metal toxicity. Recent reports suggest that dietary selenium supplementation may provide a safe and convenient method for increasing antioxidant protection in aged individuals, particularly those at risk of ischemic heart disease, or in those undergoing clinical procedures involving transient periods of oxygen depletion in the heart muscle (Venardos, et al.; 2007).

▪ Diabetes/Blood Sugar Support

Selenium is reported to mimic the action of insulin (Stapleton; 2000). In laboratory studies performed in recent years, selenium has been shown to mediate a number of insulin-like actions such as stimulating glucose uptake and regulating metabolic processes including glycolysis, gluconeogenesis, fatty acid synthesis and the pentose phosphate pathway. Selenium is also reported to play a role in reducing the oxidative stress associated with diabetes (Mukherjee, et al.; 1998) thereby retarding the progression of the secondary complications of diabetes such as neuropathy, retinopathy and cataracts. Recent reports however suggest that further clinical studies need to be done to support the use of selenium supplementation for diabetes prevention in selenium replete populations.

▪ Anti-inflammatory Support

Low selenium status has been associated with the incidence of rheumatoid arthritis (Kose, et. al; 1996), selenium therefore potentially helps to protect against this disease. Arthritic inflammation caused by prostaglandin and the morning stiffness of arthritis can be prevented with selenium. Preliminary studies indicate the beneficial role of selenium as a free radical scavenger that may thereby delay the progression of arthritis. By modulating levels of hydroperoxides, glutathione peroxidase can influence key enzymes of the arachidonic acid cascade, such as cyclooxygenases that catalyze the formation of inflammatory prostaglandins and lipoxygenase that catalyzes the formation of inflammatory leukotrienes.

In animal model studies, organoselenium compounds were found to inhibit colon cancer at the post-initiation stage. Cyclooxygenase enzyme levels are used as marker in the assessment of experimental colon cancer. The organoselenium compounds tested were found to inhibit these enzymes (Rae, et al.; 2001).

▪ Immunity

Selenium deficiency appears to result in immunosuppression, whereas supplementation with low doses of Selenium appears to result in augmentation and/or restoration of immunological functions and strengthened immune system. A deficiency of Selenium has been shown to inhibit resistance to bacterial and viral infections (Sammalkorpi; 1988). More recent studies confirm that selenium supplementation decreases coxsackievirus heart disease occurring in animal models suffering from AIDS (Sepulveda, 2002). Selenium nutritional status is reported to be the “driving force” for influenza virus mutations. Studies show that a non-virulent virus, in a selenium-deficient host, mutates to become ‘super virulent’-a "killer" virus (Nelson, et al.; 2001; Beck, et al.; 2001).

▪ Neurological & Psychological Health

Low plasma selenium status has been associated with senility and cognitive decline in the elderly and with Alzheimer’s disease. Selenium supplementation was observed to reduce the severity of epileptic seizures in children (Ramaekers, 1994). Selenium supplementation is also reported to improve confused and depressed mental states; mental fatigue and anxiety in adults (Finley,et al.; 1998). Recent studies support the beneficial role of selenium in cognitive health in the elderly (Gao, et al.; 2007).

Topical Support

The topical benefits of selenium compounds are well known and preparations containing selenium sulfide are available for the treatment of seborrhic dermatitis, dandruff and fungal infections such as Tinea versicolor,. It has been demonstrated in both human subjects and experimental animals that topical selenomethionine reduces the degree of damage to the skin induced by UV radiation (Burke, 1992, 2003). Selenomethionine is also potentially beneficial in modulating immune functions in psoriasis (Serwin, et al; 1999).

Reproductive Health

Observations in animals reflect that selenium deficiency impairs reproductive functions and that correction with selenium supplements restores normal functions. In poultry, selenium deficiency was found to reduce both egg production and hatchability. In ruminants, selenium deficiency leads to high embryonic mortality. Rats fed low selenium diets, produced hairless offspring that were growth retarded and sterile on maturity (Cronin, 2000; Rayman, 2000; Badmaev, et al.; 1996). Studies on rodents reveal that that selenium is vital for maintaining the integrity of sperm mitochondria and in facilitating sperm motility and normal testicular growth and functions (Wu, et al.; 1979).

Urinary Health

Studies in animal models confirm the beneficial role of selenium in the management of kidney stones (Kumar, et al.; 2003).

Miscellaneous

By virtue of the role of selenium containing enzymes in relieving oxidative stress and in optimizing immune and thyroid functions, selenium supplements are potentially useful in lowering the risk of SIDS (sudden infant death syndrome), cretinism and birth defects. It is proposed by researchers that adequate selenium status may offer protection against encephalopathies such as BSE (Bovine Spongiform Encephalopathy, in animals) and TSE (Transmissible Spongiform Encephalopathy, in humans) (Stockdale, 2001), as well as neurological disorders such as Parkinson's disease. Supplemental selenium may also help in cases of endemic goiter, multiple sclerosis and pregnancy related disorders such as spontaneous miscarriage. All these conditions are reported to be associated

with sub-optimal selenium status. A recent clinical study revealed that selenomethionine when used with L-thyroxine has beneficial effects on patients with autoimmune thyroditis (Duntas, et al.; 2003).

L(+)-Selenomethionine - SeleniumSeLECT® : SUPERIOR BIOAVAILABILITY

A study conducted by Vanderbilt University Medical Center found that L-(+)-Selenomethionine in the form of Sabinsa's branded SeleniumSeLECT, is twice as bioavailable as selenium in the form of selenite (Xia, et al.; 2005). The study involved 120 subjects with an average selenium intake of 10 micrograms per day, well below the recommended dietary allowance of 55 micrograms per day. Participants were given supplemental selenium in either the form of sodium selenite or selenomethionine (SeleniumSeLECT was used). The amount of selenium in both forms needed to optimize nutrient levels in the blood was determined. As compared to sodium selenite, less than half the amount of selenium as selenomethionine was needed to reach optimal blood levels. Would this be true in selenium replete subjects as well? The researchers proceeded to validate these findings in a nutritionally adequate group of subjects in the United States.

A subsequent study (Burk, et al.; 2006) was done on selenium replete subjects to measure plasma selenium biomarkers and urinary selenium excretion using different types of selenium supplements. Doses of selenium used ranged from 200mcg/d to 600 mcg/d with three types of products being used including sodium selenite, high selenium yeast, and L(+)-selenomethionine. 81 subjects were randomly put into 10 groups as placebo and 3 dose levels of each form of selenium. Urinary excretion results showed that supplemental selenium is absorbed to a greater extent in the form of selenomethionine than in the forms of yeast and selenite. Some of the subjects in this study ingested > 800 mcg selenium/day for 16 weeks. This is considerably more than the Institute of Medicine's tolerable upper level of 400 mcg/day. No signs of selenium toxicity (hair loss and nail changes) were observed, in agreement with earlier observations in Chinese subjects with intakes of 800 mcg. Moreover, plasma selenium concentrations were lower than levels determined in healthy farmers in Enshi County, an area in China with high selenium in the soil where selenium toxicity is not recognized now but was reported in the past.

REGULATORY UPDATE/MONOGRAPH

The following **qualified health claim statements** can be made for dietary supplements containing selenium (USFDA, 2003):

- (1) Selenium may reduce the risk of certain cancers. Some scientific evidence suggests that consumption of selenium may reduce the risk of certain forms of cancer. However, FDA has determined that this evidence is limited and not conclusive. *or*,
- (2) Selenium may produce anticarcinogenic effects in the body. Some scientific evidence suggests that consumption of selenium may produce anticarcinogenic effects in the body. However, FDA has determined that this evidence is limited and not conclusive.

The **United States Pharmacopeial (USP) monograph for Selenomethionine** is based on analytical methods developed for Sabinsa's Selenium SeLECT brand of L-(+)-Selenomethionine. Sabinsa Corporation also supplied the reference standard to the USP.

On August 1, 2005, the European Union scheduled to ban approximately 300 supplement ingredients as part of the **Food Supplements Directive**. Sabinsa submitted an extensive dossier containing research findings and safety data and was granted exemption from this directive for SeleniumSeLECT®. The remaining 23 member states of the European Union granted derogation or accepted the result of derogation by the United Kingdom and Denmark.

The multifaceted clinical roles of selenium offer substantial support to the argument for increasing selenium intake, particularly as a bioavailable food form, such as L(+)-Selenomethionine. It must be emphasized that supplementation at the recommended levels with L(+)-Selenomethionine would not result in cumulative toxicity. When the supplement is incorporated into the body proteins, a steady state is established that prevents the uncontrolled accumulation of selenium.

REFERENCES

1. Alfthan, G. et al. **Selenium metabolism and platelet glutathione peroxidase activity in healthy Finnish men: effects of selenium yeast, selenite, and selenate.** *Am. J. Clin. Nutr*. 1991; 53(1):120-125.
2. Badmaev V, Majeed M, Passwater RA. **Selenium: A quest for better understanding.** *Alternative Therapies* 1996; 2(4): 59-67
3. Baines A, Taylor-Parker M, Goulet AC, Renaud C, Gerner EW, Nelson MA. **Selenomethionine Inhibits Growth and Suppresses Cyclooxygenase-2 (COX-2) Protein Expression in Human Colon Cancer Cell Lines**.*Cancer Biol Ther.* 2002 Jul-Aug;1(4):370-4.
4. Beck, M.A. et al. **Selenium deficiency increases the pathology of an influenza virus infection.** *FASEB J* 2001;15(8): 1481-1483
5. Burk RF, Norsworthy BK, Hill KE, Motley AK, Byrne DW. Effects of chemical form of selenium on plasma biomarkers in a high-dose human supplementation trial. *Cancer Epidemiol Biomarkers Prev.* 2006;15(4):804-10.
6. Burke, K.E. et al. **The effects of topical and oral L-selenomethionine on pigmentation and skin cancer induced by ultraviolet radiation.** *Nutr. Cancer* 1992;17:123-137
7. Burke, KE et al. **Effects of topical L-selenomethionine with topical and oral vitamin E on pigmentation and skin cancer induced by ultraviolet irradiation in Skh:2 hairless mice.** *J Am Acad Dermatol.* 2003 Sep;49(3):458-72.
8. Cantor, A.H., et al. **Efficacy of selenium in selenium compounds and feedstuffs for prevention of pancreatic fibrosis in chicks.** *J. Nutr.* 1975; 105(1): 106-111.
9. Clark LC, et al.. **Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial.** *JAMA*. 1996;276:1957-63.
10. Cronin, J.R. **Dietary selenium: Elemental Nutrition for Muscles Immunity, Well-Being and Cancer Prevention**. *Alt. Complement. Therap*. 6 2000; (6): 342-346
11. Csallany, A. S. et al., **Effect of selenite, vitamin E and N,N'-diphenyl-p-phenylenediamine on liver organic solvent-soluble lipofuscin pigments in mice.** *J Nutr*. 1984**;** 114(9):1582-7
12. Decensi, A, Costa, AS. **Recent advances in cancer chemoprevention, with emphasis on breast and colorectal cancer**. *Eur. J. Cancer*. 2000; 36(6):694-709.
13. Duntas LH et. al. **Effects of a six month treatment with selenomethionine in patients with autoimmune thyroiditis**. *Eur J Endocrinol*. 2003 Apr;148(4):389-93
14. Finley, J.W. et al. Adequacy or deprivation of dietary selenium in healthy men: Clinical and psychological findings. *J. Trace Elem.* Exp.1998; Med. 11:11-27.
15. Gao, S et al. **Selenium level and cognitive function in rural elderly Chinese.** *Am J Epidemiol.* 2007 Apr 15;165(8):955-65.
16. Ip, C. et al. **Selenium modulation of cell proliferation and cell cycle biomarkers in normal and premalignant cells of the rat mammary gland.** *Cancer Epidemiol Biomarkers Prev.* 2000; 9(1):49-54.
17. Kose, K. et al. **Plasma selenium levels in rheumatoid arthritis.** *Biol. Trace Element Res.* 1996; 53:51-56.
18. Kumar SK, and Selvam R. **Supplementation of vitamin E and selenium prevents hyperoxaluria in experimental urolithic rats**. *J Nutr. Biochem.* 2003; 14 : 306–313
19. Letavayova L et al. **Selenium: from cancer prevention to DNA damage.** *Toxicology*. 2006 Oct 3; 227(1-2):1-14.
20. Lewis, A. J. **Bioavailability of D-amino acids and DL-Hydroxymethionine, in** C.B. Ammerman, D.H. Baker, and A.J. Lewis, **Bioavailability of Nutrients for Animals**: 67-81. 1995. San Diego: Academic Press.
21. Limburg PJ, et al.. **Randomized, placebo-controlled, esophageal squamous cell cancer chemoprevention trial of Selenomethionine and celecoxib.** *Gastroenterology*. 2005; 129(3):863-73.
22. Lyons, TP and Jacques, KA, ed. **Biotechnology in the Feed Industry.** Nottingham Uni. Press 1996; 257-267
23. Mukherjee, B. et al. **Novel implications of the potential role of selenium on antioxidant status in streptozotocin-induced diabetic mice.** *Biomed Pharmacother* 1998; 52(2):89-95
24. Nelson HK, et al. **Host nutritional selenium status as a driving force for influenza virus mutations.** *FASEB J* 2001;15:1481-3.
25. Neve, J. **Selenium as a risk factor for cardiovascular diseases**. *J. Cardiovasc. Risk* 1996; 3:42-47.
26. Ozer, N.K. et al. **New roles of low density lipoproteins and vitamin E in the pathogenesis of atherosclerosis.** *Biochem. Mol Biol. Int*. 1995; 35:117-24**.**
27. **Proceedings of the Sixth Int. Symposium of the STDA** 1998; 159-160
28. Rae CV, et al. **Chemoprevention of colon cancer by a glutathione conjugate of 1, 4-phenylene*bis* (methylene) selenocyanate - a novel organoselenium compound with low toxicity.** *Cancer Res.* 2001; 61(9):3647-52
29. Ramaekers, V.T. et al. **Selenium deficiency triggering intractable seizures.** *Lancet* 1994; 337:1443-1444.
30. Rayman, M.P. **The importance of selenium in human health.** *Lancet.* 2000; 356:223-241

31. Redman C, et al. CM, Nelson MA. **Inhibitory effect of Selenomethionine on the growth of three selected human tumor cell lines.** *Cancer Lett* 1998;125 (1-2):103-110.
32. Sammalkorpi K et al. **Serum selenium in acute infections**. *Infection* 1988; 16(4):222-4.
33. Schrauzer, G.N. **Selenomethionine and selenium yeast: appropriate forms of selenium for use in infant formulas and nutritional supplements.** *J. Med. Foods.* 1998; 1:201-206.
34. Schrauzer GN. **The nutritional significance, metabolism and toxicology of selenomethionine.** *Adv Food Nutr Res.* 2003;47:73-112.
35. Seo, YR, et al. **Selenomethionine induction of DNA repair in human fibroblasts.** *Ocogene* 2002; 21(23); 3663-9
36. Sepulveda RT et al.. **Selenium supplementation decreases coxsackievirus heart disease during murine AIDS.** *Cardiovasc Toxicol* 2002;2(1):53-61.
37. Serwin AB, et al. **Selenium nutritional status and the course of psoriasis.** *Pol Merkuriusz Lek.* 1999; 6(35):263-5
38. Stapleton, S.R. **Selenium: an insulin-mimetic**. *Cell Mol Life Sci.* 2000; 57(13-14) :1874-9.
39. Stockdale T. **A biochemical theory to explain the cause of bovine spongiform encephalopathy and other encephalopathies**. *Med Hypotheses*. 2001 Jun;56(6):608-16
40. Venardos KM, Kaye DM. **Myocardial ischemia-reperfusion injury, antioxidant enzyme systems, and selenium: a review.** *Curr Med Chem*. 2007;14(14):1539-49.
41. Whiting, R. F. In: **Selenium in Biology and Medicine**, Spallholz, J. E., Martin, J. L. and Ganther, H. E., Eds. 1981. AVI Publishing, Westport, p325
42. Wu AS, et al. **Specific effect of selenium deficiency on rat sperm.** *Biol Reprod.* 1979 May;20(4):793-8
43. **www.seleniumselect.com**
44. Xia, Y. et al. **Metabolism of Selenate and Selenomethionine by a selenium deficient population of men in China.** *J.Nutr.Biochem* 1992; 3:202.
45. Xia, Y. et al. **Effectiveness of selenium supplements in a low-selenium area of China** *Am J Clin Nutr.* 2005 Apr; 81(4):829-34.

***

EU Approved

When the National Cancer Institute began its study of selenium it could only choose one.

A single L-selenomethionine ingredient from a growing field of options. The research NCI used to make this selection was meticulous. It had to be. The study follows 32,400 men from 400 locations across the United States, Puerto Rico and Canada—the largest of its kind. The results will likely amount to the most impressive validation of the effects of selenium on human health ever compiled. So the ingredient used in the trials had to be the definitive selenium gold standard. An organic, amino acid bound selenium compound proven to be safe and highly bioavailable. One ingredient stood out from the rest. Selenium SeLECT® from Sabinsa. The National Cancer Institute chose it. Now, you can too.

NATIONAL® CANCER INSTITUTE

SABINSA CORPORATION

info@sabinsa.com
www.seleniumselect.com

Selenium SeLECT®
An ingredient of Sabinsa Corporation