Selenium and its Relationship to Cancer

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The statements "Selenium may reduce the risk of certain cancers" and "Selenium may produce anticarcinogenic effects in the body" are supported by scientific evidence. There is significant scientific agreement that daily supplementation with selenium may reduce the risk of some cancers and that selenium is anticarcinogenic. This report will examine epidemiological studies, human clinical trials, animal studies, and in vitro studies on selenium's relationship to cancer. It will examine the efficacy of different forms of selenium and of different levels of selenium supplementation.

I. Selenium

Selenium is classified in a group VIA of the periodic table of elements which includes the nonmetals, sulfur and oxygen, in the periods above selenium, and the metals, tellurium and polonium, in the period below this element (Combs and Combs, 1986a). By period, selenium lies between the metal arsenic and the nonmetal, bromine. Thus, selenium is considered a metalloid, having both metallic and nonmetallic properties. It has an atomic number of 34 and an atomic weight of 79. Elemental selenium, like its sister elements, sulfur and tellurium, can exist in either an amorphous state or one of three crystalline states.

Elemental selenium can be reduced to the -2 oxidation state (selenide), or oxidized to the +4 (selenite) or +6 (selenate) oxidation states. Hydrogen selenide (H_2Se) is a fairly strong acid in aqueous systems. The gas is colorless, has an unpleasant odor, and is highly toxic. At low pH, selenite is readily reduced to the elemental state by mild reducing agents such as ascorbic acid or sulfur dioxide. In its oxidized state (+6), selenium can exist as selenic acid or as selenate salts. Selenic acid is a strong acid. Most selenate salts are soluble in water, in contrast to the corresponding selenite salts and metal selenides. Selenates tend to be rather inert and are very resistant to reduction.

The chemical and physical properties of selenium are very similar to those of sulfur. The two elements have similar outer-valence shell electronic configurations and atomic sizes and their bond energies, ionization potentials and electron affinites are virtually the same. Despite these similarities, the chemistry of selenium and sulfur differ in two respects that distinguish them in biological systems. First, in the biological systems, selenium compounds are metabolized to more reduced states whereas sulfur compounds are metabolized to more oxidized states. The second important difference in the chemical behaviors of these elements is in the acid strengths of their hydrides. The hydride, H_2Se, is much more acidic than is H_2S. This difference in acidic strengths is reflected in the dissociation behaviors of the selenohydryl groups of selenocysteine and the sulfhydryl groups on cysteine. Hence, while thiols such as cysteine are predominantly protonated at physiological pHs, the selenohydryl groups of selenols such as selenocysteine are predominantly dissociated under the same conditions.

II. Selenocompounds in plants.

The metabolism of selenocompounds in plants has been summarized (Whanger, 1989). Selenium enters the food chain through incorporation into plant proteins, mostly as selenocysteine and selenomethionine (Semet) at normal selenium levels. However, with elevated selenium levels, Se-methylselenocysteine (SeMCYS) can be the predominant selenocompound. As many as eight other selenocompounds have been identified in plants but their concentrations

are usually very low except at high selenium levels. Indicator plants (called selenium accumulators) can accumulate extremely large amounts of selenium, ranging from 1000 to 10,000 Fg selenium per gm because they synthesize mostly nonprotein selenoamino acids (Brown and Shrift, 1981). As much as 80% of the total selenium in some accumulator plants is present as SeMCYS and until recently it was thought to be absent in nonaccumulator plants.

The selenium content of plants is dependent upon the region of growth (summarized by Whanger, 1989). Vegetables such as rutabagas, cabbage, peas, beans, carrots, tomatoes, beets, potatoes, and cucumbers contained a maximum of 6 Fg selenium per gm even when grown on seleniferous soils. Vegetables such as onions and asparagus may accumulate up to 17 Fg selenium per gm when grown on these types of soils. Plants which contain deficient levels of selenium are found in the Pacific Northwest, upper Mid-West, the New England states and along the Atlantic coast of the United States. In other parts of the country such as North and South Dakota, Colorado and Western Nebraska plants may contain high levels of this element. Plants can synthesize organic selenium compounds including Semet from inorganic selenium (Burnell and Shrift, 1977). Because of the uneven global distribution of selenium, disorders of both selenium deficiency and selenium excess are known. For example, China has regions with both the lowest and the highest selenium-containing soil in the world (Yang et al, 1989 a,b). Plants of economic importance do not have a selenium requirement for growth and thus plant selenium is for the health of animals including humans.

Although the data are lacking, synthesis of the nonprotein selenoamino acids by plants probably occurs along pathways normally associated with sulfur metabolism. Conversion of selenocysteine to SeMCYS in accumulators has been shown to involve the transfer of a methyl group from S-adenosylmethionine, analogous to the synthesis of S-methylcysteine (Neuhierl et al, 1999). Even though the primary source of selenium in soil is inorganic, mostly selenate, *Astragalus* accumulators have been shown to synthesize SeMCYS when supplied with Semet (Chen et al, 1970). The ability of the accumulators to exclude selenoamino acids from proteins has been suggested as a reason for their selenium tolerance. Similar mechanisms apparently operate in selenium enriched plants such as garlic, broccoli, onions and wild leeks where the nonprotein selenoamino, SeMCYS, is the predominant one present.

Most of the selenium in enriched wheat grain (Olson et al, 1970), corn and rice (Beilstein et al, 1991) and soybeans (Yasumoto et al, 1984) is Semet. Semet is the predominant form of selenium in selenium enriched yeast (Ip et al, 2000a). Selenium enriched yeast is the most common source of selenium available commercially (Schrauzer, 2000). The selenoamino acid, Semet, is also available for the public. The major form of selenium is SeMCYS in selenium enriched garlic (Ip et al, 2000a), onions (Cai et al, 1995), broccoli florets (Cai et al, 1995) and sprouts (Finley et al, 2001), and wild leeks (Whanger et al, 2000).

III. Selenocompounds in animals

A brief metabolic pathway for selenium metabolism in animals has been presented (Ip, 1998). Organic selenium such as Semet or inorganic selenium can be converted to a common intermediate, hydrogen selenide. There are two possible pathways for the catabolism of Semet. One is the transsulfuration pathway via selenocystathionine to produce selenocysteine, which in turn is degraded to hydrogen selenide by the enzyme, $-lyase (Mitchell and Benevenga, 1978). The other pathway is the transamination-decarboxylation pathway. It was estimated that 90% of the methionine is metabolized through this pathway and thus could be the major route also for Semet catabolism. SeMCYS is the predominant selenocompound formed in selenium enriched garlic at relatively low concentrations, but γ-glutamyl-Se methyl selenocystine is the predominant one at high selenium concentrations (Dong et al, 2001). Even though this glutamyl derivative may be the predominant one, it is hydrolyzed in the intestinal tract and the absorbed SeMCYS cleaved by a lyase to form methylselenol (Dong et al, 2001). Thus, this glutamyl derivative is metabolized like SeMCYS at the tissue level. SeMCYS is converted to methylselenol directly when cleaved by beta-lyase and unlike Semet it cannot be incorporated nonspecifically into proteins. Since

SeMCYS can be converted directly to methylselenol, this is presumably the reason it is more efficacious than other forms of selenium.

When rats are injected with selenite, the majority of the selenium is present in tissues as selenocysteine (Olson and Palmer, 1976; Beilstein and Whanger, 1988). As expected, no Semet was found under the conditions of these studies. In contrast to plants, there is no known pathway in animals for synthesis of Semet from inorganic selenium, and thus they must depend upon plant or microbial sources for this selenoamino acid. However, animals can convert Semet to selenocysteine. One day after injection of Semet there is about three times as much Semet as selenocysteine in tissues, but five or more days afterwards the majority (46-57%) of the selenium is present as selenocysteine (Beilstein and Whanger, 1986).

A total of 24 selenoproteins have been identified in eukaryotes (Gladyshev, 2001). These selenoproteins have been subdivided into groups based on the location of selenocysteine in selenoprotein polypeptides. The first group (called glutathione peroxidase, GPX) is the most abundant and includes proteins in which selenocysteine is located in the N-terminal portion of a relatively short functional domain. These include the four GPXs, selenoproteins P, Pb, W, W2, T T2 and BthD (from *Drosophila*). The second group of eukaryotic selenoproteins is characterized by the presence of selenocysteine in C-terminal sequences. These include the three thioredoxin reductases and the G-rich protein from *Drosophila*. Other eukaryotic selenoproteins are currently placed in the third group that consists of the three deiodinase isozymes, selenoproteins R and N, the 15 kDa selenoprotein and selenophosphate synthetase. The four GPXs are located in different parts of tissues and all detoxify to various degrees hydrogen peroxide and fatty acid derived hydroperoxides and thus are considered antioxidant selenoenzymes. The three deiodinases convert thyroxine to triiodothyronine, thus regulating thyroid hormone metabolism. The thioredoxin reductases reduce intramolecular disulfide bonds and, among other reactions, regenerate vitamin C from its oxidized state. These reductases can also affect the redox regulation of a variety of factors, including ribonucleotide reductase, the glucocorticoid receptor and the transcription factors (Holmgren, 2001). Selenophosphate synthetase synthesizes selenophosphate, which is a precursor for the synthesis of selenocysteine.(Mansell and Berry, 2001). The functions of the other selenoproteins have not been definitely identified.

Selenium is present in all eukaryotic selenoproteins as selenocysteine (Gladyshev, 2001). Semet is incorporated randomly in animal proteins in place of methionine. By contrast, the incorporation of selenocysteine into proteins known as selenoproteins is not random. Thus, by contrast to Semet, selenocysteine does not randomly substitute for cysteine. In fact, selenocysteine has it own triplet code (UGA) and is considered to be the 21st genetically coded amino acid. Interestingly, UGA has a dual role in the genetic code, serving as a signal for termination and also a codon for selenocysteine. Whether it serves as a stop codon or encodes selenocysteine depends upon the location of what is called the selenocysteine insertion sequence (Mansell and Berry, 2001).

A number of reviews have been written on the chemopreventive effects of selenium including most recently those by Combs and Gray (1998), Ganther (1999), Ip (1998), Schrauzer (2000), El-Bayoumy (2001) and Fleming et al (2001). The mechanism for selenium as an anticarcinogenic element is not known but several speculations have been advanced. It is well established that the most effective dose of selenium for cancer protection is at elevated levels, often called supernutritional or pharmacological levels. The suggested mechanisms for cancer prevention by selenium include its effects upon cell cycle (called apoptosis, probably the most accepted possibility), its role in selenoenzymes, its effects upon carcinogen metabolism, its effects upon the immune system, and its specific inhibition of tumor cell growth by certain selenium metabolites.

IV. Epidemiological studies.

There have been a number of epidemiological studies in the United States and throughout the world on the relationship between selenium and cancer. Shamberger and Frost (1969) reported

that the selenium status of humans may be inversely related to the risk of some kinds of cancer. Two years later, Shamberger and Willis (1971) in more extensive studies indicated that the mortality due to lymphomas and cancers of the gastrointestinal tract, peritoneum, lung, and breast were lower for men and women residing in areas of the United States that have high concentrations of selenium in forage crops than those residing in areas with low selenium content in the forages. Those studies were supported by a later analysis of colorectal cancer mortality using the same forage data (Clark et al, 1981). A 27-country comparison revealed that total cancer mortality rate and age-corrected mortality due to leukemia and cancers of the colon, rectum, breast, ovary and lung varied inversely with estimated per capita selenium intake (Schrauzer et al, 1977). Similar results were also reported in China, a country where selenium intakes range from deficient to toxic levels (Yu et al, 1985).

Lower selenium levels were found in serum collected from American subjects one to five years prior to diagnosis of cancer as compared to those who remained cancer free during this time (Willett et al, 1983). That association was strongest for gastrointestinal and prostatic cancers. Evidence that low serum selenium is a prediagnostic indicator of higher cancer risk was subsequently shown in studies conducted in Finland (Salonen et al, 1984) and Japan (Ujiie et al, 1998). In additional case-control studies, low serum or plasma selenium were found to be associated with increased risk of thyroid cancer (Glattre et al, 1989), malignant oral cavity lesions (Toma et al, 1991), prostate cancer (Brooks et al, 2001), esophageal and gastric cancers (Mark et al, 2000), cervical cancer mortality rates (Guo et al, 1994) and colorectal adenomas (Russo et al, 1997). A decade long prospective study of selenium status and cancer incidences indicated that initial plasma selenium concentration was inversely related to subsequent risks of both non-melanoma skin cancer and colonic adenomatous polyps (Clark et al, 1993). Patients with plasma selenium levels less than 128 ng/ml (the average normal value) were four times more likely to have one or more adenomatous polyps. An 8-year retrospective case control study in Maryland revealed no significant association of serum selenium level and cancer risk at sites other than the bladder (Helzlsouer et al, 1989), but those with low plasma selenium levels had a 2-fold greater risk of bladder cancer than those with high plasma selenium. In a study with Dutch patients the mean selenium levels were significantly less than that of controls in men, but no differences were found in plasma selenium levels between control women and those with cancer (Kok et al, 1987). No significant associations in three other studies were found between serum selenium concentration and risk to total cancers (Coates et al, 1988) or cancers of the lungs, stomach, or rectum (Nomura et al, 1987 and Kabuto et al, 1994). In other work, significant increases of urinary selenium excretion were found in Mexican women with cervical uterine cancer as compared to controls (Navarrete et al, 2001).

In four studies low toenail selenium values were associated with higher risks of developing cancers of the lung (van den Brandt et al, 1993a), stomach (van den Brandt et al, 1993b), breast (Garland et al, 1995) and prostate (Yoshizawa et al, 1998). In contrast, in four other studies no significant differences were found between cancer cases and controls (Noord et al, 1987, Hunter et al, 1990, Rogers et al, 1991 and Veer et al, 1990). It has been suggested that the reason for those not showing a relationship is because the selenium intakes of most of the subjects tested were below that necessary for protection (Schrauzer, 2000). Obviously these results indicate that many factors must be taken into consideration when evaluating plasma and toenail selenium concentrations in relation to cancer incidence.

V. Human Trials.

In spite of advances in diagnosis and treatment, cancer continues to be a major health burden. With the fear associated with diagnosis of cancer, it is not surprising that the public may have considerable interest in easily implemented measures, such as dietary modification or use of vitamin and trace element supplementation for cancer prevention. Promising results have been obtained, however, to indicate that selenium supplementation is effective in reduction of cancer in humans.

There have been six trials conducted on the effects of selenium supplementation on the incidence of cancer or biomarkers in humans and all of them have shown positive effects of selenium. Three of these were conducted in China and one each in India, Italy and in the United States. The first human intervention trial to prevent cancer with selenium in humans was conducted in Qidong, a region north of Shanghai, China, with a high incidence of primary liver cancer (PLC). Subjects were given table salt fortified with 15 ppm selenium as sodium selenite which provided about 30 to 50 micrograms selenium daily for eight years (Yu et al, 1991, 1997). This resulted in a drop of the PLC incidence to almost one-half (27.2 per 100,000 populations versus 50.4 per 100,000 populations consuming ordinary salt). Upon withdrawal of selenium from the treated group, the PLC incidence began to rise. In a separate study, risk populations receiving selenite salt as a source of selenium also showed a significant reduction in the incidence rate of viral infectious hepatitis, a major predisposing PLC risk factor in this region (Yu et al, 1989). The selenium fortified salt was distributed to the general population of 20,800 persons. Six neighboring townships served as controls and were given normal table salt.

In a second trial, members of families at risk of PLC were either given 200 micrograms selenium daily in the form of high-selenium yeast or a placebo (Yu et al, 1997). During the 2-year study period, 1.26% of the controls developed PLC versus 0.69% in those given selenium enriched yeast. Furthermore, of 226 Hepatitis B surface antigen carriers, seven of 113 subjects in the placebo group developed PLC during four years as opposed to no cases in those taking selenium enriched yeast.

A third human trial on the effects of selenium on cancer was also conducted in China with 3,698 subjects. This intervention trial was conducted from 1984 to 1991 in Linxian, China, a rural county in Henan Province, where the mortalities from esophageal cancer are among the highest in the world (Blot et al, 1993). The results indicated that a treatment containing selenium (50 micrograms Se/day as Se enriched yeast plus vitamin E and $-carotene) produced a modest protective effect against esophageal and stomach cancer mortality among subjects in the general population (Li et al, 1993; Taylor et al, 1994; Blot et al, 1995). Probably the reason for only a modest reduction of cancer by selenium is because only 50 micrograms were given daily in contrast to other studies where up to 200 micrograms were given per day.

In the study conducted in India, 298 subjects were used. One-half of the subjects with precancerous lesions in the oral cavity were supplemented with a mixture of four nutrients [vitamin A, riboflavin, zinc and selenium (100 micrograms daily for six months and 50 micrograms the final six months as selenium enriched yeast)] and compared to controls (also 149 patients) receiving placebos (Prasad et al, 1995). The frequency of micronuclei and DNA adducts were significantly reduced in the supplemented groups at the end of the one year study. The adducts decreased by 95% in subjects taking selenium with all categories of lesions and by 72% in subjects without lesions. No such effects were noted in the placebo group.

In the Italian study subjects were given a mixture called "Bio-selenium" which provided 200 micrograms selenium as L-selenomethionine daily plus zinc and vitamins A, C and E for five years, and compared to those taking a placebo (Bonelli et al, 1998). A total of 304 patients participated in this study and the incidence of metachronous adenomas of the large bowel evaluated. Patients with prior resected adenomatous polyps were used in a randomized trial and new adenomatous polyps were noted. The observed incidence of metachronous adenomas was 5.6% in the group given the "Bio-selenium" mixture versus 11% in the placebo group.

One of the most exciting clinical trials on selenium and cancer in humans was conducted in the United States. A simple experimental design in a double-blind, placebo-controlled trial with 1312 older Americans with histories of basal and/or squamous cell carcinomas of the skin were used (Clark et al, 1996, 1998). The use of a daily oral supplement of selenium enriched yeast (200 µg Se/day) did not affect the risk of recurrent skin cancers. However, supplementation with selenium as selenium enriched yeast reduced the incidence of lung, colon and prostate cancers respectively by 46, 58 and 64%. Restricting the analysis to the 843 patients with initially normal levels of prostate specific antigen, only four cases were diagnosed with cancer in the selenium

treated group but 16 cases were diagnosed in the placebo group after a 2-year treatment lag (Clark et al, 1998). Even though Clark et al (1996) did not observe any effect of selenium on skin cancer in their study, the results strongly indicated that other types of skin disorders may be reduced by selenium.

The author is aware of at least three human trials [two in the United States (University of Arizona; and the SELECT trial at NCI; Klein et al, 2001), and one in Europe (PRECISE, Rayman, 2000)] presently under way to confirm the results of this American investigation.

Finally, in another trial, topical application of Semet was effective in protecting against acute ultraviolet irradiation damage to skin of humans (Burke et al, 1992a). Maximal protection appeared to be attained at concentrations between 0.02% and 0.05%.[1][1]

VI. Selenium and tumors in small animals.

There have been more than 100 trials conducted with small animals on the relationship of tumor incidences to selenium status (Combs and Combs, 1986b; Combs and Gray, 1998). Interestingly, the first evidence that selenium may counteract tumors was presented in 1949 where the addition of selenium to a diet for rats significantly reduced tumors caused by ingestion of an azo dye (Clayton and Bauman, 1949). These results were ignored even by these researchers because of the negative image selenium held at that time. The first evidence of the essentiality of selenium was presented in 1957 (Schwarz and Foltz, 1957), at which time selenium was considered a carcinogenic element. A number of reviews on selenium and carcinogensis in animals have been presented which include those by Milner (1985), Ip and Medina (1987) Medina and Morrison (1988) and Whanger (1992). The chemical carcinogens used to produce tumors in liver, mammary gland, colon, skin, lungs, trachea, pancreas and stomach have been summarized (Whanger, 1992). Two thirds of the animal studies showed significant reductions by selenium in the tumor incidence with one-half showing reductions of 50% or more (Combs and Gray, 1998). In the majority of those studies selenium as selenite was used but that may not have been the most effective form (as noted later) to use. Those results with animals and the epidemiological surveys showing a positive relationship between selenium and cancer incidence were the main motivating factors for conducting human trials.

VII. Tissue cultures.

The present research efforts are primarily focused on the mechanism of cancer reduction by selenium and tissue cultures have been used advantageously to study how tumors are reduced by this element. Research with these cultures also indicates that the beta-lyase mediated production of a monomethylated selenium metabolite, namely methylselenol, from SeMCYS is a key step in cancer chemoprevention by this agent (Ip et al, 2000b). In order for SeMCYS to be effective, cells must possess this beta-lyase. One way to get around this is to use methylselenic acid, which is even effective in cells without this lyase. Although several possibilities have been suggested (Combs and Gray, 1998), the evidence indicates that the likely mechanism in which selenium reduces tumors is through its effects upon apoptosis (Unni et al, 2001; Sinha et al, 1999). Methylselenic acid produced a more robust response at one-tenth the concentration of SeMCYS in the inhibition of cell proliferation and the induction of apoptosis in mouse mammary epithelial cells (Ip et al, 2000b). Apparently these cells have low levels of the beta-lyase. Interestingly the distinction between these two compounds disappears *in vivo* where their cancer chemopreventive efficacies were found to be very similar. The reason for this is because the beta-lyase enzyme is abundant in many tissues and thus the animal has ample capacity to convert SeMCYS to methylselenol.

Work with the mouse mammary epithelial tumor cells indicate that SeMCYS mediates apoptosis by activating one or more caspases (Unni et al, 2001). Of the caspases, caspase-3 activity appeared to be activated to the greatest extent. Apparently these cells have ample lyases to convert SeMCYS to methylselenol. Further work with these same cells using methylselenic acid produced similar results, providing additional support that monomethylated forms of selenium are the critical effector molecules in selenium mediated growth inhibition *in vitro* (Sinha et al, 1999).

Further research is needed to identify why a monomethylated form of selenium that is required for this effect cannot be fulfilled by other forms of selenium.

VIII. Forms of selenium in foods and supplements.

The efficacy of various selenocompounds using the mammary tumor model has been summarized in Table 1.[2][2] SeMCYS and selenobetaine are the most effective selenocompounds identified thus far against mammary tumorigenesis in animals (table 1). Although selenobetaine is just as effective, SeMCYS is considered to be the most interesting selenocompound because it is the predominant one present in selenium enriched plants such as garlic (Ip et al, 2000a), broccoli florets (Cai et al, 1995) and sprouts (Finley et al, 2001), and onions (Cai et al, 1995). Selenobetaine has never been detected in selenium enriched plants. Therefore, SeMCYS has received the most recent attention as possibly the most useful one for cancer reduction. Except for Semet and selenocystine, the other selenocompounds listed in this table are not present in plants and thus are mostly of academic interest. However, some of them are of therapeutic interest.

Selenobetaine and SeMCYS are good precursors for generating monomethylated selenium (Ip, 1998). Selenobetaine tends to lose a methyl group before scission of the Se-methylene carbon bond to form methylselenol. SeMCYS is converted to methylselenol directly when cleaved by beta-lyase and unlike Semet it cannot be incorporated nonspecifically into proteins. Since these

Table 1. Anticarcinogenic Efficacy of Different Selenium Compounds for reduction of mammary tumors in rats.

Compound	Dose of Selenium for 50% Inhibition (ppm)
Se-methylselenocysteine	2
Selenobetaine	2
Selenobetaine methyl ester	2-3
Selenite	3
Selenomethionine	4-5
Selenocystine	4-5
PXSC*	8-10
Triphenylselenonium	10-12
Dimethylselenoxide	>10
Trimethylselenonium	(No effect at 80 ppm)

*1,4-phenylene bis (methylene) selenocyanate

Data taken from Ip and Ganther, 1993 and Ip et al, 1994a, 1994b.

selenocompounds can be converted directly to methylselenol, this is presumably the reason they are more efficacious than other forms of selenium. Dimethylselenoxide

and selenobetaine methyl ester are converted to dimethylselenide but are less effective for reduction of tumors (Ip, 1998). Trimethylselenonium is essentially not effective in tumor reduction. Thus, there is a negative correlation between the effectiveness of these selenocompounds and the degree of methylation.

Even though Semet is effective against mammary tumors, one disadvantage is that it can be incorporated directly into general proteins instead of converted to compounds which most effectively reduce tumors (Ip, 1998). When this occurs its efficacy for tumor reduction is reduced. For example, when a low methionine diet is fed there is significant reduction in the protective effect of Semet even though the tissue selenium was actually higher in animals as compared to those given an adequate amount of methionine (Ip, 1988). When methionine is limiting, a greater percentage of Semet is incorporated nonspecifically into body proteins in place of methionine because the methionine-tRNA cannot distinguish between methionine and Semet. Feeding diets with Semet to animals as the main selenium source will result in greater tissue accumulation of selenium than other forms of selenium (Ip and Lisk, 1994; Whanger and Butler, 1989). It is not known whether this stored selenium can serve as a reserved pool of this element but the evidence indicates that it is metabolically active (Waschulewski and Sunde, 1988).

With the knowledge of the effects of these selenocompounds as anticarcinogenic agents, it was of interest to investigate the most appropriate methods for delivery to the general population. One obvious approach was to investigate additional methods for expeditious ways to deliver these protective agents through the food system. One strategy in this direction was the investigation of enriching garlic with selenium (Ip et al, 1992). The addition of selenium enriched garlic to yield three micrograms selenium per gram diet significantly reduced the mammary tumor incidence in rats from 83% to 33%. Similar to garlic, selenium enriched broccoli also reduced mammary tumors from 90% to 37% (Finley et al, 2001).

Selenium enriched garlic was shown to be twice as effective as selenium enriched yeast in the reduction of mammary tumors (table 2). The total number of tumors as well as the incidence of tumors was reduced to a greater extent by enriched garlic than enriched yeast. Chemical speciation of selenium in these two products indicated that Semet was the predominant form of selenium in enriched yeast whereas SeMCYS (as the glutamyl derivative) was the predominant form of selenium in enriched garlic (Ip et al, 2000a). The glutamyl derivative is considered a carrier of SeMCYS and both of these compounds were shown to be equally effective in the reduction of mammary tumors (Dong et al, 2001). These results are consistent with those in table 1 where SeMCYS was more effective than Semet for reduction of mammary tumors. The chemical composition of selenocompounds in these two sources of selenium is apparently responsible for this difference in efficacy.

Using another model, selenium enriched broccoli florets (Finley et al, 2000; 2001; Finley and Davis, 2001) as well as enriched broccoli sprouts (Finley et al, 2001) significantly reduced colon tumors in rats. This is intriguing because colon cancer is the third most common newly diagnosed cancer in the United States, resulting in about 55,000 deaths per year due to this type of cancer (American Cancer Society, 2000).

Table 2. Mammary Cancer Prevention by Selenium enriched Garlic or Selenium enriched Yeast in the DMBA and MNU Models

Model	Treatment	Dietary Selenium (µg/g)	Tumor Incidence	Total number of Tumors	Percentage inhibitiona
DMBA	none Se-garlic	0.1 3.0 3.0	26/30 11/30b	74 25b 49c	66 34

	Se-yeast		19/30c		
MNU	none Se-garlic Se-yeast	0.1 3.0 3.0	28/30 10/30b 20/30c	80 24b 55c	70 31

aCalculated based on total tumor yield data.

bP < 0.05, compared to the corresponding Se-yeast group.

cP < 0.05, compared to the corresponding control group.

DMBA = dimethylbenz [*a*] anthracene; MNU = Methylnitrosourea

Taken from Ip et al, 2000a

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Selenium enriched broccoli was more effective than selenite, selenate or Semet in the reduction of induced colon carcinogenesis (Feng et al, 1999 and Davis et al, 1999). In contrast, selenite, selenate and Semet were more effective for induction of GPX activity than selenium enriched broccoli (Finley and Davis, 2001). This indicates that the plant converts the selenium to more effective forms for reduction of these tumors and these results emphasize the need to study the effects of selenium in food forms.

Similar to chemically induced colon tumors there were significantly fewer intestinal tumors when mice which have a genetic defect for development of intestinal tumors were fed selenium enriched broccoli (Davis et al, 2002). These results along with data above indicate that selenium enriched broccoli is effective against both chemically and genetically induced intestinal tumors. Data from work with another strain of mice which develop spontaneous intestinal tumors is consistent with these results where selenium deficiency resulted in activation of genes involved in DNA damage (Rao et al, 2001).

IX. Level of selenium necessary for nutritive benefit

The Chinese data have been used almost exclusively to establish the required levels of selenium for nutritive benefit as well as to establish the safe levels for humans (Yang et al, 1989b; Yang and Zhou, 1994). It is fortunate to have a country like China where areas vary from deficient to toxic levels of selenium, and this has made it convenient to collect critical information on the metabolism and effects of various levels of selenium in humans. Significant correlations have been found between daily selenium intake and selenium content of whole blood, plasma, breast milk, and 24 hour urine (Yang et al, 1989a). Highly significant correlations were also found between levels of whole blood selenium and hair selenium, fingernail selenium and toenail selenium, hair selenium and fingernail or toenail selenium, and whole blood selenium and toenail or fingernail selenium. Morphological changes in fingernails were used as the main criterion for clinical diagnosis of selenosis (Yang et al, 1989b). The fingernail changes and loss of hair are the main signs of excess selenium intakes. With excess selenium intakes, the fingernails become brittle and are easily cracked. The data collected on Chinese subjects are summarized in table 3.

An intake of nearly 5 mg of selenium resulted in definite occurrence of selenosis, characterized by hair and nail losses. One suggested reason the subjects were able to tolerate this high level of selenium is because they consumed a high fiber diet. The low adverse effect level of dietary selenium was calculated to range between 1540 and 1600 micrograms daily. However, some effects were noted in individuals with a daily intake of 900 micrograms. The maximum safe dietary selenium intake was calculated to be about 800 micrograms per day, but there were some individuals where an amount of 600 micrograms per day was the maximum safe intake. In order to provide a safety factor, the maximum safe dietary selenium intake was suggested as 400 micrograms per day. A level of about 40 micrograms daily was suggested as the minimum requirement, and an intake of less than 11 micrograms daily will definitely result in deficiency problems. Deficiency of selenium in humans results in a cardiac and muscular disorder called

Keshan disease, and deficiency of selenium is thought to be one of the contributing factors to another disorder called Kaschin-Beck disease.

Table 3. Health Effects of Various Levels of Dietary Selenium Intakes

Average Adult Dietary

Selenium Intakes

(μg/d) (μg/KgBW) Forms Effects on *Human Health*

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*4990 ± 1349 90 Cereal-based plant diet Occurrence of selenosis with hair & nail loss

in seleniferous area

*1660 30 Cereal-based plant diet Adverse effect level (AEL) of dietary Se intake

in seleniferous area

*1540 ± 653 28 Cereal-based plant diet Low adverse effect level of dietary Se intake

in seleniferous area (mean LOAEL)

*×900 17 Cereal-based plant diet Individual low level causes toxicity

in seleniferous area (individual LOAEL)

*819 ± 129 15 Cereal-based plant diet Maximum safe dietary Se intake

in seleniferous atea (NOAEL, mean)

*600 11 Cereal-based plant diet Individual maximum safe dietary Se intake

in seleniferous atea (NOAEL, individual)

400 - Natural Diet Suggested maximum safe dietary Se intake

40 0.7 75% of dietary Se from Suggested adequate dietary Se requirement

selenomethionine

< 11 < 0.2 Cereal-based plant diet Prevalence of Keshan disease and

in Keshan disease area Kaschin-Beck disease

*Calculated by regression equation.

Data modified from: Yang and Zhou (1994). .

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X. Conclusion.

The RDA for selenium is 55 micrograms for healthy adults, with 40 micrograms selenium as the minimum requirement. Less than 11 micrograms selenium will definitely put people at risk of deficiency that would be expected to cause damage. Daily doses of 100 to 200 micrograms

selenium inhibit genetic damage and cancer development in humans. About 400 micrograms

selenium per day is considered an upper safe limit. Clearly doses above the RDA are needed to

inhibit genetic damage and cancer. Despite concerns about the toxicity of higher dietary levels of selenium, humans consuming up to 600 micrograms of selenium daily appear to have no adverse clinical symptoms.[3][3]

Both animal and human data indicate that more than 100 and up to 200 micrograms of selenium are necessary for greatest reduction of cancer. This is because a methylated form of selenium is necessary for maximum reduction of cancer, and the methylated forms are present at highest levels with elevated intakes of this element. In most human trials, the subjects were supplemented with 200 micrograms selenium per day and in trials where only 50 micrograms were supplemented there was not as much reduction of cancer. Therefore, the selenium requirement for maximum reduction of cancer appears to be at least four times the RDA. However, since only 50 to 200 micrograms additional selenium have been used, it is not possible to indicate which level will give maximum protection. For example, it is not known whether supplemental levels of selenium above 200 micrograms daily will provide any additional protection against cancer.

Selenium enriched yeast is the most common source of selenium available commercially and it also has been the most used selenium source in human trials. Semet is the major form in enriched yeast but SeMCYS is the predominant form in enriched plants such as garlic and broccoli. Selenium enriched garlic was shown to be twice as effective as enriched yeast in reduction of mammary tumors in rats. Apparently, the reason SeMCYS is more effective is because it is converted directly to methylselenol, the suspected biologically active form of selenium for reduction of tumors. However, it is not known whether providing twice as much selenium as enriched yeast will give the same benefits as enriched garlic. Therefore, in addition to enriched yeast, selenium enriched food plants such garlic, broccoli and onions appear also to be an effective and safe method for delivery of selenium to the general population. Nevertheless, regardless of the source of selenium it is apparent that additional intakes of this element by humans will reduce the incidence of cancer.

It has been estimated that one-third of the cancers in humans are environmentally related. The results in this report indicate that on an average there could be 50% reduction of cancer through increased selenium ingestion in humans. If the 50,000 deaths due to colorectal cancer, the 41,800 deaths due to prostate cancer in men, or the 43,300 breast cancer deaths in women could be reduced by one-half with selenium, this would be a very significant contribution to human health.

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[1][1] These results are consistent with some animal data. Hairless mice treated by topical application of selenomethionine (0.02%) or given drinking water with 1.5 micrograms selenium per ml as selenomethionine had significantly less skin damage due to ultraviolet irradiation (Burke et al, 1992b). This is consistent with an earlier study which indicated that dietary selenium (one microgram/g) fed to mice significantly reduced the number of skin tumors induced by two carcinogenic chemicals plus croton oil (Shamberger, 1970).

[2][2] The incidence of breast cancer is greatest of all cancers in women but it is the third highest cause of all cancer deaths (American Cancer Society, 2000), probably reflecting the improved methods for detecting and treatment of breast cancer compared to other cancers . Although usually not mentioned, a small number of men develop breast cancer with even some deaths. About 400 men die of breast cancer each year compared to 43,300 breast cancer deaths in women.

[3][3] The author is aware of a person who consumed one mg of selenium for two years before toxic signs of selenium occurred. Thus this element appears not as toxic as often believed.