Food chain Se and human health: emphasis on intake

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Abstract

Following the publication of the landmark trial of Clark and colleagues in 1996 that showed that Se could reduce the risk of cancer, awareness of the importance of selenium (Se) to human health has markedly increased. As a result, there is now much more aggressive marketing of Se supplements and functional foods, even in situations where additional consumption of Se is inappropriate. This review addresses how Se gets into the food chain, the wide variability in Se content of foods and the very different levels of intake between countries and regions. Though it is clear that there are adverse consequences for health of both deficient and excessive intake, health effects at intermediate levels of intake are less certain. Thus it is difficult to define optimal intake which depends on a large number of factors, such as which functions of Se are most relevant to a particular disease state, which species of Se is most prominent in the Se source, which health condition is being considered, the adequacy or otherwise of intake of other nutrients, the presence of additional stressors, and lastly whether the ability to make selenoproteins may be compromised. These complexities need to be understood, particularly by policy makers, in order to make informed judgments. Potential solutions for increasing Se intake, where required, include agronomic biofortification, genetic biofortification or for individuals, increased intake of naturally Se-rich foods, functional foods or supplements. The difficulties of balancing the risks and benefits in relation to Se intake are highlighted.
Introduction
There is a much greater awareness now of the importance of selenium (Se) to human health than there was even ten years ago. This is partly due to the publication of the landmark trial of Clark and colleagues\(^\text{(1)}\) that showed that Se could reduce the risk of cancer. As a result, there is now much more aggressive marketing of Se supplements and functional foods, even in situations where additional consumption of Se is inappropriate.

Both individuals, who take a measure of responsibility for their own health and that of their families, and more importantly, advisory bodies, need to be aware of the complexities surrounding the issue of optimal Se intake in order to make informed judgments. The subject is often treated too simplistically. This review attempts to air the issues that need to be considered.

Perhaps primarily, people need to be aware of the baseline intake in their country or region and whether that intake is adequate or not. There are currently too few data on which to base this judgment, hence companies are able to market Se supplements or functional foods to populations that may already have a perfectly adequate intake of Se. Even in relatively-low Se areas, some people may consume foods of good Se content (e.g. fish) or containing potent Se species (e.g. garlic, onions, or broccoli) that may give them a higher or more effective intake than might be predicted. An appropriate intake for an individual who is a cigarette smoker or has a family history of prostate cancer may well not be the same as for an individual with a family history of squamous cell carcinoma or diabetes. People may eventually learn whether they have a compromised ability to make selenoproteins in which case they may need to increase their intake of Se-rich foods.

On the other hand, some evidence is now emerging that links the risk of more subtle adverse health effects to levels of intake well below those known to be toxic. There may even be a possibility of increased risk of one condition even where risk of another is reduced.

An understanding of these niceties requires a certain background knowledge such as:- how Se gets into the food chain; the variability of Se content of foods and how that content is affected by food preparation or cooking; how intake varies according to country of region of country; health effects in relation to level of intake and the factors modifying those effects. These issues are addressed below, following which the potential solutions for increasing Se intake, if required, are discussed. Lastly, the difficulties of balancing the risks and benefits in relation to Se intake are highlighted.

How Se gets into the food chain
Se enters the food-chain through plants: intake through drinking water is generally trivial\(^\text{(2)}\). The amount of Se in foods depends on a number of geological, geographical and other factors: while the Se concentration of the soil is primarily controlled by the underlying geology (carbonatic vs.
silicatic), the bioavailability of that Se to plants is dependent on pH, redox conditions, amounts of organic matter in the soil, competing ionic species such as sulphate, microbial activity, soil texture, compaction and mineralogy, soil temperature, level of rainfall during the growing season, irrigation and by pedoclimatic variables (temperature and rain intensity excursions) related to fluctuations of soil moisture and pH\textsuperscript{(3-10)}. The uptake of Se by the plant can be greatly inhibited by the simultaneous occurrence of a high soil content of organic matter, iron hydroxides and clay minerals, all of which can adsorb or bind Se\textsuperscript{(4)}. Se speciation in soils also affects Se bioavailability: selenate is more mobile, soluble and less-well adsorbed than selenite\textsuperscript{(8)}. Thus oxidising, alkaline conditions that favour the formation of selenate improve Se bioavailability, while reducing acid conditions that favour the formation of selenite lower bioavailability. According to Fordyce\textsuperscript{(8)}, it is important to understand that even soils that contain adequate or high total Se concentrations can result in Se deficient crops if the element is not in a form amenable to plant uptake. This is well-illustrated by data from the Keshan disease area of Hebei Province, China, that showed a high soil Se content but very low Se bioavailability owing to high organic matter content and lower pH than other soils in the region\textsuperscript{(8)}.

A further important factor is that flowering plant species (angiosperms) differ in their ability to assimilate and accumulate Se: they can be divided into three groups, non-accumulators, Se-indicators (or secondary Se accumulators) and Se accumulators\textsuperscript{(11)}. It appears that the transporters that are responsible for the uptake or translocation of Se are selective such that the ratio of Se:S in the shoots can be higher or lower than that of the solution surrounding the roots\textsuperscript{(11)}. While non-accumulators rarely accumulate more than 100 μg Se/g dry weight, Se-accumulators can contain up to 40,000 μg Se/g dry weight when grown in Se-rich environments\textsuperscript{(11)}. The only Se accumulator plant regularly used as a food source is the tree Bertholletia excelsa which produces Brazil nuts, but some crop species of commercial importance can be described as secondary Se-accumulators e.g. Brassica species (canola, broccoli), and Allium species (garlic, onions, cabbage, leeks and wild leeks)\textsuperscript{(11,12)}. Cereals crops such as wheat, oats, rye and barley are non-accumulators\textsuperscript{(8)}.

The distribution of Se in various parts of the plant depends on species, phase of development and physiological condition\textsuperscript{(12)}: in Se accumulators, Se accumulates in young leaves during the early vegetative stage of growth but during the reproductive stage it is found at much higher levels in seeds. In non-accumulator cereal crops, there is often about the same amount in grain and roots with smaller amounts in stems and leaves\textsuperscript{(12)}. 
Se content of foods is very variable

Se concentration in natural food sources has been tabulated by Rayman and colleagues(13). According to a WHO report(14), the typical Se content of foods varies as follows: organ meats and seafood, 0.4 to 1.5 $\mu$g/g; muscle meats, 0.1 to 0.4 $\mu$g/g; most agricultural crops <1 $\mu$g/g dry weight; e.g. cereals and grains, less than 0.1 to greater than 0.8 $\mu$g/g; dairy products, less than 0.1 to 0.3 $\mu$g/g; fruits and vegetables, less than 0.1 $\mu$g/g. In fact most vegetables contain a maximum of 6 $\mu$g/g even when grown on seleniferous soils and the level in both fruits and vegetables is more likely to be < 0.01 $\mu$g/g(15,16).

The variation in Se content of foods purchased in the upper Midwest of the US was 72-fold (11-774 $\mu$g Se per 100 g) for wheat flakes, 57-fold (14-803 $\mu$g Se per 100 g) for wheat, and 11-fold (19-217 $\mu$g Se per 100 g) for beef(17) while two brands of the same corn product purchased at the same time from the same store in N America had a 10-fold difference in Se concentration(18). The same foods purchased in different countries may have very different Se content e.g. an average of 57 $\mu$g Se/100g in pasta products made in the US compared to only 6 $\mu$g Se/100g in Italian pasta(17). Some idea of the Se content of foods purchased in Europe may be obtained by inspecting the values found by Barclay and colleagues(19) who measured the Se content of a range of around 100 foods purchased in the UK between 1993 and 1994. Reilly(2) has tabulated Se levels in twelve common foods from a number of countries around the world giving a good illustration of the variability that exists. He also addresses in more detail the Se content of a number of individual foodstuffs:- milk, bread and cereals, meat, fish, fruit, vegetables, Brazil and other nuts.

Brazil nuts are the richest source of food Se, but the content is very variable ranging from 0.03 - 512 $\mu$g/g in the studies quoted in the companion paper(13). Brazil nuts are harvested from an enormous area of the Amazon basin but soil levels vary from high, in the Menaus to Belem region of the lower Amazon, to low, in the Acre-Rondonia region on the upper Amazon, resulting in high variability in Se content(2). Three studies have reported a higher Se content in unshelled than shelled nuts though the reason is not known(20-22). Two of these studies have drawn attention to the fact that Brazil nuts are exceedingly high in barium, containing levels up to 4,000 $\mu$g barium/g. Lisk and colleagues(20) found that a serving of three Brazil nuts (flesh weight 13.2 g) containing 290 $\mu$g Se, also provided 26 mg of barium. Barium can be toxic causing gastroenteritis, muscular paralysis, potassium deficiency, decreased pulse rate, ventricular fibrillation and extra systoles, and 90% of the barium ingested in that study was retained in the body. The US Environmental Protection Agency’s oral reference dose for barium based on toxicological data is 0.2 mg/kg/d, which for a 75 kg person would be 15 mg/d(23). It is clear that this could readily be exceeded by a modest serving of Brazil nuts. Furthermore, Brazil nuts contain small amounts of radium, a
radioactive material. Although the amount is very small, about 1–7 pCi/g (40–260 Bq), and most of it is not retained by the body, this is 1000 times higher than in other foods (24). People relying on Brazil nuts as their Se source, of whom there are a not-inconsiderable number, in the UK at least, should be aware both of the uncertainty surrounding the quantity of Se they may be consuming and of the fact that they may be inadvertently consuming barium in amounts exceeding the oral reference dose and radium.

Effect of preparation and cooking on food Se

According to Fordyce (8) cooking reduces the Se content of most foods, and studies have shown that vegetables that are normally high in Se such as asparagus and mushrooms can lose 40% during boiling owing to leaching with water. Other studies have estimated that 50% of the Se content is lost from vegetables and dairy products during cooking especially if salt and low pH components such as vinegar are added, whereas frying foods results in much smaller Se losses (8,14,25). For Se-enriched Allium and Brassica plants such as garlic and cabbage, recent studies have estimated that 85 and 89%, respectively, of the total Se is leached into boiling water (Dr Heidi Goenaga Infante, personal communication, 2006). The distribution, concentration and speciation of Se in different edible parts of a plant may well be different: e.g. the total Se concentration in the skin of Se-enriched potatoes was found to be almost three times higher than that of the flesh though the highest percentage of Se as selenomethionine (73% of the total Se) was found in the flesh (Dr Heidi Goenaga Infante, personal communication, 2006). Thus mode of preparation of food must be taken into account when estimating magnitude or nature of Se intake.

Variability in Se intake by country/region

Intake of Se varies considerably between countries and regions of countries largely owing to the variability of the Se content of plant foods (and hence of animal forage) from one part of the world to another. Se intake data are summarised in Table 1 (7,24,26,27,31). Though the level of reliability of such intake data is somewhat variable, it is clear that there is an immense range of intakes, from toxic (≥5 mg/d) in parts of China affected by selenosis (areas of Enshi County, Hubei Province and Ziyang County, Shaanxi Province), through high [Venezuela, parts of N America (N and S Dakota, Montana and Wyoming) ≥ 200-724 μg/d] to high-adequate (rest of N. America, Japan ≥ 100-200 μg/d) to adequate/marginally adequate (Australia, Europe, New Zealand ≥ 30-90 μg/d) to low or deficient (Eastern European countries, parts of China ≥ 7-30 μg/d) as judged against current recommendations (tabulated by Rayman (7)). Though plants are the primary source of Se in the diet,
animals may be a more reliable source (at least for omnivores) as, unlike plants, they have an absolute requirement for Se which they must get through feed or forage\(^{(28)}\). For instance, organ meats such as kidney and liver are good Se sources while some sea-foods contain nearly as much. In some countries, foods of animal rather than plant origin may even be a more important source of dietary Se, as is the case in the UK\(^{(29)}\).

Human Se status is dependent not only on the Se content of locally-grown foods but on the extent of use of imported foods. During the 1950s, UK wheat constituted only 15% of the grist\(^{(11)}\), while wheat imported from Canada, which was much higher in Se content, made a much larger contribution. This situation persisted up to the mid-1980s but by 2005, the percentage of UK wheat in grists had risen to 80%\(^{(11)}\). Se intake and status in the UK has fallen in parallel with the decline in imports\(^{(30)}\) though increased use of sulphur fertilisers (competition of chemically similar species), breeding for higher grain yield per plant, lower atmospheric deposition of Se from coal combustion and the reported decline in cereal consumption are other important factors\(^{(6,11,31)}\). The opposite situation has been seen in New Zealand where Australian wheat with a higher Se content has recently made a significant contribution to Se intake, thereby improving Se status\(^{(32)}\).

**Health effects of Se in relation to level of intake**

Intake of Se ranges from clearly deficient to toxic. At intermediate levels of intake, more subtle health effects have been reported. The situations of deficiency and toxicity are relatively straightforward to describe and will be summarised first. The question of optimal intake for health is much more difficult to address as it requires consideration of the interplay between a large number of factors.

**Deficient intake**

Overt Se deficiency is associated with Keshan disease, a cardiomyopathy affecting mainly children and women of child-bearing age, frequently fatal, named after the province in the extreme northeast of China where it was endemic\(^{(33)}\). Affected areas had soils that were subject to a strong leaching effect and a high proportion of subsistence farmers who were very dependent on their local food supply\(^{(8,34)}\). The disease occurred in areas where grain crops contained < 0.04 \(\mu g\) Se/g and total daily Se intake was between 10 and 15 \(\mu g\) Se/d. Based on epidemiological studies in Keshan disease areas, Chinese workers have suggested a deficiency threshold of 0.02 \(\mu g/g\) in cereal crops for human consumption\(^{(8)}\). Large-scale Se supplementation (0.5-1 mg sodium selenite/week) between 1974 and 1977 dramatically reduced disease incidence\(^{(8)}\). Though the disease was Se-responsive, it is now thought likely that it also had a viral co-factor which in the presence of Se
deficiency in the Keshan disease area mutated to a more virulent form that caused the heart
condition, as has been shown in the case of Se-deficient mice infected with coxsackie virus.\(^\text{35}\) Coxsackie virus has been isolated from archived heart tissue from patients with Keshan disease.\(^\text{36}\)

Though Kashin-Beck disease, an osteoarthropathy found in rural areas of China, Tibet and
Siberia has also been associated with severe Se deficiency, other factors, notably low iodine status,
or the presence of fulvic acids or mycotoxins in foods appear likely to be more important.\(^\text{37,38}\) More recent data from Tibet appear to support the hypothesis that Kashin-Beck disease occurs as a
consequence of oxidative damage to cartilage and bone cells when associated with decreased
antioxidant defence, though inhibition of bone remodelling by certain mycotoxins has also been
suggested as a potential mechanism.\(^\text{39}\)

While levels of Se deficiency of this magnitude are not normally seen in the West, a number
of cases of cardiomyopathy, some of which have been shown to be Se-responsive, have been
reported in subjects on intravenous nutrition receiving inadequate selenium in their infusion
solutions.\(^\text{40,41}\)

**Excessive intake**

Overt Se toxicity in humans is far less widespread than Se deficiency.\(^\text{8}\) Se toxicity has been
studied in animals and observed in humans where signs of selenosis are hair loss, brittle, thickened
and stratified nails, garlic breath and skin.\(^\text{42}\) Chronic exposure to high levels of selenium has been
observed in several populations in seleniferous areas of the world, such as the northern great plains
of the United States, parts of Venezuela and Colombia, and one county in China (Enshi, Hubei
Province) where the average daily intake of 4.9 mg was associated with a blood Se concentration of
3,200 μg/l and symptoms of selenosis. In Enshi, selenosis was associated with consumption of
high-Se crops grown on soils derived from coal containing, on average, greater than 300 μg Se/g
(one sample exceeded 80,000 micrograms/g).\(^\text{43}\) Se from the coal entered the soil by weathering
and was available for uptake by crops because of the traditional use of lime as fertiliser in that
region. Morbidity rates reached 50% during peak prevalence years (1961-64) in the worst affected
villages which were all located in remote areas among populations of subsistence farmers.\(^\text{8}\) The
particular outbreak of human selenosis was due to a drought that caused failure of the rice crop,
forcing the villagers to eat more high-Se vegetables and maize and fewer protein-rich foods.\(^\text{43}\)

Though some plants that grow on seleniferous soils - the Se-accumulators - can take up
extremely large amounts of Se ranging from 1000 to 100,000 μg/g (air-dried), farm crops rarely
accumulate levels greater than 25-30 μg/g, even in seleniferous areas.\(^\text{15,16}\) Based on
epidemiological studies in areas affected by selenosis, Chinese workers have suggested a toxicity
threshold of 1 μg/g in cereal crops for human consumption.\(^\text{8}\) From published data, no health or
toxicity problems have been observed up to levels of intake of 819 μg Se/d in China\(^\text{44,45}\) or 724 μg Se/d in the USA\(^\text{45}\). If from cereal or rice, such intake is largely in the form of selenomethionine (SeMet) and selenate\(^\text{46}\). By contrast, the high daily intake of Se in the Inuit of North Greenland (estimated as 193-5885 μg/d), where the diet consists largely of meat and organs from marine mammals, seabirds, fish, and the whales' skin delicacy, muktuk\(^\text{47}\), may include a more substantial amount of selenocysteine (SeCys) from selenoproteins. Apart from the noted longitudinal striation on the nails, no clinical signs of selenosis have been reported in this population, notwithstanding the extremely high Se intake and blood concentrations well above 1,000 μg/L\(^2\): it would appear that Se supplied through a marine diet can be tolerated at levels much higher than normally considered safe. Similarly, despite the Se contamination of the Kesterson National Wildlife Refuge in California and levels of 96 μg/g (wet weight) in fish, up to 130 μg/g (dry weight) in the liver of aquatic birds and up to 5.3 μg/g (wet weight) in the flesh of waterfowl, no adverse health effects were seen in the local population or in domestic animals\(^\text{48}\).

Based on the classic studies of Yang and colleagues in China, the LOAEL (Low Observed Adverse Effects Level) was established as 1540 μg/d\(^\text{49}\) and the NOAEL (No Observed Adverse Effects Level) as 819 μg/d\(^\text{44}\). It should be noted, however, these values apply only to total Se and may be inaccurate for any specific form. Applying a safety factor to the NOAEL has allowed expert groups in a number of countries to define an upper level of total Se intake believed to be safe. Thus for adults, the "Tolerable Upper Intake Level" for the US and Canada is 400 μg/d, based on a NOAEL of 800 μg/d\(^\text{28}\). This same value has been adopted by the WHO\(^\text{50}\) and is to be adopted by Australia/New Zealand. The "Safe Upper Limit" in the UK is set at 450 μg/d for adults\(^\text{51}\)

Remarkably, in Enshi, China, as described above, Keshan disease and selenosis occur within 20 km of one another: their incidence is dependent on the very different geologies of the two relatively isolated areas\(^\text{8}\).

**Optimal intake**

Despite food supplies coming from diverse sources at least in developed countries, there is evidence, that in some population groups, Se intake, while not deficient, may be sub-optimal for protection against a number of adverse health conditions. Table 2 summarises studies that showed a Se-associated health benefit. Use of data from these studies allows an attempt to be made to estimate optimal intake in relation to specific health benefits.

Ascertaining the optimal intake of Se is not a trivial matter since it is dependent on a number of factors. These include consideration of the mechanism by which Se is thought to act in any particular situation, the species of Se ingested, which type of disease (or which type of cancer) is
being considered, the overall nutritional adequacy of the group or population, the extent to which genomic differences between people or populations may be relevant, and what other risk or lifestyle factors may be present within the population under consideration. These factors will be considered separately below.

**Which function of Se is being considered?**

In the case of the many disease conditions associated with oxidative stress (e.g. asthma, rheumatoid arthritis, pancreatitis, CHD), it would seem important to have an intake of Se that would at least allow full expression of selenoproteins with an antioxidant function. Current recommendations for intake of dietary Se (mean 57, range 30-85 μg/d (7)) hereinafter referred to as the RDA/RNI (Recommended Dietary Allowance/Reference Nutrient Intake), have been set with this objective in mind though we now know that some recommended intakes would be insufficient for the expression of selenoprotein-P, a selenoprotein that appears to have a special role in scavenging peroxynitrite\(^{(91,92)}\).

Furthermore, selenoprotein P is required for the transport of Se to a number of tissues after its synthesis in the liver\(^{(93)}\) and mouse knock-out studies show its absolute requirement by the brain to avoid neurological dysfunction and brainstem axonal degeneration\(^{(94,95)}\). It would seem therefore that Se intake needs to be sufficient to optimize the concentration of plasma selenoprotein P.

Though we do not yet know what level of intake that would require, we do know that current intakes in some parts of Europe, specifically Eastern Europe, and parts of China are inadequate for full expression of GPx let alone for full expression of selenoprotein-P\(^{(92)}\).

Apart from the selenoproteins, small molecular weight Se compounds such as Se-methyl selenocysteine and γ-glutamyl-Se-methyl selenocysteine are thought to be precursors of the potent anti-cancer agent methyl selenol\(^{(96)}\) which is purported to cause apoptosis, cell-cycle arrest, inhibition of tumour cell invasion and angiogenesis\(^{(97)}\). Though small amounts of these compounds are found in members of the *Allium* and *Brassica* families, production of adequate amounts for cancer prevention by metabolism of Se compounds more commonly found in foods probably requires a considerably-larger intake, perhaps up to 290 μg Se/d, as was the case in NPC trial subjects\(^{(1)}\).

**Nature of Se species in food/supplements consumed**

The predominant species of Se in the food (or supplement) consumed will affect the level of intake considered to be optimal as it will affect bioavailability (absorption and retention), usefulness for synthesis of selenoproteins and ability to produce methyl selenol metabolites. For instance, Se from high-Se broccoli (mainly Se-methyl-selenocysteine, a precursor of methyl selenol) does not
accumulate in tissues or increase GPx enzyme activity to the same extent as selenite or selenoamino acids\(^{(98)}\). Selenite, on the other hand, can be effectively used for selenoprotein synthesis, but it cannot be stored in the body for later use. Selenomethionine (e.g. from cereals or high-Se yeast) can act as a storage form of Se in body proteins from which it can slowly be released by catabolism to maintain Se requirements over a longer period. Burk’s group has shown\(^{(92)}\) that when Se was supplemented to Chinese subjects in the form of selenomethionine, maximum enzyme activity was reached with a supplement dose of 37 \(\mu\)g/d (on top of a background intake of 10 \(\mu\)g Se/d). When the supplement was selenite, a daily dose of 66 \(\mu\)g was required to reach the same maximum level. Thus, selenium in the form of selenomethionine was almost twice as effective as selenium in the form of selenite in supporting plasma GPx activity. These issues are addressed in depth in the companion paper\(^{(13)}\).

**Which health condition is being considered?**

**Mortality:** As mortality reflects vulnerability to a number of diseases combined, it is worthy of consideration despite the fact that there have been very few studies on plasma Se and mortality in elderly populations. Furthermore, such studies are particularly prone to confounding as plasma Se concentrations are known to be higher in fit and well-nourished elderly people and lower in those who are frail, poorly-nourished and unwell\(^{(99)}\). Such a criticism cannot be leveled at randomized controlled trials (RCTs): in a meta-analysis of RCTs, Bjelakovic and colleagues\(^{(100)}\) found that Se supplementation tended to reduce mortality. In the 9-year longitudinal EVA study of 1389 elderly French individuals living independently where various potential confounding factors (sociodemographic characteristics, dietary habits, health, and cognitive factors) were controlled for, low plasma selenium concentrations were associated with higher mortality i.e. for a reduction of 16 \(\mu\)g/L in plasma Se, relative risk (RR) of death was 1.54 (95% CI, 1.25-1.88)\(^{(52)}\). With a mean plasma Se concentration in the EVA study population of 87 \(\mu\)g/L, a considerable proportion of the participants may not have had a sufficient Se intake for optimal selenoprotein expression\(^{(32)}\). This study therefore suggests that the RNI/RDA level of intake may benefit longevity.

**Cognitive function:** There can be no doubt that Se is important to the brain\(^{(101)}\): (i) animal models of neurodegenerative disease show enhanced cell loss in Se depletion; (ii) genetic inactivation of cellular glutathione peroxidise (GPx) increases the sensitivity towards neurotoxins and brain ischemia while increased GPx activity as a result of increased Se supply or overexpression ameliorates the outcome; (iii) genetic inactivation of selenoprotein P leads to a marked reduction in
brain Se content with a corresponding movement disorder and spontaneous seizures in animal models\(^{(102)}\).

Data from elderly French and Chinese populations of low-moderate Se status (mean baseline plasma Se 86.0 μg/L and mean toenail Se 0.21-0.61 μg/g respectively) suggest that being at the top rather than the bottom of the low-moderate range of Se status is sufficient to reduce the risk of cognitive decline (see Table 2\(^{(53-55)}\)). This should be achieved by an RDA/RNI level of intake.

In the context of cognitive function in the elderly, it should be appreciated that low plasma Se may at least partly reflect a lower production of plasma glutathione peroxidase (GPx3) by a less efficient kidney\(^{(103)}\). Failing kidneys also leak homocysteine, a known risk factor for dementia, into the bloodstream\(^{(104)}\). Whether toenail Se would reflect plasma Se in this context is unknown.

**Immune function:** The studies in Table 2 show that the cell-mediated (Th1) immune response can be improved by an additional 100 or 200 μg Se/d even in healthy US volunteers whose baseline Se intake and status is already sufficient to optimize selenoenzyme activity\(^{(56-59)}\). In line with these findings, the UK researchers concluded that in the UK population, an additional 100 μg Se/d may be insufficient to support optimal function\(^{(59)}\).

**Antiviral effects/HIV:** Though animal studies have shown that adequate Se for antioxidant GPx1 activity is important for the avoidance of viral mutation to more virulent forms\(^{(104)}\), the success of supplementation studies with 100 or 200 μg Se/d suggests that this level of intake on top of basic diet may be necessary for anti-viral effects in humans\(^{(59,60,66,67)}\) (Table 2). It has been suggested that retroviruses such as HIV and Coxsackie B3 have the potential to deplete the host’s Se supply by incorporating the Se into viral selenoproteins for their own protection, as has been demonstrated for the DNA virus, *Molluscum contagiosum*\(^{(106-108)}\). Although unproven, this is a potential explanation for the requirement for a Se intake higher than the RNI/RDA.

**Fertility and reproduction:** The selenoproteins phospholipid glutathione peroxidase (GPx4) and sperm nuclei selenoprotein are required for sperm motility and sperm maturation respectively\(^{(109,110)}\). The level of Se intake required to optimise the activities of these selenoproteins is probably somewhere within the range of currently recommended intakes (RDA/RNI), say between 55 and 75 μg/d, as both are high in the hierarchy of selenoprotein expression\(^{(111,112)}\). It follows that the fertility of men whose Se intake is lower than that required to optimise selenoenzyme activity may be improved by supplementation as was demonstrated in sub-fertile Scottish men who showed a significant increase in sperm motility when supplemented with 100 μg
Se/d for three months\(^{69}\) (Table 2). There is however a suggestion that relatively high intakes (around 300 \(\mu g/d\)) may decrease sperm motility\(^{113}\).

It seems likely that the risk of miscarriage and the pregnancy disease, pre-eclampsia, may also require an intake sufficient to give optimal selenoprotein expression. This can be concluded from studies in UK pregnant women where those with higher Se status had a significantly lower risk of first-trimester or recurrent miscarriage\(^{70,71}\) and of pre-eclampsia\(^{72}\) (see Table 2). As UK Se intake has been measured as 29-39 \(\mu g/d\)^{31}, it is clear that raising it to the RDA/RNI level of intake would be sufficient to optimise female reproductive success.

*Cancer:* Results of the numerous prospective studies and trials are summarised in Table 2. From prospective studies, the mean/median level of plasma Se required for a significant reduction in cancer risk ranges from > 84 \(\mu g/L\) (e.g. for oesophageal and gastric cardia cancer in China\(^{74}\)) to 147 \(\mu g/L\) (e.g. for prostate cancer in Hawaii\(^{114}\)) according to the study, while from trial data, the minimum mean plasma Se for significant reduction in cancer risk in an Eastern US population in the NPC Trial ranged from 105 \(\mu g/L\) (all cancers)\(^{80}\) to 123 \(\mu g/L\) (prostate cancer)\(^{81}\). The minimum Se intake required to achieve these plasma concentrations ranges from just below the RNI/RDA level to a total intake of around 140 \(\mu g/d\) from dietary Se (or Se-yeast, which is similarly absorbed and retained\(^{115}\)). This assertion is based on results of a UK supplementation study in healthy volunteers with a baseline dietary intake of approximately 40 \(\mu g/d\) in which a further 100 \(\mu g Se/d\) as Se-enriched yeast raised plasma Se from 90.3 to 148.4 \(\mu g/L\)\(^{116}\).

The significant benefit of Se treatment effect in the NPC trial was restricted to males and to those with baseline plasma Se \(\leq\) 105.2 \(\mu g/L\). In fact there was a non-significant increased risk of cancer among those in the highest tertile (baseline plasma Se >121.6 \(\mu g/L\)) and a significantly increased risk of squamous cell carcinoma in NPC participants with baseline plasma selenium in the top two tertiles\(^{80,117}\). In addition, further analysis of NPC trial data has shown an increased risk of self-reported Type-2 diabetes in those supplemented with Se, though the effect was significant only in those in the top tertile of plasma Se at baseline\(^{118}\). Though such secondary end-point analyses must be regarded with caution, the advisability of supplementing individuals of already-replete status (say 120-125 \(\mu g/L\) or more\(^{119}\)) with Se must be questioned.

Certainly it should be apparent that in populations that already have a mean baseline intake at the level associated with reduced cancer risk e.g. the Prostate, Lung, Colorectal and Ovarian Cancer Trial population where mean plasma Se was 141.3 \(\mu g/L\)\(^{120}\), no significant benefit at higher intake/status should be expected, nor indeed was seen in that population. Such populations should not be exposed to additional dietary Se or supplementation.
To date, no cancer trial has used a level of dose that would give a total intake of 140 μg Se/d as suggested above, all having opted for 200 μg Se/d or more.

Thyroid effects: Since the selenoenzymes GPx and thioredoxin reductase are crucial to the protection of the thyroid from the hydrogen peroxide that is produced there for thyroid hormone synthesis\(^\text{121}\) and the selenoenzyme iodothyronine deiodinase is required for the production of active thyroid hormone, it might be expected that an intake of around the RDA/RNI which would optimize the activities of these selenoproteins would be sufficient for the protective effects of Se on the thyroid (see Table 2). However, it was found that a dose of 200 μg/d sodium selenite or selenomethionine was required to decrease inflammation and thyroid autoantibody concentrations in patients with autoimmune thyroiditis, the lower dose of 100 μg/d selenomethionine being ineffective\(^\text{85}\). The reason for this rather surprising result is not known.

Coronary heart disease (CHD): Evidence that Se affects CHD risk has generally been equivocal despite a good biological rationale for optimal selenoprotein activity/concentration conferring benefit. However, a recent excellent meta-analysis of 25 observational studies, found the pooled relative risk in a comparison of the highest with the lowest selenium concentration categories to be 0.85 (95% CI: 0.74, 0.99) in 14 cohort studies and 0.43 (0.29, 0.66) in 11 case-control studies\(^\text{90}\) though the authors warn that observational studies have provided misleading evidence for other antioxidants. Only two randomized trials have used Se as a single agent, one in Finland that found a significant reduction in risk\(^\text{122}\) and the other in the US that did not\(^\text{123}\), though the latter was in a Se-replete population with respect to selenoprotein activity/concentration. Inspection of the serum/plasma/toenail values reported in the meta-analysis together with the randomized trial evidence suggests that achieving the RDA/RNI level of intake may generally be sufficient to reduce CHD risk.

Conclusion on optimal intake for health effects: Partly because of the presence of potential confounding in observational studies from which most of the above data is derived, it is difficult to be categorical about the intake required to minimize the risk of any particular condition. However, it does seem clear that the optimal intake of Se depends on the health effect being considered, the risk apparently being reduced at the RDA/RNI level of intake in many cases while others such as cancer and the immune response appear to require a higher intake. Results of many studies are consistent with a threshold effect i.e. an intake (as represented by serum/plasma/toenail concentration) of Se above which risk is uniformly decreased\(^\text{73, 74,80,124}\).
General nutritional adequacy

The intake of other nutrients needs to be taken into account when establishing Se requirements. If a population is well-nourished, for instance, with good intake levels of vitamin E and other antioxidant micronutrients, the requirement for Se is likely to be somewhat lower than may be the case for a poorly-nourished population such as some of those described in Chinese studies\(^{(125)}\). Thus, the strongest effect of Se on cancer risk has been shown among those subjects with the lowest levels of dietary antioxidant vitamins and carotenoids, and particularly at low \(\alpha\)-tocopherol concentrations (reviewed by Rayman\(^{(75)}\)). Where the population is iodine deficient (e.g. the Democratic Republic of Congo), Se intake should not be increased until iodine status has been optimized, as there may be adverse effects on brain development\(^{(126)}\).

If ability to make selenoproteins is compromised, additional Se intake may be needed

The ability to make selenoproteins may be reduced in people with failing liver (selenoprotein P) or kidney (GPx3) function\(^{(103,127)}\). To some extent, by analogy with studies in mice, increased Se intake may be able to compensate for a deficit in selenoprotein activity, at least with respect to colon cancer risk, by increasing the concentration of low-molecular weight selenium metabolites that can produce methyl selenol\(^{(128)}\).

People differ substantially in their ability to increase selenoprotein activity in response to additional dietary Se\(^{(129)}\). This inter-individual variation may to some extent be accounted for by single nucleotide polymorphisms (SNPs) in selenoprotein genes that determine the efficiency with which individuals can incorporate Se into selenoproteins\(^{(130-132)}\). Selenoprotein synthesis is a complex process requiring multiple factors, many of which are encoded by polymorphic genes, for the successful insertion of Se as SeCys\(^{(133)}\). This results in inter-individual and inter-racial variation in the efficiency with which selenoproteins are expressed.

A notable example is the \((GPx1)\) gene polymorphism at proline/leucine 198 where possession of the leucine-198 allele is associated with an increased risk of bladder cancer\(^{(134)}\) in a Japanese population and of lung cancer in Caucasians but not among ethnic Chinese who do not appear to show this polymorphism\(^{(132)}\). A Danish study found a highly significant correlation between the GPx1 polymorphism and erythrocyte GPx activity such that GPx1 catalytic activity was lowered 5% for each additional copy of the variant leucine-allele (\(P = 0.0003\))\(^{(135)}\).

Furthermore, the activity of GPx-1 derived from the leucine-containing allele was found to be less responsive to increasing Se supplementation than that from the proline-containing allele\(^{(130)}\). Thus requirements for dietary Se for optimal protection against cancer may be higher in individuals carrying particular functional selenoprotein SNPs (reviewed by Rayman\(^{(75)}\)).
Epigenetic inactivation of selenoprotein gene expression may also have the potential to alter Se requirements. For instance, a high frequency of GPx3 promoter hypermethylation and progressive loss of GPx3 expression has been found in Barrett’s adenomacarcinomas and associated lesions\(^{(136)}\). GPx3 biallelic hypermethylation and inactivation increased significantly with progression toward neoplasia. It is currently unknown whether increased Se intake can compensate for such loss of selenoprotein expression though the work of Irons and colleagues\(^{(128)}\) suggests that that may be the case.

**Presence of additional stressors**

A number of factors may increase Se requirements and need to be considered when deciding on optimal intake.

Cigarette smokers have lower plasma Se\(^{(99)}\) presumably because of higher levels of oxidative stress and may therefore require a higher Se intake. Similarly exposure to arsenic, as occurs from drinking water in Bangladesh and Taiwan, may increase the Se requirement since Se can interact with arsenic to reduce its toxicity, possibly by the formation of a Se-arsenic-glutathione conjugate formed in the liver and excreted into bile\(^{(137)}\). It is also postulated that a high mercury intake may limit the availability of Se through strong chemical binding\(^{(41)}\).

Other factors known to be associated with lower Se status that may increase oxidative stress and therefore Se requirements are obesity, occurrence of cardiovascular disease, infection or inflammation\(^{(99,138)}\).

**Potential solutions for increasing Se intake**

If further evidence accrues that a certain level of Se intake or status is optimal for reduced disease risk, appropriate solutions for increasing intake will vary according to whether a public-health or an individual solution is envisaged.

Public-health solutions range from fortification of the food supply, to addition of Se to fertilizers (agronomic fortification), as practiced successfully in Finland since 1984\(^{(11,139)}\), to supplementation of animal feed, which is more effective if the supplement is organic. The latter two solutions have the merit of introducing a biological barrier that protects the target population from the effects of accidental overdose\(^{(140)}\). Genetic biofortification is a more novel solution where food crops are enriched with Se by selecting or breeding crop varieties with enhanced Se-accumulation characteristics\(^{(11)}\). This method may also minimise the need to use Se fertilizers in all but the lowest soil Se situations. It also has the potential for breeding crop varieties with higher
concentrations of specific forms of Se, such as Se-methyl selenocysteine or γ-glutamyl-Se-methyl selenocysteine that can readily be converted to methyl selenol.

Individual solutions may encompass an increased intake of Brazil nuts, offal, fish or shellfish which are good sources of Se\(^{(2)}\) or the increasingly-available and widening-range of functional foods that have been created with market demand in mind. High-Se bread, potatoes, garlic, onions, broccoli, beer, tea and mussels can be sourced through the internet, Se-enriched mushrooms providing a good source of bioavailable Se are now produced in N. Ireland\(^{(141)}\) while Korea has a chain of restaurants selling pork fed with organic selenium “Selenpork”\(^{(142)}\). Se-enriched eggs are produced more than in 25 countries world-wide and enjoy a substantial market share in Russia (Prof Peter Surai, personal communication, 2007). Interestingly, the pork, the mushrooms and the eggs are claimed to have improved shelf-life.

Supplements are a popular way of increasing Se intake for more affluent consumers. Se from selenomethionine was found to be 1.6 times more bioavailable and much more effective in raising plasma Se than was sodium selenite\(^{(92, 119)}\). Se consumed in this way appears to reach its target as shown by significantly increased concentration of Se in prostate tissue in men that consumed Se supplements for up to one month\(^{(143-145)}\). Se-methyl selenocystine is also available as an over-the-counter supplement though there is as yet no published human data on the pharmacokinetics, toxicity, or health benefits of this supplement.

According to Taylor and Greenwald\(^{(146)}\), at- or near-physiologic doses of Se are the appropriate choice in a public-health fortification plan while higher doses might be considered if individual supplementation (or consumption of functional foods) is contemplated.

**Striking a balance**

Though there are clearly individuals and populations that might benefit from a higher level of intake of Se than they currently have, the evidence presented in this review highlights the large number of factors that need to be taken into account before reaching a conclusion on optimal intake.

Furthermore, though full knowledge of all the relevant factors in any particular set of circumstances can never be achieved, advisory bodies are obliged to do their best to make appropriate public-health recommendations. An attempt must be made to balance risks and benefits. While there seems no downside to optimising intake to the RDA/RNI level, is it sensible to increase Se intake to the level apparently required to reduce the risk of prostate cancer if it may simultaneously increase the risk of squamous cell carcinoma or Type-2 diabetes\(^{(81,117,118)}\)? Potential benefits in terms of immune response, cancer risk, thyroid auto-immune disease must be balanced against the potential risks that may be associated with a supra-physiological intake.
It is very important to be aware of background intake in any particular country or region as what may be an appropriate additional intake in one country may well be excessive in another. For instance, in those with a background level of intake that already gives them a plasma Se concentration of ≥ 122 μg/L, cancer risk may potentially be increased with further Se intake\(^{(80)}\). This is a concern in the current SELECT trial where US participants, of mean plasma Se 125 μg/L (as found in NHANES III\(^{(147)}\)) are being supplemented with 200 μg Se/d as the highly-bioavailable selenomethionine. Similarly, high users of multivitamin/multimineral supplements should also be aware that they may place themselves at excess risk by topping up their Se intake with additional single supplements\(^{(148)}\).

With a view to balancing risks and benefits, it would seem sensible to aim just to reach the appropriate threshold level of intake for any particular individual or indeed for a population insofar as it may be judged.

Acknowledgements

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References


13. Rayman et al. companion paper


<table>
<thead>
<tr>
<th>Country</th>
<th>Selenium intake (μg/person/d)</th>
<th>Information source</th>
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<tr>
<td>Australia</td>
<td>57-87</td>
<td>Fardy et al. 1989&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Austria</td>
<td>48</td>
<td>Simma &amp; Pfannhauser 1998&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Belgium</td>
<td>28-61</td>
<td>Robberecht et al. 1994&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Brazil</td>
<td>28-37</td>
<td>Maihara et al. 2004&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>Czech Republic</td>
<td>10-25 (estimate)</td>
<td>Kvicala et al. 1996&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Canada</td>
<td>98-224</td>
<td>Gissel-Nielsen 1998&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>China</td>
<td>7-4990</td>
<td>Combs, 2001&lt;sup&gt;26&lt;/sup&gt;</td>
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<td>Croatia</td>
<td>27</td>
<td>Klapec et al. 1998&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Denmark</td>
<td>38-47</td>
<td>Danish Government Food Agency, 1995&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Egypt</td>
<td>29</td>
<td>Reilly 1996&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>France</td>
<td>29-43</td>
<td>Lamand et al. 1994&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Germany</td>
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<td>Alftan G &amp; Neve J, 1996&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>27-48</td>
<td>Mahalingam et al. 1997&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>104-199</td>
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<td>Nepal</td>
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<td>Moser et al. 1998&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>van Dokkum 1995&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>New Guinea</td>
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<td>Poland</td>
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<td>Reis et al. 1990&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>Saudi Arabia</td>
<td>15</td>
<td>Al-Saleh et al. 1997&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>Serbia</td>
<td>30</td>
<td>Djujic et al. 1995&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Pokom et al. 1998&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>Diaz-Alarcon et al. 1996&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>Sweden</td>
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<td>Swedish Natl Food Admin. 1989; Kumpulainen, 1993&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Kumpulainen, 1993&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>UK</td>
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<td>Venezuela</td>
<td>200-350</td>
<td>Combs &amp; Combs, 1986&lt;sup&gt;a&lt;/sup&gt;</td>
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<sup>a</sup> cited by Combs 2001<sup>26</sup>; <sup>b</sup> cited by Rayman 2004<sup>7</sup>; <sup>c</sup> cited by Surai 2006<sup>27</sup>
<table>
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<th>Condition/effect</th>
<th>Evidence</th>
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<tr>
<td>Mortality (RDA/RNI)</td>
<td>- After adjustment for confounding factors, low plasma Se concentration was significantly associated with higher mortality in the 9-year longitudinal EVA study of 1389 elderly French individuals of mean baseline plasma Se = 87 µg/L(^{(52)}).</td>
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<td>- Cerebral palsy and multiple sclerosis were significantly associated with low plasma Se concentration at baseline (53).</td>
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<td></td>
<td>- Lower toenail Se was significantly associated with lower cognitive score in rural elderly Chinese(^{(55)}).</td>
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<td>Cognitive decline</td>
<td>- After adjustment for various confounding factors, a significantly increased risk of cognitive decline (OR = 1.58; CI 95% = 1.08-2.31) over a four-year period was found in French subjects aged 60 to 70 from the EVA cohort with low plasma Se concentration at baseline(^{(53)}).</td>
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<tr>
<td>(RDA/RNI)</td>
<td>- After controlling for potential confounders, cognitive decline was significantly associated with the magnitude of plasma Se decrease over a nine-year period in the EVA cohort(^{(54)}).</td>
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<td>- Lower toenail Se was significantly associated with lower cognitive score in rural elderly Chinese(^{(55)}).</td>
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<tr>
<td>Immune system (Add. 100-200 µg/d, Europe/US)</td>
<td>- Supplementation with 100 µg Se/d (as Se-enriched yeast) restored the age-related decline in immune response in elderly Belgians(^{(56)}).</td>
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<td>- Supplementation with 200 µg Se/d enhanced the cellular immune response of US healthy volunteers and head-and-neck cancer patients(^{(57,58)}).</td>
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<td>- Se supplementation of UK adults with 100 µg Se/d for 15 weeks in a double-blind study significantly enhanced the cellular immune response(^{(59)}).</td>
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<tr>
<td>Anti-viral effects</td>
<td>- Low Se status increases the risk of developing primary liver cancer in hepatitis B/C positive patients while supplementation of men carrying the hepatitis B surface antigen with 200-500 µg Se/d significantly reduced their</td>
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</tbody>
</table>
- Se supplementation of UK adults with 50 or 100 μg/d sodium selenite for 15 weeks in a double-blind study resulted in faster clearance of attenuated polio virus with fewer mutations in the viral genome\(^{59}\).
- In US patients with relatively-low Se status (plasma Se <85 μg/L), HIV infection progressed more rapidly to AIDS with higher mortality\(^{64,65}\).
- In a RCT in 262 HIV-1-seropositive US men and women, the majority of whom were receiving antiretroviral therapy, selenium supplementation (200 μg as Se-yeast) significantly suppressed the progression of HIV-1 viral burden and indirectly improved CD4 count\(^{67}\).
- In a Tanzanian observational study involving 949 HIV-positive pregnant women, mortality decreased by 5% for every 8 μg/L increase in plasma Se above 85 μg/L (p for trend = 0.01) over a five-year follow up period\(^{68}\).

**Male and female reproduction**

(RNI/RDA/100 μg/d)

- Sub-fertile Scottish men supplemented with 100 μg Se per day for three months had significantly increased sperm motility\(^{69}\).
- Significantly lower serum Se was found in UK women who suffered either first-trimester or recurrent miscarriages compared to women who did not miscarry\(^{70,71}\).
- UK women in the bottom third of Se status were 4.4-times more likely to develop pre-eclampsia than those in the top two-thirds\(^{72}\).

**Anti-cancer effects**

(RDA/RNI-additional 200 μg/d)

- Prospective studies have provided strong evidence for a beneficial effect of Se on risk of lung (meta-analysis\(^{73}\)), oesophageal/gastric-cardia cancers\(^{74}\) and prostate cancer (see review\(^{75}\) and meta-analyses\(^{76,77}\)).
- The risk of recurrence of colorectal adenoma, a pre-cancerous condition, in US subjects with baseline serum/plasma Se in the highest quartile (median 150 μg/L), was significantly lower than in those in the lowest quartile (median 113 μg/L), (OR 0.66; 95% CI 0.50, 0.87)\(^{78}\).
- Supplementation with 200 μg Se/d reduced risk of colorectal adenomas in NPC trial subjects with plasma Se in the
bottom tertile (<105 μg/L) at baseline\textsuperscript{(79)}.

- The Nutritional Prevention of Cancer (NPC) trial showed a significant reduction in cancer mortality and in incidence of total cancer, prostate, colorectal and lung cancers\textsuperscript{(1)} though in follow-up analyses, only total and prostate cancer incidence remained significant\textsuperscript{(80-82)} except in the bottom Se-tertile.

- Chinese trials with Se as Se-yeast (200 μg/d) or sodium selenite (500 μg/d) have shown that Se supplementation significantly reduces the risk of hepatocellular carcinoma (RR 0.50, 95% CI 0.35, 0.71)\textsuperscript{(63)}.

- There is some evidence that Se may affect not only cancer risk but also progression and metastasis\textsuperscript{(75)}.

<table>
<thead>
<tr>
<th>Protection of the thyroid (Additional 200 μg/d, Europe)</th>
<th>Se supplementation decreased inflammation and thyroid autoantibody concentrations in patients with autoimmune thyroiditis\textsuperscript{(83-85)}.</th>
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<tr>
<td>- An inverse association was found between Se status and thyroid volume, thyroid tissue damage and goitre in French women\textsuperscript{(86)}.</td>
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<td>- A positive association was found between the incidence of thyroid cancer and low prediagnostic serum Se concentration in a Norwegian population\textsuperscript{(87,88)}.</td>
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<td>- Se supplementation during pregnancy and the postpartum period with 200 μg/d selenomethionine in an RCT reduced thyroid inflammatory activity and the incidence of permanent hypothyroidism\textsuperscript{(89)}.</td>
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</tr>
</tbody>
</table>

| Coronary heart disease (RDA/RNI) | A meta-analysis of 25 observational studies showed that a 50% increase in Se concentrations was associated with a 24% (95% CI 7%, 38%) reduction in coronary heart disease risk while in six randomized trials, the pooled relative risk in a comparison of supplements containing Se with placebo was 0.89 (0.68, 1.17)\textsuperscript{(90)}. |