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COMPREHENSIVE INVITED REVIEW

Selenium in Human Health and Disease

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Abstract

This review covers current knowledge of selenium in the environment, dietary intakes, metabolism and status, functions in the body, thyroid hormone metabolism, antioxidant defense systems and oxidative metabolism, and the immune system. Selenium toxicity and links between deficiency and Keshan disease and Kashin-Beck disease are described. The relationships between selenium intake/status and various health outcomes, in particular gastrointestinal and prostate cancer, cardiovascular disease, diabetes, and male fertility, are reviewed, and recent developments in genetics of selenoproteins are outlined. The rationale behind current dietary reference intakes of selenium is explained, and examples of differences between countries and/or expert bodies are given. Throughout the review, gaps in knowledge and research requirements are identified. More research is needed to improve our understanding of selenium metabolism and requirements for optimal health. Functions of the majority of the selenoproteins await characterization, the mechanism of absorption has yet to be identified, measures of status need to be developed, and effects of genotype on metabolism require further investigation. The relationships between selenium intake/status and health, or risk of disease, are complex but require elucidation to inform clinical practice, to refine dietary recommendations, and to develop effective public health policies. *Antioxid. Redox Signal.* 14, 1337–1383.

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I. Introduction

In the last century, interest in selenium and health was focused primarily on the potentially toxic effects of high intakes in humans, stimulated by reports of alkali disease in livestock raised in seleniferous areas (341). The essentiality of selenium was demonstrated in the mid-1950s (326), when rats fed a highly purified casein diet developed a fatal liver disease, which was prevented by certain foods, including brewer's yeast; selenium was identified as the active ingredient (327).

In recent years, there has been growing interest in selenium in relation to Keshan disease (an endemic cardiomyopathy) and also possible protective effects against cancer and other chronic diseases. In a large-scale supplementation trial, selenium had an anticarcinogenic effect (86), and although investigations into the protective role of selenium had been undertaken for many years before this, both in animals and case–control studies in humans, the results were difficult to interpret because neoplastic tissue sequesters selenium (311 cited in 402), and therefore the impact of selenium status on the initiation and progression of various cancers could not be evaluated.

There is a relatively narrow margin between selenium intakes that result in deficiency or toxicity, with health effects being related to level of exposure and selenium status. Further, the species of selenium is another determinant of its health effect. This review covers the functions of selenium, absorption and metabolism, dietary intakes and recommendations, clinical deficiency disorders and toxicity, the effects of environmental factors and genotype on selenium status, and the relationship between selenium and health outcomes, including cardiovascular disease (CVD), cancer, diabetes, inflammatory disorders, and male fertility.

II. Selenium in the Environment

A. Soil selenium

Globally, total soil selenium concentrations typically lie within the range 0.01–2.0 mg/kg with an overall mean of 0.4 mg/kg (130). Much greater concentrations (up to 1200 mg/kg) are found in soils derived from seleniferous parent materials, including shales, sandstones, limestones, slate, and coal series (130, 191). Seleniferous soils are widespread in parts of the United States, Canada, South America, China, and Russia. Although parent geology is the primary long-term determinant of selenium in soils, significant inputs of selenium to soils occur following deposition of selenium from natural (volcanoes, sea spray, volatilization/recycling *via* biotic cycling) and anthropogenic (*e.g.*, fossil fuel combustion, sewage, and agricultural inputs such as fertilizers and lime) sources (64, 191). Annually, fluxes of selenium to soils from anthropogenic activities are greater than those from

all natural sources combined. The effect can be seen in long-term agricultural experiments, where fossil fuel combustion practices correlate with selenium deposition to crops and soils (157).

Crop selenium uptake is influenced greatly by the availability and chemical species of selenium in soils. Inorganic selenium occurs in three soil-phases—fixed, adsorbed, and soluble—and only adsorbed/soluble forms of selenium are thought to be available for plant uptake. In addition, availability of selenate (+6 oxidation state) and selenite (+4) forms to plants varies markedly, with selenate taken up much more rapidly than selenite under most soil conditions. Until recently, it was possible to quantify selenium species in different soil phases only from soils with high adsorbed/soluble selenium loads (50–9000 μg soluble selenium per kg soil) using Hydride Generation Atomic Absorption Spectroscopy techniques (351). However, anion-exchange liquid chromatography (LC) coupled to inductively coupled plasma mass spectrometry (ICP-MS) have enabled selenium species to be quantified in soils of low selenium concentrations (<20 μg soluble selenium per kg soil) (351). In UK soils of low selenium status, adsorbed/soluble selenium concentrations are generally two orders of magnitude lower than total soil selenium, and consist primarily of selenite and organic selenium forms (351).

B. Food sources and selenium species

The amount of selenium in the diet largely depends on where crops are grown and cultivated, the soil/fodder to which animals are exposed, and the actual foods consumed. The effect of selenium species on bioavailability has been reviewed recently (117) and data on the selenium content of foods are available (117, 135, 302, 372). The main food groups providing selenium in the diet are bread and cereals, meat, fish, eggs, and milk/dairy products (Fig. 1). Some Brazil nuts are a particularly rich source, with selenium concentrations ranging from ~0.03–512 mg/kg fresh weight (302).

1. Bread and cereals. The selenium content of bread and cereals can vary widely from ~0.01–30 mg/kg (302). On average, bread and cereals provide a quarter of the selenium intake in the UK (Fig. 1). The predominant species of selenium in wheat and bread are selenomethionine (usually ~55%–85%), selenocysteine (~4%–12%), and selenate/ite (~12%–19%) (400, 405).

2. Meat, fish, and eggs. The selenium content of meat depends on many factors. Offal contains relatively high levels of selenium, in particular liver and kidneys; the selenium concentrations of kidney, liver, and heart tissue from beef were 4.5, 0.93, and 0.55 mg/kg, respectively, whereas muscle was in the region of 0.2 mg/kg (193). Supplementation of cattle with selenium-enriched yeast increased muscle selenium concentration to ~0.6 mg/kg (193). In the United States, the average selenium content of chicken is ~0.2 mg/kg and beef ~0.25–0.3 mg/kg (372). Meat generally provides a relatively large proportion of the selenium intake in omnivorous populations, and in the UK, it provides one quarter of the total estimated intake (Fig. 1). The predominant species of selenium in edible portions of meat may be selenomethionine (~50%–60% of total extractable selenium species) and selenocysteine (20%–31% and ~50% of total extractable selenium species in chicken and lamb, respectively) (47). However, the total content and species depends mainly on the animals' diet.

The selenium content in fish is between 0.1 and ~5.0 mg/kg (117, 302, 310); some marine fish are relatively high in selenium; for example, the selenium content of cod, shark, and canned tuna is ~1.5, 2.0, and 5.6 mg/kg, respectively (117, 310). In the UK, the average selenium content of fish is ~0.42 mg/kg (136). The main selenium species in fish are selenomethionine (29%–70%) and selenite/selenate (12%–45%) (77, 117, 302) with the species profile differing between fish species and the total selenium content.

Hens' eggs contain from ~3 to ~25 μg selenium per whole egg (224). Selenium supplementation of the hen's diet may increase the selenium content of eggs to 0.34–0.58 mg/kg

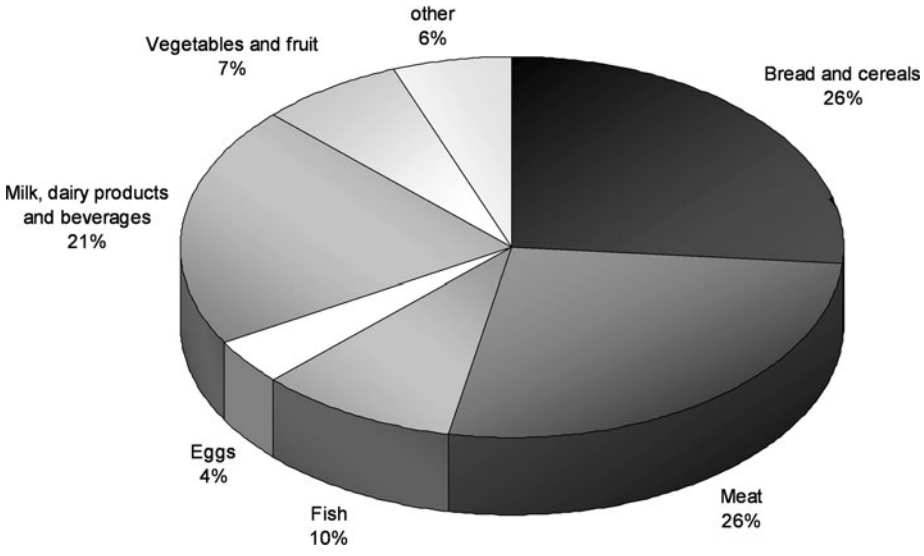

FIG. 1. Contribution of each food group to total population dietary exposure in the UK. Adapted from data presented in the UK Food Standards Agency document (136).

(232); selenium-enriched eggs are widely produced around the world (125). The main selenium species in eggs are selenocysteine, selenomethionine, and possibly selenite, with selenomethionine and selenocysteine as the predominant species (>50%) in egg white and egg yolk, respectively (224).

3. Milk, dairy products, and beverages. The selenium content of milk and dairy products varies widely; in the UK, milk and dairy products contain ~0.01–0.03 mg/kg selenium. The predominant selenium species in cows' milk are selenocysteine and selenite (256). Supplementation of dairy cows with selenium-enriched yeast alters the species profile in the milk and the major species after supplementation are selenocysteine, selenomethionine, and selenite (256).

4. Fruit and vegetables. Fruit and vegetables typically contain relatively small amounts of selenium. In unenriched vegetables with low levels of selenium, the major species may be, for example, selenate in onions (207) or selenomethionine (53%), γ-glutamyl-Se-methylselenocysteine (31%), Se-methylselenocysteine (12%), and selenate (4%) in garlic with natural selenium content of <0.5 mg/kg (207). However, certain vegetables, such as onions, garlic, and broccoli when grown on selenium-rich soil can accumulate selenium, resulting in selenium-enrichment from <0.5 mg/kg up to 140–300 mg/kg. The main selenium species in Se-enriched food such as onions is γ-glutamyl-Se-methylselenocysteine, accounting for ~63% of the species, with a relatively smaller proportion of ~10% selenate and 5% selenomethionine, plus other species (174, 207). In Se-enriched garlic, similar to Se-onions, γ-glutamyl-Se-methylselenocysteine may be the predominant species (~73%) with also ~13% selenomethionine, 4% γ-glutamyl-selenomethionine, 3% Se-methylselenocysteine, and 2% selenate (181). Selenium-enriched broccoli sprouts may contain predominantly Se-methylselenocysteine (~45%) with smaller amounts (~12%–20%) of selenate and selenomethionine, plus other species of selenium (*e.g.*, adenosylselenohomocysteine) (124). In summary, in vegetables such as broccoli, onions, and garlic the selenium species profile is variable depending on the total level of selenium enrichment, the forms of selenium used for enrichment, and the type of vegetable; predominant species in selenium-enriched vegetables analyzed to date are Se-methylselenocysteine or γ-glutamyl-Se-methylselenocysteine; these forms of selenium in foods have received attention due to purported protection against cancer in animal models when compared with other forms of selenium (123, 183).

5. Selenium-enriched foods. The only permitted species of selenium added to foods for particular nutritional use in Europe, including baby formula milk and total parental nutrition foods, are sodium selenate, sodium selenite, and sodium hydrogen selenite (127), whereas the predominant selenium species in most natural and unenriched foods is selenomethionine (Fig. 2). Selenium-enrichment through fertilization or feeding supplements to animals changes the selenium species profile in some foods, for example, eggs, onions, garlic, and broccoli (124, 183, 207, 224), but wheat and meat tend to retain the predominant selenium species as selenomethionine (47, 405). The selenium speciation of foods and the effect of processing and cooking on the species profile is a priority for future research.

C. Selenium intake

1. Dietary surveys. The contribution to selenium intake from drinking water (130) and air is insignificant, except for individuals working in industries with an occupational exposure risk (*e.g.*, metal recovery and paint production). Dietary selenium intakes can be estimated from dietary surveys, food composition tables, market basket type surveys, and/or composite dietary analyses. There are inherent uncertainties in using all of these data, since dietary surveys are prone to misreporting, and robust primary data on the selenium concentration of different foodstuffs are often lacking or below

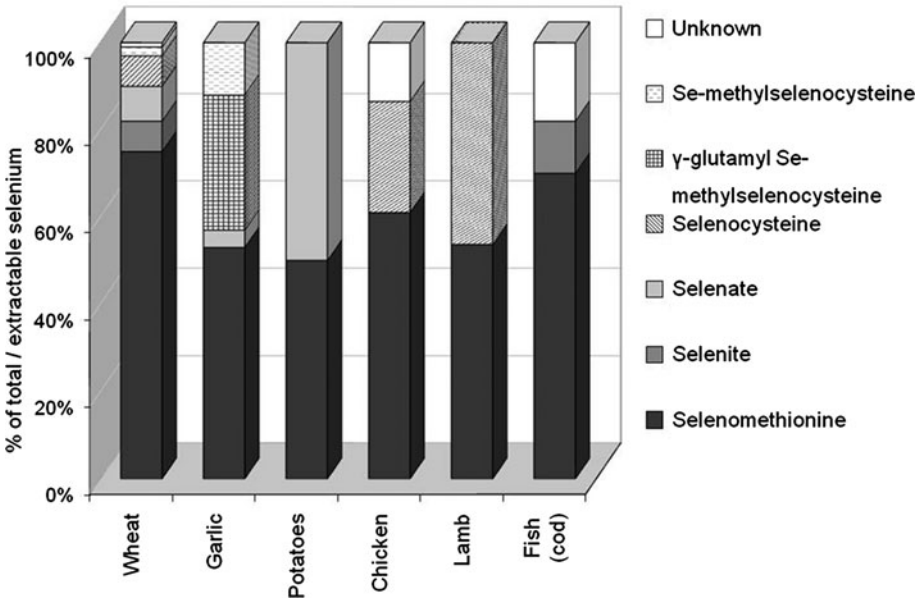

FIG. 2. Species of selenium in natural un-enriched foods, % contribution of each type of selenium to total/extractable selenium. This figure was produced from data presented in references (47, 117, 207, 302, 400, 405) with the percentage of total/extractable selenium species presented for natural un-enriched foods with typical selenium contents (fresh weight) for wheat, 0.1–30 mg/kg; garlic, <0.5 mg/kg; potatoes, 0.12 mg/kg; chicken, 0.5 mg/kg; lamb, 0.4 mg/kg; fish (cod), 1.5 mg/kg.

technical limits of detection and/or quantification. For example, in the UK, the most recent published dietary survey reporting mineral intakes is the National Diet and Nutrition Survey (NDNS) (158, 165). However, under-reporting is ~25% (307), and there can be over-reporting of foods perceived to be healthy, for example, cereals and vegetables (275, 385). Food composition tables may lack robust selenium concentration data for many food groups. For example, the Sixth Summary Edition of McCance and Widdowson's The Composition of Foods contains mineral concentration data for up to 3423 types of food and drink products (135). Of these, selenium data are not reported for 1161 products, "trace" or zero selenium is reported for 467 products, and the selenium contents of a further 470 products are estimates. Among the 1325 products for which selenium concentration data are reported, 241 products have the lowest reported selenium concentration of 1 μg/100 g, which may introduce rounding errors. In the UK's 2006 Total Diet Survey, a market basket survey of 24 UK towns reported selenium concentration data above the limit of quantification for only 7 out of 20 food groups (136). However, subject to these caveats, it is still possible to provide estimates of selenium intake, and even target-specific food groups, by integrating dietary survey data with food composition data (62).

2. Global variation in selenium intake. Individual dietary selenium intakes across the world are estimated to range from 3 to 7000 μg/day (130, 297, 300, 410). The highest levels of intake have been recorded in seleniferous regions of China [>4990 μg/day (422)] and Venezuela (130, 298, 299). For European countries where estimates are available, mean intakes are typically <50 μg/day per person (298, 299), which is close to or below the recommended nutrient intake level (127, 300). In regions of relatively high selenium intake in India, intakes were estimated to be 475 μg/day for women and 632 μg/day for men, with >80% of the selenium intake provided by consumption of cereals grown in high selenium soil in the local region (164). For large areas of the world (*e.g.*, Africa and many parts of Asia and Latin America), dietary selenium intake estimates are unavailable. Examples of selenium intakes across the world are shown in Figure 3.

With respect to selenium intake from habitual diet, the UK is one of the countries with the lowest estimated selenium intake (Fig. 3). The mean selenium intake from food sources for men and women (aged 19–64) were 55 and 43 μg/day, respectively. In comparison, intakes in the United States are much higher: the mean intake from food in the United States was 133.5 ± 2.42 μg/day for men and 92.6 ± 1.57 μg/day for women (370). There is a very wide variation in selenium

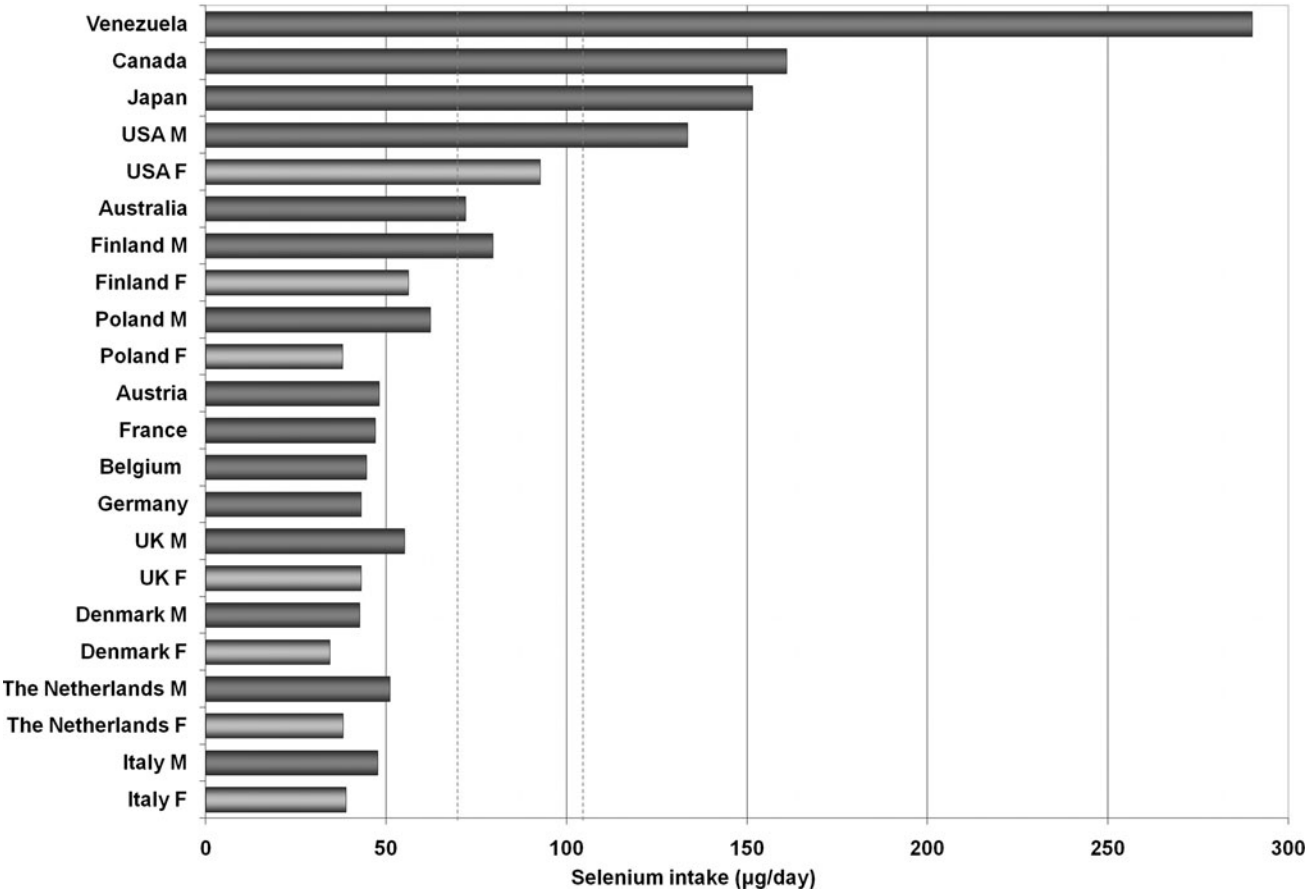

FIG. 3. Global variation in selenium intake. Data shown in Figure 3 were compiled from selenium intake data presented in references (127, 137, 300, 370). Data are presented for the intakes for males (M) and females (F) where available, with the latter shown in a lighter shade. The dotted lines represent the intake required to reach maximal plasma GPx3 and selenoprotein P expression, at ~70 and ~105 μg/day (174, 365).

intake around the world, and when undertaking risk–benefit analysis, an important task due to the narrow safe range of selenium, it is also important to take the use of dietary supplements into account.

3. Selenium intake from dietary supplements. There are many different formulations of supplements available worldwide with varying doses and species of selenium, and selenium is often included in multivitamin/mineral supplements. The selenium content of supplements analyzed in the United States indicates that they provide between 10 and 200 μg/day (371). Dietary supplement use in the United States and Europe is common, with over 50% of the population surveyed in the United States regularly consuming dietary supplements (289). In the UK, 35% of adults (27% of men and 41% of women) reported taking supplements, predominantly fish oils and multivitamins/minerals (137), some containing selenium. Denmark and Finland report 32%–60% use of supplements, and in Poland and Spain 8%–11% of men and 10%–18% of women consume dietary supplements (127). A recent evaluation and comparison of national intake survey data from several countries in Europe, comparing intake from supplements and habitual diet, estimated that the contribution from dietary supplements was between 6% and 45% of the total estimated selenium intake for adult men and women, with country-specific differences (127). In Finland, where selenium fertilizers are mandatory, the mean estimated selenium intake from the habitual diet for men and women is 79.5 and 56.1 μg/day, respectively. Consumption of dietary supplements by 32% of men and 58% of women was calculated to provide an extra 5.3 μg/day for men and 10.5 μg/day for women (127).

The contribution of selenium-containing supplements is likely to provide an average additional intake of 5–30 μg/day, but obviously this will vary widely depending on habitual diet and the content/formulation of the supplement. Also, the absorption and metabolism of selenium depends on the selenium species in the supplement as well as the dose/amount consumed and selenium status of the individual. A substantial proportion of supplements available contain one species of selenium (mainly in multivitamin/mineral supplements), as selenomethionine, Se-methylselenocysteine, selenite, or selenate. However, selenium-enriched yeast is a complex mixture of several different species of selenium and usually contains more than four different species, including $\sim$ 23%–84% selenomethionine, 3%–21% selenocysteine, 1%–20% Se-methylselenocysteine/γ-glutamyl Se-methylselenocysteine, 0.5%–5% Se-adenosyl-selenohomocysteine, $\sim$ 4% selenate, plus other selenium species that may vary according to the media and growth conditions of the selenium-enriched yeast (302, 400).

III. Selenium Absorption and Metabolism

There is limited knowledge about the biochemical interconversions involved in the metabolism of the different selenium species in mammals, and information concerning tissue specificity of pathways remains scant. The absorption of selenium for assimilation and excretion through these pathways potentially involves multiple membrane transport mechanisms, but it is a topic that has received little attention to date.

A. Absorption of dietary selenium

The identity of the transporter proteins responsible for the absorption of dietary selenium remains uncertain. Membrane transport proteins with the capacity to mediate uptake of organic forms of selenium have been identified on the basis of quantification of the total selenium content of *Xenopus laevis* oocytes expressing individual transporters (from injected *in vitro*-transcribed mRNA) and provided with different test substrates. These studies revealed that the selenoamino acids selenomethionine, methylselenocysteine, and selenocysteine, but not the seleonoderivatives selenobetaine or selenocystamine, are transported effectively by a suite of intestinal (and renal) amino acids transporters, in particular by the B^0 and b^{0+}rBAT systems (263). The SLC26 multifunctional anion exchanger family are good candidates for intestinal selenate transport, based on published observations concerning inhibition of selenate transport in various experimental epithelial systems by the SLC26 inhibitor, 4,4′-diisothiocyano-2,2′-disulfonic acid stilbene (DIDS), and by substrates including sulfate and oxalate (336, 406). This view is substantiated by unpublished data demonstrating expression of several SLC26 family members in human intestine and in the intestinal cell line Caco-2 and inhibition by selenate of sulfate uptake by Caco-2 cells (Dianne Ford, pers. comm.).

B. The biochemical interconversion of selenium species

Assimilation of dietary selenium into selenoproteins occurs through a series of interconversions about which many details are still lacking. An overview of the metabolic pathways is given in Figure 4. For clarity, selenide (H_2Se) is considered as a central point in the metabolic interconversions of both organic and inorganic selenium compounds. Dietary selenomethionine is converted to selenocysteine (also obtained directly from the diet, as is Se-methylselenocysteine) *via* the intermediate selenocystathionine through the action of cystathionine β-synthase and then cystathionine γ-lyase (97, 267). Selenomethionine released through protein catabolic processes enters the process of metabolic interconversion in the same way and, unlike selenocysteine, is incorporated nonspecifically in place of methionine into proteins, depending on availability. Selenocysteine β-lyase releases selenide (H_2Se) from selenocysteine (97, 267); an alternative route for the release of selenide from selenomethionine may be through the action of gut bacterial methionase (97). Dietary Se-methylselenocysteine can be converted to methylselenol (CH_3SeH) in a cystathione γ-lyase-catalysed reaction (287), which can in turn be demethylated to produce selenide (356). Selenite can be reduced to selenide directly through the action of thioredoxin reductase (TXNRD, itself a selenoprotein) plus thioredoxin (229) or it can react with glutathione to form selenodiglutathione (229). Selenodiglutathione is a substrate for reduction to glutathioselenol by glutathione reductase (229); glutathioselenol then reacts with glutathione to yield selenide (229). Selenate is, presumably, assimilated into proteins through reduction to selenide *via* the same pathways; however, the mechanism for reduction of selenate to selenite remains unclear but may involve the activity of TXNRD in the presence of glutathione and thioredoxin (229). Further steps in the assimilation of selenide into selenoproteins involve generation of the highly reactive selenium donor selenophosphate through the activity

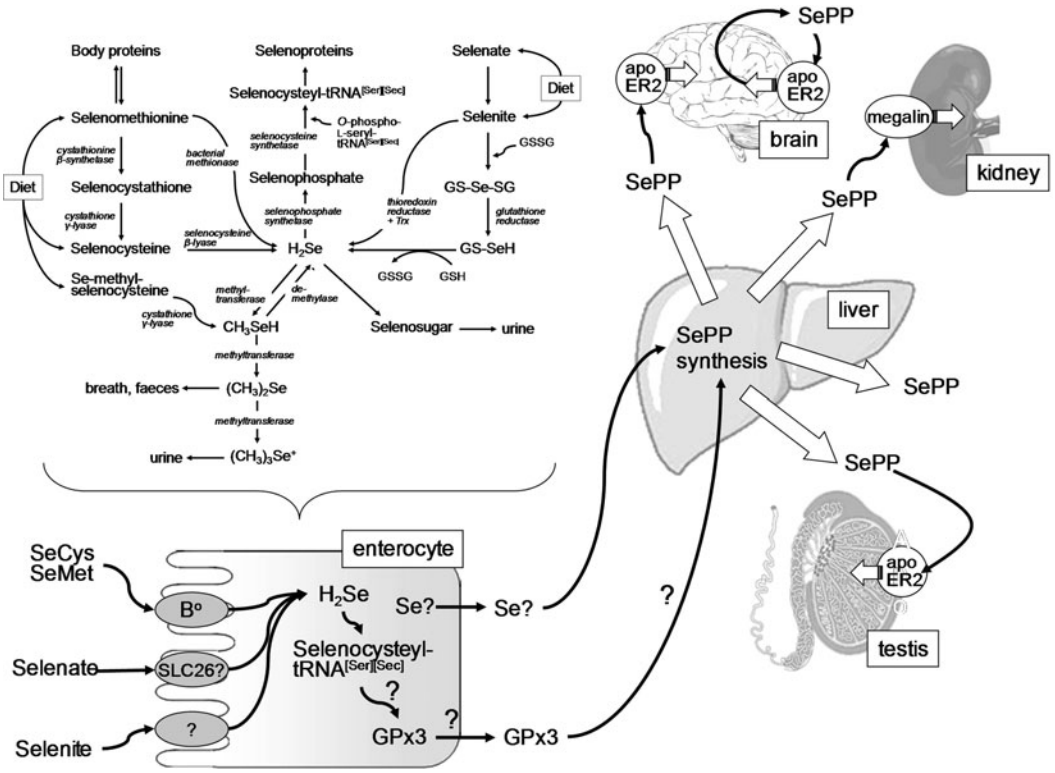

FIG. 4. A scheme for selenium absorption, metabolism, and distribution. Tissues/cells represented are the enterocyte, liver, kidney, brain, and testis, as labeled. The metabolic interconversions of selenium compounds shown may include ubiquitous reactions; other reactions may be specific to particular tissues. The scheme serves to show the details of the pathways through which selenium obtained as dietary selenocysteine, selenomethionine, Se-methylselenocysteine, selenite, and selenite, absorbed from the intestinal lumen potentially involving transport proteins as indicated, are converted to selenide (H_2Se), and how this intermediate is incorporated into selenoproteins as selenocysteine. Enzymes catalyzing the various steps are shown in italics. Major routes of excretion for selenosugar and the methylated metabolites (breath, feces, and urine) are indicated. For full details, refer to the text. Incorporation of absorbed dietary selenium into secreted GPx3 is proposed as a pathway through which dietary selenium may enter the portal circulation, to reach the liver for incorporation into SePP. Other, unidentified mechanisms may also/alternatively transport dietary selenium to the liver. Uptake of SePP by the testis, brain, and kidney *via* the apoER2 receptor and megalin is indicated. Other mechanisms for delivery of selenium carried as SePP to tissues are unknown. Local synthesis, release, and reuptake of SePP by the brain (SePP cycle; important under selenium-depleted conditions) is indicated. B^0, amino acid transport system B^0; GPx3, glutathione peroxidase 3; GS-Se-GS, selenodiglutathione; GS-SeH, glutathioselenol; GSSG, glutathione disulfide; SeCys, selenocysteine; SeMet, selenomethionine; SePP, selenoprotein P.

of selenophosphate synthetase (360) and then incorporation of selenium into selenocysteyl-tRNA $^{[Ser][Sec]}$ through conversion of *O*-phospho-L-seryl-tRNA$^{[Ser][Sec]}$ (141). Selenide is also the intermediate metabolite for selenium excretion; at lower levels of intake it is incorporated into selenosugar for excretion in urine, and at higher levels of intake methyltransferases add methyl groups sequentially to convert selenide to methylselenol then dimethylselenide, which is excreted in the breath and in the feces, then trimethylselonium, which is excreted in the urine (210, 267).

C. Systemic transport of selenium

Plasma selenoprotein P (SePP) is the major circulating transport form of selenium, accounting for the majority of selenium in plasma [up to 60% (162)], and is responsive to changes in level of dietary exposure (99, 174, 414). In humans, full-length SePP is a glycosylated protein of 366 amino acids. Approximately two-thirds of the molecule (amino acid residues 1–244) is folded into an N-terminal domain that includes one selenocysteine residue, whereas the smaller C-terminal domain includes nine selenocysteines, providing the selenium transport capacity (67). Thiol-redox function has been attributed to the N-terminal domain, based on the presence of a thioredoxin fold and on measured functional properties (314, 359). Truncated isoforms of SePP have been described (67) and in humans two major forms resolve as proteins with different molecular mass ($\sim$50 and $\sim$60 kDa) on SDS-PAGE. The relative ratio of the two isoforms has been reported to be influenced by genotype with respect to two single nucleotide polymorphisms (SNPs) in the SePP gene, the effect of which was abrogated under conditions of selenium supplementation (243). SePP synthesis is reduced under conditions of dietary selenium deficiency and plasma concentrations fall (67).

The phenotypic features of SePP knockout mice are consistent with a role in systemic selenium transport. These features include reduced body selenium content and reduced concentration in some tissues, with accompanying changes in

the activity of selenoproteins (163, 325). A noteable exception is the thyroid gland, for which mechanisms for prioritization of selenium supply (see section V.A.2) appear to include SePP-independent supply of selenium (323). Although SePP is expressed in most tissues, the current model is that SePP synthesis in the liver incorporates selenium into SePP for distribution to other tissues (306). Local SePP biosynthesis appears to be important in protecting the brain against selenium loss under selenium-deficient conditions (328).

Uptake of SePP from the plasma into tissues, including testis, kidney, and brain, is emerging as a receptor-mediated process. For example, mouse Sertoli cells were observed by immunohistochemistry to contain *SePP1*-positive vesicles, and apolipoprotein E receptor-2 (apoER2) was found to be associated with SePP in preparations of mouse testis (273). Another member of the lipoprotein receptor family—megalin (Lrp2)—is believed to mediate SePP uptake from the glomerular filtrate in the kidney (271).

In summary, the form in which absorbed dietary selenium enters the portal circulation appears to have received little attention, and is likely to vary depending on the dietary source (*e.g.*, organic or inorganic). The scheme proposed for the absorption and metabolic interconversion of selenium compounds (Fig. 4) reveals multiple potential points of interaction with other molecules and/or processes that may lead to influences of selenium on health and disease and so provide important targets for future research. Membrane transport proteins that are involved in the absorption of dietary selenium should be identified, and potential interactions with dietary components and oral pharmaceuticals investigated to aid the development of dietary recommendations and health policy. Establishing the extent to which specific metabolic interconversions of selenium compounds are tissue- or organ-specific, or ubiquitous, will provide a more detailed model for selenium handling on a whole-body level, including identification of the molecular forms in which selenium is transported between the tissues; the view that SePP produced in the liver is the major circulating from of selenium is substantiated by robust evidence, but it is likely that other selenoproteins, or other forms of selenium, are also important transported forms, perhaps with some element of tissue specificity with respect to production and uptake. Notable in this context is the form in which selenium leaves the intestinal enterocyte and in which it is presented to the liver, ultimately for incorporation into SePP. While receptor-mediated endocytosis, involving specific receptor molecules, is emerging as the mechanism for uptake of SePP in specific tissues, the mechanisms involved in delivery of selenium to the tissues in general remains unknown. A good understanding of selenium metabolism and transport on a whole-body level is essential if research aimed to establish the relationships between selenium, health, and disease is to be optimally targeted, so these gaps in knowledge should be addressed as a matter of priority.

IV. Selenium Status

A. Measurement of status

Methods to assess the selenium status of populations have been reviewed extensively (23, 130, 191). In some situations, the overall selenium status of large populations can be predicted by examining the chemical composition of the terrestrial environment, in particular soil selenium content, and by analyzing the selenium composition of generic foodstuffs and dietary habits. At an individual level, selenium status can be assessed from hair, toenail, and urinary analysis, or more directly by assaying the selenium concentration of blood (whole blood, plasma, serum, or erythrocyte/platelet fractions), and bioassays of selenoproteins in different blood fractions may provide more accurate estimates of functional/physiological selenium status.

The analysis of selenium in hair and toenails is useful as a long-term biomarker (23). As both tissues are easy to access and are noninvasive, they are also suitable for fieldwork, but samples must be prepared with care to avoid contamination. For example, hair samples can be affected by selenium-containing shampoo residues. Wide variation in hair selenium concentration has been reported in populations of contrasting selenium status in China (<0.1 to >100 mg/kg hair) (130), but positive correlations have been found between selenium status and toenail selenium concentrations (316). Urinary selenium excretion can also be used to determine absorption in bioavailability studies, or to assess compliance in intervention studies and is a useful responsive biomarker (23).

Plasma or serum selenium is one of the most commonly used biomarkers of selenium status, and in a meta-analysis of 14 studies plasma selenium responded to selenium-supplementation or selenium-depletion across all subgroups (23). Plasma selenium is relatively easy to obtain provided trace element-free collection tubes are available. Whole blood selenium also responds significantly to supplementation and is therefore also a useful biomarker. However, there are only a limited number of studies reporting whole blood selenium, so the interindividual heterogeneity is unclear and the length of time needed to incorporate selenium into red blood cells renders it less responsive than plasma to changes in selenium intake. It is possible to assess the selenium concentration of erythrocytes and platelets although samples require almost immediate processing. Since much of the selenium in red blood cells is associated with hemoglobin (144), erythrocyte selenium is again less responsive than plasma selenium.

Although serum/plasma selenium is a useful measure of selenium status and short-term responses to changes in intake, it is not ideal for assessing selenium status in populations due to the high level of interindividual heterogeneity (23). Serum/plasma selenium is also affected by confounding factors, including smoking, alcoholism, and some disease states. For example, HIV/AIDS appears to lower plasma selenium levels (9, 105). There is also an apparent decline in plasma selenium in the elderly in certain populations (92, 269, 380), which may occur independently of intake, and one study suggested that the bioavailability of selenium is influenced by aging (269). In addition, there is a large effect of dietary selenium species on plasma selenium concentrations. For example, organic species of selenium are readily incorporated into plasma albumin unlike inorganic species (68, 262).

Expression of individual selenoproteins may be useful measures of selenium status (23, 174, 281). There are a total of 25 human genes that express selenoproteins (211); quantification of a combination of the selenoproteins may be needed to measure selenium status (111). The most commonly used group of selenoproteins are the glutathione peroxidases; GPx1, GPx3, and GPx4. GPx activities in plasma, erythrocytes, and platelets generally respond to supplementation only in

selenium-deficient populations since plasma GPx3 activity normally plateaus with intakes $\geq$65 μg/day. The selenium intake required to achieve maximal activity of plasma GPx activity has been used to set dietary reference intake (DRI) values in the United States (274) (section XI). Plasma SePP responds in a dose-dependent way to selenium supplementation (23, 99, 162, 174, 253, 414) and may be a more sensitive selenium status biomarker over a wider range of intake/status than some other markers, for example, platelet GPx1 or GPx3 (174, 414); SePP concentration may reach a maximum at a plasma selenium concentration in the region of 125 ng/ml (to convert to μM divide by 78.96) and an intake $\sim$100 μg/day (174).

B. Global variation in status

As with global estimates of selenium intake, there is very wide geographical variation in plasma and serum selenium concentrations (87, 130, 297, 377, 410). In areas of China in which Keshan Disease and Kashin-Beck Disease (an endemic, chronic, degenerative osteoarthropathy—see section VI.A) are prevalent, serum selenium concentrations as low as $\sim$12–20 ng/ml have been reported, whereas in seleniferous regions of the United States, serum selenium can rise to 200 ng/ml (410). For healthy adults, the proposed reference range is 39.5–197.4 ng/ml (410). However, this range carries considerable uncertainties with regard to sufficiency since maximal plasma GPx activity occurs at plasma selenium concentrations $\sim$70–90 ng/ml (262, 365), and maximal SePP activity occurs at a plasma selenium concentration $\sim$120 ng/ml (174). Fordyce reports a more conservative normal range of serum selenium of 60–105 ng/ml (130). In a review of 65 studies published between 1995 and 2003, serum or plasma selenium concentrations in European healthy adults ranged from 50.22 to 145.29 ng/ml but with the skewed range, most fell below the mean selenium concentration of 78.96 ng/ml (1.00 μM) (377).

C. Changes in selenium status in relation to environmental factors

Case studies from New Zealand, China, Finland, and the UK clearly demonstrate a link between supply of selenium in the soil-to-crop pathway and changes in selenium intake and status among populations. In New Zealand, increased selenium intakes correlated with imports of Australian wheat that contain higher levels of selenium (366, 368, 395). In China, a detailed geochemical analysis of areas with high incidence of Keshan disease in the late 1990s showed that total soil selenium was not inversely correlated with Keshan disease incidence, as expected, but Keshan disease incidence was, however, inversely correlated with water soluble soil selenium [reviewed by Johnson *et al.* (191)].

In Finland, the link between the supply of selenium in the soil-to-crop pathway and changes in selenium intake and status among populations has been demonstrated [reviewed by Broadley *et al.* (64)]. In 1983, legislation was introduced to incorporate selenium into all multinutrient fertilizers (20, 114–116, 297, 378, 379). The policy aimed to produce a 10-fold selenium-enrichment of cereal grains (379). Multinutrient fertilizer formulations were altered to include 16 mg selenium/kg fertilizer for arable and horticultural crops and 6 mg selenium/kg fertilizer for fodder crop and hay production. Initially, crop selenium concentrations increased by more than 10-fold and a single level of supplementation of 6 mg selenium/kg fertilizer commenced in June 1990 (379). In 1998, selenium supplementation was increased to 10 mg selenium/kg fertilizer for all crops (64).

Selenium fertilizers in Finland increased crop selenium content, dietary intakes, and the selenium status of the Finnish population (64, 116, 297). The selenium concentration of wheat bran increased 10-fold and fruit and vegetable crops 10-to-100-fold (114); pig muscle meat and liver increased from 0.08 and 0.49 mg/kg, respectively, in 1985 to a peak of 0.30 and 0.73 mg/kg in 1989 (379). Average selenium intakes rose from 25 μg/day in 1975/1976 to 124 μg/day in 1989 (116). Between 1975/6 and 1989, intake of selenium from cereals increased from 9 to 30 μg/day, from fruit and vegetables from 0.4 to 4 μg/day, and more modest (<10-fold) increases were reported in meat, fish, dairy products, and eggs (116). Increases in blood (378) and serum (392) selenium concentrations were also reported, including a study of Finnish children (<15 years), whose serum selenium increased from a mean of 69 ng/ml (range: 43–114 ng/ml) in 1985 to 100 ng/ml (range: 76–124 ng/ml) in 1986 (392). In adults, serum selenium increased from 82 ng/ml (range: 49–107 ng/ml) in 1985 to 103 (range: 69–136 ng/ml) in 1986.

In the UK, there is also evidence to support an environmental link between selenium supply and selenium status, although more subtle than in Finland. Selenium intake is relatively low, $\sim$50–60 μg per day, and some populations may not be consuming sufficient selenium for optimal plasma GPx3 activity or optimal SePP concentration [$\sim$100 μg/day (174)]. The evidence for a decline in selenium intake in the UK since the 1970–80s shows that in 1974 and 1985 estimates of selenium intake were $\sim$60 μg/day, but by 1991, estimated intakes of 24–31 to 60 μg/day per person were reported (136, 248). In studies from 1994, 1995, 1997, and 2000, selenium intakes ranged from 29 to 43 μg/day, but in 2006 an increase to 48–58 μg/day per person was reported, with the caveat that there are analytical uncertainties for 13 out of 20 food groups analyzed for selenium (136).

There are several reasons for the apparent decline in selenium intake and status in the UK over the last 30 years (2, 49, 163, 252). Cereals, and especially wheat, comprise $\sim$30% of the energy intake of the average UK diet (137) and the single largest dietary change affecting selenium intake and status is likely to be a reduction in consumption of imported milling wheat containing higher levels of selenium in the grain, and increased consumption of UK-grown wheat containing low levels of grain selenium. In 1970 > 5 Mt of wheat was imported into the UK, mostly used for milling and human consumption (Fig. 5A) (120). Of this, 2.2 Mt came from the United States and Canada (235). Since 1990, wheat imports to UK have averaged 1.2 Mt/year (range 0.73–1.67 Mt). In 2005, of the 1.35 Mt/year imported to UK, 0.37 Mt was imported from Canada and 0.10 Mt from the United States (Fig. 5B), and by the 2007/08 season, 82% of wheat for human consumption was reportedly being grown in the UK (64). The primary reason for the decline in imports was the widespread adoption of the Chorleywood Bread Process in the early 1960s, which enabled UK (and other European Union, EU)-grown milling wheat to replace higher protein content North American–grown wheat in bread production. Subsequently, the UK became a member of European Economic Community (EEC) in 1973, which introduced EU import tariffs and led to a rapid decline in non-EU sourced wheat.

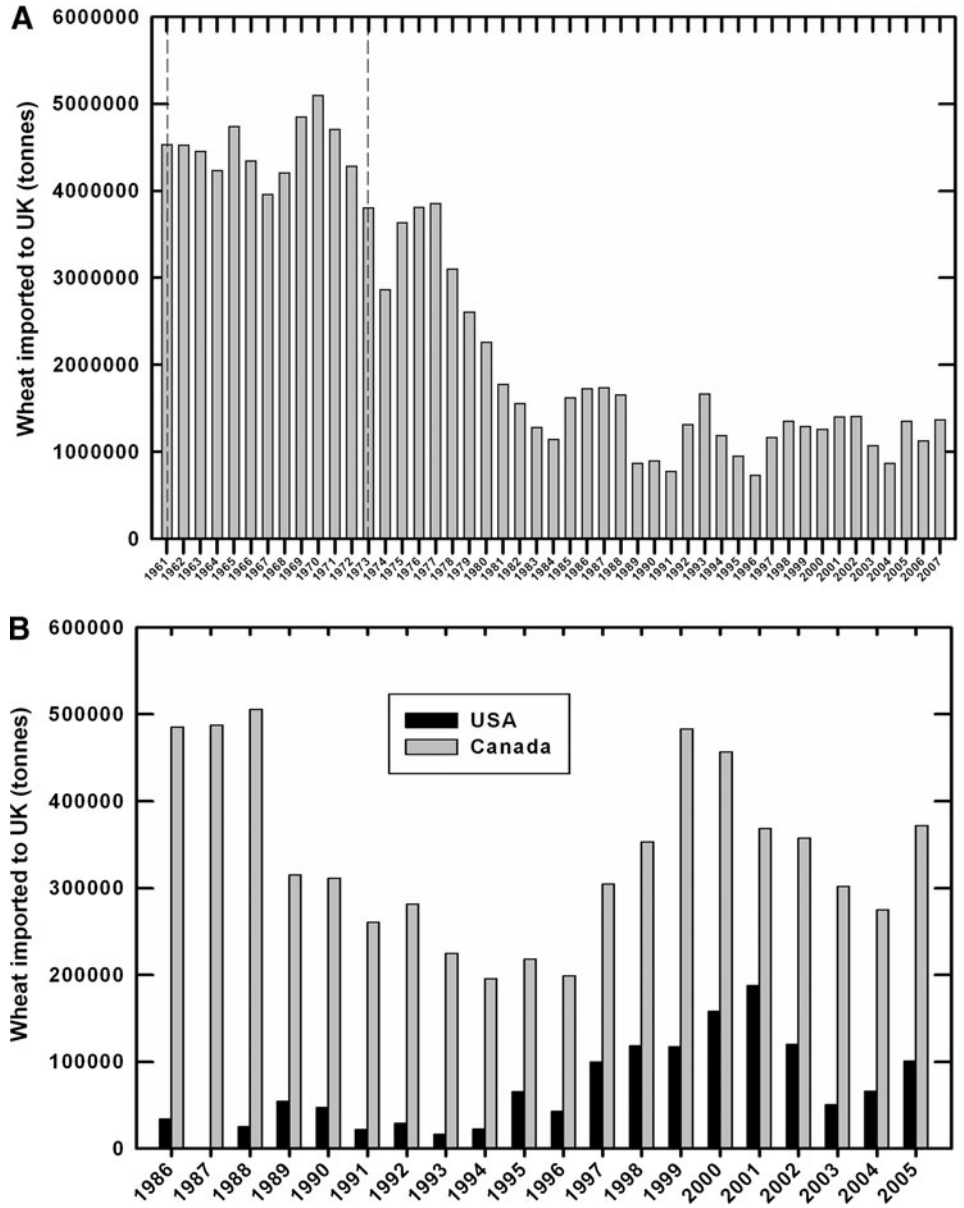

FIG. 5. Wheat imports to UK. (A) Wheat imports to UK from all sources 1961–2007. Wheat imports to UK from all sources 1961–2007 data obtained from reference (120). The introduction of the Chorleywood Bread Process in 1961 is highlighted with a dashed line; this process enabled use of UK and EU wheat in bread making instead of North American wheat. The second dashed line represents the year when the UK became a member of the European Economic Community in 1973. **(B)** Wheat imports to UK from United States and Canada 1986–2005. Wheat imports to UK from United States and Canada 1986–2005 data obtained from reference (120).

Recently, it has been shown that UK wheat grain selenium concentration can be increased by 16–26 ng/g fresh grain, for each gram of selenium applied per hectare (applied as sodium selenate (Na_2SeO_4)) (63). The concentration of selenium in UK-sourced wheat grain is usually 28 ng/g, with a narrow interquartile range of $\leq$19 ng/g, $n = 452$). There has been little apparent change since the early 1980s (2), although increased sulfur usage may cause a decrease in selenium uptake by wheat (352). In contrast, the selenium concentration of U.S. -sourced wheat grain is 457 [$n = 190$; (148)] and 370 [$n = 290$; (407)] ng/g and Canadian-sourced wheat grain is reportedly 760 ng/g (58). The higher concentration of selenium in U.S. and Canadian wheat grain is primarily due to the higher plant-available selenium concentrations found naturally in soils of their wheat-growing regions and lower-yielding (*i.e.*, typically more mineral dense) grain. Most soils in the UK are naturally low in selenium (64, 130) and there is no evidence for soil selenium depletion due to more intensive cropping (119). However, since coal is a rich source of selenium, general reductions in coal usage and desulfurization technologies may also have reduced selenium inputs to crops (2, 157). Changes in dietary patterns, such as decreased consumption of offal, is a further contributing factor (191).

Rice is another staple food that affects selenium status in certain populations. Williams *et al.* recently conducted a spatially resolved analysis of variation in selenium concentration in polished rice grains (403). Over 1000 samples of rice were purchased from major rice-producing/exporting countries and there is wide variation between and within countries. For example, rice sourced from the United States and India had average levels of selenium >30 times greater than rice sourced from Egypt (Fig. 6). Within countries, rice selenium concentration varied by up to 10-fold. Therefore, for public health policy spatial links between geochemistry, crop uptake, dietary intake, and plasma/serum selenium concentration need to be resolved.

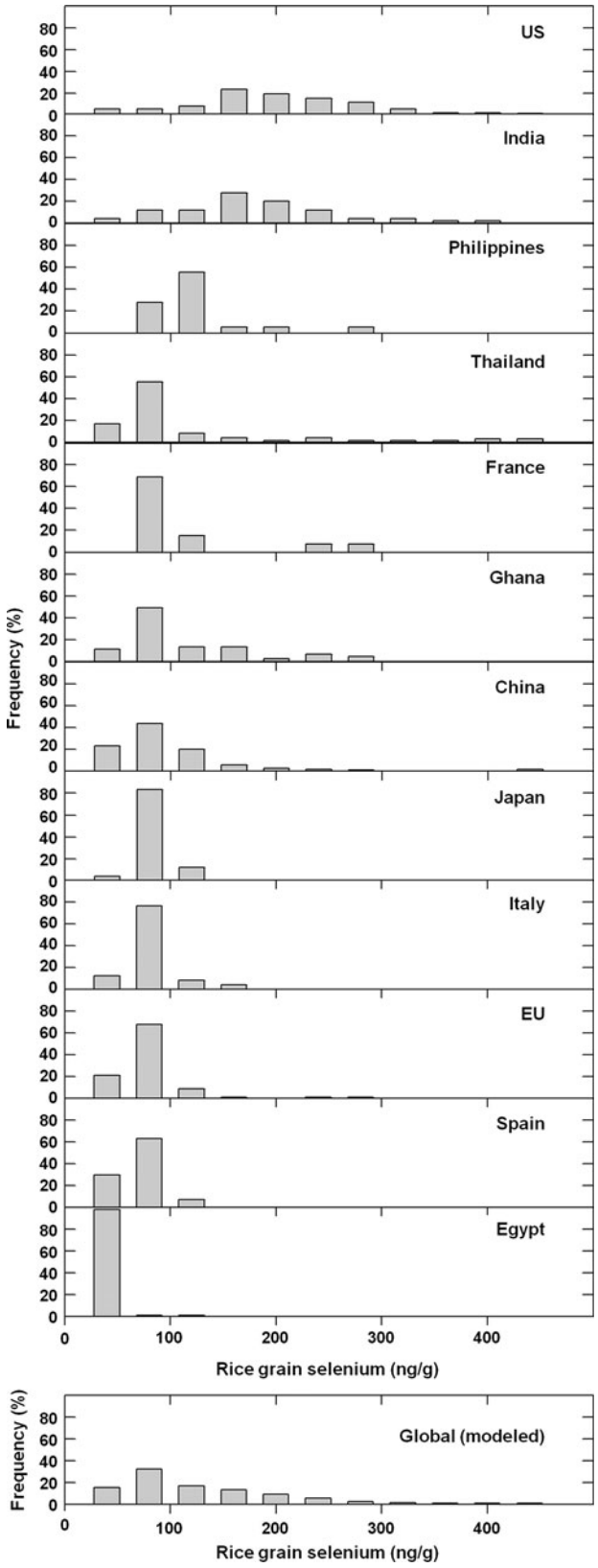

FIG. 6. Selenium content in rice produced from different countries. Selenium concentration of white (polished) rice from market stores between 2005 and 2008, from countries representing 61.5% of production and 71.1% export pools globally. Redrawn from Williams *et al.* (403). Data are given as percentage frequency distributions from a sample size $n = 1092$.

V. Functions of Selenium in the Human Body

A. Thyroid hormone metabolism

The redox-protective effects of selenoproteins may be of particular importance in the thyroid gland, whose long-lived cells generate H_2O_2 (and so also reactive oxygen species [ROS]) required for the synthesis of thyroid hormones. This likely role is reflected in the abundance of selenium in the thyroid gland (206) and perhaps by the high priority given to maintaining selenium supply to the thyroid gland under conditions where availability is restricted. Also of particular relevance is the direct involvement of selenoenzymes, the iodothyronine deiodinases (DIOs), in thyroid hormone metabolism.

1. Thyroid hormone synthesis and the role of selenoproteins in thyroid gland function and protection. The pathway for synthesis of the thyroid hormones tetra-iodothyronine (T4) and 3,3′,5′ tri-iodothyronine (T3) is shown schematically as Figure 7, based on evidence from a variety of sources (48, 134, 145, 322, 343), and highlighting the roles of selenoproteins. Expression in the thyrocyte of several selenoproteins, including glutathione peroxidases (GPx1, GPx3 [secreted], and GPx4), thioredoxin reductases 1 and 2 (TXNRD1 and TXNRD2), deiodinases 1 and 2 (DIO1 and DIO2), Sep15, SePP, and selenoproteins M and S (319) may contribute to its high selenium content, and the ability of some of these (GPx1, GPx3, GPx4, TXNRD1, and TXNRD2), along with intracellular catalase and peroxiredoxins, to degrade excess H_2O_2, may be important in antioxidant defense and redox control (205). An additional protective role for selenium in the thyroid gland is indicated by the positive outcomes of clinical trials involving selenium supplementation to reduce antibody load in cases of autoimmune thyroiditis (257).

2. Prioritization of the selenium supply to the thyroid gland and to DIOs. Observations made in rats fed severely selenium-deficient diets provided early evidence that selenium supply to the thyroid gland is prioritized. Whereas levels of GPx activity and GPx1 mRNA became virtually undetectable in liver and heart, mRNA levels were maintained in the thyroid gland and activity was reduced by only 50%. Similarly, DIO activity and DIO1 mRNA were maintained in thyroid but reduced in liver (43). There is also evidence that the DIOs, both in the thyroid gland and in nonthyroid tissues, are preferentially supplied above other selenoproteins with selenium to retain activity. For example, 5′-deiodinase activity and DIO1 mRNA were retained under conditions of selenium depletion sufficient to reduce GPx activity and GPx1 mRNA in an epithelial cell line (147). The clinical phenotype of an abnormality in thyroid hormone metabolism resulting from a mutation in SBP2 (selenocysteine insertion sequence [SECIS] binding protein 2, which interacts with the 3′UTR SECIS of selenoproteins to recode the UGA [stop] codon to facilitate selenocysteine incorporation) appeared to be dominated by effects on DIO activity (103), perhaps reflecting an important role for SBP2 in the prioritization of selenium supply to the DIOs. Further evidence that functionality of the SECIS is important in selenium prioritization more generally includes the identification of a wide range (up to 1000-fold) in the UGA-recoding activity of different human SECIS sequences (213).

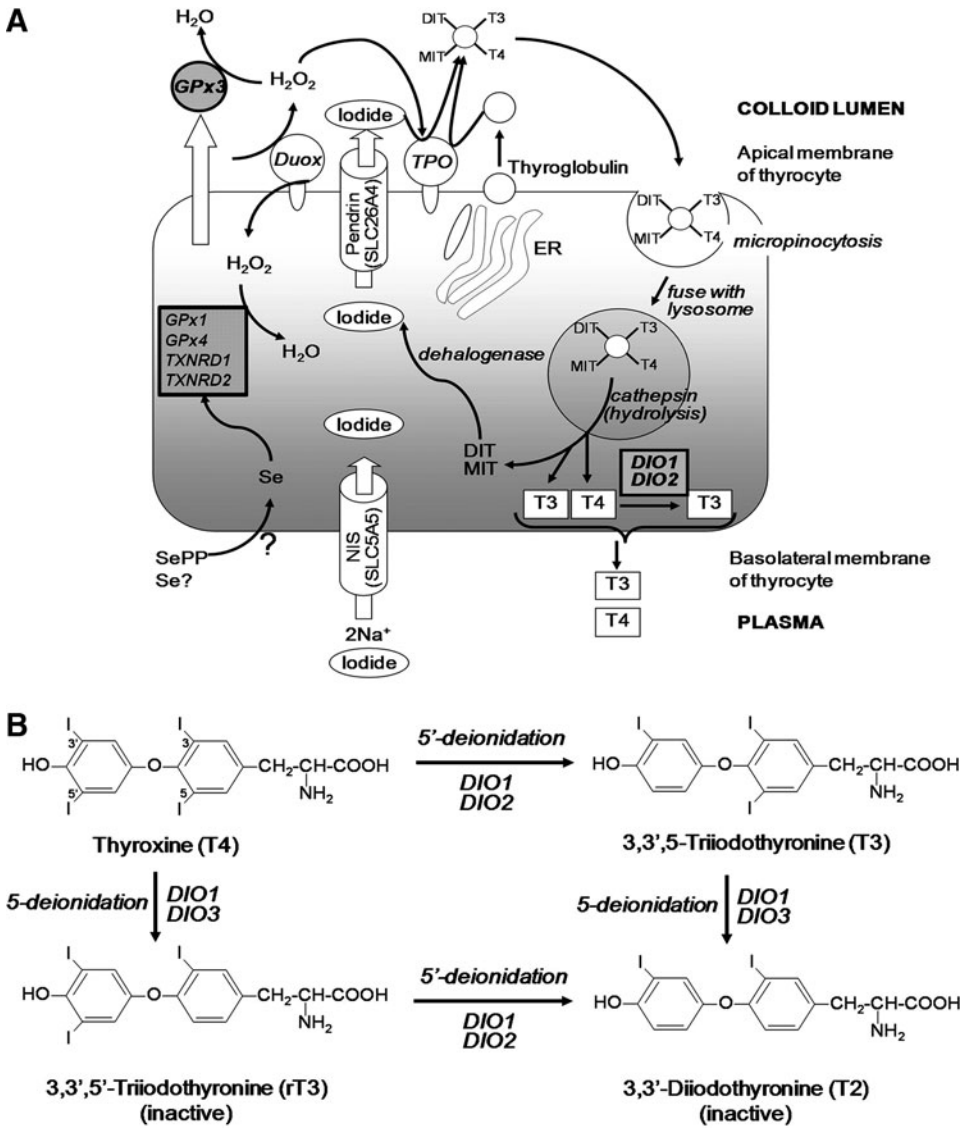

FIG. 7. Thyroid hormone metabolism, highlighting roles of selenoproteins. (A) The generation of T3 and T4 in the thyrocyte. Apical and basolateral membranes are indicated, facing the colloid lumen and plasma, respectively. The route for passage of iodide for thyroid hormone synthesis from plasma to colloid lumen is indicated, and then incorporation as MIT, DIT, T3, and T4 side chains of the thyroglobulin backbone (produced in the ER then secreted) (thyroglobulin iodination) is shown. Thyroglobulin iodination (organification of iodine) is catalyzed by TPO and requires an H_2O_2 cofactor, generated by Duox. Excess H_2O_2 is indicated as being inactivated by secreted GPx3 or by intracellular selenoproteins (GPx1, GPx2, TNXRD1, and TXNRD2). Iodinated thyroglobulin is taken across the apical membrane by micropinocytosis, as indicated, and then fusion of vesicles with lysosomes leads to cathepsin-catalyzed cleavage to release T4 and T3, which diffuse into the plasma, and DIT and MIT, from which iodide is released by dehalogenase and recycled. The form and route through which selenium enters the thyrocyte is unknown, as indicated. Selenoproteins are highlighted in bold-italic text in shaded shapes. **(B)** Chemical interconversions of the major thyroid hormones and their metabolites by the DIOs. Deiodination at the 5′-position is an activating step and is catalyzed by DIO1 and DIO2. Deiodination at the 5-position is an inactivating step and is catalyzed by DIO1 and DIO3. DIO1, iodothyronine deiodinase 1; DIO2, iodothyronine deiodinase 2; DIO3, iodothyronine deiodinase 3; DIT, diiodothyronine; Duox, dual oxidase (thyroxidase); ER, endoplasmic reticulum; GPx1, glutathione peroxidase 1; GPx3, glutathione peroxidase 3; GPx4, glutathione peroxidase 4; MIT, monoiodothyronine; NIS, sodium-iodide symporter; TXNRD1, thioredoxin reductase 1; TXNRD2, thioredoxin reductase 2.

3. Functions of the DIOs and their potential role in health and disease. Thyroid hormones are important signaling molecules with essential roles in cell function and in tissue development and physiology; thus, perturbations in their levels, potentially including through effects of selenium status on their synthesis, have potential consequences for health. While some T4 deiodination occurs in the thyroid gland, it has been estimated that around 80% of circulating T3 is generated through DIO activity in the peripheral tissues (345). DIO2 is now recognized to be the deiodinase primarily responsible for deiodination of the pro-hormone T4 at the 5′ position to generate active T3 (345). The roles of the three DIOs in interconversion of the thyroid hormones, including inactivation by 5-deionidation, are shown in Figure 7.

A wealth of evidence supports the view that the relative levels of expression of the different DIOs in specific tissues and at specific developmental stages or in response to challenges such as tissue injury, illness, and nutritional deficiency is balanced to promote appropriate control of cell proliferation and/or differentiation through control of thyroid hormone activation and inactivation, as reviewed recently (345). For example, compensatory increases in tissue DIO2 activity observed in iodine deficiency or hypothyroidism increased local T3 production (112, 282). Adequate selenium nutrition may thus be particularly important in cases of hypothyroidism to facilitate increased DIO activity in tissues for which the selenium supply is a lower priority than for the thyroid gland.

Variation in DIO genes appears to influence thyroid hormone metabolism and activity (283). Two SNPs in the *DIO1* gene that have been associated with alterations in the ratio of active T3 to the inactive metabolite 3,3′,5′ triiodothyronine (rT3) are of particular interest because they are located in the 3′UTR of the mRNA, so may [in a manner similar to SNPs in the 3′UTR regions of GPX4 and SePP (241, 243)] mediate effects through selenocysteine incorporation into DIO1, and so, speculatively, may show an interaction with selenium status.

In conclusion, given the evidence that the nonthyroid tissues have lower priority for supply with selenium under conditions of restriction and that DIO induction may be an important adaptive response of tissues to particular challenges, more information on the interactions and processes is required to understand links between selenium, health, and disease.

B. Antioxidant defense system and oxidative metabolism

1. Glutathione peroxidases. Among the selenoproteins are four GPxs: cytosolic GPx (GPx1), gastrointestinal-specific GPx (GPx2), plasma GPx (GPx3), and phospholipid hydroperoxide GPx (GPx4). These are well-characterized major selenoenzymes of the human antioxidant defense systems (230). GPx1-3 catalyzes the reduction of hydrogen peroxide and organic hydroperoxides, whereas GPx4 can directly reduce phospholipid hydroperoxides and cholesterol hydroperoxides. GPx6 is an olfactory epithelium and embryonic tissue-specific GPx (211). GPx1 and GPx2 have well-characterized antioxidant functions, as indicated by the greater susceptibility of mice lacking both GPx1 and 2 to an oxidative challenge (85). Responses of transgenic mice lacking or overexpressing GPx1 suggest novel roles for GPx1 in relation to both reactive oxygen species and reactive nitrogen species, and a link to insulin secretion and insulin resistance (217, 394). GPx3 is a key antioxidant enzyme in the plasma and acts as a functional parameter for selenium status assessment, and GPx3 deficiency has been associated with CVD and stroke (46, 399).

GPx activity and expression have been used in many human studies as biomarkers for selenium status (355). It has been shown in GPx1$^{(-/-)}$ mice that GPx1 deficiency plays a major role in cardiac dysfunction in angiotensin II-dependent hypertension (18). Further, there have been attempts to correlate genetic polymorphism of selenoenzymes with risk of disease, including cancer and heart disease. A recent study provided some evidence that SNPs in GPx1 and GPx4, and their interaction with variants in other selenoprotein genes, may influence colorectal cancer risk (242). In another study, with a population that had advanced distal colorectal carcinoma, SNPs in *SEPP1* and *TXNRD1* were identified to be associated with adenoma risk but not the *GPX1-4* variants investigated (286).

2. Thioredoxin reductases. TXNRDs are involved in the control of cellular proliferation, cell survival, and apoptosis through the control of thioredoxin (Trx) activity and redox state, and play a crucial role in biological response to oxidative stress. Three TXNRDs have been identified in mammals: TXNRD1 in the cytosol/nucleus, TXNRD2 in mitochondria, and thioredoxin glutathione reductase in the testis, with the last also possessing glutathione and glutaredoxin reductase activity (279). TXNRD, Trx, and NADPH constitute the thioredoxin system, a major cellular redox system present in all living organisms (19). TXNRDs have a wide range of substrates, including small molecules such as hydrogen peroxide, lipid hydroperoxides, and ascorbate, lipoic acid, ubiquinone, and Trx (413). ROS are a major contributing factor to the pathogenesis of CVD. The thioredoxin system plays an important role in scavenging ROS. Trx, glutaredoxin, peroxiredoxin, and their isoforms are involved in interaction with signaling pathways, thus making them attractive targets for clinical intervention (3). TXNRD is the only known enzyme able to reduce oxidized Trx, which regulates a plethora of redox signaling events (153). Reduced Trx provides electrons to ribonucleotide reductase, essential for DNA synthesis, by converting ribonucleotide to deoxyribonucleotides. Moreover, the Trx system participates in many cellular signaling pathways by controlling the activity of transcription factors containing critical cysteines in their DNA-binding domains, such as nuclear factor kappa B (NFκB), activator protein-1 (AP-1), p53, and the glucocorticoid receptor (223).

There is growing evidence that redox regulation by the TXNRD systems plays a crucial role in the biological response against oxidative stress and in cell proliferation, apoptosis, and the modulation of inflammation (70, 342, 362). Trx can bind to apoptosis signal regulating kinase 1 (ASK1) and modulates apoptosis (223, 258, 315). TXNRD is also overexpressed in many tumor cells and contributes to drug resistance; therefore, TXNRD was considered a new target for anticancer drugs (140). In addition to selenium, dietary phytochemicals such as isothiocyanates and polyphenols can also upregulate TXNRD and GPx2 expression in both tumor and normal cell lines *via* the Keap1-Nrf2-ARE pathway (203, 220, 429).

3. Other selenoproteins involved in the antioxidant defense system. Recently, it has been suggested that selenoproteins, including SelW, SelM, SelT, and the 15 kDa selenoprotein, are members of a novel redox protein family that share the common feature of containing a thioredoxin-like fold with a CxxSec redox fold (1, 39). Further, overexpression of SelW in cultured cells led to lower sensitivity to challenge from hydrogen peroxide (190), suggesting that SelW has an antioxidant function. Selenoprotein H (SelH) is a nucleolar thioredoxin-like protein with a unique expression pattern, and structural studies suggest that SelH is a redox-sensing DNA binding protein (266, 278). A recent study described a knock-out mouse deficient in selenoprotein MsrB1 (SelR) with increased levels of malondialdehyde, protein carbonyls, protein methionine sulfoxide, and glutathione disulfide as well as reduced levels of free and protein thiols, indicating that MsrB1 plays an important role in redox regulation (128). SePP has a purported thiol-redox function as a member of the thioredoxin superfamily (67) and may protect against oxidative damage (347). In addition, selenoproteins N and K may have antioxidant roles (17, 228).

In summary, several of the selenoproteins may be involved in the antioxidant defense system as highlighted in section V.B. above; there are many other important functions of the human selenoproteins such as the role of SelW and SelN in muscle function, reviewed recently in Lescure *et al.* (218), and other functions discussed throughout this review, for

example, throughout chapter VI: clinical disorders section below. For recent reviews focused in detail on selenoproteins, refer to refs. (39, 230, 279, 301, 332, 433).

C. Immune system

Studies in experimental and farm animals indicate that selenium deficiency affects both cell-mediated and humoral components of the immune response (21, 167, 344). In humans, limited data suggest that when intakes of selenium are sub-optimal selenium supplements can enhance immune responses (167). Low serum selenium in humans is associated with low levels of natural killer cells (304), and selenium supplementation (200 μg/day) increased T-lymphocyte-driven tumor lysis and lymphocyte proliferation (200). In rats, selenium deficiency lowers levels of IgA, M, and G; selenium-deficient lymphocytes show lower mitogen-stimulated proliferation, and in cell culture, selenium promotes human neutrophil function (21). Despite these observations the details of how selenium intake influences the immune system remain poorly understood, with the most information being available on the effects of severe selenium deficiency and selenoprotein knockout in response to viral infection.

A landmark discovery in selenium biology during the past 30 years was the observation by Chinese scientists that Keshan disease, a myocarditis found in selenium-deficient areas of China, is associated with a combination of low selenium intake and Coxsackie virus B (CVB) infection (see section VI.A.1). Molecular hybridization and immunohistochemistry analysis of postmortem material has shown CVB3 to be present in the majority of Keshan diseases cases. Further, feeding mice a selenium-deficient diet in combination with CVB infection leads to pathological changes in the myocardium similar to those found in Keshan disease (multiple necrosis lesions of the myocardium and inflammatory cell infiltration). Overall, these data demonstrate that enteroviruses, especially CVB, are closely associated with the viral myocarditis of Keshan disease (107, 431).

Selenium intake has subsequently been found to affect the progression of other viral infections in animals (34). For example, selenium deficiency results in greater lung pathology in mice infected with influenza virus compared with selenium-adequate mice; selenium-deficient mice showed an altered immune response to an infection with a virulent strain of influenza virus and the viral genome changed to a more virulent genotype. Selenium deficiency also has a significant impact on the morphology and influenza-induced host defense responses in human airway epithelial cells (35). Porcine circovirus type 2 replication in PK-15 cells is inhibited by DL-selenomethionine in a concentration-dependent manner (277). Except for Keshan disease no causal links between selenium intake and viral response have been demonstrated in humans, but selenium status and viral responses are associated. For example, selenium supplementation was shown to modulate the response of healthy volunteers of marginally low plasma selenium status to a disabled polio virus (65), confirming that selenium status determines the ability to respond to a viral infection. In addition, epidemiological studies suggest a correlation between severity of AIDS and selenium deficiency, but to date it is not clear whether this reflects a protective role for selenium during HIV infection or an altered nutritional selenium status as a result of the disease (31, 167, 227). Similar observations have been made with the influenza virus. Not only does selenium status modulate responses to influenza virus (261), but also GPx1 activity is important in determining the response (33, 337). However, the extent to which other selenoproteins are involved in determining the effects of selenium status on responses to viral infection is poorly understood, although selenium depletion was shown in a cell culture model to affect influenza virus-induced cytokine production in bronchial epithelial cells (189).

Immune responses are intimately linked to inflammatory processes and these in turn are inter-related to production of ROS and redox control processes. For example, ROS production can increase expression of inflammatory cytokines through increased NF-κB activity (369). It is possible that selenium modulates inflammatory and immune processes through redox functions. To some extent this is illustrated by the observations that transgenic mice with a mutant Secys-tRNA that causes depletion of all selenoproteins, but with variations in extent between selenoprotein and tissues, showed changes in the pattern of certain cytokines (*e.g.*, interferon–γ) (337). In addition, the potential importance of redox signaling *via* selenoproteins is also shown by the effects of GPx1 knockout on viral infection. However, mutant Secys-tRNA mice failed to show differences in lung pathology after influenza virus infection, suggesting that a basal threshold level of GPx1 is sufficient to maintain response to the virus. It was recently reported that the selenoprotein thioredoxin reductase 1, also a key factor in redox control, can negatively regulate the activity of the HIV-1-encoded transcriptional activator, Tat, in human macrophages (194).

White blood cells such as lymphocytes, macrophages, and neutrophils require ROS and pro-inflammatory molecules for their activation, differentiation, and phagocytosis (132). Thus, since selenoproteins may influence these signaling pathways they may in turn be expected to be crucial for these cell functions. For example, neutrophils require oxidative radical production to achieve microbial killing and selenium deficiency lowers the ability of neutrophils to kill ingested microbes, probably partly due to lower GPx1 activity and thus impaired radical metabolism (21). Macrophages are key cells in the signaling and activation of inflammatory responses, but this action also produces ROS; therefore, it must be carefully controlled and counteracted. Studies in which selenium-supplemented macrophages were stimulated with LPS (a bacterial endotoxin) found that supplementation with selenium suppressed TNF-α and COX-2 (cyclooxygenase-2) expression (386). However, Carlson *et al.* (79) found that macrophages without any selenoproteins still exhibited normal inflammatory responses, although higher levels of ROS were seen. In a similar experiment, mice with selenoprotein-less T-cells also exhibited increased ROS levels, reduced numbers of mature T-cells, and defective antibody responses (340).

Low selenium status has been associated with reduced serum IL6 in elderly people (388), an observation that is consistent with links between selenium, selenoproteins, and inflammatory signaling. In addition to potential metabolic links between GPx1, ROS, and inflammatory cytokines such as the interleukins, results from a series of studies suggest that selenium levels affect eicosanoid metabolism. Studies of both severely selenium-deficient animals and selenium-deficient cells in culture suggest that selenium supply, through its influence on GPxs, has an inhibitory regulatory effect on

5′ lipoxygenase activity in lymphocytes (179, 397) and thus on generation of pro-inflammatory leukotrienes. In addition, overexpression of GPx4 in transfected basophils has also been reported to suppress 5′ lipoxygenase activity. Further evidence for a metabolic link between GPx4 and leukotrienes has come from the finding that individuals with different allelic variants of a common SNP in the *GPX4* gene (rs713041) have been found to have different levels of 5′ lipoxygenase product in their lymphocytes (382), suggesting that lymphocyte GPx4 activity influences pro-inflammatory leukotriene activity in lymphocytes.

A combination of severe selenium and iodine deficiency causes a thyroid atrophy that does not respond to iodine supplementation due to inflammatory damage to the thyroid, and this has led to studies of selenium in thyroiditis (205). Indeed, several clinical trials have reported that selenium supplementation reduces inflammatory markers in patients with autoimmune thyroiditis, and this has led to the hypothesis that even a moderate selenium deficiency can be a causative factor in autoimmune thyroid disease in patients who have genetic susceptibility to autoimmune disorders.

In summary, there is a growing body of evidence that selenium status affects immune function, in particular the ability to respond to viral infection. The mechanisms underlying these effects are poorly understood but may involve modulation of ROS and inflammatory signaling pathways through the antioxidant and redox functions of selenoproteins.

VI. Clinical Disorders

A. Deficiency

1. Keshan disease. Keshan disease is an endemic cardiomyopathy observed in selenium-deficient areas of China. Its name originates from a severe outbreak in Keshan County, Heilongjiang Province, China in 1935. The main clinical features of Keshan disease are acute or chronic episodes of a heart disorder characterized by cardiogenic shock and/or congestive heart failure. Keshan disease can be clinically classified into four types: acute, sub-acute, chronic, and latent. Dilatation of the heart is commonly observed (143).

The etiology of Keshan disease is not yet fully understood. Originally, the proposed risk factors included Coxsackie virus (CVB), type A streptococci, and organic toxicants produced by parasitic fungi on cereals or putrid organic substances in water and/or soil environments. In the 1970s, the low selenium status of the inhabitants in Keshan disease-endemic areas became evident, and subsequently, the preventive effect of selenium supplementation on Keshan disease was identified. Further improvements in selenium status were associated with a decline in Keshan disease in the endemic areas and confirmed the link between selenium and Keshan disease.

In China, the selenium-deficient zone from the northeast to the southwest involves 16 provinces, and historical data indicated that the population at risk was >100 million. Keshan disease surveillance has been a national program since 1990, an important component of which is the determination of selenium levels in Keshan disease-endemic areas (425).

The geographical distribution of topsoil selenium in China and its relationship to Keshan disease (and Kashin-Beck disease) indicates that the selenium concentrations in topsoil of affected areas are typically below 0.125 mg/kg. In contrast, the concentration in areas without disease is 0.224 mg/kg, and the excessive level is >3 mg/kg (361). Nutritional studies showed that the mean hair selenium contents were <0.122 mg/kg in endemic areas and >0.200 mg/kg in non-Keshan disease–endemic zones, whereas the average blood selenium concentration of people in Keshan disease endemic areas was no more than 253 n*M* (20 ng/ml). The selenium content of muscle, heart, liver, and kidney in Keshan disease patients is up to 10-fold lower than that in healthy subjects (143).

Recent studies suggest that genetic polymorphisms in selenoproteins may be associated with susceptibility to Keshan disease. Lei *et al.* measured the concentration of blood selenium and the activity and polymorphisms of cellular GPx1 in 71 Keshan disease patients and 290 controls (216). Results suggested that selenium deficiency in carriers with the GPx1 leucine-containing allele is associated with low GPx1 enzyme activity, which may, in turn, increase the incidence of Keshan disease.

The link between selenium and Keshan disease was further strengthened with results of a selenium supplementation trial. Between 1974 and 1977, sodium selenite or placebo tablets were given to children at high risk of Keshan disease. Concurrent with an increase in blood selenium concentrations in the treated group ($n = 6767$), 17 acute and sub-acute Keshan disease cases were reported compared with 106 in the placebo group ($n = 5445$). After 4 years, there had been 53 deaths in the controls, whereas only one selenium-treated subject had died (421). Supplementation of individuals with selenium tablets (as sodium selenite) has been effective in preventing the development of Keshan disease (418). However, as not all people living in the low selenium areas suffered from Keshan disease, other causal factors such as virus infections were proposed.

In animal studies, Bai *et al.* demonstrated that mice fed grains from Keshan disease areas developed a deficiency in selenium (28). When these mice were infected with a strain of Coxsackie virus B4 that was isolated from a Keshan disease victim, the mice developed severe heart pathology, whereas mice that were fed grains from non-Keshan disease–endemic areas developed only mild heart pathology when infected with the virus. This study suggested that together with the deficiency in selenium, an infection of CVB was required for the development of Keshan disease (28). A further study demonstrated that selenium deficiency was responsible for driving changes in the viral genome and changing a normally avirulent pathogen into a virulent one (36). Moreover, influenza virus exhibits increased virulence toward the selenium-deficient mice (34).

Selenium deficiency may affect expression of selenoenzymes such as GPX1. One study showed that 50% of GPx1 knockout mice (GPx−/−) infected with CVB3/0 developed myocarditis, whereas infected wild-type mice (Gpx1+/+) were resistant (no mice developed myocarditis) (33). This study suggests that antioxidant protection is important for protection against CVB3-induced myocarditis.

After the isolation of enteroviruses from patients with Keshan disease during outbreaks of the disease in selenium-deficient rural areas of southwestern China, an association of enterovirus infection with Keshan disease and its outbreaks in selenium-deficient areas has been established (284). To date, many studies strongly suggest a dual etiology that involves both a nutritional deficiency of selenium as well as an infection with an enterovirus (34, 173).

There is an interest in identifying potential protective dietary compounds, for example, sulforaphane (SFN), a hydrolysis product of glucosinolate from cruciferous vegetables that is a potent inducer for a battery of antioxidant enzymes, including quinone oxidoreductase, glutathione transferases, UDP-glucuronyltransferase, γ-glutamylcysteine synthetase, heme oxygenase, aldo-keto reductase, thioredoxin reductase, and GPxs. The mechanism of interactions between selenium and SFN in antioxidant enzyme expression was mainly *via* Nrf2/Keap1 system (60). Sun *et al.* conducted a study to investigate whether SFN can protect the myocardium of selenium-deficient mice against viral infection and demonstrated that GPx activity in groups given SFN was significantly higher than in the control groups without SFN (353). Further, both the incidence and extent of myocardium injury in viral groups with SFN were significantly lower than those in the viral groups without SFN. It was therefore concluded that SFN affords a degree of protection against Coxsackie virus B3m-induced mouse cardiomyopathy.

2. Role of selenium in Kashin-Beck disease. Kashin-Beck disease (KBD) is an endemic, chronic, degenerative osteoarthropathy that is present in selenium-deficient areas in the world, and is mainly found in a diagonal belt from northeast to southwest China, and also in Mongolia, Siberia, and North Korea. The disease was first described in 1848 by Nickolay Kashin in the Bajkal area of Russia (196) and later in 1906 by Eugene Beck (32). The etiology of KBD is largely unknown. The risk factors seem to include mycotoxins such as Trichothecene mycotoxin (T-2) from contaminated storage grains, and organic substances such as humic acid and fulvic acid in drinking water, Coxsackie B3 virus infection, and deficiency in trace elements, mainly selenium and iodine (348). The original theory proposed by Russian researchers was that KBD had been caused by a mycotoxin. However, the focus on the disease gradually shifted to China, where the causal theory was based on the effects of selenium deficiency and interactions with mycotoxins (8). Among all the risk factors, selenium was the most studied, and disturbances of selenoprotein expression and/or function are associated with both Keshan and Kashin-Beck diseases (204).

In the KBD-endemic areas the levels of selenium in both soil and human biological samples are much lower than that in areas without KBD. Ge and Yang reported that average hair selenium concentrations in residents of KBD-endemic areas were 1.19 ± 0.34 nmol/g compared with 4.81 ± 2.27 nmol/g in nonendemic areas (143). Blood GPx activities were 74.0 ± 12.8 kU/l in endemic groups of the population and 95.6 ± 8.9 kU/l in nonendemic groups. Oral supplementation of the endemic group with sodium selenite (1–2 mg/wk) for 2 months increased GPx activity to 94.0 ± 11.5 kU/l, indicating that the population was selenium deficient (389). Many epidemiological studies conclude that KBD is mainly common in low selenium areas where patients are in a selenium-deficient condition, and selenium supplementation is effective at preventing a worsening of metaphysis change and in promoting repair (75, 83). For example, in the KBD region in China, serum selenium concentration was on average $36–37 \pm 17$ ng/ml, compared with a similar region with no evidence of KBD where serum selenium was $\sim 63 \pm 15$ ng/ml. A majority (>50%) of participants in the KBD area had serum selenium <37 ng/ml, compared with only 16% in the nondisease area [data from 2006–reported in Shi *et al.* (338)]. There was 13% prevalence of Kashin-Beck in certain regions of China (338).

In areas where severe selenium deficiency is endemic, iodine deficiency is also a risk factor for KBD (252) and correction of iodine deficiency should be undertaken before selenium supplementation to avoid hypothyroidism. However, in another study, Zhang *et al.* studied selenium, iodine, and fungal contamination in the Yulin District, including three villages where KBD was endemic, whereas there were no cases of KBD in the fourth village. Results showed that low hair selenium concentration and presence of fungal cereal contamination were significantly associated with an increased risk of KBD, but low urine iodine was not (430).

T-2 is a naturally occurring mold byproduct of *Fusarium* sp. fungus that is toxic to humans and animals and was found at high levels ($2.0 \sim 1549.9$ ng/g) in contaminated grain (353). T-2 toxin-containing food can lead to some pathologic changes in the cartilage of guinea pigs that are similar to the changes observed in KBD patients (415). Therefore, the T-2 toxin contamination was proposed as a possible cause of KBD (424). In support of this hypothesis, cell culture studies demonstrated that T-2 toxin can inhibit aggrecan synthesis in human chondrocytes, promote aggrecanases and pro-inflammatory cytokines expression, and aggrecan degradation; selenium can inhibit the effects of T-2 toxin (222). A previous study by the same group showed that selenium can partly block T-2 toxin-induced apoptosis in chondrocytes (82).

In human studies, Cao *et al.* demonstrated that there was significant aggrecanase-mediated proteoglycan degradation in both adult and child KBD patients and altered CD44 metabolism was also involved in KBD pathogenesis (76). Again in a cell culture study, Wojewoda *et al.* found that selenium decreased ROS generation and increased the level and activity of antioxidant enzymes such as GPx and TXNRD (404).

So far, the contribution of any particular genotype toward the risk of developing KDB is unknown. Recently, the associations between genetic variation in selenoprotein genes and susceptibility to KBD were studied. The genotypic and allelic frequency of GPx1 Pro198Leu were significantly different between KBD patients and the control group ($p = 0.013$, $p = 0.037$, respectively). A significant increased KBD risk was observed in individuals with Pro/Leu or Leu/Leu (odds ratio, OR = 1.78; 95% confidence interval: $1.13 \sim 2.81$) compared with Pro/Pro. Moreover, the GPx activity in whole blood decreased significantly in a subgroup of individuals representing Pro/Leu and Leu/Leu compared with Pro/Pro ($p < 0.01$) (416). In contrast, in this study, no associations were found between KBD risk and other gene polymorphisms such as *TXNRD2*, *SEPP1*, and *DIO2*. Moreover, Shi *et al.* suggest that variants of the chromosomal short tandem repeats D11S4094, D11S4149, D2S338, and D2S305 might be associated with KBD (338). Downey *et al.* studied the effects of skeletal selenoprotein deficiency using a transgenic mouse line to trigger Trsp gene deletions in osteochondroprogenitors (96). Trsp encodes selenocysteine tRNA[Ser]Sec, which is required for the incorporation of selenocysteine residues into selenoproteins. The mutant mice exhibited growth retardation, epiphyseal growth plate abnormalities, and delayed skeletal ossification, as well as marked chondronecrosis of articular, auricular, and tracheal cartilages. Phenotypically, the mice replicated a number of the pathological features of KBD (96), supporting the notion that selenium deficiency is important to the development of KBD.

Moreno-Reyes *et al.* reported that selenium supplementation in Tibet had no effect on established KBD, growth, or thyroid function once iodine deficiency was corrected (251). Therefore, it was suggested that iodine, but not selenium, deficiency should be corrected in Tibetan children with KBD. The results of a systematic review demonstrated no convincing evidence that selenium, vitamin A, vitamin C, or the combination product of selenium, vitamin A, C, and E is effective in the treatment of any type of arthritis (75). A meta-analysis of five randomized controlled trials (RCTs) and 10 non-RCTs assessed the efficacy of selenium supplementation for prevention of KBD osteoarthropathy in children (435). Significant effects were demonstrated and the results indicated that current evidence supports the benefits of selenium supplementation for prevention of KBD in children although evidence was limited by potential biases and confounders. Results from a 3-year trial in which 1064 children aged 3–10 have been given iodine and selenium and either a cocktail of micronutrients (copper, manganese, zinc, and vitamins A, C, and E), or a placebo are expected to be published soon by Mathieu and colleagues, which may help resolve the controversy.

Recent comparative microarray analysis of gene expression profiles between primary knee osteoarthritis (OA) and KBD demonstrated a clear difference in the gene expression profile in cartilage from patients with KBD compared with that from patients with OA (98), implying that there are different mechanisms responsible for the development and progression of these two diseases (393). The genes with a lower expression in KBD than normal cartilage included chondrocyte metabolism, ECM, DNA modification, and transcription factors, and genes with a higher expression in KBD than normal cartilage included signaling transduction, cell cycle, and apoptosis. The differential gene expression specific for KBD may indicate a specific mechanism that is responsible for the destruction of the articular cartilage in KBD. The data also suggest that cartilage degeneration, apoptosis induction pathways, and matrix metabolism might be more important in KBD cartilage.

Finally, the development of protein chip technology has enabled the application of high-throughput proteomics to identify potential biomarkers for a variety of diseases, including KBD. Wang *et al.* reported marked serum proteomic changes in KBD using surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (391), and it would be plausible to use this technique in human intervention trials to examine the effect of selenium supplementation.

B. Toxicity

Although much less common than selenium deficiency, selenium toxicity can affect individuals as a result of oversupplementation (234), accidental or deliberate (suicidal) ingestion of very high doses (215), or through high levels in the food supply. Characteristic features of selenosis occur in population groups exposed to unusually high levels of dietary selenium, and include brittle hair and brittle, thickened, stratified nails, leading to loss in some cases, along with an odor of garlic on the breath and skin (234, 300). Additional symptoms, including vomiting and pulmonary oedema, are a feature of more acute selenium poisoning (215).

In Enshi, in the Chinese province of Hubei, an outbreak of illness in which the most notable and prevalent symptoms were loss of nails and hair reached a peak between 1961 and 1964, when it affected almost half of the population. This condition was later diagnosed as severe selenosis, attributed to soil with very high selenium content (422). It was identified that the period of peak prevalence of selenosis was due to drought causing failure of the (lower selenium) rice crop, leading to consumption of alternative crops, with higher selenium content. Analysis of vegetables and cereals grown in the area after the period of peak prevalence confirmed high levels of selenium, which were up to 1500-fold greater than levels measured in the same foods taken from a nearby selenium-deficient area, where Keshan disease was endemic. Average daily intake of selenium was estimated to be 4990 μg. Analysis of samples of human hair, blood, and urine from residents of the affected area revealed that selenium concentrations were far in excess of concentrations measured in samples from individuals resident in a selenium-adequate area.

In parts of the Punjab State, in the northwestern region of India, crops and fodder contain very high selenium levels and selenosis is observed in cattle. Signs of selenium toxicity are observed in people consuming locally grown food (Fig. 8) (164). Daily intakes of selenium were estimated to be 632 and 475 μg/day in men and women, respectively, and corresponding values from nonseleniferous areas were 65 and 52 μg/day (94). Policies to manage the situation include nonconsumption of crop produce by the farmers, dilution with produce from nonendemic regions, and application of manures to reduce selenium accumulation in crops (95).

Levels of dietary exposure at which selenium becomes toxic and selenosis develops are difficult to establish, because toxicity is affected by the form in which selenium is available in the food supply, and probably also by combination with other dietary components and, possibly, interactions with

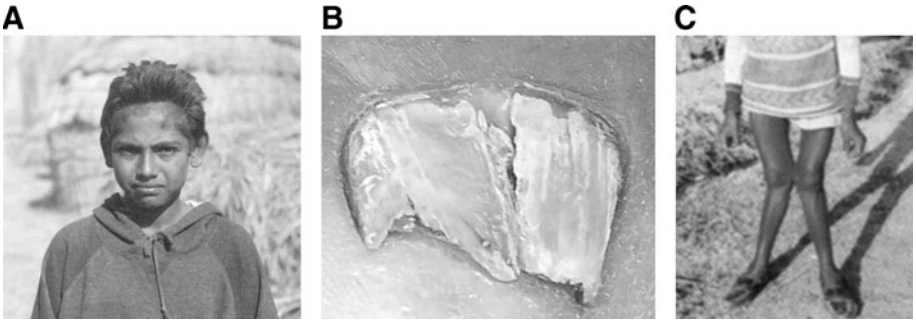

FIG. 8. Effects of consuming locally grown foods from selenium toxic areas in Punjab. (A) Hair loss, **(B)** keratosis, and **(C)** rickets. Photographs provided by Dr. N. Tejo Prakash of Thapar University, Patiala, India, and Professors K.S. Dillon and U.S. Sadana, Punjab Agricultural University, Ludhiana, India.

genotype. High levels of selenium in diets based predominantly on meat sources appear to be particularly well-tolerated, as exemplified by the high daily selenium intake of the Inuit of North Greenland, estimated as 193–5885 μg (150). This intake results in blood selenium concentrations in the order of 1000 μg/l (300), but is not associated with symptoms of toxicity. Comparison of levels of selenium in blood and urine in the Enshi study population and also in samples from populations in South Dakota (169) revealed toxicity associated with lower concentrations than those that result in symptoms of selenosis in Venezuela (422), probably reflecting exposure to dietary selenium in different forms. Suicide by exposure to very high levels of selenium has been associated generally with ingestion of selenite or selenate (215), an observation that probably reflects the form of selenium in substances used in suicide attempts, rather than necessarily being indicative of greater toxicity of inorganic compared with organic selenium compounds.

The mechanisms underlying selenium toxicity remain unknown; suggested mechanisms include induction of oxidative stress (375) and the replacement of sulfur with selenium in hair and keratin, leading to structural defects (376). Research on this topic, based on various *in vitro* and *in vivo* models [reviewed in Valdiglesias *et al.* (375)] is complicated by likely effects on measured outcomes of the form and dose of selenium administered and limitations with respect to extrapolating results from *in vitro* assays to human exposure. The eventual evolution of systems-biology-based approaches to describing selenium metabolism and interactions with cells and tissues will guide the most relevant experimental systems for understanding selenium toxicity at a molecular and whole body level.

VII. Effects on Health

A. Cardiovascular disease

Selenium is essential for selenium-dependent antioxidant enzymes such as GPxs, TXNRD, SePP, and other selenoproteins. Because of the antioxidant properties of selenium and/or selenoenzymes, it has been hypothesized that selenium may prevent CVD. Many observational studies investigating the association of low selenium concentrations with cardiovascular outcomes and randomized trials investigating whether selenium supplements prevent coronary heart disease (CHD) have been inconclusive.

A meta-analysis (126) synthesized results from observational studies of the association of selenium biomarkers with CHD endpoints and from results of clinical trials of the efficacy of selenium supplements in preventing CHD. The conclusions were that observational studies showed an inverse association between selenium concentrations and CHD incidence, although the data need further validation, whereas randomized trials were inconclusive with respect to the effect of selenium supplementation. Another meta-analysis of 13 prospective cohort studies found a moderate inverse relationship between plasma/serum selenium and CHD although the interpretation of these data are complicated by potential residual confounding and publication bias (260). Finally, a recent report by Xun *et al.* examined the longitudinal association between toenail selenium levels and subclinical atherosclerosis over an 18-year period, and no associations were observed between toenail selenium and measures of subclinical atherosclerosis among young American adults (417).

Selenium supplementation does not appear to reduce the risk of CVD in healthy individuals. Supplements of 200 μg/day in individuals free of CVD at baseline were not significantly associated with any CVD endpoints during 7.6 years follow-up of the entire blinded phase of the Nutritional Prevention of Cancer Trial (1983–1996) (350), and a randomized, placebo-controlled trial in healthy men given 300 μg/day of selenium as high-selenium yeast for 48 weeks suggested that selenium supplements were not likely to improve endothelial function or peripheral arterial responsiveness in healthy North American men receiving adequate selenium from their diets (155). Moreover, increased consumption of wheat biofortified with selenium does not modify biomarkers of cancer risk, oxidative stress, or immune function in healthy Australian males (412).

Although it appears that selenium supplementation has no effect on CVD risk in healthy individuals, in a very recent AtheroGene study, low selenium concentration was associated with future cardiovascular death in patients with acute coronary syndrome, although no effect on stable angina pectoris (232). Further, in the selenium Therapy in Coronary Artery disease Patients (SETCAP) Study, supplementation of sodium selenite increased GPx1 activity in endothelial cells and in coronary artery disease (CAD) patients. Therefore, long-term studies are needed to demonstrate whether CAD outcome can be improved by selenium (320). A cross-sectional study on the association of serum selenium with the prevalence of peripheral arterial disease among 2062 U.S. men and women 40 years of age or older participating in the National Health and Nutrition Examination Survey (NHANES), 2003–2004, suggested that the effects of selenium on athlerosclerosis are nonlinear and may follow a U-shaped relationship (54).

In summary, the observational evidence that low selenium concentrations are associated with cardiovascular risk should be treated as suggestive but not definitive. There is uncertainty about cause and effect; therefore, time-resolved and prospective studies are needed in different pathological settings. Further, when investigating the relationship between selenium and disease risk, future studies need to determine not only selenium status but also genotype in relation to selenoproteins and related pathways (301).

B. Cancer

There are a multitude of studies investigating the effect of selenium on cancer; several recent reviews focus on the potential mechanisms of action using evidence from *in vitro* cell culture studies and *in vivo*, mainly animal model, studies (187, 231, 332, 433). Proposed mechanisms of the effects of selenium on cancer are summarized in Figure 9. They include regulation of cell cycle and apoptosis, antioxidant effect through the action of selenoproteins, in particular, GPx1, GPx4, Sep15, SEPP1, and TXNRD1 (301, 433), modulation of angiogenesis (231), and the extracellular matrix (79, 175), histone deacetylase inhibition (287), carcinogen detoxification, induction of GSTs, alteration of DNA damage, and repair mechanisms, and also immune system modulation (187, 231, 332, 433). However, the effects of selenium on cancer are species-specific, dose-specific, and cancer type-specific and may be affected by genotype and the bioavailability of selenium (Fig. 9), discussed in more detail below. In this review we discuss data from human studies, including RCTs and epidemiological

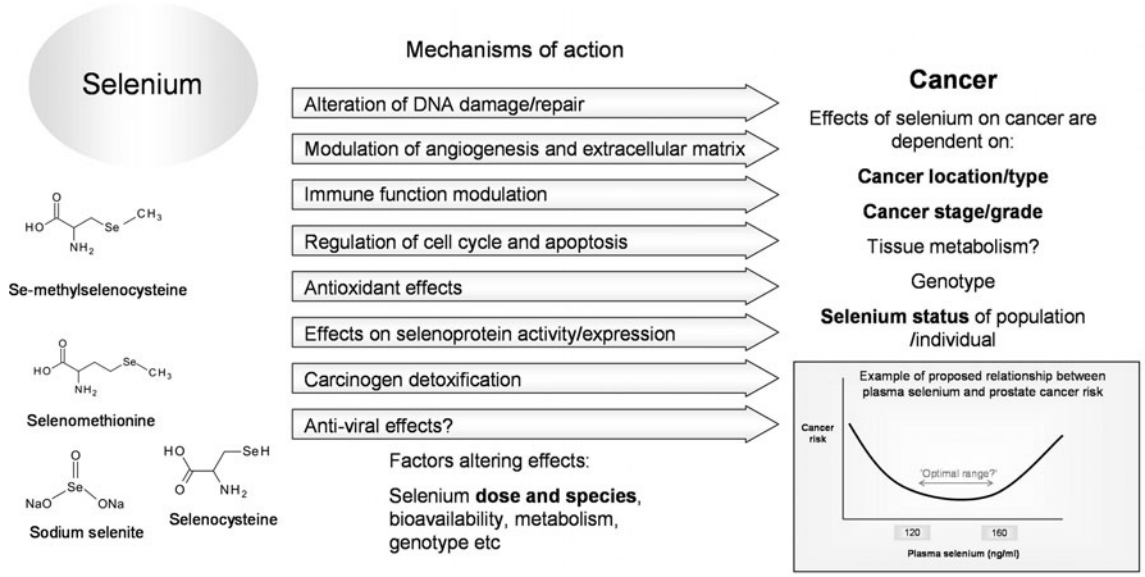

FIG. 9. Purported mechanisms of action of selenium against cancer and key factors modulating the effect of selenium.

data, with a particular focus on the species and dose of selenium in interventions and plasma/serum selenium status.

1. Total cancer incidence and mortality. Willett *et al.* (401) reported an association between selenium and cancer in which the relative risk (RR) of cancer was higher in individuals with low plasma selenium concentrations (<115 ng/ml compared with 128 to >154 ng/ml) (Fig. 10A). The Nutritional Prevention of Cancer (NPC) trial showed a protective effect of selenium-enriched yeast supplements (200 μg/day) on total cancer mortality (86), and also total cancer incidence, but only for men with low plasma selenium concentrations (<121.6 ng/ml at baseline) (101). Participants with baseline plasma selenium >121.6 ng/ml who consumed selenium-enriched yeast 200 μg/day had a trend toward elevated cancer incidence (101).

In one of the large nutrition intervention trials in Linxian, China, with over 20,000 participants, supplementation for ~5 years with 15 mg β-carotene, 30 mg α-tocopherol and 50 μg/day selenium resulted in a small significant decrease in total cancer mortality (55, 56, 390). In the SU.VI.MAX trial (138) the antioxidant status of participants at baseline was related to the risk of cancer in men but not women, and a large 2-year intervention study with selenium and allitridum (a synthetic compound similar to bioactive forms in garlic) with follow-up of cancer incidence for 5 years showed a reduced RR of all tumors in men but not women (221). A meta-analysis investigating the effect of antioxidant supplements on primary cancer incidence and mortality by Bardia *et al.* concluded that selenium supplementation was associated with reduced cancer incidence in men but not women (29).

2. Gastrointestinal cancers. A meta-analysis of five studies published up to 2007 on the effect of selenium on gastrointestinal cancers showed that selenium supplementation was associated with a ~25%–60% reduction in gastrointestinal cancers (overall RR: 0.59, 95% CI: 0.46–0.75) (49); gastrointestinal cancer included esophageal, gastric, small intestine, colorectal, pancreatic, liver, and biliary tract (49). The RR for esophageal cancer was 0.40, and for gastric, colorectal, and hepatocellular carcinoma the RRs were 0.76, 0.48, and 0.56, respectively.

A dietary intervention trial in China showed a significant decrease in esophageal cancer prevalence (364), and also a significant decrease in total mortality and gastric cancer mortality (56, 288, 390). The reduction in esophageal cancer mortality was observed after 10 years of supplementation in the population group <55 years of age (288). Overall, while the results are very striking, the anticancer effects cannot be attributed to selenium alone since the population was also supplemented with vitamin E and β-carotene.

Another large intervention trial in China, with over 5000 participants, investigated the effect of a combined dose of selenium (50 μg/day as sodium selenite) and garlic compound, allitridum (200 mg/day), compared with placebo group on gastric cancer and total cancer incidence (221). The concentration of plasma/serum selenium was not reported in this study, and it is not known whether the effects were due to selenium alone, allitridium alone, or the combination. However, the intervention with selenium and allitridium for 2 years and the follow-up of cancer incidence for 5 years following the intervention period showed that the RRs of all tumors and gastric cancer were reduced, but in men only (221).

As part of a large prospective study conducted in the Netherlands (The Netherlands Cohort Study), the selenium status (toenail selenium) of a subgroup of cases with esophageal cancer and controls (total $n = 2750$) were compared. An inverse association between toenail selenium content and esophageal squamous cell carcinoma and gastric cardia carcinoma was observed (346). The multivariable adjusted RR for esophageal squamous cell carcinoma and gastric cancer were 0.37 (95% CI: 0.16–0.86) and 0.52 (95% CI: 0.27–1.02) respectively, for the highest quartile selenium status (toenail selenium >0.613 μg/g) compared with the lowest quartile (toenail selenium $\leq$0.498 μg/g) (346). The blood selenium concentrations

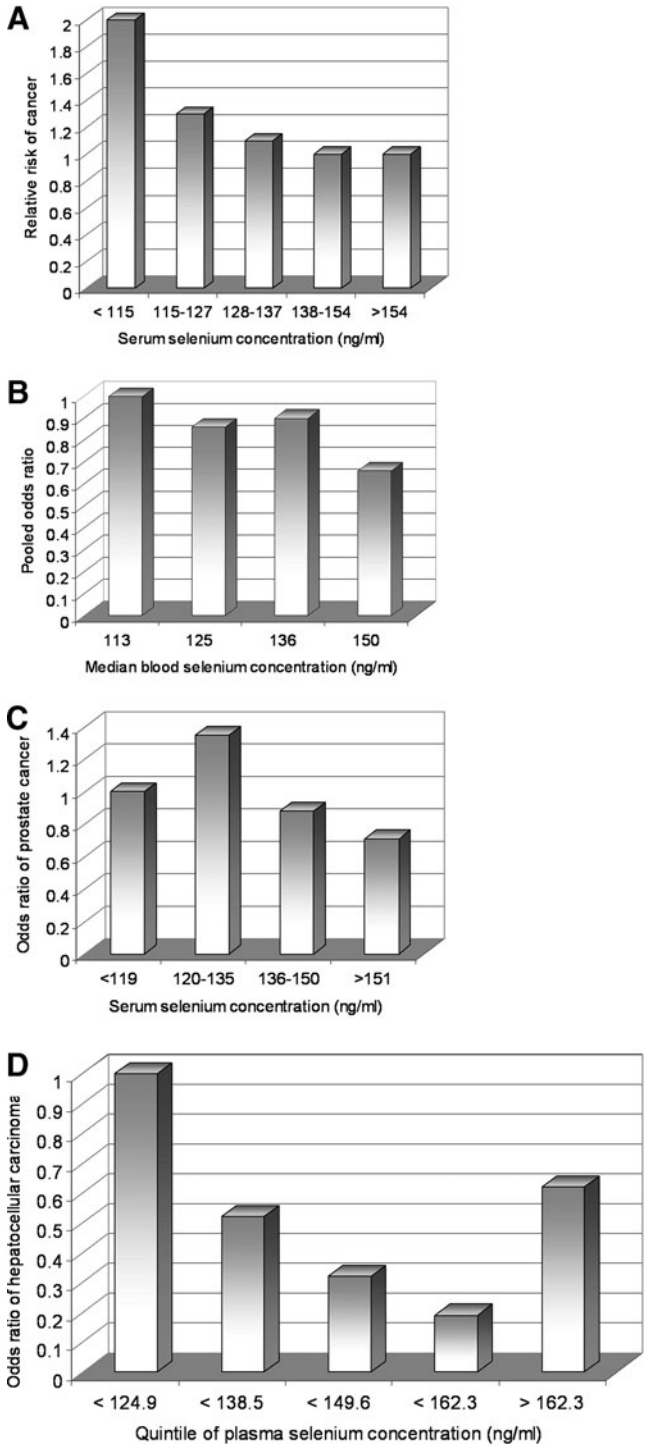

FIG. 10. Cancer risk over a range of blood selenium concentrations/levels from several studies. (A) Relative risk of cancer by quintile of serum selenium level as described by Willet *et al.* (401). **(B)** Pooled analysis of adjusted odds ratios for colorectal adenoma as published by Jacobs *et al.* (188). **(C)** Odds ratios of prostate cancer by quartile of serum selenium as described by Vogt *et al.* (384). **(D)** Adjusted odds ratios for hepatocellular carcinoma by quintile of plasma selenium level as described by Yu *et al.* (426).

and selenium intakes were not reported, but the mean intake of selenium in the Netherlands is estimated to be relatively low, $\sim$43 and 57 μg/day for women and men, respectively (127).

Selenium-enriched yeast supplements (200 μg/day) in the NPC trial significantly reduced the incidence of colorectal cancer and adenomas in participants with low baseline selenium status who were current smokers (304); the mean baseline plasma selenium concentration for all volunteers on the study was 114 ng/ml, and only the group with baseline plasma selenium $<$105.5 ng/ml had a significantly reduced risk of colon cancer after selenium supplementation. Colorectal adenoma cancer patients in Norway were given a daily supplement containing 101 μg selenium, 15 mg β-carotene, 150 mg vitamin C, 75 mg vitamin E, and 1.6 g calcium for 3 years, but there was no overall effect of the supplement on the incidence of colon polyps or the growth of adenomas. However, patients $<$60 years and those with lower incidence of adenomas at inclusion potentially benefited more from the supplement compared with the placebo (168).

Patients with colon adenomas had significantly reduced serum selenium concentration (57 ± 3.97 ng/ml) and other markers of selenium status compared with a control group (serum selenium of 71 ng/ml) (10). Supplementation of these patients with 500 μg/day selenite increased serum selenium concentration to $\sim$87 ng/ml, and in the colon tissue there were specific effects on different biomarkers; for example, GPx increased slightly in response to supplementation. However, markers of cancer growth and progression and biomarkers of effect were not quantified in this study (10). Comparing colorectal cancer tissue with normal mucosa showed a significant reduction or even a loss of SePP mRNA in colon cancer tissue compared with normal tissue. This result was specific for SePP since gastrointestinal GPx differed between tumor and normal tissues, but overall was not significantly different (12). In colon cancer there is likely to be a differential regulation of various selenoproteins and initial evidence points to the relative importance of SePP.

Pooled analysis of the effects of blood selenium concentration on colorectal adenoma risk, from three randomized trials, the polyp prevention trial (317), the wheat bran fiber trial (239), and the polyp prevention study (146), as described by Jacobs *et al.* (188), demonstrated that those who had plasma selenium concentrations in the highest quartile (median 150 ng/ml) had statistically significant lower odds of developing new colorectal adenomas than those with selenium levels in the lowest quartile (median 113 ng/ml), refer to Figure 10B (188). The baseline blood selenium concentration in the three studies was $\sim$130 ng/ml.

Generally, the relationship between selenium and risk of esophageal or gastric cancer is unclear since the human studies to date have investigated low dose selenium (50 μg/day) with a combination of other supplements, or have looked at the association with selenium over a relatively narrow range of selenium status. There is, however, an indication of a protective effect of selenium against colorectal cancer, although the dose–response has not yet been elucidated.

3. Prostate cancer. A case–control study in the United States showed that serum selenium concentrations $>$151 ng/ml were associated with reduced risk of prostate cancer

compared with serum selenium below 119 ng/ml (Fig. 10C). The effect was also associated with serum α-tocopherol concentration: men with low serum α-tocopherol and high serum selenium concentration were at decreased risk of prostate cancer (384). A meta-analysis of epidemiological studies, including case–control and nested case–control studies reporting selenium status (in toenail, serum, or plasma) and prostate cancer incidence ($n = 20$ studies included up to 2005) shows an inverse association between serum levels and risk of cancer (61). Another meta-analysis of epidemiological data of selenium intake and prostate cancer risk (113) indicated that the level of selenium intake and the stage of prostate cancer were important factors. In a comparison of studies reporting prostate cancer risk relative to selenium intake and disease status Etminan *et al.* reported that men with late stage prostate cancer and high level of selenium intake had a pooled RR of 0.69 (95% CI: 0.48–1.01), suggesting that in this population a relatively high selenium intake may reduce cancer risk by ~30% (113). West *et al.* found that for men (aged 68–74) with aggressive prostate cancer and with estimated high intake of selenium (in the two highest quartiles, 139–183 μg/day and >183 μg/day) the RR was increased up to 1.8 (95% CIs were 0.7–4.3 and 0.8–4.4 respectively), compared with lower intakes of selenium (<106 μg/day) (398). This indicates that there is likely to be a relatively narrow range of benefit in terms of selenium intake and chemopreventive effect, and the optimal intake requires further elucidation in different populations.

Selenium supplementation, together with other antioxidants, decreased the risk of prostate cancer (244), but the effects were related to prostate specific antigen (PSA) score; in men with normal PSA concentration <3 μg/l, the reduction in prostate cancer risk was significant, whereas with PSA > 3 μg/l the supplementation was associated with slightly increased risk. In the Nutritional Prevention of Cancer (NPC) trial, baseline PSA also appeared to be linked to the effect of selenium, the protective effect of the selenium-yeast supplement being more effective for men who had baseline PSA 4 ng/ml (100). In a group of men with high-grade prostatic intraepithelial neoplasia (PIN), daily supplementation with 200 μg selenium (as selenomethionine) plus 60 mg vitamin E and 100 mg isoflavanoids (42 mg genistein, 22.8 mg glycitin, and 35.2 mg daidzin) for 6 months decreased PSA concentration and was associated with a trend in decreased prostate cancer diagnosis in repeat biopsy prostate tissue (192). Unfortunately, the study design did not include a placebo or control group (192) and further research is required to investigate the potential reduction in prostate cancer with the supplementation regimen and to investigate which supplement component(s) may be most effective.

More recently, the largest randomized placebo-controlled trial to date investigating the effect of selenium (as selenomethionine) on prostate cancer risk, the SELECT trial (226) did not show a reduction in prostate cancer risk for the population of relatively healthy men studied who consumed 200 μg/day selenomethionine supplement ($n = 8752$) compared with the placebo group ($n = 8696$) over 5 years. Supplementation with L-selenomethionine (200 μg/day) plus vitamin E (400 IU/day all rac-α-tocopheryl acetate) as part of the SELECT study, in a healthy selenium replete group, did not reduce prostate cancer risk either (226). This can probably be attributed to the relatively high selenium status (median baseline plasma selenium concentration ~135 ng/ml) of the population studied, and because selenomethionine may not be the most effective anticarcinogenic form of selenium (182, 183, 290). The NPC trial showed that selenium-enriched yeast may be associated with a reduction in prostate cancer risk, and this protection was confined to those men who had a low baseline plasma selenium concentration <123.2 ng/ml (86, 100). All participants on the SELECT trial were also allowed to consume a multivitamin tablet (containing 400 IU/day of vitamin D_3, plus other multivitamins) and were freely supplied with this multivitamin (225). Other studies have shown that multivitamin use may not protect against cancer, and may increase the risk of certain types of cancer (214). Finally, the World Cancer Research Fund (WCRF) meta-analyses of the studies to date published on selenium and prostate cancer suggest that selenium may be more effective in protecting against aggressive prostate cancer and its progression (408), so selenium may be beneficial for patients who already have prostate cancer.

The effects of selenium are clearly specific to cancer type and stage (61, 113, 408), and the relative risks and benefits of low/replete/high selenium status should be considered carefully. For example, the NPC trial (86) demonstrated that 200 μg/day selenium-enriched yeast reduced prostate, lung, and colon cancer risk but slightly increased the risk of skin cancer in the cohort who had previously had skin cancer (86). The dose is critical as illustrated by the fact that a relatively high dose of selenium-yeast, 400 μg/day, did not reduce total cancer incidence (303), whereas 200 μg/day selenium-yeast did (86). For selenium and prostate cancer the dose, species, status of the population, and cancer type/grade are all important factors linked to outcome and cancer prevention. From a review of the literature, it seems probable that plasma/serum selenium between >120 and <160 ng/ml may be associated with a protective effect; this level of plasma selenium is normally achieved through consumption of ~100–150 μg selenium/day. Improving our understanding of the relationship between selenium and risk and progression of prostate cancer and the underlying mechanisms is a current research priority. One such interesting future research area may surround the action of selenium on viral infection in cancer; for example, some patient cohorts in the United States with malignant prostate cancer have recently been found to have xenotrophic murine leukemia virus-related (XMRV) virus present (318). The relative importance of SePP in prostate may also be a key interesting target, since SePP concentration has been found to be significantly reduced in serum (245) and SEPP1 gene expression downregulated in some types of malignant prostate cancer compared with normal prostate tissue (74). Studies in healthy humans show that SePP reaches a maximum at ~120–125 ng/ml plasma selenium (174), and optimal selenium intake for certain populations with prostate cancer requires further determination.

4. Other cancers. Many cell culture and animal model experiments have focused on the mechanisms of action of selenium on breast cancer, reviewed by El-Bayoumy and Sinha (109), but there are only a few human studies investigating selenium status and breast cancer. An association between GPx1 polymorphism and breast cancer risk was reported (295). Further, a large study investigating the association between several polymorphisms in 10 key genes

associated with oxidative damage repair in >4000 women with breast cancer linked two polymorphisms in GPx4 with increased risk of mortality (373). In a population-based case–control study, using data from the Shanghai breast cancer study with over 1000 participants, breast cancer risk was increased in women with the manganese superoxide dismutase (SOD2) Ala/Ala genotype compared with the Val/Val genotype, especially in those women who were premenopausal and had a higher body mass index (73). In a recent study, toenail selenium content was inversely associated with levels of chromosome damage in BRCA1 carriers with estimated selenium intake of 90 μg/day and toenail selenium concentration of 1.00 μg/g (208). The authors suggested that "selenium supplementation may be beneficial for BRCA1 carriers." However, any potential effect of selenium supplementation on the reduction in chromosome damage is likely to be limited to low intake/status populations.

A meta-analysis of epidemiological studies published on selenium and lung cancer concluded that selenium may protect against lung cancer in low selenium regions, intake <55 μg/day and serum selenium <100 ng/ml (432).

In relation to skin cancer, a combined supplement containing selenium-enriched yeast (providing a daily dose of 120 mg vitamin C, 30 mg vitamin E, 6 mg β-carotene, 100 μg selenium and 20 mg zinc) was associated with increased incidence, in particular melanoma skin cancer, in women when compared with the placebo group over a follow-up period of ~7.5 years in the SU.VI.MAX trial (159). In patients who had a history of skin cancer (nonmelanoma), consumption of 200 μg/day selenium-enriched yeast increased the risk of skin cancer (squamous cell carcinoma and total melanoma skin cancer) compared with the placebo group (86, 102). It seems unlikely that "optimal selenium status" or selenium supplementation regimes can offer protection against skin cancer from the human study data to date and higher selenium status and intakes may be associated with increased risk of skin cancer.

A long-term intervention trial in China with selenized table salt fortified with 15 ppm sodium selenite for over 8 years in over 20,000 individuals showed that the incidence of primary liver cancer decreased by 35% in the selenium-supplemented group compared with the control nonsupplemented group (427). Supplementation with selenium-enriched yeast (200 μg/day) reduced the incidence of primary liver cancer in hepatitis B surface antigen-positive individuals compared with the placebo group (427). Hepatitis B viral infection was prevalent in ~15% of the population in the Qidong region of China, where this intervention study was completed; those who had hepatitis B had a 200-fold increased risk of primary liver cancer. Selenium reduced the incidence in this population but the exact mechanisms for this protection against liver cancer are not known.

In a study carried out in Taiwan, men who were hepatitis B positive and had hepatocellular carcinoma had a significantly lower mean plasma selenium level of 131.6 ng/ml compared with the hepatitis B negative control group (150.2 ng/ml) (426). Among the men who had hepatitis virus infection, the plasma selenium concentration was associated with a difference in odds ratio for hepatocellular carcinoma (Fig. 10D). There was a decrease in hepatocellular carcinoma with an increase in plasma selenium concentration, but the effect in terms of cancer protection was nonlinear; >162.3 ng/ml the number of hepatocellular carcinoma cases started to increase and the odds ratio was on a trend upward, indicating perhaps >160 ng/ml was above the associated protective range of plasma selenium. Overall, men who had hepatitis virus infection and plasma selenium between 150 and 160 ng/ml had significantly less risk of developing hepatocellular carcinoma compared with men who had plasma selenium <124.9 ng/ml.

5. Summary of selenium and cancer research, and ranges that may offer protection. Although direct comparisons of odds ratios, hazard ratios (HR), and relative risks for many studies are not possible because the results are study specific, there is a consistent trend throughout several of the human studies demonstrating potential protective effects with plasma/serum selenium between ~120–160 ng/ml and reduced risk of some types of cancer when compared with the low plasma selenium status, namely <120 ng/ml. Above 160 ng/ml the cancer protective effect is likely to diminish and the risk perhaps increases for some types of cancer. Literature from the 1950s and 1960s showed that an inappropriately high dose range of selenium may actually increase the incidence of certain types of cancer in animal models and selenium used to be classed as a carcinogen in animals when used at high exposure (84, 334). Therefore, a careful balance ensuring selenium intakes and selenium status fall in the relatively narrow base of the U-shaped risk-response curve is critical for potential modulation of certain cancer-type-specific risk profiles.

6. Selenium supplementation as an adjuvant therapy in radiation or chemotherapy treatment. Initial evidence for the role of optimal selenium status in protecting against toxicity and unwanted effects of chemotherapy and radiotherapy in cancer patients seems to be promising, especially considering the often observed depleted selenium status in many cases of cancer. Several studies have shown the potentially protective and beneficial effects of selenium (mainly selenite) supplementation, to protect against toxicity and side effects of radiotherapy and chemotherapy treatments, in particular cisplatin therapy (22, 66, 170, 434, 255). However, the effect of selenium and other antioxidants may only be beneficial for reducing the chemotherapy side effects for certain types of cancer in certain combinations. For example, Weijl *et al.* found no reduction in organ toxicity or other markers of toxicity with a supplementation regimen of selenium plus vitamins C and E (110, 396). The potential beneficial effects of selenium supplementation and therapy treatment for cancer patients are also likely to be selenium dose and species specific, and are also treatment and cancer specific. For example, large superdoses (>2000 μg/day) of selenomethionine to increase plasma selenium to >15–20 μM in cancer patients (various types of cancer including colorectal, small and nonsmall lung cancer, sarcoma, and urachal) undergoing treatment with irinotecan did not seem to provide any overall additional benefit to the patient and did not decrease the toxicity of the treatment (118).

In certain at-risk populations, selenium supplementation and optimization of selenium status should be tested further as an adjuvant to radio- and chemotherapy. The potential mechanisms of action of selenium and radiotherapy treatment of prostate cancer may include effects on DNA damage pathway, cell cycle control, and antioxidant effects (357).

7. Effect of genotype and polymorphisms relating to selenium and cancer risk. Various SNPs in selenoprotein genes *SEPP1, GPX1, GPX4,* and *SEP15* have been associated with cancer risk in humans (including lung, colorectal, head and neck, prostate, breast, bladder, lymphoma, and liver cancers) (section VII.F below) (160, 301, 433).

Other SNPs have also been linked to the effect of selenium on cancer. In a case–control study investigating selenium intake and esophageal squamous cell carcinoma risk and the involvement of two polymorphisms (in aldehyde dehydrogenase-2, *ALDH2* and x-ray repair cross-complementing 1, *XRCC1*), the cohort with *ALDH2* Lys/Lys and *XRCC1* 399Gln/Gln or Gln/Arg genotypes, plus low selenium intake from the diet (<14.6 μg/day) and exposure to tobacco and alcohol, had significantly increased risk of esophageal squamous cell carcinoma (72). The population cohort studied ($n = 633$ in total) was from a selenium-deficient region in China (median selenium intake estimated to be 25.9 μg/day) and where esophageal cancer has the highest worldwide incidence rate (72). Nearly 60% of the patients investigated with esophageal cancer had a selenium intake <14.6–22.1 μg/day, and there was a lower risk of esophageal cancer in the highest selenium intake group (≥43.2 μg/day) (72).

Genetic variants of the gene encoding manganese superoxide dismutase (*SOD2*) were linked with the association of selenium and prostate cancer risk; men who had the AA genotype and higher plasma selenium concentration (>139.8 ng/ml) had a lower risk of aggressive prostate cancer (RR: 0.60, 95% CI: 0.32–1.12), whereas men with the VV or VA genotype and higher selenium concentration (>139.8 ng/ml) had an increased risk (RR: 1.82, 95% CI: 1.27–2.61). The overall suggestion from this cohort study with prostate cancer patients ($n = 489$) from the United States indicated that the association between plasma selenium concentration and prostate cancer risk may be modified by different *SOD2* genotype (81). Cooper *et al.* (89) showed that there was an interaction between *SOD2* and *SEPP* SNPs and prostate cancer risk in a large ($n = 4871$ in total) population case–control study in Sweden. Men who had the SOD2Ala16 + and were homozygous for SEPP1Ala234 had a significantly higher risk of prostate cancer and aggressive prostate cancer (OR: 1.43, 95% CI: 1.17–1.76; OR: 1.60, 95% CI: 1.22–2.09) compared with SOD2val16 homozygotes. This relationship between the *SOD2* and *SEPP1* polymorphisms and prostate cancer risk was more pronounced in smokers (89).

The SEPP1Ala234Thr and rs7579 polymorphisms may also be linked to the relative abundance of the two isoforms (50 and 60 kDa forms) of selenoprotein P in plasma; the 60 kDa form of selenoprotein P was significantly reduced in the plasma of colorectal cancer patients compared with controls and this was linked to *SEPP1* genotype (243). In a relatively small case–control cohort study ($n = 80$ participants in total) investigating the effect of GPX1Pro198Leu and Sep15 1125G/A polymorphisms on selenium status and gene expression in bladder cancer patients compared with healthy controls, the *GPX1* and *SEP15* polymorphisms were not associated with the gene expression levels of *GPX1*, *GPX3*, *SEP15*, or *SEPP* or with plasma selenium concentration, but in patients with bladder cancer *SEP15* and *GPX3* were correlated with grade of cancer. The expression levels of genes *GPX1*, *GPX3*, *SEP15*, and *SEPP1* were significantly decreased (1.3–2.0-fold) in leukocytes from bladder cancer patients compared with the healthy controls (309). In a selenium supplementation trial, *BRCA1* mutation carriers had increased levels of DNA damage marker (8-oxodG) in leukocyte DNA compared with the control group without the BRCA1 mutation, and after supplementation with 300 μg/day sodium selenite, the DNA damage marker level significantly decreased (106).

Genetic variation in selenoprotein genes and other genes may impact both the response to selenium and cancer risk/outcome, which adds complexity to the relationship between selenium and cancer and requires further investigation to pinpoint the key genetic associations and mechanisms of effect.

C. Diabetes

The evidence supporting an effect of selenium on the risk of diabetes is variable, occasionally conflicting, and limited to very few human studies. Following a trial investigating the effect of selenium supplementation (200 μg/day) on skin cancer, subsequent analysis showed that there was an increased risk of developing type 2 diabetes in the supplemented group (349). The participants in the trial were North American and generally selenium replete. Supplementation over a period of 7 years increased plasma selenium concentrations to ~180–190 ng/ml (HR: 1.55, 95% CI: 1.03–2.33), and it was observed that the risk for developing diabetes was greatest in participants with the highest tertile of baseline selenium status, >121.6 ng/ml (HR: 2.70, 95% CI: 1.30–5.61). These findings suggest that the Upper Tolerable Intake Level for selenium, currently set at 400 μg/day by the United States DRI committee (274), may need to be revised, and that there could be adverse effects associated with higher dietary intakes that are not as overt as the typical toxicity signs associated with selenosis (51).

Evidence from analysis of NHANES III (52) supports these findings; the adjusted mean serum selenium concentrations were slightly, but significantly, higher in diabetics compared with those without the disease; comparison of the highest (>137.66 ng/ml) with the lowest (<111.62 ng/ml) quintile gave an odds ratio of 1.57 (95% CI: 1.16–2.13). Conversely, recent evidence from a European population suggests that the incidence of diabetes was greater in men with lower median plasma selenium concentrations compared with higher concentrations (71.06 ng/ml *vs.* 101.86 ng/ml) (4). This study, conducted in an elderly French population, found a sex-specific protective effect of higher selenium status at baseline on later occurrence of dysglycemia; that is, risk of dysglycemia was significantly lower in men with plasma selenium in the highest tertile (93.96–155.55 ng/ml) compared with those in the lowest tertile (14.21–78.96 ng/ml) (HR: 0.48, 95% CI: 0.25–0.92), but no significant relationship was observed in women.

Cross-sectional case–control analyses have also given mixed results. A number of studies have found a lower selenium status in diabetic patients compared with controls (202, 259), which is in contrast to the findings from the NHANES III analysis (52, 212). Analysis of the Health Professionals Follow-up Study found the prevalence of diabetes to be greater in men with the lowest tertile of toenail selenium (OR: 0.43, 95% CI: 0.28–0.64) compared with the highest tertile (291). The study also analyzed men with both diabetes and CVD compared with controls, but no association was found. Due to the global variations in selenium status these studies may not be

directly comparable, and the results may in fact indicate a U-shaped risk curve, which could be further complicated by other diseases associated with diabetes.

The mechanisms behind this potential U-shaped risk association have not yet been clearly defined. In its role as an antioxidant, particularly within the GPxs, selenium is likely to be important in reducing oxidative stress, an important risk factor for developing diabetes. There are also plausible suggestions that selenium can influence glucose metabolism. However, at high intakes it is also conceivable that reactive oxygen species could be generated or selenium may accumulate in the organs associated with glucose metabolism (51). In patients with diabetes, selenium supplementation (960 μg/day) reduced NF-κB levels to those comparable with nondiabetic controls (121). Animal model work has also suggested a role for selenium supplementation in reducing some biochemical effects of diabetes. Hwang *et al.* (176) found that selenium supplementation of NOD (nonobese diabetic mice) counteracted ER stress through stimulation of PERK-eIF2 and IRE1-JNK pathways and also activating the insulin-signalling pathway. The study also suggested that treatment with selenium may influence aspects of other chronic diseases associated with diabetes, for example, by decreasing the levels of serum markers of liver damage. SelS was first isolated (at the time called Tanis) during work on diabetic rats and is thought to be an important link in the relationship between diabetes, inflammation, and CVD (387). Expression of SelS was found to be significantly lower in diabetic rats in a fed state compared with normal control animals and appears to be regulated by glucose. The importance of SelS in inflammatory responses is described further in section VII.D. Whatever the mechanisms responsible, current evidence implies that both low and high selenium intakes could influence the risk of diabetes, and this relationship requires further investigation through good quality human studies.

D. Inflammation and inflammatory disorders

In addition to being an important antioxidant, selenium has anti-inflammatory properties. The underlying mechanisms have recently been reviewed elsewhere (104). In summary, there are a number of ways in which selenium can influence inflammatory responses, including the inhibition of the NF-κB cascade, which induces the production of interleukins and tumor necrosis factor-α (TNF-α) (209). Evidence also suggests that SelS has a key role in inflammatory responses, first identified in diabetic rats (387). Serum amyloid A (SAA) is an acute phase response protein produced in the liver, and SelS has been identified as a potential receptor for the protein (387), thus also establishing a link between selenium and CVD (as SAA is incorporated into HDL cholesterol). Polymorphisms in the *SELS* gene have been linked to variations in markers of inflammation, with one particular variant $-105\text{G} \rightarrow \text{A}$ showing significantly impaired expression of SelS (91). However, a recent case–control study indicated that there is no association between six polymorphisms in the *SELS* gene and autoimmune inflammatory disorders, including arthritis and diabetes (238). There is evidence to suggest a sex-specific effect of selenium on inflammatory responses (324), which may explain some of the variation in findings related to inflammatory disorders. There is a degree of sexual dimorphism in the distribution of selenium throughout the organs of the body, which could impact on selenium status and prioritization of certain systems or tissues in times of deficiency. However, presently little consideration is given to the effect of sex in either animal or human experimentation (324).

Chronic inflammatory disorders are normally associated with a decrease in selenium status, and cross-sectional case–control studies have suggested that patients with inflammatory disorders such as cystic fibrosis (247), acne (246), and inflammatory bowel disease (268) may have a lower selenium status than healthy controls. Therefore, supplementation with selenium could possibly alleviate some of the symptoms of such disorders through increasing antioxidant activity and suppressing inflammatory conditions. Unlike the potential preventative benefits of selenium seen for other health issues, most of the research surrounding inflammatory disorders has been focused on supplementation as an alternative therapy, or treatment, for patients.

A systematic review (6) of selenium supplementation for chronic asthma patients found only one RCT of sufficient quality to assess the efficacy of intervention. In this study (151) significant improvements were seen in the overall clinical evaluation of patients in the supplemented group; however, these differences were not seen in the individual parameters measured. All other assessed studies were either not randomized or before–after trials, and therefore did not meet the inclusion criteria for the review. The authors therefore concluded that although there was some indication of a positive effect of selenium supplementation, high-quality evidence is currently lacking. A more recent larger RCT (333) concluded that selenium supplementation did not result in any significant improvements in either lung function or asthma-related quality-of-life scores.

Other studies have indicated a varied response to supplementation for asthma patients. One hypothesis for the variation in intervention results is that although selenium may have important antioxidant properties, it can also enhance the immune reactions responsible for the allergic responses of the disorder (167). Mouse model work has suggested that low and high selenium status may produce smaller allergic responses than a moderate selenium status (166). This may explain some of the variation in human trial results, assuming that patients supplemented in the various studies had diverse selenium status at baseline. However, a large European-wide case–control analysis of selenium levels in asthma patients and healthy matched controls revealed no association between status and risk of the disease (71). There are, of course, other variables to consider, such as the specific type of asthma, population characteristics, and concurrent use of asthma drugs, which are likely to further complicate an already intricate relationship.

Selenium has also been postulated as a potential therapy for rheumatoid arthritis (RA) patients. Like many other inflammatory disorders, selenium status appears to be lower in RA patients than in controls [summarized in Tarp (363)]. A recent systematic review of the use of antioxidants for treatment of arthritis concluded that the five trials identified (for selenium and RA) were generally of poor quality and that few conclusions could be drawn on the efficacy of supplementation. No meta-analysis was performed because in some instances data reporting was incomplete, but most of the included studies did not report any significant effect of selenium supplementation on clinical outcomes (75).

Although there appears to be good evidence from case–control studies suggesting lower selenium status in patients with inflammatory conditions compared with healthy controls, there is little supporting evidence from high-quality RCTs for a therapeutic effect of selenium supplementation. This could, in part, be explained by the dual functionality of selenium, influencing both antioxidant and immune responses. Further high-quality interventions are required to establish these relationships.

E. Fertility

The use of selenium supplements for fertility problems in some domestic animal species prompted an investigation into the relationship between selenium and impaired fertility in both men and women, and reproductive outcomes. Much of the current evidence has been focused on the role of selenium in male spermatogenesis and semen quality (*e.g.*, sperm count, semen volume, motility, and morphology), but links have also been made to female reproductive issues such as pre-eclampsia and miscarriage (296). The evidence supporting a role for selenium in female fertility is limited, although there are data to suggest that women with unexplained infertility may have lower selenium levels in the follicular fluid than those with explained infertility (280). A study in which couples were assessed over a period of 5 years found that the pregnancy rate was greatest in the mid-range of selenium status (50); however, status was only measured in the semen of the men, and therefore these findings require cautious interpretation as the exposure of both partners would not necessarily be similar.

There is a larger body of evidence supporting a potential role for selenium, and antioxidants in general, in postconception physiology and complicated pregnancies. Infants born to mothers with the lowest selenium status in the early stages of pregnancy have significantly lower birthweights than those born to mothers with higher selenium status (57). Cross-sectional analysis suggests that women with pre-eclampsia have both a significantly lower selenium status in the latter stages of pregnancy and lower levels of placental GPx at delivery than healthy pregnant women (24). Pre-eclampsia is characterized by an increase in the usual inflammatory responses that occur during pregnancy. Subsequently, following the discovery that SelS is associated with inflammatory responses (91), a retrospective genetic analysis of a case–control study in Norway identified an increased risk of pre-eclampsia in women carrying the allele associated with impaired SelS expression (254). Miscarriage has also been linked with selenium status; Barrington *et al.* (30) found that women recently suffering a miscarriage in the first trimester of pregnancy had significantly lower selenium status than pregnant women at the same gestational age. A decrease in antioxidant enzyme activity (particularly the GPxs) is attributed to the effect (428).

The relationship between selenium and male fertility has been widely studied using animal models and cross-sectional analyses of semen samples. However, the effect of dietary supplementation on fertility measures has not been widely studied through human interventions, and has thus far given inconsistent results. Behne *et al.* (38) showed that the testis are a primary target for selenium within the body (Fig. 4), and during times of deficiency the supply of the micronutrient to the male gonads appears to be prioritized. The selenium content of the testis is high, and increases during puberty. SePP is required to transport selenium, particularly to the testis, where apoER2 is known to act as a receptor (273). In *Sepp1* knock-out mice the semen quality is severely compromised, and wildtype mice fed low selenium diets show almost identical problems, but these are reversed upon feeding a high-selenium diet (270, 272).

The majority of selenium found within the testis is incorporated into the selenoprotein GPx4, which is expressed in particularly large amounts and is now thought to have multiple roles within spermatogenesis. The selenium-containing GPx enzymes are considered to have key antioxidant activities, scavenging and protecting cells from reactive oxygen species. GPx4 fulfils this role within the testis, and is highly expressed and active during the process of sperm maturation. GPx4 also has a structural role within the mature spermatozoa, most of the selenium content of mature spermatozoa is still present as GPx4; however, the activity of the enzyme is negligible (374). During the final phases of sperm maturation, GPx4 forms interlinking structures and comprises >50% of the mitochondrial containing capsule of mature spermatozoa, a unique example of a GPx enzyme forming a keratin-like structure and subsequently losing its activity (374). The position of the capsule, in the mid-piece of the spermatozoa, is likely to explain the structural defects commonly seen in selenium-deficient animals, particularly the brittle and weak connection between the head and tail regions (411). Two recent animal studies that used spermatocyte-specific GPx4 knockouts or mice lacking expression of mitochondrial GPx4 both found that these mice were infertile, characterized by a reduced number of spermatozoa plus increased abnormalities (178, 321). Other selenoproteins present in the testis include selenoproteins V, W, K, 15ka, and S, but the specific function of these within the testis remains unknown (59).

Three different measures of selenium content in semen can be made: the selenium concentration in the semen as a whole, the concentration in the seminal plasma, and the concentration in the sperm. The choice of compartment is critical in assessment of selenium concentration. Sperm selenium content is well regulated and does not appear to be heavily influenced by dietary intake. Seminal plasma, however, is largely composed of secretions from other glands (notably the prostate) and therefore may not accurately reflect the selenium present within the testis. Semen selenium takes both measures into account, but it is, to a certain extent, dependent upon sperm density (37).

Semen selenium values are typically about a third of the value of blood plasma selenium (312) and extremes of semen concentration have been associated with reduced semen quality, particularly motility (50). Many cross-sectional analyses have been conducted to attempt to establish a relationship between infertility and selenium content of semen. Takasaki *et al.* (358) found no significant difference between the selenium concentration in whole semen or seminal plasma of fertile and infertile men, although the sperm selenium content was significantly higher in the infertile group. The exact proportion of semen selenium that is contributed by sperm appears to vary, and not only according to the sperm count. Behne *et al.* (37) found a correlation between the sperm count of men seeking treatment for infertility and the contribution of sperm selenium to whole semen concentrations, but

the proportion ranged from 0% to 41% and was not in agreement with previous studies that suggested a value of around 15% regardless of sperm count (50).

Since the discovery of the importance of the GPxs to male fertility, particularly GPx4, a number of cross-sectional analyses of their relevance to measures of male fertility have been conducted. Alkan *et al.* (5) reported that levels of GPx in the seminal plasma of infertile men were lower than those of fertile men, which in turn led to higher levels of reactive oxygen species. GPx4 expression is significantly lower in the spermatozoa of some men with reduced fertility, but this only appears to account for about a quarter of infertile men (180). A comparison of the rescued GPx4 activity of specimens from fertile and infertile men found the range of activity to be significantly lower in the latter (131).

Relatively few intervention studies have been conducted, and these have yielded mixed results. Scott *et al.* (330) showed that supplementation with selenium (100 μg/day, as L-selenomethionine) improved motility after 3 months. However, the patients recruited for the trial had a low initial selenium status and had low motility levels at onset of treatment. An earlier study administering 200 μg/day as either selenium-enriched yeast or sodium selenite showed no significant effect on semen quality measurements in either group (184). A controlled feeding trial, in which men were given either high (297 μg/day) or low (13 μg/day) selenium-containing diets for 99 days, found no changes in sperm selenium or androgen levels throughout the trial (156). However, there was a significant decrease in the fraction of motile sperm in the high-selenium group, and an overall decrease in sperm count in both groups. It was hypothesized that the latter could be a result of seasonal fluctuations in sperm production. Selenium supplementation with selenium-enriched yeast (247 μg/day) also resulted in no significant changes in testosterone levels or ratios in a small group of healthy adult males (108).

In one of the largest intervention trials to date, Safarinejad and Safarinejad (313) conducted a 2×2 factorial trial to study the effects of selenium and *N*-acetyl-cysteine (NAC) on a group of 468 infertile men. A dose of 100 μg of selenium/day was administered to one group for 26 weeks, which resulted in an increase in testosterone and all semen quality parameters. Similar patterns were seen in the NAC group and the size of effect was increased in the group receiving both types of supplement. The authors suggest that the positive effects seen in this trial may have been a result of the larger study groups, the population setting (with selenium status likely to be influential), the form of selenium administered, and the specific targeting of their study to a group of infertile men with conditions most likely to respond to supplementation. A further intervention trial by Hawkes *et al.* (154) supplemented healthy men with 300 μg/day selenium-enriched yeast for 48 weeks and found no effect on testosterone levels or semen quality measures. However, semen volume and sperm selenium decreased, and velocity and normal morphology increased in both the supplemented and placebo groups. The study also confirmed that sperm selenium levels are almost entirely unaffected by recent dietary intakes, as the concentration in the supplemented group did not alter despite large significant increases in blood selenium levels.

In addition to selenium supplementation trials, a number of studies have assessed combinations of micronutrients as a therapy for infertility in male patients. Keske-Ammar *et al.* (197) compared a combination of selenium (as "Bio-selenium," 225 μg/day) and vitamin E with a control of B vitamins (a standard therapy) in infertile men. Although a significant improvement was seen in mobility after 3 months in the vitamin E-selenium group, less than half of the originally recruited patients completed the study. A small study ($n = 9$) supplementing infertile men with a combination of selenium (100 μg/day organic selenium) and vitamin E reported significant improvements in motility, normal morphology, and percentage of live spermatozoa after a treatment period compared with a baseline control period (381).

The disparity in results from intervention and observational studies makes it difficult to disentangle selenium–semen quality relationships. The considerable natural variation in semen parameters, even within defined fertility categories, makes large sample sizes imperative. Further, the selenium status of the population, form of selenium administered, and duration of intervention all varied in the few intervention trials conducted. Duration could be particularly important if seasonal variations can account for large differences in semen measures, as suggested by Hawkes *et al.* (156). Few studies have actually looked at reproductive outcomes associated with semen parameters and selenium intake. One intervention trial reported a paternity rate of 11% in the supplemented group (330), and a cohort followed up reproductive outcomes for up to 5 years, reporting that pregnancy rate was highest in the mid-ranges of semen selenium (50). It is clear, however, that much is still unanswered regarding the influence of selenium on male fertility and, in particular, actual reproductive outcomes. Further high-quality interventions are required to establish whether selenium has any discernable therapeutic effects for male infertility, and if so in which populations and circumstances. Evidence to date suggests that high dietary intakes (although below the upper safety limits) may be as detrimental as deficiency to male fertility, and therefore determining the optimal range for health is all the more pertinent.

F. Genetics of selenoproteins

Theoretically, there are three broad routes by which selenoprotein function can differ between individuals: first, different dietary intakes affect selenoprotein synthesis and activity; second, genetic variants in a selenoprotein gene (mutations or SNPs) lead to altered protein function or regulation; third, a combination of dietary intake and genetic variants affect selenoprotein function. It is well established that selenoprotein synthesis varies with dietary intake and that there is a hierarchy in sensitivity to selenium intake (39, 42). In addition, a small number of mutations have been identified in selenium-related genes that lead to clinical disease. For example, a mutation in the gene encoding SECIS Binding Protein 2, SBP2, causes an amino acid change that results in altered selenocysteine incorporation into selenoproteins, and as a result impaired thyroid hormone action due to low deiodinase expression (103). Recently, newly identified nonsense mutations in this gene have been shown to lead to a complex syndrome that includes myopathic, thyroid, and neurological features (122). In addition, a congenital muscular dystrophy has been associated with a rare mutation in the region of the selenoprotein N gene predicted to correspond to the SECIS within the 3′UTR (7). In these cases the effect of the

rare mutation is independent of selenium intake—they give rise to genetic diseases. In contrast, links between common SNPs, alone or in combination with sub-optimal dietary selenium, and risk of multifactorial diseases such as cancer and heart disease remain to be established. However, over the past few years a number of SNPs in selenoprotein or selenium-related genes have been shown to have functional consequences and thus to be worthy of study in relation to disease risk.

Selenocysteine incorporation occurs during translation by a mechanism that requires a specific RNA stem-loop structure (SECIS) in the 3′ untranslated region (3′UTR) of the mRNAs (39, 160); therefore, it is important to consider SNPs selenoprotein gene regions corresponding to 3′UTR sequences and not only those in promoter or coding regions. Indeed in selenoprotein genes SNPs identified as being functional have been found in coding, promoter, and 3′UTR regions.

The first coding region SNP identified in a selenoprotein gene was rs1050450, which causes a Pro to Leu amino acid change in GPx1 and which alters enzyme thermal stability and enzyme activity (133). The variant has been found to alter the relationship between plasma selenium and blood cell GPx1 activity (185). More recently, a coding region SNP in the *SEPP1* gene (rs3877899) was identified (240), and this is predicted to cause a Thr to Ala change in the amino acid sequence. The SNP apparently alters SEPP function since it leads to altered responses of blood cell GPx1, GPx4, and TR1 to selenium supplementation and also affects the proportion of SePP isoforms in plasma (240, 243).

Reporter genes have proved useful in assessing the functionality of promoter region polymorphisms in the selenoprotein genes. For example, the promoter region of the *SePP1* gene contains a TC repeat sequence, and a SNP in this sequence has been found to cause lower promoter activity when linked to a reporter gene and expressed in a liver cell line (11). More recently, eight linked variants have been identified in the promoter region of the *GPx3* gene; reporter studies have suggested differences in promoter activity between the two haplotypes, suggesting that there are functional variants within these groups (383). In addition, a SNP has been found in the promoter region of the *Selenoprotein S* gene at position −105, and this variant has been found to alter both the levels of markers of inflammation such as TNF-α and interleukin 1β and the response to endoplasmic reticulum-related stress (91).

Reporter genes have also proved useful in exploring the functionality of SNPs in gene regions corresponding to the 3′UTR of selenoprotein mRNAs. Approximately 10 years ago two SNPs, a C/T substitution at position 811 (rs5845) and a G/A at position 1125 (rs5859), were found in the region of the *Sep15* gene that corresponds to the 3′UTR of the mRNA, and expression studies using the sequences linked to a reporter gene showed that the combination of the variants influenced read-through at a UGA codon (172). In addition, a variant in the 3′UTR region of the *GPX4* gene (rs713041) has also been found to determine selenoprotein deiodinase reporter gene activity in transfected Caco-2 cells; the two allelic variants of this rs713041 SNP in *GPx4* promote reporter activity to differing extents in selenium-deficient and selenium-supplemented conditions (46). The C variant promotes reporter gene activity to a greater extent and this would be expected to result from greater selenocysteine incorporation into the deiodinase reporter. In addition, *in vitro* RNA–protein binding assays show that transcripts corresponding to the T and C variants differ in their ability to form RNA–protein complexes (241), with the C variant having the stronger binding properties. Further, data from a selenium supplementation trial showed that this SNP affected responses of GPx4, GPx1, and GPx3 protein expression or activity in response to selenium supplementation or withdrawal (241). In addition, a G/A variant has been found at position 25191 in the 3′UTR region of the *SEPP1* gene (rs7579) and on the basis of results from a human selenium supplementation trial the SNP appears to be functional. Rs7579 was found to modulate both plasma and lymphocyte GPx activities, plasma concentrations of SePP post-supplementation, and the proportion of SEPP isoforms found in plasma (240).

The allele frequencies of a limited number of these SNPs have been assessed in disease association studies [reviewed in Hesketh (160) and Rayman (301)] and although the cohorts analyzed have been relatively small the analyses have led to suggestions that some of the variants may be associated with disease risk. Variants in the family of GPx gene family have been linked to cancer risk. The Leu variant of GPx1 (rs 1050450) has been reported to increase susceptibility to lung, breast, and bladder cancer, possibly when combined with the influence of either a second SNP in the gene encoding the antioxidant defense protein manganese superoxide dismutase or environmental factors such as alcohol consumption and smoking (90, 171, 177, 293, 295). These studies suggest that this allele, in combination with increased cell stress, affects disease susceptibility.

To date, studies of the association of rs713041 (a T/C SNP in the 3′UTR of *GPX4*) have produced contradictory results with one small UK study indicating that the T variant is associated with a lower risk of colon cancer (44), but a recent larger study in a Czech population showing that the T variant is associated with a higher risk of colorectal cancer (CRC) (242). In addition, results from a large association study suggest a link between genotype at this SNP and susceptibility to breast cancer (373). Other variants have been reported in the *GPx4* gene, but there was no clear relationship between any of these variants and sperm viability or fertility. SNPs in the promoter region of the *GPx3* gene fall into two haplotype groups, and the group that showed a lower activity in reporter gene assays was also present at higher frequency in children and young adults with arterial ischemic stroke (383).

Since SePP has a key role in selenium transport, it might be expected that variants in this gene would influence risk of diseases in which selenium intake has been implicated as a determining factor. However, the evidence for such associations is limited. Initial studies suggested that neither the TC promoter polymorphism nor the Ala-Thr SNP in *SEPP1* (rs3877899) show altered allele frequencies in colorectal cancer patients (11, 12). However, a more recent study has studied different SNPs in the *SEPP1* gene and reported that a combination of several SNPs in *SEPP1* promoter modify risk of colorectal adenoma (286). Recent studies have suggested that rs7579 is associated with altered risk of CRC and rs3877899. In combination with the rare allele for the manganese superoxide dismutase SNP rs4880 affects risk of prostate cancer in smokers (89).

An association between the combined rs5845 and rs5859 variants in *Sep15* and breast cancer risk has been reported; in addition, the genotype for rs5859 has been observed to

influence lung cancer risk in smokers (186). Two small association studies have showed no evidence that the −105G → A SNP in the promoter of *SelS* affects risk of ulcerative colitis or other autoimmune inflammatory diseases (331). However, a recent study in a Japanese population has suggested the variant affects the risk of gastric cancer (338). In addition, a recent association study has linked another variant in *SelS* (rs 34713741) to CRC risk (242).

In summary, genetic variants in regions of selenoprotein genes corresponding to promoter, coding region, or 3′UTR have been identified and shown to cause functional changes. To date, disease association studies of these SNPs have been inconclusive and there is a need to carry out more extensive studies of larger cohorts so as to incorporate analysis of an appropriate range of SNPs to assess variation across the selenoprotein pathway as a whole, and in combination with selenium status/intake. Results of the small association studies carried out to date suggest that such future extensive studies will be important, especially when they consider interactions between different variants and also take environmental and dietary factors into account.

VIII. Selenium in Critical Illness

Selenium is generally accepted as an essential component of total parenteral nutrition since in its absence deficiency symptoms are observed (198, 292), and it has been shown to have a positive effect on immune function in patients on home parenteral nutrition for short-bowel syndrome (285).

Critically ill patients, including those with burns (40), have reduced plasma GPx activity and selenium concentrations (236, 237), in particular selenoprotein P (129). The magnitude of the decrease in plasma selenium appears to reflect the severity of the disease (15) and the concentration continues to fall over time for patients in intensive care (152). There is an accompanying increase in urinary selenium excretion (201) although these losses are not enough to account for the reduction in plasma selenium concentrations, which must reflect the redistribution of body selenium. In the light of these observations it has been suggested that there is a higher demand for selenium in critical illness, and recommendations made for selenium to be included in parenteral nutrition and/or for selenium to be administered intravenously (25, 335).

The reason for the transfer of selenium from plasma into other body compartments is not known, and the underlying mechanisms have yet to be elucidated. In critical illness, TSH, thyroxine, and thyroxintriodothyronine (T3) are low and reverse T3 is elevated (195). Although the etiology and consequences of changes in thyroid hormones are unclear, it is likely to be a direct effect of cytokines rather than selenium insufficiency *per se* (142). The hierarchy in synthesis of selenoproteins when selenium supply is inadequate gives preference to the three iodothyronine deiodinases involved in thyroid metabolism (45). Further, selenium supplementation has no effect on thyroid hormone levels in critically ill patients (16).

Excessive oxidative stress plays a key role in the development of complications of critical illness, such as systemic inflammatory response syndrome (SIRS). Several selenoproteins are enzymes involved in antioxidant defences and redox regulation, such as the GPxs, thioredoxin reductases, and methionine sulfoxide reductase. Sepsis is an important cause of mortality in intensive care unit patients; infection and endotoxemia provoke a cascade of localized and systemic responses, including increased free radical production, cytokines, and lipid peroxidation (139). It has been proposed that low GPx activity in critically ill patients and low total, but increased glutathione disulfide levels, plus increased free radicals in body compartments may contribute to multiorgan failure (149). Selenium supplementation (158–454 μg/d) was found to increase plasma selenium and GPx activity in severely septic patients in intensive care, but thyroid function tests, C-reactive protein, and F2 isoprostanes were unaffected (250). An intriguing hypothesis to explain the observed redistribution of selenium in septic shock and SIRS is that selenoprotein P binds strongly to the endothelium and hence the fall in plasma concentration, which is particularly notable just before death (129).

High-dose selenium supplementation has been reported to decrease mortality in septic shock, especially when using a bolus administration, whereas studies using a continuous administration fail to find any benefit. In septic shock patients given high-dose selenium administration by continuous infusion (selenium as sodium selenite (4000 μg on the first day, 1000 μg/day for the 9 following days) or placebo), there was no difference in mortality rates or adverse events rates. Conversely, when patients with severe SIRS, sepsis, and septic shock were given 1000 μg of selenium as sodium-selenite as a 30-min bolus injection, followed by 14 daily continuous infusions of 1000 μg intravenously, or placebo, mortality rate was reduced (14).

Heyland *et al.* (161) undertook a systematic review to investigate whether antioxidant supplementation (including selenium) improved the survival of critically ill patients. Subgroup analysis of seven studies showed a trend [RR: 0.59, 95% CI: 0.32, 1.08 $p = 0.09$] toward lower mortality with high dose (500–1000 μg/d) selenium supplements, either alone or in combination with other antioxidants, but not with lower doses (<500 μg/d); there was no effect of selenium on infectious complications. A Cochrane Review on the impact of selenium supplementation in critically ill adults was published in 2004 and updated in 2007 (27). Ten randomized trials involving 1172 patients were included, but they were reported to be generally poor quality (inadequate size and/or methodology). The administration of intravenous sodium selenite was not demonstrated to result in a significant reduction in mortality of intensive care patients. There was also no effect on the development of infection, or number of days on a ventilator, length of intensive care unit stay, length of hospital stay, or quality of life. Since these systematic reviews were published, the results of a trial examining the influence of early antioxidant supplementation (selenium, zinc, vitamin C, and thiamine) on clinical outcome of critically ill patients in intensive care with conditions characterized by oxidative stress, namely, cardiac valve or coronary bypass surgery with postoperative complications, major trauma, and severe subarachnoid hemorrhage, have been published (41). Plasma selenium increased and C-reactive protein decreased faster in the test *versus* the placebo group, but infectious complications did not differ and length of stay in hospital was only reduced in the trauma group.

In conclusion, despite the well-documented fall in circulating selenium in critical illness, there is limited evidence for any meaningful improvement in the outcome that can be

attributed to selenium supplementation. A large trial (SIGNET) in critical care patients has recently been completed to determine whether selenium and glutamine offer any potential to enhance host defence and thereby reduce infections and mortality (13). Another trial (CRISIS) is currently underway, investigating the prophylactic effect of enteral supplementation with zinc, selenium, and glutamine on nosocomial infections and sepsis in critically ill children (78). When the results of these trials are published, it will hopefully be possible to develop a transparent and robust policy for selenium administration in critical illness.

IX. Dietary Reference Intakes

The range of intake between which selenium deficiency and toxicity occurs is relatively narrow, with current estimates suggesting that intakes below 30 μg/day are inadequate and those exceeding 900 μg/day are potentially harmful (409, 420). Globally, dietary intakes traverse both of these guidelines due to the influence of geochemistry on the quantity of selenium in foods. The best known examples of the influence of local geochemistry on selenium intakes are within China, where there are areas with extremely low and high selenium consumption. Much of the data pertaining to the risks of excessive and deficient intakes have been derived from these areas.

The methodology and terminology of DRIs can be confusing. Essentially, DRIs encapsulate a range of different values recommended by expert bodies, although even the term DRI is not exclusive, with dietary reference values and nutrient intake values having similar definitions. Although there have been attempts to align the terminology (199), at present it is as diverse as the values themselves. Each set of DRIs typically includes values equivalent to an estimated average requirement (EAR), the mean intake level that would meet the needs of half the population, and a recommended dietary allowance (RDA), the intake level at which the needs of 97.5% of the population are met (2 SDs above the EAR; Fig. 11). In addition, many bodies have issued advice on the tolerable upper intake level, the highest daily intake level that poses no adverse effects to health and normally includes the application of an uncertainty factor; some have also designated a lower level of intake, normally defined as the minimum intake required to maintain proper function or prevent deficiency symptoms.

Not only do current dietary recommendations aim to prevent overt deficiency, but also, in most cases, the DRIs have been set to achieve an optimum status. For selenium, the most commonly used marker for deriving current recommendations is the optimization of plasma GPx3 activity. Despite this, DRIs for selenium are diverse (Fig. 12). This variation is largely due to the selection of articles from which to derive an evidence base, the use of varying average body weights, and the interpolation techniques applied. The DRIs for adults published by a selection of countries and expert bodies are shown in Table 1. Some of the recommendations, notably the UK (93) and the European Food Safety Authority (EFSA) (329) DRIs, are almost 20 years old, and since then further data from studies have become available. However, when the Nordic Nutrition Council and the World Health Organization (WHO) updated their recommendations in 2004 (265, 410), they concluded that there was no significant new evidence to incorporate into their decisions and the reference values were left unchanged, despite nearly a decade elapsing since the previous reports. Two of the most recently published recommendations, WHO (410) and Australia and New Zealand (AU/NZ) (26), are quite different, with the Recommended Dietary Intake (RDI, RDA equivalent) of AU/NZ more than twice the value of the equivalent Recommended Nutrient Intake (RNI) set by WHO. The AU/NZ recommendations are in fact more in line with those published by the UK back in 1991 (Table 1).

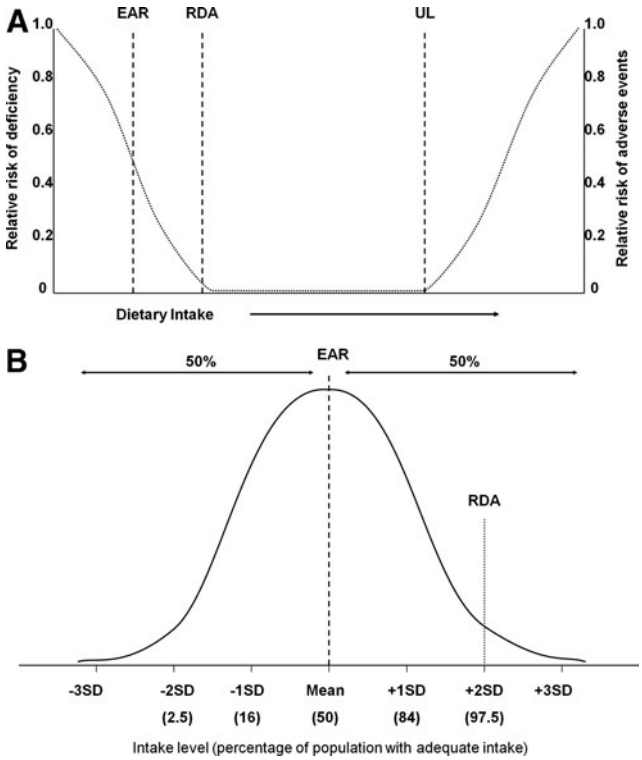

FIG. 11. (A) Theoretical dose–response curves used in the derivation of Dietary Reference Intakes. (B) Theoretical distribution graph for determining recommended dietary allowances from estimated average requirements. EAR, estimated average requirement; RDA, recommended dietary allowance; UL, tolerable upper intake level.

The choice of data for determining recommendations and its interpretation are often specific to the country or the committee setting the DRIs. The UK panel chose to set recommendations based on assessments of intake and status data from dietary surveys within its own country. From these data they concluded that, at the time of review, the whole blood selenium concentrations within the population were just over the 100 μg/l value suggested for optimization of GPx activity (367); therefore, the average diet consumed by UK residents was adequate to meet requirements. The Reference Nutrient Intake (RNI, RDA equivalent) value was calculated using the current intakes and set at an equivalent to 1 μg/kg per day (93), but there were insufficient data to derive an EAR. In comparison, WHO recommendations were set on the basis of two-thirds maximal plasma GPx3 activity rather than full saturation (the end point used by most expert bodies) because they saw no obvious health benefit of maximal saturation. Further, the average body weight used by the committee was

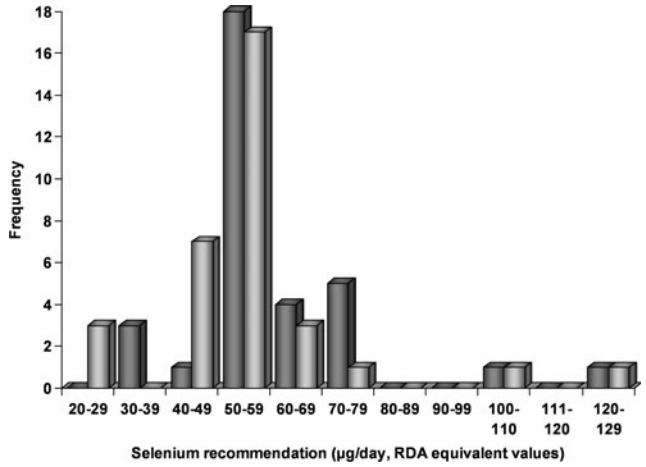

FIG. 12. Current diversity in selenium recommendations by sex. Compiled using the EURRECA Nutri-RecQuest database (80). Where recommendations are given as ranges, the midpoint has been used. Recommendations for males (M) and females (F) are shaded as dark gray or light gray bars, respectively.

65 kg for men, significantly less than in many Western countries, to better reflect the needs of populations in developing countries (410). WHO set their recommendations using data from a trial in which severely depleted individuals were supplemented with varying amounts of selenium over time (423).

Several other DRI committees have also used data from the trials conducted in China by Yang *et al.* (423), including EFSA (329), the Nordic Nutrition Council (265), and the Institute of Medicine (IOM) (274). The latter, however, averaged the suggested requirement of 41 μg/day from the Yang trial (423) (interpolated to 52 μg/day for American males) with a study from New Zealand (99) that suggested a figure of 38 μg/day to arrive at their EAR of 45 μg/day for adults. The panel reviewing the literature for the AU/NZ DRIs in 2005 (26) also used evidence from the Duffield *et al.* (99) study in which New Zealanders with low blood selenium concentrations were selected for a supplementation trial where various doses of selenomethionine (up to 40 μg/day) were provided, on top of a habitual dietary intake just under 30 μg/day, for 20 weeks. Plasma GPx3 activity only reached a plateau in the 40 μg/day supplement group, suggesting an intake of around 70 μg/day is necessary for deficient populations. However, the panel also used evidence from a more recent trial that was conducted in China and involved groups supplemented with either selenomethionine or selenite up to doses of 66 μg/day, plus a habitual average intake estimated as 10 μg/day, also for 20 weeks (414). GPx3 activity reached a plateau in the selenomethionine group at a supplemental intake of 37 μg/day and in the selenite group at 66 μg/day.

Many countries and bodies have chosen not to distinguish recommended intakes for men and women, selecting instead just one value for adults. The IOM concludes that although Keshan disease has been recorded in women of reproductive age, this was only an issue in extremely deficient populations and not currently of concern, even in China, given recent improved intakes. The DRIs, however, are calculated on a basis of average male body weight and therefore are more than adequate to meet female needs (274). The majority of differences in the gender-specific recommendations are as a result of calculations made on average body weights. The Japanese recommendations have assigned different values for the Tolerable Upper Intake Level for each gender (Table 1), which is not the practice of the majority of panels as the value already incorporates an uncertainty factor (249). None of the recommendations discriminate between different forms of selenium, although this might be of relevance for upper limits.

DRI panels tend to set requirements for children and adolescents by extrapolating data from the adult values on the basis of metabolic body weight. Although far from ideal, there is currently very limited evidence for setting EARs for these population groups. Infants under the age of 1 year are not covered by this method of estimation. Instead, an adequate intake is set which is based on observations and evidence from the literature of intakes that appear to be adequate to meet the population needs. These estimations are usually based on average measurements from human milk, which are assumed to be adequate during the first year of life.

The process of setting DRIs using data from trials conducted in populations exposed to very different selenium intakes could potentially be misleading. There is evidence to suggest that there is a significant adaptation to usual intakes within a

Table 1. Current Dietary Reference Intakes for Adults (μg Selenium/Day) of Selected Countries and Bodies

Country or body	*Year*	*EAR*[a]	*RDA*[b]	*UL*[c]	*LI*[d]
UK (93)	1991	*Not derived for selenium*	60 (F), 75 (M)	450	40
USA and Canada (274)	2000	45	55	400	—
Nordic (265)	2004	30 (F), 35 (M)	40 (F), 50 (M)	—	20
WHO/FAO (410)	2004	20 (F), 27 (M)	26 (F), 34 (M)	400	—
EFSA (EU) (329)	1993	40	55	450	20
AU/NZ (26)	2005	50 (F), 60 (M)	60 (F), 70 (M)	400	—
Japan (249)	2005	20 (F), 25–30 (M)	25 (F), 30–35 (M)	350 (F), 450 (M)	—

[a]EAR, estimated average requirement (USA, UK, AU/NZ, and Japan); equivalent to AR, average requirement (EFSA, Nordic); ANR, average normative requirement (WHO).
[b]RDA, recommended dietary allowance (USA, Japan); equivalent to RNI, reference nutrient intake (UK); PRI, population reference intake (EFSA); RNI, recommended nutrient intake (WHO/FAO); RDI, recommended dietary intake (AU/NZ); RI, recommended intake (Nordic).
[c]UL, tolerable upper intake level (USA, Japan, WHO/FAO); equivalent to UL, upper level of intake (AU/NZ); maximum safe intake (UK, EFSA).
[d]LI, lower level of intake (Nordic); equivalent to LRNI, lower reference nutrient intake (UK); LTI, lowest threshold intake (EFSA).
EFSA, European Food Safety Authority.

population, and therefore historical intakes will affect the selenium balance of an individual. This theory is supported by trials in American men (219) in whom an intake of 80 μg/day was necessary to balance losses. Conversely, Luo *et al.* (233) conducted a similar study in Chinese men and estimated the figure to be 7.4 μg/day. The wide variation in these figures can partly be attributed to differences in body weight of the subjects, but also the difference in selenium body pool size.

The choice of plasma GPx3 as a biomarker for use in setting dietary reference values is subject to debate. The two trials that served as the basis for the AU/NZ recommendations (99, 414) both reported that plasma selenoprotein P did not plateau in any of their intervention groups, suggesting that it reaches a maximum at intakes in excess of 70 μg/day. The Nordic Nutrition Council conceded that although intakes of 30–40 μg/day appear adequate to optimize plasma GPx3, other GPxs may require considerably higher intakes to reach a plateau (265). The choice of biomarker has a significant impact on the reference value that is derived, as does the cut-off point chosen. A recent systematic review of selenium biomarkers concluded that for most measures of selenium status there are insufficient data to determine the conditions for which different biomarkers are useful (23). There is also currently some debate as to whether recommendations should be set to prevent overt deficiency symptoms or to maximize optimal health. This discussion is further fuelled by evidence that suggests that intakes higher than current recommendations may reduce the risk of certain chronic diseases, such as cancer and CVD (see Section VII.A, B). Currently, although many DRI expert bodies acknowledge these relationships, the general conclusion is that the evidence is not sufficient to use for deriving DRI values.

In a recent risk modeling exercise, Renwick *et al.* (308) compared the data used for setting the current DRIs with other potential, but less substantiated, health effects. In the model, the range of intake that provided a very low (<0.001%) risk of deficiency or toxicity, according to data used by DRI committees, was 90–500 μg/day. The potential complications (Fig. 13) of using alternative health end-points was illustrated

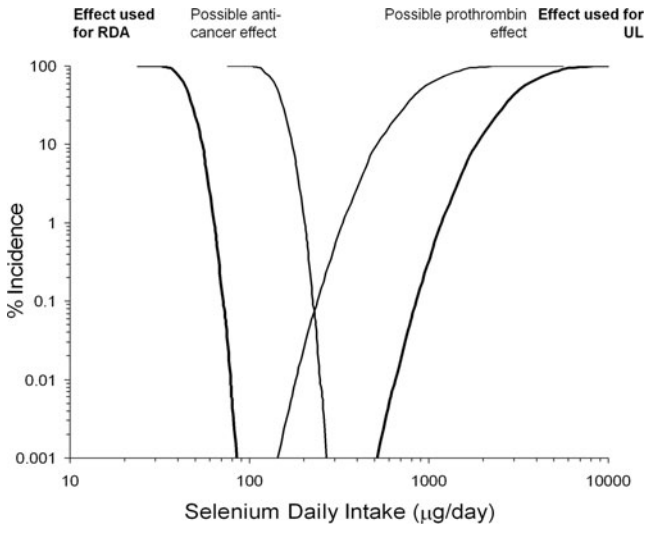

FIG. 13. Risk modeling comparing the data used to set the UL and RDA values with other potential effects associated with dietary intake. Adapted with permission from Renwick *et al.* (308).

by the addition of lines modeled for an anticancer effect [using data from Clark *et al.* (86)] and an increased prothrombin time effect [using data from Yang *et al.* (419)]. This eliminates the safe range, and results in an overlap for beneficial and adverse effects, thereby highlighting the complications of including risk–benefit assessment as part of the DRI process.

A further consideration that is pertinent to DRIs is selenium bioavailability. Although the bioavailability of selenium compounds is generally high (compared with iron, for example), there are marked differences in the absorption of the organic and inorganic forms (117). The bioavailability of different species of selenium from varying food sources is not well defined and requires further research. In addition, the quantity of selenium within specific foods, even those grown in the same region, can vary considerably, and therefore a larger error factor is sometimes applied to selenium requirements to counteract inconsistencies in intake.

The EURRECA Network of Excellence is a European Commission Framework Programme 6 (FP6)–funded project that aims to address some of the discrepancies currently evident in dietary recommendations throughout Europe. During the first stage of the research activities current data on the recommendations set by panels were collated and transformed into an online database (80), which will be a resource to the wider community interested in DRIs. Further work is planned to develop a series of instruments designed to revise and standardize the way micronutrient reference values are derived. In addition, it is hoped that the Network will identify areas of research that are needed to progress DRI development, and also address the concept of personalized nutrition. The influence of genotype on nutrient requirements is still an emerging field, but evidence suggests that certain polymorphisms may alter the metabolism of dietary selenium (240, 241) (see section VII.F). One particular remit of the Network is to pay special attention to vulnerable groups within populations. There is evidence to suggest that those on parenteral nutrition, HIV-positive patients, alcoholics, and the chronically ill may all be at risk of poor selenium status. No DRI panel has yet issued advice for specific population subgroups, but it may be the first step toward a more personalized approach, and it is increasingly evident that the identification of at risk groups is extremely important for the development of public health policies.

X. Conclusions and Perspectives

As outlined throughout this review a great deal of research is needed to improve our understanding of selenium metabolism, which is currently rather limited compared with many other nutrients. The mechanisms of absorption have not yet been identified, and various roles of selenium within the body are awaiting characterization. Robust measures of status in relation to short- and long-term exposure and biochemical, functional, and health outcomes need to be developed. Existing possible relationships between blood selenium concentration and selenium function or health effects are summarized (Fig. 14). However, the relationship between selenium intake/status and risk of disease is complex, as exemplified by the observation that the effects of selenium supplementation trials are cancer type specific (location of tumor and grade/severity of disease) and specific to populations or individuals, being dependent on baseline selenium

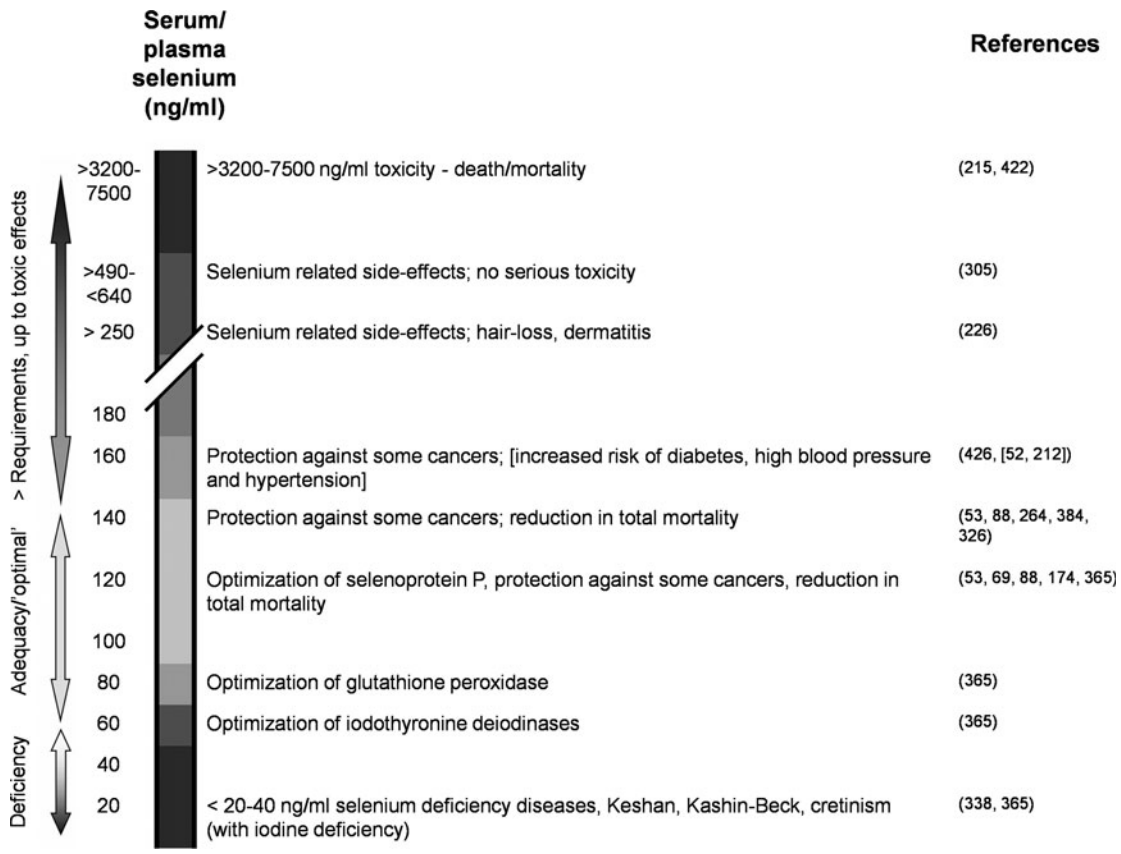

FIG. 14. Range of blood selenium concentrations with possible related health effects from deficiency to toxicity. Various parameters associated with selenium function or health have been assessed in relation to a range of selenium intakes and blood selenium concentrations. The plasma/serum selenium concentration ranges and associated health effects were compiled from published literature (refer to references displayed in the figure) to give some indication of how these parameters are affected by selenium status. Precise relationships between selenium intake/status and health effects remain to be defined.

status, intake, metabolism, and genotype. The potential for some selenium species to inhibit certain types of cancer and their possible role as an adjuvant in cancer therapy requires further investigation. Greater understanding of the relationship between selenium and health will be assisted by a more complete knowledge about the functions of selenoproteins and interactions with other metabolites, which can be achieved using a systems biology approach. The impact of genotype, in particular polymorphisms, is a key component of personalized nutrition/medicine, which will aid preventive medicine and therapeutic clinical practice. Gender is another important parameter that is all too often ignored during the design of trials and during the analyses. Finally, and most urgently, in view of on-going activities in the United States and Europe to update current dietary reference intakes, biomarkers that can be used to derive selenium requirements are needed to refine current dietary recommendations and to develop public health policies.

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Abbreviations Used

AIDS = acquired immune deficiency syndrome
AKR = aldo-keto reductase
ALDH2 = aldehyde dehydrogenase 2
AP-1 = activator protein-1
ApoER2 = apolipoprotein E receptor 2
ASK1 = apoptosis signal-regulating kinase 1
CAD = coronary artery disease
CHD = coronary heart disease
CNS = central nervous system
CRC = colorectal cancer
CVB = Coxsackie virus B
CVD = cardiovascular disease
DIDS = diisothiocyano-2,2′-disulphonic acid stilbene
DIO = iodothyronine deiodinase
DIO = iodothyronine deiodinase gene

Abbreviations Used (Cont.)

DRI = dietary reference intake
EAR = estimated average requirement
EEC = European Economic Community
EFSA = European Food Safety Authority
EU = European Union
EURRECA = European Micronutrient Recommendations Aligned
GCS = γ-glutamylcysteine synthetase
GI = gastrointestinal
GPx = glutathione peroxidase
GPX = glutathione peroxidase gene
GST = glutathione transferase
HIV = human immunodeficiency virus
HO = heme oxygenase
HR = hazard ratio
ICP-MS = inductively coupled plasma mass spectrometry
IOM = Institute of Medicine
KBD = Kashin-Beck disease
LC = liquid chromatography
LI = lower level of intake
mnSOD = manganese superoxidase dismutase
NAC = *N*-acetyl cysteine
NDNS = National Diet and Nutrition Survey
NF-κB = nuclear factor kappa B
NHANES = National Health and Nutrition Examination Survey
NPC = Nutritional Prevention of Cancer trial
OA = osteoarthritis
OR = odds ratio
PIN = prostatic intraepithelial neoplasia
PSA = prostate-specific antigen
QR = quinone oxidoreductase
RA = rheumatoid arthritis
RCT = randomized controlled trial
RDA = recommended dietary allowance
RNI = recommended nutrient intake
ROS = reactive oxygen species
RR = relative risk
rT3 = 3,3′,5′ triiodothyronine
SBP2 = SECIS binding protein 2
SECIS = selenocysteine insertion sequence
SelH = selenoprotein H
SelM = selenoprotein M
SelR = selenoprotein R
SelS = selenoprotein S
SelT = selenoprotein T
SelW = selenoprotein W
SEP15 = 15 kDa selenoprotein gene
SePP = selenoprotein P
SEPP = selenoprotein P gene
SEPS = selenoprotein S gene
SEPW = selenoprotein W gene
SFN = sulforaphane
SNP = single nucleotide polymorphism
SOD = superoxide dismutase
SOD2 = manganese superoxide dismutase gene
T-2 = trichothecene mycotoxin
T3 = 3,3,5′ tri-iodothyronine
T4 = tetra-iodothyronine or thyroxine
TNF-α = tumor necrosis factor-α
Trx = thioredoxin
TXNRD = thioredoxin reductase
TXNRD = thiredoxin reductase gene
UGT = UDP-glucuronyltransferase
UL = tolerable upper intake level
WCRF = World Cancer Research Fund
WHO = World Health Organization
XMRV = Xenotropic murine leukemia virus-related virus
XRCC1 = x-ray repair cross-complementing 1