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Dietary Selenium Across Species

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Abstract

This review traces the discoveries that led to the recognition of selenium (Se) as an essential nutrient and discusses Se-responsive diseases in animals and humans in the context of current understanding of the molecular mechanisms of their pathogeneses. The article includes a comprehensive analysis of dietary sources, nutritional utilization, metabolic functions, and dietary requirements of Se across various species. We also compare the function and regulation of selenogenomes and selenoproteomes among rodents, food animals, and humans. The review addresses the metabolic impacts of high dietary Se intakes in different species and recent revelations of Se metabolites, means of increasing Se status, and the recycling of Se in food systems and ecosystems. Finally, research needs are identified for supporting basic science and practical applications of dietary Se in food, nutrition, and health across species.

Contents

1. INTRODUCTION

Within only a few decades, selenium (Se) emerged from being viewed as a toxic element in soils and consequently forages of grazing animals to an essential nutrient for many species and humans, with possible metabolic roles beyond its traditionally recognized nutritional necessity. Schwarz and colleagues were among the very first to suggest a nutritional role of Se by revealing its effectiveness in preventing liver necrosis in rats (145) and exudative diathesis in chicks (144). Subsequent work showed that combined deficiencies of Se and vitamin E produced lesions in turkey poults; hepatic, cardiac, and smooth muscle pathologies in pigs; skeletal myopathies (white muscle disease) in lambs and calves; placental retention in cows; and reproductive failure in turkey toms and bulls

(30). Because these lesions were prevented by supplementing those diets with either vitamin E or Se, a phenomenon referred to as nutritional sparing, and because vitamin E was known to have an antioxidant function, Se, too, became regarded as an antioxidant—the dominant paradigm for almost 20 years.

In 1973, a more accurate mechanistic understanding of the nutritional role of Se became available with the discovery of Se as an essential constituent of cellular glutathione peroxidase (GPX1) (139). This finding revealed Se as having an essential role in the multicomponent cellular antioxidant defense system and provided the first framework for our current knowledge of the function of Se in selenoproteins.

2. SOURCES OF DIETARY Se

2.1. The Soil, Plant, and Animal Interface

The Se content of foods and feeds ultimately depends on the Se content of soils and the capacity of plants to obtain the element from soils. Although Se is not essential for higher plants, it may promote plant growth in some cases (131, 180). Plants readily take up Se from the soil and incorporate it into organic compounds using Se assimilation enzymes (131). Due to similar chemical properties between Se and sulfur (S), Se assimilation into plants typically occurs through the substitution of S in the formation of S-containing amino acids, primarily selenomethionine (SeMet), selenocysteine (Sec), and Se-methylselenocysteine (205). The incorporation of Se into plants is considered luxury accumulation and is reflective of the resident concentration of Se in the soil. Therefore, an accurate soil nutrient mapping can predict the Se content of forages grown in the area.

The Se content of most soils is 0.01 to 2 mg/kg. Soils containing <0.5 mg/kg are classified as Se deficient. Se-deficient soils are found throughout China in a geographic belt that extends from the southwest to the northeast, accounting for 35% of available agricultural soils in the country (214). High Se levels in soils also occur worldwide, including >4 mg/kg in northwest India (36), approximately 30 mg/kg in northern California (188), and more than 100 mg/kg in Enshi, Hubei Province, China (231). In the northern high plains of the United States, soil Se concentrations tend to be high (14); thus, forages grown in these areas commonly have adequate levels of Se. This is reflected in the tissue Se concentrations of cattle raised from these areas (65).

Most plants can respond metabolically to Se treatments (59, 152). Florets of broccoli (*Brassica oleracea*) fertilized with selenate showed increased contents of free amino acids, sulforaphane, and glucosinolates (84). Se-containing sprays are used on forage crops to increase the Se intakes of grazing animals. Foliar application of sodium selenate providing 120–480 g of Se per hectare substantially increased the Se content of Bermuda grass (*Cynodon dactylon*) (186). Alfalfa (*Medicago sativa*) hay produced on fields receiving such spray applications showed increases in Se content (57). Most of the Se in Se-treated forages and feedstuffs is in the form of SeMet, with lesser amounts of Sec and Se-methylselenocysteine (64, 205). These forms of plant Se are highly available to ruminants and are more effective than inorganic Se in increasing the Se status of cattle (149).

2.2. Determinants of Se Uptake by Plants and Animals

The two forms of Se that are most available to plants are soluble in aqueous environments: selenite (Se^{+4}) and selenate (Se^{+6}). Selenate dominates in alkaline, well-oxidized soils; selenite dominates in acidic and neutral soil (43). Accordingly, Se is better taken from sandy soils than from loamy ones, likely due to adsorption to clay, humic acid, and iron oxides in the latter. Plant roots take up both forms of Se (selenate by sulfate transporters, selenite passively). Selenate is translocated to shoot tissues, thus composing the dominant Se species in xylem sap, while selenite is metabolized to SeMet and tends to remain in the root (87). Absorbed Se is converted into organic compounds

through the substitution of S in the formation of Se-containing amino acids, that is, SeMet and, to a lesser extent, Se-methylselenocysteine (131, 205). Foods such as cruciferous vegetables, which are naturally rich in S, can accumulate nutritionally significant amounts of Se (1–10 mg/kg) if grown on high-Se soils or if fertilized with selenite or selenate salts. Wheat grain may contain Se levels of >2–5 mg/kg if produced in parts of the northern plains of North America but as little as 0.1 mg/kg in Kansas or New Zealand and only 0.005 mg/kg in Shaanxi Province, China. Plants grown in proximity to coal-powered electrical generators can receive Se in the fallout of Se-containing fly ash. Sulfur in acid precipitation and groundwater can antagonize the root uptake of Se (13). Reduced soil pH decreases the ability for plants to accumulate Se. High S in plant tissues can impair the utilization of Se by animals consuming them (73). The Se intakes of grazing livestock reflect the Se content of their forages, while those of livestock fed in confinement reflect the Se content of the ingredients composing their mixed feeds. The use of Se-containing feed supplements, which typically contain sodium selenite, has reduced geographic variation in the Se content of animal products. In addition, ruminants (foregut fermenters) and species that practice coprophagy (some hindgut fermenters) are exposed to and/or ingest Se-containing compounds produced by their enteric bacteria (203).

2.3. Se in Human Diets

Human diets contain Se predominantly in the form of SeMet. Because animals metabolize ingested Se into proteins (55–65% as SeMet, with 5–15% as Sec) (170), the Se contents of animal products tend to be correlated with their protein contents; for example, muscle meats contain 0.3 to 0.5 mg/kg (fresh weight), and organ meats usually contain amounts that are 4 to 15 times higher. Most plant-based foods, with notable exceptions (such as the *Brassicas* species), have Se concentrations positively related to protein contents. Therefore, most of the Se in human diets tends to be provided by the major sources of dietary protein, and the bioavailability of Se in foods is largely dependent on the availability of their constituent Se-containing proteins. Individuals with chronically low protein intakes are at risk for Se deficiency. Interestingly, in American diets, fewer than two dozen foods provide most of the total dietary Se, with five foods contributing half: beef, bread, pork, chicken, and eggs (143). Estimated daily Se intakes (μg/person) in 18 countries varied from 3 in parts of China to 224 in parts of Canada and Venezuela (28) to a level as high as 6,690 in endemic Se intoxication areas in Enshi County, Hubei Province, China (212).

3. UTILIZATION OF DIETARY Se

3.1. Digestion and Absorption

In general, dietary sources of Se are well digested and absorbed by simple-stomached animals and humans. For Se-containing amino acids, this process involves digestion of their respective proteins and absorption of the digestive products by active transport. For inorganic forms of Se, this process involves direct absorption by simple (selenite) or carrier-mediated (selenate) diffusion (183, 187). Wastney et al. (196) found that the enteric absorption of Se from single doses (200 μg) by humans was 98% for SeMet and 84% for selenite. The high Se absorption rate seems to be independent of Se status (15). The commonly used feed supplements of selenite and selenate are well absorbed from the intestine (50–90%).

The bioavailability of dietary Se ranges from 29 to 98% across species (3, 170, 200). In ruminants, bioavailability of Se in forage plants is lower than in concentrate-based diets (30% versus 60%) (122). The fractional absorption of Se by ruminants is less than that of nonruminants, likely due to reduction of dietary Se into insoluble forms in the rumen and/or incorporation of Se into ruminal microbial protein. The reduced form of Se, selenide (Se^{-2}), is not absorbed in the rumen;

however, the rumen microbial population is capable of converting a significant portion to organic forms, which are absorbed intestinally. Thus, little to no absorption of Se occurs in the rumen or abomasum, whereas the greatest absorption occurs in the small intestine and cecum (114).

The Se-containing proteins ingested by ruminants are degraded by ruminal microbes, incorporated into ruminal microbial protein, and mixed with other feed ingredients (3, 106). The mixture flows out of the forestomach complex into the gastric portions (true stomach) and intestines, where it is acted upon by acids and gastric enzymes, and intestinal enzymes, respectively, as in nonruminants. Digestive actions release SeMet and Sec, both of which follow S transporter pathways into the enterocyte. Likewise, basolateral transport of Se-containing amino acids follows the transport pathways into the venous blood and reaches the liver via the hepatic portal vein. Selenite and selenate cross the intestinal barrier by different mechanisms as described above (107).

3.2. Intermediate Metabolism

Upon absorption, Se enters the mesenteric venous drainage and flows to the liver (58). In the liver, various forms of Se are rapidly metabolized to selenide (HSe^-). This species in biological systems at the −2 oxidation state may be present alone or in association with other species such as glutathione. This central metabolite can be utilized in three major ways by simple-stomached animals: incorporation into selenoproteins, methylation and excretion, and conversion to selenosugars (**Figure 1**).

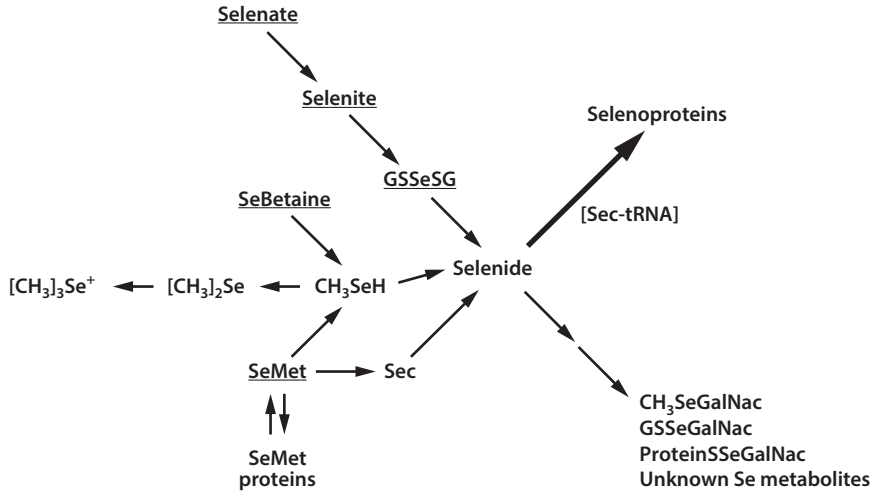


Figure 1

Schematic diagram of Se metabolism into selenoproteins. Selenate is reduced to selenite; selenite can react with GSH to form GSSeSG, which is then further reduced to selenide. SeMet is degraded via transsulfuration to Sec, which can be metabolized to selenide, or SeMet is degraded via transamination to methaneselenol and then selenide. Alternatively, SeMet can be incorporated into general body proteins as a methionine analog. SeBetaine is degraded to release methaneselenol. Methaneselenol can be metabolized to volatile dimethyl selenide or urinary trimethyl selenonium ion. Selenide is the precursor used for Sec-tRNA-mediated selenoprotein incorporation from the five underlined tracer selenocompounds, as assessed by SDS-PAGE. Metabolites not detected by SDS-PAGE include the low-MW selenosugars, high-MW selenosugar-decorated proteins, and other unknown metabolites. Abbreviations: GSH, glutathione; GSSeSG, selenodiglutathione; MW, molecular weight; SDS-PAGE, sodium dodecyl sulfate–polyacrylamide gel electrophoresis; Se, selenium; SeBetaine, selenobetaine; Sec, selenocysteine; SeMet, selenomethionine; tRNA, transfer RNA. Figure adapted with permission from Reference 46.

3.2.1. Incorporation into selenoproteins. The novel metabolic fate of selenide is its incorporation into selenoproteins as Sec. This selenoamino acid is synthesized via a cotranslational process involving the conversion of tRNA-bound serine to Sec, occurring on a unique $tRNA^{Sec}$ with an anticodon specific for UGA (normally a stop codon) and proceeding via a tRNA-bound phosphoserine intermediate RNA (83). Selenoprotein transcripts have in-frame UGA codons at the position of Sec incorporation. These transcripts are distinguished from others with premature or nonsense UGA stop codons by having a stem loop Sec insertion sequence (SECIS) motif in their 3′ untranslated regions (UTRs) (11). Incorporation of Sec is facilitated by the SECIS element, which recruits novel factors that bind the $tRNA^{Sec}$ such that the latter outcompetes release factors and inserts the Sec into the growing peptide chain (82, 83).

SeMet is incorporated into proteins during translation by a different mechanism. Because it can charge $tRNA^{Met}$, SeMet is incorporated directly, but nonspecifically, in lieu of methionine into proteins (104). Because Sec does not readily compete with cysteine in charging the $tRNA^{Cys}$ (217), a substantial misincorporation of Sec in place of cysteine is unlikely to occur during translation. When SeMet-containing proteins are degraded, the free SeMet can be metabolized by either the transamination pathway to Sec or the transsulfuration pathway to selenide. The nonspecific incorporation of SeMet into proteins can markedly increase tissue Se levels beyond those associated with Sec proteins. This, in effect, renders SeMet a storage form of Se. As its mobilization depends on protein turnover, it does not usually provide a readily accessible reserve for maintaining selenoprotein expression (195). Because plants lack Sec proteins (203), SeMet is the major tissue form (10).

3.2.2. Formation of selenosugars. Selenosugar (seleno-*N*-acetyl-D-galactosamine, SeGalNac), with the Se directly linked to the 1 carbon of galactosamine, was identified as GSH-SeGalNac in the liver of rats and birds, whereas an apparent derivative, 1β-methyl-SeGalNac, was identified as the dominant form of Se in human urine (81). These metabolites are thought to be generated from an inorganic selenide-GSH pool. They have also been found in rat liver and kidney (55, 172), pig liver (97), and quail plasma and liver (2). Recent studies have found that SeGalNac accounts for a large amount of the Se in the liver of turkey. It was found to be linked via Se-S bonds to general proteins, composing a greater portion of liver Se than Sec in selenoproteins (80). Supranutritional levels of dietary selenite (2 or 5 μg Se/kg) further increased hepatic levels of selenosugars linked to low molecular weight thiols as well as selenosugar-decorated proteins (80). Studies in rats on early ^{75}Se metabolism found very rapid Se metabolism from a diverse set of inorganic and organic selenocompounds to a common selenide-level intermediate used for synthesis and incorporation of ^{75}Se into the major selenoproteins in a variety of tissues. The missing ^{75}Se in these selenoprotein profiles, especially at early time points, further suggested that substantial tissue Se in Se-supplemented animals was present in both low- and high-molecular-weight selenosugars in addition to selenoproteins (**Figure 1**) (46).

3.2.3. Methylation and other conversions. Early studies have revealed that selenide can be methylated into forms that are excreted in the urine: methylselenol ($[CH_3]_2Se$) and trimethyl selenonium ($[CH_3]_3Se^+$). Another metabolite, dimethyl selenide ($[CH_3]_2Se$), which is excreted from the lung, is formed at higher Se intakes. Meanwhile, ingested Se can be converted to other metabolites. A selenoimidazole, selenoneine (2-Se-*N*,*N*,*N*-trimethyl-L-histidine), occurs as the major circulating form of Se in tuna and is also found in tissues of chickens and pigs (210). This metabolite is present in zebrafish embryos as well, where it appears to reduce the accumulation of methylmercury (209). However, its metabolic origin is unclear.

Several apparent Se-binding proteins that do not appear to contain Sec have been reported. These include a 14-kDa protein with a peptide sequence similar to that of the fatty acid binding

protein (6) and several 56- to 58-kDa proteins similar to the acetaminophen-binding protein (110, 134). These proteins, however, do not appear to incorporate Se during their synthesis, as pretreatment with cycloheximide does not block the radioactive Se labeling (45). These observations may also be due to contamination by true selenoproteins of similar weights. A highly conserved 56-kDa species is now designated as Se binding protein-1 (SBP1), which also has methane thiol oxidase activity (182) and is expressed in mammalian tissues as well as plants (42). The polypeptide contains a single cysteine residue, a likely Se binding site. Expression of SBP1 is low in many cancers and is associated with poor clinical outcomes (42).

3.3. Excretion and Balance

Under conditions of low to moderate Se intakes, body Se balance is maintained primarily through urinary excretion (114). Metabolic tracer studies have shown that, over a 12-day period, Se-adequate adults excreted ~17% of Se from an oral selenite dose but only ~11% of Se from an oral SeMet dose (129). The longer turnover of the latter is thought to be due to its nonspecific incorporation into body proteins under normal circumstances, when there appears to be only a small enterohepatic circulation of absorbed Se. Therefore, fecal Se constitutes mostly unabsorbed dietary Se. High Se intakes in rats resulted in increased urinary excretion of $[CH_3]_3Se^+$, whereas acute subtoxic Se intakes led to an excretion in the breath as $[CH_3]_2Se$ (77). Thus, the significance of various routes of Se excretion depends on both the magnitude and form of ingested Se as well as the level of body Se reserves. Other elements (arsenic, copper, lead, and mercury) have also been implicated as effectors of Se absorption and retention (114, 119, 170).

4. FUNCTIONS AND REGULATIONS OF SELENOPROTEOMES AND SELENOGENOMES

4.1. Biochemical and Metabolic Properties of Selenoproteins

The vertebrate selenoproteome has been characterized using Sec and SECIS transcript elements as a signature to screen annotated genomes for selenoproteins (10, 54, 100, 166). This approach has identified 25 selenoproteins in humans, pigs, cattle, sheep, and horses (100) but only 24 selenoproteins in rodents and chickens (**Table 1**). Of these, two were found only in the chicken (SELENOU, SELENOP2) (**Figure 2*a***). Although *SEPHS2* was not found in the early chicken genome assembly (90), it was identified in some EST sequences from *Gallus gallus* (101), and its transcript was detected in the adipose tissue of chickens (91). Two selenoproteins found in mammals (GPX6 and SELENOV) are missing in chickens (90). The selenoproteome of pigs (**Figure 3*a***) resembles those of humans and rodents, but porcine GPX1 surprisingly shows the closest evolutionary relationships with that of sheep and cattle among eight domestic species (24).

Selenoproteins are predominately oxidoreductases. With a few exceptions, their Sec moieties are located in the polypeptide backbone of the active site (**Table 1**). The best characterized selenoproteins are the glutathione peroxidases (GPX1–4), which catalyze the reduction of peroxides using reducing equivalents from glutathione. Other selenoproteins include the iodothyronine 5′ deiodinases (DIO1–3), which regulate thyroxine hormone function by reductive deiodination; the thioredoxin reductases (TXNRD1–3), which contain Sec as the penultimate C-terminal amino acid and reduce thioredoxin, glutaredoxin, and other low-molecular-weight compounds using reducing equivalents from NADPH; a methionine sulfide reductase (MSRB1), which also contains zinc and repairs oxidized methionine residues in proteins; and selenophosphate synthase 2 (SEPHS2), which catalyzes the ATP-dependent formation of selenophosphate from selenide in the first step in forming Sec-tRNA^{Sec} in all vertebrates. SELENOP is secreted predominately by liver into the plasma, where it can account for half of plasma Se. Human and rodent SELENOPs

Table 1 Comparative selenoproteomes of humans, rodents, and avian species

Selenoprotein	Gene	Outcome of global knockout in mice	Number of AA(H/R/A)[a]	Position of Sec (H/R/A)	Accession number	Main function(s)	Note
Glutathione peroxidases	*GPX1*	Viable	203/201/195	49/47/39	NP_000572.2/ NP_110453.3/ NP_001264782	Redox modulation as free radical scavengers; involved in metabolism of macronutrients, cell survival and death, and reproduction	Global *Gpx4*$^{-/-}$ is ELTM but DTTH
	GPX2	Viable	190/190/191	40/40/41	NP_002074.2/ NP_899653.2/ NP_001264783		
	GPX3	Viable	226/226/219	73/73/71	NP_002075.2/ NP_071970.2/ NP_001156704		
	GPX4	Embryonic lethal	197(170)/197 (170)/202 (194, 191)	73(46)/73(46)/ 70(70, 67)	NP_002076.2 (NP_001354761.1)/ NP_058861.3 (NP_001354972.1)/ NP_989551.2 (NP_001333378.1, NP_001333377.1)		
	GPX6	Knockout model unavailable	221/NA/NA	73/NA/NA	NP_874360.1/ NA/NA		Sec in only humans and pigs
Iodothyronine 5′ deiodinases	*DIO1*	Viable	249/257/246	126/126/124	NP_000783.2/ NP_067685.5/ NP_001091083.1	Thyroid hormone metabolism	Deficiency of any of the three genes is intolerant to humans
	DIO2	Viable	273/262/279	133/130/132	NP_054644.1/ NP_113908.4/ NP_989445		
	DIO3	Viable	304/304/274	170/170/139	NP_001353.4/ NP_058906.3/ NP_001116120.1		
Thioredoxin reductases	*TXNRD1*	Embryonic lethal	551(499)/580 (499)/499(498)	550(498)/579 (498)/498(497)	NP_003321.3 (NP_877419.1)/ NP_001338913.1 (NP_001338912.1)/ NP_001025933 (NP_001338952.1)	Acting as oxidoreductase to reduce cytosolic and/or mitochondrial thioredoxin and/or glutaredoxin in all tissues or specifically in testis (TXNRD3)	Global *Txnrd1*$^{-/-}$ is ELTM, and the deficiency is also intolerant to humans

(*Continued*)

Table 1 (*Continued*)

Selenoprotein	Gene	Outcome of global knockout in mice	Number of AA(H/R/A)[a]	Position of Sec (H/R/A)	Accession number	Main function(s)	Note
	TXNRD2	Embryonic lethal	524/526/514	523/525/513	NP_006431.2/ NP_072106.1/ NP_001116163		Global *Txnrd2*$^{-/-}$ is ELTM but DTTH
	TXNRD3	Knockout model unavailable	643(607)/652 (615)/606	642(606)/651 (614)/605	NP_443115.1 (NP_001166984.1)/ NP_001171641.1 (NP_001100079.2)/ NP_001116249		
Methionine sulfide reductase	*MSRB1*	Viable	116/116/111	95/95/93	NP_057416.1/ NP_001037750.2/ NP_001129030	Repair of oxidized methionine in proteins	
Selenophosphate synthase 2	*SEPHS2*	Knockout model unavailable	448/451/NA	60/62/NA	NP_036380.2/NP-001073358.2/NA	Selenoprotein synthesis	Not found in early genome of chickens, but identified from EST sequences and expression
Selenoprotein P	*SELENOP*	Viable	385/385/393	59, 264, 282, 323, 335, 357, 371, 373, 380, 382/59, 264, 282, 323, 335, 357, 371, 373, 380, 382/55, 287, 300, 313, 331, 343, 356, 358, 365, 379, 381, 388, 390	NP_062065.2/ NP_001077380.1/ NP_001026780.2	Se transport	10 Sec in mammals; 13 Sec in avian species
	SELENOP2	Knockout model unavailable	NA/NA/263	NA/NA/59	NA/NA/NP-001335698.1	Unknown, but putative functions similar to SELENOP	Avian and fish only
Selenoprotein W	*SELENOW*	Viable	87/88/85	13/13/13	NP_003000.1/ NP_037159.4/ NP_001338303.1 (NP-001159799.1)	Putative antioxidant, muscle integrity?	

(*Continued*)

Table 1 (*Continued*)

Selenoprotein	Gene	Outcome of global knockout in mice	Number of AA(H/R/A)[a]	Position of Sec (H/R/A)	Accession number	Main function(s)	Note
Selenoprotein T	*SELENOT*	Embryonic lethal	195/195/199	49/49/53	NP_057359.2/ NP-001014275.2/ NP_001006557	Oxidoreductase in Golgi, ER, and cytosol, involved in redox regulation and anchorage	Global *Selenot*$^{-/-}$ is ELTM, and the deficiency is also intolerant to humans
Selenoprotein V	*SELENOV*	Viable	346/326/NA	273/253/NA	NP_874363.1/ NP_001159868.1/ NA	Regulation of lipogenesis and energy expenditure	Placental animal only
Selenoprotein U	*SELENOU*	Knockout model unavailable	NA/NA/224	NA/NA/85	NA/NA/ NP_001180448.1 (NP_001180447.1)	Unknown	Avian only
Selenoprotein H	*SELENOH*	Knockout model unavailable	122/116/129	44/38/51	NP_734467.1/ NP_001308221/ NP_001264794.1	In nucleus, regulation of redox sensing and transcription	
Selenoprotein I	*SELENOI*	Embryonic lethal	397/398/400	386/388/384	NP_277040.1/ NP_001128226.2/ NP_001264794.1	Catalyzing phosphatidyl ethanolamine biosynthesis	Global *Selenoi*$^{-/-}$ is ELTM
Selenoprotein M	*SELENOM*	Viable	145/145/152	48/48/37	NP_536355.1/ NP_001108485.1/ NP_001264788.1	ER-resident protein, involved in body weight and energy metabolism control; highly expressed in brain with neuroprotective properties	
Selenoprotein F	*SELENOF*	Viable	165/162/160	96/93/91	NP_004252.2/ NP_579831.2/ NP_001012944.2NP-	ER-resident thioredoxin-like oxidoreductase, quality control of protein folding in ER	

(*Continued*)

Table 1 (*Continued*)

Selenoprotein	Gene	Outcome of global knockout in mice	Number of AA(H/R/A)[a]	Position of Sec (H/R/A)	Accession number	Main function(s)	Note
Selenoprotein N	*SELENON*	Viable	590(556)/ 557(510)/530	427(428)/ 427(381)/402	NP_065184.2 (NP_996809.1)/ XP_038967216.1 (XP_008762412.3)/ NP_001108444.1	Localized to ER, muscle development	Mutations cause multi-minicore disease and other myopathies
Selenoprotein O	*SELENOO*	Viable	669/666/670	667/664/668	NP_113642.1/ NP_001078954.1/ NP_001108489.3	In mitochondria, containing a CXXU motif, possible redox and kinase function	
Selenoprotein K	*SELENOK*	Viable	94/94/95	92/92/93	NP_067060.2/ NP_997472.2/ NP_001020612.1	Localized to ER, involved in Ca flux in immune cells and chaperone-like function in ER-associated degradation of misfolded proteins	
Selenoprotein S	*SELENOS*	Knockout model unavailable	189/190/194	188/189/193	NP_060915.2/ NP_775143.2/ NP_001919905.1	Localized to ER, involved in ER-associated degradation and anti-inflammation	

[a] Alternate forms of the same protein listed in parentheses.

Abbreviations: AA, amino acid; DTTH, deficiency tolerant to humans; ELTM, embryonic lethal to mice; ER, endoplasmic reticulum; H/R/A, humans/rodents/avian species; NA, not applicable or existing in the given species.

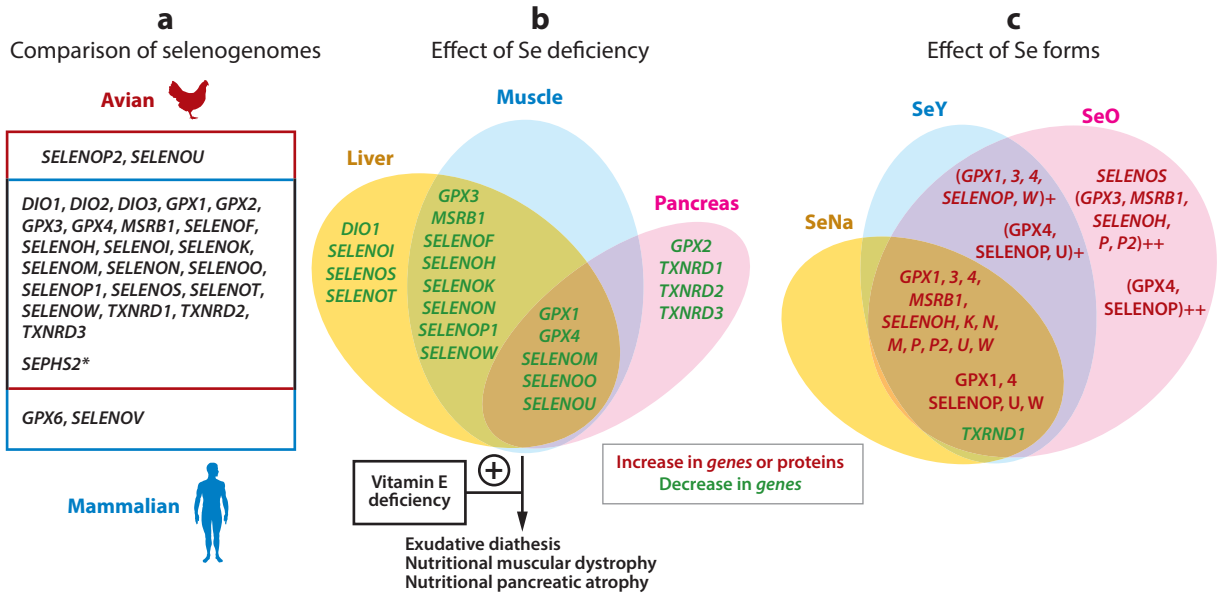


Figure 2

(*a*) Comparative selenogenomes of avian (chicken, in *red* box) and mammalian (human, in *blue* box) species. Common genes in both species are shown in the middle overlap area of the two boxes. The asterisk indicates that whereas *SEPHS2* was not found in the early chicken genome assembly (90), it was identified in some EST sequences from *Gallus gallus* (101), and its transcript expression was detected in the adipose tissue of chickens (91). (*b*) Effects of dietary Se deficiency (<0.06 mg/kg), in comparison with Se adequacy (>0.2 mg/kg), on selenotranscriptome expression (decreases) in the liver (*yellow*), pectoral muscle (*blue*), and pancreas (*pink*) of chickens (2–6 weeks of age). Genes showing similar changes in the three tissues and between liver and muscle are listed in the respective overlap areas. Genes showing specific changes within a given tissue are listed in that tissue only. (*c*) Effects of three forms of supplemental dietary Se on the selenotranscriptome (*italic*) expression and selenoprotein production in the liver and pectoral and thigh muscles of chickens (3–6 weeks of age). Genes or proteins in red indicate an increase; genes in green indicate a decrease; genes and proteins listed in the overlap area of the three compounds were compared with the Se-deficient basal diet; genes and proteins listed in the overlap area of SeY and SeO with a plus symbol were compared with the SeNa group; and genes and proteins listed in the SeO area with two plus symbols were compared with the SeNa and SeY groups. SeO upregulated the *SELENOS* mRNA compared with the Se-deficient basal diet. In all panels, DIO1, 2, and 3 equal iodothyronine deiodinase 1, 2, and 3, respectively; GPX1, 2, 3, 4, and 6 equal glutathione peroxidase 1, 2, 3, 4, and 6, respectively; MSRB1 equals methionine-R-sulfoxide reductase 1; SELENOF, H, I, K, M, N, O, P, P2, S, T, U, V, and W equal selenoprotein F, H, I, K, M, N, O, P, P2, S, T, U, V, and W, respectively; SEPHS2 equals selenophosphate synthetase 2; and TXNRD1, 2, and 3 equal thioredoxin reductase 1, 2, and 3, respectively. Abbreviations: SeNa, sodium selenite; SeO, 2-hydroxy-4-methyl selenobutanoic acid; SeY, seleno-yeast. Figure adapted from References 90, 159, and 225.

have 10 Secs in the peptide and two SECIS elements in the 3′ UTR. The Sec located in the middle of the sequence may have peroxidase activity. The additional Secs located in the C terminus appear to be without catalytic activity, instead functioning to transport Se. Circulating SELENOP binds to ApoER2 receptors that have been identified in testes and brain, facilitating the targeted transfer of Se to tissues, particularly under conditions of Se deficiency. In birds, SELENOP has 13 Sec residues, with 12 of its 13 Sec residues located in the C terminus. However, SELENOP2 has only a single Sec residue (90, 166).

Several other selenoproteins including SELENOW, SELENOT, SELENOH, and SELENOV appear to be oxidoreductases. Each contains Sec in a CXXU sequence located in a thioredoxin fold. Deletion of SELENOV affected tissue Se distribution (22) and elevated lipogenesis and decreased energy expenditure in male mice, leading to the accumulation of body fat via a cascade of SELENOV–O-GlcNAc transferase–AMP-activated protein kinase (21).

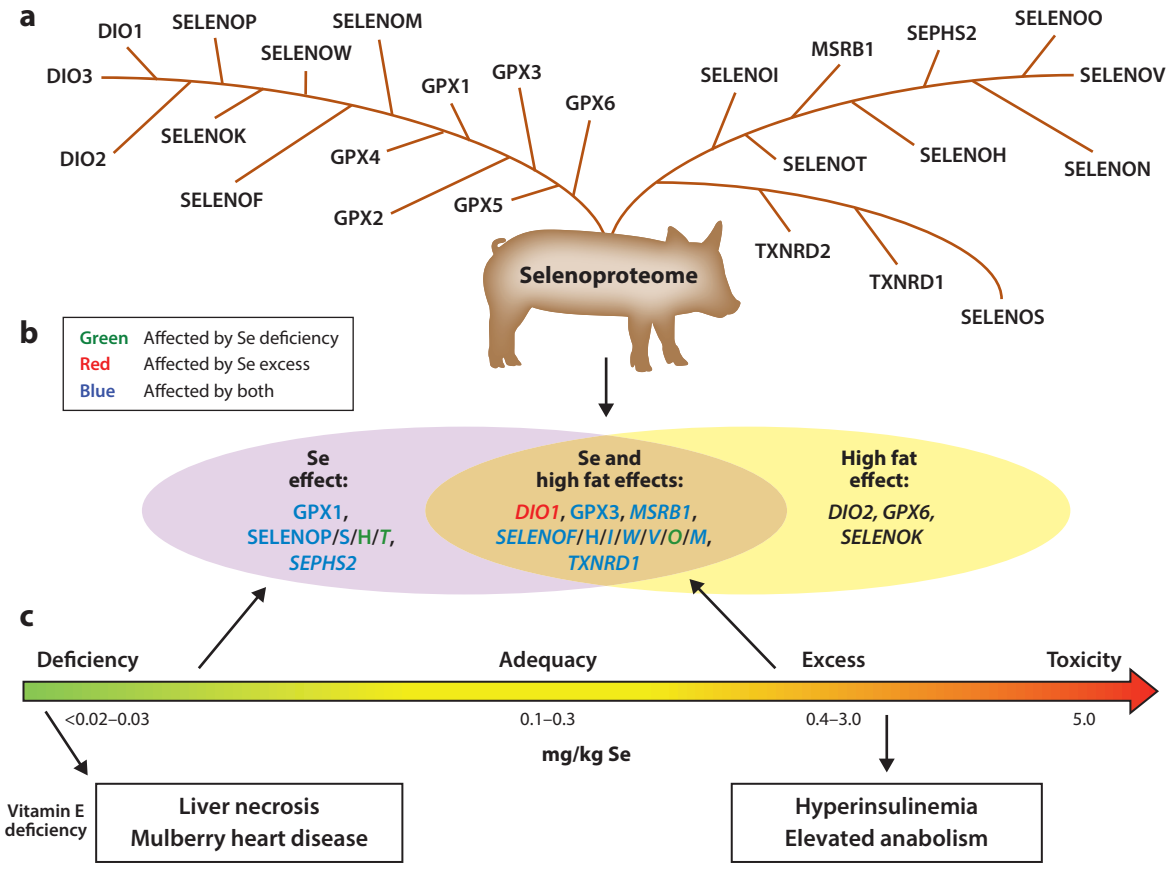


Figure 3

(*a*) Phylogenetic scheme of the 25 identified porcine selenoproteins that fall into two primitive groups and three parallel branches. (*b*) Effects of dietary concentrations of Se (mg/kg) (deficiency: <0.02 to 0.03 and excess: 0.4 to 3.0 in comparison with adequacy: 0.1 to 0.3) and fat (wt/wt%) (high fat: 3–7% lard in comparison with normal fat: <0.83% crude fat) on expression of selenotranscriptome (*italic*) and production of selenoproteins in the liver and other tissues of pigs (2–6 months of age and 20–120 kg of body weight). Genes and proteins affected by both dietary Se and fat concentrations are listed in the overlap area between the pink and yellow circles; those affected by dietary concentrations of only Se or fat are listed in the pink and yellow circles, respectively. Genes and proteins in blue were affected by both dietary Se deficiency and excess; those in red were affected by dietary Se excess; and those in green were affected by dietary Se deficiency. (*c*) Dose-dependent effects of dietary Se concentrations on susceptibility to classical Se–vitamin E deficiency diseases, expression of selenotranscriptome and production of selenoproteome, risk of abnormal metabolism, and overt toxicity in pigs. In all panels, DIO1, 2, and 3 equal iodothyronine deiodinase 1, 2, and 3, respectively; GPX1, 2, 3, 4, and 6 equal glutathione peroxidase 1, 2, 3, 4, and 6, respectively; MSRB1 equals methionine-R-sulfoxide reductase 1; SELENOF, H, I, K, M, N, O, P, P2, S, T, U, V, and W equal selenoprotein F, H, I, K, M, N, O, P, P2, S, T, U, V, and W, respectively; SEPHS2 equals selenophosphate synthetase 2; and TXNRD1, 2, and 3 equal thioredoxin reductase 1, 2, and 3, respectively. Figure adapted from Reference 24 and based on data from Reference 224.

SELENOI has phosphatidyltransferase activity, catalyzing formation of phosphatidyl ethanolamine. SELENOM and SELENOF are located in the endoplasmic reticulum (ER); they also have thioredoxin-like folds and are associated with the elimination of misfolded proteins. SELENOK and SELENOS each have a single transmembrane domain; they, too, are associated with elimination of misfolded proteins (63). SELENOO is the largest selenoprotein with unknown function. SELENON functions in muscle differentiation and development, and its

mutations are associated with early onset muscular disorders in humans, implying a possible involvement in white muscle diseases in animals (146). While knockout models of *Selenoh*, *Selenoo*, *Selenos*, *Sephs2*, and *Txnrd3* are not reported, global knockouts of the remaining 19 selenoprotein genes in mice caused embryonic lethality in only five homozygous lines (*Gpx4*$^{-/-}$, *Trxnd1*$^{-/-}$, *Trxnd2*$^{-/-}$, *Selenoi*$^{-/-}$, and *Selenot*$^{-/-}$) (**Table 1**). Humans may tolerate the deficiency of *GPX4* or *TXNRD2* but not the loss of any of the DIO enzymes (140).

4.2. Regulation of Selenoproteome and Selenogenome

Effects of dietary Se on selenoprotein production in several species have been reviewed (24, 70, 90, 166, 224). In general, production of many, but not all, selenoproteins is decreased by deprivation of Se and restored by Se supplementation. The production is reported to be affected by dietary vitamin E and fat concentrations (67, 223), but dietary vitamin E deficiency in otherwise healthy rats showed no direct effect on concentrations of liver Se or activities of plasma GPX3, red blood cell GPX1, liver GPX1, and liver GPX4 (168). This suggests that selenoproteome changes are more likely due to downstream effects of dietary vitamin E deficiency.

Likewise, expression of many, but not all, selenotranscripts responds to changes in dietary Se intakes. These responses appear to vary with species, tissue, and subcellular location and seem to imply the biological relevance of those encoded proteins. As described above, global knockouts of 19 selenoprotein genes in mice caused embryonic lethality in only five homozygous lines. All heterozygous knockouts, with only 50% of protein or activity of the altered selenoproteins, seemed to be viable and/or to breed well under nonstressed conditions. Therefore, we should be cautious to directly relate numerical changes of tissue selenotranscriptome or selenoproteome expression, despite statistical significances, to body metabolic outcomes.

4.2.1. Rodents. Many studies have used only two to three concentrations of dietary Se and determined their effects on functional expression of several selenoprotein genes in two or three tissues. In contrast, a comprehensive rat study used 10 graded levels (0–0.8 mg Se/kg) of selenite supplementation in a basal diet (0.007 mg Se/kg) and measured concentrations of Se; activities of GPX1, GPX3, and GPX4; and transcript expression of 24 selenoproteins in the liver, kidney, muscle, and/or blood (7). Dietary Se deficiency decreased hepatic transcript expressions of just 11 of the 24 selenoproteins. Relative to the Se-adequate levels, liver mRNA levels of *Gpx1* were decreased to <10%, *Selenoh* and *Selenow* to <25%, and *Dio1*, *Gpx3*, *Selenot*, and *Txnrd3* to <50%. The Se response curve analyses indicated that liver GPX1 activity, plasma GPX3 activity, all tissue GPX4 activities, and liver Se concentration reached plateaus at ≤0.1 mg Se/kg of diet, whereas kidney Se concentration, GPX1 activity, and muscle GPX1 activity needed 0.1 to 0.15 mg Se/kg to be saturated. However, the full selenoprotein transcript expression occurred at <0.07 mg Se/kg (165).

Transcript expression of selenoproteins in mice also showed varied responses to dietary Se or fat (228). Thirteen genes (*Gpx1*, *Gpx3*, *Gpx4*, *Selenok*, *Selenoh*, *Selenom*, *Selenop*, *Selenos*, *Selenow*, *Selenox*, *Txnrd2*, and *Txnrd3*) were downregulated by Se deprivation in the liver. Twelve genes were affected by both dietary Se and fat concentrations including those five genes encoding ER-resident proteins (*Dio2*, *Selenof*, *Selenok*, *Selenom*, and *Selenos*) (228). Five genes showed relatively low or little response (*Gpx2*, *Selenon*, *Selenoo*, *Selenov*, and *Sephs2*) to either dietary Se or fat concentrations.

4.2.2. Pigs. Regulation of selenotranscript expression by dietary Se in pigs is largely similar to that in rodents. Only *DIO2*, *DIO3*, *SELENOF*, and *SELENOI* showed different responses to Se deprivation from those of the mouse genes (224). Production of porcine GPX1, SELENOP, SELENOS, and SELENOH were readily decreased in several tissues by Se deprivation (224), while expressions of *GPX4*, *DIO2*, *SELENOK*, *TXNRD2*, or *TXNRD3*) were less affected

(93, 95, 98). High dietary fat intakes up- or downregulated expressions of most selenoprotein genes (except for *TXNRD2* and *TXNRD3*) and seemed to affect the expressions of *DIO2*, *GPX6*, and *SELENOK* that were unaffected by dietary Se concentrations (93, 194, 223) (**Figure 3*b***). The effects of high dietary fat intakes were associated with changes in plasma levels of tumor necrosis factor alpha and interleukin-6 (223). Supplemental dietary serine elevated the mRNA levels and/or activities of GPX1, GPX2, TXNRD1, TXNRD2, and/or SELENOI in the skeletal muscle and liver of pigs (96). Heat and immune (via the administration of lipopolysaccharide) stresses altered selenoprotein gene expression in porcine cell lines and tissues, respectively (224).

4.2.3. Birds. In chickens, expression of *GPX1*, *GPX4*, *SELENOM*, *SELENOO*, and *SELENOU* was downregulated by dietary Se deficiency in the liver, muscle, and pancreas, whereas the same effect on the remaining genes was relatively weak and/or tissue specific (90) (**Figure 2*b***). Compared with sodium selenite, two sources of organic Se induced greater levels of transcripts, proteins, and/or activities of several selenoproteins in the liver and muscle of chickens (159, 225) (**Figure 2*c***). Different from that of rodents, *GPX4* mRNA in chickens was readily decreased by Se deprivation (67, 69, 89, 164, 208). In both chickens and turkeys, *GPX3* and *GPX4* transcript changes did not consistently lead to changes in selenoprotein levels (69, 164). In turkey liver, only *SELENOU*, *DIO1*, *SELENOP1*, and *SELENOP2* were significantly decreased by Se deficiency as assessed by differential expression of individual genes, whereas 13 selenotranscripts contributed to the significant downregulation of the selenotranscriptome as shown by gene set enrichment analysis (178).

5. HEALTH EFFECTS OF Se AND NEW PATHOLOGICAL MECHANISMS

5.1. Molecular Mechanisms of Se Deficiency Disorders in Various Species

Although the first pathologies associated with Se deficiency were reported in 1957, fundamental mechanisms for the pathogeneses of those Se deficiency diseases have remained elusive. Several recent studies have replicated a few of these classical deficiency symptoms in chicks, pigs, and cows for elucidating the underlying molecular bases.

5.1.1. Liver necrosis in pigs. The mechanisms underlying the development of liver necrosis are partially understood. The condition was manifested as apoptosis and necroptosis, apparently due to the activation of the oxidative stress pathway (222) accompanied by a shift of the tricarboxylic acid cycle to glutamine catabolism with impaired hepatic lipid synthesis (173).

5.1.2. Exudative diathesis in chickens. Exudative diathesis involves increased vascular permeability, resulting in edema in depending (a special term referring to lower anatomical regions in which body fluids tend to pool) aspect of the body. In the chick, the condition was associated with downregulation of *GPX1*, *GPX4*, *SELENOW*, *SELENON*, *SELENOP1*, *SELENOO*, and *SELENOK* transcripts in the liver and muscle (67). The incidence and mortality were completely prevented by supplemental dietary Se but only partially decreased by supplemental α-tocopherol acetate. Interestingly, supplementing α-tocopherol acetate decreased ($P < 0.05$) hepatic *GPX1*, *SELENOI*, *TXNRD1*, and *TXNRD2* transcripts. The inverse relationship between hepatic expression of these redox-related selenoprotein genes and vitamin E status underscores the complex roles of Se and vitamin E in preventing exudative diathesis.

5.1.3. Nutritional myopathies in chickens. Se-deficient chicks showed apoptosis in the pectoral and other skeletal muscles, associated with decreased gene expression of ER-resident

selenoproteins (*SELENON*, *SELENOT*, *SELENOK*, and *SELENOS*) (216). This finding indicated increased susceptibility of myocytes to oxidative cell death, which in Se-adequate animals was prevented by metabolizing endogenously produced peroxides and regulating redox/apoptotic signaling (69).

5.1.4. Nutritional pancreatic atrophy in chickens. Digital gene expression analysis of nutritional pancreatic atrophy of chicks indicated that Se deprivation altered the expression of 884 unigenes, with 360 of them upregulated and 524 of them downregulated, in the pancreatic transcriptome. Of the differentially expressed genes, 530 unigenes were annotated and 65 of them were classified into pathways related to Se-compound metabolism and apoptosis (68).

5.1.5. Impaired reproduction in cattle. Dietary Se deficiency has a well-known association with increased rates of retained placenta and embryonic loss and decreased fertilization rate. The direct mode of action was speculated to be connected to the regulation of oxidative stress in the periparturient cows (154). Additionally, improved fertility by supplemental Se might result from increased progesterone concentrations during the early luteal phase, particularly when cows consumed organic sources of Se with greater bioavailability (18, 20). Increased progesterone concentrations during this period might enhance successful pregnancy outcomes, particularly in lower fertility cows (211).

5.2. Se Deficiency–Associated Diseases in Humans

Severe endemic Se deficiency is linked with two diseases in humans: Keshan disease (KD), a juvenile cardiomyopathy, and Kashin-Beck disease (KBD), an osteoarthropathy. These disorders were described in rural, mountainous areas of central and northeastern China and Russia (eastern Siberia) where food systems were exceedingly low in Se (soils <125 μg/kg; grains <40 μg/kg) and humans had blood Se concentrations of <25 ng/ml (compared with 85–200 ng/ml in the United States).

5.2.1. Keshan disease. KD is a multifocal myocarditis primarily affecting children 2–10 years of age and, to a lesser extent, women of child-bearing age. Diagnosis is based on signs of acute or chronic cardiac insufficiency, cardiac enlargement, arrhythmia, and electrocardiographic abnormalities (51). Affected individuals may show cardiogenic shock or congestive heart failure. In the 1970s, Chinese scientists found Se to be effective in preventing the disease (25). This discovery led to the widespread use of Se supplements (oral doses of sodium selenite at 0.5 to 1 mg Se/week, or table salt fortified with selenite at 10 to 15 mg Se/kg of salt) (23). Such interventions have virtually eliminated KD from previously affected areas. The disease might be caused by cardiophilic RNA viruses, whose mutations could be potentiated in severe Se deficiency (8, 9).

Expression profile analysis of Se-related genes in peripheral blood mononuclear cells (PBMCs) of patients with KD identified 16 upregulated and 11 downregulated Se-related genes compared with those in healthy controls. These genes were involved in apoptosis, metabolism, transcription regulation, ion transport, and growth and development (94). Proteomic analysis of the patient serum revealed 9 significantly altered proteins among 27 differentially expressed proteins compared with that of healthy adults (161). The differentially expressed proteins were mainly involved in complement coagulation pathways. Another proteomic analysis of the patient serum samples identified 105 differentially expressed proteins including 19 Se-associated proteins involved in hypoxia-inducible factor 1 signaling and apoptosis pathways (192).

5.2.2. Kashin-Beck disease. KBD is an osteoarthropathy affecting the epiphyseal and articular cartilage and epiphyseal growth plates of growing bones. It presents as enlarged joints (especially of fingers, toes, and knees); shortened fingers, toes, and extremities; and, in severe cases, dwarfism. A meta-analysis of 15 clinical trials (232) suggested that Se supplementation had some value in preventing the disease. However, additional factors, including iodine deficiency and exposure to fungal toxins, have been implicated as etiological factors.

Transcription profile of selenoprotein in PBMCs of KBD patients showed 17 downregulated and 2 upregulated (*GPX4* and *SELENOM*) selenotranscripts. The transcripts of *GPX2*, *GPX3*, *DIO1*, *TXNRD1*, *TXNRD3*, and *SPS2* were most closely associated with those of apoptosis-related genes in the patients (215). Further genome-wide differential methylation analyses revealed distinct differentially methylated regions in conjunction with corresponding differentially methylated genes and enriched functional pathways in KBD and osteoarthritis; these genes are all key to regulating cartilage/skeletal physiologic and pathologic processes (48).

5.3. Role of Se in Anticarcinogenesis

That Se may be anticarcinogenic was proposed in the late 1960s on the basis of inverse relationships of cancer mortality rates and forage crop Se contents in the United States (150). Subsequent epidemiology found blood Se concentrations to be inversely associated with the prevalence of colorectal and prostate cancer (31).

5.3.1. Animal studies. Hundreds of studies with tumor models have found both inorganic and organic forms of Se to be effective in preventing carcinogenesis. In fact, this has been the finding in every model examined, including models of primary tumorigenesis in which tumors are induced by chemical or viral agents and models of secondary tumorigenesis in which tumors are induced by transplanting primary tumor cells. The antioxidant functions of selenoproteins would suggest anticarcinogenic functions (60, 230). Tumors have been found to express variant forms of *GPX1* (66) and to underexpress *GPX1*, *GPX3*, and *SELENOP* (111). The i^6A^- transgenic mouse, which has reduced expression of most selenoproteins due to a dysfunctional $tRNA^{[Ser]SeCys}$, shows accelerated prostate carcinogenesis (37). Single-nucleotide polymorphisms of several selenoproteins have been linked to cancer risk (4, 137).

These effects would appear to be maximized in animals fed nutritionally adequate levels of Se, for example, 0.1–0.2 mg/kg of diet. However, in all animal tumor model studies, anticarcinogenesis has been observed with supranutritional exposures to Se, that is, levels substantially greater (10–20 times) than those needed for maximal selenoprotein expression. This observation implies mechanisms unlikely to involve selenoproteins, with the possible exception of SELENOW, the mRNA for which has been reported to be upregulated under conditions of supranutritional Se treatment (61). Evidence suggests other underlying mechanisms (74): production of reactive oxygen species (ROS) by the redox cycling of selenides; modification of protein thiols by selenides; and substitution of SeMet for methionine in key proteins, increasing their sensitivity to ROS.

5.3.2. Human interventions. The anticarcinogenic potential of Se remains a subject of debate. Only a few clinical trials have been conducted to test the hypothesis that Se may reduce cancer risk in humans (12, 26, 176, 218). Systematic reviews have differed in their assessments of those results (34, 141, 189), influenced by apparently conflicting results of two major intervention trials.

The Nutritional Prevention of Cancer (NPC) Trial (26) showed that supplemental Se (200 μg/day in the form of a high-Se yeast) significantly reduced risks to total cancers and to prostate and colorectal carcinomas over more than 7 years of intervention. The larger Selenium

and Vitamin E Cancer Trial (SELECT) (92) found no protection by the same dose of Se, provided as SeMet, against prostate cancer over a 5-year intervention period. Consideration of the blood Se levels of each cohort shows that, in fact, their results were consistent: SELECT subjects had relatively high baseline plasma Se levels (averaging 136 ng/ml), that is, comparable with those of NPC subjects that did not show prostate cancer risk reduction by Se [risk reduction was noted only among NPC subjects in the lowest tertile of baseline plasma Se status, i.e., <106 ng/ml (38)]. Many have missed this point. Overall, it appears that supplemental Se may reduce the risk of certain cancers in many people, especially in those with low or nutritionally adequate, but not high, Se status.

6. BIOMARKERS OF BODY Se STATUS AND DIETARY Se REQUIREMENTS

6.1. Biomarkers of Se Status

The word status is a term of art in the field of nutrition referring to the amount of metabolically active or potentially metabolically active Se or other nutrients in various tissues. Accordingly, Se status is a product of an individual's intake, retention, and metabolism of this micronutrient. It has four components: Se intake, tissue Se, Se excretion, and Se function (29).

The establishment of dietary requirements for Se (or any essential nutrient) requires parameters (biomarkers) that are both accessible and measurable with levels and activities that vary in predictable ways according to the magnitude of exposure to that nutrient. Useful biomarkers of Se status include gene transcript, protein abundance, and enzyme activity of selenoproteins and tissue Se concentrations. The levels of these biomarkers fall upon Se deprivation, thus distinguishing adequate from deficient status.

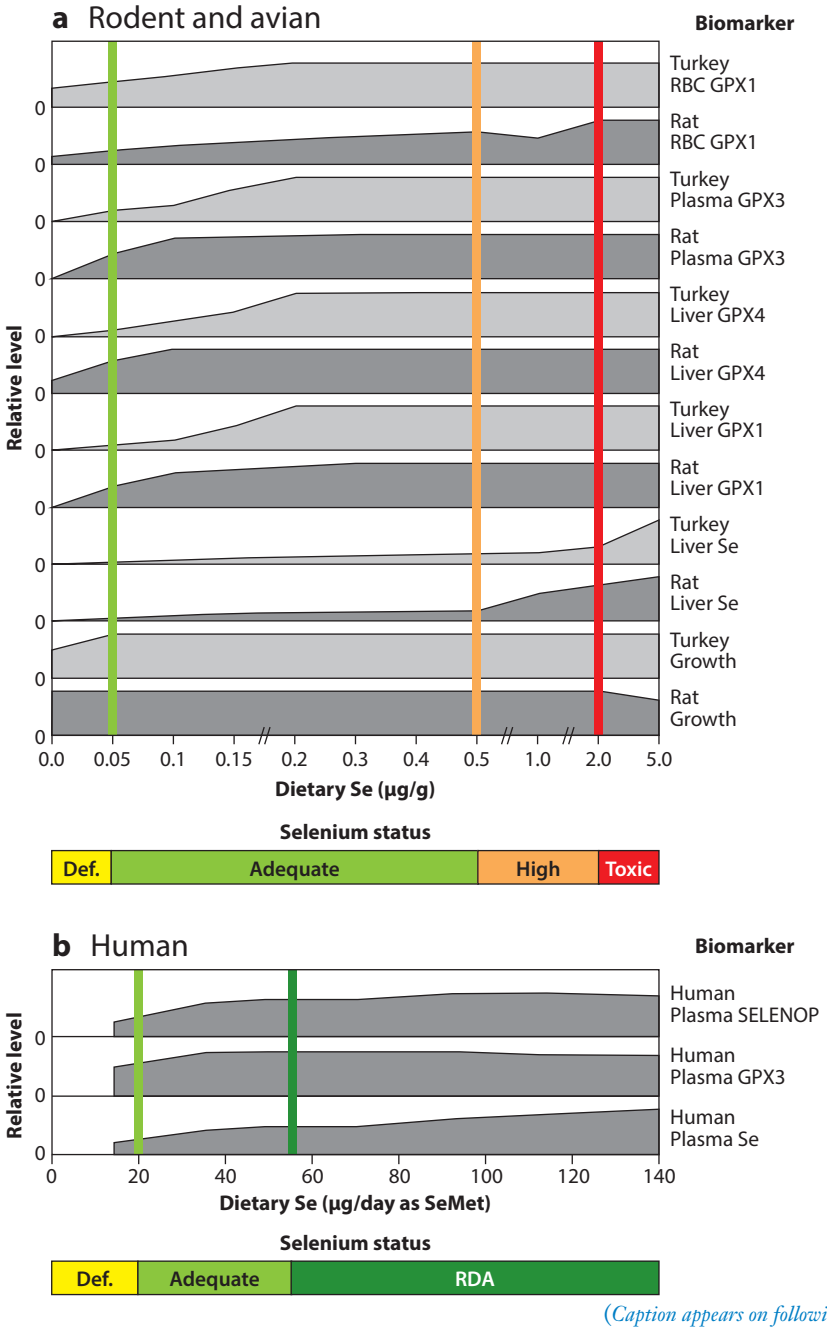
The most useful biomarkers of Se status are those that consistently show well-defined dose-response functions. These include plasma GPX3 activity, liver GPX1 activity, and liver GPX4 activity for animals (165) (**Figure 4*a***), and plasma GPX3 activity and SELNOP concentration for humans (15, 207) (**Figure 4*b***). Simply, erythrocyte GPX1 activity and tissue Se are less useful, because although they decrease in Se deficiency, they increase over a wide range of Se intakes, overshooting the levels required to prevent deficiency disease. Dose-response curves of Se biomarkers can be constructed to impute dietary Se requirements. However, responses of a given biomarker to dietary Se and other treatments could be very different or even opposite between tissues (228). Thus, multiple biomarkers in several tissues should be considered to provide a full and accurate spectrum of Se status.

6.2. Recommended Dietary Se Intakes for Animals

Recommended dietary Se concentrations or intakes for laboratory, food- and wool-producing, and companion animals are established by expert panels convened by the National Academies of Science, Engineering, and Medicine, formerly the National Research Council (NRC) of the National Academy of Sciences. The recommendations are based, as much as possible, on published research; where necessary, they are extrapolated from such data. These currently available recommendations are summarized in **Table 2** and briefly discussed below.

6.2.1. Laboratory animals. The recommended Se level of 0.15 mg/kg for growing rats was based on the minimal amount (0.1 mg/kg) required to support maximal expression of GPX1 activity in the liver (86, 185, 199) and a slightly higher level (0.15 mg/kg) required to protect against microvascular lesions in rats fed high-sucrose diets (40). Subsequent studies with multiple dietary

Se concentrations and biomarkers supported this recommendation (7). A higher dietary Se concentration of 0.4 mg/kg was recommended for pregnant and lactating rats (116). That concentration was rationalized by the lack of plateau of erythrocyte GPX1 activity, liver GPX1 activity, and liver Se concentration to graded dietary Se concentrations up to 0.3 mg/kg in young adult nulliparous females through lactation day 18 (153). Later studies showed that the Se needs for



(*Caption appears on following page*)

Figure 4 (*Figure appears on preceding page*)

(*a*) Example rodent and avian biomarkers of Se status. Shown are relative responsive levels of indicated biomarkers of Se status in rats and turkeys. Weanling rats and day-old turkeys from Se-adequate parents were fed Se-deficient diets supplemented with indicated levels of dietary Se as selenite for 4 weeks. Responses of tissue Se concentrations may depend in large part on the nature of consumed Se, as SeMet supports much greater tissue Se deposit than do selenite or selenate, particularly when dietary methionine is not in excess. Growth performance may not be a very responsive or specific biomarker of dietary Se changes in many species. Data are from References 135, 165, 177, and 179. (*b*) Human biomarkers of Se status. Shown are relative responsive levels of indicated biomarkers of Se status of low-Se Chinese subjects consuming 14 μg/day and supplemented with additional Se as SeMet for 40 weeks. Deficient Se status is shown as 19 μg/day [average of the male and female adult basal safe mean Se intake levels by the World Health Organization (204)] and recommended dietary allowance (RDA) as 55 μg/day. Data are from Reference 207.

pregnancy and lactation were not substantially greater than those of rapidly growing rat pups (163). There is also no evidence that the Se requirements of rats change with age (167).

The NRC recommendation of a dietary Se concentration of 0.15 mg/kg for mice was based on the above-described apparent need of the rats. Moderate differences in Se intakes of otherwise adequately nourished mice did not affect growth, although low Se concentrations decreased activities of GPX1 in erythrocytes and liver as well as the Se content of liver (49, 165). Maximal activities of GPX3 in plasma and GPX1 and GPX4 in kidney were achieved with dietary Se concentrations of 0.05–0.08 mg/kg, while erythrocyte GPX1 activity plateaued at 0.12 mg/kg. These studies indicate that a dietary Se concentration of 0.2 mg/kg is adequate for mice. The recommended dietary Se concentrations for gerbils, guinea pigs, and hamsters (0.1 to 0.15 mg/kg) were based on the needs of the rats and apparently require experimental verification.

6.2.2. Other nonruminants. Recommendations of dietary Se concentrations for five domestic, simple-stomached mammals are in the range of 0.10 to 0.42 mg/kg (**Table 2**). Among these species, the estimates for pigs were the best studied and were based on maximal GPX activities in blood and other tissues. A study with growing pigs found maximal activities of GPX1 in liver, GPX4 in heart, and GPX3 in plasma at dietary Se concentrations of 0.2 mg/kg (85). That Se concentration also reduced in vivo lipid oxidation (F_2 isoprostanes in plasma and liver). Fast-growing neonatal and weanling pigs may require greater Se intakes than grower or finisher pigs. Supplementing sows with Se-enriched yeast (79) or SeMet (47, 220) may help meet that need of weanling piglets. Boars are particularly susceptible to dietary Se deficiency. When fed low dietary Se concentrations, for example, <0.07 mg/kg, they developed characteristic changes in testicular structure (169).

The most recent NRC (120) recommendations of dietary Se for dogs and cats are 0.35 and 0.30 mg/kg of diet or 90 and 19 μg/day, respectively. Earlier recommendations for these species were based on intakes of metabolizable energy and Se levels for protection against lesions observed in Se-deficient animals and/or the needs of other simple-stomached species. Because commercial diets for cats and dogs often contain high levels of animal protein and may be contaminated by a variety of pro-oxidants, it is suggested that those diets be supplemented with Se up to 0.5 mg/kg. However, the actual estimated Se requirements for kittens (197) and puppies (198), on the basis of responses of plasma and erythrocyte GPX activities, plasma Se concentrations, and plasma T3 concentrations to multiple dietary Se concentrations (kittens: 0.027 to 0.31 mg/kg; puppies: 0 to 0.52 mg/kg), were 0.15 and 0.21 mg/kg, respectively. The current NRC recommendation of dietary Se concentration (0.1 to 0.3 mg/kg) for horses falls in the same range of earlier estimates (157) and translates into a minimal intake of 1 to 1.25 mg Se/day for a horse with a 500-kg body weight (BW).

Table 2 Recommended dietary Se intakes for animals and humans

Species	Recommendation	Reference
Laboratory animals (mg/kg diet)		
Rats	0.15	116
Mice	0.15	116
Gerbils	0.15–0.4	116
Guinea pigs	0.15	116
Hamsters	0.10	116
Nonhuman primates	0.11	118
Domestic nonruminants (mg/kg diet)		
Pigs	0.15–0.3	124
Dogs	0.35	120
Cats	0.30	120
Minks	0.05–0.42	113
Horses	0.1–0.3	121
Birds (mg/kg diet)		
Meat chickens, all ages	0.15	115
White egg–laying strains	0–6 weeks: 0.15 6 weeks, first egg: 0.10	115
Brown egg–laying strains	0–6 weeks: 0.14 6 weeks, first egg: 0.10	115
Turkeys, all ages	0.2	115
Ducks, 0–2 weeks	0.2	115
Japanese quails, all ages	0.2	115
Ruminants		
Beef cattle (mg/kg DMI)	0.1	112
Dairy cattle (mg/kg DMI)	0.3	117
Sheep (mg/day)	Maintenance: 0.00025 mg/kg BW ÷ AC Growth: 0.50 mg/kg BW gain ÷ AC Pregnancy (last trimester): 0.0025 mg/kg litter birth weight ÷ AC Lactation: 0.14 mg/kg milk yield ÷ AC Wool: 0.38 mg/kg clean fleece weight ÷ AC	122
Goats (mg/day)	Maintenance: (0.015 mg/kg DMI + 0.083 mg) ÷ AC Growth: 0.5 mg/kg BW gain ÷ AC Pregnancy (last trimester): 0.0021 mg/kg litter birth weight ÷ AC Lactation: 0.10 mg/kg milk yield ÷ AC Mohair: 0.38 mg/kg clean fleece weight ÷ AC	122
Donkeys (μg/kg BW)	1–1.5	122
Camels (mg/day) (New World camelids)	0.74	122
Fish (mg/kg diet)		
Rainbow trout (*Oncorhynchus mykiss*)	0.15	123
Channel catfish (*Ictalurus punctatus*)	0.25	123
Hybrid striped bass (*Morone saxatilis* × *M. chrysops*)	0.25	123
Grouper (*Epinephelus* spp.)	0.7	123
Pacific white shrimp (*Litopenaeus vannamei*)	0.2–0.4	123

(*Continued*)

Table 2 (*Continued*)

Species	Recommendation	Reference
Humans (μg/day)		
Based on plasma GPX3 activity	55	72
Based on plasma GPX3 activity	30 (women), 40 (men)	204
Based on plasma SELENOP concentration	75	207

Abbreviations: AC, absorption coefficient (0.31 for forages and 0.60 for concentrates); BW, body weight; DMI, dry matter intake.

6.2.3. Birds. The recommended dietary Se concentrations for various types of birds are 0.1 to 0.2 mg/kg. The Se concentration of 0.15 mg/kg for broiler chickens was based on studies of day-old chicks fed corn-soy or semipurified diets (78) containing 0.17 to 0.18 mg Se/kg and their responses of weight gain and feed intake compared with those fed basal diets containing 0.06 to 0.08 mg Se/kg. The recommendation was also supported by earlier studies for preventing poor growth and exudative diathesis (181) as well as pancreatic exocrine atrophy (56) and maximizing plasma GPX3 activity in chicks (126). Studies with a more recent breed of rapidly growing male broiler chicks fed adequate amounts of vitamin E showed that Se supplementation of a Se-deficient diet with 0.025 mg/kg significantly improved growth. Se supplementation of 0.10 to 0.13 mg/kg raised activities of GPX3 in plasma, GPX1 in liver, and GPX4 in gizzard to plateau levels (89). However, activities of pancreatic GPX1 and GPX4 did not plateau with these increases in dietary Se, suggesting that chickens may require an increase in dietary Se to 0.2 mg/kg.

The NRC recommendation for all classes of turkeys (dietary Se concentration of 0.2 mg/kg) was based on the studies of Scott and colleagues (148). They found that addition of Se at 0.1 mg/kg into a practical (basal) diet containing 0.08 mg/kg and supplemental vitamin E for turkey poults prevented poor growth and development of gizzard myopathy that occurred in poults fed the basal diet. Subsequent studies found that total dietary Se concentrations of 0.13–0.17 mg/kg were required to maximize plasma GPX3 activity (17). A recent study found that a dietary Se concentration of at least 0.05 mg/kg was needed to support normal growth of vitamin E–fed male poults. However, dietary Se concentrations of 0.25–0.35 mg/kg were required for maximal activities of GPX3 in plasma, GPX1 in pancreas and liver, and GPX4 in kidney and skeletal muscle (179). These results suggest that recommended dietary Se concentrations should be increased to 0.4 mg/kg for growing turkeys.

6.2.4. Ruminants. Estimates of the Se needs of ruminant species, while based on the best available data, are still not well defined. The recommendation for beef cattle, 0.1 mg/kg of dry matter intake (DMI), assumes adequate dietary vitamin E (112). Adjusting those data for projected DMI associated with differing rates of gain resulted in projected Se needs somewhat higher than those reported for dairy cattle (117). Results of Australian studies supported Se needs of 0.04 mg/kg of DMI (33). The recommendation for dairy cattle, 0.3 mg/kg of DMI, also assumes adequate dietary vitamin E (112, 117).

The Se recommendation for sheep, 0.1 mg/kg of DMI, was imputed from beef cattle data using a factorial approach and assuming utilization efficiencies of 30% for Se in forages and 60% for Se in concentrate-based diets, respectively. The factorial method is applied to calculate Se requirements by sheep and goats for maintenance, growth, pregnancy, lactation, and wool production on the basis of BW, BW gain, litter BW, milk yield, and clean fleece weight, respectively (122). After being adjusted to the predicted DMI level, these estimates are within the ranges of those for dairy and beef cattle. Results of Australian studies supported Se needs of 0.05 mg/kg of DMI (33).

6.2.5. Fishes. It is challenging to determine the dietary Se requirements of fish because there are a large number of species, different life stages, wide ranges of environmental conditions, and variations in harvest time and daily managements (16). Blood and tissue GPX activities and Se concentrations are often used as biomarkers to assess Se status and requirements of fish. Intriguingly, estimated dietary Se requirements of several types of fish and shrimp fall largely in the ranges (0.15 to 0.42 mg/kg) of those for food-producing mammals.

6.3. Dietary Reference Intakes for Humans

Recommended dietary allowances (RDAs) for Se were not set until 1989; they were revised as dietary reference intakes (DRIs) in 2000 (72). These standards were based on Se intakes associated with maximal expression of a single selenoenzyme, GPX3, from only two small human studies. The first study involved Chinese adults with baseline Se intakes averaging 11 μg/day. When supplemented with graded levels of selenite, they showed increases in GPX3 activity that plateaued at a total daily Se intake of 41 μg (213). Adjustment for the mean BWs of Americans yielded an estimated Se requirement of 52 μg/day. The second study involved adult New Zealanders with a baseline Se intake of 28 μg/day (39). When supplemented with Se, as SeMet, those subjects responded to a 10-μg daily dose of Se with increased GPX3 activity, suggesting a requirement of 38 μg/day. The average of these estimates, 45 μg/day, was taken as the estimated average requirement, and the RDA was set at 55 μg/day for both men and women. RDAs for children were extrapolated from this value on the basis of BW. Those for infants, however, were based on projected Se intakes from breast milk (birth to 6 months: 15 μg/day) and from breast milk plus complementary foods (6 months to 1 year: 20 μg/day). Additional Se was recommended during pregnancy and lactation, bringing those RDAs to 60 μg/day and 70 μg/day, respectively.

In assessing available data, the World Health Organization (WHO) (204) established basal adult Se intake levels of 16 and 21 μg/day as intake levels below which signs of Se deficiency might occur. Subsequently, the WHO based its recommendations on amounts of Se needed to support two-thirds of maximal plasma GPX3 activity according to the study of Yang et al. (213). That Se intake was imputed to be 26 μg/day. Adjusting for BW and assumed interindividual variation, the WHO-recommended Se intakes for men and women were set at 40 and 30 μg/day, respectively. Neither of these groups considered the bioavailability differences of selenite and the major form of Se in foods, SeMet. The latter is known to be more effective in supporting GPX3 activity by low-Se individuals (206).

A higher value was suggested by the results of a 40-week randomized intervention trial with Chinese subjects with baseline Se intakes averaging 14 μg/day (207). When supplemented with graded doses of SeMet, plasma GPX3 activity increased to plateau levels with total intakes of 35 μg/day, while maximization of plasma SELENOP concentration occurred with total intakes of 49 μg/day. Using SELENOP optimization as the key parameter and adjusting for BW and individual variation, Xia et al. (207) proposed a daily Se need of 75 μg through the dominant food form, SeMet, for Americans. In the United Kingdom, the recommendation for dietary Se intake, called reference nutrient intake, is 60 μg/day for women and 75 μg/day for men (72).

7. ADVERSE EFFECTS AND TOXICITIES OF Se

7.1. Metabolic Effects of High Se Intakes on Animals

Dietary Se concentrations up to 5 mg/kg impaired growth and, occasionally, survival of rats (102, 135) but had no effect on turkey poults (177). Mice have been found to tolerate Se in the form of selenate or selenite in their drinking water at levels of 2–3 μg/L (142). Such high dietary concentrations do, however, increase the deposition of Se in the livers of various species (e.g., by 6- to

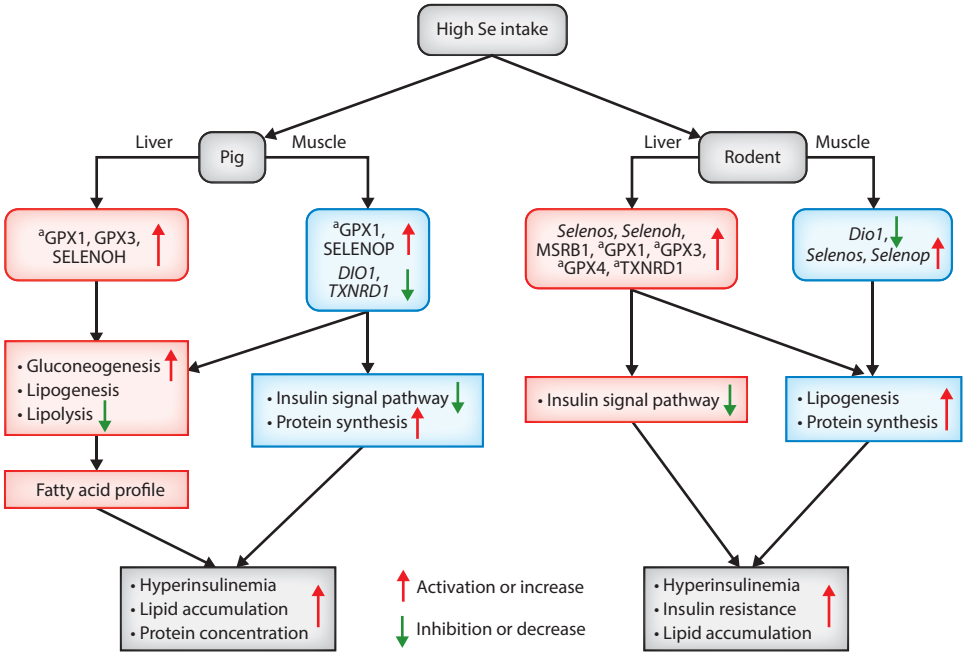


Figure 5

Overview of regulatory pathways and mechanisms for the metabolic impacts of high dietary Se intakes (1 to 3 mg/kg of diet) in comparison with adequate or deficient Se intakes in pigs and rodents. Abbreviations: a, activity; DIO1, iodothyronine deiodinase 1; GPX1, 3, and 4, glutathione peroxidase 1, 3, and 4; MSRB1, methionine-R-sulfoxide reductase 1; SELENOH, P, and S, selenoprotein H, P, and S; TXNRD1, thioredoxin reductase 1. Figure adapted from Reference 24.

7-fold) (95, 127, 135, 177, 227, 230). In rats and chicks, this effect is greater for organic Se than for selenite (160, 202). High Se intakes typically do not affect the expression of selenoenzymes, most of which are maximized at nutritional intakes, that is, <0.5 mg/kg (165). In both rats and turkey poults, high dietary Se concentrations had no effects on hepatic levels of selenoprotein transcripts (135, 177). However, pigs fed a dietary Se level of 3 mg/kg showed elevated activities of GPX3 in plasma and GPX1 in liver, muscle, and thyroid compared with those fed 0.3 mg/kg (95, 230).

Excessive Se intakes seem to exert no global regulation of transcript expression across individual selenoprotein genes or tissues. Studies with pigs have shown that a dietary Se level of 3.0 mg/kg caused increases of *GPX3* expression in liver and muscle (95), decreases of *SELENOW* expression in liver (88, 95, 221), increases of *SELENOW* expression in muscle (88, 95), and no changes in *GPX1*, *SELENOP*, or *SELENOS* expression in these tissues (95, 227, 230). In comparison, rats fed a dietary Se level of 5 mg/kg showed a 20% decrease in growth rate and had altered expression of 4% of the transcriptome (1,193 liver transcripts), whereas rats fed a dietary level of ≤2 mg/kg had <10 altered transcripts (135). The overall impacts of high dietary Se intakes on biochemical responses and macronutrient metabolism in pigs and rodents are outlined in **Figure 5**.

RNA sequencing (RNA-seq) studies revealed only a small number of differentially expressed transcripts in turkeys fed dietary Se levels of 2 or 5 mg/kg, without transcripts showing a consistent pattern of expression altered or associated metabolic pathways or biological functions affected by excess Se. Gene set enrichment analyses revealed that excessive dietary Se intakes (2 to 5 mg Se/kg of diet) resulted in no consistently altered gene sets in turkeys (178) but 27 upregulated gene sets in rats fed 5 mg Se/kg of diet (162). Cross-species comparison of transcript expression in rats and

turkeys revealed no common gene sets consistently regulated by excess Se. The fact that a dietary Se level of 5 mg/kg dramatically increased liver differentially expressed transcripts and GSEA gene sets in rats, while a lower, supranutritional concentration (2 mg/kg) did not, suggests a level of subclinical toxicity associated with the higher level. The turkeys fed the same level of Se did not show increases in differentially expressed transcripts and thus seemed to tolerate that high level of Se exposure. Microarray and RNA-seq studies using multiple, high-level Se supplements found no specific transcripts, pathways, biological states, or processes that were directly linked with high Se status, suggesting accommodation to excessive Se beyond transcriptional regulation.

7.2. Diabetogenic Risk of High Se Status in Humans

Recent animal experiments have shown unexpected risks of prolonged high Se intakes (0.4 to 3.0 mg/kg of diet) (95, 219, 227, 229) or overproduction of selenoproteins (103) in potentiating insulin resistance and type 2 diabetes mellitus (T2DM). The underlying mechanisms for these observations remain unclear, but they seem to involve elevated activity or production of selenoproteins including GPX1, MSRB1, SELENOS, and SELENOP; diminished intracellular ROS; dysregulated insulin synthesis, secretion, and signaling (193, 229); and dysregulated gluconeogenesis, lipogenesis, and protein synthesis (227, 228) (**Figure 5**).

However, the translational significance of these animal studies to humans is questionable (109). Observational studies have indicated associations of high plasma/serum Se and risk of T2DM and/or elevated fasting plasma glucose, though the associations are often nonlinear (190). Interestingly, deficient Se status has also been associated with risk of hypoglycemia (194). Using toenails as an indicator of Se status, the risk of T2DM was found to be lower across increasing quintiles of Se (128, 136). Clinical studies have not shown such effects; of six randomized controlled trials that evaluated the effects of Se supplementation on T2DM risk, only one trial found effects on unconfirmed T2DM (158). A larger trial, SELECT, which detected 1,782 cases in a cohort of >30,000 subjects, found no effect of supplemental Se on T2DM risk (92), nor did supplemental Se appear to affect pancreatic β cell function, insulin sensitivity, or glycemic indices (1, 76).

7.3. Acute and Chronic Toxicities

Most reported cases of Se intoxication of animals involve cattle and sheep grazing in regions with Se-accumulating native plants. Such plants, which are prevalent on seleniferous soils of the northern Great Plains of the United States, are capable of synthesizing a variety of methylated selenides, selenoamino acids, and selenowaxes and accumulating Se at 20–100 mg/kg of dry matter (30). The high level of Se was found to cause neuropathies in horses and cattle (blind staggers, alkali disease) in the 1940s, and subsequent investigations have characterized selenosis in both its acute and chronic forms (30). Cattle and sheep have a learned postingestive feedback mechanism that helps them avoid the consumption of toxic plants (133); they both also appear to consume forages selectively to avoid excessive Se intakes (130).

Acute selenosis has occurred in humans due to accidental ingestion of gram quantities of Se in such high-Se solutions as gun bluing, sheep drench, and antidandruff shampoo (30, 72). Each case involved rapid development of severe gastrointestinal and neurological symptoms followed by acute respiratory failure, myocardial infarction, and renal failure.

Chronic selenosis has occurred in both animals and humans. In grazing animals, it is caused by dietary Se levels of 3–8 mg/kg of DMI (170). In humans, endemic selenosis was identified in the early 1960s in Enshi, Hubei Province, China, where residents consumed foods containing very high levels of Se (several hundred mg/kg) due to the use of local high-Se coal ash to amend agricultural soils (212). During the years of peak prevalence (1961–1964), the five most heavily

affected villages experienced morbidity rates approaching 50%, and some individuals had blood Se levels as high as 3,200 μg/L. The most common signs were hair and nail loss, and sometimes lesions of the skin, nervous system, and teeth. Dietary Se intakes, estimated a few years later, averaged ~5 mg/day, with individuals with Se intakes <1.5 mg/day showing no adverse effects. Acute Se doses of >30 mg/day in humans can cause diarrhea, hair loss, nail pathology, and nausea.

Intoxication due to apparent misformulation of Se supplements is a real concern. Acute Se toxicity occurred in 201 humans who took an over-the-counter supplement that was found to contain 200-fold of the dose stated on the label. This overdose resulted in Se intakes of 3 to 245 mg/day (median 42 mg/day) over a period averaging 29 days (99). Ingestion of another misformulated Se preparation that contained 27.3 mg/tablet (187-fold of the amount stated on the label) for up to 2.5 months resulted in similar symptoms (62). A group of 21 polo ponies experienced fatal pulmonary hemorrhages after administration of a veterinary supplement that contained a 1,000-fold excess of Se (35).

7.4. Maximal Tolerable Se Levels

Guidelines for maximal amounts of dietary Se supplementations and maximal tolerable levels of Se across species have been established to prevent the adverse effects and toxicities of excessive Se intakes outlined above. Overall, data for these guidelines were of good quality for terrestrial animals but less so for aquatic species and only minimal for humans. However, mainly, the well-being and survival of different species were considered in setting up these maximal levels of Se. The potential impacts of these levels on the ecological sustainability and biosafety of Se accumulation in the food chain should not be neglected.

7.4.1. Guidelines for Se supplementation in animal feeds. In 2005, the NRC set the following maximum tolerable levels for Se in animal feeds (119): 5 mg/kg for cattle, sheep, horses, rats, and mice; 4 mg/kg for swine; 3 mg/kg for chickens, turkeys, and ducks; and 2 mg/kg for fishes. Since that time, additional data have supported new recommendations for beef cattle of 3–8 mg/kg of DMI (112). In many countries, the supplementation of Se in animal feeds is controlled. In the United States, selenite, selenate, Se-enriched yeast, and/or selenomethionine hydroxy analog can be added to complete feeds for chickens, turkeys, ducks, cattle (beef and dairy), sheep, and/or swine at levels that provide no more than 0.3 mg of Se/kg of diet (184). In the European Union, selenate or SeMet may be added to all livestock feeds in amounts that bring total dietary Se levels to no more than 0.5 mg of Se/kg of diet (41). In essence, both sets of guidelines are designed to limit feed Se levels to 0.5 mg/kg.

7.4.2. Guidelines of maximal intakes for humans. The US Food and Drug Administration (FDA) set a no observed adverse effect level (NOAEL) for Se in whole blood at 1,000 μg/L; this level was calculated to correspond to a dietary intake of 853 μg/day in an adult male (115). The Institute of Medicine (72) set a tolerable upper Se intake level for adults at 400 μg/day, that is, approximately half the NOAEL. The European Food Safety Authority set a tolerable upper Se level for adults at 300 μg/day (147). Other national bodies adopted similar recommendations of 350–450 μg/day for adults (71).

8. INCREASING Se STATUS

8.1. Providing Se to Animals

Many natural feed ingredients produced in the world do not contain adequate amounts of Se to meet the nutrient requirements by domestic species. Dietary Se supplementations of inorganic or

organic forms, Se biofortifications of plant feeds, and direct Se injections in animals have been widely used in animal production after Se was approved as a feed additive. Notably, new forms of Se supplements, along with the intended amount, time, and route, require FDA approval. The most important considerations of different methods for providing Se to various species include efficacy, safety, and ecological impact of the supplements.

8.1.1. Feed supplementation. Addition of Se to feeds is a reliable means of increasing and assuring the Se status of animals. This is typically done by adding Se compounds to vitamin-mineral premixes used in formulated feeds. This practice has become routine in manufacturing most formulated diets, particularly those for chickens, pigs, horses, cats, dogs, fish, and laboratory animals.

Another approach is the use of free-choice mineral mixes containing Se. In most countries, the principal approach is the use of free-choice, salt-based supplements fortified with Se and other minerals (105). This approach can be confounded by nonuniform intakes of the free-choice supplements and by the presence of S, which can antagonize the utilization of Se (5).

Providing supranutritional Se in the diets of gestating cattle or sheep has little impact on growth (138) but increases blood and muscle Se concentrations (19, 174). In dairy cattle, the practice has been reported to increase milk production and colostrum quality (171), which may relate to increased mammary gland vascularity (191). Supranutritional dietary intakes of Se may enhance cow-calf nutrient transport capabilities, as treated cows showed increased vascularity of maternal intestinal tissues (155).

Se supplementation of maternal diets has resulted in responses of offspring in developmental programming involving epigenetic effects. Evidence of such effects includes increased growth and development of lambs produced by Se-supplemented ewes (138). The basis of such responses would appear to involve changes in early embryonic gene expression that affects metabolism. This hypothesis was supported by findings that, by gestational day 50, six genes associated with selenoproteins and glutathione metabolism were responsive to moderate changes in maternal Se supply (32).

8.1.2. Direct supplementation. Direct treatment has been found effective in providing Se to grazing ruminants. Injectable preparations containing Se can be used to avert effects of confounders. Studies have found this approach effective in raising liver Se contents in cattle and sheep that could persist for at least a month (52, 132). This approach is viewed as a particular utility for treating beef calves of deficient or marginal Se status at the time of weaning. Ruminal boluses or pellets designed to provide a sustained slow release of Se have been used in dairy cows and sheep. This approach has been effective in increasing blood Se levels in dairy cows over extended periods of time (75). Sprinkle et al. (156) found that the use of long-acting trace element boluses for cows grazing extensive rangeland decreased calving intervals and increased calf weaning weights.

8.1.3. Indirect application. Se-containing sprays have been used on forage crops to increase the Se intakes of grazing animals. Foliar application of sodium selenate providing 120–480 g of Se per hectare substantially increased the Se contents of Bermuda grass (186). Alfalfa hay produced on fields receiving spray applications of sodium selenate showed increases in Se content (57).

8.2. Increasing Se in Food Systems for Humans

Sustainable increases in Se contents of foods can be accomplished using approaches that take advantage of and enhance the cycling of Se in the ecosystem. These approaches have been done in Se-deficient parts of Finland through the use of Se-containing fertilizers to increase the Se contents of feeds and foods for preventing veterinary morbidities (53) and improving the Se status of

humans (44). Within a few years, the program effectively raised per capita Se intake from deficient (~25 μg/day) to adequate (110 to 120 μg/day) levels. That rise resulted in a marked increase in adult serum Se concentrations from an average of ~70 to ~119 ng/ml (44).

8.3. Biofortification of Animal-Sourced Foods with Se

As elaborated above, cattle grazing forages in areas of elevated Se concentrations produce Se-enriched beef (64). Taylor et al. (175) reported that Se-enriched beef was as acceptable to consumers as control beef. In fact, eggs, meat (chicken, turkey, pork, beef, and lamb), and milk are readily enriched with Se by feeding animals high dietary concentrations of Se. Se contents could be enhanced to 30–35 μg/egg and 20–45 μg per 100 g of fresh meat (50, 108). The enrichments enable ingestion of one egg or 100 g of meat to meet approximately 40–60% of the DRI of Se. There are large variations in the reported concentrations of Se in the milk of cows and goats (2 to 50 μg/L) and their responses to dietary Se supplementations (3). Elevating dietary Se intakes of these species resulted in increases in Se contents linearly in the goat milk but nonlinearly in the cow milk (27).

Supplemental organic Se, including SeMet, Se-enriched yeast, and seleno-hydroxy-methionine, is more effective than inorganic Se in enriching Se in eggs, meats, and milk (**Figure 2*c***). The chemical form of Se also affects the Se deposition destination: The inorganic Se is deposited predominantly in the yolk, whereas SeMet and Se-enriched yeast are transferred mainly to the albumen (125). The Se enrichments do not seem to alter the physical or sensory properties of eggs, meats, and milk but do improve their oxidative resilience and shelf life (50, 108).

The bioavailability of Se in various meats, based on rodent liver GPX activity and other responses (151, 201), was similar to that of selenite or SeMet. Long-term benefits of these Se-enriched animal foods to humans need intervention verifications. Interestingly, the Se-enriched porcine serum (5.4–6.2 μmol/L) exerted a strong growth inhibition on several types of human cancer cells (160). It is unlikely that consuming Se-enriched animal foods at typical intakes will exceed the safe or maximal tolerable levels for humans enough to cause chronic toxicity concern. However, a recent study indicated that the total target hazard quotient for Se, Pb, Cd, As, Hg, and Cr contamination in Se-enriched eggs might predispose children aged 2–9 years to noncarcinogenic health risks (226).

9. CONCLUDING REMARKS

Among all the essential micronutrients, Se is perhaps the most unique because of its multiphased roles in nutrition and health, the identifications of selenogenome and selenoproteome sets, and the narrowest gap (with the possible exception of iodine) between the amounts required to prevent clinical signs of deficiency and those leading to adverse effects or toxicities. However, specific and collective functions of many selenoproteins, along with their regulation by dietary Se and their contribution to the pathogeneses of the Se-deficiency diseases, remain unclear. Many of the dietary Se recommendations currently used in animal and human nutrition need to be revised with clearly defined metabolic goals and fully validated biomarkers supported by advances in Se biology. Although current biomarkers for assessing Se deficiency status are largely usable, future research is needed to identify correspondingly good biomarkers for high Se status. Those novel tools would help to better characterize safe levels of dietary Se intakes. While several forms of inorganic (selenite and selenite) and organic (SeMet and Se-enriched yeast) Se are widely used in food fortification and feed manufacture, there is a continued interest in searching for new forms and sources of Se to improve the efficacy and safety of Se supplementation and to prevent environmental contamination of Se. As global Se deposits on Earth are rather limited and unevenly

distributed, the recycling of Se in food and ecological systems should be optimized for an efficient and sustainable supply of Se to meet the dietary requirements of humans and various species of animals.

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