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Review article

Selenium and breast-feeding

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The objective of the present review is to discuss Se nutrition during breast-feeding, encompassing environmental and maternal constitutional factors affecting breast-milk-Se metabolism and secretion. A literature search of Medline and Webofscience was used to retrieve and select papers dealing with Se and breast milk. Although Se in natural foods occurs only in organic form, breast milk responds to organic and inorganic Se in supplements. Inorganic Se (selenite, selenate), which is largely used in maternal supplements, is not detectable in breast milk. The mammary-gland regulating mechanism controls the synthesis and secretion of seleno-compounds throughout lactation, with a high total Se level in colostrum that decreases as lactation progresses. Se appears in breast milk as a component of specific seleno-proteins and seleno-amino-acids in milk proteins that are well tolerated by breast-fed infants even in high amounts. Se in breast milk occurs as glutathione peroxidase (4–32 % total Se) > selenocystamine > selenocystine > selenomethionine. The wide range of breast-milk Se concentrations depends on Se consumed in natural foods, which reflects the Se content of the soils where they are grown. Se prophylaxis, either through soil Se fertilization or maternal supplements, is effective in raising breast-milk Se concentration. In spite of wide variation, the median Se concentration from studies worldwide are 26, 18, 15, and 17 μg/l in colostrum (0–5 d), transitional milk (6–21 d), mature milk (1–3 months) and late lactation (>5 months) respectively. Se recommendations for infants are presently not achieved in 30 % of the reported breast-milk Se concentrations; nevertheless Se status is greater in breast-fed than in formula-fed infants.

Selenium: Lactation: Speciation: Glutathione peroxidase

Se deficiency, well documented in livestock, was only recently recognized in man consuming food grown in Se-poor soil in remote areas. Manifest human Se deficiency is associated with Keshan disease and Kaschin-Beck osteoarthropathy. Besides being a constituent of glutathione peroxidase (GPX), the most important protective agent against free radicals induced by xenobiotics, Se acts against chemical carcinogens and counteracts the toxicity of heavy metals. The importance of Se in biology and medicine has been well discussed by others (Whanger, 1992; Allan *et al.* 1999; Kohrle *et al.* 2000; Rayman, 2000; Combs, 2001). However, its interaction with thyroid metabolism merits consideration.

Thyroid hormone metabolism depends on deiodination reactions carried out by three deiodinase selenoenzymes (Kohrle *et al.* 2000). Two deiodinases, type I and type II 5′-deiodinase, catalyse the reductive 5′-(phenolic ring) of the prohormone L-thyroxine (3,3′,5,5′-tetraiodo-L-thyroxine) to thyromimetically active 3,3′,5-triiodo-L-thyronine. Type III 5-deiodinase removes the iodide in 5-position from the tyrosyl ring of 3,3′,5,5′-tetraiodo-L-thyroxine and forms thyromimetically inactive 3,3′,5′-triiodothyronine (reverse 3,3′,5′-triiodothyronine). Animal studies have shown that the mammary alveolar cell contains thyroxine-5′-deiodinases that are positively correlated with lactation intensity (Jack *et al.* 1994). Deiodinase activity is also present in milk cellular components (Slebodzinski & Brzezinska–Slebodzinska, 1991). As a consequence, a new interest in the interaction between I and Se is emerging.

Se appears in major staple foods mainly as L(+)-selenomethionine. Schrauzer (2001) reviewed the subject showing that 8 % total Se in maize, wheat and soyabean

Abbreviation: GPX, glutathione peroxidase.

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Table 1. Summary of studies reporting mean selenium concentrations (μg/l or μg/kg) and glutathione peroxidase (GPX) activity in breast milk

Reference	Country	Se concentration	GPX activity (units)	Stage of lactation	Observations
Al-Awadi & Srikumar (2001)	Kuwait	20·0	182·0	0–6 m	Kuwaiti
		18·0	130·0	0–6 m	Non-Kuwaiti
		16·0	126·0	6–12 m	Kuwaiti
		16·0	115·0	6–12 m	Non-Kuwaiti
		15·0	128·0	12–18 m	Kuwaiti
		14·0	104·0	12–18 m	Non-Kuwaiti
Debski *et al.* (1987)	USA	15·1	36·0	NG	
Debski *et al.* (1989)	USA	22·2	40·1	4–6 m	Vegetarian
		16·8	27·5	4–6 m	Non-vegetarian
Dodge *et al.* (1998)	China	22·6	70·0	Early	Xichang
		6·3	40·0	Late	Xichang
		26·0	78·0	Early	Beijing
		15·8	68·0	Late	Beijing
		83·0	69·0	Early	Enshi
		94·8	61·0	Late	Enshi
Dodge *et al.* (1999)	New Zealand	12·9	34·0	1–90 d	Supplemented
		9·4	39·0	1–90 d	Non-supplemented
Ellis *et al.* (1990)	USA	32·4	29·7	3 d	Term
		26·0	36·8	7 d	Term
		23·7	39·2	21 d	Term
		21·3	35·4	42 d	Term
		31·6	39·7	3 d	Preterm
		26·8	28·8	7 d	Preterm
		25·3	30·1	21 d	Preterm
		22·9	33·2	42 d	Preterm
		32·4	28·2	3 d	Very preterm
		26·0	28·2	7 d	Very preterm
		24·5	22·9	21 d	Very preterm
		25·3	29·5	42 d	Very preterm
Funk *et al.* (1990)	Gambia	21·0	51·0	Early	Dry season
		19·4	40·8	Late	Dry season
Hojo (1986)	Japan	34·2	66·0	4 d	
		24·0	46·0	7–8 d	
		22·5	38·8	36–86 d	
Hojo (1987)	Japan	22·5	38·8	1–3 months	
L'Abbe & Friel (2000)	Canada	NG	73·0	1–12 weeks	Term
		NG	85·8	1–12 weeks	Preterm
Mannan & Picciano (1987)	USA	15·6	68·1	4–16 weeks	Fore-milk
		18·1	90·4	4–16 weeks	Hind-milk
Milner *et al.* (1987)	USA	14·4	136·0	1–12 months	
Moore *et al.* (2000)	China	7·4	54·0	1 d	Control
		8·7	80·0	1 week	Control
		9·3	88·0	2 weeks	Control
		11·7	91·0	3 weeks	Control
		8·4	82·0	4 weeks	Control
		6·3	19·0	12 weeks	Control
		16·7	70·0	1 d	100 μg selenomethionine/d
		17·9	90·0	1 week	100 μg selenomethionine/d
		19·8	88·0	2 weeks	100 μg selenomethionine/d
		16·9	90·0	3 weeks	100 μg selenomethionine/d
		16·2	83·0	4 weeks	100 μg selenomethionine/d
		9·9	45·0	12 weeks	100 μg selenomethionine/d
Trafikowska *et al.* (1996)	Poland	9·2	82·7	1 month	
		15·9	80·7	1 month	200 μg yeast Se/d
		15·0	92·7	2 months	200 μg yeast Se/d
		14·4	74·9	3 months	200 μg yeast Se/d
Trafikowska *et al.* (1998)	Poland	8·9	80·0	0 months	Control
		8·9	75·0	0 months	Yeast Se
		8·9	70·0	0 months	Selenite
		8·9	71·0	1 month	Control
		16·0	72·0	1 month	Yeast Se
		12·9	90·0	1 month	Selenite
		9·0	72·0	2 months	Control
		14·5	80·0	2 months	Yeast Se
		13·0	145·0	2 months	Selenite
		6·0	80·0	3 months	Control
		13·0	70·0	3 months	Yeast Se
		14·0	150·0	3 months	Selenite
Williams (1983)	New Zealand	7·6	31·0	29–33 d	

NG, not given; m, months.

consists of selenomethionine, and in yeast it reaches more than 90 %. Other selenocompounds (methylselenocysteine, selenocystathionine, γ-glutamyl-methylselenocysteine) are normally found in small amounts in edible plants. Se in higher plants (Terry *et al.* 2000) and in the global food systems (Combs, 2001) has been the subject of specific reviews. Selenomethionine is easily absorbed and incorporated into body proteins in place of methionine and linked to protein turnover (Thomson *et al.* 1993). Although existing naturally, selenite (SeO_3^{2-}) and selenate (SeO_4^{2-}) are not recognized as commonly occurring components of plant or animal tissue in natural foods. Inorganic Se salts are readily reduced to selenide and made into selenophosphate, the precursor of selenocysteine (Allan *et al.* 1999). These salts are largely used as nutritional supplements and in infant formulas (Schrauzer, 2001). In spite of this, selenomethionine is a less bioavailable source of metabolic Se than inorganic Se in supplements.

The human infant is born with Se reserves, but also depends on the Se supplied by human milk. Thus, human milk is fundamental for the infant's optimum Se status, as reports consistently show a higher plasma Se concentration and GPX activity in breast-fed infants compared with formula-fed infants (Jochum *et al.* 1995; Sievers *et al.* 2001). The objective of the present review is to discuss Se nutrition during breast-feeding, encompassing environmental and maternal constitutional factors affecting breast-milk-Se metabolism and secretion.

The scientific literature was searched through MEDLINE (www.ncbi.mlm.nih.gov) and WEBOFSCIENCE (Thompson ISI, USA).

Selenium species in breast milk

Se is secreted in breast milk as organic compounds and its partition is mostly associated with protein in the water-soluble fraction. After ultracentrifugation, 62 % total Se was found in the supernatant fraction (Debski *et al.* 1987). Dialysable Se (28 %) varies proportionally with total Se, but not with stage of lactation (Debski *et al.* 1987; Milner *et al.* 1987). Studies have shown the occurrence of up to nine selenoproteins (Milner *et al.* 1987), with GPX accounting for 3·6–14·3 (Hojo, 1987; Avissar *et al.* 1991) or 15–30 % Se in milk (Milner *et al.* 1987; Bhattacharya *et al.* 1988). Most, if not all, of this enzyme was derived from its maternal plasma selenoprotein form (Avissar *et al.* 1991).

Studies by Michalke & Schramel (1997, 1998) found mainly GPX > selenocystamine > selenocystine > selenomethionine and no inorganic Se (selenite and selenate) in pre-concentrated breast-milk samples. Al-Awadi & Srikumar (2001) showed that selenomethionine was the major Se form associated with breast-milk whey, and that the selenocysteine content was negligible. They also showed a distinct pattern of Se compounds between human and cows' milk and could not detect inorganic Se. Michalke & Schramel (1998) and Michalke (2000) calculated a mass balance (sum of Se species:total Se) in breast milk of 94–100 %. However, in seleniferous areas of Venezuela, breast-milk samples with very high Se concentrations (1240–1930 μg/kg DM) showed a mass balance of 87 % corresponding to four peaks in the whey fraction (Negretti de Bratter *et al.* 1995) and a unique selenoprotein pattern that differed from that of cows' milk and soyabean-formula (Bratter *et al.* 1998).

Animal studies have shown that organic Se is more efficiently incorporated into milk proteins than the inorganic form. In dairy animals, selenite and selenate supplements were only as half as effective as yeast Se in raising total milk Se (Ortman & Pehrson, 1999). However, the effect of inorganic Se on sows' milk GPX activity was higher than its organic forms (Mahan, 2000). This is consistent with easier formation of selenocysteine, the active form of selenoprotein (Allan *et al.* 1999). Indeed, differences in milk Se concentrations due to type of diet (Debski

Table 2. Summary of studies comparing mean selenium concentrations (μg/kg or μg/l) in fore- and hind-milk

Reference	Country	Fore-milk	Hind-milk	Stage of lactation	Observations
Bratter *et al.* (1991*b*)	Germany	NG	NG	NG	16 % increase in hind-milk
Cumming *et al.* (1983)	Australia	11·8	–	8–23 weeks	Users and non-users of oral contraceptives, fore-milk
Cumming *et al.* (1992*b*)	Australia	–	12·0	6–12 weeks	Boys
		–	12·5	6–12 weeks	Girls
Cumming *et al.* (1992*a*)	Australia	10·8	13·9	6–12 weeks	
Dorner *et al.* (1990)	Germany	31·0	–	2 weeks	
		24·3	–	5 weeks	
		21·3	–	8 weeks	
		18·7	–	12 weeks	
		17·6	–	16 weeks	
Mandic *et al.* (1995)	Croatia	11·3	10·4	1 week – >60 d	Smokers
		11·5	10·2	1 week – >60 d	Two deliveries
		–	11·9	1 week – >60 d	Two deliveries
Mannan & Picciano (1987)	USA	15·6	18·1	4–16 weeks	
Smith *et al.* (1982)	USA	15·7	16·3	2 weeks	
		14·4	15·2	1 month	
		14·1	15·9	2 months	
		13·9	16·4	3 months	
Walivaara *et al.* (1986)	Sweden	14·3	14·2	NG	

NG, not given.

Table 3. Summary of studies that measured selenium concentrations in breast milk and maternal plasma or serum

Reference	Country	Mean Se concentration (μg/l)		Stage of lactation	Observations
		Plasma or serum	Milk		
Al–Awadi & Srikumar (2001)	South Arabia	126·0	20·0	0–6 months	Kuwaiti
		87·0	18·0	6–12 months	Kuwaiti
		79·0	16·0	12–18 months	Kuwaiti
		87·0	16·0	0–6 months	Non-Kuwaiti
		79·0	15·0	6–12 months	Non-Kuwaiti
		63·0	14·0	12–18 months	Non-Kuwaiti
Alegria *et al.* (1998)	Spain	74·7	9·6	NG	Whole blood
Arnaud *et al.* (1993*b*)	Niger	62·0	20·0	5 d	Serum
		89·0	15·0	90 d	Serum
		88·0	12·0	180 d	Serum
Arnaud *et al.* (1993*a*)	Niger	62·41	18·9	Colostrum	Serum
		60·83	19·8	Colostrum	Serum
		90·85	15·0	3 months	Serum
		90·85	14·2	3 months	Serum
		89·27	11·9	6 months	Serum
		90·0	13·4	6 months	Serum
Bratter *et al.* (1997)	Venezuela	229·0	42·9	20–24 d	Yaracuy, serum
		327·0	56·6	20–24 d	Portugueza 1 region
		621·0	112·2	20–24 d	Portugueza 1 region
Cumming *et al.* (1992*b*)	Australia	81·0	11·9	6–12 weeks	Serum
Cumming *et al.* (1983)	Australia	77·4	11·8	8–23 weeks	Plasma
Dodge *et al.* (1998)	China	15·8	6·3		Plasma, Xichang
		86·8	15·8		Plasma, rural Beijing
		552·7	94·8		Plasma, Enshi
Grandjean *et al.* (1995)	Faroe Islands	NG	19·1	NG, transitional milk	
Higashi *et al.* (1983)	Japan	148·0	17·0	3 months	Serum
Hojo (1987)	Japan	153·3	4·2	1–3 months	
Kantola *et al.* (1997)	Finland	11·8	22·1	Colostrum	Serum
	Estonia	63·0	13·1	Colostrum	Serum, Rakvere
	Estonia	48·2	11·2	Colostrum	Serum, Tallin
	Russia	88·3	21·9	Colostrum	Serum
Kumpulainen *et al.* (1985)	Finland	55·0	11·0	5–6 d	Unsupplemented
		84·0	10·4	4 months	Unsupplemented
		54·0	11·6	5–6 d	Selenite supplemented
		105·0	11·0	4 months	Selenite supplemented
		56·0	11·6	5–6 d	Yeast Se supplemented
		142·0	13·4	5–6 d	Yeast Se supplemented
Levander *et al.* (1987)	USA	136·0	20·0	1 month	Plasma
		137·0	15·0	3 months	Plasma
		138·0	15·0	6 months	Plasma
Mannan & Picciano (1987)	USA	97·0	16·8	4–16 weeks	
Micetic-Turk *et al.* (2000)	Slovenia	62·0	29·0	2–3 d	Serum
Michalke & Schramel (1998)	Austria	70·0	15·8	NG	
Moore *et al.* (2000)	China	35·0	7·4	1 d	Control
		–	8·7	1 week	Control
		48·0	9·3	2 weeks	Control
		–	11·7	3 weeks	Control
		50·0	8·4	4 weeks	Control
		30·0	6·3	12 weeks	Control
		100·0	16·7	1 d	100 μg selenomethionine/d
		–	17·9	1 week	100 μg selenomethionine/d
		88·0	19·8	2 weeks	100 μg selenomethionine/d
		89·0	16·9	3 weeks	100 μg selenomethionine/d
		80·0	16·2	4 weeks	100 μg selenomethionine/d
		–	9·9	12 weeks	100 μg selenomethionine/d
Moser *et al.* (1988)	Nepal	8·2*	10·0	2–6 months	
	USA	17·4*	15·0	NG	
Rossipal *et al.* (2000)	Austria	69·5	32·7	1 d	Serum
Schramel *et al.* (1988*a*)	Germany	80·0	43·0	1 d	Whole blood
		–	21·0	Mature milk	
Trafikowska *et al.* (1996)	Poland	54·0	9·2	1 d	Baseline, plasma
		101·0	15·9	1 month	200 μg Se/d, plasma
		127·0	15·0	2 months	200 μg Se/d, plasma
		116·0	14·4	3 months	200 μg Se/d, plasma
Trafikowska *et al.* (1998)	Poland	50·0	8·9	0 months	Control
		50·0	8·9	0 months	Yeast Se
		50·0	8·9	0 months	Selenite

Table 3. *Continued*

Reference	Country	Mean Se concentration (μg/l)		Stage of lactation	Observations
		Plasma or serum	Milk		
		50·0	8·9	1 month	Control
		105·0	16·0	1 month	Yeast Se
		90·0	12·9	1 month	Selenite
		50·0	9·0	2 months	Control
		130·0	14·5	2 months	Yeast Se
		100·0	13·0	2 months	Selenite
		49·0	6·0	3 months	Control
		115·0	13·0	3 months	Yeast Se
		100·0	14·0	3 months	Selenite
Wasowicz *et al.* (2001)	Poland	34·9	22·8	0–4 d	Plasma
		44·6	11·3	5–9 d	Plasma
		54·3	9·2	10–30 d	Plasma
Williams (1983)	New Zealand	46·0	7·6	29–35 d	Whole blood

NG, not given.
* nmol/l.

et al. 1989) or chemical forms of Se in supplements (Dodge *et al.* 1999) were also reported in lactating mothers. In undialysed fractions of lacto-ovo-vegetarians' breast-milk, the protein concentration was similar for both vegetarians and non-vegetarians, but an increase in milk Se was associated with protein <100 kDa (Debski *et al.* 1987).

Either as specific seleno-proteins or as the result of unspecific Se incorporation with S-containing amino acids, there is a positive correlation between total Se and protein content in human milk (Walivaara *et al.* 1986). Se in natural foods consumed by Chinese mothers from Xichang (low-Se region) and Enshi (high-Se region) provinces showed differences in total Se (0·26 *v.* 1·0 μmol/l respectively), but similar GPX activity in early breast-milk (1–7 d). However, in late lactation (2–10 months), the milk GPX activity in mothers from Xichang had decreased to significantly lower levels (Dodge *et al.* 1998). Absorption, retention and utilization (appearance in milk) were greater in a selenomethionine- than in a selenite-supplemented group (Mangels *et al.* 1990; Moser-Veillon *et al.* 1992; Trafikowska *et al.* 1998). Therefore, maternal Se either in natural food or supplements (organic and inorganic) also influences Se speciation in breast milk. A summary of mean GPX activity in breast milk is shown in Table 1.

Hind-milk is richer in fat than fore-milk (Dorea *et al.* 1982), but less than 5 % Se was found in the milk fat (Debski *et al.* 1987; Milner *et al.* 1987). Therefore, the significant difference in Se concentration between fore- and hind-milk reported by some (Smith *et al.* 1982; Mannan & Picciano, 1987; Bratter *et al.* 1991*b*; Cumming *et al.* 1992*a*), but not by others (Millar & Sheppard, 1972; Walivaara *et al.* 1986; Dorner *et al.* 1990), may be a statistical artifact due to variability in milk Se (Table 2). The overall median Se concentration is 10 μg/l milk, but extreme concentrations of 2·6 and 283 μg/l may change the proportion of organic forms as well as distribution within milk fractions (whey, milk fat). Although there exists a wide variation (Tables 1–9), the worldwide median Se concentration from studies dealing with maternal intake of Se from natural foods is 26, 18, 15, and 17 μg/l for colostrum (0–5 d), transitional milk (6–21 d), mature milk (1–3 months) and late lactation (>5 months) respectively. It is possible that some of the variation in breast-milk Se concentrations is due to differences in methodology.

Maternal constitutional factors

Although breast-milk Se is influenced by maternal Se intake, mechanisms of Se complexation with S-containing amino-acids modulates Se incorporation into milk proteins. These milk proteins are responsible for total Se secretion into breast milk and explains its decline during lactation, especially after the protein-rich colostrum. Nevertheless, no decline or even increase in total Se was reported by Kawamoto *et al.* (1994). Therefore, Se is higher in plasma than in breast milk (Table 3). Bratter *et al.* (1991*b*) showed that breast-milk Se concentration is 6–7-fold lower than maternal serum Se concentration. Recently, Rossipal *et al.* (2000) showed Se in colostrum was equivalent to 47 % total Se in maternal sera. Values of mean serum or plasma Se:milk Se ratios are highly variable, but there is a direct relationship between these two variables, and indeed, significant correlations have been reported (Williams, 1983; Kumpulainen *et al.* 1985; Levander *et al.* 1987; Mannan & Picciano, 1987; Bratter *et al.* 1991*b*), with some exceptions (Higashi *et al.* 1983; Micetic-Turk *et al.* 2000).

The Se complexation with S-containing amino acids facilitates its incorporation into protein. Se in fish fat can reach 59 % of the total amount found in muscle (Burger *et al.* 1992). In mammals, experiments show that muscles of cynomologus macaques (*Macaca fascicularis*) also have a higher concentration of Se than adipose tissue and a much higher capacity to retain supplemented Se (Hawkes *et al.* 1994). In lactating women, urine Se is influenced by creatinine excretion and therefore by lean-body mass (Thomson *et al.* 2001). Nevertheless, breast-milk

Table 4. Summary of studies comparing mean selenium concentrations (μg/kg or μg/l) in breast milk of term and preterm mothers

Reference	Country	Term	Preterm	Stage of lactation	Observations
Aquilio *et al.* (1996)	Italy	14·8	18·1	2–6 d	
		16·1	16·7	12–16 d	
		17·3	17·4	21 d	
Campfield *et al.* (1987)	USA	–	24·6	<60 d	
Daniels *et al.* (1997)	Australia	–	13·0	NG	
Ellis *et al.* (1990)	USA	32·4	31·6	3 d	
		26·0	26·8	7 d	
		23·7	25·3	21 d	
		21·3	22·9	42 d	
		–	32·4	3 d	Very preterm
		–	26·0	7 d	Very preterm
		–	24·5	21 d	Very preterm
		–	25·3	42 d	Very preterm
Ladodo *et al.* (1997)	Russia	33·3	26·8	Colostrum	
		48·2	35·7	Mature milk	
	Vietnam	–	12·2	Colostrum	
		–	11·0	Mature milk	
Perrone *et al.* (1993)	Italy	370*	520·0	1 week	
		340*	410·0	2 weeks	
		330*	370·0	3 weeks	
		320*	230·0	>3 weeks	
Sluis *et al.* (1992)	New Zealand	–	19·8	23 d	
Smith *et al.* (1991)	USA	–	26·0	1 d	
		–	24·0	1 week	
		–	24·0	2 weeks	
		–	23·0	3 weeks	

NG, not given.
* μg/kg DM.

Se was not correlated with maternal BMI (Bianchi *et al.* 1999), nor with infants' birth weights (Yoshinaga *et al.* 1991).

Events related to length of gestation and reproductive experience were investigated and results comparing term and preterm total milk Se are summarized in Table 4. Total Se and GPX activity in sera of parturients delivering preterm was reported to be low (Dobrzynski *et al.* 1998). However, the GPX activity was higher in preterm human milk (Ellis *et al.* 1990; L'Abbe & Friel, 2000) and even increased as milk protein content declined (L'Abbe & Friel, 2000). Reports showed no significant differences between preterm and term milk (Aquilio *et al.* 1996; Ladodo *et al.* 1997) except at 1 week (Perrone *et al.* 1993). In addition, the Se concentrations in preterm milk reported by Campfield *et al.* (1987), Smith *et al.* (1991) and Sluis *et al.* (1992) were within the range of Se reported for term milk (Table 4).

With regard to reproductive experience, there were no significant differences in maternal serum Se (Kumpulainen *et al.* 1985) or in breast-milk Se (Mandic *et al.* 1995) due to parity status. Indeed, Arnaud *et al.* (1993*a*) found no significant correlation between milk Se with parity or maternal age (Grandjean *et al.* 1995). However, Funk *et al.* (1990) found an inverse correlation between parity and milk Se only in late lactation. Although there is a significant correlation between Se status (toenail Se) and smoking (Virtanen *et al.* 1996), there was no significant difference in milk Se between smoking and non-smoking mothers (Mandic *et al.* 1995).

There are few studies dealing with the effects of medication on Se metabolism during lactation. A positive correlation between plasma oestrogen and plasma Se concentrations (Smith *et al.* 2000) and an increase in serum Se due to oral contraceptives have been reported (Verlinden *et al.* 1983; Heese *et al.* 1988). Nevertheless, the progestagen-only pill had no effect on serum or breast-milk Se concentrations (Cumming *et al.* 1983). However, a non-hormonal medication (selenium disulfide, 25 g/kg) used topically as an anti-seborrhoeic was described by Sugathan & Riyaz (1990) to suppress lactation.

Environmental factors

The Se content of foods depends on the Se concentration of soils where they are grown (Yang *et al.* 1989*b*; Terry *et al.* 2000). In certain areas of the world where Se fertilization of soil was carried out, there was an increase in the Se content of food and especially of breast milk. Wang *et al.* (1998) reported that Se fertilization of soil in Finland brought about an improvement in the Se status of the population that resulted in a substantial increase in milk Se (Koivistoinen, 1980; Kantola & Vartiainen, 1991). However, for a given stage of lactation, breast-milk Se may remain stable in a population over the years, provided there is no change in dietary Se supply. Tiran *et al.* (1993) showed that milk I in Austria increased after 2 years of dietary I supplementation, but in the absence of

Table 5. Summary of mean breast-milk selenium concentrations μg/kg or μg/l in studies comparing countries or regions in the same country

Reference	Country	Se concentration	Stage of lactation	Observations
Aro *et al.* (1994)	Russia	96·0	NG	Tanga
		76·0	NG	Chelutai
Bratter *et al.* (1991*a*)	Germany	15·1	10–20 d	Berlin
		15·2	12–63 d	Luberk
		16·4	12–62 d	Wurzberg
Debski *et al.* (1992)	Poland	8·6	1–2 months	Siedlce
		16·1	1–2 months	Piotrkow Trybunalski
		14·5	1–2 months	Warsaw
Dodge *et al.* (1998)	China	22·6	1–7 d	Xichang (low Se region)
		6·3	2–18 months	Xichang (low Se)
		83·0	1–7 d	Enshi (high Se region)
		94·8	2–18 months	Enshi (high Se region)
Hadjimarkos & Shearer (1973)	USA	21·0	51 d	OR, USA
	Greece	20·0	67 d	
Kantola & Vartiainen, 1991	Finland	15·8	4 months	Urban, rural residents 1990 May, September
		17·2		
Kantola *et al.* (1997)	Finland	22·1	Colostrum	
	Finland	19·2	Mature milk	Supplementation 1992-4
	Estonia	11·2	Colostrum	Tallin
	Estonia	18·2	Mature milk	Tallin
	Estonia	13·1	Colostrum	Rakvere
	Estonia	9·5	Mature milk	Rakvere
	Russia	11·5	Colostrum	Karelia
	Russia	21·9	Colostrum	St. Petersburg
Kantola & Vartiainen (2001)	Finland	16·6	4–6 weeks	Helsinki (urban) 1987
		16·14	4–6 weeks	Kuopio (rural) 1993–5
		17·3	4–6 weeks	Helsinki (urban) 1987
		19·4	4–6 weeks	Kuopio (rural) 1993–5
KD (1979)	China	3·0		Low Se region
		20·0		Moderate Se region
		283·0		High Se region
Ladodo *et al.* (1997)	Russia	26·8	Colostrum	
		35·7	Mature milk	
	Vietnam	12·2	Colostrum	
		11·0	Mature milk	
Palma & Howell (1982)	Mexico	150·0	NG	
	USA	50·0	NG	
Parr *et al.* (1991)	Guatemala	19·2	3 months	
	Hungary	13·9	3 months	
	Nigeria	24·2	3 months	
	Philippines	33·2	3 months	
	Sweden	13·1	3 months	
	Zaire	19·3	3 months	
Pilecki & Zachara (2001)	Poland	10·4–10·5*	14–58 d	Seven municipalites
Radzanowski *et al.* (1997)	Australia	9·4	1–12 months	
	Canada	10·4	1–12 months	
	Chile	9·4	1–12 months	
	China	5·6	1–12 months	
	Japan	10·5	1–12 months	
	Mexico	7·2	1–12 months	
	Philippines	12·1	1–12 months	
	UK	8·3	1–12 months	
Schramel *et al.* (1988*b*)	Germany	13–21*		Five areas in Bavaria
Shearer & Hadjimarkos (1975)	USA	13–28*	>10 d	Seventeen states
Yang *et al.* (1989*a*)	China	15		Low Se, Enshi county
		30·9		Moderate Se, Enshi county
		120·5		High Se, Enshi county
Zachara & Pilecki (2000)	Poland	8·8–11·6*		Sixteen provinces

NG, not given.
* Range.

any form of Se supplementation, mean breast-milk Se concentration was unchanged in the same period (1990–2). On the other hand, there are studies reporting that in countries with a decline in dietary Se supply, there is an impact on the Se status of their populations. Bratter *et al.* (1991*b*) summarized data from Germany indicating a decrease in breast-milk Se from 1976–87. In the UK, blood Se declined 50 % between 1974 and 1991 (Brown *et al.* 2000), but unfortunately there are no records of trends in breast-milk Se over the same period.

Table 6. Summary of studies comparing breast-milk selenium concentrations (μg/kg or μg/l) in relation to natural-food selenium intake and dietary habits

Reference	Country	Groups		Stage of lactation	Description of groups	
		1	2		1	2
Al-Awadi & Srikumar (2001)	Kuwait	20·0	16·0	0–6 months	Kuwaiti	Non-Kuwaiti
		18·0	15·0	6–12 months	Kuwaiti	Non-Kuwaiti
		16·0	14·0	12–18 months	Kuwaiti	Non-Kuwaiti
Arnaud *et al.* (1993*a*)	Niger	89·0	90·8	3 months	Control	Fe-supplemented
		89·0	90·0	6 months	Control	Fe-supplemented
Debski *et al.* (1989)	USA	16·8	22·2	4–6 months	Control	Lacto-ovo-vegetarian
Funk *et al.* (1990)	Gambia	21·0	15·3	1–6 months	Dry season	Rainy season
		19·4	17·5	13–19 months	Dry season	Rainy season
Kantola & Vartiainen (1991)	Finland	17·2	14·6	4 weeks	1990, May	1990, September
Rodriguez *et al.* (1998)	Spain	14·4	–	7–14 d	Combined seasons	
		16·8	–	23–30 d	Combined seasons	
		16·0	–	3 months	Combined seasons	
Snook *et al.* (1987)	USA	13·0	15·0		Columbus OH	Amish community

Variation in breast-milk Se among countries or regions within a country is shown in Table 5. Shearer & Hadjimarkos (1975) compared seventeen regions of the USA, reporting a mean range of 13–28 μg/l. Studies in Poland reported a range of 8·8–11·6 μg/l in sixteen provinces (Zachara & Pilecki, 2000), but a more uniform distribution (10·41–10·65 μg/l) among seven municipalities of western Poland (Pilecki & Zachara, 2001). Parr *et al.* (1991) compared breast-milk Se in six countries in four continents and reported a range of 13–32 μg/l. Moser *et al.* (1988) compared Se intake and breast-milk Se of Nepalese (2–6 months) and US mothers. US women, who had a dietary intake of Se 3·6-fold greater than that of Nepalese mothers, had a milk Se concentration only 1·5-fold greater. After the Se fertilization of soil in Finland, breast-milk Se concentration was higher than in neighbouring Russia and Estonia (Kantola *et al.* 1997). Nevertheless, breast-milk Se in Russia was higher than in Vietnam (Ladodo *et al.* 1997). Areas of low soil Se in China (KD, 1979; Yang *et al.* 1989*b*) as well as seleniferous regions of Venezuela (Bratter & Negretti de Bratter, 1996) and China (KD, 1979; Yang *et al.* 1989*b*) showed

Table 7. Summary of studies comparing breast-milk selenium concentrations (μg/l or μg/kg) and maternal dietary intake (μg/d) of selenium in natural foods

Reference	Country	Milk Se concentration	Maternal Se intake	Stage of lactation	Observations
Bianchi *et al.* (1999)	Brazil	14·1	71·0	7–210 d	
Bratter *et al.* (1991*b*)	Venezuela	46·0	220·0	NG	Caracas
		60·0	300·0	NG	Turen, La Laguna
		90·0	450·0	NG	El Aji, La Colonia, El Cedral
Bratter & Negretti de Bratter (1996)	Venezuela	42·9	205·0	20–24 d	Yaracuy
		56·6	274·0	20–24 d	Portugueza 1 region
		112·2	552·0	20–24 d	Portugueza 2 region
Debski *et al.* (1989)	USA	16·8	106·0	4–6 months	Non-vegetarian
		22·2	101·0	4–6 months	Vegetarian
Dodge *et al.* (1998)	China	6·3	11·0	2–18 months	Xichang
		110·0	15·8	2–18 months	Rural Beijing
		94·8	759·0	2–18 months	Enshi
Kumpulainen *et al.* (1983)	Finland	10·7	NG	1 month	1976, domestic wheat
		5·8	36·0	3 months	1976, domestic wheat
		5·6	36·0	6 months	1976, domestic wheat
Kumpulainen *et al.* (1984)	Finland	11·8	33·0	1 month	1976, US wheat
		10·9	NG	3 months	1976, US wheat
		10·0	NG	6 months	1976, US wheat
Levander *et al.* (1987)	USA	20·0	84·0	1 month	
		15·0	84·0	2 months	
		15·0	87·0	3 months	
Moser *et al.* (1988)	Nepal	10·0	23·0	2–6 months	
	USA	15·0	84·0	NG	
Yang *et al.* (1989*a*)	China	15·0	62·0	NG	Enshi region
		31·0	198·0	NG	Enshi region
		121·0	1238·0	NG	Enshi region

NG, not given.

Table 8. Summary of breast-milk selenium concentrations (μg/l) compared with selenium prophylaxis studies

Reference	Country	Se concentration		Stage of lactation	Type of prophylaxis
		Control	Prophylaxis		
Dodge *et al.* (1999)	New Zealand	12·9	9·4	1–90 d	50 μg as Se Methionine/d
Dylewski & Picciano (1999)	USA	24·0	33·0	3 months	6 months after 20 μg Se/d
Kantola & Vartiainen (1991)	Inland	–	6·5	4 months	1980 soil fertilization
		–	10·9	4 months	1984 soil fertilization
		–	14·3	4 months	1986 soil fertilization
		–	15·7	4 months	1987 soil fertilization
Kantola & Vartiainen (2001)	Finland	–	16·4	4–6 weeks	1987 soil fertilization
		–	18·9	4–6 weeks	1993 soil fertilization
Koivistoinen (1980)	Finland	50·0	110·0	NG	Before (1975–7) and after (1986) Se fertilization
Kumpulainen *et al.* (1985)	Finland	11·0	11·6	5–6 d	Selenite supplement (100 μg/d)
		10·1	11·4	2 months	Selenite supplement (100 μg/d)
		10·4	11·0	4 months	Selenite supplement (100 μg/d)
		9·0	10·6	6 months	Selenite supplement (100 μg/d)
		–	11·6	5–6 d	Yeast Se supplement (100 μg/d)
		–	14·1	2 months	Yeast Se supplement (100 μg/d)
		–	13·4	4 months	Yeast Se supplement (100 μg/d)
		–	13·4	6 months	Yeast Se supplement (100 μg/d)
McGuire *et al.* (1993*b*)	USA	18·0	16·6	1 month	Yeast Se
		–	16·0	1 month	Selenomethionine
		15·4	17·7	2 months	Yeast Se
		–	19·9	2 months	Selenomethionine
		13·2	14·2	3 months	Yeast Se
		–	10·4	3 months	Selenomethionine
		10·7	11·0	4 months	Yeast Se
		–	11·3	4 months	Selenomethionine
Moore *et al.* (2000)	China	7·4	16·7	1 d	+ 100 Selenomethionine/d
		8·7	17·9	1 week	+ 100 Selenomethionine/d
		9·3	19·8	2 weeks	+ 100 Selenomethionine/d
		11·7	16·9	3 weeks	+ 100 Selenomethionine/d
		8·4	16·2	4 weeks	+ 100 Selenomethionine/d
		6·3	9·9	12 weeks	+ 100 Selenomethionine/d
Trafikowska *et al.* (1996)	Poland	9·2	–	1 month	
		–	15·9	1 month	200 Yeast Se (μg/d)
		–	15·0	2 months	200 Yeast Se (μg/d)
		–	14·4	3 months	200 Yeast Se (μg/d)
Trafikowska *et al.* (1998)	Poland	8·9	8·9	0 months	Selenite supplement
		–	8·9	0 months	Yeast Se supplement
		8·9	16·0	1 month	Selenite supplement
		–	12·9	1 month	Yeast Se supplement
		9·0	14·5	2 months	Selenite supplement
		–	13·0	2 months	Yeast Se supplement
		6·0	13·0	3 months	Selenite supplement
		–	14·0	3 months	Yeast Se supplement
Walivaara *et al.* (1986)	Sweden	17·6	14·2	Colostrum	1978 and 1983*
		11·4	NG	6–10 d	1978 and 1983
		9·4	11·9	12–150 d	1978 and 1983

NG, not given.
* Se enrichment of animal feed started in 1980.

mean breast-milk concentrations in low and high ranges respectively (Table 5).

Within a food system, maternal dietary habits can influence Se status and modulate breast-milk Se (Table 6). Studies by Shultz & Leklem (1983) suggested a direct relationship between Se status (blood Se) and consumption of meat, milk and wheat products. Kadrabova *et al.* (1995) showed that vegetarians have a lower Se status (plasma Se and GPX activity) than non-vegetarians. Therefore, vegetarians showed different expression of milk GPX activity under identical total Se intake. In studies of Se metabolism in lacto-ovo-vegetarian nursing mothers with similar dietary Se intake (101 μg/d), it was observed that their milk had 146 % higher GPX activity than non-vegetarian (dietary intake 106 μg/d) controls (Debski *et al.* 1989). Comparing groups of mothers within a country, but with different dietary habits and Se status, showed differences in breast-milk Se fractions. Expression of milk GPX activity was significantly higher in middle-class Kuwaiti mothers consuming natural foods than in non-Kuwaiti mothers (Al-Awadi & Srikumar, 2001).

A summary of studies presented in Table 6 compares breast-milk Se concentrations in relation to maternal intake of Se in natural foods as affected by season or dietary habits. Funk *et al.* (1990) reported lower milk Se during the rainy season in the Gambia, while Rodriguez *et al.* (1998) found that breast-milk Se was higher in spring than in autumn in Spain. Although significant

Table 9. Summary of studies that measured breast-milk selenium concentrations (μg/kg or μg/l) in breast milk from different parts of the world

Reference	Country	Se concentration			Stage of lactation
		Minimum	Median	Maximum	
Alegria *et al.* (1996)	Spain	12·0	–	21·7	NG
Al-Saleh *et al.* (1997)	South Arabia	16·2	16·9	19·5	<3 months–<6 months
Anal *et al.* (1995)	Turkey	–	48·6	–	8 weeks
Benemaryia *et al.* (1995)	Burundi	5·2	9·2	16·9	2–4 d 10 months
Bratakos & Ioannu (1991)	Greece	17·0	23·0	41·0	1–3 d – 20–180 d
Bratter (1996)	Germany	–	59·0	–	NG
Bratter *et al.* (1987)	Germany	–	58·8	–	12–14 weeks
Clemente *et al.* (1982)	Italy	–	13·3	–	5 d–3 months
Cocho *et al.* (1992)	Spain	–	11·7	–	Mature milk
Dolamore *et al.* (1992)	New Zealand	–	13·4	–	Mature milk
Dylewski *et al.* (2001)	USA	19·0	27·0	105·0	1 d–12 months
Farrè *et al.* (1981)	Spain	–	11·4	–	3–10 d
Foster *et al.* (1996)	UK	–	20·6	–	Mature milk
Garg *et al.* (1993)	India	–	45·0	–	3–5 d
Grimanis *et al.* (1978)	Greece	15·0	16·0	48·0	0–3 d–30 d
Hadjimarkos (1963)	USA	–	21·0	–	67 d
Higashi *et al.* (1983)	Japan	17·0	18·0	80·0	Colostrum–5 months
Jochum *et al.* (1995)	Germany	–	9·9	–	4 months
Johnson *et al.* (1993)	USA	16·3	18·7	22·7	2–16 weeks
Kawamoto *et al.* (1994)	Japan	24·5	–	40·8	1 week–1 month
Kim *et al.* (1998)	South Korea	15·1	–	28·6	Colostrum–Mature milk
Krachler *et al.* (1998)	Austria	12·5	16·0	32·7	1–3 d – 42–60 d
Krachler *et al.* (2000)	Austria	–	17·0	–	Transitional milk
L'Abbe *et al.* (1996)	Canada	–	17·7	–	43–84 d
Levander (1982)	USA	7·0	–	33·0	NG
Li *et al.* (1990)	Japan	–	29·2	–	Transitional milk
Li *et al.* (1999)	Austria	7·0	13·5	23·9	1–7 d – 293 d
Litov *et al.* (1989)	USA	–	23·0	–	1–8 weeks
Lombeck *et al.* (1978)	Germany	28·3	30·5	84·0	0–3 d – 173 d
Micetic-Turk *et al.* (2000)	Slovenia	–	29·0	–	2–3 d
Michalke & Schramel (1998)	Germany	–	15·8	–	Pooled, 14–17 d
Millar & Sheppard (1972)	New Zealand	9·8	13·3	22·6	Colostrum–Mature milk
Oster *et al.* (1986)	Germany	–	17·8	–	10 d
Rivero-Martino *et al.* (2001)	Spain	–	14·1	–	NG
Robberecht *et al.* (1995)	Burundi	5·2	9·2	16·9	2–4 d – 10 months
Robberecht *et al.* (1985)	Belgium	9·7	12·7	15·3	0–3 d – 3 months
Rossipal *et al.* (2000)	Austria	–	32·7	–	2–3 d
Sachde & Bundt (1989)	Germany	–	46·0	–	NG
Shen *et al.* (1996)	Belgium	–	12·7	–	NG
Sorvacheva *et al.* (1996)	Russia	16·7	19·6	20·1	1–4 months
Tamari & Mohri (1991)	Japan	11·2	19·6	30·7	1–21 d
Tamari *et al.* (1995)	Japan	9·0	21·0	118·0	1–150 d
Tamari *et al.* (1996)	Korea	10·0	17·0	50·0	2–90 d
Tamari & Kim (1999)	Korea	9·6	24·0	38·7	0–90 d
Thorn *et al.* (1978)	UK	10·0	–	20·0	Mature
Tiran *et al.* (1993)	Austria	8·0	–	9	21–36 d
Torres *et al.* (1999)	Spain	5·3	10·7	11·4	<5 d – >2 months
Varo *et al.* (1980)	Finland	–	10·0	–	NG, pooled
Varo *et al.* (1988)	Finland	–	14·3	–	NG
Yanardag & Orak (1999)	Turkey	11·2	11·5	13·2	
Yoshinaga *et al.* (1991)	Japan	–	29·0	–	5–9 d
Zachara *et al.* (1994)	Poland	9·5	11·2	25·5	Colostrum – Mature milk

NG, not given.

differences in Se status between rural and urban residents of the USA were reported by Snook *et al.* (1983), no significant difference in milk Se was observed between rural (Amish community) and urban (Columbus, OH) US mothers (Snook *et al.* 1987), or in Finnish mothers before and after the programme of Se fertilization of soil (Kantola & Vartiainen, 1991). However, in their latest study, Kantola & Vartiainen (2001) reported a significant difference in breast-milk Se concentrations between rural (Kuopio) and urban (Helsinki) Finnish mothers.

It is worth noting that mothers eating natural foods grown in seleniferous areas of Venezuela (Bratter *et al.* 1991*b*) and China (KD, 1979; Yang *et al.* 1989*b*) show particularly high concentrations of breast-milk Se (Tables 3 and 7). Mothers with representative habitual dietary intakes of Se of 150, 800, and 3000 μg/d consumed by the population of certain areas of China showed breast-milk Se concentrations of 15·0, 31·0 and 120·5 μg/kg respectively (Yang *et al.* 1989*b*). The mammary gland secretes Se quite effectively. Even wider ranges of mean

breast-milk Se concentrations were found in Keshan disease areas and seleniferous areas of China (KD, 1979): 2·86 (low-Se region) and 283·00 (high-Se region) μg/l. A 20-fold increase in Se intake from 62·0 to 1283·5 μg/d found in the female population of these regions corresponded to a 90-fold increase in milk Se (3 to 283 μg/l).

Table 7 summarizes studies showing breast-milk concentrations and respective maternal Se intake. Besides the complexity of food Se composition and bioavailability, the methods used to estimate maternal Se intake varied among studies. Dodge *et al.* (1998) reported results from studies by others. Bratter *et al.* (1991*b*) used extrapolation of Se intake *v.* breast-milk Se reported in several countries and claimed a linear relationship, which was used to estimate maternal daily Se intake in their study (Bratter *et al.* 1991*a*). Dietary assessment was used to estimate maternal Se intake. Debski *et al.* (1989) used Se values of food in the USA, while Bianchi *et al.* (1999) estimated Se intake using food Se values of food grown in countries other than Brazil. Direct determination of Se in maternal diets by atomic absorption spectrophotometry has been used by only a few researchers. Bratter & Negretti de Bratter (1996) determined Se in Venezuelan diets, while Kumpulainen *et al.* (1983, 1984) analysed maternal diets in Finland. Before soil fertilization, the results of Kumpulainen *et al.* (1983, 1984) did not show substantial differences in maternal Se intake, but showed an increase in breast-milk Se concentrations attributed to consumption of wheat imported from the USA in 1980. Levander *et al.* (1987) also determined Se in diets of US mothers by fluorimetry.

Estimated maternal Se intakes from natural foods (Table 7) varies from 23·0 to 1238·5 μg/d, whereas breast-milk Se varies from 5·6 to 283·0 μg/l in the same reports. Studies summarized in Table 3 show that Se concentrations in plasma or serum are higher than in milk. Although the Se content of diets worldwide may vary 700-fold (Combs, 2001), the extremes of mean breast-milk Se are narrower (108-fold). Considering that a substantial part of breast-milk Se is present as functional selenoenzymes, the breast-fed infant is less susceptible to sub-optimal Se supplied in cows' milk formulas.

Selenium prophylaxis and breast-feeding

Combs (2001) compiled worldwide data on Se intake of adults from natural foods, showing that *per capita* intake can vary from 7 to 4990 μg/d. In the countries surveyed (twenty-six), there were eighteen population reports of adult groups with estimated intakes below current requirements (<55 μg/d). As a consequence, women of reproductive age in those countries may not support maximal expression of the Se enzymes. Rayman (2000) discussed current levels of Se requirement suggesting a high (73 μg Se/d) or even higher (80–100 μg Se/d) level of intake required for full expression of plasma GPX. The UK nutrient reference intake of 60 μg Se/d (Rayman, 2000) was determined as that required to optimize plasma GPX, whereas plasma or serum Se concentration required to optimize GPX was estimated at 95 μg Se/l. Therefore, there is clearly a need for Se prophylaxis to be carried out directly or indirectly.

Direct maternal Se prophylaxis with Se supplements, or indirectly with Se in the food chain, either through selenized fertilizers or Se enrichment of animal feed, are effective in raising total Se in breast milk. Indeed breast-milk Se increased after the programme of Se fertilization of soil in Finland (Table 8). Selenization of fertilizers results in organic Se in foods (Terry *et al.* 2000). However, the Se status of mothers seems to interact with the chemical form of supplement modulating breast-milk Se. Studies showed marked differences in total milk Se output in mothers from countries with low and adequate Se supply. Trafikowska *et al.* (1996) reported that Polish mothers taking 200 μg Se/d (as yeast Se) had 66 % more milk Se than unsupplemented mothers, while Dylewski & Picciano (1999) reported that only one-tenth of that amount (20 μg Se as sodium selenite/d) given to US mothers (from 3 to 6 months) raised the total milk Se by 37·5 %. Studies comparing sources of organic Se showed that supplementation with selenomethionine (200 μg Se/d) raised milk Se by 25 % after 1 month, but no significant increase was observed in the group of mothers taking yeast Se. Nevertheless, yeast Se prevented the early decline of breast-milk Se seen in unsupplemented mothers (McGuire *et al.* 1993*b*).

Comparing yeast Se and selenite, Trafikowska *et al.* (1998) observed that plasma Se:milk Se ratio increased from 5·9 before supplementation to 6·4 and 8·5 after supplementation with yeast Se and selenite respectively. They also found that after 3 months of maternal supplementation (200 μg Se/d), no significant differences were observed in milk Se due to yeast Se (16 μg/l) or selenite (14 μg/l) at 1 month after the start of treatment or subsequently. Both supplemented groups, however, showed significantly higher concentrations of milk Se than the non-supplemented group. However, GPX activity did not change significantly after yeast Se supplementation, but did after the first month of selenite supplementation (Trafikowska *et al.* 1998). Kumpulainen *et al.* (1985) also reported that yeast Se (100 μg Se/d) was more effective than selenite in raising milk Se. Moser-Veillon *et al.* (1992) suggested that the more metabolically active selenite was better retained in lactating women, compensating for losses of Se in milk.

A substantial proportion (15–30 %) of total milk Se occurs as GPX; therefore, differences in breast-milk responses to the organic and inorganic forms of Se supplements are expected. After 3 months of Se supplementation (50 μg/d selenomethionine), milk Se of New Zealand mothers increased significantly, but the increase in GPX activity was not significant (Dodge *et al.* 1999). Dodge *et al.* (1998) observed that in early lactation (1–7 d) of Chinese mothers, even in the presence of significantly low milk Se concentrations there was no difference in milk GPX activity between low and high intakes of habitual dietary Se. Similar observations were made by Moore *et al.* (2000) after supplementation with 100 μg Se (selenomethionine from yeast)/d of Chinese mothers with habitually low Se intake. In spite of an increase in maternal plasma Se and plasma GPX, as well as milk Se,

no significant difference was observed in the milk enzyme activity. When comparing organic (yeast Se) and inorganic (selenite) Se, Trafikowska *et al.* (1998) showed that GPX activity in milk of selenite-supplemented mothers increased 2-fold after 3 months, but no changes in the milk enzymatic activity were observed in yeast-Se group. This is consistent with an earlier study (Trafikowska *et al.* 1996) showing that in spite of a 37 % increase in maternal GPX there was no response in the enzyme activity of breast milk.

Selenium interactions and breast-feeding

Se is the most studied nutrient affecting the toxicity of Hg (Whanger, 1992). Besides being part of GPX, Se also reacts with metals to form selenides or protein complexes. Animal studies indicate that Se plays a role in inhibiting organic Hg bioaccumulation in the sucking rat. Interaction of Se with Hg in the lactating rat model showed that selenite supplementation to the dam resulted in an increased transport of inorganic Hg to milk (Sundberg *et al.* 1991; Nielsen & Andersen, 1995). Mean Hg in breast milk varies from 0·15 to 7·60 μg/l and occurs mainly because of maternal fish intake (Barbosa & Dorea, 1998). However, fish is also a good source of Se (Dorea *et al.* 1998). Fortunately for breast-fed infants, the concentration of Se in human milk is much higher than Hg (Donangelo & Dorea, 1998). The Se:Hg molar ratio of the mean metal concentrations in the breast milk of subjects from several countries are as follows: Germany 16 and 26 (Schramel *et al.* 1988*a*,*b* respectively), Sweden 10, Zaire 18, Hungary 24, Nigeria 28, Guatemala 31, Philippines 49 (Parr *et al.* 1991), India 33 (Garg *et al.* 1993), Faroe Islands 20 (Grandjean *et al.* 1995), Yugoslavia 15 to 22 (Kosta *et al.* 1983). Considering that at high Hg burden, the molar ratio of Se:Hg in tissues approaches 1 (Drasch *et al.* 2000), breast milk has a greater proportion of Se over Hg.

Se status (serum Se) of mothers on self-selected diets affects milk Se as well as the milk fatty-acid profile (Dotson *et al.* 1991). A significant correlation between milk linoleic acid and GPX activity, but not with total milk Se, was found by Debski *et al.* (1989). Dodge *et al.* (1999) reported that maternal Se supplementation (50 μg/d as selenomethionine) increased the polyunsaturated fatty acids (especially linoleic acid) and decreased saturated fatty acids in breast milk. Dodge *et al.* (1998), studying Se metabolism in seleniferous areas of China, reported that milk linoleic acid was also high in the women from Enshi (extremely high Se intake). A discrepant report of this trend was the study of Moore *et al.* (2000) in Chinese mothers from a low-Se area. They showed no significant difference in milk fatty acid profile after supplementation with 100 μg/d. In addition, after Se supplementation of soil in Finland, there was no significant correlation between milk Se and polyunsaturated fatty acids (Walivaara *et al.* 1986).

Although preterm infants fed Fe-supplemented formula (12 mg/l) showed no adverse effect on plasma Se (Rudolph *et al.* 1981), Lonnerdal & Hernell (1994) reported that plasma GPX activity was lowest in infants fed formulas with the highest Fe concentrations (7 mg/l). Nevertheless, after maternal Fe supplementation during pregnancy, cord-blood Se decreased, but did not influence the breast-milk Se concentration (Arnaud *et al.* 1993*a*).

Although taurine and Se in breast milk were found to occur in a similar pattern, the correlation between them was not significant (Kim *et al.* 1998). Nevertheless, there exists an association in the similarity of the pattern of changes in Zn (Dorea, 2000) and Se (Tamari *et al.* 1995) concentrations in breast milk throughout lactation. Al-Awadi & Srikumar (2000, 2001) showed a similar pattern of the two trace elements when comparing breast milk of Kuwaiti and non-Kuwaiti mothers. The concentration of both elements decreases as lactation proceeds, with a sharp decline after the colostrum phase. Because maternal dietary Se intake influences breast-milk Se, the pattern of decrease is sharper and more consistent in the case of Zn. Nevertheless, Bratter *et al.* (1997) reported that breast-milk Zn was modulated by both maternal Se status, with breast-milk Se concentrations showing an inverse relationship between the mean breast-milk concentrations of Se and Zn. Recently, Kantola & Vartiainen (2001) observed that after the selenization of fertilizers in Finland, the increase in breast-milk Se was accompanied by a decrease in breast-milk Zn concentrations between 1987 and 1995.

In spite of the role of Se in I metabolism, there are few studies exploring their nutritional interaction. Studies with rats showed that Se plays an important role in determining the severity of the hypothyroidism associated with I deficiency (Beckett *et al.* 1993). In lactating ewes challenged with goitrogens (glucosinolate and sodium nitrate), supplementation with both I and Se was more effective in raising I concentrations in milk (Kursa *et al.* 2000). Although there are no direct studies of Se and I interaction in breast-fed infants, Darlow *et al.* (1995) reported no change in thyroid hormone metabolism in formula-fed infants supplemented with sodium selenite. Older children, however, with low Se status, had increased thyroxine due to reduced type I iodothyronine-5′-deiodinase activity (Terwolbeck *et al.* 1993).

Se has an important role in sparing vitamin E metabolism (Levander, 1982). There is evidence of a Se and vitamin E interaction in defence against mastitis in cattle (Hemingway, 1999) and that Se supplementation improved the transfer of dietary α-tocopherol to cows' milk (Nicholson *et al.* 1991). Such studies are yet to be carried out in human subjects. Nevertheless, concentrations of vitamin E and total Se were higher in colostrum than in transitional breast-milk (Millar & Sheppard, 1972; Walivaara *et al.* 1986; Deschuytere *et al.* 1987), but were not significantly correlated (Walivaara *et al.* 1986). Moore *et al.* (2000) showed that Se supplementation affected plasma Se but did not affect plasma vitamin E in lactating women.

Studies in animals showed a gender-related effect of Zn on Se metabolism (Behne *et al.* 1992). In formula-fed preterm infants a gender-related effect on Se metabolism was reported by Friel *et al.* (1993). In Poland, a gender-linked hormonal response to concomitant Se and I deficiency in older children (7–16 years) with goitre was reported by Zagrodzki *et al.* (2000). In breast-fed infants, Yoshinaga

et al. (1991) showed a significant association between milk Se and gender, but Cumming *et al.* (1992*b*) reported no significant difference in breast-milk Se due to the infant's gender.

Excess selenium in breast milk

Symptoms of selenosis in man have occurred under occupational exposure to high Se levels, or after accidental ingestion of wrongly prepared supplements (Litov & Combs, 1991). There were also cases of selenosis among populations consuming foods naturally high in Se levels every day throughout each individual's lifetime (Yang *et al.* 1989*a*; Bratter *et al.* 1991*a*). Although high concentrations of milk Se can adversely affect pigs nursed by sows fed excess inorganic Se (>7 μg/kg diet) (Kim & Mahan, 2001), there are no reported cases of selenosis in the breast-fed infant. In spite of an inverse correlation between maternal serum Se and triiodothyronine (Bratter & Negretti de Bratter, 1996) in lactating mothers exposed to excess Se in natural foods (554 μg/d), there are no reports of adverse effects on breast-fed infants in seleniferous regions of Venezuela (Bratter *et al.* 1991*a*). In China, a much higher maternal daily intake of Se that raised breast-milk Se to 283 μg/l (KD, 1987) seems to be without adverse effects on the breast-fed infant. The organic Se in foods of seleniferous areas most likely appears as Se-containing amino acids in breast-milk proteins and is tolerated by the breast-fed infant.

In the rat model, selenite and selenate show similar potency (Palmer & Olson, 1974), but there are marked differences in neurotoxic effects between selenite and selenomethionine. Selenite showed a 43-fold higher toxicity than selenomethionine (Ammar & Couri, 1981). This is consistent with Kim & Mahan's (2001) observation that nursing pigs are capable of buffering against excess of milk Se (organic) by storing more Se in body tissues. Levander (1989) discussed upper limits of Se in infant formulas, which contain Se salts, suggesting that 75–160 μg Se/d might adversely affect infants.

Breast-feeding and the infant's selenium status

Milk Se bioavailability is related to the gastric digestibility of milk proteins. Shen *et al.* (1996), using *in vitro* methods based on simulated gastric digestion and Se dialysability, showed different indices of Se bioavailability: human milk (11·1 %) > cows' milk (6·8 %) > goats' milk (6·2 %) > sheep milk (<2 %). Studies in term and preterm infants showed that cows' milk-based formula resulted in a negative Se balance (Dorner *et al.* 1990). Coupled with this, regional variation in soil Se content can result in even lower concentrations of cows'-milk Se (Debski *et al.* 1992). Debski *et al.* (1992) showed differences of Se incorporation in cows'-milk protein from different regions of Poland. Besides lower bioavailability, compared with human milk, infant feeding with cows' milk will result in lower Se intakes due also to its lower Se concentration (Millar & Sheppard, 1972; Friel *et al.* 1997). While breast milk has only half of the protein content of cows milk, breast-milk protein contains twice as much Se as cows' milk (Millar & Sheppard, 1972).

The superiority of breast milk in maintaining higher Se status was shown in both term and preterm infants (Smith *et al.* 1982, 1991; Kumpulainen *et al.* 1987; Bratter *et al.* 1991*b*; Dolamore *et al.* 1992; Johnson *et al.* 1993; McGuire *et al.* 1993*a*; Jochum *et al.* 1995; Rossipal & Tiran, 1995; Daniels *et al.* 1997; Lonnerdal & Hernell, 1994; Friel *et al.* 1999; Sievers *et al.* 2001). Studies showing a higher Se status in breast-fed infants compared total Se intake, milk sources and supplemental Se forms. In some studies, total Se intake was higher in human milk than in cows' milk-based formulas (Smith *et al.* 1988), while in others it was the opposite. However, even under such circumstances, Se status was better in the breast-fed group. Kumpulainen *et al.* (1987) compared infants fed breast-milk Se (14 μg/l) with formula-fed Se (20 μg/l) as selenite. Infants fed a soyabean formula supplemented with selenite had plasma and erythrocyte Se values lower than breast-fed infants; however, plasma and erythocyte GPX were similar (Johnson *et al.* 1993). Friel *et al.* (1997) reported that breast-fed infants had higher erythrocyte GPX than infants fed an evaporated-milk formula (5 μg Se/d) or formula (13 μg Se/d). However, Litov *et al.* (1989) observed that infants with good Se status at birth showed no significant differences in Se status between breast- and formula-feeding with or without Se supplementation. A few studies, however, indicate a unique utilization of Se in relation to other trace elements. Comparing formula- and breast-feeding, Cu and Zn status (plasma metal concentrations) were not significantly different, but Se status was better in the breast-fed group (Hatano *et al.* 1985). Part of the beneficial effects of breast-milk Se may relate to its GPX activity (Rossipal & Tiran, 1995). In this regard, studies showed that freezing does not affect Se concentration, but decreases milk GPX activity (Milner *et al.* 1987).

It is worth noting that in the sucking-rat model, there was no difference in absorption of extrinsically labelled selenite from three milk diets (infant formula, cows'

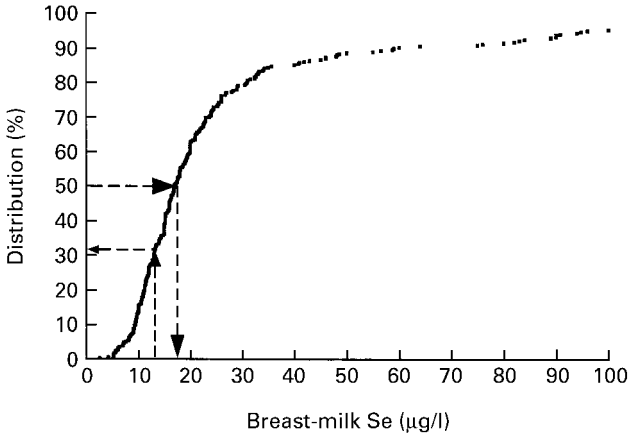

Fig. 1. Distribution of mean selenium concentrations in breast milk of non-supplemented mothers from studies worldwide (actual values in Tables 1–9). Arrows indicate percentage of studies reporting milk-Se concentrations that can meet benchmarks of 10 and 12 μg/d.

milk and breast milk), although absorption of selenomethionine was 2-fold higher than selenite (Raghib *et al.* 1986). Nevertheless, differences in milk composition of nutrients such as vitamin E, which is intimately associated with Se metabolism, may also contribute to better nutritional status of breast-fed infants. Millar & Sheppard (1972) showed that in the first month, breast-fed infants received more α-tocopherol (13-fold) and Se (2·5-fold) than formula-fed infants.

The distribution of mean breast milk Se concentration from studies around the world is shown in Fig. 1. Mothers eating natural foods without Se supplements showed a wide range of mean concentrations (2·6–283 μg/l) with a median of 17 μg/l. Considering a mean breast-milk intake of 750 ml/d, such a median level could provide 12 μg/d, but a substantial proportion (30 % below 13·3 μg/l) of median breast milk concentrations cannot meet the minimum of 10 μg/d proposed by Levander (1989). In populations consuming food produced in low-Se soil, the incidence of low breast-milk Se concentration can be high. Zachara & Pilecki (2000) surveyed all provinces of Poland (905 samples) and estimated that infant Se intake was only 64–85 % of minimum safe intake (10 μg/d). However, worldwide, the proportion of low Se intake of adult population is higher (Combs, 2001).

With regard to Se, studies of the nutritional status of infants nursed by mothers supplemented with organic and inorganic Se indicate that infant plasma Se is readily raised by organic Se. Organic (yeast Se) and inorganic (selenite) forms of Se when given to lactating mothers were shown to influence the Se status of breast-fed infants (Kumpulainen *et al.* 1985; Trafikowska *et al.* 1998). Yeast Se was more effective than selenite in raising breast-milk Se and infant Se status. The source of organic Se, however, does not seem to affect infant nutritional status. McGuire *et al.* (1993*a*) reported that plasma Se in infants nursed by mothers supplemented either with selenomethionine or yeast Se was similar with regard to total Se intake, and the GPX activity was unrelated to breast-milk Se. McGuire *et al.* (1993*a*) reported that plasma GPX activity was unrelated to total breast milk Se intake, but the decline in erythrocyte Se was prevented by both forms of maternal organic Se supplements (selenomethionine, yeast Se).

Conclusions

Maternal Se status reflects Se intake and modulates Se concentrations in human milk. Se bioavailability in natural foods (organic) or maternal supplements (organic and inorganic) has an important impact on breast-milk Se compounds. As a consequence, total Se in breast milk shows a wide variation, reflecting the content of natural foods grown in different soils. Se prophylaxis is effective in raising maternal Se status and increasing both breast-milk Se and milk GPX activity. The mammary gland secretes Se quite effectively as Se-containing amino acids in milk proteins and such a chemical form protects the infant from excessive maternal Se. Current estimates of Se intakes of adults place most diets as sub-optimal in meeting daily Se requirements. Although maternal Se status under most diets may not be sufficient to provide optimal serum Se concentrations and full expression of GPX activity, breast-fed infants consistently show higher Se status than formula-fed infants.

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