Scientific Advisory Committee on Nutrition

SACN POSITION STATEMENT ON SELENIUM AND HEALTH

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INTRODUCTION

1. The purpose of this statement is to provide an overview of the implications for health of current dietary intakes of selenium in the UK population. Members of the Scientific Advisory Committee on Nutrition (SACN) were asked to consider the statement and assess the need for a full risk assessment and its timing. As this is a position statement rather than a full risk assessment, it is not intended to be comprehensive but is a narrative review of the key issues and main studies. It also will not include public health recommendations.

2. This statement considers evidence on the association of various exposures to dietary selenium and the occurrence of cancers, cardiovascular disease, impaired immune, reproductive, thyroid and cognitive function published since 1996 and builds on the previous assessment by the Committee on Medical Aspects of Food and Nutrition Policy (COMA) in 1998 (Food Safety Information Bulletin 1998).

3. In 1998 COMA concluded that there was no evidence of adverse health consequences associated with selenium intakes in the UK at that time. However, COMA recommended that intakes and indicators of selenium status should be monitored to ascertain whether dietary selenium intakes of the population were adequate (Food Safety Information Bulletin 1998).

BACKGROUND

4. Selenium is an essential trace element. It is present in foods largely in the amino acids selenocysteine and selenomethionine in which selenium is analogous to the sulphur moiety of cysteine and methionine. Selenocysteine, for which a specific transcriptional codon exists is the biologically active form of selenium in selenoproteins, whereas selenomethionine is incorporated non-specifically into proteins in place of methionine, as the methionine-tRNA cannot distinguish between methionine and selenomethionine (Whanger *et al*., 2002). Selenomethionine is the predominant form in plants. The uptake of selenium by plants depends on the selenium content of soil, soil pH, redox potential and water content. In general, selenium is less readily taken up by plants growing in more acidic, impervious soils (Diplock 1993; Fordyce 2005).

5. In animals, including man, the body burden of selenium is homeostatically regulated. This operates principally through its excretion. At customary levels of exposure this is mediated by the hepatic formation of trimethylated selenium or selenosugars which are excreted in the urine. At increasingly high exposures excess selenium is converted to dimethylselenide which is exhaled in the breath (Rayman *et al*. 2008). It is now appreciated that faecal loss of selenium increases with high exposures to the element but the mechanism responsible is not clear.

6. Both inorganic [selenite (SeO_3^{2-}) and selenate (SeO_4^{2-})] and organic forms (selenium-enriched yeast and selenomethionine) of selenium are used in dietary supplements and food fortificants. Human supplementation trials to date have primarily used either sodium selenite, selenomethionine or selenium-enriched yeast (in which selenomethionine predominates as the selenium form). All forms of dietary selenium are easily absorbed; however, selenomethionine is regarded as more bioavailable than inorganic forms (Thomson 1998; Xia *et al*., 2005; Burk *et al*., 2006).

7. Selenium is essential for a wide range of biochemical functions within the body. These functions are mediated by 25 human selenoproteins, such as the glutathione peroxidases (GPx), which contain selenocysteine at their active site. They play a key role in a number of redox reactions involving antioxidant systems, thyroid hormone protection, immune function and sperm morphology (Rayman 2012; Terry and Diamond 2012).

8. The global prevalence of actual selenium deficiency or of those at a significant public health risk of deficiency is unknown, because the spectrum of biochemical and functional sequelae of inadequate selenium supply has not been fully characterised. Selenium deficiency manifest by a cardiomyopathy e.g. Keshan disease in China (Ge & Yang. 1993), is now uncommon, but there are concerns that selenium deficiency impairing the deiodinases involved in the function of thyroid hormones contributes to the risk of hypothyroidism in central African populations. These problems are associated with low selenium content or availability from the soils on which these populations subsist, but other factors may be involved in the pathogeneses: for example extremes of temperature and more particularly inter-current infections with Coxsackie RNA viruses are thought to precipitate Keshan disease. Where Keshan disease is prevalent, population whole blood median selenium levels were found to be around 21µg/l and mean intakes of selenium to be 19µg/24h (WHO/FAO/IAEA 1996), however similar values in markers of exposure have been noted without discernible adverse sequelae in other populations including at one time those on synthetic diets used in the management of Phenylketonuria (Lombek et al., 1984). Thus the thresholds at which clinical deficiency occurs are unclear, and although selenium responsive cardiomyopathy has been recorded in patients on parenteral nutrition the extent of severity and potential exacerbating factors have not been fully assessed (Rayman 2012).

9. In humans, excess intakes of selenium result in selenosis, where symptoms include vomiting, diarrhoea, hair and nail loss and lesions of the skin and nervous system. In certain areas of China with high soil selenium concentrations, cases of selenosis were observed at intakes ranging from 3.2-6.99mg/day (Yang *et al*., 1983). Toxic effects in people with a whole blood selenium concentration greater than 12.7µmol/L, which equates to an intake of over 850µg/day have also been reported (Yang & Zhou 1994).

Sources

10. Fish, Brazil nuts and offal are rich sources of selenium (Table 1). However, intakes of these foods, particularly offal, represent a small percentage of estimated selenium intakes in the UK due to dietary patterns (Table 2). The main sources of selenium in the UK diet are breads, cereals, fish and meat (Total Diet Study 2006; Food Standards Agency 2009). It should be noted that the entry of selenium into the terrestrial food chain depends on the selenium content of soil and soil geochemistry (Fordyce 2005) (see paragraph 4) and consequently there is a large, but as yet poorly characterised, variation in the selenium contents of food. This means that food composition tables and estimates of dietary intakes based on these may be of limited reliability for determining actual selenium intakes, especially if the analyses were not completed recently.

11. An example of the variability in the selenium content of food is the difference in selenium content of wheat grown in the UK compared to wheat grown in the US. The selenium content of wheat from cereal-growing areas throughout the UK was analysed in 1982, 1992 and 1998 with mean concentrations reported to be at 0.025, 0.033 and 0.025mg selenium/kg respectively (Adams *et al*., 2002) compared to 0.370 and 0.457mg selenium/kg in US wheat (Hahn *et al.,* 1981; Wolnik *et al.,* 1983). Wheat grown in the US is higher in selenium primarily because it has been grown on higher selenium soils.

Table 1. Selenium content of foods

Food	**Mean selenium (µg/per 100g)**
Brazil nuts, kernel only	85-690 [a]
Kidney, pigs, stewed	250 [a]
Tuna canned in sunflower oil	87 [b]
Liver, lamb, fried	62 [a]
Baked, cod, flesh only	44 [b]
Prawns, coldwater, cooked	30 [b]
Egg, whole, boiled, chicken	27 [c]
Salmon, farmed, grilled	19.5 [d]
Chicken, breast, grilled without skin	16 [a]
Beef, rump steak, grilled	10 [a]
Wholemeal bread*	7 [a]
White bread*	6 [a]
Corn flakes	5 [a]
Lamb, loin chops grilled	4 [a]
Muesli, Swiss style*	5 [e]

[a] Taken from The Composition of Foods, 6th edition, 2002. (FSA 2002);
[b] Taken from Fish Analytical Survey, DH, 2012 (unpublished);
[c] Taken from Eggs Analytical Project, DH 2012;
[d] Taken from Nutrient Analysis Catch Up Project, FSA, 2004
[e] Taken from Breakfast cereals analytical Survey, FSA, 2004
*based on UK wheat sources

Table 2. Estimated intake of selenium from different foods in the UK in 2006*

Food	Estimated contribution to total selenium intake µg/day (%)	Selenium content (µg/100g fresh weight)
Miscellaneous cereals	9 (16)	7
Meat products	8.5 (15)	14
Bread	6.4 (11)	6
Beverages	6.3 (11)	<0.5
Fish	5.9 (10)	42
Milk	3.4 (6)	1.4
Poultry	3.2 (6)	17
Carcass meat	2.8 (5)	14
Eggs	2.5 (4)	19
Dairy products	2.5 (4)	3
Sugars & preserves	1.7 (3)	<3
Other vegetables	1.6 (3)	1.8
Potatoes	1.1 (2)	<1
Nuts	0.9 (2)	30
Offal	0.8 (1)	77
Oils & fats	0.7 (1)	<3
Canned vegetables	0.5 (1)	1.4
Fresh fruit	0.4 (1)	<0.5
Fruit products	0.3 (<1)	<0.5
Green vegetables	0.2 (<1)	0.7
Total	39 (100)	-

*Table adapted Food Standards Agency Survey information sheet of the 2006 Total Diet Study (2009)

12. Selenium is also present in a number of food supplements at doses up to 200µg/day. Supplementation studies at this level have not demonstrated overt signs of toxicity (Expert Group on Vitamins and Minerals (EVM) 2003). Study participants have been supplemented daily with 200µg of selenium over a ten year period (mean treatment time 4.5 years) without the occurrence of adverse effects (Clark *et al*., 1996).

Dietary recommendations

13. In 1991 COMA set Dietary Reference Values (DRVs) for selenium (Table 3). These were set based on the functional role of selenium in GPx and limited evidence that whole blood GPx activity reaches a plateau at a whole blood selenium concentration of 100µg/l (Thomson et al., 1977). At the time the DRVs were set, mean selenium concentrations of whole blood in the UK were just above 100µg/l, therefore it was assumed, that UK intakes of selenium permitted functional saturation of whole blood GPx, and the Reference Nutrient Intake (RNI)[1] was established at a level to maintain this, at 1.0µg (13nmol) Se/kg body weight (Department of Health (DH) 1991). The values for children were derived from those set for adults, with an additional requirement for growth, and are therefore uncertain. The Lower Reference Nutrient Intake (LRNI)[2] for selenium is displayed in Table 4.

[1] The RNI represents the amount of a nutrient likely to meet the needs of 97.5% of the population.
[2] The LRNI represents the amount of a nutrient likely to meet the needs of 2.5% of the population

Table 3. Reference Nutrient Intakes for selenium (COMA 1991)

Age	Males µg/d (µmol/d)	Females µg/d (µmol/d)
0-3 months*	10 (0.13)	10 (0.13)
4-6 months*	13 (0.16)	13 (0.16)
7-9 months	10 (0.13)	10 (0.13)
10-12 months	10 (0.13)	10 (0.13)
1-3 years	15 (0.19)	15 (0.19)
4-6 years	20 (0.25)	20 (0.25)
7-10 years	30 (0.38)	30 (0.38)
11-14 years	45 (0.57)	45 (0.57)
15-18 years	70 (0.89)	60 (0.76)
19-50 years	75 (0.95)	60 (0.76)
50+ years	75 (0.95)	60 (0.76)
Pregnancy	-	No increment
Lactation	-	+15 (+0.19)

* The RNI for infants aged 0-6 months is for breast fed infants

Table 4. Lower Reference Nutrient Intakes for selenium (COMA 1991)

Age	Males µg/d (µmol/d)	Females µg/d (µmol/d)
0-3 months	4 (0.05)	4 (0.05)
4-6 months	5 (0.06)	5 (0.06)
7-9 months	5 (0.06)	5 (0.06)
10-12 months	6 (0.08)	6 (0.08)
1-3 years	7 (0.09)	7 (0.09)
4-6 years	10 (0.13)	10 (0.13)
7-10 years	16 (0.20)	16 (0.20)
11-14 years	25 (0.32)	25 (0.32)
15-18 years	40 (0.51)	40 (0.51)
19-50 years	40 (0.51)	40 (0.51)
50+ years	40 (0.51)	40 (0.51)
Pregnancy	-	-
Lactation	-	+ 15 (+0.19)

14. The lower limit of the World Health Organization (WHO) safe range of the population mean intake to meet selenium requirements is 40µg/day based on a body weight of 60kg (WHO 2004).

Selenium tolerable upper limit

15. High intakes of selenium can be toxic. The Expert Group on Vitamins and Minerals (EVM 2003) set a safe upper limit for selenium intake at 450µg/day. In North America an upper level of tolerable intake at 400µg/day was agreed (Institute of Medicine 2000).

Selenium intakes in the UK

16. Selenium intake is measured as part of the National Diet and Nutrition Survey (NDNS) rolling programme. Results of Year 1 and 2 of the rolling programme were published in July 2011. This is the first time selenium intake has been measured as part of the NDNS programme, providing UK intake data of individuals (Bates *et al*., 2011).

17. For the majority of age groups reported mean selenium intake was below the RNI, with only boys and girls aged 1.5-10 years consuming over the RNI on average (Table 5 & 6). For males and females aged 11 years and over mean selenium intakes were around 70-80% of the RNI (Table 6).

18. Around half of females aged 11-18 years and 19 years and over had selenium intakes below the LRNI (Table 7). The percentage of males with selenium intakes below the LRNI was lower than for females: 34%, 39% and 41% of males aged 11-18 years. Adults 19-64 years and 65 plus years respectively had selenium intakes from all sources below the LRNI (Table 7).

19. Prior to the selenium intake being measured as part of the NDNS rolling programme, selenium intake in the UK was estimated from the UK Total Diet Study (TDS) (Food Standards Agency 2009; Food Standards Agency 2004; Ministry of Agriculture 1999). The TDS assesses the likely dietary exposure by analysing 20 composite food samples representative of broad food categories (for example, 'oils and fats' and 'beverages'). Choice of sub-samples making up these composites are based on household purchase data[3], with all purchases made annually in 24 towns across the UK. The composite samples can then be chemically analysed for metals, trace elements or other components of interest. This information, combined with data on quantity of food groups purchased, taken from the Family Food Module of the Living Costs and Food Survey, provides an estimate of likely average intakes for each food group and for the diet as a whole. TDS estimates are based on food purchases by households rather than food consumed by individuals. It should also be noted that foods purchased for consumption out of the home are excluded.

[3] Household purchase data from the National Food Survey until 2000; and then its successors, the Expenditure and Food Survey (2001-2007) and the Living Costs and Food Survey (from 2008).

20. The data from the TDS indicate that dietary selenium intake of the UK population decreased between 1974 and 2000 but then appears to have increased in 2006 (Table 8). Selenium levels in foods are known to be very variable and for some foods, such as wheat it depends on the levels in soil (see paragraph 11). One explanation for the apparent decrease in intakes is the declining usage of North American wheat flour in the UK, and the corresponding increased use of European flours, which contain less selenium (Rayman 1997; Broadley *et al*., 2006). Biochemical data from Scotland also suggests that a decline in mean plasma selenium concentration from 118 to 71µg/L (1.5 to 0.9µmol/l) occurred in Scotland between 1985 and 1994 (Macpherson *et al*., 1997). The TDS data further show a sudden decrease between 1991 and 1994. This change should be interpreted with caution as there were no known sudden changes in food supply between 1991 and 1994 and the TDS methodology means that year on year changes may be due to differences in the choice of foods purchased. Changes in the analytical laboratory used between surveys and possible improvements in analytical methods over time may also contribute to the differences.

Table 5. Reported daily selenium intake in the UK (year 1 & 2 combined NDNS rolling programme 2008/09 and 2009/10)

		Average daily selenium intake (µg)*									
Age	**n**	**Food sources**					**All sources (including supplements)**				
		Mean	**Median**	**SD**	**Upper 2.5 percentile**	**Lower 2.5 percentile**	**Mean**	**Median**	**SD**	**Upper 2.5 percentile**	**Lower 2.5 percentile**
Males											
4-10 years	210	34	33	10	60	18	35	33	11	60	18
11-18 years	238	44	43	16	84	19	44	43	16	84	19
All boys	448	40	37	15	73	19	40	37	15	73	19
19-64 years	346	54	50	25	110	25	56	51	30	128	25
65 + years	96	51	47	22	101	17	59	48	49	290	17
Females											
4-10 years	213	32	31	10	57	15	32	31	10	57	15
11-18 years	215	35	34	13	65	13	36	35	13	65	14
All girls	428	34	33	12	62	15	34	33	12	62	15
19-64 years	461	43	39	18	89	18	46	40	24	101	18
65 + years	128	41	38	13	70	23	43	40	17	99	23
Total											
1.5-3 years	219	25	24	10	45	10	25	24	10	45	10
4-10 years	423	33	32	10	59	17	33	32	11	59	17
11-18 years	453	40	37	15	73	16	40	37	15	73	16
19-64 years	807	48	45	22	101	19	51	46	28	116	19
65+ years	224	45	43	18	90	21	50	44	35	110	22

*To convert units 1µmol = 79µg
Standard deviation (SD)

Table 6. Reported daily selenium intake as a percentage of the RNI in the UK (year 1 & 2 combined NDNS rolling programme 2008/09 and 2009/10)

		Daily selenium intake as a percentage of the RNI (%)					
Age	**n**	**Food sources**			**All sources (including supplements)**		
		Mean	**Median**	**SD**	**Mean**	**Median**	**SD**
Males							
4-10 years	210	136	129	39	137	131	40
11-18 years	238	80	74	33	80	74	33
All boys	448	105	99	46	105	99	46
19-64 years	346	72	67	33	75	68	40
65 + years	96	68	63	29	78	64	65
Females							
4-10 years	213	129	118	48	129	118	48
11-18 years	215	69	65	28	70	66	28
All girls	428	96	86	49	96	87	49
19-64 years	461	71	65	30	76	67	40
65 + years	128	68	63	22	72	67	29
Total							
1.5-3 years	219	163	157	66	164	159	66
4-10 years	423	133	126	44	133	126	44
11-18 years	453	74	69	31	75	69	31
19-64 years	807	72	66	31	76	68	40
65+ years	224	68	63	25	75	64	48

Table 7. Proportion with average reported intakes below the LRNI, between the LRNI and the RNI, and at or above the RNI in the UK (year 1 & 2 combined NDNS rolling programme 2008/09 and 2009/10)

Age	Selenium intake from food sources			Selenium intake from all sources (including supplements)		
	% Below LRNI	% Between LRNI and RNI	% at RNI and above	% Below LRNI	% Between LRNI and RNI	% at RNI and above
Males						
4-10 years	0	16	84	0	16	84
11-18 years	22	57	21	22	57	21
19-64 years	24	63	13	24	61	15
65 + years	30	58	13	30	52	18
Females						
4-10 years	2	27	72	2	27	72
11-18 years	48	41	12	47	40	12
19-64 years	53	34	13	49	33	18
65 + years	52	42	6	50	40	10
Total						
4-10 years	1	21	78	1	21	78
11-18 years	34	49	17	34	49	17
19-64 years	39	48	13	37	47	16
65+ years	42	49	9	41	46	13

Note: The DRV for selenium is based on data with a number of assumptions and caution should be exercised when assessing the adequacy of intakes using the LRNI.

Table 8. Estimated selenium intakes in the UK from the Total Diet Study

Year	Intake (µg/day)
1974	60 [a]
1985	63
1991	60
1994	43
1995	39 [b]
1997	39
2000	32-34 [c]
2006	48-58 [b,c]

[a] It should be noted that data collected before 1981 are not directly comparable to those in subsequent years because of reorganisation of the TDS in 1981 (Peattie *et al*., 1983)

[b] Exposure estimates for the 2006 and the 1995 TDS and are not directly comparable with those from other years as they are based on analyses of composite samples of each food from all the towns in the TDS rather than the upper bound mean concentrations of analyses of each food group from each town.

[c] In the 2000 and 2006, TDS the elemental exposures were estimated from upper and lower bound mean concentrations of food samples and expressed as a range. In all other years, only upper bound mean concentrations were reported. If the concentration in a sample is lower than the limit of detection for that element, the upper bound is taken as being equal to the limit of detection

Measurement of selenium status

21. Dietary assessment methods may be poor measures of selenium intake because the selenium content of the foods consumed and recorded is ascertained from compositional data, which may not adequately capture the varying levels of selenium in particular foods (see paragraph 10) (Longnecker *et al*., 1996). Due to the difficulty of assuring reliable estimates of the intake of selenium, various markers of intake or function are used in research studies and the population monitoring of deficiency and excess. These markers may be concentrations of selenium in tissues (erythrocytes, platelets or nails) or bodily fluids (whole blood, serum plasma or urine), concentration of selenoproteins or activity of selenoenzymes (Diplock 1993;Longnecker *et al*., 1996).

22. The interpretation of markers as indicators of selenium adequacy, deficiency or excess status is complex. A systematic review (Ashton *et al*., 2009) assessed the usefulness of such markers by examining controlled trials (not all randomised) that reported values at baseline and after supplementation or depletion. The authors concluded that further trials are required to investigate the observed heterogeneity of response and the applicability of markers for use in different population groups. Markers are influenced by factors other than the dietary intake. These can include body pools of selenium, intake of other nutrients, age, health, inflammation, infection and genotype (Rayman 2008 Hesketh 2008; Meplan *et al*., 2009). In general, selenium present in plasma, serum and urine reflects recent intakes, whereas red blood cell selenium represents intake over a longer period, due to the lifespan of erythrocytes being 120 days (Nève 1995). Therefore, changes in availability of a nutrient to tissues may not be reflected in the selected status markers in "real time". Additionally, the relationship between selenium intake and the selected markers may not be linear across the full range of intakes. Numerous mechanisms buffer the body against very high and low intakes of nutrients, typically resulting in a flattening of the response at either extreme of intake. This implies that different individual or combined markers might need to be used to assess the possibilities of deficiency, adequacy or excess.

23. Plasma selenium concentration is commonly used as an indicator of selenium exposure in epidemiologic and clinical studies (Åkesson *et al*., 1997). Following supplementation a marked increase in plasma selenium concentration is observed in subjects with low plasma selenium concentrations at baseline (Duffield *et al*., 1999; Xia *et al*., 2005). Even those who have a high plasma selenium concentration at baseline show an increase if supplemented with organic selenium (selenomethionine or selenium-yeast) (Burk *et al*., 2006; Hawkes *et al*., 2008). Due to the large geographic variation in plasma selenium concentration, no internationally or nationally standardised range for "normal" limits has been agreed (Thomson 2004a). Plasma selenium concentration has also been shown to decrease with infection or inflammation (Ghayour-Mobarhan *et al*., 2005) when there is a systemic inflammatory response, cytokines are produced that inhibit the expression of plasma selenoprotein P, a major contributer to plasma selenium (Renko *et al*. 2009).

24. Glutathione peroxidase (GPx), a selenoprotein which catalyses the removal of hydrogen peroxide and lipid hydroperoxides (Arthur 2000), is often used as a functional indicator of selenium status. It has a number of isoforms: GPx1 is found in the cytosol, GPx2 is largely associated with the gastrointestinal tract, GPx3 is an extracellular protein found in plasma and the thyroid follicular lumen and GPx4 is a membrane associated protein which uses phospholipid hydroperoxide as a substrate (Arthur 2000). GPx activity can be measured in plasma, whole blood, erythrocytes and platelets, however it reaches plateau (or saturation) at a blood selenium level of approximately 100µg/l (Thomson et al., 1977). In selenium-replete subjects, plasma GPx activity did not respond to supplementation (Burk *et al.,* 2006). While in subjects with a low estimated selenium intake (of 10µg/day), enzyme activity rose proportionally from 49.1µg/l and 36.7µg/l, in men and women respectively, with increasing doses until saturation was achieved with an additional intake of 37µg/day selenium (Xia *et al*., 2005). Consequently, GPx activity is only useful indicator in people with low selenium intakes at baseline. Plasma GPx activity will also fall with suboptimal function of the kidney, which synthesises GPx3 (Yoshimura *et al*., 1996).

25. Selenoprotein P (Sepp1), accounts for a large proportion of selenium present in plasma (Hill *et al*., 1996), however, as with plasma selenium there appears to be a large geographical variation in Sepp1 concentration (Marchaluk *et al*., 1995). Sepp1 is vital for selenium homeostasis and transport, notably to the brain, testis and proximal tubule cells of the kidney (Burk & Hill 2009). In selenium replete individuals, Sepp1 does not respond to supplementation (Burk *et al*., 2006), whereas in subjects of lower selenium status, supplementation leads to rapid increases in Sepp1concentrations (Duffield *et al*., 1999; Xia *et al*., 2005&2010). Heterogeneity however exists in the results. In subjects from New Zealand with baseline Sepp1 concentration of 0.6mg/l, maximal concentrations were achieved at doses of ~30µg/d selenium, whereas in Chinese subjects baseline Sepp1 concentrations of 1.5mg/l and 1.2mg/l for men and women respectively, concentrations continued to rise with increasing doses of selenium up to 75µg/d.

26. Nail, particularly toenail, samples have been used in epidemiological studies investigating the links between selenium exposure and chronic disease (van den Brandt *et al*., 1993, van den Brandt *et al*., 2003). The selenium content of toenails may reflect longer term intakes than plasma, over a period of 26-52 weeks (Longnecker *et al*., 1993), however is less sensitive. Selenium concentration in hair has also been related to long term selenium intake (Yang *et al.,* 1989); however, some shampoos contain selenium, which limits the value of hair samples (Hawkes *et al.,* 2008b).

27. Daily urine excretion has been found to be correlated with dietary intake over the short term (Swanson 1990; Åkesson *et al*., 1997; Yang *et al*., 1989; Longnecker *et al*; 1996; Burk *et al*., 2006; Hawkes *et al*., 2008). Yang *et al*., (1989) reported that, over a large range of intakes (<40-1700µg/day), the percentage of selenium excreted in urine fell within a fairly narrow range (40-45%). Burk *et al*., (2006) found no significant differences in the percentage of selenium excreted when different doses of selenium supplements (200-600µg/day) were given to US subjects. In order to accurately measure the amount of selenium excreted a 24 hour urine collection is required, but this is a more intensive sampling method than taking spot urines.

28. In considering the evidence base for the health effects of selenium and comparing values for selenium status between studies, it is important to identify the following factors: how the marker is being used (either to infer intake or functional status); the analytical method (as standard reference methods are not available); the assumptions being made and the validity of the range over which the marker is used.

Selenium status in the UK

29. The results of Year 1 and 2 of the NDNS rolling programme provide recent data on the selenium status of those aged 11 years and over (Table 9). Selenium status was assessed through plasma selenium concentration. These results show that selenium status was higher in females than males and in adults compared to adolescents. The small sample size to date of the rolling programme limits further exploration of this data – including geographical differences. When compared to previous data from children and adults (Annex 1), these results indicate very slight increases in the selenium status of the UK.

Table 9. Plasma selenium concentration (year 1 and 2 combined NDNS Rolling Programme 2008/09 and 2009/10).

	n	**Plasma Selenium concentration µmol/L (µg/L)**				
Males		Mean	Median	SD	Lower 2.5 percentile	Upper 2.5 percentile
Boys 11-18 years	84	0.90 (71.1)	0.89 (70.3)	0.161 (12.7)	0.60 (47.4)	1.29 (101.9)
Men 19-64 years	136	1.08 (85.3)	1.09 (86.1)	0.195 (15.4)	0.76 (60.0)	1.56 (123.2)
Females						
Girls 11-18 years	65	0.92 (72.7)	0.94 (74.3)	0.132 (10.4)	0.66 (52.1)	1.18 (93.2)
Women 19-64 years	201	1.03 (81.4)	1.03 (81.4)	0.171 (13.5)	0.75 (59.3)	1.41 (111.4)
Total						
All 11-18 years	149	0.91 (71.9)	0.90 (71.1)	0.148 (11.7)	0.66 (52.1)	1.29 (101.9)
All 19-64 years	337	1.06 (83.7)	1.06 (83.7)	0.180 (14.2)	0.76 (60.0)	1.48 (116.9)

* To convert units 1µmol/L = 79µg/L

Selenium intakes in other countries

30. Selenium intake varies widely around the world, mainly due to the differences in the selenium availability from the soil. Countries reported as having low selenium intakes include: UK with an average adult intake of 48µg/day from food sources (51µg/day from all sources, including supplements) (Bates *et al*., 2011); Denmark with average intakes from food sources 42.6 and 34.3µg/day for men and women respectively and Italy average intakes from food sources 47.6 and 38.8µg/day for men and women respectively (Flynn *et al.,* 2009); Germany; Poland and New Zealand (Combs 2001). Certain areas of China, where overt clinical signs of selenium deficiency e.g. Keshan disease are evident, have reported average intakes of less than 11µg/day (Yang & Zhou 1994).

31. In the 1997 New Zealand National Nutrition Survey, median intakes were estimated to be 56 and 39 µg/day for men and women, respectively (Russell *et al*., 1999). However, the 2003/04 New Zealand Total Diet Survey, indicated intakes of 67µg and 49µg/day for men and women, respectively. The observed increase in selenium intakes in New Zealand is likely to be multifactorial, due in part to the importation of Australian wheat and wheat products, predominantly to the North Island of New Zealand (Thomson 2004b).

32. Countries that are considered to have moderate to high selenium intakes include: Finland (after 1984 when selenium was added to fertilisers for cereal production) with an average intake of 60-80µg/day between 1994 and 2009 (Alfthan *et al*., 2011), the United States (US) with average intakes from food sources of 133.7µg/day and 93.6µg/day for men and women respectively (USDA 2012 - NHANES 2009-2010), Canada and Japan (Combs 2001). In certain areas of China intakes can reach very high levels and cases of selenium toxicity have been documented at intakes of 4990µg/day (Yang *et al*., 1989).

SELENIUM AND HEALTH OUTCOMES

33. Some laboratory experiments, clinical trials and epidemiological studies have suggested that there might be a preventative association between selenium and a number of conditions (Rayman 2012; Terry and Diamond 2012) including; cancers (Clark *et al*., 1996), thyroid hormone production (Schomburg & Köhrle 2008), thyroid disease (Toulis *et al*., 2010), cardiovascular disease (Blankenberg *et al*., 2003; Flores-Mateo *et al*., 2006), male infertility (Foresta *et al.,* 2002), female reproduction (Rayman *et al.,* 2003), cognitive decline (Berr *et al.,* 2000 and Akbaraly *et al.,* 2007), immunity and viral infection (Beck *et al.*, 2001, Broome *et al*., 2004).

34. This statement provides a review of the evidence of the association between selenium and cancers, cardiovascular disease, immune function, reproduction, thyroid function and cognitive function. Studies considered in this report were published from 1998 to July 2011, subsequent to the COMA statement in 1998 (Food and Safety Information Bulletin 1998), although some later reviews have been included (Tables 10-36).

35. A PubMed search was conducted from 1998 to July 2011 for any relevant evidence, The statement focuses on randomised controlled trials, cohort studies, case-control studies and meta-analysis. Cross-sectional studies have been excluded. Only studies that have reported adjusted measures of relative risk have been included. Definitions of study types are listed in Annex 2.

36. Typically SACN gives more weight to good quality randomised controlled trials and less weight to observational studies (SACN Framework for the evaluation of evidence). Observational studies, including cohort and case-control studies are potentially subject to bias, reverse causality and confounding by other lifestyle factors. Observational studies can also only show associations rather than cause-effect relationships between exposure and outcomes. Randomised controlled trials can provide evidence for causal relationships but can also be subject to limitations including; sample size, duration and compliance.

37. A number of variants within the genes encoding selenoproteins and components of the selenoprotein synthetic machinery have been identified (Hesketh, 2008). These variants have been associated with the risk of cancer and other health conditions (Sutherland *et al*., 2010;Meplan *et al*., 2009; Rayman 2012). However, a review of the genetics of selenium metabolism is beyond the scope of this statement.

SELENIUM AND CANCER

38. A number of cohort and case-control studies suggest that higher selenium concentrations in plasma/toenail samples are associated with a decrease in cancer incidence. The proposed mechanism for this phenomenon is the role of selenium in selenoproteins with antioxidant and other properties (World Cancer Research Fund (WCRF) 2007). This statement focuses on prostate, lung, breast and colorectal cancer as these cancers have been the most studied (Tables 10-23).

39. In 1998 COMA concluded that there was insufficient evidence to demonstrate a causal or protective link between dietary selenium intake and cancer (DH 1998; Food Safety Information Bulletin 1998).

40. The WCRF report included systematic literature reviews which investigate selenium intake, both from dietary and supplementary sources, and selenium status markers and the risk of developing site specific cancers (WCRF/ American Institute for Cancer Research (AICR) 2007). The 2007 report considered evidence up until the end of 2006. The WCRF published their Continuous Update Project on breast cancer in (Norat *et al*., 2008) and colorectal cancer in 2011 (WCRF 2011), this evidence has been included in this statement.

Prostate cancer

41. Seven studies investigating the relationship between prostate cancer and selenium intake and 16 studies assessing selenium status from concentrations in nails, plasma and serum are detailed in Tables 10, 11 and 12.

42. A US randomised controlled trial, the National Prevention of Cancer (NPC) study, n=1312 (Clark *et al*., 1996, Clark *et al*., 1998), with skin cancer as the primary outcome, demonstrated that selenium supplementation (dose 200µg/day) significantly lowered the risk of prostate cancer. A follow- up study (Duffield-Lillico *et al*., 2002;Duffield-Lillico *et al*., 2003), which extended the blinded treatment period to 1996, found that the risk of developing prostate cancer remained significantly lower among those receiving selenium supplements (RR 0.48; 95% CI 0.28-0.80; p=0.005), with the effect being strongest in men in the bottom third of selenium status at baseline (i.e. plasma selenium <106 µg/L).

43. The selenium and vitamin E cancer prevention trial (SELECT) also based in the US aimed to investigate whether the findings of Clark *et al*., (1996) could be replicated, but using prostate cancer as the primary endpoint (the risks of lung cancer, colon cancer and all cancers were included as secondary endpoints). The SELECT trial randomised 35,533 men into four groups who either received selenium alone (200µg/day), vitamin E alone (400 IU/day), selenium and vitamin E or a placebo. The SELECT trial was intended to have a maximum duration of 12 years, however, this trial was stopped after seven years following an independent review of the data by the data and safety monitoring committee (Hoque *et al*., 2001;Lippman *et al*., 2005; Lippman *et al*., 2009). The committee agreed that based on the evidence from the seven year interim analyses, there was no benefit from either study agent and no possibility of a benefit with additional follow up. Analysis on a median of five and a half years of follow up, based on 1758 cases, demonstrated that there was no evidence that the supplements taken alone or in combination prevented prostate cancer or any other secondary outcome.

44. The subjects in the SELECT trial were followed without the intervention supplements for a further three years to study the long-term effects of the supplementation and results were published in October 2011, after the cut-off for this statement (Klein *et al*., 2011). The authors reported that the rate of prostate cancer detection was greater in all treatment groups compared to placebo but was not significant in any of the selenium intervention groups.

45. The SELECT trial and the NPC study varied both in the form of selenium supplemented and the baseline selenium status of the participants, which may have influenced the results. The NCP study supplemented with high selenium yeast (where selenomethionine predominated as the selenium form) and the SELECT trial used an equivalent dose of *l*-selenomethionine, based on the rationale that variation in yeast formulation between batches exists. The subjects in SELECT had a higher baseline plasma selenium than the subjects in the NPC trial i.e. mean plasma selenium 114µg/L in NPC vs. median plasma selenium 135µg/L in SELECT.

46. The results of a multi-centre randomised controlled trial investigating prostate cancer progression were published in 2010 (Stratton *et al*., 2010). In this trial 140 subjects with prostate cancer, from nine sites within the US, were randomised to either a placebo, 200µg/day selenium or 800µg/day selenium for five years. Mean plasma selenium at baseline was 134.5µg/l. Overall, selenium supplements did not protect against prostate cancer progression (defined by an elevated prostate specific antigen (PSA) but with negative biopsy). The authors also reported a statistically significantly higher PSA velocity (p=0.018), (rate of change of the PSA level) for men in the highest quarter of baseline plasma selenium concentration taking 800µg/day selenium compared to the placebo and therefore concluded that high levels of selenium supplementation could have detrimental effects on PSA velocity in men with modestly high levels of plasma selenium.

47. Hartman *et al*., (1998) analysed dietary data recorded from subjects within a randomised controlled trial that supplemented subjects with α-tocopherol or β-carotene, and found that there was no association between selenium intake (lowest quarter <71.5µg/day vs. highest quarter >111.1µg/day) and prostate cancer risk. It should be noted that this study was conducted in Finland shortly after the introduction of soil fertilisers fortified with selenium. Baseline serum selenium was not reported. Peters *et al*., (2008) also reported no significant association between dietary selenium intake and the risk of prostate cancer in a US cohort study. A UK cohort of men with localised prostatic adenocarcinoma reported no association between baseline selenium levels and progression of the disease (Venkitaraman *et al*., 2010). In comparison, one US cohort study (Lawson *et al*., 2007) demonstrated an increased risk for total and localised, but not advanced, prostate cancer with increasing selenium supplement intake. This effect appeared to be dominated by men who took supplements more than seven times per week, as no significant association was observed for subjects who reported lower levels of supplement use.

48. Three nested case-control studies (Brooks *et al*., 2001;Nomura *et al*., 2000;Yoshizawa *et al*., 1998) and one case cohort study (see Annex 2 for definition) (van den Brandt *et al*., 2003) reported that subjects with higher baseline selenium status markers had a significantly reduced risk of prostate cancer. Yoshizawa *et al.,* (1998) found that this relationship remained significant even after adjusting for geographic region by soil selenium content. Nomura *et al.,* (2000), reported that when the analyses were stratified by smoking status the relationship only remained significant for smokers. One nested case-control study (Helzlsouer *et al*., 2000) found that those with the highest toenail selenium concentrations were significantly less likely to have prostate cancer than those with the lowest concentrations. Three nested case-control studies (Goodman *et al*., 2001;Peters *et al*., 2007;Allen *et al*.,2008) found no association of selenium status markers with prostate cancer. Gill *et al*., (2009) reported no overall association between selenium and prostate cancer, although an inverse association was observed in African American men and Li *et al*., (2004) found a significant protective association for advanced prostate cancer only.

49. Two case-control studies reported a significantly reduced risk of prostate cancer in subjects with higher serum selenium concentrations (Pourmand *et al*., 2008; Steinbrecher *et al*., 2010). Three other case-control studies (Allen *et al*., 2004;Ghadirian *et al*., 2000;Lipsky *et al*., 2004) found no association between nail selenium concentration and prostate cancer and another (Lee *et al*., 1998) reported no significant association between selenium intake and the risk of prostate cancer.

50. A meta-analysis reporting associations between selenium status and prostate cancer risk (Brinkman *et al*., 2006) included one cohort, one case-cohort, nine case-control and nine nested case control studies. Meta-analysis of the 11 serum studies resulted in a statistically significant difference between selenium levels in cases and controls, with smaller non-significant associations for toenail and plasma studies, suggesting that men with lower selenium status are at increased risk of prostate cancer.

51. The WCRF considered the available evidence up to 2006 for both selenium intake (one randomised controlled trial, three cohort studies, seven case control studies and two ecological studies) and status (15 cohort studies, seven case control studies, one ecological study). Studies investigating intake included both dietary and supplemental sources of selenium, and status referred to research looking at selenium concentration in plasma/serum or nails. The WCRF concluded that foods containing selenium probably protect against prostate cancer (WCRF/AICR 2007), however, there remains uncertainty about whether this relationship is causal due to the inconclusive nature of the evidence

52. A more recent meta-analysis (Hurst *et al*., 2012) included studies published up to November 2010, using the search strategy and protocol described by WCRF. Twelve studies were included in a dose response meta-analysis and indicated that the association between higher selenium status and reduced prostate cancer risk may be over a relatively narrow range (plasma selenium 120-170µg/l and toenail selenium 0.85-1.0µg/g).

Ongoing studies

53. Marshall *et al.,* (2006) reported on the progress of a US double blind randomised controlled trial investigating selenium supplementation (200µg/d L-selenomethionine) on the risk of developing prostate cancer in men with high grade prostatic intraepithelial neoplasia (HGPIN). HGPIN is considered as a pre-malignant lesion for prostate cancer and subjects with this condition are at higher risk of developing the disease. Results of the study were published in November 2011, after the cut-off date of this statement, and indicated no significant effects of selenium (Marshall *et al*., 2011)

Summary

54. Since COMA reported in 1998, the moderate amount of new evidence on selenium intake and status in relation to reducing the risk of prostate cancer has shown inconsistent results. Randomised trials with prostate cancer as the primary outcome have not supported the protective association observed by the NPC study, prospective studies have not demonstrated a clear relationship between selenium and the risk of prostate cancer and results from case-control studies are also conflicting. Reasons for this may lie in differences in the health of participants, heterogeneous design of supplement trials or the range of baseline selenium levels studied. The applicability of studies to the UK population is also important; the published randomised controlled trials for example, were all conducted in the US where participants had higher mean baseline plasma selenium levels than those currently seen in adult men in the UK.

55. There is a moderate amount of evidence available but overall, at the levels of selenium intake and status studied, the data do not suggest a protective association between selenium and the risk of prostate cancer.

Table 10. Studies of estimated selenium intake and prostate cancer[a]

Study Reference	Country	Population (no. & characteristics)	Age (yrs)	Selenium intake-mean (SD)	Mean follow up (yrs)	Adjusted relative risk (95% CI)	Comments
Clark *et al.,* 1996 &1998 Nutritional Prevention of Cancer Trial (NPC)	US	1312 subjects with history of basal cell or squamous cell carcinoma of the skin 48 prostate cancer cases	18-80	Mean (SD) plasma selenium at baseline, 114 (23) µg/l. Intervention: 200µg/day of selenium vs. placebo	4.5 treatment, 6.4 follow up.	RR: 0.37 (0.18-0.71) p=0.002 HR: 0.35 (0.18-0.65) p= 0.001	Significant inverse effect with selenium supplementation.
Lippman *et al*., 2009 Selenium and vitamin E cancer prevention trial (SELECT)	US	35,533 men with no prior prostate cancer 1758 prostate cancer cases	50 plus	Baseline median plasma selenium in intervention and placebo groups, 135µg/l Interventions: 200µg/day selenium vs. 400IU/d vitamin E vs. both vs. placebo.	5.46 (median follow up) 4.17-7.33 (range)	Selenium & vitamin E group HR: 1.05 99% CI (0.88-1.25) p=0.52 Selenium only HR: 1.04 99% CI (0.87-1.24) p=0.62	No significant effect .
Stratton *et al.,* 2010	US	140 men with localised prostate cancer	Mean age 72.8	Baseline plasma selenium of study population 134.5 (41.5) µg/l. Interventions: 200µg/day of selenium vs. 800µg/day of selenium vs. placebo	5	Difference in PSA velocity 200µg/day vs. placebo p=0.328 800µg/day vs. placebo p= 0.613	No significant difference in prostate cancer progression between groups

[a] Please note that only studies published after 1996 are included in this statement
HR – hazard ratio, RR - relative risk

Table 10 continued

Study Reference	Country	Population (no. & characteristics)	Age (yrs)	Selenium intake- mean (SD)	Mean follow up (yrs)	Range	Adjusted relative risk (95% CI)	Comments
Cohort								
Hartman *et al*., 1998	Finland	29,133 subjects 127 cases from alpha-tocopherol supplement group 190 cases from non supplemented group	50-69	FFQ selenium including supplements (µg/day) Total mean intake: Prostate cancer cases 93.9 (40.2) No prostate cancer 95.9 (36.5)	9	Top fourth vs. bottom fourth	0.84 (0.43-1.67) p= 0.64 1.27 (0.70-2.20) p=0.49	No significant association.
Lawson *et al*., 2007 National Institutes of Health (NIH) – AARP Diet and Health Study	US	295,344 subjects 10241 prostate cancer cases 8765 Localised Prostate cancer cases 1476 Advanced prostate cancer cases	50-71	Selenium supplement intake: no. of times/week 130 cases >7 times/ week 109 cases >7 times/ week 21 cases >7 times/ week	6	>7 times/ week vs. never	1.39 (1.09-1.77) p trend=0.003 1.37 (1.05-1.78) p trend=0.004 1.53 (0.82-2.85) p trend=0.36	A significant positive association with increasing supplement intake. A significant positive association with increasing supplement intake. No significant association.
Peters *et al*., 2008 VITAL study	US	22,089 subjects	50-76	Supplement intake: 26.6µg Dietary selenium intake: 138.9µg	10	10 years >50µg/day vs. Never	HR: 0.90 (0.62-1.3) p trend=0.97	No significant association.

Case control								
Lee *et al*., 1998	China	265 controls 133 prostate cancer cases	40-≥70	FFQ (µg/day) Mean intake cases- 65.4 (2.6) Controls- 58.0 (1.5)	N/A	Cases vs. controls	1.0 (0.99-1.04) p= 0.75	No significant association.

[a] Please note that only studies published after 1996 are included in this statement

FFQ-food frequency questionnaire; NA- not applicable. HR – hazard ratio, RR - relative risk

Table 11. Cohort and nested case-control studies of selenium status and prostate cancer[a]

Study Reference	Country	Age (yrs)	Population (no. & characteristics)	Sample	Mean concentration (SD/range)	Mean follow up (yrs)	Range	Adjusted relative risk (95% CI)	Comments
Cohort									
van den Brandt *et al*., 2003 The Netherlands Cohort Study	The Netherlands	55-69	522 cases with prostate cancer 1211 subcohort	Toenail (µg/g)	Cases: 0.53 (0.09) Subcohort: 0.55 (0.13)	6.3	Top fifth vs. bottom fifth	0.70 (0.48-1.01) p trend=0.012	Significant inverse association.
Venkitaraman *et al*., 2010	UK	48-77	104 cases with localised prostatic adenocarcinoma	Serum (µmol/l)	1.19	2.5	NR	HR: 0.99 (0.985-1.011) p trend=0.76	No significant association between baseline selenium levels and time to disease progression.
Nested case control									
Allen *et al*., 2008 EPIC	Europe – Denmark, Germany, Greece, Italy, Netherlands, Spain, Sweden & UK	43-76	959 cases 1059 controls	Plasma (µg/l)	Cases: 70.6 Controls: 71.9	4.3	Top fifth vs. bottom fifth	0.96 (0.70-1.31) p trend= 0.25	No significant association.
Brooks *et al*., 2001	US	45-74	52 cases 96 controls	Plasma (µg/l)	Cases: 122 (19) Controls: 117 (17)	N/A	Top fourth vs. bottom fourth	0.24 (0.07-0.77)	Significant inverse association when comparing the three highest quarters to lowest quarter. No p trend given.

Gill *et al*., 2009 Multiethnic cohort	US	42-75	467 cases 936 controls	Serum (µg/g)	Cases: 0.13 Control: 0.14	NR	Top fourth vs. bottom fourth	0.82 (0.59-1.14) p trend= 0.25	No significant association. When the analysis was repeated by ethnic groups there was a statistically significant inverse association in the African-American men. Third quarter vs. first quarter (95% CI 0.38-0.93).
Goodman *et al*., 2001 Carotene & Retinol Efficacy Trial (CARET)	US	45-74	235 cases with prostate cancer 456 controls	Plasma (µg/l)	Cases: 114.8 (19.6) Control: 114.3 (20.4)	4.7	Top fourth vs. bottom fourth	1.02 (0.65-1.60) p trend= 0.69	No significant association.
Helzlsouer *et al*., 2000	US	Mean 66.4	117 cases with prostate cancer 233 controls	Toenail (µg/g)	Median Cases: 0.77 (0.07-2.27) Controls: 0.79 (0.48-1.98)	6	Top fifth vs. bottom fifth	0.38 (0.17-0.85) p trend= 0.12	No significant trend, but a significant association was observed when comparing the highest fifth with lowest fifth.

Study Reference	Country	Age (yrs)	Population (no. & characteristics)	Sample	Mean concentration (SD/range)	Mean follow up (yrs)	Range	Adjusted relative risk (95% CI)	Comments
Li *et al*., 2004 Physicians' Health Study	US	40-84	586 cases with prostate cancer 577 control subjects	Plasma (µg/l)	Cases: 106 (18) Controls: 108 (18)	13	Top fifth vs. bottom fifth	0.78 (0.54-1.13) p trend= 0.16	All prostate cancer - No significant association
			384 cases with localised prostate cancer					0.97 (0.64-1.49) p trend= 0.91	Localized cases - No significant association
			171 cases with advanced prostate cancer					0.52 (0.28-0.98) p trend= <0.05	Advanced cases - Significant inverse association.
Nomura *et al*., 2000	Hawaii	45-85	249 cases with prostate cancer 249 controls	Serum (µg/l)	Cases: 129.9 (72.8-205.0) Controls: 134.1 (77.1-227.7)	>20	Top fourth vs. bottom fourth	0.50 (0.3-0.9) p trend=0.02	Significant inverse association

Peters *et al*., 2007 Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial	US	55-74	724 incident total cases 879 controls	Serum (µg/l)	Controls: 141.3 (26.0)	8	Top fourth vs. bottom fourth	0.84 (0.62-1.14) p trend= 0.70	No significant association.
Steinbrecher *et al*., 2010 EPIC-Heidelberg cohort	Germany	Mean 58.1	248 cases with prostate cancer 493 controls	Serum (µg/l)	Cases: 86.2 Controls: 87.7	NR	Top fourth vs. bottom fourth Third fourth vs. first fourth	0.78 (0.49-1.22) 0.61 (0.38-0.98) p=0.04	No significant association. Significant inverse association in the third fourth compared to the first fourth.
Yoshizawa *et al*., 1998 Health Professionals Follow Up Study	US	40-75	181 cases with prostate cancer 181 controls	Toenail (µg/g)	Cases: 0.82 Controls: 0.96 (0.53-7.09)	7	Top fifth vs. bottom fifth	0.35 (0.16-0.78) p trend=0.03	Significant inverse association

[a] Please note that only studies published after 1996 are included in this statement
HR – hazard ratio, NR – not reported
N/A- Not applicable

Table 12. Case control studies of selenium and prostate cancer[a]

Study Reference	Country	Age (yrs)	No. of cases	No. of controls	Sample	Selenium status measure & mean concentration (SD/range)	Range	Adjusted relative risk (95% CI)	Comments
Allen *et al*., 2004	UK	44-77	300 prostate cancer 211 Localised prostate cancer 89 Advanced prostate cancer	300 211 89	Fingernail (µg/g)	Cases: 0.62 Controls: 0.61	Top fourth vs. bottom fourth	1.24 (0.73-2.10) p trend= 0.58 1.45 (0.78-2.70) p trend= 0.31 0.78 (0.27-2.25) p trend=0.48	No significant association. No significant association. No significant association.
Ghadirian *et al*., 2000	Canada	35- 84	232 Prostate cancer	688	Toenail (µg/g)	Cases: 0.91 (0.15) Controls: 0.89 (0.14)	Top fourth vs. bottom fourth (-0.79 vs. +1.00)	1.14 (0.46-2.83) p trend=0.624	No significant association.
Lipsky *et al*., 2004	Austria	48-95	70 Prostate cancer	80 controls with non-malignant urologic disease	Toenail (µg/g)	Median Cases: 0.53 (0.39-4.27) Controls: 0.50 (0.20-0.83)	Cases vs. Controls	0.74 (0.22-2.71) p= 0.58	No significant association.
Pourmand *et al*., 2008	Iran	47-90	62 Prostate cancer	68	Serum (µg/l)	Cases: 66.3 (25.5-112) Controls: 77.5 (25-123.2)	Top third vs. bottom third	0.16 (0.06-0.47) p= 0.001	Significant inverse association.

[a] Please note that only studies published after 1996 are included in this statement

Lung cancer

56. Three studies investigating the relationship between lung cancer and selenium intake and six studies assessing selenium status are detailed in Tables 13, 14 and 15.

57. The Nutritional Prevention of Cancer (NPC) trial, n=1312 (Clark *et al*., 1996), with skin cancer as the primary outcome, found that 200µg/day selenium supplementation decreased the risk of developing lung cancer but this was of borderline statistical significance when the results were analysed up to 1993. When the treatment period was extended by a further three years, the association between selenium intake and lung cancer was no longer significant (RR 0.74; 95% CI 0.44-1.24, p=0.26) (Duffield-Lillico *et al*., 2002). Lung cancer was measured as a secondary outcome in the SELECT trial and selenium supplementation had no effect on the incidence of lung cancer (Lippman *et al*., 2009).

58. One nested case-control study (Knekt *et al*., 1998) in Finland demonstrated that low serum selenium concentrations at baseline (highest tertile >60.6µg/l vs. lowest tertile <45.5µg/l) were associated with an increased risk of lung cancer at 10 years follow up (RR 0.41; 95% CI 0.17-0.94 p trend = 0.046). It should be noted however, that in this study, baseline measurements were taken prior to the introduction of selenium supplementation of fertilisers in Finland. A Finnish case-control study, nested within the Alpha-Tocopherol Beta Carotene Cancer Prevention Study, investigated the association of selenium status with the risk of developing lung cancer in male smokers (Hartman *et al*., 2002). Mineral fortification of fertilisers had been introduced a few months prior to commencement of this study, therefore the analysis was performed by year of entry in order to capture any effects of the population's increasing selenium intake. The authors reported that those who entered the study early and had the highest toenail selenium concentrations were significantly less likely to be diagnosed with lung cancer, whereas, for subjects who were entered in the fifth year of the study no associations were observed between toenail selenium concentrations and lung cancer incidence. Two other nested case-control studies Goodman *et al*., (2001) conducted in the US and Ratnasinghe *et al*., (2000) conducted in China found no association between selenium status and lung cancer.

59. A case-control study in Polish smokers (Jablonska *et al*., 2008) observed lower plasma selenium concentrations in cases of lung cancer than in controls. However, the authors reported significantly increased risk of lung cancer in those with plasma selenium <49µg/l compared to those between 50–89µg/l. They also suggest that genetic variations in the population may alter the risk susceptibility to lung cancer in those of low selenium status. One case-control study (Gromadzinska *et al*., 2003) demonstrated a significant decreased risk of lung cancer among subjects with plasma selenium levels above 63.2 µg/l. One case-control study Mahabir *et al*., (2007) reported that selenium intake was inversely associated with the incidence of lung cancer in men only.

60. Zhuo *et al.,* (2004) conducted a meta-analysis of cohort and case-control studies investigating selenium intake and/or status measured using toenail or serum samples. Sixteen studies were included, 13 presented measures of relative risk (RR) and the remaining three provided means only. The summary relative risk was 0.74 (95% CI 0.57-0.97), indicating that those with higher selenium exposures (status and intake) were less likely to develop lung cancer. When stratified by method of analysis, only higher levels of toenail selenium were inversely associated with lung cancer (0.46; 95% CI 0.24-0.87; p=0.03), but there was no significant association observed for serum selenium or selenium intake (0.80; 95% CI 0.58-1.10, 1.00; 95% CI 0.77-1.30, respectively). The protective association between selenium exposure and reduced risk of lung cancer appeared to be greater in populations where average selenium levels were lower (Zhuo *et al*., 2004).

61. The WCRF report concluded that there is limited evidence to suggest a link between selenium exposure (intake and status) and lung cancer. Their report considered two case-control studies and two ecological studies investigating selenium intake, and 13 cohort studies, seven case-control studies and four ecological studies measuring selenium concentrations in plasma/serum or nails. Due to the paucity of data, the WCRF considered there to be insufficient evidence to infer a causal relationship (WCRF 2007).

Summary

62. Since COMA reported in 1998, there has been a moderate amount of new evidence from nested case-control and case-control studies to suggest a protective association between higher selenium intake or status and lower risk lung cancer. However, this is not supported by the trial data, as the effect initially identified from the NPC study was not statistically significant at the end of the treatment period and was not supported by the results of the SELECT trial.

63. Overall, the available evidence, at the levels of selenium intake and status studied, does not suggest a protective association between selenium and the risk of lung cancer.

Table 13. Studies of estimated selenium intake and lung cancer[a]

Study Reference	Country	Study design	Population (no. & characteristics)	Age (yrs)	Selenium intake- mean (SD)	Mean follow up (yrs)	Range	Adjusted relative risk (95% CI)	Comments
Randomised controlled trials									
Clark *et al.,* 1996 Nutritional Prevention of Cancer Trial	US	RCT	1312 patients with history of basal cell or squamous cell carcinoma of the skin. 48 lung cancer cases	18-80	Plasma selenium at baseline, 114 (23) µg/l. Intervention: 200µg/day of selenium vs. placebo	4.5 years treatment, 6.4 years follow up.		HR: 0.56 (0.31-1.01) p= 0.05	Significant inverse effect with selenium supplementation
Lippman *et al*., 2009 Selenium and vitamin E cancer prevention trial (SELECT)	US	RCT	35,533 men with no prior prostate cancer 1758 prostate cancer cases	50 plus	Baseline median plasma selenium in intervention and placebo groups, 135µg/l 200µg/day selenium vs. 400IU/d vitamin E vs. both vs. placebo.	5.46 (median follow up) 4.17-7.33 (range)		Selenium & vitamin E group HR: 1.16 99% CI (0.76-1.78) Selenium only HR: 1.12 99% CI (0.73-1.72)	No significant effect.
Case-control									
Mahabir *et al*., 2007	US	Case control	1676 lung cancer cases 1676 controls 902 male lung cancer cases 829 male	Mean cases 61.13, controls 60.96 Mean male cases	Selenium from food (µg/day): Cases: 90.40 (32.01) Controls: 91.74 (34.24) Cases: 99.80 (32.41) Controls: 102.34 (34.24)	N/A	Top fourth vs. bottom fourth Top fourth vs. bottom fourth	0.86 (0.64-15) p trend= 0.14 0.93 (0.61-1.40) p trend= 0.04	No significant association Significant inverse association.

Study Reference	Country	Study design	Population (no. & characteristics)	Age (yrs)	Selenium intake- mean (SD)	Mean follow up (yrs)	Range	Adjusted relative risk (95% CI)	Comments
			controls	61.48, controls 61.97					
Mahabir *et al*., 2007 continued			774 female lung cancer cases 847 female controls	Mean female cases 60.72, controls 59.97	Selenium from food (µg/day): Cases: 79.44 (27.80) Controls: 81.35		Top fourth vs. bottom fourth	0.87 (0.54-1.38) p trend= 0.35	No significant association

[a] Please note that only studies published after 1996 are included in this statement
HR- hazard ratio

Table 14. Nested case-control studies of selenium status and lung cancer[a]

Study Reference	Country	Study design	Age (yrs)	Population (no. & characteristics)	Sample	Mean concentration (SD/range)	Mean follow up (yrs)	Range	Adjusted relative risk (95% CI)	Comments
Goodman *et al*., 2001	US	Nested case-control study	45-74	356 cases with lung cancer 356 controls	Serum selenium (µg/l)	Cases 119.1 (1.96) Controls 117.7 (1.85)	4.7	Top fourth vs. bottom fourth	1.20 (0.77-1.88) p trend=0.49	No significant association.
Hartman *et al*., 2002 Alpha-tocopherol, Beta-carotene Cancer Prevention Study Cohort	Finland	Nested case control	Mean 63 yrs	250 male cases with lung cancer 250 male controls	Toenail selenium (µg/g)	Mean cases: 0.54 (0.13) Mean controls: 0.55 (0.13)	5-8	Top third vs. bottom third	0.20 (0.09-0.44) Randomised early in trial 0.61 (0.27-1.41) Randomised later in trial	Significant inverse association. No significant association.
Knekt *et al*., 1998	Finland	Nested case-control study	Mean - cases 57.7, controls 57.6	95 cases of lung cancer 190 healthy controls	Serum selenium (µg/l)	Cases: 53.2 (24.3) Controls: 57.8 (16.9)	Max 19	Top third vs. bottom third	0.41 (0.17-0.94) p trend = 0.05	Significant inverse association.
Ratnasinghe *et al*., 2000	China	Nested case-control study	~35-74	108 male cases with lung cancer, 216 healthy controls	Serum selenium (µg/l)	Cases: 46.5 Controls: 45.0	6	Top third vs. bottom third	1.20 (0.6-2.4) p trend=0.52	No significant association.

[a] Please note that only studies published after 1996 are included in this statement

Table 15. Case-control studies of selenium status and lung cancer[a]

Study Reference	Country	Age (yrs)	No. of cases	No. of controls	Sample	Selenium status measure & mean concentration (SD/range)	Range	Adjusted relative risk (95% CI)	Comments
Gromadzinska *et al*., 2003	Poland	43-78	152 lung cancer	210	Plasma selenium (µg/l)	Cases: 48.4 (16.5) Controls: 53.7 (14.3)	Cases vs. controls for those with >63.2 µg/l	0.72 p=0.010	No CIs or P trend stated. Significant inverse association when comparing cases with controls, analysis by thirds was conducted.
Jablonska *et al*., 2008	Poland	30-78	325 lung cancer	276	Plasma selenium (µg/l)	Cases: 49.4 Controls: 53.3	Cases vs. controls	Plasma selenium 4-49 µg/l 1.90(1.30-2.77) p=0.001 Plasma selenium 50-60 µg/l 1.00 Plasma selenium 70-89 µg/l 1.21(0.67-2.20) p=0.531	Significant increased risk for selenium concentrations up to 49µg/l

[a] Please note that only studies published after 1996 are included in this statement

Breast cancer

64. Four studies investigating the relationship between breast cancer risk and selenium intake and four studies assessing selenium status are detailed in Tables 16, 17 and 18.

65. The Nutritional Prevention of Cancer trial (Clark *et al*., 1996), with skin cancer as the primary outcome, found no association between selenium intake and the risk of breast cancer. After extending the treatment period of the trial, selenium supplementation still appeared to have no effect on the risk of developing breast cancer (HR 1.89; CI 0.69-5.14; p=0.21) (Duffield-Lillico *et al*., 2002).

66. One US nested case-control study (Dorgan *et al*., 1998) found no association between serum selenium (≤112.9 vs. 1.31.9-156.4µg/l) and breast cancer risk. Two case-control studies, one conducted in Finland (Männistö *et al*., 2000) and the other Netherlands (Ghadirian *et al*., 2000), found no association between toenail selenium concentrations and breast cancer. No association was also reported in two case-control studies investigating selenium intake and the risk of breast cancer (Challier., 1998;Moorman *et al*., 2001). Challier *et al*., (1998), conducted in France, found no association when comparing selenium intakes of ≤86.5 vs. 129.1µg/day and (Moorman *et al*., 2001) conducted in the US found no association between subjects taking selenium supplements and those not taking any. However, only a small number of people reported taking selenium supplements in the study, therefore there might not have been sufficient power to detect an effect of selenium intake.

67. Navarro Silvera & Rohan (2007) conducted a review of the evidence on trace elements and different cancers. The review found no association between selenium and breast cancer. The majority of the cohort and case-control studies included in the review were published pre 1998 and have therefore not been included in this statement.

68. The WCRF report could draw no firm conclusions in terms of breast cancer and selenium exposure (intake and status) (WCRF 2007). The WCRF Continuous Update Project identified two further studies showing that selenium intake (Raven-Haren *et al*., 2006) and selenium content of breast tissue (Cui *et al*., 2007) were not related to breast cancer risk. However, they concluded that the evidence remained limited (Norat *et al*., 2008)

Summary

69. Since COMA reported in 1998, the majority of studies investigating selenium and breast cancer risk have reported no association. However, the evidence is mainly limited to a small number of case-control studies, which are prone to bias and confounding.

70. Overall, there is insufficient evidence to establish whether selenium, at the intake or status levels studied, is associated with breast cancer risk.

Table 16. Studies of estimated selenium intake and breast cancer[a]

Study Reference	Country	Population (no. & characteristics)	Age (yrs)	Selenium intake-mean (SD)	Mean follow up (yrs)	Range	Adjusted relative risk (95% CI)	Comments
Randomised controlled trials								
Clark *et al.,* 1996 Nutritional Prevention of Cancer Trial	US	1312 patients with history of basal cell or squamous cell carcinoma of the skin 12 cases with breast cancer	18-80	Plasma selenium at baseline, 114 (23) µg/l. Intervention: 200µg/day of selenium vs. placebo	4.5 years treatment, 6.4 years follow up.		HR 2.95 (0.80-10.9) p=0.11	No significant effect.
Case control								
Challier *et al*., 1998	France	345 cases with breast cancer 345 controls	NR	Dietary intake µg/day	NA	Top fifth vs. bottom fifth (≤86.5 vs. >129.1)	1.10 (0.61-1.95) p trend= 0.99	No significant association.
Moorman *et al*., 2000	US	15 cases with breast cancer 12 controls[b]	20-74	Selenium supplements-any use	NA	No use vs. any use	0.97 (0.38-2.49)	No significant association.
Ravn-Haren *et al.,* 2006	Denmark	377 cases, 377 control	50-64	Selenium intake (µg/d) Cases 62µg/d, Controls 59µg/d	3-7yrs	Per 10 µg/d increase	1.01 (0.97-1.06)	No significant association.

[a] Please note that only studies published after 1996 are included in this statement

[b] The entire study consisted of 861 cases and 790 controls however only a small number reported taking selenium supplements.

NA – not applicable, NR - not reported

Table 17. Nested case-control study of selenium status and breast cancer[a]

Study Reference	Country	Study design	Age (yrs)	Population (no. & characteristics)	Sample	Mean concentration (SD/range)	Mean follow up (yrs)	Range	Adjusted relative risk (95% CI)	Comments
Cui *et al*., 2007	US	Nested case control	NR	252 cases, 252 controls	Breast tissue selenium level (ng/cm^2)	Median Se levels cases 0.031 ng/cm^2, controls 0.027 ng/cm^2	NR	Top fifth vs. bottom fifth	1.10 (0.72-1.68) p trend =0.76	No significant association.
Dorgan *et al*., 1998	US	Nested case control	40-75	105 cases with breast cancer 209 controls	Serum selenium (µg/l)	NR	9.5	Top fourth vs. bottom fourth	0.9 (0.4-1.8) p trend= 0.99	No significant association.

[a] Please note that only studies published after 1996 are included in this statement
NR – not reported

Table 18. Case-control studies of selenium status and breast cancer[a]

Study Reference	Country	Age (yrs)	No. of cases	No. of controls	Sample	Selenium status measure & mean concentration (SD/range)	Range	Adjusted relative risk (95% CI)	Comments
Ghadirian *et al*., 2000	The Netherlands	35-79	414 breast cancer	688	Toenail selenium (µg/g)	Cases: 0.92 (0.23) Controls- 0.93 (0.16)	Top fourth vs. bottom fourth	0.72 (0.40-1.31) p trend= 0.19	No significant association.
			102 pre-menopausal breast cancer	31		Cases: 0.92 (0.15) Controls: 0.93 (0.18)		1.20 (0.38-3.80) p trend= 0.93	No significant association.
			204 post-menopausal breast cancer	85		Cases: 0.90 (0.26) Controls: 0.91 (0.17)		0.61 (0.30-1.26) p trend= 0.18	No significant association.
Männistö *et al*., 2000	Finland	25-75	112 pre-menopausal breast cancer	168	Toenail selenium (µg/g)	Cases: 0.80 (0.16) Controls: 0.84 (0.17)	Top fifth vs. bottom fifth	0.5 (0.2-1.1)	No significant association.
			177 post menopausal breast cancer	265		Cases: 0.77 (0.16) Controls: 0.80 (0.14)		0.8 (0.4-1.4)	No significant association.

[a] Please note that only studies published after 1996 are included in this statement

Colorectal cancer

71. Five studies investigated the relationship between colorectal cancer and selenium intake or status; two randomised controlled trial using selenium supplements and three case-control studies either measuring selenium intake, toenail concentration or serum concentration (Table 19 and 20).

72. The Nutritional Prevention of Cancer (NPC) trial, n=1312 (Clark *et al*., 1996), with skin cancer as the primary outcome, found that subjects supplemented with selenium (200µg/day) had a significantly lower risk of developing colorectal cancer than those in the placebo group, based on 27 cases. When the treatment period was extended by three years, data from 1250 subjects suggested an effect in the direction of benefit, although it did not reach the criterion for statistical significance (HR 0.46; 95% CI 0.21-1.02; p=0.057, based on 28 cases) (Duffield-Lillico *et al*., 2002). The SELECT trial included colorectal cancer as a secondary endpoint, concluding that selenium supplementation was not significantly associated with the development of this cancer (Lippman *et al*., 2009).

73. In case-control studies, a significant decreased risk of colorectal cancer was associated with increasing selenium intake (12 vs. 50µg/day) (Ravasco *et al*., 2005) and toenail selenium concentration (Ghadirian *et al*., 2000). When the results were stratified by gender, this relationship remained significant for women only (Ghadirian *et al*., 2000). A US case-control study, (Connelly-Frost *et al*., 2009) observed a reduced risk of colorectal cancer in subjects who had a high serum selenium concentration (>140µg/L) and high folate intake (>354µg/day).

Colorectal adenomas

74. Four studies have investigated selenium and colorectal adenoma. These consist of one randomised controlled trial on selenium intake and three nested case-control studies investigating selenium status (Tables 21, 22 and 23).

75. A sample of 598 subjects, taken from the NPC trial, who reported colorectal cancer screening, were assessed for the occurrence of adenomas (Reid *et al*., 2006). Overall, no effect of selenium supplement intake and the risk of colorectal adenoma was observed. However, selenium supplementation appeared to reduce prevalent adenomas significantly among subjects in the lowest third (<105 µg/l) of plasma selenium (OR 0.27, CI 0.09-0.77 p-value 0.01). Prevalent adenomas were defined as adenomas identified at the first screening procedure. No effect was observed for incident adenomas, which were defined as lesions that developed over the course of the trial (Table 21).

76. From the nested case-control studies, Wallace *et al*., (2003), conducted in the US, found no association between the risk of colorectal adenomas and selenium status, where mean serum selenium levels of the first and fifth quintile ranged from 116-147µg/l. One Spanish study (Fernandez-Banares *et al*., 2002) showed that those with a higher selenium status (>82.1µg/l), appeared to have a decreased risk of developing colorectal adenomas and the other US study (Peters *et al*., 2006) demonstrated a significant decreased risk for colorectal adenomas with increasing serum selenium. Mean serum selenium levels of the first and fifth quintile ranged from 108 to 174µg/l. When the findings were analysed by gender, significant associations were observed only in men. When the analysis was stratified by smoking status the relationship was only significant for recent smokers (Peters *et al*., 2006).

77. A meta-analysis by Bjelakovic *et al.,* (2006) reviewed eight randomised controlled trials that investigated the effect of antioxidant supplementation (ß-carotene, vitamins A, C, E and selenium given either individually or in combination) with the risk of colorectal adenoma. Single analysis of selenium was derived from two trials and, overall, neither of the models used demonstrated an association with the risk of developing colorectal adenomas (Bjelakovic *et al*., 2006).

78. Jacobs *et al.,* (2004) performed a pooled analysis of observational data generated in three randomised controlled trials, to investigate the association between serum or plasma selenium concentrations and colorectal adenoma risk. The analyses included data from the Wheat Bran Fiber Trial, Polyp Prevention Trial and Polyp Prevention Study. When the lowest quarter was compared to the highest, only the Polyp Prevention Study demonstrated that serum selenium was significantly associated with a reduced risk of colorectal adenoma recurrence. However, the pooled analysis of all three studies, (two of which measured selenium in serum and the other analysed plasma) demonstrated a decreased risk with increasing plasma and serum selenium concentrations. The median blood selenium level in the first and fourth quartile of the pooled analysis ranged from 113 to 150 µg/l (Jacobs *et al*., 2004).

79. The WCRF report (WCRF 2007) stated that there is some evidence from case-control studies to suggest that greater selenium exposure could be related to reduced risk of colorectal cancer. However, due to the limited nature of the evidence, causality could not be inferred. In terms of dietary selenium, the available data were derived mainly from case-control studies. Only one randomised controlled trial (the NPC trial) and one cohort study investigating the impact of selenium supplementation were available. The WCRF Continuous Update Project (2011) identified one further trial on selenium and colorectal cancer risk and concluded that overall the evidence was sparse and inconsistent.

Summary

80. Since COMA reported in 1998, the trials investigating colorectal cancer have had heterogeneous methodology and inconsistent findings. The evidence from case-control studies and nested case- control studies suggest that selenium maybe beneficial for reducing colorectal cancer risk and colorectal adenomas, however these types of study cannot provide evidence of a cause-effect relationship (see paragraph 36).

81. There is currently insufficient evidence to establish whether selenium at the intake or status levels studied, is associated with colorectal cancer risk.

Table 19. Studies of estimated selenium intake and colorectal cancer[a]

Study Reference	Country	Population (no. & characteristics)	Age (yrs)	Selenium intake- mean (SD)	Mean follow up (yrs)	Range	Adjusted relative risk (95% CI)	Comments
Randomised controlled trials								
Clark *et al.,* 1996 Nutritional Prevention of Cancer Trial	US	1312 patients with history of basal cell or squamous cell carcinoma of the skin. 27 cases of colorectal cancer	18-80	Plasma selenium at baseline, 114 (23) µg/l. Intervention 200µg/day of selenium vs. placebo	4.5 years treatment, 6.4 years follow up.		HR 0.39 (0.17-0.90) p=0.03	Significant inverse effect.
Lippman *et al*., 2009 Selenium and vitamin E cancer prevention trial (SELECT)	US	35,533 men with no prior prostate cancer 1758 prostate cancer cases	50 plus	Baseline median plasma selenium in intervention and placebo groups, 135µg/l 200µg/day selenium vs. 400IU/d vitamin E vs. both vs. placebo.	5.46 (median follow up) 4.17-7.33 (range)		Selenium & vitamin E group HR 1.28 99% CI (0.82-2.00) Selenium only HR 1.05 99% CI (0.66-1.67)	No significant effect.
Case control								
Ravasco *et al*., 2005	Portugal	70 cases with colorectal cancer 70 control	Mean – Cases 62 Controls 61	Median selenium intake µg/day <u>Men</u> Cases 32 (24-42) Controls 57 (41-69) <u>Women</u> Cases 35 (26-43) Controls 58 (48-71)	N/A	Top fourth vs. bottom fourth	0.36 (0.29-0.40) p trend= 0.001	Significant inverse association

[a] Please note that only studies published after 1996 are included in this statement

[b] In this study prevalent adenomas were defined as adenomas identified at the first screening procedure following randomisation. Incident adenomas were classified as those being detected at subsequent screening appointments.

N/A- not applicable

Table 20. Case control studies of selenium status and colorectal cancer[a]

Study Reference	Country	Age (yrs)	No. of cases	No. of controls	Sample	Selenium status measure & mean concentration (SD/range)	Range	Adjusted relative risk (95% CI)	Comments
Connelly-Frost *et al*., 2009	US	40-80	532 subjects with primary diagnosis of invasive adinocarinoma of the colon	832	Serum (µg/L)	Cases Males: 126 Females: 125 Controls Males: 132 Females: 129	Top fifth vs. bottom fifth (with low and high folate intake)	Low folate intake 0.9 (0.6-1.5) High folate intake 0.4 (0.2-0.6)	Inverse association in subjects that also had a high folate intake
Ghadirian *et al.,*2000	Canada	35-79	92 colon cancer	202	Toenail concentration (µg/g)	Cases: 0.86 (0.14) Controls: 0.91 (0.16)	Top fourth vs. bottom fourth (-0.79 vs. +1.00)	0.42 (0.19-0.93) p= 0.009	Significant inverse association.
			49 male colon cancer	82		Cases: 0.86 (0.15) Controls: 0.89 (0.14)		0.54 (0.16-1.76) p= 0.25	No significant association.
			43 female colon cancer	120		Cases: 0.86 (0.13) Controls: 0.93 (0.18)		0.38 (0.11-1.27) p= 0.05	Significant inverse association.

[a] Please note that only studies published after 1996 are included in this statement

Table 21. Studies of estimated selenium intake and colorectal adenoma[a]

Study Reference	Country	Study design	Population (no. & characteristics)	Age (yrs)	Selenium intake-mean (SD)	Mean follow up (yrs)	Range	Adjusted relative risk (95% CI)	Comments
Reid *et al*., 2006 Nutritional Prevention of Cancer Trial (NPC)	US	RCT	598 subjects reported CRC screening 99 cases with prevalent colorectal adenoma[b] 61 cases with incident colorectal adenoma[b]	Mean 62.8 yrs	Baseline plasma selenium 114 (23) µg/l. 200µg/day high selenium baker's yeast vs. placebo	7.9		0.67 (0.43-1.05) p=0.08 0.98 (0.57-1.68) p=0.08	No significant effect. No significant effect.

[a] Please note that only studies published after 1996 are included in this statement

[b] In this study prevalent adenomas were defined as adenomas identified at the first screening procedure following randomisation. Incident adenomas were classified as those being detected at subsequent screening appointments.

Table 22. Nested case-control studies of selenium status and colorectal adenomas[a]

Study Reference	Country	Age (yrs)	Population (no. & characteristics)	Sample	Mean concentration (SD/range)	Mean follow up (yrs)	Range	Adjusted relative risk (95% CI)	Comments
Peters *et al*., 2006 Prostate, Lung, Colorectal & Ovarian Cancer Screening Trial	US	55-74	759 cases with advanced distal colorectal adenoma 767 controls 228 women advanced distal colorectal adenoma 235 controls 530 men advanced distal colorectal adenoma 532 controls	Serum (µg/l)	Cases: 134.2 (23.3) Controls: 137.3 (23.3)	N/A	Top fifth vs. bottom fifth	0.76 (0.53-1.10) p trend=0.01 1.22 (0.59-2.52) p trend=0.40 0.57 (0.36-0.89) p trend=0.001	Significant inverse association. No significant association. Significant inverse association
Wallace *et al.,*2003	US	Mean 61.5	276 cases with colorectal adenoma 276 controls	Plasma concentration-total (µg/l) Plasma concentration-bound (µg/l)	Cases: 131.5 (19.7) Controls: 130.3 (17.8) Cases: 133.1 (19.6) Controls: 130.9 (16.8)	4	Top fifth vs. bottom fifth	0.76 (0.44-1.30) p=0.50 0.60 (0.34-1.05) p=0.20	No significant association. No significant association.

[a] Please note that only studies published after 1996 are included in this statement

N/A- not applicable.

Table 23. Case-control studies of selenium status and colorectal adenomas[a]

Study Reference	Country	Age (yrs)	No. of cases	No of controls	Sample	Selenium status measure & mean concentration (SD/range)	Range	Adjusted relative risk (95% CI)	Comments
Case control									
Fernandez-Banares *et al.,*2002	Spain	Mean 60-61	28 subjects with large sporadic adenomatous polyps.	35	Serum (µg/l)	Cases - <60y 57.9 (4.3) >60y 49.6 (5.5) Controls - <60y 88.9 (8.0) >60y 44.7 (6.6)	Top fourth vs. all subjects below (≥82.11 vs. <82.11)	0.17 (0.03-0.84)	Significant inverse association. More marked in subjects <60y. ≥82.11µg/l was stated as being in the 75th percentile of plasma selenium.

[a] Please note that only studies published after 1996 are included in this statement

Summary of evidence for selenium and cancer

82. Since COMA reported in 1998, the majority of research on selenium and cancer has focused on prostate cancers, with smaller numbers of studies focusing on other cancers including lung, breast and colorectal cancers. Some studies have suggested that higher selenium intake or status may be associated with a lower risk of cancers. However, overall in the context of the levels studied, data do not suggest a protective association between higher selenium intake or status in relation to prostate or lung cancers, and data are insufficient to establish whether or not selenium is associated with the risk of developing breast or colorectal cancers. Furthermore systematic review of the evidence of selenium exposure and cancer incidence (Dennert *et al*., 2011 The Cochrane Collaboration) found inconclusive evidence of a causal relationship.

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SELENIUM AND CARDIOVASCULAR DISEASE

83. Due to the role of selenoproteins in antioxidant systems, it has been hypothesised that selenium may help prevent cardiovascular disease (CVD).

84. Two US randomised controlled trials have investigated selenium supplementation and the incidence of CVD as a secondary outcome. The Nutritional Prevention of Cancer (NPC) trial (Stranges *et al*., 2006) found no association between CVD and the consumption of selenium supplements or baseline plasma selenium concentrations. In the SELECT trial, after a median follow up of 5.5 years selenium supplementation also did not appear to provide any significant benefit (Lippman *et al*., 2009) (see Table 24).

85. Eight prospective cohort studies investigated CVD and selenium status (Table 25). One cohort study (Blankenberg *et al*., 2003) demonstrated a decreased risk of cardiovascular events with increasing GPx1 activity. It should be noted that this study was conducted in an at risk population, as subjects were recruited if they were suspected of having coronary artery disease, as determined by presence of angina. The authors observed that at baseline, the level of GPx1 was significantly lower among those who died from cardiac causes or had a nonfatal myocardial infarction. Lubos *et al*., (2010) observed significantly lower selenium levels in subjects with acute coronary syndrome (ACS) who died from cardiovascular causes, compared to survivors (61.0 vs. 75.1µg/l). However, only baseline selenium measures were taken. One cohort study (Wei *et al*., 2004) found no association between heart disease or stroke mortality and serum selenium. Although when subjects in the top three quarters were compared to the bottom quarter (≤60.8 vs. >60.8µg/l), a protective association was observed for heart disease mortality (p=0.05). Kilander *et al*., (2001) observed no significant association between serum selenium levels and cerebro- and cardiovascular mortality. Marniemi *et al*., (1998) observed lower serum selenium in subjects who died of vascular causes (75.6 vs. 78.1µg/l), however this was not significantly different. Bleys *et al*., (2008) reported no association between serum selenium levels and cardiovascular mortality in the NHANES III cohort, whereas Eaton *et al*., (2010) observed low serum selenium levels <98µg/l were associated with increased risk of coronary heart disease mortality in subject aged over 35 years in the same NHANES III cohort. This association was significant in subjects that also suffered from impaired renal function. Xun *et al*., (2010) observed no association between toenail selenium and measures of subclinical atherosclerosis.

86. One nested case-control study (Yoshizawa *et al*., 2003) found no association between coronary heart disease overall and toenail selenium concentration. When investigating the occurrence of non-fatal myocardial infarction, a lower risk was observed among subjects with the highest toenail selenium concentrations, but no significant effect was identified with increasing levels of selenium across the fifths (p trend = 0.07). Another nested case-control study (Rajpathak *et al*., 2005) found no association between toenail selenium concentration and the risk of CVD in diabetic men.

87. One case control study (Alissa *et al*., 2006) demonstrated that patients with CVD had significantly lower serum selenium concentrations, but higher urine selenium excretion compared to controls (Table 26).

88. Flores-Mateo *et al.,* (2006) conducted a meta-analysis of studies investigating selenium and the risk of coronary heart disease. They reviewed 14 cohort and 11 case control studies that assessed associations with selenium status, and six randomised controlled trials that evaluated selenium supplementation. Within cohort and case-control studies, higher selenium status was associated with a decreased risk of coronary heart disease (RR 0.85; CI 0.71-0.99, 0.43 CI; 0.29-0.66, respectively). However, no effect was observed from the randomised controlled trial data (RR 0.89; CI: 0.68-1.17). The authors noted that only two trials supplemented with selenium alone, that they were small and few of the studies measured clinical endpoints. They concluded that there was inadequate evidence for selenium being protective against coronary heart disease (Flores-Mateo *et al*., 2006).

Summary

89. Since COMA reported in 1998, the observational studies assessing the relationship between selenium intake or status and the risk of cardiovascular disease have shown inconsistent results. Data from trials do not show any effect of selenium supplementation on the incidence of CVD.

90. Overall, the available evidence does not suggest a protective association between selenium intakes and/or status and CVD risk, at the levels studied.

Table 24. Randomised controlled trials of selenium intake and cardiovascular disease[a]

Study reference	Country	Population (no. & characteristics)	Age (yrs)	Selenium intake	Mean follow up (yrs)	Adjusted relative risk (95% CI)	Comments
Lippman *et al*., 2009 Selenium and vitamin E cancer prevention trial (SELECT)	US	35,533 men with no prior prostate cancer 1050 cases of cardio-vascular events	50 plus	Baseline median plasma selenium in intervention and placebo groups, 135µg/l 200µg/day selenium vs. 400IU/d vitamin E vs. both vs. placebo.	5.46 (median follow up) 4.17-7.33 (range)	Selenium group: HR 1.02 (99% CI 0.92-1.13) Selenium and Vitamin E group HR 0.99 (99% CI 0.89-1.10)	No significant effect.
Stranges *et al*., 2006 Nutritional Cancer Prevention Trial	US	1004 patients with history of basal cell or squamous cell carcinoma of the skin. 199 CVD events 122 coronary heart disease cases 77 cerebrovascular accident cases	Mean ~ 62	Baseline plasma selenium 114 (23) µg/l. 200 µg selenium baker's yeast tablet	7.6	1.03 (0.78-1.37) p=0.81 1.04 (0.73-1.49) p=0.81 1.02 (0.65-1.59) p=0.94	No significant effect. No significant effect. No significant effect.

[a] Please note that only studies published after 1996 are included in this statement
CVD- cardiovascular disease

Table 25. Studies of selenium status and cardiovascular disease[a]

Study Reference	Country	Age (yrs)	Population (no. & characteristics)	Sample	Mean concentration (SD/range)	Mean follow up (yrs)	Range	Adjusted relative risk (95% CI)	Comments
Cohort									
Blankenberg *et al*., 2003	Germany	Mean: no CVD event-60.9 CVD event-67.0	636 subjects in cohort (patients with suspected coronary heart disease) 83 cardiovascular events	GPx red cell concentration (U/g haemoglobin)	49.2 (11.6)	4.7 (median)	Top fourth vs. bottom fourth	0.29 (0.14-0.60) p trend= 0.001	Significant inverse association.
Bleys *et al*., 2008 NHANES III Cohort	US	20-90	13887 subjects in NHANES III cohort	Serum concentration (µg/l)	Mean 125.6	12	Top third vs. bottom third	Cardiovascular mortality 0.94 (0.77-1.16) CHD mortality 0.99 (0.67-1.47) Stroke mortality 1.23 (0.66-2.28)	No significant association.
Eaton *et al*., 2010 NHANES III Cohort	US	35 plus	10531 subjects in NHANES III cohort (aged +35yrs) 1038 deaths from CHD	Serum concentration (µg/l)	Mean 124 (SD18.2; range 39-622)	13.4	Low selenium (<98µg/l) vs. normal selenium (>98µg/l)	HR 1.26 (0.94-1.69) HR: 2.06 (1.13-3.75) (subjects with low selenium and impaired renal function)	Significant inverse association.

Kilander *et al*., 2001	Sweden	50	2301 mean 301 CVD deaths	Serum selenium	NR	25.7	NR	0.97 (0.84-1.12)	No significant association
Lubos *et al*., 2010	Germany	Subjects with SAP– 61.3, 65.8 [b] Subjects with ACS – 60.8, 67.6 [b]	1724 subjects with) 190 deaths from cardiovascular causes	Serum selenium (µg/l)	Subjects with SAP: 74.8(±28.1), 73(±28.1) [b] Subjects with ACS: 71.5(±22.3), 61.0(±22.5) [b]	6.1	Top third vs. bottom third	HR: 0.38 (0.16-0.91) p trend = 0.03 Subjects with ACS	Significant inverse association in subjects with ACS with cardiovascular mortality.
Marniemi *et al*., 1998	Finland	≥65	344 elderly 142 deaths from CVD	Serum selenium (µg/l)	Alive: 82.2 (24) CVD death: 78.1 (23)	13	Top third vs. bottom third	1.08 (0.68-1.72)	No significant association
Wei *et al.,* 2004	China	40-69	1103 subjects in cohort. 116 deaths from CHD 167 deaths from stroke	Plasma concentration (µg/l)	Mean: 73	15	Top fourth vs. bottom fourth	0.66 (0.41-1.08) p trend= 0.17 1.43 (0.89-2.30) p trend= 0.82	No significant association. No significant association.
Xun *et al*., 2010 Cardia Trace Element Study	US	18-30	3112 subjects	Toenail selenium (µg/l)	Fifths (median) 1- 0.69 2- 0.78 3- 0.84 4- 0.92 5- 1.04	18	Top fifth vs. bottom fifth	0.95 (0.67-1.35) (Odds ratio)	No significant association between toenail selenium and measures of subclinical atherosclerosis.

Rajpathak *et al*., 2005 Health Professionals Follow Up Study	US	26-79	202 cases diabetic men with CVD 361 controls	Toenail selenium (µg/g)	Geometric mean Cases: 0.60 Controls: 0.71	~11	Top fourth vs. bottom fourth	0.58 (0.29-1.05) p=0.08	No significant association observed.
Yoshizawa *et al.,* 2003 Health Professionals Follow Up Study	US	40-75	470 cases with CHD 470 controls	Toenail concentration (µg/g)	Cases: 0.95 (0.43) Controls: 0.93 (0.29)	5	Top fifth vs. bottom fifth	0.86 (0.55-1.32) p trend= 0.75	No significant association.
			225 cases of non-fatal MI 465 controls					0.54 (0.31-0.93) p trend= 0.07	Significant inverse association with non-fatal MI for subjects in the highest fifth.

[a] Please note that only studies published after 1996 are included in this statement

[b] Patients with cardiovascular mortality

NR- not reported, HR- hazard ratio, CHD-coronary heart disease, MI – myocardial infarction, CVD- cardiovascular disease, SAP- stable angina pectoris, ACS- acute coronary syndrome, GPx – glutathione peroxidase**.**

Table 26. Case control studies of selenium status and cardiovascular disease[a]

Study Reference	Country	Age (yrs)	No. of cases	No of controls	Sample	Selenium status measure & mean concentration (SD/range)	Range	Adjusted relative risk (95% CI) *	Comments
Alissa *et al*., 2006	Saudi Arabia	Cases 55 yrs, controls 55.6 yrs	130 men with CVD	130 male controls	Serum selenium (µg/l)	Mean cases: 90 (0.05) Mean controls: 150 (0.08)	Case vs. control	0.07 (0.02-0.31) p= 0.001	Significant inverse association.
					Urine selenium (µg/mol creatinine)	Mean cases: 120 (0.13) Mean controls: 90 (0.13)	Case vs. control	3.34 (1.40-7.99) p= 0.007	Significant association.

[a] Please note that only studies published after 1996 are included in this statement
CVD- cardiovascular disease

SELENIUM AND IMMUNE FUNCTION IN RESPONSE TO VIRAL CHALLENGE

91. Data from animal studies suggest that selenium deficiency affects immune response to infection (Beck *et al*., 2001). Four human studies have investigated the relationship between selenium and viral infection in terms of the potential effects of selenium on immune function and viral handling (Table. 37).

92. One study reported an increase in immune function following challenge with influenza virus in 725 institutionalised elderly subjects supplemented with 100µg/day of selenium (Girodon *et al*., 1999). However, this study also supplemented with 20mg/day zinc, which may complicate the conclusions. In a randomised controlled trial in 66 UK volunteers, supplementation with selenium (50 and 100µg/day) augmented the cellular immune response to live attenuated poliovirus through increased production of interferon-γ and other cytokines and earlier peak T-cell proliferation, compared to placebo. The 100µg/day group showed a significantly greater T-cell response (Broome *et al.,* 2004). Furthermore, a more rapid clearance of poliovirus was seen in the selenium supplemented groups and there were fewer mutations in the viral genome than occurred in the placebo group.

93. Hawkes *et al.,* (2001) did not report any significant differences in antibody response to influenza vaccine in 11 men consuming a diet high or low in selenium for 120 days, although greater differences were observed following vaccination with diphtheria. The authors stated that their study duration might have been too short to observe the full effects of selenium supplementation.

94. A UK randomised, controlled trial investigated the relationship between dietary selenium intake and immune function in 119 subjects to identify functional markers of selenium status. As part of this trial the expression of selenoprotein W (SePW1), selenoprotein S (SEPS1) and selenoprotein R (SEPR) after supplementation with different forms and doses of selenium and the changes in response to influenza vaccine were measured. Participants received a placebo, 50, 100 or 200 µg /day Se-enriched yeast or meals containing unenriched or Se-enriched onions (50 µg /day). SEPW1 and SEPR were not sensitive markers to different forms and doses of selenium and did not change after vaccination with the influenza virus. However, a dose specific response in SEPS1 expression was noted following vaccination (Goldson *et al*., 2011).

Summary

95. Results from the randomised controlled trials on selenium and response to viral challenge identified since COMA reported in 1998 are inconsistent. There is currently insufficient evidence to establish a cause-effect relationship between selenium intakes, at levels studied, and human response to viral challenge.

Table 27. Randomised controlled trials of selenium intake and immune function[a]

Study reference	Country	Population (no. & characteristics)	Age (yrs)	Baseline selenium status- mean & SD (plasma µg/l)	Selenium intake	Trial duration	Comments
Girodon *et al.,* 1999	France	725 long term institutionalised elderly patients	>65 yrs	Placebo: 56 (19.7) Interventions: 56 (14.2) and 47 (14.2)	1) 20mg zinc + 100µg selenium 2) 120mg ascorbic acid + 6mg β-carotene + 15mg α-tocopherol 3) both supplements from 1 + 2 4) Placebo	2 yrs	A higher proportion of patients in the mineral supplement group remained free from respiratory tract infections compared to the other groups, though it was not significant (p=0.06). The antibody response to the influenza vaccine was better in group 1 and 2 and at 28 and 90 days there was a higher number of serologically protected patients in group 1 and 2.
Broome *et al.,* 2004	UK	66 healthy free living adults with relatively low selenium concentrations	20-47	Plasma selenium (µg/l) Placebo: 79 (2.4) 50µg group : 78 (1.6) 100µg group : 82 (1.6)	50µg/d or 100µg/d of sodium selenite or a placebo	15 weeks	Following vaccination the supplemented groups had a significantly higher production of IFN- γ on day 7 than the placebo group after vaccination. IL-10 production was significantly higher in the supplemented groups. In the placebo group IFN-γ and IL-10 production peaked at day 14 compared to day 7 in the supplemented groups. Poliovirus PCR products were significantly lower in the supplemented group after vaccination and further analysis of these products showed the presence of additional bands on the gel indicating mutation in the placebo group.

Goldson *et al.,* 2011	UK	119 healthy adults with sub optimal selenium status (<110µg/l)	50-64	Plasma selenium at baseline 95.7 (± 11.5) µg/l	Daily placebo or selenium-enriched yeast tablets containing 50, 100, or 200µg selenium, selenium-enriched onion meals, providing the equivalent of 50 µg Se/d), or unenriched onion meals	12 weeks	SEPW1 and SEPR were not sensitive makers to different forms and doses of selenium and did not change after vaccination with the influenza virus. However, a dose specific response in SEPS1 expression was noted following vaccination
Hawkes *et al.,* 2001	US	11 healthy males confined to metabolic unit	26-45	Low Se diet: 118 (7.9) High Se diet: 106 (18.9)	For 99 days either: Low selenium diet (13µg/d) or high selenium diet (297µg/d) dietary intake following 21 day run-in period	120 days	No significant difference following challenge with influenza vaccine. Mean white blood cell count decreased 5% in the high selenium group and increased 10% in the low selenium group. Lymphocyte counts increased transiently in the high selenium group, with a maximum of 17% at day 45. At the end of the trial there was a slight increase in both groups. Selenium aided secondary immune response to diphtheria vaccine.

[a] Please note that only studies published after 1996 are included in this statement

SELENIUM AND REPRODUCTION

Male Fertility

96. Selenium is essential for the normal development of spermatozoa and for sperm motility. Selenoproteins in the mid-peice portion of spermatozoa play a structural role stabilising the integrity of the sperm flagella (Ursini *et al.,* 1999).

97. Four randomised controlled trials have investigated selenium and indicators of male fertility. A trial conducted in the UK (Scott *et al*., 1998), which supplemented 69 men with 100µg selenium alone or selenium plus vitamins A, C and E, found no association between selenium supplementation and sperm motility or sperm count. However, when both of the treatment groups were combined, sperm motility was significantly increased compared to placebo. One randomised controlled trial (Sarfarinejad & Sarfarinejad 2009) investigated the effects of supplementing 200µg selenium or 600mg N-acetyl cysteine or both in 468 infertile men. Selenium supplementation alone for 26 weeks significantly increased sperm count (p=0.02) and sperm motility (p=0.03) in men with baseline plasma selenium 77.7µg/l. Hawkes *et al*., (2009) reported an increase in seminal selenium concentration in 54 healthy males supplemented with 300µg selenium, however this had no effect on sperm concentration or motility (Table 28).

98. No cohort or case-control studies were identified of sufficient quality.

Summary

99. There is currently insufficient evidence that selenium intake, at levels studied is causally related to male fertility.

Table 28. Randomised controlled trials of selenium intake and sperm motility and/or male infertility [a]

Study reference	Country	Population (no. & characteristics)	Age (yrs)	Baseline selenium status- mean & SD (plasma µg/l)	Selenium intake	Mean follow up (yrs)	Comments
Hawkes *et al*., 2009	US	54 healthy males	18-45	Blood plasma Selenium group : 1.80µmol/l Placebo: 1.85µmol/l	Either: 1) 300µg selenium 2) placebo	48 weeks treatment, 48 weeks follow up	Blood plasma and seminal selenium concentration increased in the supplemented group by 61% and 49% respectively. Sperm concentration and motility did not change in either group during the intervention.
Safarinejad & Sarfarinejad. 2009	Iran	468 infertile men with idiopathic oligo-asthenoteratospermia	25-48	Selenium group 77.7 (6.8) N-acetyl cysteine (NAC) group: 80.1 (6.6) Selenium & NAC group: 78.2 (6.8) Placebo group: 81.7 (6.8)	Either: 1) 200µg selenium 2) 600mg N-acetyl cysteine (NAC) 3) 200µg selenium and 600mg NAC 4) placebo	26 weeks treatment, 30 weeks follow up	At 26 weeks total sperm count had significantly increased in all supplemented groups compared to the placebo groups (p=0.02 selenium only group). Sperm motility also significantly increased in the selenium (p= 0.03) and selenium and NAC groups. These were no longer significant at 30 weeks follow up.
Scott *et al.,* 1998	UK	64 men attending a subfertility clinic	Mean 33.3	81.4 (NR)	Either: 1)100µg/d selenium 2)100µg/d selenium, 1mg vit A, 10mg vit C, 15mg vit E 3) placebo	3 months treatment 2 weeks follow up	No significant difference between the sperm count among the three groups. No significant difference in sperm motility between selenium treatment groups, however, when they were combined and compared to the placebo group, a significant increase in sperm motility was observed (p=0.02).

[a] Please note that only studies published after 1996 are included in this statement
NR- not reported

Recurrent miscarriages, pre term birth and pre-eclampsia

100. Selenium intake and status has been linked to pre-term birth and pre-eclampsia.

101. A randomised controlled trial supplemented 166 pregnant women from their first trimester until delivery with 100µg selenium or a placebo to investigate the risk of premature (pre-labour) rupture of membranes (Tara *et al*., 2010b) and pre-eclampsia (Tara *et al*., 2010a). The incidence of premature rupture of membranes was significantly lower in the selenium group compared to the placebo group, (Tara *et al*., 2010b). Tara *et al*., (2010a) reported no cases of pre-eclampsia in 83 women supplemented to selenium compared to three cases in 83 women taking a placebo; the difference was not statistically significant (Table 29).

102. A cohort study of 1197 Dutch women (Rayman *et al*., 2011) showed that serum selenium at 12 weeks gestation was significantly lower in women who had a pre-term birth than among those who delivered at term mean 75.8µg/l vs. 80.6µg/l ($p = 0.001$). Women with the lowest quarter of serum selenium (<72.7µg/l) had twice the risk of a preterm birth as women in the upper three quarters (Table 30).

103. Case control studies exploring the relationship between selenium concentrations and the risk of pre-eclampsia have provided contradictory results (Table 31). Rayman *et al*., (2003) found that toenail selenium concentrations were significantly lower in women with pre-eclampsia, whereas Mahomed *et al.,* (2000) found that pre-eclamptic women had significantly higher leukocyte selenium concentration at delivery.

Summary

104. There is currently insufficient evidence that low selenium intake or status are associated with premature delivery and pre-eclampsia.

Table 29. Randomised controlled trials of selenium intake and premature rupture of membranes and pre eclampsia[a]

Study reference	Country	Population (no. & characteristics)	Age (yrs)	Baseline selenium status- mean & SD (serum µg/l)	Selenium intake	Mean follow up (yrs)	Comments
Tara *et al*., 2010a&b	Iran	166 Pregnant women up to 12 weeks gestation	16-35	Se group 122.5 (+/- 23.2) µg/l Control group 122.9 (+/- 26.9) µg/l	Se group 100µg supplement or placebo group.	First trimester until delivery	Two papers published on the same study population looking at different outcomes following supplementation. The incidence of premature rupture of membranes was significantly lower ($p<0.01$) in the selenium group compared to the placebo group. There was no significant difference in incidence of preeclampsia however, study may have been underpowered for this outcome.

[a] Please note that only studies published after 1996 are included in this statement

Table 30. Cohort study of selenium status and preterm birth and pre-eclampsia[a]

Study Reference	Country	Age (yrs)	Population (no. & characteristics)	Sample	Mean concentration (SD/range)	Mean follow up (yrs)	Range	Adjusted odds ratio (95% CI)	Comments
Rayman *et al.*, 2011	Netherlands	Term birth – 30.5 Preterm birth – 29.9	1197 pregnant women of which 60 women with preterm birth	Serum (µmol/l)	1.01µmol/l (1.02µmol/l term births) (0.96µmol/l preterm births)	From 12 weeks gestation to birth	Top fourth vs. bottom fourth	Low selenium level (<25th percentile at 12 wk gestation) and preterm birth 2.18(1.25-3.77)	Whether the women had cervicovaginal or intrauterine infections during pregnancy, an important risk factor for premature rupture, was not recorded in this study

[a] Please note that only studies published after 1996 are included in this statement

Table 31. Case control studies of selenium status and pre-eclampsia[a]

Study Reference	Country	Age (yrs)	No. of cases	No of controls	Sample	Selenium status measure & mean concentration (SD/range)	Range	Adjusted relative risk (95% CI)	Comments
Mahomed *et al.,* 2000	Zimbabwe	Mean 25	171	184	Leucocytes (µg/g total protein)	Cases: 3.23 Controls: 2.80 (≤1.89-≥ 4.01)	Top fourth vs. bottom fourth	3.38 (1.53-7.45)	Cases had significantly higher leukocyte selenium concentration. Women in the highest quarter had a 3.4 fold increase risk of pre-eclampsia compared with women in the lowest quarter.
Rayman *et al.,* 2003	UK	Mean 31	53	53	Toenail (µg/g)	Cases: 0.56 (0.51-0.64) Controls: 0.62 (0.57-0.69)	Top third vs. bottom third	4.4 (1.6-14.9) p=0.029.	Significant increased risk of pre-eclampsia associated with the lowest third. The cases that delivered their infants before 32 weeks had a significantly lower selenium status.

[a] Please note that only studies published after 1996 are included in this statement

SELENIUM AND THYROID FUNCTION

105. In addition to the established role of iodine (Zimmerman 2009), selenium is important in thyroid function (Schomburg and Köhrle 2008). It has a role in iodothyronine deiodinases and glutathione peroxidases (GPx3). Iodothyronine deiodinase converts thyroxine (T4) to tri-iodothyronine (T3) and GPx3 reduces the potential oxidative damage arising from hydrogen peroxide produced during thyroid hormone synthesis, (Arthur *et al.,* 1999). A number of trials have investigated the relationship between selenium intake and thyroid function (Table 32).

Selenium and thyroid hormone production

106. A double blind randomised controlled trial (Rayman *et al*., 2008) allocated 501 (368 completed) elderly UK participants to either 100, 200, 300µg/day high selenium yeast or a placebo for six months. Although plasma selenium levels increased in the subject receiving the selenium this had no effect on thyroid function (as measured by levels of thyroid stimulating hormone (TSH), T4, T3 or T4/T3 ratio).

107. A US randomised placebo controlled trial in 42 healthy men (Hawkes *et al.,* 2008a) administered 300µg/day high-selenium yeast for 48 weeks. Serum levels of thyroid hormones T3 or T4 did not change during the study.

108. Supplementation studies performed in New Zealand found no association between selenium status and thyroid hormone levels (Thomson *et al*., 2005). A further study in 102 older adults compared the effects of 12 weeks 100µg/day selenium and 80µg/day iodine supplementation, either separately or combined on thyroid hormone status (Thomson *et al*., 2009). Significant reductions in thyroglobulin were seen in the iodine and iodine and selenium groups but no significant effects on thyroid hormone levels in any group.

109. Hess (2010) reviewed the evidence on interactions between selenium and iodine in relation to thyroid metabolism. They concluded that evidence from randomised controlled trials does not confirm the hypothesis that selenium deficiency adversely effects thyroid function. However, the subjects in the existing trials may have had baseline selenium levels above those where effects might have been seen.

Selenium, thyroditis and auto immune thyroid disease

110. Selenium may ameliorate effects on the thyroid in patients with thyroiditis and autoimmune thyroid disease (Table 33). Nacamulli *et al*., (2010) supplemented 76 patients with autoimmune thyroditis not receiving L-T4 replacement therapy, with either 80µg/day selenium or placebo. The results showed that selenium supplementation prevented decline of thyroid echogenicity after 6 months and reduced serum levels of auto-antibodies after 12 months. A meta-analysis of studies comparing L-T4 treatment in Hashimoto's thyroiditis with and without selenium supplementation (Toulis *et al*., 2010), found that selenium significantly lowered auto- antibody levels at three months.

111. Postpartum thyroiditis has been reported to occur in between 7-9 % of pregnancies (Kennedy *et al*., 2010). It is characterised by a period of high thyroid activity followed by a period of hypothyroidism. In some cases, it can result in permanent hypothyroidism. In a placebo controlled study, Negro *et al.,* (2007) showed that, in women with anti-thyroid peroxidase antibodies, selenium supplementation at 200 µg/day significantly reduced the presence levels of the antibodies, reduced thyroid inflammatory activity and the incidence of hypothyroidism.

Summary

112. There is evidence to show that selenium intake, at levels studied, does not affect thyroid hormone production. However, selenium supplementation may benefit patients with autoimmune thyroid conditions.

Table 32. Randomised controlled trials of selenium intake and thyroid function[a]

Study Reference	Country	Population (no. & characteristics)	Age (yrs)	Selenium intake-mean (SD)	Follow up	Range	Adjusted relative risk (95% CI)	Comments
Hawkes *et al*., 2008	USA	42 healthy men	18-45	Baseline plasma se Supplements 300 µg/d as high sodium selenite yeast	48 weeks		NR	No significant change in T3, T4, thyroxine or thyrotropin
Rayman *et al*., 2008	UK	501 older adults	60-74	Baseline plasma Se 91.3µg/l Supplements 100, 200µg, 300µg selenium as high selenium yeast or placebo yeast.	6 months		NR	No significant effect on T3, T4, T3:T4 or THS
Thomson *et al.*, 2005	New Zealand	72 smokers low selenium status	19-52	Baseline plasma Se 0.97µmol/l Supplements: 100µg/d selenium as selenomethionine tablet or placebo	20 weeks		NR	No significant effect on T4 or T3:T4 ratio
		172 healthy adults	18-65	Baseline plasma Se 1.11µmol/l Supplements, placebo yeast or 200µg/d se-enriched yeast containing selenomethionine.	21 weeks		NR	No significant effect on T4 or T3:T4 ratio

Thomson *et al*., 2009	New Zealand	100 healthy older adults	60-80	Baseline plasma Se 1.20µmol/l Supplements 100µg Se as selenomethionine, 100µg Se and 80µg iodine, 80µg iodine or placebo	12 weeks		NR	No significant effect on T3, T4, T3:T4 or THS

[a] Please note that only studies published after 1996 are included in this statement

Table 33. Randomised controlled trials of selenium intake and thyroditis[a]

Study Reference	Country	Population (no. & characteristics)	Age (yrs)	Selenium intake-mean (SD)	Follow up	Adjusted relative risk (95% CI)	Comments
Nacamulli *et al.,* 2010	Italy	76 patients with Auto immune thyroditis	15-75 (mean 43)	Supplements 80 µg/d sodium selenite vs. placebo	12 months	NR	Se prevented reduction in thyroid echogenicity after 6 mo, reduced auto antibodies after 12 months but did not modify T$ or TSH.
Negro *et al.,* 2007	Italy	232 pregnant women positive for thyroid peroxidase antibodies	18-36	200 µg/d selenomethionine, placebo or matched control group	12 wk gestation to term	NR	Selenium supplementation at 200 µg/day significantly reduced the presence levels of the antibodies, reduced thyroid inflammatory activity and the incidence of hypothyroidism. Subject also advised to use iodized salt.

[a] Please note that only studies published after 1996 are included in this statement

SELENIUM COGNITIVE FUNCTION AND MOOD

113. Two small studies published before the COMA statement reported a beneficial effect of selenium supplementation on mood (Benton and Cook 1991;Hawkes and Hornbostel 1996). However, one larger randomised controlled trial in 500 elderly volunteers (Rayman *et al*., 2006) found no effect of selenium supplementation on mood measures (Table 34).

114. One cohort study (Berr *et al*., 2000) demonstrated that subjects with low plasma selenium <76µg/l were at increased risk of cognitive decline (Table 35). Following a nine year follow up of the same cohort, Akbaraly *et al*., (2007) demonstrated that the association between cognitive function and selenium status remained significant and that those subjects who experienced a greater fall in plasma selenium were at increased risk of cognitive decline.

Summary

115. There is insufficient evidence to demonstrate that low selenium intakes are associated with impairment of cognitive function.

Table 34. Randomised controlled trial of selenium intake and mood and cognitive function[a]

Study reference	Country	Population (no. & characteristics)	Age (yrs)	Baseline selenium status- mean & SD (plasma µg/l)	Selenium intake	Trial duration (yrs)	Comments
Rayman *et al.,* 2006	UK	467	60-74	92 (20) µg/l	100, 200 or 300µg selenium via selenised yeast Placebo: identical yeast supplement	2 years, analysis of mood was conducted after 6 months	No effect was found between selenium supplementation and mood score, even after detailed stratified analysis.

[a] Please note that only studies published after 1996 are included in this statement

Table 35. Cohort study of selenium status and mood and cognitive function[a]

Study Reference	Country	Age (yrs)	Population (no. & characteristics)	Sample	Mean concentration (SD/range)	Mean follow up (yrs)	Range	Adjusted relative risk (95% CI)	Comments
Berr *et al*., 2000 EVA Study	France	60-70	1166 subjects	Plasma selenium (µg/L)	87 (15.8)	4	(bottom fourth vs. all subjects above) (<76 vs. ≥ 76 µg/L)	1.58 (1.08-2.31) p= 0.02	Significant association

[a] Please note that only studies published after 1996 are included in this statement

SUMMARY

116. When the relationship between selenium and health was last considered by COMA in 1998 they concluded that there was "no evidence of adverse health consequences from [current] intakes" of selenium in the UK at that time. This position statement provides an overview of the key evidence on selenium and health published between 1996 and July 2011.

117. Selenium is an essential trace element that is required for many important biochemical processes in the body. Intakes around the world are highly variable, partly due to the differences in the nature of soil in which crops are grown.

118. According to the National Diet and Nutrition Survey (NDNS) rolling programme, teenagers and adults are estimated to have mean selenium intakes below the reference nutrient intake (RNI). Only boys and girls aged 1.5-10 years have a mean intake above the RNI. It should be noted however, that the selenium dietary reference values were set on very limited data and caution should be exercised when using the RNI or LRNI to infer the adequacy of selenium intake in the population.

119. A range of markers have been used to assess selenium adequacy. These include plasma, whole blood, nail and hair selenium concentrations, plasma selenoprotein P levels, various blood indices of GPx activity and selenium urinary excretion. However, there is no single marker of selenium status that can be used to confirm selenium deficiency, adequacy or excess and each measure has limitations which need to be considered when interpreting data. Plasma selenium concentration is the most frequently used measure yet there is no agreement of what is considered to be a suitable reference range. The NDNS rolling programme shows that adults aged 19-64 years in the UK have a mean plasma selenium concentration of 83.7µg/l (1.06µmol/l) with a lower and upper 2.5 percentile of 60.0µg/l (0.76µmol/l) and 116.9µg/l (1.48µmol/l) respectively.

120. Some studies have suggested that low selenium intake or status are associated with an increased risk of diseases and other outcomes. However, the evidence is insufficient to infer that selenium exposure at intakes representative of the UK diet, is statistically significantly associated with breast or colorectal cancer, immune function, human reproduction or cognitive function and there is a moderate amount of evidence suggesting no beneficial association with risk for prostate and lung cancer, cardiovascular disease and thyroid hormone production.

121. The majority of epidemiological studies considered in this paper did not include functional markers of selenium adequacy. The heterogeneous design of the existing randomised controlled trials also limits comparability, with differences existing in the form of selenium supplemented, the health and range of baseline selenium status of participants. Further, there is potentially a range of baseline selenium levels above which associations between health and additional selenium intake are not seen. There is a need for further research to characterise functional markers of selenium status, in particular how they respond to

different levels of intakes and how they relate to various health outcomes in order to define adequate selenium exposure.

CONCLUSION

122. Current UK selenium intakes are generally below the RNI (see Table 7).

123. Having reviewed the research on associations between selenium and a range of health outcomes, no adverse health consequences of dietary intakes at the levels typically seen in the UK or benefits of higher intakes have been convincingly demonstrated. Evidence from well-designed randomised, controlled trials across the range of usual human intakes and using functional indicators of selenium status might clarify some of the uncertainties in the current evidence base.

124. Overall, there is currently insufficient evidence of a public health issue or rationale to justify undertaking a more detailed full risk assessment on selenium and health. However, it is advisable to keep a watching brief on the arising evidence, including through continuing to monitor selenium intake and status of the UK population in the National Diet and Nutrition Survey rolling programme.

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Annex 1: Selenium status data from previous National Diet and Nutrition Surveys

125. Prior to the NDNS rolling programme which started fieldwork in 2008/2009, data on selenium status were captured in the NDNS surveys of adults (19-64 years), children and young people (4-18 years) and a subset of older adults (65+ years). These surveys provide further information on differences in selenium status between population groups in the UK.

126. In 1997 selenium concentration in plasma and red blood cells (RBC) and GPx activity in whole blood were measured in children and adolescents aged 4-18 years as part of the NDNS (Bates *et al*., 2002b) (Table 36). Plasma and RBC selenium were well correlated with each other and both indices were positively associated with age. From these observations it may be inferred that the selenium supply was sufficient for GPx to reach maximal activity in this population. Socioeconomic status was associated with plasma selenium, with children living in more affluent households being more likely to have higher selenium levels. Children of Afro-Caribbean or south Asian origin had significantly higher levels of plasma and red blood cell selenium than children of white European origin.

Table 36. Mean plasma selenium concentration, red cell selenium and erythrocyte GPx activity for young people aged 4-18 years.

	Plasma selenium µmol/L*		Red cell selenium µmol/L*		Blood GPx (nmol/mg Hb/min)	
Boys						
Age	Mean	SD	Mean	SD	Mean	SD
4-6 years	0.83	0.15	1.41	0.27	91.0	18.6
7-10 years	0.87	0.15	1.44	0.26	88.3	17.1
11-14 years	0.84	0.14	1.44	0.28	88.8	14.7
15-18 years	0.89	0.14	1.46	0.25	92.8	24.0
All boys	0.86	0.15	1.44	0.26	90.0	18.7
Girls						
Age	Mean	SD	Mean	SD	Mean	SD
4-6 years	0.82	0.15	1.46	0.30	90.1	18.8
7-10 years	0.90	0.16	1.56	0.35	90.7	18.0
11-14 years	0.85	0.14	1.57	0.31	98.1	20.3
15-18 years	0.91	0.14	1.67	0.32	93.0	18.8
All girls	0.88	0.15	1.58	0.33	93.5	19.2

*To convert µmol/L to µg/L multiply by 78.96.

127. The NDNS of adults aged 19-64 years (Rushton *et al*., 2004) (Tables 37 and 38) showed mean plasma selenium concentrations increased significantly with age for both men and women ($p<0.01$). Red cell selenium was higher in women compared to men across all age groups, except for 50-64 year olds. Men aged 19-24 years had significantly lower red cell selenium concentrations relative to other age groups ($p<0.05$), whereas no age differences were observed for

women. Mean activities of GPx in whole blood were significantly higher in women ($p<0.05$), but no age differences were evident for either men or women. Mean plasma selenium was significantly less for men and women living in households receiving benefits (financial support) than non-benefit households ($p<0.05$) (table 38). For women only, mean red cell selenium was significantly lower in households receiving benefits ($p<0.01$).

Table 37. Mean plasma selenium concentration, red cell selenium and erythrocyte GPx activity for adults in the UK.

	Plasma selenium (µmol/L)*		Red cell selenium (µmol/L)*		Blood GPx (nmol/mg Hb/min)	
Men						
Age	Mean	SD	Mean	SD	Mean	SD
19-24 years	1.03	0.150	1.42	0.286	118.5	24.20
25-34 years	1.10	0.160	1.60	0.328	119.5	27.45
35-49 years	1.13	0.182	1.64	0.356	123.4	31.06
50-64 years	1.15	0.199	1.64	0.422	124.1	29.36
All men	1.11	0.182	1.60	0.369	121.9	28.79
Women						
Age	Mean	SD	Mean	SD	Mean	SD
19-24 years	1.03	0.151	1.73	0.276	134.0	36.39
25-34 years	1.07	0.205	1.83	0.453	122.5	30.49
35-49 years	1.09	0.176	1.80	0.457	126.8	31.93
50-64 years	1.17	0.332	1.82	0.816	129.2	27.85
All women	1.10	0.240	1.80	0.569	127.2	31.14

*To convert µmol/L to µg/L multiply by 78.96.

Table 38. Mean plasma selenium concentration, red cell selenium and erythrocyte GPx activity for adults whether receiving benefits in the UK.**

	Plasma selenium (µmol/L)*		Red cell selenium (µmol/L)*		Blood GPx (nmol/mg Hb/min)	
Men	Mean	SD	Mean	SD	Mean	SD
Receiving benefits	1.05	0.193	1.54	0.347	119.8	25.78
Not receiving benefits	1.12	0.178	1.61	0.372	122.3	29.24
Women						
Receiving benefits	1.01	0.171	1.65	0.362	123.3	32.26
Not receiving benefits	1.12	0.249	1.84	0.603	128.2	30.82

*To convert µmol/L to µg/L multiply by 78.96.

** financial support to provide additional income when unemployed and looking for work, earnings are low, if bringing up children, retired, care for someone, are ill or have a disability.

128. Selenium status was measured in a random sample of adults aged 65 years and over taken from the 1994-1995 NDNS and consisted of free living (n=833) and institution based (n=251) elderly individuals (Bates *et al*., 2002a). Plasma selenium concentration significantly decreased with age in both the free-living group ($p<0.0001$) and the institution group ($p=0.04$) (Table 39). It was noted that those of lower socio-economic status and who experienced poor health had lower plasma selenium concentrations. The correlation between plasma selenium concentration and whole blood GPx activity was weak ($p=0.21$) and it was less strongly associated with indices of frailty and health compared to plasma selenium.

Table 39. Mean plasma selenium concentration for free living and institution based elderly people in the UK.

Free-living sample	Plasma selenium (µmol/L)*	Institution sample	Plasma selenium (µmol/L)*
Men		Men	
Age	Mean	Age	Mean
65-74 years	1.00	65-74 years	0.79
75-84 years	0.93	75-84 years	0.76
85+ years	0.84	85+ years	0.73
Women		Women	
Age	Mean	Age	Mean
65-74 years	0.98	65-74 years	0.84
75-84 years	0.92	75-84 years	0.79
85+ years	0.84	85+ years	0.77
All of sample	0.94	All of sample	0.77

*To convert µmol/L to µg/L multiply by 78.96.
No standard deviations given

129. Some regional differences in selenium status were observed in the stand alone NDNS surveys, however the reason for these are unknown. It may be due to differences in food or lifestyle choices across the UK or it could be attributed to varying regional soil selenium content. The British Geological Survey (BGS) has currently mapped soil selenium concentrations for some areas, however peoples' food choices are not necessarily dependant on locally grown produce. Please see the full published NDNS reports for further details.

Annex 2: Study Design Definitions
(taken from World Cancer Research Fund systematic literature review manual 2002)

Randomised controlled trial (RCT)

This is an (epidemiological) experimental study in which conditions are controlled and manipulated by the investigator. Study subjects are randomly allocated to intervention or control groups. Results are assessed by comparison of disease rates or other outcome among intervention and control groups.

Randomised means allocation to study group entirely based on chance. Randomisation should follow a strict plan, usually some form of centralised randomisation scheme, an on-site computer system or sealed opaque envelopes.

Based on these principles, different design features can be differentiated:

RCT- Factorial design

In a factorial experimental design, the effects of a number of different factors can be investigated at the same time. The interventions are formed by all possible combinations that can be formed from the different factors. For example there are two interventions A and B and a control group C. The possible combinations are AB AC BC A B C so allowing the independent effects of each intervention to be assessed, as well as any interaction between them.

Testing of more than one intervention in one study (but not in one subject). Each participant is randomly allocated to intervention A or control B, and separately to intervention C or control D.

Prospective cohort study

(Synonyms: concurrent study, follow-up study, incidence study longitudinal study, prospective study).

In cohort studies exposure is measured in the present and outcome ascertained in the future. Cohort studies sample from groups of people with different levels of exposure (but unknown or unmeasured outcome). The sample for a cohort study is not always selected to represent the distribution within the whole population; it may be weighted to maximize heterogeneity of exposure.

A defined population (the cohort) is identified that consists of exposed and unexposed (to the exposure of interest) subjects. Exposure is assessed and then disease incidence (or other outcomes) is ascertained during the (prospective) follow-up period.

Single centre and multi-centre studies are possible.

Nested case-control study

This is a case-control study where cases and controls are drawn from the population of a prospective cohort study. The cases arising in the cohort become the cases and a sample of unaffected subjects from the cohort become the controls. Exposure is characterised prior to outcome being known. Single centre and multi-centre studies are possible. Migrant population may be included.

Case-cohort study

This is a method of sampling from an assembled epidemiological cohort study or a (clinical) trial. A random sample of the cohort (sub-cohort) is used as a comparison for all cases that occur in the cohort. This design is used when the assessment of covariates is too expensive to collect on all study subjects.

Single centre and multi-centre studies are possible.

Case-Control Study

(Synonyms: case comparison study, case history study, case referent study, retrospective study)

In case-control studies outcome is measured in the present and the past exposure is ascertained. Case-control studies sample from the population of people with the outcome of interest (with unknown levels of exposure). This study starts with the identification of cases, then selection of appropriate controls. Exposure is assessed retrospectively.

Case-control studies can be multi-centre studies, in which cases are recruited and corresponding controls are selected in an identical manner at different study centres.

Migrant populations can be selected for the study.

Cross-sectional studies

This is used to estimate the distribution (or joint distribution) of certain quantities (e.g. dietary exposure and disease rate) in a target population at a certain moment in time. Special characteristic is the simultaneous assessment of exposure and outcome.
Cross-sectional studies measure both exposure and outcome in the present and at the same point in time. Generally cross-sectional studies sample from the population in such a way as to reflect the population characteristics for both exposure and outcome.