LIST OF TABLES

Table 1. Selenium content of foods
Table 2. Estimated intake of selenium from different foods in the UK in 2006
Table 3. RNI for selenium (COMA 1991)
Table 4. LRNI for selenium (COMA 1991)
Table 5. Average reported daily selenium intake in the UK (year 1 & 2 of NDNS rolling programme)
Table 6. Reported daily selenium intake as a percentage of the RNI in the UK (year 1 & 2 of NDNS rolling programme)
Table 7. Proportion with average reported intakes below the LRNI in the UK (year 1 & 2 of NDNS rolling programme)
Table 8. Estimated selenium intakes in the UK from the Total Diet Study
Table 9. Selenium status Table (year 1 & 2 of NDNS rolling programme)
Table 10. Studies of estimated selenium intake and prostate cancer
Table 11. Cohort and nested case-control studies of selenium status and prostate cancer
Table 12. Case control studies of selenium and prostate cancer
Table 13. Studies of estimated selenium intake and lung cancer
Table 14. Nested case control studies of selenium status and lung cancer
Table 15. Case control studies of selenium status and lung cancer
Table 16. Studies of estimated selenium intake and breast cancer
Table 17. Nested case control study of selenium status and breast cancer
Table 18. Case control studies of selenium status and breast cancer
Table 19. Studies of estimated selenium intake and colorectal cancer
Table 20. Case control studies of selenium status and colorectal cancer
Table 21. Studies of estimated selenium intake and colorectal adenoma
Table 22. Nested case control studies of selenium status and colorectal adenomas
Table 23. Case control studies of selenium status and colorectal adenomas
Table 24. Randomised controlled trials of selenium intake and cardiovascular disease
Table 25. Studies of selenium status and cardiovascular disease
Table 26. Case control studies of selenium status and cardiovascular disease
Table 27. Randomised controlled trials of selenium intake and immune function
Table 28. Randomised controlled trials of selenium intake and sperm motility and or male fertility
Table 29. Randomised controlled trials of selenium intake and premature rupture of membranes and pre eclampsia
Table 30. Cohort study of selenium status and preterm birth and pre-eclampsia
Table 31. Case control studies of selenium status and pre-eclampsia
Table 32. Randomised controlled trials of selenium intake and thyroid function
Table 33. Randomised controlled trials of selenium intake and thyroditis
Table 34. Randomised controlled trials of selenium intake and mood and cognitive function.
Table 35. Cohort study of selenium status and mood and cognitive function
Table 36. Mean plasma selenium, red cell selenium and erythrocyte GPx activity for young people aged 4-18 years.
Table 37. Mean plasma selenium, red cell selenium and erythrocyte GPx activity for adults in the UK.
Table 38. Mean plasma selenium, red cell selenium and erythrocyte GPx activity for adults whether receiving benefits in the UK.
Table 39. Mean plasma selenium for free living and institution based elderly people in the UK.
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

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

<sup>a</sup>Taken from The Composition of Foods, 6th edition, 2002. (FSA 2002);
<sup>b</sup>Taken from Fish Analytical Survey, DH, 2012 (unpublished);
<sup>c</sup>Taken from Eggs Analytical Project, DH 2012;
<sup>d</sup>Taken from Nutrient Analysis Catch Up Project, FSA, 2004
<sup>e</sup>Taken from Breakfast cereals analytical Survey, FSA, 2004
<sup>*</sup>Based on UK wheat sources
Table 2. Estimated intake of selenium from different foods in the UK in 2006*

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

*Table adapted from 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 (DRV)s 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)

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

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

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

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

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)

<table>
<thead>
<tr>
<th>Age</th>
<th>n</th>
<th>Food sources</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Upper 2.5 percentiles</th>
<th>Lower 2.5 percentiles</th>
<th>All sources (including supplements)</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Upper 2.5 percentiles</th>
<th>Lower 2.5 percentiles</th>
</tr>
</thead>
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<tr>
<td>Males</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>4-10 years</td>
<td>210</td>
<td></td>
<td>34</td>
<td>33</td>
<td>10</td>
<td>60</td>
<td>18</td>
<td>35</td>
<td>33</td>
<td>11</td>
<td>60</td>
<td>18</td>
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</tr>
<tr>
<td>11-18 years</td>
<td>238</td>
<td></td>
<td>44</td>
<td>43</td>
<td>16</td>
<td>84</td>
<td>19</td>
<td>44</td>
<td>43</td>
<td>16</td>
<td>84</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>All boys</td>
<td>448</td>
<td></td>
<td>40</td>
<td>37</td>
<td>15</td>
<td>73</td>
<td>19</td>
<td>40</td>
<td>37</td>
<td>15</td>
<td>73</td>
<td>19</td>
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</tr>
<tr>
<td>19-64 years</td>
<td>346</td>
<td></td>
<td>54</td>
<td>50</td>
<td>25</td>
<td>110</td>
<td>25</td>
<td>56</td>
<td>51</td>
<td>30</td>
<td>128</td>
<td>25</td>
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</tr>
<tr>
<td>65 + years</td>
<td>96</td>
<td></td>
<td>51</td>
<td>47</td>
<td>22</td>
<td>101</td>
<td>17</td>
<td>59</td>
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</tr>
<tr>
<td>Females</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-10 years</td>
<td>213</td>
<td></td>
<td>32</td>
<td>31</td>
<td>10</td>
<td>57</td>
<td>15</td>
<td>32</td>
<td>31</td>
<td>10</td>
<td>57</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>11-18 years</td>
<td>215</td>
<td></td>
<td>35</td>
<td>34</td>
<td>13</td>
<td>65</td>
<td>13</td>
<td>36</td>
<td>35</td>
<td>13</td>
<td>65</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>All girls</td>
<td>428</td>
<td></td>
<td>34</td>
<td>33</td>
<td>12</td>
<td>62</td>
<td>15</td>
<td>34</td>
<td>33</td>
<td>12</td>
<td>62</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>19-64 years</td>
<td>461</td>
<td></td>
<td>43</td>
<td>39</td>
<td>18</td>
<td>89</td>
<td>18</td>
<td>46</td>
<td>40</td>
<td>24</td>
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<td>1.5-3 years</td>
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<td>10</td>
<td>25</td>
<td>24</td>
<td>10</td>
<td>45</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>4-10 years</td>
<td>423</td>
<td></td>
<td>33</td>
<td>32</td>
<td>10</td>
<td>59</td>
<td>17</td>
<td>33</td>
<td>32</td>
<td>11</td>
<td>59</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>11-18 years</td>
<td>453</td>
<td></td>
<td>40</td>
<td>37</td>
<td>15</td>
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<td>16</td>
<td>40</td>
<td>37</td>
<td>15</td>
<td>73</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>19-64 years</td>
<td>807</td>
<td></td>
<td>48</td>
<td>45</td>
<td>22</td>
<td>101</td>
<td>19</td>
<td>51</td>
<td>46</td>
<td>28</td>
<td>116</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>65+ years</td>
<td>224</td>
<td></td>
<td>45</td>
<td>43</td>
<td>18</td>
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<td>21</td>
<td>50</td>
<td>44</td>
<td>35</td>
<td>110</td>
<td>22</td>
<td></td>
</tr>
</tbody>
</table>

*To convert units 1µmol = 79µg
Standard deviation (SD)
<table>
<thead>
<tr>
<th>Age</th>
<th>n</th>
<th>Food sources</th>
<th>All sources (including supplements)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>Median</td>
</tr>
<tr>
<td>Daily selenium intake as a percentage of the RNI (%)</td>
<td></td>
<td>Mean</td>
<td>Median</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-10 years</td>
<td>210</td>
<td>136</td>
<td>129</td>
</tr>
<tr>
<td>11-18 years</td>
<td>238</td>
<td>80</td>
<td>74</td>
</tr>
<tr>
<td>All boys</td>
<td>448</td>
<td>105</td>
<td>99</td>
</tr>
<tr>
<td>19-64 years</td>
<td>346</td>
<td>72</td>
<td>67</td>
</tr>
<tr>
<td>65+ years</td>
<td>96</td>
<td>68</td>
<td>63</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-10 years</td>
<td>213</td>
<td>129</td>
<td>118</td>
</tr>
<tr>
<td>11-18 years</td>
<td>215</td>
<td>69</td>
<td>65</td>
</tr>
<tr>
<td>All girls</td>
<td>428</td>
<td>96</td>
<td>86</td>
</tr>
<tr>
<td>19-64 years</td>
<td>461</td>
<td>71</td>
<td>65</td>
</tr>
<tr>
<td>65+ years</td>
<td>128</td>
<td>68</td>
<td>63</td>
</tr>
<tr>
<td>Total</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1.5-3 years</td>
<td>219</td>
<td>163</td>
<td>157</td>
</tr>
<tr>
<td>4-10 years</td>
<td>423</td>
<td>133</td>
<td>126</td>
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<td>11-18 years</td>
<td>453</td>
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<tr>
<td>19-64 years</td>
<td>807</td>
<td>72</td>
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</tr>
<tr>
<td>65+ years</td>
<td>224</td>
<td>68</td>
<td>63</td>
</tr>
</tbody>
</table>
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)

<table>
<thead>
<tr>
<th>Age</th>
<th>Selenium intake from food sources</th>
<th>Selenium intake from all sources (including supplements)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Below LRNI</td>
<td>% Between LRNI and RNI</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-10 years</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>11-18 years</td>
<td>22</td>
<td>57</td>
</tr>
<tr>
<td>19-64 years</td>
<td>24</td>
<td>63</td>
</tr>
<tr>
<td>65 + years</td>
<td>30</td>
<td>58</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-10 years</td>
<td>2</td>
<td>27</td>
</tr>
<tr>
<td>11-18 years</td>
<td>48</td>
<td>41</td>
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<tr>
<td>19-64 years</td>
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<td>34</td>
</tr>
<tr>
<td>65 + years</td>
<td>52</td>
<td>42</td>
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<tr>
<td>Total</td>
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<td></td>
</tr>
<tr>
<td>4-10 years</td>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>11-18 years</td>
<td>34</td>
<td>49</td>
</tr>
<tr>
<td>19-64 years</td>
<td>39</td>
<td>48</td>
</tr>
<tr>
<td>65+ years</td>
<td>42</td>
<td>49</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Intake (µg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1974</td>
<td>60&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>1985</td>
<td>63</td>
</tr>
<tr>
<td>1991</td>
<td>60</td>
</tr>
<tr>
<td>1994</td>
<td>43</td>
</tr>
<tr>
<td>1995</td>
<td>39&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>1997</td>
<td>39</td>
</tr>
<tr>
<td>2000</td>
<td>32-34&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2006</td>
<td>48-58&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> 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).

<sup>b</sup> 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.

<sup>c</sup> 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 contributor 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 (Burr & 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 Sepp1 concentrations (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) |                          |                          |                          |                          |                          |
|-------------------------|-----|-------------------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                         |     | Mean | Median | SD | Lower 2.5 percentile | Upper 2.5 percentile |
| Males                   |     |      |        |    |                      |                        |
| Boys 11-18 years        | 84  | 0.90 | 0.89   | 0.161 | 0.60 | 1.29 |
|                         |     | (71.1)| (70.3) | (12.7)| (47.4)| (101.9) |
| Men 19-64 years         | 136 | 1.08 | 1.09   | 0.195 | 0.76 | 1.56 |
|                         |     | (85.3)| (86.1) | (15.4)| (60.0)| (123.2) |
| Females                 |     |      |        |    |                      |                        |
| Girls 11-18 years       | 65  | 0.92 | 0.94   | 0.132 | 0.66 | 1.18 |
|                         |     | (72.7)| (74.3) | (10.4)| (52.1)| (93.2) |
| Women 19-64 years       | 201 | 1.03 | 1.03   | 0.171 | 0.75 | 1.41 |
|                         |     | (81.4)| (81.4) | (13.5)| (59.3)| (111.4) |
| Total                   |     |      |        |    |                      |                        |
| All 11-18 years         | 149 | 0.91 | 0.90   | 0.148 | 0.66 | 1.29 |
|                         |     | (71.9)| (71.1) | (11.7)| (52.1)| (101.9) |
| All 19-64 years         | 337 | 1.06 | 1.06   | 0.180 | 0.76 | 1.48 |
|                         |     | (83.7)| (83.7) | (14.2)| (60.0)| (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.
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.

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.

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.

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.

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\(^a\)

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

\(^a\)Please note that only studies published after 1996 are included in this statement  
HR – hazard ratio, RR - relative risk
### Table 10 continued

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Country</th>
<th>Population (no. &amp; characteristics)</th>
<th>Age (yrs)</th>
<th>Selenium intake- mean (SD)</th>
<th>Mean follow up (yrs)</th>
<th>Range</th>
<th>Adjusted relative risk (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Hartman et al., 1998</td>
<td>Finland</td>
<td>29,133 subjects</td>
<td>50-69</td>
<td>FFQ selenium including supplements (µg/day)</td>
<td>9</td>
<td>Top fourth vs. bottom fourth</td>
<td>0.84 (0.43-1.67) p=0.64 1.27 (0.70-2.20) p=0.49</td>
<td>No significant association.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>127 cases from alpha-tocopherol supplement group</td>
<td></td>
<td>Total mean intake: Prostate cancer cases 93.9 (40.2) No prostate cancer 95.9 (36.5)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>190 cases from non supplemented group</td>
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</tr>
<tr>
<td>Lawson et al., 2007</td>
<td>US</td>
<td>295,344 subjects</td>
<td>50-71</td>
<td>Selenium supplement intake: no. of times/week</td>
<td>6</td>
<td>&gt;7 times/ week vs. never</td>
<td>1.39 (1.09-1.77) p trend=0.003</td>
<td>A significant positive association with increasing supplement intake.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10241 prostate cancer cases</td>
<td></td>
<td>130 cases &gt;7 times/ week</td>
<td></td>
<td></td>
<td>1.37 (1.05-1.78) p trend=0.004</td>
<td>A significant positive association with increasing supplement intake.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8765 Localised Prostate cancer cases</td>
<td></td>
<td>109 cases &gt;7 times/ week</td>
<td></td>
<td></td>
<td>1.53 (0.82-2.85) p trend=0.36</td>
<td>No significant association.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1476 Advanced prostate cancer cases</td>
<td></td>
<td>21 cases &gt;7 times/ week</td>
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</tr>
<tr>
<td>Peters et al., 2008</td>
<td>US</td>
<td>22,089 subjects</td>
<td>50-76</td>
<td>Supplement intake: 26.6µg Dietary selenium intake: 138.9µg</td>
<td>10</td>
<td>10 years &gt;50µg/day vs. Never</td>
<td>HR: 0.90 (0.62-1.3) p trend=0.97</td>
<td>No significant association.</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Controls</td>
<td>Cases</td>
<td>FFQ (μg/day)</td>
<td>Cases vs. controls</td>
<td>p-value</td>
<td>Note</td>
<td></td>
</tr>
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<tr>
<td>Lee et al., 1998</td>
<td>China</td>
<td>265 controls 133 prostate cancer cases</td>
<td>40-70</td>
<td>Mean intake cases- 65.4 (2.6) Controls- 58.0 (1.5)</td>
<td>N/A</td>
<td>1.0 (0.99-1.04)</td>
<td>p= 0.75</td>
<td>No significant association</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Country</th>
<th>Age (yrs)</th>
<th>Population (no. &amp; characteristics)</th>
<th>Sample</th>
<th>Mean concentration (SD/range)</th>
<th>Mean follow up (yrs)</th>
<th>Range</th>
<th>Adjusted relative risk (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort</strong></td>
<td></td>
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<tr>
<td>van den Brandt</td>
<td>The Netherlands</td>
<td>55-69</td>
<td>522 cases with prostate cancer 1211 subcohort</td>
<td>Toenail (µg/g)</td>
<td>Cases: 0.53 (0.09) Subcohort: 0.55 (0.13)</td>
<td>6.3</td>
<td>Top fifth vs. bottom fifth</td>
<td>0.70 (0.48-1.01) p trend=0.012</td>
<td>Significant inverse association.</td>
</tr>
<tr>
<td>et al., 2003</td>
<td></td>
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<tr>
<td>The Netherlands Cohort Study</td>
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</tr>
<tr>
<td>Venkitaraman et al., 2010</td>
<td>UK</td>
<td>48-77</td>
<td>104 cases with localised prostatic adenocarcinoma</td>
<td>Serum (µmol/l)</td>
<td>1.19</td>
<td>2.5</td>
<td>NR</td>
<td>HR: 0.99 (0.985-1.011) p trend=0.76</td>
<td>No significant association between baseline selenium levels and time to disease progression.</td>
</tr>
<tr>
<td><strong>Nested case control</strong></td>
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<tr>
<td>Allen et al., 2008 EPIC</td>
<td>Europe – Denmark, Germany, Greece, Italy, Netherlands, Spain, Sweden &amp; UK</td>
<td>43-76</td>
<td>959 cases 1059 controls</td>
<td>Plasma (µg/l)</td>
<td>Cases: 70.6 Controls: 71.9</td>
<td>4.3</td>
<td>Top fifth vs. bottom fifth</td>
<td>0.96 (0.70-1.31) p trend= 0.25</td>
<td>No significant association.</td>
</tr>
<tr>
<td>Brooks et al., 2001</td>
<td>US</td>
<td>45-74</td>
<td>52 cases 96 controls</td>
<td>Plasma (µg/l)</td>
<td>Cases: 122 Controls: 117</td>
<td>N/A</td>
<td>Top fourth vs. bottom fourth</td>
<td>0.24 (0.07-0.77)</td>
<td>Significant inverse association when comparing the three highest quarters to lowest quarter. No p trend given.</td>
</tr>
<tr>
<td>Study</td>
<td>Location</td>
<td>Age Range</td>
<td>Cases Controls</td>
<td>Measure Type</td>
<td>Cases: Median (IQR)</td>
<td>Control: Median (IQR)</td>
<td>Analysis</td>
<td>Odds Ratio (95% CI)</td>
<td>p Value</td>
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</tbody>
</table>
| Gill et al., 2009            | US       | 42-75     | 467 cases 936 controls | Serum (µg/g) | Cases: 0.13  
Control: 0.14 | 4.7 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         | 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. |
<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Country</th>
<th>Age (yrs)</th>
<th>Population (no. &amp; characteristics)</th>
<th>Sample</th>
<th>Mean concentration (SD/range)</th>
<th>Mean follow up (yrs)</th>
<th>Range</th>
<th>Adjusted relative risk (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al., 2004</td>
<td>US</td>
<td>40-84</td>
<td>586 cases with prostate cancer</td>
<td>Plasma (µg/l)</td>
<td>Cases: 106 (18)</td>
<td>13</td>
<td>Top fifth vs. bottom fifth</td>
<td>0.78 (0.54-1.13) p trend= 0.16</td>
<td>All prostate cancer - No significant association</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>577 control subjects</td>
<td></td>
<td>Controls: 108 (18)</td>
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<td></td>
<td></td>
<td>384 cases with localised prostate cancer</td>
<td></td>
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<td></td>
<td></td>
<td>0.97 (0.64-1.49) p trend= 0.91</td>
<td>Localized cases - No significant association</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>171 cases with advanced prostate cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.52 (0.28-0.98) p trend= &lt;0.05</td>
<td>Advanced cases - Significant inverse association.</td>
</tr>
<tr>
<td>Nomura et al., 2000</td>
<td>Hawaii</td>
<td>45-85</td>
<td>249 cases with prostate cancer</td>
<td>Serum (µg/l)</td>
<td>Cases: 129.9 (72.8-205.0)</td>
<td>&gt;20</td>
<td>Top fourth vs. bottom fourth</td>
<td>0.50 (0.3-0.9) p trend=0.02</td>
<td>Significant inverse association</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>249 controls</td>
<td></td>
<td>Controls: 134.1 (77.1-227.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Age Range</td>
<td>Cases/Controls</td>
<td>Type (µg/l)</td>
<td>HR [95% CI]</td>
<td>Trend</td>
<td>Significance</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Peters et al., 2007</td>
<td>US</td>
<td>55-74</td>
<td>724/879</td>
<td>Serum (µg/l)</td>
<td>Controls: 141.3 (26.0)</td>
<td>Top fourth vs. bottom fourth</td>
<td>0.84 (0.62-1.14) p trend= 0.70</td>
<td>No significant association.</td>
<td></td>
</tr>
<tr>
<td>Steinbrecher et al., 2010</td>
<td>Germany</td>
<td>Mean 58.1</td>
<td>248/493</td>
<td>Serum (µg/l)</td>
<td>Cases: 86.2</td>
<td>Top fourth vs. bottom fourth</td>
<td>0.78 (0.49-1.22)</td>
<td>No significant association.</td>
<td></td>
</tr>
<tr>
<td>Yoshizawa et al., 1998</td>
<td>US</td>
<td>40-75</td>
<td>181/181</td>
<td>Toenail (µg/g)</td>
<td>Cases: 0.82</td>
<td>Top fifth vs. bottom fifth</td>
<td>0.35 (0.16-0.78) p trend=0.03</td>
<td>Significant inverse association</td>
<td></td>
</tr>
</tbody>
</table>

* 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

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

*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>
<thead>
<tr>
<th>Study Reference</th>
<th>Country</th>
<th>Study design</th>
<th>Population (no. &amp; characteristics)</th>
<th>Age (yrs)</th>
<th>Selenium intake- mean (SD)</th>
<th>Mean follow up (yrs)</th>
<th>Range</th>
<th>Adjusted relative risk (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomised controlled trials</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clark <em>et al.</em>, 1996</td>
<td>US</td>
<td>RCT</td>
<td>1312 patients with history of basal cell or squamous cell carcinoma of the skin. 48 lung cancer cases</td>
<td>18-80</td>
<td>Plasma selenium at baseline, 114 (23) µg/l. Intervention: 200µg/day of selenium vs. placebo</td>
<td>4.5 years treatment, 6.4 years follow up.</td>
<td></td>
<td>HR: 0.56 (0.31-1.01) p= 0.05</td>
<td>Significant inverse effect with selenium supplementation</td>
</tr>
<tr>
<td>Lippman <em>et al.</em>, 2009</td>
<td>US</td>
<td>RCT</td>
<td>35,533 men with no prior prostate cancer 1758 prostate cancer cases</td>
<td>50 plus</td>
<td>Baseline median plasma selenium in intervention and placebo groups, 135µg/l 200µg/day selenium vs. 400IU/d vitamin E vs. both vs. placebo.</td>
<td>5.46 (median follow up) 4.17-7.33 (range)</td>
<td></td>
<td>Selenium &amp; vitamin E group HR: 1.16 99% CI (0.76-1.78) Selenium only HR: 1.12 99% CI (0.73-1.72)</td>
<td>No significant effect.</td>
</tr>
<tr>
<td><strong>Case-control</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mahabir <em>et al.</em>, 2007</td>
<td>US</td>
<td>Case control</td>
<td>1676 lung cancer cases 1676 controls 902 male lung cancer cases 829 male</td>
<td>Mean cases 61.13, controls 60.96</td>
<td>Selenium from food (µg/day): Cases: 90.40 (32.01) Controls: 91.74 (34.24)</td>
<td>N/A</td>
<td>Top fourth vs. bottom fourth</td>
<td>0.86 (0.64-1.5) p trend= 0.14</td>
<td>No significant association</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Study Reference</td>
<td>Country</td>
<td>Study design</td>
<td>Population (no. &amp; characteristics)</td>
<td>Age (yrs)</td>
<td>Selenium intake- mean (SD)</td>
<td>Mean follow up (yrs)</td>
<td>Range</td>
<td>Adjusted relative risk (95% CI)</td>
<td>Comments</td>
</tr>
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</tr>
<tr>
<td>Mahabir et al., 2007 continued</td>
<td></td>
<td></td>
<td>controls</td>
<td>61.48, controls 61.97</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>774 female lung cancer cases 847 female controls</td>
<td>Mean female cases 60.72, controls 59.97</td>
<td>Selenium from food (µg/day):</td>
<td></td>
<td></td>
<td>0.87 (0.54-1.38) p trend= 0.35</td>
<td>No significant association</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cases: 79.44 (27.80) Controls: 81.35</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Table 14. Nested case-control studies of selenium status and lung cancer

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

*Please note that only studies published after 1996 are included in this statement*
Table 15. Case-control studies of selenium status and lung cancer

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Country</th>
<th>Age (yrs)</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>Sample</th>
<th>Selenium status measure &amp; mean concentration (SD/range)</th>
<th>Range</th>
<th>Adjusted relative risk (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gromadzinska et al., 2003</td>
<td>Poland</td>
<td>43-78</td>
<td>152 lung cancer</td>
<td>210</td>
<td>Plasma selenium (µg/l)</td>
<td>Cases: 48.4 (16.5) Controls: 53.7 (14.3)</td>
<td>Cases vs. controls for those with &gt;63.2 µg/l</td>
<td>0.72</td>
<td>p=0.010</td>
</tr>
<tr>
<td>Jablonska et al., 2008</td>
<td>Poland</td>
<td>30-78</td>
<td>325 lung cancer</td>
<td>276</td>
<td>Plasma selenium (µg/l)</td>
<td>Cases: 49.4 Controls: 53.3</td>
<td>Cases vs. controls</td>
<td>Plasma selenium 4-49 µg/l 1.90(1.30-2.77) p=0.001</td>
<td>Significant increased risk for selenium concentrations up to 49 µg/l</td>
</tr>
</tbody>
</table>

*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\(^a\)

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

\(^a\) 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>
<thead>
<tr>
<th>Study Reference</th>
<th>Country</th>
<th>Study design</th>
<th>Age (yrs)</th>
<th>Population (no. &amp; characteristics)</th>
<th>Sample</th>
<th>Mean concentration (SD/range)</th>
<th>Mean follow up (yrs)</th>
<th>Range</th>
<th>Adjusted relative risk (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cui et al., 2007</td>
<td>US</td>
<td>Nested case control</td>
<td>NR</td>
<td>252 cases, 252 controls</td>
<td>Breast tissue selenium level (ng/cm²)</td>
<td>Median Se levels cases 0.031 ng/cm², controls 0.027 ng/cm²</td>
<td>NR</td>
<td>Top fifth vs. bottom fifth</td>
<td>1.10 (0.72-1.68) p trend =0.76</td>
<td>No significant association.</td>
</tr>
<tr>
<td>Dorgan et al., 1998</td>
<td>US</td>
<td>Nested case control</td>
<td>40-75</td>
<td>105 cases with breast cancer 209 controls</td>
<td>Serum selenium (µg/l)</td>
<td>NR</td>
<td>9.5</td>
<td>Top fourth vs. bottom fourth</td>
<td>0.9 (0.4-1.8) p trend=0.99</td>
<td>No significant association.</td>
</tr>
</tbody>
</table>

*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

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

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 (β-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

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

*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

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

* Please note that only studies published after 1996 are included in this statement.
Table 21. Studies of estimated selenium intake and colorectal adenoma

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

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

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

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

*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

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Country</th>
<th>Age (yrs)</th>
<th>No. of cases</th>
<th>No of controls</th>
<th>Sample</th>
<th>Selenium status measure &amp; mean concentration (SD/range)</th>
<th>Range</th>
<th>Adjusted relative risk (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fernandez-Banares et al., 2002</td>
<td>Spain</td>
<td>Mean 60-61</td>
<td>28 subjects with large sporadic adenomatous polyps.</td>
<td>35</td>
<td>Serum (µg/l)</td>
<td>Cases -</td>
<td>&lt;60y 57.9 (4.3) &gt;60y 49.6 (5.5) Controls -</td>
<td>&lt;60y 88.9 (8.0) &gt;60y 44.7 (6.6)</td>
<td>Top fourth vs. all subjects below (≥82.11 vs. &lt;82.11)</td>
</tr>
</tbody>
</table>

*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.
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

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Country</th>
<th>Population (no. &amp; characteristics)</th>
<th>Age (yrs)</th>
<th>Selenium intake</th>
<th>Mean follow up (yrs)</th>
<th>Adjusted relative risk (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Lippman et al., 2009    | US      | 35,533 men with no prior prostate cancer  
1050 cases of cardiovascular 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   | 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.                                                                         |

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

CVD- cardiovascular disease
<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Country</th>
<th>Age (yrs)</th>
<th>Population (no. &amp; characteristics)</th>
<th>Sample</th>
<th>Mean concentration (SD/range)</th>
<th>Mean follow up (yrs)</th>
<th>Range</th>
<th>Adjusted relative risk (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Blankenberg <em>et al.</em>, 2003</td>
<td>Germany</td>
<td>Mean no CVD event-60.9 CVD event-67.0</td>
<td>636 subjects in cohort (patients with suspected coronary heart disease) 83 cardiovascular events</td>
<td>GPx red cell concentration (U/g haemoglobin)</td>
<td>49.2 (11.6)</td>
<td>4.7 (median)</td>
<td>Top fourth vs. bottom fourth</td>
<td>0.29 (0.14-0.60) p trend= 0.001</td>
<td>Significant inverse association.</td>
</tr>
<tr>
<td>Bleys <em>et al.</em>, 2008</td>
<td>US</td>
<td>20-90</td>
<td>13887 subjects in NHANES III cohort</td>
<td>Serum concentration (µg/l)</td>
<td>Mean 125.6</td>
<td>12</td>
<td>Top third vs. bottom third</td>
<td>Cardiovacular mortality 0.94 (0.77-1.16) CHD mortality 0.99 (0.67-1.47) Stroke mortality 1.23 (0.66-2.28)</td>
<td>No significant association.</td>
</tr>
<tr>
<td>Eaton <em>et al.</em>, 2010</td>
<td>US</td>
<td>35 plus</td>
<td>10531 subjects in NHANES III cohort (aged +35yrs) 1038 deaths from CHD</td>
<td>Serum concentration (µg/l)</td>
<td>Mean 124 (SD18.2; range 39-622)</td>
<td>13.4</td>
<td>Low selenium (&lt;98µg/l) vs. normal selenium (&gt;98µg/l)</td>
<td>HR 1.26 (0.94-1.69) HR: 2.06 (1.13-3.75) (subjects with low selenium and impaired renal function)</td>
<td>Significant inverse association.</td>
</tr>
<tr>
<td>Kilander et al., 2001</td>
<td>Sweden</td>
<td>50</td>
<td>2301 mean 301 CVD deaths</td>
<td>Serum selenium</td>
<td>NR</td>
<td>25.7</td>
<td>NR</td>
<td>0.97 (0.84-1.12)</td>
<td>No significant association</td>
</tr>
<tr>
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<td>----</td>
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<td>-----------------</td>
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</tr>
<tr>
<td>Lubos et al., 2010</td>
<td>Germany</td>
<td>Subjects with SAP – 61.3, 65.8 a Subjects with ACS – 60.8, 67.6 b</td>
<td>1724 subjects with) 190 deaths from cardiovascular causes</td>
<td>Serum selenium (µg/l)</td>
<td>Subjects with SAP: 74.8(±28.1), 73(±28.1) b Subjects with ACS: 71.5(±22.3), 61.0(±22.5) b</td>
<td>6.1</td>
<td>Top third vs. bottom third</td>
<td>HR: 0.38 (0.16-0.91) p trend = 0.03 Subjects with ACS</td>
<td>Significant inverse association in subjects with ACS with cardiovascular mortality.</td>
</tr>
<tr>
<td>Marniemi et al., 1998</td>
<td>Finland</td>
<td>≥65</td>
<td>344 elderly 142 deaths from CVD</td>
<td>Serum selenium (µg/l)</td>
<td>Alive: 82.2 (24) CVD death: 78.1 (23)</td>
<td>13</td>
<td>Top third vs. bottom third</td>
<td>1.08 (0.68-1.72)</td>
<td>No significant association</td>
</tr>
<tr>
<td>Wei et al., 2004</td>
<td>China</td>
<td>40-69</td>
<td>1103 subjects in cohort. 116 deaths from CHD 167 deaths from stroke</td>
<td>Plasma concentration (µg/l)</td>
<td>Mean: 73</td>
<td>15</td>
<td>Top fourth vs. bottom fourth</td>
<td>0.66 (0.41-1.08) p trend= 0.17 1.43 (0.89-2.30) p trend= 0.82</td>
<td>No significant association. No significant association.</td>
</tr>
<tr>
<td>Xun et al., 2010</td>
<td>US</td>
<td>18-30</td>
<td>3112 subjects</td>
<td>Toenail selenium (µg/l)</td>
<td>Fifths (median) 1- 0.69 2- 0.78 3- 0.84 4- 0.92 5- 1.04</td>
<td>18</td>
<td>Top fifth vs. bottom fifth</td>
<td>0.95 (0.67-1.35) (Odds ratio)</td>
<td>No significant association between toenail selenium and measures of subclinical atherosclerosis.</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Age Range</td>
<td>Cases</td>
<td>Controls</td>
<td>Variable</td>
<td>Grouping</td>
<td>Odds Ratio</td>
<td>95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>-------</td>
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<td>---------</td>
</tr>
<tr>
<td>Rajpathak <em>et al.</em>, 2005</td>
<td>US</td>
<td>26-79</td>
<td>202 cases diabetic men with CVD</td>
<td>361 controls</td>
<td>Toenail selenium (µg/g)</td>
<td>Geometric mean</td>
<td>Cases: 0.60</td>
<td>Controls: 0.71</td>
<td>~11</td>
</tr>
<tr>
<td>Yoshizawa <em>et al.</em>, 2003</td>
<td>US</td>
<td>40-75</td>
<td>470 cases with CHD</td>
<td>470 controls</td>
<td>Toenail concentration (µg/g)</td>
<td></td>
<td>Cases: 0.95</td>
<td>Controls: 0.93 (0.29)</td>
<td>5</td>
</tr>
</tbody>
</table>

* Please note that only studies published after 1996 are included in this statement

* Patients with cardiovascular mortality

### Table 26. Case control studies of selenium status and cardiovascular disease

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

*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>
<thead>
<tr>
<th>Study reference</th>
<th>Country</th>
<th>Population (no. &amp; characteristics)</th>
<th>Age (yrs)</th>
<th>Baseline selenium status- mean &amp; SD (plasma µg/l)</th>
<th>Selenium intake</th>
<th>Trial duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girodon et al., 1999</td>
<td>France</td>
<td>725 long term institutionalised elderly patients</td>
<td>&gt;65 yrs</td>
<td>Placebo: 56 (19.7) Interventions: 56 (14.2) and 47 (14.2)</td>
<td>1) 20mg zinc + 100µg selenium 2) 120mg ascorbic acid + 6mg β-carotene + 15mg α-tocopherol 3) both supplements from 1 + 2 4) Placebo</td>
<td>2 yrs</td>
<td>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.</td>
</tr>
<tr>
<td>Broome et al., 2004</td>
<td>UK</td>
<td>66 healthy free living adults with relatively low selenium concentrations</td>
<td>20-47</td>
<td>Plasma selenium (µg/l) Placebo: 79 (2.4) 50µg group : 78 (1.6) 100µg group : 82 (1.6)</td>
<td>50µg/d or 100µg/d of sodium selenite or a placebo</td>
<td>15 weeks</td>
<td>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.</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Participants</td>
<td>Age Range</td>
<td>Baseline Selenium</td>
<td>Intervention</td>
<td>Duration</td>
<td>Findings</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------</td>
<td>--------------</td>
<td>-----------</td>
<td>-------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>----------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Goldson et al., 2011</td>
<td>UK</td>
<td>119 healthy adults with sub-optimal selenium status (&lt;110 µg/l)</td>
<td>50-64</td>
<td>Plasma selenium at baseline 95.7 (± 11.5) µg/l</td>
<td>Daily placebo or selenium-enriched yeast tablets containing 50, 100, or 200 µg selenium, selenium-enriched onion meals, providing the equivalent of 50 µg Se/d, or unenriched onion meals</td>
<td>12 weeks</td>
<td>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</td>
</tr>
<tr>
<td>Hawkes et al., 2001</td>
<td>US</td>
<td>11 healthy males confined to metabolic unit</td>
<td>26-45</td>
<td>Low Se diet: 118 (7.9)</td>
<td>For 99 days either: Low selenium diet (13 µg/d) or high selenium diet (297 µg/d) dietary intake following 21 day run-in period</td>
<td>120 days</td>
<td>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.</td>
</tr>
</tbody>
</table>

*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-piece 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>
<thead>
<tr>
<th>Study reference</th>
<th>Country</th>
<th>Population (no. &amp; characteristics)</th>
<th>Age (yrs)</th>
<th>Baseline selenium status- mean &amp; SD (plasma µg/l)</th>
<th>Selenium intake</th>
<th>Mean follow up (yrs)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawkes <em>et al.</em>, 2009</td>
<td>US</td>
<td>54 healthy males</td>
<td>18-45</td>
<td>Blood plasma Selenium group : 1.80µmol/l Placebo: 1.85µmol/l</td>
<td>Either: 1) 300µg selenium 2) placebo</td>
<td>48 weeks treatment, 48 weeks follow up</td>
<td>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.</td>
</tr>
<tr>
<td>Safarinejad &amp; Sarfarinejad. 2009</td>
<td>Iran</td>
<td>468 infertile men with idiopathic oligo-asthenoteratospermia</td>
<td>25-48</td>
<td>Selenium group 77.7 (6.8) N-acetyl cysteine (NAC) group: 80.1 (6.6) Selenium &amp; NAC group: 78.2 (6.8) Placebo group: 81.7 (6.8)</td>
<td>Either: 1) 200µg selenium 2) 600mg N-acetyl cysteine (NAC) 3) 200µg selenium and 600mg NAC 4) placebo</td>
<td>26 weeks treatment, 30 weeks follow up</td>
<td>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.</td>
</tr>
<tr>
<td>Scott <em>et al.</em>, 1998</td>
<td>UK</td>
<td>64 men attending a subfertility clinic</td>
<td>Mean 33.3</td>
<td>81.4 (NR)</td>
<td>Either: 1)100µg/d selenium 2)100µg/d selenium, 1mg vit A, 10mg vit C, 15mg vit E 3) placebo</td>
<td>3 months treatment 2 weeks follow up</td>
<td>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).</td>
</tr>
</tbody>
</table>

*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>
<thead>
<tr>
<th>Study reference</th>
<th>Country</th>
<th>Population (no. &amp; characteristics)</th>
<th>Age (yrs)</th>
<th>Baseline selenium status- mean &amp; SD (serum µg/l)</th>
<th>Selenium intake</th>
<th>Mean follow up (yrs)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tara et al., 2010a &amp; b</td>
<td>Iran</td>
<td>166 Pregnant women up to 12 weeks gestation</td>
<td>16-35</td>
<td>Se group 122.5 (+/- 23.2) µg/l Control group 122.9 (+/- 26.9) µg/l</td>
<td>Se group 100µg supplement or placebo group.</td>
<td>First trimester until delivery</td>
<td>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&lt;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.</td>
</tr>
</tbody>
</table>
### Table 30. Cohort study of selenium status and preterm birth and pre-eclampsia\(^a\)

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

\(^a\)Please note that only studies published after 1996 are included in this statement

### Table 31. Case control studies of selenium status and pre-eclampsia\(^a\)

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Country</th>
<th>Age (yrs)</th>
<th>No. of cases</th>
<th>No of controls</th>
<th>Sample</th>
<th>Selenium status measure &amp; mean concentration (SD/range)</th>
<th>Range</th>
<th>Adjusted relative risk (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahomed et al., 2000</td>
<td>Zimbabwe</td>
<td>Mean 25</td>
<td>171</td>
<td>184</td>
<td>Leucocytes (µg/g total protein)</td>
<td>Cases: 3.23 Controls: 2.80 (≤1.89–≥ 4.01)</td>
<td>Top fourth vs. bottom fourth</td>
<td>3.38 (1.53-7.45)</td>
<td>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.</td>
</tr>
<tr>
<td>Rayman et al., 2003</td>
<td>UK</td>
<td>Mean 31</td>
<td>53</td>
<td>53</td>
<td>Toenail (µg/g)</td>
<td>Cases: 0.56 (0.51-0.64) Controls: 0.62 (0.57-0.69)</td>
<td>Top third vs. bottom third</td>
<td>4.4 (1.6-14.9) p=0.029.</td>
<td>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.</td>
</tr>
</tbody>
</table>

\(^a\)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 autoimmune 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 thyroditis with and without selenium supplementation (Toulis *et al.*, 2010), found that selenium significantly lowered auto-antibody levels at three months.

111. Postpartum thyroditis 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\textsuperscript{a}

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Country</th>
<th>Population (no. &amp; characteristics)</th>
<th>Age (yrs)</th>
<th>Selenium intake-mean (SD)</th>
<th>Follow up</th>
<th>Range</th>
<th>Adjusted relative risk (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawkes et al., 2008</td>
<td>USA</td>
<td>42 healthy men</td>
<td>18-45</td>
<td>Baseline plasma selenite yeast Supplements 300 µg/d as high sodium selenite yeast</td>
<td>48 weeks</td>
<td>NR</td>
<td>No significant change in T3, T4, thyroxine or thyrotropin</td>
<td></td>
</tr>
<tr>
<td>Rayman et al., 2008</td>
<td>UK</td>
<td>501 older adults</td>
<td>60-74</td>
<td>Baseline plasma Se 91.3µg/l Supplements 100, 200µg, 300µg selenium as high selenium yeast or placebo yeast.</td>
<td>6 months</td>
<td>NR</td>
<td>No significant effect on T3, T4, T3:T4 or THS</td>
<td></td>
</tr>
<tr>
<td>Thomson et al., 2005</td>
<td>New Zealand</td>
<td>72 smokers low selenium status</td>
<td>19-52</td>
<td>Baseline plasma Se 0.97µmol/l Supplements: 100µg/d selenium as selenomethionine tablet or placebo</td>
<td>20 weeks</td>
<td>NR</td>
<td>No significant effect on T4 or T3:T4 ratio</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>172 healthy adults</td>
<td>18-65</td>
<td>Baseline plasma Se 1.11µmol/l Supplements, placebo yeast or 200µg/d se-enriched yeast containing selenomethionine.</td>
<td>21 weeks</td>
<td>NR</td>
<td>No significant effect on T4 or T3:T4 ratio</td>
<td></td>
</tr>
<tr>
<td>Thomson et al., 2009</td>
<td>New Zealand</td>
<td>100 healthy older adults</td>
<td>60-80</td>
<td>Baseline plasma Se 1.20µmol/l</td>
<td>Supplements 100µg Se as selenomethionine, 100µg Se and 80µg iodine, 80µg iodine or placebo</td>
<td>12 weeks</td>
<td>NR</td>
<td>No significant effect on T3, T4, T3:T4 or THS</td>
</tr>
</tbody>
</table>

*Please note that only studies published after 1996 are included in this statement*
Table 33. Randomised controlled trials of selenium intake and thyroditis

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Country</th>
<th>Population (no. &amp; characteristics)</th>
<th>Age (yrs)</th>
<th>Selenium intake-mean (SD)</th>
<th>Follow up</th>
<th>Adjusted relative risk (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nacamulli et al., 2010</td>
<td>Italy</td>
<td>76 patients with Auto immune thyroditis</td>
<td>15-75 (mean 43)</td>
<td>Supplements 80 µg/d sodium selenite vs. placebo</td>
<td>12 months</td>
<td>NR</td>
<td>Se prevented reduction in thyroid echogenicity after 6 mo, reduced auto antibodies after 12 months but did not modify T$ or TSH.</td>
</tr>
<tr>
<td>Negro et al., 2007</td>
<td>Italy</td>
<td>232 pregnant women positive for thyroid peroxidase antibodies</td>
<td>18-36</td>
<td>200 µg/d selenomethionine, placebo or matched control group</td>
<td>12 wk gestation to term</td>
<td>NR</td>
<td>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.</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Country</th>
<th>Population (no. &amp; characteristics)</th>
<th>Age (yrs)</th>
<th>Baseline selenium status- mean &amp; SD (plasma µg/l)</th>
<th>Selenium intake</th>
<th>Trial duration (yrs)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rayman et al., 2006</td>
<td>UK</td>
<td>467</td>
<td>60-74</td>
<td>92 (20) µg/l</td>
<td>100, 200 or 300µg selenium via selenised yeast</td>
<td>Placebo: identical yeast supplement</td>
<td>2 years, analysis of mood was conducted after 6 months</td>
</tr>
</tbody>
</table>

*aPlease note that only studies published after 1996 are included in this statement

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

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

*aPlease 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.

ACKNOWLEDGEMENTS

The Committee would like to thank Prof. Margaret Rayman for her contribution to this statement.
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Department of Health, Eggs Analytical Project, 2012,

Department of Health, Fish Analytical Survey, 2012 (unpublished)


Food Standards Agency, Breakfast Cereals Analytical Survey, 2004

Food Standards Agency, Nutrient Analysis Catch Up Project, 2004


SACN Framework for the evaluation of evidence (2012)


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 | Red cell selenium | Blood GPx       |
|                 | µmol/L*         | µmol/L*         | (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.

<table>
<thead>
<tr>
<th></th>
<th>Plasma selenium (µmol/L)*</th>
<th>Red cell selenium (µmol/L)*</th>
<th>Blood GPx (nmol/mg Hb/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19-24 years</td>
<td>1.03 ± 0.150</td>
<td>1.42 ± 0.286</td>
<td>118.5 ± 24.20</td>
</tr>
<tr>
<td>25-34 years</td>
<td>1.10 ± 0.160</td>
<td>1.60 ± 0.328</td>
<td>119.5 ± 27.45</td>
</tr>
<tr>
<td>35-49 years</td>
<td>1.13 ± 0.182</td>
<td>1.64 ± 0.356</td>
<td>123.4 ± 31.06</td>
</tr>
<tr>
<td>50-64 years</td>
<td>1.15 ± 0.199</td>
<td>1.64 ± 0.422</td>
<td>124.1 ± 29.36</td>
</tr>
<tr>
<td>All men</td>
<td>1.11 ± 0.182</td>
<td>1.60 ± 0.369</td>
<td>121.9 ± 28.79</td>
</tr>
</tbody>
</table>

| **Women** |                           |                             |                           |
| Age    |                           |                             |                           |
| 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.

<table>
<thead>
<tr>
<th></th>
<th>Plasma selenium (µmol/L)*</th>
<th>Red cell selenium (µmol/L)*</th>
<th>Blood GPx (nmol/mg Hb/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Receiving benefits</td>
<td>1.05 ± 0.193</td>
<td>1.54 ± 0.347</td>
<td>119.8 ± 25.78</td>
</tr>
<tr>
<td>Not receiving benefits</td>
<td>1.12 ± 0.178</td>
<td>1.61 ± 0.372</td>
<td>122.3 ± 29.24</td>
</tr>
</tbody>
</table>

| **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.

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

*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.