Selenium and Health
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### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>AIDS</td>
<td>Acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>COMA</td>
<td>Committee on Medical Aspects of Food Policy</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>FSA</td>
<td>Food Standards Agency</td>
</tr>
<tr>
<td>GSH</td>
<td>Glutathione</td>
</tr>
<tr>
<td>GSHPx</td>
<td>Glutathione peroxidase enzyme</td>
</tr>
<tr>
<td>GSSG</td>
<td>Reduced glutathione</td>
</tr>
<tr>
<td>$\text{H}_2\text{O}_2$</td>
<td>Hydrogen peroxide</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>MAFF</td>
<td>Ministry of Agriculture, Fisheries and Food</td>
</tr>
<tr>
<td>NADP</td>
<td>Nicotinamide adenine dinucleotide</td>
</tr>
<tr>
<td>NADPH</td>
<td>Oxidised form of nicotinamide adenine dinucleotide</td>
</tr>
<tr>
<td>RNI</td>
<td>Reference nutrient intake</td>
</tr>
<tr>
<td>SIDS</td>
<td>Sudden infant death syndrome</td>
</tr>
<tr>
<td>SPS2</td>
<td>Selenoprotein synthetase</td>
</tr>
<tr>
<td>T3</td>
<td>Triiodothyronine</td>
</tr>
<tr>
<td>T4</td>
<td>Thyroxine</td>
</tr>
<tr>
<td>TR1, TR2, TR3</td>
<td>Thioredoxin reductase enzymes</td>
</tr>
<tr>
<td>LRNI</td>
<td>Lower reference nutrient intake</td>
</tr>
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</table>
Selenium and Health

SUMMARY

Selenium is an essential trace element, which is present in most foods, with brazil nuts, fish and offal containing the highest amounts. The selenium concentration of plants is determined by the content and availability of the element in the soil in which they are grown. The selenium content of plant foods, therefore, varies from country to country, being generally low in UK and Europe. There are also regional variations. The amount of selenium in animal foods reflects the feeding patterns of livestock.

The UK reference nutrient intake (RNI) for selenium is 75 and 60 μg/day for adult males and females respectively. Selenium intake in the UK has fallen over the last 25 years, largely due to the reduction in the import of high selenium wheat from North America. The most recent Total Diet Study, carried out by the Ministry of Agriculture, Fisheries and Food in 1997, estimated current intake to be 39 μg/day (MAFF 1999). Whilst the estimated intake from this study cannot be compared directly with reference nutrient intakes, concern has been expressed about this level being at the lower end of the recommended reference range for adults. There is also some evidence to support a corresponding fall in blood selenium levels.

At high doses, selenium has been shown to be toxic and a maximum safe intake of 450 μg/day has been proposed. The use of selenium supplements has become increasingly popular in the UK and could confer a risk of selenium toxicity at high doses.

Selenium is present in foods mainly as the amino acids selenomethionine and selenocysteine. Around 80% of dietary selenium is usually absorbed but the amount is affected by the chemical form in the diet and a range of other factors including intake of protein and the presence of any appreciable levels of toxic elements in the diet, such as mercury and arsenic. The major route of excretion is via the urine and under normal physiological conditions this constitutes the prime method of body selenium regulation.

Selenium, in the form of selenocysteine, is incorporated into a range of enzymes (selenoproteins) in the body, which are crucial to human health. The best known of these is glutathione peroxidase, which plays an important role in protecting cell membranes from damage by free radicals. There is now considerable evidence that selenium plays a key role in the functioning of the immune system and in thyroid hormone metabolism, and that the trace element is needed for successful reproduction.

Selenium can be measured in a variety of media including plasma or serum, whole blood, red cells, platelets, hair and nails. Of the blood components, red cells probably provide the more accurate assessment of long-term intake. Toenail clippings are easy to collect and have been used in large epidemiological studies. Status can also be assessed by estimating the activity of the selenium-containing enzymes, such as glutathione peroxidase.

Selenium deficiency occurs in cattle and sheep grazing on low selenium soils in the UK unless supplementation is provided. Deficiency signs for selenium in animals include vascular changes, poor growth and reproductive failure. There are two major human selenium deficiency-related conditions – Keshan disease (an endemic cardiomyopathy) and Kashin-Beck disease (a deforming arthritis). These diseases have occurred in areas of selenium-deficient soils in central and western China and neighbouring regions.

Links between less overt deficiency and many other disorders have been suggested. Epidemiological evidence to examine the role of selenium in cancer risk is accumulating. A recent trial in the US showed a substantial reduction in cancer mortality in those taking selenium supplements and large trials are now underway to assess the validity of these findings. Some studies have also shown an association between low blood selenium levels and heart disease risk, although this has not been confirmed by others. The finding that blood levels of selenium influence the outcome in HIV infection has also raised interest in the role of selenium in the progression of this disease. Selenium supplementation has been advocated for many other conditions in humans, including Down's syndrome, cystic fibrosis, muscular dystrophy, sudden infant death syndrome, multiple sclerosis and defective immunoresponses. However, any link with these conditions is likely to be an outcome of the disease process.

The recognition of the importance of selenium in health has led to considerable concern about the falling intake in the UK. Some countries that have experienced a similar decline in selenium intake
have instituted special measures. For example in Finland an agricultural fertilisation programme has been implemented in order to raise cereal selenium concentrations and boost dietary intakes. Since this programme was implemented in 1985, the selenium intake in Finland has more than tripled and the prevalence of coronary heart disease and some forms of cancer has fallen. The contribution of increased selenium intake to this decline, however, is unclear since several other aspects of the diet have improved simultaneously.

The adoption of fertilisation or fortification programmes has been advocated in the UK. A review by the Committee on Medical Aspects of Food and Nutrition Policy (COMA) in 1998 concluded that there was insufficient evidence of adverse health consequences from selenium intakes to warrant action at that time, but recognised the need to continue to monitor intake and status.

In order to establish whether or not current average intakes are acceptable and to define intakes that are consistent with good health, selenium is one of the nutrients that has been studied within MAFF’s Optimal Nutrition Status programme of research (responsibility for this programme was transferred to the Food Standards Agency on 1st April 2000). Other identified objectives of this programme included the development of accurate measures of bioavailability from foods and the identification of functional markers of selenium status. This Briefing Paper summarises current nutritional knowledge on selenium and places in context the work on selenium conducted within MAFF’s research program.
1 BACKGROUND

In April 1999, the British Nutrition Foundation was awarded a nine month contract by the Ministry of Agriculture, Fisheries and Food (MAFF) to produce a critical review of the research being conducted within MAFF's Optimal Nutrition Status programme, to place this research within the context of other relevant work being conducted nationally and internationally, to produce a list of future research recommendations to aid policy makers and advisors and, not least, to disseminate the findings to a wide audience. Management and funding responsibility for the Optimal Nutrition Status research programme was transferred to the Food Standards Agency (FSA) when it was established on 1st April 2000. Nutrients studied in the review originally commissioned by MAFF included calcium, iron, selenium, vitamins C, D, E, K and folate. Using the information derived from the part of the review covering selenium, this Briefing Paper provides a detailed and up-to-date summary of the role of selenium in health, and has been written to aid the dissemination process. A description of ongoing FSA (previously MAFF) funded projects in this area and an outline of the future research priorities recommended by the British Nutrition Foundation on completion of its review of the Optimal Nutrition Status research programme can be found in the Appendix.

2 INTRODUCTION

Recent international research has revealed exciting new aspects of the essential trace element selenium, both in terms of its metabolic roles and of its relevance to human health. Selenium plays an important role in several functions, including the control of thyroid hormone metabolism, reproduction and the removal of peroxides by glutathione peroxidase enzymes. Some epidemiological evidence has suggested a link between selenium deficiency and diseases as diverse as cancer, heart disease, arthritis and AIDS. Evidence that dietary intake is falling in some parts of the world, including the UK, therefore, merits careful examination.

This Briefing Paper provides detailed information on the sources of selenium in the UK diet. This is followed by a description of the recent trends in selenium intake in the UK, in the context of existing recommendations for minimum and maximum intake. Current knowledge about the metabolic regulation and function of selenium in the body is outlined, together with the methods available for the assessment of selenium status. Finally, symptoms of selenium deficiency are described and the evidence for links between less overt deficiency and diseases such as cancer and heart disease reviewed.

3 SOURCES OF SELENIUM

3.1 Origins of selenium in food and water

Selenium is ubiquitous, occurring in all soils, and is taken up and accumulated by plants, even though it is not generally required for their growth (Reilly 1996a). Overall, selenium occurs at a concentration of about 50-200 μg/kg in rocks and soil but its geographical distribution is uneven and, depending on geological and other factors, it can be present in greater or lesser amounts. Highly siliceous rocks, such as granite, produce low selenium soils, while coals and shales provide higher levels. Acid soils promote binding to clay particles and iron complexes, thus reducing the uptake of selenium by plants, as in many parts of Europe (Reilly 1996a). Percolating ground and surface waters can also have an effect on soil selenium concentrations. Heavy rainfall can cause leaching of the soluble form of selenium from the soil. Selenium is particularly concentrated and available from the alkaline soils of some dry regions such as Wyoming and South Dakota, USA, while selenium deficient areas include wetter regions such as the South Island of New Zealand and the island of Tasmania off Australia. Selenium-containing fertilisers are used in several countries, such as Finland, to raise levels in deficient soils.

Food, by far, constitutes the principal route of exposure to selenium for the general population. Selenium is efficiently transferred up the soil-plant-animal-human food chain, so geographical differences in the availability of the selenium in soil for uptake by plants result in substantial variation in the selenium content of foods (Combs 2001). In Britain, animal feeds have been supplemented with selenium at nutritional levels since 1978, a practice that has virtually eliminated financial losses due to selenium deficiency diseases in farm animals. Drinking water generally contributes negligible amounts of selenium, except perhaps in some localised highly seleniferous areas (National Research Council 1980). Air contributes little except in regions of excessive pollution as a consequence of industrial emission of selenium into the environment.
3.2 The selenium content of common foods in the UK

The publication *Composition of Foods* (Holland et al. 1991) and subsequent supplements, compiled by MAFF, provide information on the average selenium content of foods in Britain. As part of MAFF's rolling programme of nutrient analyses (recently transferred to the Food Standards Agency), the concentrations of selenium in various foods are periodically analysed and revised. Recent analyses of selenium levels in foods include marine and shellfish (MAFF 1998) and breads (MAFF 2000a). In 1995, Barclay and colleagues carried out a study on behalf of MAFF to update and extend the availability of analytical values for selenium to include a wide range of foods (Barclay et al. 1995). This was the first comprehensive study of the selenium content of UK foods since that of Thorn et al. in 1978 (Thorn et al. 1978). It covered the whole of mainland UK and included 100 different types of food, representing a wide range of products. Regional data were collected for a variety of foods including bread, cereals, dairy products, shellfish, offal, brazil nuts and tea. Table 1 provides the most up-to-date information available on the selenium composition of selected UK foods.

### Table 1: THE SELENIUM CONTENT OF SELECTED FOODS

<table>
<thead>
<tr>
<th>Food group</th>
<th>Food item</th>
<th>Average selenium content (µg/100g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuts*</td>
<td>Brazil</td>
<td>254</td>
</tr>
<tr>
<td></td>
<td>Cashew</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Cockles</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Cod</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Cod fish fingers</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Crab</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>Haddock</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Herring</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Lobster</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>Mackerel</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Mussels</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Plaice</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Red fish</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>Scallops</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Shrimps (brown)</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Shrimps (pink)</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>Squid</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Whiting</td>
<td>24</td>
</tr>
<tr>
<td>Offal*</td>
<td>Kidney (pork, lamb, ox)</td>
<td>145</td>
</tr>
<tr>
<td></td>
<td>Liver (pork, lamb, ox)</td>
<td>42</td>
</tr>
<tr>
<td>Meat*</td>
<td>Beef</td>
<td>7.8</td>
</tr>
<tr>
<td></td>
<td>Pork</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Lamb</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>Turkey (white meat)</td>
<td>10</td>
</tr>
<tr>
<td>Bread*</td>
<td>White</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Wholemeal</td>
<td>0.9</td>
</tr>
<tr>
<td>Flour*</td>
<td>White</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>Brown</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>Strong</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>Wholemeal</td>
<td>5.9</td>
</tr>
<tr>
<td>Rice*</td>
<td>Brown</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>1.3</td>
</tr>
<tr>
<td>Cereals*</td>
<td>Cornflakes</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>Muesli</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>Bran based</td>
<td>3.6</td>
</tr>
<tr>
<td>Cheese*</td>
<td>Cheddar</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td>Parmesan</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Stilton</td>
<td>8</td>
</tr>
<tr>
<td>Vegetables*</td>
<td>Mung beans</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Soya beans</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Mushrooms</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Celery</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Garlic</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Parsnip</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Carrots</td>
<td>1</td>
</tr>
<tr>
<td>Fruit*</td>
<td>Raisins</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td>Apricots (ready-to-eat)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Peaches</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Bananas</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Oranges</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Chicken eggs</td>
<td>11</td>
</tr>
<tr>
<td>Eggs*</td>
<td>Whole</td>
<td>1.5</td>
</tr>
<tr>
<td>Milk*</td>
<td>Skimmed</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Foods analysed in raw state
*Estimated values

Selenium appears to occur in a number of foodstuffs. Brazil nuts, on average, are the richest natural source of selenium, with levels of up to 5300 μg/100g reported in brazil nuts sold in the UK (Thorn et al. 1978). However, the content is highly variable (Reilly 1999, Barclay et al. 1995, Thorn et al. 1978), depending on how effectively the tree from which the nuts are harvested takes up the element from the soil in which it grows. This is determined by the maturity of the root system and the tree variety (Reilly 1999). In general, fish represent the next most concentrated food source of the mineral. The most recent MAFF analyses found selenium concentrations of 57 μg/100g in shellfish and 29 μg/100g in other fish, with crab containing the most selenium (130 μg/100g) (MAFF 1998). Cod fingers contained slightly lower concentrations (11 μg/100g) than unprocessed fish samples (26μg/100g) (MAFF 1998). Egg yolks and meat, particularly organ meats, are also a potentially good source but the selenium content of food products of animal origin depends heavily on soil and fodder levels, in addition to the intake of supplements added to feed (levels of which vary between countries). Certain grains and cereal products contribute significantly to the dietary intake of selenium but, again, variations in selenium content are possible in different samples of the same foodstuffs. Rice has the highest selenium content of the cereal grains, with levels being greatest in long grain varieties. The selenium levels in bread in the UK have dropped considerably since the 1980s (MAFF 2000a, Barclay et al. 1995) and recent analyses have found levels in white and wholemeal bread to be 6 and 9 mg/100g respectively (MAFF 2000a). In the US, levels in bread are higher, being 32 μg/100g in white bread and 44 μg/100g in wholemeal bread (Agency for Toxic Substances and Disease Registry 1996). In general, fruits and vegetables provide very little selenium. In summary, selenium is most concentrated in high protein foods but the content is greatly influenced by growth conditions. Selenium is also present in a variety of dietary supplement products.

In general, food tables cannot be used to provide an accurate assessment of selenium intake because there may be variation of up to 100-fold in the selenium content of a particular foodstuff, depending on the soil in which the plant was grown or the diet of livestock (Barclay & MacPherson 1992, Barclay et al. 1995; Molnar et al. 1995). The Total Diet Study, an annual government surveillance programme previously carried out by MAFF but now conducted by the Food Standards Agency, includes a regular assessment of the levels of a range of trace elements, including selenium, in a variety of foods and drinks. The contribution of each food group to average dietary selenium intake can then be assessed very crudely using population average consumption data from the National Food Survey (Table 2).

<table>
<thead>
<tr>
<th></th>
<th>Selenium content (μg/100g fresh weight)</th>
<th>Consumption (g/day)</th>
<th>Estimated contribution to total selenium intake (μg/day) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bread/cereals</td>
<td>Bread</td>
<td>4.4</td>
<td>108</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous cereals</td>
<td>3.9</td>
<td>101</td>
</tr>
<tr>
<td>Meat</td>
<td>Carcass meat</td>
<td>11.5</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Offal</td>
<td>49.2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Meat products</td>
<td>13.0</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Poultry</td>
<td>18.5</td>
<td>19</td>
</tr>
<tr>
<td>Fish</td>
<td>Fish</td>
<td>36.0</td>
<td>14</td>
</tr>
<tr>
<td>Fats</td>
<td>Oils &amp; fats</td>
<td>0.3</td>
<td>27</td>
</tr>
<tr>
<td>Dairy products/eggs</td>
<td>Milk</td>
<td>1.4</td>
<td>281</td>
</tr>
<tr>
<td></td>
<td>Dairy produce</td>
<td>3.2</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Eggs</td>
<td>19.4</td>
<td>14</td>
</tr>
<tr>
<td>Vegetables</td>
<td>Green vegetables</td>
<td>0.8</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Other vegetables</td>
<td>2.2</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>Canned vegetables</td>
<td>1.4</td>
<td>33</td>
</tr>
<tr>
<td>Fruit</td>
<td>Fresh fruit</td>
<td>0.1</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Fruit products</td>
<td>0.07</td>
<td>44</td>
</tr>
<tr>
<td>Other</td>
<td>Nuts</td>
<td>25.1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Beverages</td>
<td>0.04</td>
<td>937</td>
</tr>
<tr>
<td></td>
<td>Sugars and preserves</td>
<td>0.9</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Potatoes</td>
<td>0.3</td>
<td>123</td>
</tr>
<tr>
<td>TOTAL</td>
<td>Estimated total intake</td>
<td>191.7</td>
<td>2075</td>
</tr>
</tbody>
</table>

Source: MAFF 1999
In the UK diet, bread, cereals, fish, poultry and meat are the main contributors to selenium intake (MAFF 1999). In 1997, 22% of selenium intake was derived from bread and cereal products, 45% from meat and fish, and 22% from eggs and dairy products (Figure 1).

**Figure 1: ESTIMATED INTAKE OF SELENIUM FROM DIFFERENT FOOD GROUPS IN THE UK IN 1997**

![Pie chart showing the percentage of selenium intake from different food groups](chart.png)

- **Dairy Products/eggs (22%)**
- **Other foods (5%)**
- **Bread/cereals (22%)**
- **Fish (13%)**
- **Meat/meat products (32%)**

*Source: MAFF 1999*

### 3.3 Effect of food processing on the selenium content of foods

Very little work has been done to identify the effect of cooking and general preparation on the selenium content of foods. Milling has been shown to reduce the amount of selenium in cereal products (Yang et al. 1989); wholemeal bread has a higher selenium content than white bread (MAFF 2000a). However, losses during milling do not appear to be excessive as selenium is thought to be evenly distributed throughout the wheat kernel (Ferretti & Levander 1974). Studies investigating the effect of cooking and processing have not always demonstrated losses (Dudek et al. 1989) and the amount lost appears to vary according to both the type of food and the process used. In general, the harsher the cooking conditions the greater the selenium loss (Reilly 1996a). Most studies have, however, suggested that the loss of selenium during usual cooking procedures is likely to be negligible for most foods (World Health Organisation 1987).

### 3.4 The selenium content of cows’ milk and infant formula

Since breast milk or infant formula is usually the only source of food for infants during the first months, it is essential that it contains all necessary nutrients in adequate amounts. This is particularly important for nutrients, such as selenium, for which body stores are not extensive and sufficient quantities must be supplied regularly to maintain optimal growth and development.

In contrast to breast milk, in which there is usually similarity in selenium content between different regions, the selenium content of cows’ milk shows marked geographical variations and depends on environmental levels. Even within countries there can be considerable variations in the concentrations of selenium in milk samples from different districts and even between farms in the same district (Reilly 1996a).

The precise amount of selenium that should be present in milk formulas is unclear and recommendations for intakes amongst non-breast fed babies have been based on estimates. There is evidence that selenium is less well absorbed from infant formulas than from human milk and that intakes amongst formula-fed infants are generally low. Levander (1989), amongst others, has suggested that the selenium content of infant formulas should be raised to 10-45 μg/day. This has been interpreted by some as a suggestion that infant formulas need to be supplemented with selenium (Lombeck et al. 1975). However, alternative approaches have been advocated, including the use of ingredients naturally rich in selenium to prepare the formulas or the use of manufacturing procedures that reduce losses of the element during processing (Reilly 1996a).

### 3.5 Conclusions

- For the general population, the primary pathway of exposure to selenium is food.
- Levels of selenium in plants vary considerably with soil nature and content. The selenium content of foods can, therefore, vary by region and by country, depending upon the local geochemical environment. In the UK, most plant foods will be sourced by retailers from a variety of
national and international locations, making estimation of dietary intake extremely difficult.

- Rich dietary sources of selenium include brazil nuts, fish and offal. In the UK diet, breads, cereals, fish, poultry and meat are the main contributors to selenium intake.
- More research on the effects of food processing on the selenium content of foods is required, but most studies have suggested losses to be minimal.
- Variations in levels of selenium in breast milk are not as great as those found in cows’ milk. The precise amount of selenium that should be present in infant formulas remains unclear.

4 DIETARY REQUIREMENTS AND RECOMMENDED INTAKES

4.1 Existing recommendations for minimum intake

The Department of Health Committee on Medical Aspects of Food Policy (COMA) (Department of Health 1991) has set reference nutrient intakes (RNI) for selenium of 75 µg/day and 60 µg/day for men and women respectively. The RNI is defined as the amount of the nutrient that will meet the requirements of almost all individuals and is, therefore, higher than most people need. It is based on an intake where blood selenium levels are above the concentration (100 ng/ml) at which the activity of glutathione peroxidase, a selenium-dependent enzyme located within the red blood cells, reaches a plateau (Casey 1988). The UK lower reference nutrient intake (LRNI), which is the amount sufficient only for those with low needs (the bottom 2.5% of the distribution of requirements), is set at 40 µg/day for adults and is based on observations from studies in China. The recommendations for all age groups are listed in Table 3. In addition, it is thought that an extra 15 µg/day is needed during lactation, which is based on the level of selenium in human milk of around 10-20 ng/ml (Thorn et al. 1978).

The World Health Organisation has recently released data on trace element requirements, and recommends selenium intakes of 40 µg/day and 30 µg/day for males and females respectively (Levander 1997). The current US recommended dietary allowance (RDA) for selenium is 55 µg/day for both men and women (National Academy of Sciences Food and Nutrition Board 2000), about 10% lower than the UK RNI.

The UK recommendations for selenium intakes amongst children are shown in Table 3. These are slightly below the so-called adequate intakes and recommended daily amounts recently published in the US (National Academy of Sciences Food and Nutrition Board 2000).

There is debate about whether recommended dietary intakes should apply only to the prevention of deficiency diseases (with an allowance to take variations between individuals into account) or generally to the promotion of growth, maintenance of good health and the reduction of risk of other diseases. In this context, some have argued that the dietary selenium recommendation should be increased to reflect possible beneficial effects for chronic diseases such as cancer and heart disease (Levander & Whanger 1996). However, at present the role of selenium in protecting against such conditions remains uncertain (see Section 10).

<table>
<thead>
<tr>
<th>Age</th>
<th>Lower reference nutrient intake (µg/day)</th>
<th>Reference nutrient intake (µg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3 months</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>4-6 months</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>7-9 months</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>10-12 months</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 years</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>4-5 years</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>7-10 years</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td>11-14 years</td>
<td>25</td>
<td>45</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-18 years</td>
<td>40</td>
<td>70</td>
</tr>
<tr>
<td>19-50 years</td>
<td>40</td>
<td>75</td>
</tr>
<tr>
<td>50+ years</td>
<td>40</td>
<td>75</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-18 years</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>19-50 years</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>50+ years</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>No increment</td>
<td>No increment</td>
</tr>
<tr>
<td>Lactation</td>
<td>+15</td>
<td>+15</td>
</tr>
</tbody>
</table>

Source: Department of Health 1991

4.2 Existing recommendations for maximum intake

High doses (1 mg or more daily) of selenium are toxic. The toxicity of different selenium compounds varies. Selenite, selenate and selenomethionine are among the most toxic selenium compounds, while selenium sulphide is much less toxic as a result of its insolubility (see Section 6 for further information about different forms). In animals, acute toxicity is characterised by central nervous system toxicity, growth failure and degenerative changes in the liver. Symptoms of chronic selenium toxicity (selenosis) in humans include vomiting, diarrhoea, hair and nail loss and lesions of the skin and nervous system.
In the UK, the recommended maximum safe selenium intake from all sources is 450 μg/day in adult males (6 μg/kg/day). This is based on evidence of disturbed selenium homeostasis at intakes above 750 μg/day (Department of Health, 1991). The Nordic Project Group (1995) considered an intake of 4-5 μg/kg of selenium to be safe and tolerable. For a 70 kg man this would be equivalent to an intake of 280-350 μg/day. The World Health Organisation (1996) recommends an upper safe limit of 400 mg/day. The US National Academy of Sciences’ recent review of selenium requirements set a threshold (known as an upper level of tolerable intake) at 400 μg/day (National Academy of Sciences Food and Nutrition Board 2000).

Selenium supplements have become increasingly popular in the UK, predominantly as a consequence of claims of a protective effect against some forms of cancer. The use of high dose supplements, however, confers a risk of selenium overdose. The maximum daily dose recommended by the Council of Responsible Nutrition (a Trade Association for the UK supplements industry) is 200 μg of selenium per day for long-term supplement intake and 700 μg per day for short-term supplementation (these levels correspond to approximately 3 and 10 fold excesses over the RNI). A ceiling of 200 μg per day has also been recommended as the maximum upper safe level by the European Federation of Health Food Manufacturers (Shrimpton 1997) and by Consumers for Health Choice (1998). A recent large scale human intervention trial in the US found no dermatological changes or other signs of selenium toxicity with long-term supplementation (up to 10 years) at this dosage (Olark et al. 1996).

Recently, an Expert Group on Vitamins and Minerals has been established, which is now under the auspices of the Food Standards Agency, to consider the safety of vitamins and minerals, including selenium, in food supplements. In their recent review of selenium (Expert Group on Vitamins and Minerals 1999) they drew attention to a previous report entitled Dietary Supplements and Health Foods – Report of the Working Group (MAFF 1991), which proposed that supplements should only contain one-tenth of the identified daily undesirable dose. For selenium adverse effects were observed at intakes of 1000 μg per day, suggesting a maximum level for selenium supplements of 100 μg per day. The final recommendations of this Expert Group are expected to be published shortly.

4.3 Conclusions

- In the UK the reference nutrient intakes for selenium are 75 μg/day for men and 60 μg/day for women
- At high doses, selenium is toxic and a maximum safe intake of 450 μg/day has been recommended in the UK. The use of high dose supplements should, therefore, be avoided.

5 SELENIUM INTAKE IN THE UK

A recent review by Combs (2001) demonstrated wide variation in global selenium intakes and status and suggested that consumption in several countries may be inadequate to support maximal expression of selenoproteins (see Section 7).

5.1 Current intake

The variation in the selenium content of food products (Barclay & MacPherson 1992, Barclay et al. 1995, Molnar 1995) creates problems for the assessment of selenium intake. Food composition tables are likely to substantially over- or underestimate the true selenium content of some foods (Barclay et al. 1995) and cannot be used to obtain an accurate conversion of food consumption into nutrient intake for an individual (Judd et al. 1997). In the UK, MAFF monitors the average selenium intake of the population by analysing levels in samples of food collected during the Total Diet Study and estimating consumption of various foods using data from the annual National Food Survey. Data from the Dietary and Nutritional Survey of British Adults has also been used to assess the mean intake and distribution of intakes in the adult population (Gregory & Lowe 1996).

The 1997 Total Diet Study estimated the average selenium intake in the UK population to be 39 μg/day (Table 2), which is at the lower end of the reference range for adults recommended by COMA (the LRNI is 40 μg/day, see Section 4.1). For comparison, the average intake of selenium from food in the US has been estimated to be 71 to 152 μg/day (Expert Group on Vitamins and Minerals 1999). Scientists have suggested that, as the average intake in Britain falls well below the recommended intake (RNI) and is close to the LRNI, this implies that current intakes are inadequate for most of the UK population. It should, however, be noted that intakes estimated from the Total Diet Study are based on food consumption data from the National Food Survey of households which include children (who have lower requirements) as well as adults. Direct comparisons with the RNI or LRNI for specific age groups are not, therefore, possible. Using the 1997 Total Diet Study the mean and upper intakes (97.5 percentile) amongst adult consumers have been estimated to be 54 μg/day and 1000 μg/day respectively.

There is little information on the selenium intake of specific population groups. Data from the National Diet and Nutrition Survey of people aged 65 years and over (Finch et al. 1998) found a high proportion with daily selenium intakes below recommended levels (95%<RNI, 52%<LRNI) (Thane & Bates
2000), raising concern that status may be sub-optimal amongst the elderly in the UK. Average selenium intakes were 47 and 37 µg/day for men and women respectively (the respective RNIs are 75 and 60 µg/day). Further analysis of this data set revealed significant differences according to a number of socio-economic factors; selenium intake was lower in those of manual social class or with no educational qualifications, and male smokers tended to have lower intakes than non-smokers.

The intake of vegetarians is of particular concern because animal foods, such as fish and meat products, usually make substantial contributions to the average dietary selenium intake of the general population. A recent duplicate study found the mean dietary intake of vegetarians to be 28 µg/day, which is lower than that in the general population (MAFF 2000b). Whilst vegetarians have been shown to have lower concentrations of toenail selenium than omnivores (Judd et al. 1997), the National Diet and Nutrition Survey of young people aged 4-18 years (Gregory et al. 2000) actually found higher selenium status amongst those who adopted a vegetarian diet.

In terms of geographical differences within the UK, Barclay et al. (1995) found the lowest selenium intakes to be in the North of England, with the highest levels in the North West (Table 4) (Barclay et al. 1995). Northern Ireland has been described as a low selenium area, and lower selenium status has been reported compared with elsewhere in the UK (McMaster et al. 1991). Recent findings from a MAFF funded project demonstrated a low average selenium intake of 43 µg/day (although energy intakes suggested a high proportion of under-reporters) and sub-optimal functional selenium status in an area of Scotland (Shortt et al. 1997) (see Section 13.1, project AN0512).

### Table 4: REGIONAL SELENIUM INTAKES

<table>
<thead>
<tr>
<th>Estimated intake (µg/person/day)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>34.4</td>
</tr>
<tr>
<td>South East/East Anglia</td>
<td>39.6</td>
</tr>
<tr>
<td>South West</td>
<td>30.7</td>
</tr>
<tr>
<td>East Midlands</td>
<td>32.1</td>
</tr>
<tr>
<td>West Midlands</td>
<td>31.4</td>
</tr>
<tr>
<td>Yorkshire/Humberside</td>
<td>35.5</td>
</tr>
<tr>
<td>North West</td>
<td>40.7</td>
</tr>
<tr>
<td>North of England</td>
<td>39.2</td>
</tr>
<tr>
<td>Scotland</td>
<td>32.2</td>
</tr>
<tr>
<td>Wales</td>
<td>32.3</td>
</tr>
</tbody>
</table>

*Calculated using compositional data from Barclay et al. (1995) and weight of food eaten from the Total Diet Study*

*Source: Barclay et al. 1995*

### 5.2 Trends in intake and status

#### 5.2.1 Intake

There appears to have been a substantial drop in selenium intake in the UK in recent years. Thorn et al. reported an average intake in Britain in 1976 of 60 µg/day (Thorn et al. 1978), a level which approaches the current RNI of 75 µg/day for men and 60 µg/day for women. In contrast, in 1993/4 Barclay and colleagues (Barclay et al. 1995) estimated the national average intake to be 34 µg/day, using their own analytical data for the selenium content of UK foods in conjunction with National Food Survey estimates of the quantities consumed. Estimates from the Total Diet Study have not provided sufficient evidence to support a trend in declining selenium intakes in recent years but data for two additional time points have suggested that selenium intake is around 35% lower than the levels estimated from the 1991 and 1985 Total Diet Studies (Table 5). Changes in the organisation of the Total Diet Study from 1981 onwards means that previous estimates of exposure are not directly comparable.

#### Table 5: ESTIMATED POPULATION SELENIUM INTAKE (µg/d)

<table>
<thead>
<tr>
<th>Year</th>
<th>Population*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1974</td>
<td>60</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>range 29-39**</td>
</tr>
<tr>
<td>1997</td>
<td>39</td>
</tr>
</tbody>
</table>

*Calculated from estimated mean concentration of selenium from the Total Diet Study and average consumption of each food group from the National Food Survey*

**Estimate from 1995 Total Diet Study not directly comparable as based on analyses of composite samples of each food from all the towns rather than individual samples of each food group from each town

*Source: MAFF, 1999*

#### 5.2.2 Status

Information on blood selenium levels of various population groups in the UK is limited. However, studies have suggested that falling intakes have been reflected in diminishing serum and whole blood selenium concentrations. Longitudinal studies have demonstrated substantial reductions in selenium status over the last 20 years (Rayman 1997) and low levels have been reported in some groups in the UK (Rayman 1997, Scott et al. 1998, Shortt et al. 1997). The latter reference applies to a MAFF funded study (see Section 13.1, project AN0512).
The Department of Health (COMA 1998) has recognised the lack of information on the selenium status in specific population and age groups in the UK. As a consequence, they have commissioned further analyses from blood samples collected from previous National Diet and Nutrition Surveys and will include measurements of selenium status (such as red cell selenium, plasma selenium and glutathione peroxidase) in future surveys in order to inform government recommendations in the future. Measurements of blood parameters (plasma selenium and GSH-Px) were provided in the recently published National Diet and Nutrition Survey of young people aged 4-18 years (Gregory et al. 2000). Plasma levels did not show any evidence of frank selenium deficiency in this age group.

5.3 Conclusions

- The population average intake of selenium in the UK has recently been estimated to be 39 µg/day.
- While this estimated population intake cannot be compared directly with recommended intakes for different age and sex groups, this figure is well below the UK RNI of 75 µg/day and 80 µg/day for adult men and women respectively.
- Average intake has fallen substantially since the beginning of the 1990s and this is largely due to a reduction in the import of high selenium wheat from North America. There is some evidence to suggest a parallel reduction in blood selenium status.
- Information on selenium intake and status in specific population and age groups in the UK is limited.
- Concern about the health implications of the fall in selenium levels has been expressed but a recent government advisory committee review concluded that there is currently no evidence of adverse health effects from current intakes. The need for continued monitoring of the situation and further research was, however, recognised.

6 METABOLIC REGULATION OF SELENIUM

6.1 Dietary forms of selenium

Selenium is present in foods mainly as the amino acids selenomethionine (found primarily in cereals) and selenocysteine (from animal products) (Department of Health 1991). However, in some plants, including the leaves of beets and cabbage, and in garlic, up to 50% of the selenium present may be in the form of selenate (Agency for Toxic Substances and Disease Registry 1996). Selenium may also be consumed in nutritional supplements in the form of selenite, selenate, selenomethionine or other selenium compounds (Table 6).

6.2 Absorption

Selenium metabolism in humans is not well characterised. However, it is known that the chemical form affects its absorption, retention and subsequent utilisation. Rat studies have shown that selenomethionine is actively absorbed, sharing a transport mechanism with the amino acid, methionine. Selenocysteine may share a common active transport mechanism with basic amino acids. Selenate is absorbed by a sodium-mediated carrier transport mechanism shared with sulphur. Selenite is absorbed by passive diffusion (Fairweather-Tait 1997).
<table>
<thead>
<tr>
<th>Form</th>
<th>Name</th>
<th>Main Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic forms:</td>
<td>Selenomethionine</td>
<td>Cereals, nuts, dietary supplements</td>
</tr>
<tr>
<td></td>
<td>Selenocysteine</td>
<td>Animal products</td>
</tr>
<tr>
<td>Inorganic forms:</td>
<td>Selenite</td>
<td>Dietary supplements/food fortificants</td>
</tr>
<tr>
<td></td>
<td>Selenate</td>
<td>Dietary supplements/food fortificants and some plants</td>
</tr>
</tbody>
</table>

In general, absorption appears to play no role in the homeostatic regulation of selenium. The proportion of selenium absorbed from foods is usually independent of the exposure and is unaffected by nutritional status, although in some instances absorption can increase when selenium deficiency exists. Overall absorption of selenium from food has been shown to be around 80% (Reilly 1996a). Uptake of inorganic selenium appears to be less effective than absorption of the organic forms (Reilly 1996a). However, the amount of selenium absorbed from food is not the only important factor; the retention of selenium in the body over time also appears to vary according to its form. Various human studies have shown that selenomethionine is absorbed and retained more efficiently than selenite or selenate, and that selenite is absorbed more efficiently than selenite but is not as efficient at maintaining selenium status (Fairweather-Tait 1997). Although selenomethionine is retained in tissue proteins to a greater extent than selenocysteine and the inorganic forms (owing to direct non-specific incorporation into albumin and haemoglobin in place of methionine), the selenium is not necessary immediately available for the synthesis of functional selenoproteins (Thomson 1998), and utilisation may depend on the rate of protein catabolism.

### 6.3 Bioavailability

Apart from its chemical form, a number of dietary factors affect the bioavailability of dietary selenium (Combs 1988), although most of these probably only affect absorption of inorganic forms of selenium. Reported enhancers of bioavailability include protein (the amino acid methionine), high levels of vitamin A and high levels of vitamin E. Inhibitors include heavy metals and high dietary sulphur intake. The interaction of selenium with toxic metallic compounds generally reduces their toxicity by forming inert metal selenide complexes. In this context, selenium appears to play a protective role against mercury toxicity (Grandjean et al. 1992). Selenium is present in sufficient quantities in seafoods, which are the most likely source of mercury in the diet. The simultaneous presence of selenium and mercury in these foods can reduce the absorption of the toxic metal (although this is at the expense of selenium absorption). This is likely to be an important factor for people whose diet includes a large amount of marine foods (Turner et al. 1980). There is evidence that the presence of arsenic in the diet can also affect the uptake and retention of selenium in a similar manner (Pederson et al. 1991). Other factors implicated in reducing selenium absorption in humans include guar gum and vitamin C (Fairweather-Tait 1997).

The need to develop accurate measures of the bioavailability of selenium from foods was a stated objective of the MAFF Optimal Nutrition Status programme. Research funded in this area includes a study using stable isotope methodology to determine the relative bioavailability of selenium from different foodstuffs (see Section 13.1, project AN0510).

### 6.4 Metabolism

The major fate of all selenium absorbed by the body, whatever its original form when ingested, is incorporation into proteins. After absorption, selenium is transported from the gut and reduced to selenide within various tissues (such as red blood cells and liver) before being transported in the blood bound to protein. It is then deposited within various organs and target tissues, and incorporated into specific selenoproteins as selenocysteine. Selenium concentrations in body tissues are related to the total amount and chemical form in the diet (Foster & Sumar 1997).

### 6.5 Excretion

Excretion of selenium is primarily through the urine (Reilly 1996a). As dietary intake increases from the deficient into the adequate range, urinary excretion of the element increases (Burk et al. 1972). Thus under physiological conditions, urinary excretion is the prime method of body selenium regulation.

### 6.6 Conclusions

- Selenium in food is found in either an organic (e.g. selenomethionine, selenocysteine, other selenium compounds) or inorganic (e.g. selenite, selenate) form.
- The chemical form of the element has
been shown to affect both absorption and subsequent utilisation.

- Selenium compounds are readily absorbed from the human gastrointestinal tract. Apart from chemical form, a number of dietary factors have been suggested to affect the bioavailability. Enhancers include protein (methionine), high levels of vitamin E and high levels of vitamin A. Inhibitors include toxic elements (e.g. arsenic, mercury), high levels of sulphur, guar gum and vitamin C.
- Following absorption, selenium is incorporated into proteins such as enzymes (selenoproteins).
- Excretion is primarily via the urine and, under normal physiological conditions, this is the main method of selenium regulation.

7 BIOLOGICAL FUNCTIONS OF SELENIUM

This section outlines the roles of selenium in the body. For information regarding the possible implications for health, see Section 10.

7.1 The role of selenoproteins

Selenium is an essential nutrient for many biochemical pathways, primarily in the form of a range of selenium-containing proteins selenoproteins. To date, about 30-35 selenoproteins have been identified, about half of which have been characterised in mammalian systems (Table 7). These proteins contain selenium in the form of selenocysteine. The selenoproteins are strictly selenium-dependent and their synthesis is reduced when dietary intake of the element is restricted.

The recognition of selenium’s role in the enzyme glutathione peroxidase (GSHPx), in 1973, helped to identify selenium as a nutritionally important trace element (see Section 7.2). Four distinct glutathione peroxidases have been identified: namely, ‘classical’ or intracellular GSHPx, plasma or extracellular GSHPx, phospholipid hydroperoxide GSHPx and, most recently, a gastrointestinal form (Wingler et al. 1999) (for further details see Section 7.2.5). Together, these enzymes protect cells against free radical damage from lipid and phospholipid peroxides and hydrogen peroxide. Selenium has also been shown to be a constituent of three iodothyronine deiodinase enzymes (Type I, Type II and Type III), involved in thyroid hormone metabolism, and of three thioredoxin reductase enzymes (TR1 and TR3 expressed in a variety of tissues especially liver, TR2 preferentially expressed in testes) (Sun et al. 1999), which are involved in DNA synthesis and possibly antioxidant activity (Stadtman 1999).

More recently characterised selenoproteins include selenoprotein P, which is an extracellular membrane-bound selenoprotein that may have a role in antioxidant defence (Burk & Hill 1999) and has been shown to function as a phospholipid hydroperoxide GSHPx in extracellular fluids (Salto et al. 1999). Recent studies have suggested that selenoprotein P might protect endothelial cells against peroxidative damage during inflammation, particularly from peroxynitrite (a reactive nitrogen species formed by the reaction between nitric oxide and superoxide under inflammatory conditions) (Arteel et al. 1999).

Selenoprotein W, may also have a role in antioxidant defence and be involved in muscle metabolism. Selenophosphate synthetase (SPS2) is an enzyme required for the incorporation of selenocysteine into selenoproteins. Sperm capsule

<table>
<thead>
<tr>
<th>Selenoprotein</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSHPx1</td>
<td>Classical (or intracellular) glutathione peroxidase</td>
</tr>
<tr>
<td>GSHPx2</td>
<td>Gastrointestinal glutathione peroxidase</td>
</tr>
<tr>
<td>GSHPx3</td>
<td>Plasma glutathione peroxidase</td>
</tr>
<tr>
<td>GSHPx4</td>
<td>Phospholipid hydroperoxide glutathione peroxidase</td>
</tr>
<tr>
<td>Sperm capsule selenoprotein (now known to be a form of GSHPx4)</td>
<td></td>
</tr>
<tr>
<td>Iodothyronine 5'-deiodinase – Type I, II, III</td>
<td></td>
</tr>
<tr>
<td>Thioredoxin reductases (TR1, TR2, TR3)</td>
<td></td>
</tr>
<tr>
<td>Selenoprotein P</td>
<td></td>
</tr>
<tr>
<td>Selenoprotein W</td>
<td></td>
</tr>
<tr>
<td>Selenoprotein synthetase (SPS2)</td>
<td></td>
</tr>
</tbody>
</table>

Act as antioxidant enzymes, removing hydrogen peroxide and lipid and phospholipid hydroperoxides

Protects developing sperm cells from oxidative damage, structural role in mature sperm

Thyroid hormone metabolism

DNA synthesis, antioxidant activity

Appears to protect endothelial cells from peroxidative damage

Muscle function

Selenoprotein synthesis
Selenoprotein is now recognised to be a form of phospholipid hydroperoxide GSHP\(x\) (GSHP\(x\))-dependent peroxidase. This protects developing sperm cells from oxidative damage and appears to polymerise into a protein mesh that contributes to the structural integrity of the male germ cell cytoskeleton (Ursini et al. 1999).

### 7.2 The role of selenium in defence against oxidative damage

Selenium has no antioxidant capacity of its own but was shown to be an integral part of the enzyme glutathione peroxidase (GSHP\(x\)) over 25 years ago (Rotruck et al. 1973). This enzyme acts as part of the body's defence mechanism to protect important molecules (e.g. lipids, DNA) and cell membranes against the consequences of damage by free radicals.

#### 7.2.1 Free radicals, reactive oxygen species and cell damage

Free radicals are molecules which contain an unpaired electron and are, therefore, highly reactive. Examples include the oxygen free radicals superoxide (\(O_2^-\)) and the hydroxyl radical (OH\(^-\)). The term 'reactive oxygen species' is a collective one that includes not only free radicals of oxygen but also some non-radical derivatives of oxygen, such as hydrogen peroxide (\(H_2O_2\)) and singlet oxygen. Hydrogen peroxide can be easily broken down, particularly in the presence of transition metal ions (e.g. Fe\(^{2+}\)), to produce the highly reactive hydroxyl radical. Other reactive species can also promote damage. For example, the nitrogen reactive species, peroxynitrite (ONOO\(^-\)), is formed by the reaction between nitric oxide and superoxide under inflammatory conditions.

Reactive oxygen species are formed as part of normal biological processes, for example when oxygen is reduced to water during the respiratory process. They can readily oxidise and damage essential biological molecules such as lipids, proteins and DNA. Polysaturated fatty acids, found in the phospholipid components of cell membranes, are particularly susceptible to oxidation. This can lead to a chain of events known as lipid peroxidation. This results in the production of many damaged unsaturated fatty acids which can lead to structural defects in the cell membrane and ultimately to loss of cell function.

#### 7.2.2 Antioxidant defence

Under normal physiological conditions, the cell is protected against free radical damage by the synergistic action of several enzymes, including catalase, superoxide dismutase (the two forms of which require either manganese, or copper and zinc) and the selenium-dependent GSHP\(x\), and by various dietary antioxidants including vitamin E.
vitamin C and β-carotene (other plant antioxidants, such as flavanoids, may also prove to be important). A range of food-derived substances, therefore, interact in effecting the body’s defence mechanism (Figure 2).

Vitamin E and β-carotene are thought to be able to stop the chain reaction of lipid peroxidation by removing free radicals, forming lipid hydroperoxides. One of the suggested functions of vitamin C is to act as a reducing agent, which converts the oxidised vitamin E back to its active form.

GSHPx is involved in this system by removing the damaging hydrogen peroxide, lipid and phospholipid hydroperoxides. The reaction catalysed is:

\[
\text{GSHpx} \quad \text{glutathione peroxidase}
\]

\[
2\text{GSH} + \text{ROOH} \longrightarrow \text{GSSG} + 2\text{ROH}
\]

Where \( R \) is hydrogen or an alkyl group

Where \( R \) is hydrogen this reaction is:

\[
\text{GSHpx} \quad \text{(glutathione peroxidase)}
\]

\[
2\text{GSH} + \text{H}_2\text{O} \rightarrow \text{GSSG} + 2\text{H}_2\text{O} \quad \text{(reduced hydrogen glutathione (water) peroxide)}
\]

Reduced glutathione is then regenerated by glutathione reductase and NADPH.

\[
\text{GSSG reductase}
\]

\[
\text{GSSG} + 2\text{NADPH} \longrightarrow 2\text{GSH} + 2\text{NADP} \quad \text{(glutathione (reduced glutathione))}
\]

Lipid hydroperoxides are unstable end products which, in the presence of transition metals, such as iron, can decompose to give further reactive free radicals and cytotoxic aldehydes (Diplock 1994).

Such secondary products may initiate more lipid peroxidation, promote atherosclerosis, damage DNA and metabolically activate carcinogens (Diplock 1994) (see Section 10).

7.2.3 The interaction between selenium and vitamin E

Selenium and vitamin E, in particular, appear to have overlapping and partly compensative functions (Hoekstra 1975, Levander 1992, Levander et al. 1995, Meydani 1992). Whilst the family of selenium-dependent glutathione peroxidase enzymes reduce hydrogen peroxide and damaging lipid and phospholipid hydroperoxides to harmless products (water and alcohol), vitamin E is involved in quenching free radicals and thus avoiding their attack on lipids. Thus, in vitamin E deficiency, selenium has a beneficial effect in removing the products of free radical attack on lipids and, conversely, in selenium deficiency, vitamin E has a protective effect by removing the radicals. When selenium is adequate but vitamin E is not, tissues which have a low innate activity of GSHPx are especially susceptible to lipid peroxidation, while tissues with high activity of GSHPx are not. When the supply of selenium is deficient while vitamin E is adequate, membrane lipid peroxidation will be inhibited but tissues with high peroxide production and low innate catalase activity will still be at risk from peroxidative damage. In the absence of vitamin C, the vitamin E radical can be reduced to vitamin E by reaction with glutathione, a process catalysed by a membrane specific enzyme, phospholipid GSHPx, which is a seleno-enzyme. Thus selenium has a direct role in the recycling of vitamin E (Maierino et al. 1989).

7.2.4 Oxidative stress

Normally, a balance exists between formation and destruction of radicals. However, if exposure to free radicals exceeds the protective capacity of the antioxidant defence system (a phenomenon known as ‘oxidative’ stress), damage to molecules can occur and lead to the development of disease. The list of conditions in which free radicals have been implicated include heart disease, cancer, ageing, emphysema, ulcerative colitis, diabetes, multiple sclerosis, rheumatoid arthritis and Parkinson’s disease (Bonorden & Pariza 1994). The nutrients involved in the body’s mechanism of defences against these radicals have been suggested to play a protective role in many of these conditions.

7.2.5 Characteristics of identified glutathione peroxidase enzymes

Four distinct selenium-containing glutathione peroxidases have been identified and shown to function in different compartments in the cell.

Classical, or intracellular (cytosolic), GSHPx was the first selenoprotein to be clearly characterised and is found in virtually all cells, where it regulates intracellular hydroperoxide concentrations. This may occur only under conditions where relatively large amounts of hydrogen peroxide or lipid hydroperoxides are produced in the cell cytosol.

Plasma or extracellular GSHPx was identified in 1986 as another distinct enzyme (i.e. different to intracellular GSHPx) though it may have many similar antioxidant functions, with glutathione acting as a reducing substrate for both enzymes. However, since glutathione is present in very low concentrations in extracellular fluids, it may be that plasma GSHPx has a function other than as a glutathione peroxidase. Arthur (1992) has suggested that its function in the kidney could be to protect membranes involved in blood filtration and urine production, in addition to serving as an antioxidant in endothelial cells.

Phospholipid hydroperoxide GSHPx was identified
as a distinct enzyme in 1982, although it took almost a decade before it was satisfactorily characterised. This enzyme is capable of metabolising fatty acid hydroperoxides esterified to phospholipids, which are likely to occur in cell membranes undergoing oxidative stress. It has been suggested that the main nutritional interaction between vitamin E and selenium may be the protection against cell membrane peroxidation provided by phospholipid GSHPx and the vitamin (Ursini & Bindoli 1987).

Sperm capsule selenoprotein is identical to phospholipid GSHPx and protects developing sperm cells from oxidative damage (Ursini et al. 1999). This selenoprotein changes its physical characteristics and biological functions during sperm maturation, forming a structural protein in mature spermatozoa (Ursini et al. 1999).

A gastrointestinal form of GSHPx has also been identified and the stability of this selenoprotein in selenium deficiency points to a vital role (Wingler et al. 1999). Its location suggests that this enzyme may protect against the adverse effects of ingested hydroperoxides (Wingler et al. 2000). Recent research suggests a possible role in colon cancer resistance (Mork et al. 1998) but further studies are needed in this area.

Other selenium containing enzymes such as selenoprotein P and selenoprotein W may also be involved in oxidant defence.

7.3 The role of selenium in thyroid hormone metabolism

Selenium plays an important role in thyroid hormone metabolism. The iodine containing hormone, thyroxine (T₄), produced by the thyroid gland, is deiodinated to the metabolically active triiodothyronine form (T₃) by an enzyme in the liver called Type I iodothyronine deiodinase (or thyroxine 5' deiodinase I). This is a selenoprotein that has selenocysteine at its active site, and is sensitive to selenium deficiency (Arthur et al. 1996). Selenium is also a constituent of Type II deiodinase, the enzyme responsible for local formation of T₃ within target tissues.

![Delodinase diagram]

Selenium deficiency is, therefore, associated with elevated levels of circulating T₄ and depressed levels of the active hormone, T₃. Selenium is also involved in iodine metabolism by protecting the thyroid gland from hydroperoxide damage. Thus, when iodine intake is marginal, inadequacy of selenium can be a contributory factor in the development of iodine deficient conditions such as goitre and cretinism. However, the suggestion that selenium deficiency impedes urinary iodine loss indicates that supplementation with selenium alone may exacerbate the situation where there is combined iodine and selenium deficiency (Nordic Project Group 1995) (see Section 9.2.3).

7.4 Selenium and immune function

There is now considerable evidence that selenium plays a key role in the functioning of the immune system. The immune system is extremely sensitive to oxidative damage. Many immune cells produce reactive oxygen species as part of the body’s defence against infection and rely on adequate protection by antioxidants, such as selenium, to prevent damage to the cells. Such damage can result in an impaired ability to elicit an immune response. Selenium is found in significant amounts in tissues involved in the immune response, such as the lymph nodes, spleen and liver (Spallholz et al. 1990) and various components of the immune system become impaired when dietary intake of selenium is inadequate (McKenzie et al. 1998) (see Section 10.3).

7.5 Selenium and reproduction

Selenium is important for normal reproductive performance. Sperm capsule selenoprotein (now known to be phospholipid GSHPx) is a structural selenoprotein found in the midpiece region of the sperm tail (Wallace et al. 1987, Ursini et al. 1999). In selenium deficiency, morphological abnormalities in this region give rise to spermatozoa with impaired motility (Behne et al. 1996). A recent study showed supplementation with selenium in sub-fertile men with low selenium status to increase blood selenium concentration and improve sperm motility (Scott et al. 1998). However, not all patients in this study responded to the selenium supplementation, with 44% showing no beneficial effect. Both low and high sperm selenium concentrations have been reported to have a negative influence on the number and motility of spermatozoa in human studies, and the optimal sperm selenium concentration remains to be defined (Hansen & Deguchi 1996) (see Section 10.6).

Selenium is also needed for normal testosterone metabolism and testicular morphology, which may explain the presence of several other selenoproteins in the male gonads (Behne et al. 1996).

7.6 Conclusions

- Selenium is incorporated into a range of proteins which are referred to as selenoproteins. Their activity depends upon an adequate supply of selenium in the diet.
The best known of these are the antioxidant glutathione peroxidase enzymes, which remove hydrogen peroxide and lipid and phospholipid hydroperoxides generated by free radicals and other oxygen-derived species before they can cause harm. In this capacity selenium works with other antioxidant nutrients in the body, including vitamin E, to prevent free radical damage to the tissues and cells, which has been implicated in the risk of developing a variety of degenerative diseases.

Selenium also plays an important role in the control of thyroid hormone metabolism. The enzyme responsible for the conversion of the hormone thyroxine (T4) to its active form, triiodothyronine (T3), is a selenoprotein called iodothyronine deiodinase.

There is now considerable evidence that selenium plays a key role in the functioning of the immune system. Supplementation with selenium appears to boost cell mediated immune responses, enhance antibody production and protect against oxidative damage. In contrast, in selenium deficiency, several components of the immune system become impaired, particularly if there is concomitant vitamin E deficiency.

Selenium appears to be important for reproduction in animals and studies have demonstrated its involvement in sperm motility via a sperm capsule selenoprotein (phospholipid GSHPx).

Despite strong evidence of several important biological roles for selenium, findings regarding its function have often been inconsistent. For example, both high and low selenium concentrations have been reported to have a negative influence on sperm motility.

8. ASSESSMENT OF SELENIUM STATUS

8.1 Indicators of selenium status

Nutritional status can be assessed by measuring dietary intake, by clinical examination, or by the measurement of the nutrient of interest in blood or other tissue (i.e. in biological samples). Due to limitations in the first two methods, increasing emphasis is being placed on the identification, validation and exploitation of sensitive biochemical markers and functional indicators of nutrient status. The amount of a nutrient present in a biochemical sample, such as blood or urine, can be used to estimate dietary exposure to that nutrient and may also inform about absorption, utilisation, excretion and storage. A functional indicator should change in response to dietary exposure but should also relate directly to disease appearance. These biomarkers reflect the body’s defence mechanisms to dietary exposure and, from a biological perspective, are likely to be more reliable and informative estimates.

8.1.1 Biochemical markers of selenium intake

Selenium can be measured in a variety of media including plasma or serum, whole blood, red cells, platelets, urine, hair and nails. A serum or plasma level of 70 ng/ml is the minimum concentration of selenium that might be expected under conditions of maximal expression of plasma/serum GSH-Px (Nève 1995). Rayman has suggested using a slightly higher value of 100 ng/ml serum as a criterion of nutritional adequacy (Rayman 1997). Red blood cell (erythrocyte) selenium level probably provides a more accurate assessment of long-term intake than serum or plasma concentrations. The level of selenium measured in hair has been well correlated with blood levels in China (Chan et al. 1980) but the use of selenium-containing shampoos represents a major source of contamination in developed countries. Toenail clippings are less exposed to environmental contamination and are more easily collected, transported and stored than blood and urine samples. Since growth is slow, toenail selenium levels reflect long-term selenium intake (Longnecker et al. 1993).

A study of free-living US adults (Longnecker et al. 1996) found that the concentration of selenium in a single specimen of whole blood, serum or toenails, could provide a reasonable measure for ranking subjects according to long-term intake but could not provide an accurate assessment of individual intake. Several biological samples for each subject must, be used in order to estimate actual, rather than relative, intake in human studies.

Good correlations have also been observed between 24-hour urinary excretion and selenium intake, but random urine samples are greatly affected by recent dietary intake (Robinson et al. 1985).

8.1.2 Functional markers

As selenium is involved in several metabolic systems in cells through ‘functional proteins’, there is potential for investigating the activity of these selenoproteins as functional markers of selenium status (Arthur 1999). For example, selenium intake can be assessed by measuring the antioxidant function of the selenium-dependent enzyme glutathione peroxidase, measured in plasma, serum, erythrocytes, platelets or whole blood. Glutathione peroxidase activity is reduced among subjects with low serum selenium status (Thomson et al. 1977) and has been shown to increase with supplementation in deficient subjects (Thomson et al. 1985). Enzyme activity, however, plateaus in individuals with a high selenium intake and is, therefore, a poor measure of intake in people with
moderate or high exposure. Measures of GSHPx also vary considerably from one laboratory to another making inter-study comparisons difficult.

Investigations in human subjects suggest that selenoprotein P may also be a suitable indicator of selenium status. Hill and colleagues (1996) observed a marked increase in the plasma selenoprotein P concentration of a group of Chinese men and boys after supplementation with 100 μg selenium per day for 14 days. Plasma selenoprotein P was correlated with plasma selenium concentrations, leading them to suggest that selenoprotein P concentration in plasma is an index of selenium nutritional status that is as sensitive as other indices in common use. Persson-Moschos et al. (1998) also observed a significant increase in plasma selenoprotein P levels after supplementation of Finnish men, with a low initial selenium status, with 200 μg selenium per day in various forms. However, this effect was not seen in a similar group of subjects with a higher initial selenium status. In a study of subjects from New Zealand, increases in selenoprotein P were greater than those for selenium and GSHPx at all supplement intakes, with a plateau reached at intakes of around 30 μg/day (Duffield et al. 1999).

A human study conducted within the MAFF programme found the ratio of T3 to T4 to correlate significantly with plasma selenium concentration (see Section 13.1, project AN0512). A similar relationship has been demonstrated with red blood cell GSHPx activity (Oliverer et al. 1996) and suggests that reduced peripheral conversion of T4 can be used as a functional marker of selenium status.

Because of the diverse range of functions of selenium in the body, Arthur (1999) has suggested that it may prove impossible to find one indicator of functional selenium status that will be useful for every circumstance. The result, therefore, may be a range of markers that are specific to certain aspects of sub-optimal selenium status, such as plasma or whole blood selenium concentrations, plasma or erythrocyte GSHPx activities, selenoperoxidase activity in white cells, and levels of thyroid hormone. Patching and Gardiner (1999) have also suggested that the accurate assessment of selenium status ideally requires the simultaneous determination of a number of functional selenoproteins. The need for further research in this area was recognised as a key objective in the MAFF Optimal Nutrition Status research programme and a study has been funded to attempt to identify functional biomarkers for selenium (see Section 13.1, project AN0543).

8.2 Factors affecting selenium status

Smokers have been shown to have lower levels of blood and toenail selenium (Hunter et al. 1990, Lloyd et al. 1983) and reduced GSHPx activity (Bunker et al. 1988, Lloyd et al. 1983), but it is not known whether this is due to lower intake or a direct effect of smoking on selenium metabolism. Serum selenium also appears to be reduced in alcoholics (Korpela et al. 1985), perhaps because alcoholic beverages are low in selenium and thus dietary selenium is reduced in those consuming a high proportion of calories from alcohol. The effect of moderate alcohol consumption on selenium status is minimal (Hunter et al. 1990). Selenium status may vary with other dietary conditions, such as iodine or vitamin E deficiencies, which may interact with selenium deficiency (Arthur 1999). A MAFF funded study recently observed a wide range of individual responses to selenium supplementation through changes in the activity of GSHPx. This large variation has been suggested to reflect differences in vitamin E status (see Section 13.1, project AN0512).

8.3 Conclusions

- Measurement of dietary intake, while indicative of the general status of the population, is not sufficient for the determination of the selenium status of an individual. Variations in the selenium content of foods and uncertainty about the absorption of different forms of the element has led to increasing emphasis on the measurement of biomarkers and functional indicators of selenium in the body.

- A diverse range of biological media can be used to measure selenium concentrations, including serum or plasma, whole blood, red blood cells, platelets, urine, hair and nails. Of these biochemical markers, nails and red blood cells provide a better estimate of long-term intake.

- The activities or concentrations of a range of selenium-containing enzymes can also be determined as functional markers of selenium status. GPx activity is widely used for this purpose but there are limitations in the use of this biomarker. The ratio of the thyroid hormones T3 and T4 can also provide an indication of the activity of the selenium-dependent deiodinase enzymes.

- Smokers and heavy drinkers have been shown to have lowered selenium status. Other dietary factors may also affect status, including vitamin E and iodine deficiencies.

9 SELENIUM DEFICIENCY IN ANIMALS AND MAN

9.1 Deficiency symptoms in animals

In animals, selenium deficiency has been
associated with a wide range of symptoms, including growth retardation, vascular changes and reproductive failure (Table 8). The critical level for dietary selenium, below which deficiency signs have been observed, is approximately 0.02 mg/kg for ruminants and 0.03 to 0.05 mg/kg for poultry. In farm animals the deficiency causes skeletal and cardiac myopathies (white muscle disease), the latter often proving fatal. In addition, symptoms such as liver necrosis, haemolysis and degeneration of several organs, such as the kidney and pancreas, have also been reported. These outcomes probably occur in animals with combined selenium and vitamin E deficiency. Selenium deficiency in animals has also been associated with impaired immune response, increases in cardiotoxicity of Coxsackie B4 virus and impairment of thyroid hormone metabolism.

<table>
<thead>
<tr>
<th>Table 8: RECOGNISED SELENIUM-DEFICIENCY DISEASES IN ANIMALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>White muscle disease (myopathy of skeletal/heart muscle)</td>
</tr>
<tr>
<td>Ill-thrift (growth depression – muscle mass affected)</td>
</tr>
<tr>
<td>Impaired reproduction (sperm and embryo affected)</td>
</tr>
<tr>
<td>Liver necrosis</td>
</tr>
<tr>
<td>Exudative diathesis (damage to capillary walls)</td>
</tr>
<tr>
<td>Pancreatic degeneration</td>
</tr>
</tbody>
</table>

Source: Rayman (Personal Communication 2001)

9.2 Deficiency symptoms in humans

9.2.1 Keshan disease
In humans, selenium deficiency is thought to be linked to Keshan disease, an endemic cardiomyopathy which occurred until the 1980s in the Keshan region of China, where selenium intake was extremely low. The disease is characterised by cardiac insufficiency, heart enlargement and arrhythmia. The middle layer of the walls of the heart, which are normally composed of muscle tissue, are replaced with fibrous tissue. Changes in the thyroid gland have also been noted. Keshan disease can be organised into 4 types depending on severity: acute, sub-acute, chronic and insidious (latent). No specific test exists for the disease and its diagnosis is dependent on clinical judgement based on established criteria. The populations most susceptible to the disease in China were the young peasant women and growing children living in rural areas, who had a limited and unvaried diet. It was localised primarily in those living in certain hilly and mountainous regions with low soil selenium concentrations.

Whilst selenium supplementation has decreased the incidence of the disease (Ge & Yang 1993), certain epidemiological features cannot be explained solely on the basis of inadequate selenium nutrition. For example, the seasonal variation in the prevalence of the disease is not accompanied by changes in body selenium stores. Whilst factors such as mycotoxins in food and other nutrient deficiencies (e.g. protein deficiency) may be implicated, the most common hypothesis suggests that a cardiotoxic agent, such as a virus, might also be necessary for the disease to occur (Ge & Yang 1993). Several viruses have been found in people with Keshan disease, including a coxsackie B4 virus, which causes extensive damage to heart muscle when injected into mice fed on a low selenium diet (Ge et al. 1987). Deficiency of selenium and vitamin E have been shown to impair immune function and increase the virulence of viruses (Beck et al. 1995) (see Section 10.3).

Whilst Keshan disease clearly results from a combination of factors, the preventative effect of selenium indicates that selenium deficiency is the fundamental underlying condition which predisposes a person to the disease. For more than half a century following a severe outbreak in 1935, Keshan disease has constituted a serious problem in many areas of China. A public health programme of selenium supplementation was embarked upon during the 1970s.

In recent years, with the improved availability of selenium supplements and better selenium status of residents, as well as an improvement in living conditions (e.g. better sanitation, increased medical attention, access to a better and more varied diet) in China, the disease has now virtually been eliminated from several formerly endemic areas. Cardiomyopathies have also been seen in patients receiving total parenteral nutrition for prolonged periods where inadequate levels of selenium are present in the infusion fluids (see Section 9.2.4).

9.2.2 Kashin-Beck disease
Kashin-Beck, or enlarged joint, disease is another selenium-responsive endemic disease which occurs in low selenium areas of China and responds favourably to selenium supplements (Ge & Yang 1993). The disease is characterised by a chronic disabling degenerative osteoarthritis. The principle pathological change is degeneration and necrosis of the hyaline cartilage tissue. Initial symptoms include limb weakness, stiffness, swelling and acute pain in the finger joints, gradually progressing to osteoarthritides of the elbows and knees, and ankle joint enlargement. The disease typically has its onset during the first
or second decade of life (Sokoloff 1985). As well as selenium deficiency, a number of other aetiological factors have been suggested including iodine deficiency (Moreno-Reyes et al. 1998), mycotoxins in grain, mineral imbalance and organic contaminants in drinking water (Levander 1987).

Although there are well known and extensive regions of selenium-deficient soils in other countries, such as New Zealand, neither Keshan disease nor Kashin-Beck disease has been found to occur outside China and its northern neighbours. Comparable intakes to those reported in Keshan disease areas of China have been found in children following restrictive diets for phenylketonuria (an inherited defect of metabolism that interferes with the conversion of the amino acid phenylalanine into tyrosine) but these children showed no signs of any selenium deficiency illness (Reilly 1996a). This is likely to be due to difference in the overall quality of the diet and to the limited diet of the Chinese Keshan disease victims which together probably lead to a range of nutrient deficiencies, including low intakes of other antioxidant nutrients. The effects of selenium deficiency may, therefore, be compensated for by an otherwise well balanced and varied diet, in so far as antioxidant protection is concerned.

9.2.3 Hypothyroidism
Iodine deficiency produces a spectrum of disorders including endemic goitre, hypothyroidism, cretinism and congenital abnormalities. Selenium is an essential component of iodothyronine deiodinase, which converts thyroxine (T4) to the more biologically active hormone, triiodothyronine (T3). The selenium-containing enzyme GSH-Px is also an important antioxidant in the thyroid gland.

In animal studies, selenium deficiency lowers deiodinase activity and adversely affects thyroid metabolism (Beech et al. 1995). A reduction in GSH-Px activity may increase oxidative damage to the thyroid by hydrogen peroxide, which is produced in high amounts in the iodine-deficient thyroid as a result of raised levels of thyroid stimulating hormone (TSH) (Corvillain et al. 1993). In rats, concurrent selenium and iodine deficiency produced a significant increase in thyroid weight and TSH and a decrease in thyroidal iodine when compared with either single selenium or iodine deficiency, suggesting that selenium deficiency may exacerbate the hypothyroidism observed in iodine deficiency (Beckett et al. 1993). In humans, cross-sectional studies have suggested that poor selenium status may be associated with impaired thyroid metabolism and myxodematous cretinism in iodine-deficient populations (Thilby et al. 1993).

This has led to the investigation of selenium supplementation in iodine deficient patients. However, such studies have demonstrated a need for caution. Selenium supplementation in iodine-deficient cretins has been shown to induce a dramatic fall in the already impaired thyroid function (Contempré et al. 1991) and it has been proposed that selenium deficiency may actually provide protection against iodine deficiency and brain damage in such iodine-deficient populations. Selenium supplementation should not, therefore, be attempted before iodine deficiency has been corrected.

9.2.4 Total parenteral nutrition (TPN) induced selenium deficiency
Selenium deficiency is a recognised problem for patients receiving total parenteral nutrition (TPN) for prolonged periods of time because of inadequate intake from the infusion fluids. When adequate selenium is not supplied, blood levels can decline in TPN patients to levels found in sufferers of Keshan disease. Although such levels are not accompanied by symptoms of Keshan or Kashin-Beck disease, cardiomyopathies and less severe symptoms, including muscular pain and tenderness and reduced mobility, have been reported (van Rij et al. 1979).

9.3 Conclusions
- Selenium deficiency symptoms in animals include growth retardation, myopathy of skeletal and heart muscle (white muscle disease), vascular changes, reproductive failure and impaired immune response.
- Clinical deficiency symptoms in man include an endemic cardiomyopathy (Keshan disease) and a deforming arthritis (Kashin-Beck disease).
- Keshan disease was named after the region of China in which it was first recognised. The disease is thought to involve both selenium deficiency and a viral infection in its aetiology.
- Kashin-Beck disease is another selenium responsive endemic disease found in selenium deficient areas. It is characterised by a chronic disabling degenerative osteoarthritis. This condition is also believed to have other causative cofactors.
- When dietary iodine is inadequate, a deficiency of selenium may exacerbate symptoms of iodine deficiency, such as hypothyroidism and cretinism. However, selenium supplementation should not be undertaken without concomitant iodine supplementation in an iodine and selenium deficient population.

10 SELENIUM IN HEALTH AND DISEASE
The concept of optimal nutrition has shifted the focus on the role of micronutrients in the diet from
Table 9: DISEASES AND CONDITIONS FOR WHICH SELENIUM SUPPLEMENTATION HAS BEEN SUGGESTED TO BE BENEFICIAL

<table>
<thead>
<tr>
<th>Some evidence</th>
<th>Little/no evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>Acne</td>
</tr>
<tr>
<td>Asthma</td>
<td>Ageing</td>
</tr>
<tr>
<td>Cancer</td>
<td>Cataracts</td>
</tr>
<tr>
<td>Heart disease</td>
<td>Coeliac disease</td>
</tr>
<tr>
<td>Infectious/viral disease (HIV infection)</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>Infertility in men</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Mood</td>
<td>Down’s syndrome</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Infertility in women</td>
</tr>
<tr>
<td></td>
<td>Kwashiorkor</td>
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<tr>
<td></td>
<td>Macular degeneration</td>
</tr>
<tr>
<td></td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td></td>
<td>Muscular dystrophy</td>
</tr>
<tr>
<td></td>
<td>Sudden infant death syndrome</td>
</tr>
<tr>
<td></td>
<td>Ulcerative colitis</td>
</tr>
</tbody>
</table>

prevention of overt nutritional deficiencies to include the maintenance of good health and the reduction of chronic disease. In the light of selenium’s role as an antioxidant and in the immune and inflammatory response, there is increasing awareness that sub-clinical selenium deficiency may have several adverse health effects. As a consequence selenium supplementation has been suggested as beneficial for a variety of degenerative human diseases (Table 9). In many of these conditions, however, scientific evidence of any association is lacking. The risk of toxicity from high dose supplementation must also be considered.

10.1 Cancer

10.1.1 Animal studies
There has been considerable research into the possible protective properties of selenium against several types of cancer. A range of animal studies have shown selenium compounds to inhibit the development and growth of chemically or virally induced tumours. These protective effects have been demonstrated in animals provided with sufficient selenium to correct a deficient status. However, antitumorigenic activities have been shown in animal models when selenium is administered at levels greater than those associated with nutritional needs, suggesting a beneficial effect of selenium supplementation in animals with a nutritionally adequate intake. Studies have not, however, always found this effect and some have even reported selenium to increase tumour development (Birt 1988, Anon 1999).

10.1.2 Suggested mechanisms
The toxic effect of oxygen free radicals has been suggested to have carcinogenic properties. In its role as an antioxidant selenium may, therefore, exert a chemo-preventative effect. Selenium supplementation of individuals with low, or overtly deficient, habitual intakes of selenium would be expected to enhance antioxidant protection by increasing the expression of the selenium-dependent enzymes, glutathione peroxidase and thioredoxin reductase. However, protective effects have been demonstrated at levels of selenium supplementation which are substantially greater than those associated with maximal expression of the known selenium-containing enzymes, suggesting that other mechanisms may be more important. Selenium has been shown to have a role in several other functions that may be related to the formation and growth of tumours. For example, it has been shown to enhance the immune response (promoting the destruction of tumour cells) and to produce anti-tumorigenic metabolites (e.g. methyl selenol or its precursors) that can disturb tumour-cell metabolism, inhibit angiogenesis and stimulate programmed cell death (apoptosis) of cancer cells (Rayman 2000, Combs 1999).

10.1.3 Ecological studies
Ecological studies have suggested regions and countries with low selenium intakes or status to have higher rates of cancer death. Over 30 years ago, Schramberger and Frost showed that mortality from cancer in the US was inversely related to selenium concentrations in forage crops (Schramberger & Frost 1969). This finding was extended to international comparisons by Schrauzer and colleagues (1976), who investigated the relationship between dietary intake of selenium and cancer mortality in 27 countries. A strong inverse association was found between selenium intake and mortality from several forms of cancer, including prostate, colon and rectal cancer, whilst correlations for other types such as bladder, pancreas and skin were weaker. Whilst several
similar studies have been published (Jansson et al. 1978, Clark 1985), they have been criticised for a number of reasons including the lack of consistency and strength of the association, failure to exclude confounding factors, such as pollution, and the use of inaccurate food composition data.

10.1.4 Case-control studies

A number of case-control studies have measured blood and tissue selenium in cancer patients and compared them with similar measurements in subjects who were not suffering from the disease. In most studies of this type, cancer patients were found to have lower concentrations of selenium (Knekt et al. 1998, Shamberger et al. 1973). However, biochemical measures of selenium determined during acute illness should be interpreted with care. Blood levels have been shown to decline as the disease progresses and patients with advanced disease tend to have lower concentrations (Shamberger et al. 1973). Low levels in cancer patients may, therefore, be the consequence, rather than the cause, of the disease. This prevents these case-control studies from providing valid evidence of a causal link between selenium status and cancer.

10.1.5 Prospective studies

Prospective studies have generally provided better evidence of a role for selenium in cancer prevention. Willett and colleagues, in the USA, followed up more than 10,000 men and women over a 5 year period (1973-8). Blood samples collected at the beginning of the study were analysed for those subjects who developed cancer and a group of matched controls. The initial serum selenium level in the control group was significantly higher than in the subjects who went on to develop cancer. The cancer incidence in the low blood selenium group at baseline was significantly higher than expected, with the risk in the lowest quintile (<115 µg/ml) being twice that in the highest quintile (>154 µg/ml). Unfortunately there were insufficient cases to investigate the relationship with specific cancers, but a consistent trend of low serum status with some forms, such as prostate cancer, was demonstrated. The risk of cancer was also related to low blood vitamin E and retinol concentrations (Willett et al. 1983).

Salonen and colleagues followed 8,000 men and women in Finland for 8 years and also found a significantly increased risk of cancer amongst those with serum selenium levels below 45 µg/l at baseline (Salonen et al. 1985). Those who were in the lowest third of selenium status had a 6-fold risk of fatal cancer compared to those in the highest tertile. Again this study could not investigate cancers at different sites, although some differences did seem to be present. In both studies, the strength of the association was increased when blood levels of vitamin A and vitamin E were included in the analysis. A comparison of these two large studies has, however, raised the criticism that the highest levels of selenium in the Finnish subjects were below those in the lowest group of the American cohort, yet the total incidence of cancer (standardised for the population) in Finland is lower than in the US. There have now been several prospective studies which have investigated the link between selenium intake and cancer in a variety of populations. In general, more consistent associations have been found in populations with low or moderate selenium intake (Van den Brandt et al. 1993, Kok et al. 1987, Knekt et al. 1989) than in those with high intake (Willett et al. 1983, Coates 1988, Garland et al. 1995). This has led to the suggestion that selenium may exert its protective effect only when the basic level is low in relation to oxidative stress (Knekt et al. 1999) or may provide protection only in certain circumstances, or in combination with other antioxidants.

A recent prospective study in the US has, however, provided stronger evidence for a relationship between selenium and prostate cancer. The Health Professionals’ Cohort Study of 34,000 men found a one-half to two-thirds reduction in the risk of advanced prostate cancer for men with the highest compared to lowest selenium status (measured from toenails) (Yoshizawa et al. 1998). This study had a number of strengths including the large number studied, nearly complete follow-up, control for several potential confounding factors and the exclusion of cases diagnosed less than 2 years after collection of the samples.

10.1.6 Supplementation trials

The main intervention trial conducted to date that supports the protective role of high selenium intake against cancer is a study of 1,312 patients (mostly men) in the US, with a previous history of skin cancer, supplemented either with placebo or 200 µg selenium per day over 4.5 years (Clark et al. 1996). Significant reductions in the risk of total cancer incidence (37%) and mortality (60%) were observed. Whilst selenium was not found to have a protective effect against recurrent skin cancer, the selenium treated group had substantial reductions in the incidence of lung, colorectal and prostate cancers, of 46%, 58% and 63% respectively. The strongest treatment effect was observed in subjects in the lowest tertile of plasma selenium at the beginning of the study, a category into which most of the UK population would fall. Although these data need confirmation, they suggest that adequate selenium intake might be important for cancer prevention.

Intervention studies have also shown selenium supplementation to reduce the incidence of liver cancer in those with the hepatitis virus (Li et al. 1992, Yu et al. 1997) or with a family history of the disease (Li et al. 1992, Yu et al. 1991). The Linxian Intervention Trial, carried out in a region of China with extremely high rates of oesophageal and stomach cancer and very low selenium levels, showed supplementation with a combination of selenium, vitamin E and β-carotene to reduce
cancer mortality by 13%. The greatest reduction was for stomach cancer mortality, which was 21% lower in this intervention group (Blot et al. 1993). There is clearly a need for further supplementation trials in this area. A large European intervention trial (PRECISE) is being set up, which will be a five-year study of the effect of selenium supplementation (in the range of 100-300 µg/d) on the incidence of cancer in a normal healthy population (Rayman & Clark 1999). Two pilot studies are currently underway, in the UK and in Denmark. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) in the US will investigate the link between supplementation with selenium and vitamin E on the risk of prostate cancer.

However, concern has been raised about the long-term use of high doses of selenium in intervention trials (Vinceti et al. 1998a). This followed the demonstration of an increased incidence of melanoma in an Italian cohort exposed to high levels of environmental selenium (inorganic selenium in tap water) (Vinceti et al. 1998b).

10.1.7 Summary
In summary, evidence for an association between selenium and cancer is accumulating and has created much interest in the possible use of selenium compounds as potential chemoprotective agents. In 1998 COMA reviewed the research in this area and concluded that there was insufficient evidence at that time to support any specific links for selenium in the causation, or in the prevention, of cancer (Department of Health 1998). The demonstration that selenium also appears to be able to stimulate tumour development in rodent models (Birt 1988) suggests that any use of selenium as a cancer preventative agent should be approached with caution (Anon 1989).

10.2 Heart disease

10.2.1 Suggested mechanisms
There is growing support for the belief that antioxidants play an important protective role against cardiovascular disease (CVD) and in this context a possible role for low selenium status in the pathogenesis of CVD has been suggested. Mechanisms whereby selenium might protect against heart disease include increased resistance of low density lipoproteins (LDL) to oxidative modification (a process which enhances the formation of atherosclerotic lesions), modulation of prostaglandin synthesis and platelet aggregation (the tendency of blood to clot) and protection against heavy metals (e.g. mercury) that exert toxic effects on the cardiovascular system.

10.2.2 Evidence for an association
Supportive evidence for an association between low selenium status and heart disease has been provided in the form of descriptive ecological (Shamberger 1978), cross-sectional (Moore et al. 1984) and case-control studies (Beaglehole et al. 1990). However, this evidence is, at best, suggestive because of the potential sources of biases and the inability of such studies to determine whether low selenium status might be the cause, or the consequence, of the disease.

A causal link, however, can be better investigated by prospective studies in which selenium status is measured years before the onset of the disease. Whilst some prospective studies have shown an association between low selenium status and heart disease (Virtamo et al. 1985, Salonen et al. 1982, Suadicani et al. 1992), others have yielded conflicting results (Miettinen et al. 1983, Kok et al. 1987, Ringstad & Fonnum 1987, Salonen et al. 1985, Salvini et al. 1995). Two of the studies that did find an association (Salonen et al. 1982, Virtamo et al. 1985) were conducted in Finland, where selenium intake has been very low until recently. For example, a study by Salonen and colleagues (Salonen et al. 1982) demonstrated a 3.6 fold increase in coronary deaths and a 2.7 fold increase in heart attacks amongst men who had very low serum selenium levels (<45 µg/l). In contrast, studies in populations with higher selenium intakes have not found an association (Miettinen et al. 1983, Kok et al. 1987, Ringstad & Fonnum 1987, Salvini et al. 1995). It is, therefore, conceivable that cardiovascular risk might be influenced only by very low selenium status. A recent case-control study combined data from 9 different European countries and found no association between toenail selenium levels and risk of a non-fatal heart attack when smoking habits were taken into account (Kardinaal et al. 1997). This study, however, also suggested that there may be a link when selenium status is low because a separate analysis in the individual countries found a significant association only in Germany where selenium levels were the lowest.

10.2.3 Interaction with other antioxidants
It has been postulated that the relationship between selenium status and risk of CVD might be influenced by the status of the other antioxidants. Kok et al. reported no interaction between serum selenium and serum vitamin E and risk of CVD death in a prospective study (Kok et al. 1987). However, in a case-control study by the same researchers, patients with severe atherosclerosis had significantly lower plasma selenium levels (relative to serum polyunsaturated fatty acids) than patients with mild atherosclerosis, but only in the subgroup with low plasma vitamin E status (Kok et al. 1991). The EUROMIC study found a stronger inverse association between selenium status and heart attacks at low vitamin E status compared to higher vitamin E status but did not find any significant interaction between selenium and vitamin E or beta-carotene (Kardinaal et al. 1997). The interaction between these two nutrients requires further research in the context of cardiovascular disease.
10.2.4 Summary

In summary, there is little evidence that, in a well-nourished population, blood selenium levels affect the incidence of cardiovascular disease. Although such a relationship may occur at very low selenium levels (Nordic Project Group 1995), the available evidence, even within low selenium areas, remains inconsistent. Since selenium is potentially toxic, Diplock (Diplock 1987) has opined that therapeutic supplementation with the element as a preventative measure against CVD is not warranted.

10.3 Infectious/viral disease

Selenium deficiency impairs the immune system and increases susceptibility to infectious disease. It has been shown to impair neutrophil function, antibody production (particularly if associated with vitamin E deficiency), the proliferation of T and B cells (lymphocytes) in response to mitogens, and the activity of natural killer cells and lymphokine-activated killer cells, which are important defence mechanisms against tumours and viral infections (Kiremidjian-Schumacher et al. 1994).

Supplementation with selenium appears to boost cell-mediated immune responses (e.g. fighting infection), as well as protecting against oxidative damage. Peretz and colleagues (1991) demonstrated that selenium supplementation in elderly institutionalised subjects increased the production of T cells, in response to pokeweed mitogen, after 4-6 months of receiving the supplement compared with baseline values. Subsequently, Kiremidjian-Schumacher et al. (1994) have shown that supplementation with selenium, in selenium replete subjects, resulted in a 118% increase in cytotoxic-mediated tumour cytotoxicity, and a 82% increase in natural killer cell activity after 8 weeks compared with baseline values, even though the supplementation regimen did not produce significant changes in blood selenium levels.

The exact mechanisms whereby selenium affects the immune system remain unknown. However, studies have shown selenium to increase the number of interleukin-2 receptors on the surface of the T cells in various systems (Roy et al. 1994), thereby giving an enhanced response to interleukin-2. Interleukin-2 is a cytokine which acts on the T cells to increase the production and activity of other cells in the immune system.

Selenium deficiency is also linked to the occurrence, virulence or disease progression of some viral infections, including the influenza or flu virus (Beck 2001). Recent work in animals suggests that in a selenium or vitamin E deficient host, harmless viruses can become virulent and a virulent strain of a virus can become more virulent (Beck et al. 1995, Beck et al. 1998). This may result from an enhanced ability of a virus to replicate in a deficient host, thereby increasing the chances of a mutation occurring. This would have implications for populations with poor nutritional status, since once the mutations have occurred, even those with adequate nutrition will be susceptible to the virus-induced disease.

The research funded by the Food Standards Agency (and previously by MAFF) in this area includes an investigation of the effect of two different levels of selenium supplementation on immune response and on the mutation rate of an orally administered rotavirus (see Section 13.1, project AN0545). Another study is investigating the effect of selenium supplementation on the immune response to defined antigens in UK subjects to determine whether changes in biochemical indices of selenium status are associated with functional effects (see Section 13.1, project AN0543). A wider discussion of nutrition and immune function can be found in a recent British Nutrition Foundation Task Force Report on adverse reactions to food (Buttriss 2001).

The demonstrated antiviral and immune-altering effects of selenium have led to the suggestion that supplementation may reduce the onset, progression or severity of infectious and viral diseases. Beneficial effects have been demonstrated in some vulnerable groups. Selenium supplementation has been shown to reduce the incidence of infectious disease in the elderly (Girodon et al. 1997), promote recovery from respiratory tract infection in children (Liu et al. 1997) and reduce the risk of hepatitis B virus infection in a high risk population (Yu et al. 1999). There is also some evidence that supplementation may be of benefit in children with Down’s syndrome who are particularly prone to bacterial infection. These children often have low blood selenium concentrations and altered oxidative metabolism. Whilst research in this area is very limited, there is some evidence to suggest that supplementation with selenium may help protect against the risk of infection in these children (Anneren et al. 1990).

10.3.1 HIV/AIDS

The status of many micronutrients deteriorates as a consequence of malnutrition and malabsorption in sufferers from human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS). A number of studies have documented a decline in blood selenium levels and decreased GSHPx activity in individuals with HIV and AIDS (Dworkin et al. 1988, Cirelli et al. 1991, Mantero-Atienza et al. 1991, Allavena et al. 1995). Patients with AIDS tend to have more severe deficits than those with earlier stages of HIV infection (Dworkin 1994). However, a decline in blood status has been shown to occur even in the early stages of the disease, when malnutrition and malabsorption cannot be a factor (Look et al. 1997).
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13 APPENDIX

13.1 Objectives of the Optimal Nutrition Status programme

MAFF’s Optimal Nutrition Status Research Programme began in 1991 with two main objectives. Firstly, to understand the link between optimal nutrition status and the maintenance of good health (particularly interactions between micronutrients at different stages of life and their role in the reduction of specific diseases). Secondly, the programme aims to develop accurate measures of bioavailability from foods, using studies in the whole body to take account of interactions between nutrients at the gut level and the effective transport of these nutrients to where they are needed. Responsibility for the programme was transferred to the Food Standards Agency in April 2000. To date over 40 projects have been funded, mostly concerned with one of more of the following nutrients: iron, copper, selenium, vitamin E, vitamin C, calcium, vitamin D, vitamin K and folate/folic acid.

13.2 Structure of the Review

In April 1999, the British Nutrition Foundation was awarded a nine month contract to produce a critical review of the research being conducted within the Optimal Nutrition Status Programme. Nutrients were grouped together in terms of function (e.g. selenium, vitamin E and vitamin C) and published research reviewed to summarise current knowledge from an international prospective. Workshops consisting of MAFF contractors and other experts were held to establish the underlying consensus of the available data, help identify work in process outside the programme and to prioritise future research needs.

For further details of the programme and the review process see Buttriss and Hughes, 2000.

13.3 Recent MAFF/FSA funded research in this area

Table 10 provides a summary of recent and ongoing studies formerly funded by MAFF on various aspects of selenium. The funding of the ongoing studies was transferred to the Food Standards Agency when it was established on 1st April 2000.
Table 10: SUMMARY OF THE PROJECTS ON SELENIUM IN THE MAFF FUNDED PROGRAMME

<table>
<thead>
<tr>
<th>Project number, title, contractor, research centre and duration</th>
<th>Summary of the project</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAFF Project no. AN0510/AN0514</td>
<td>The aim of this project was to observe the relationship between the form of selenium, and its absorption and metabolism in healthy human subjects. This information is required in order to determine dietary requirements for selenium. Accurate measures of the bioavailability of selenium from foods have been established, and the influence of the amount and form of dietary selenium on selenium status has been assessed. Methods have also been developed for measuring selenium levels in various foods, and in blood and urine.</td>
</tr>
<tr>
<td>3 year project (extension to March 1999)</td>
<td></td>
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<tr>
<td>Dr S Fairweather-Tait</td>
<td></td>
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<tr>
<td>Institute of Food Research, Norwich</td>
<td></td>
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<tr>
<td>Dr HM Crews</td>
<td></td>
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<tr>
<td>Central Science Laboratory, York</td>
<td></td>
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<tr>
<td>MAFF Project no. AN0512</td>
<td></td>
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<tr>
<td>Selenium intake: effect on selenoprotein function</td>
<td></td>
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<tr>
<td>3 year project (completed in 1998)</td>
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<tr>
<td>Dr J Arthur</td>
<td></td>
</tr>
<tr>
<td>Division of Micronutrient and Lipid Metabolism, Rowett Research Institute, Aberdeen</td>
<td></td>
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<tr>
<td>MAFF Project no. AN0543</td>
<td></td>
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<tr>
<td>(Food Standards Agency Project no. N05010)</td>
<td></td>
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<tr>
<td>Biochemical and molecular markers of functional selenium status in man</td>
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<tr>
<td>3 year project (completed in January 2001)</td>
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<tr>
<td>Dr J Arthur</td>
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<tr>
<td>Division of Micronutrient and Lipid Metabolism, Rowett Research Institute, Aberdeen</td>
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<tr>
<td>MAFF Project no. AN0545</td>
<td></td>
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<tr>
<td>(Food Standards Agency Project no. N05012)</td>
<td></td>
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<tr>
<td>Functional markers of selenium in man</td>
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<tr>
<td>3 year project (due to be completed in October 2001)</td>
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<tr>
<td>Professor M Jackson</td>
<td></td>
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<tr>
<td>Department of Medicine, University of Liverpool, Liverpool</td>
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</tr>
</tbody>
</table>

13.4 Recommendations for further research

Table 11 outlines the recommended priorities for future research which were identified by the British Nutrition Foundation during the review of MAFF's Optimal Nutrition Status research programme.
### Table 11: RECOMMENDED PRIORITIES FOR FUTURE RESEARCH IDENTIFIED DURING THE REVIEW OF THE MAFF PROGRAMME

<table>
<thead>
<tr>
<th>MAFF programme objectives</th>
<th>Research priorities identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>To understand the links between Optimal Nutrition Status and the maintenance of good health</td>
<td>• To establish the general relationships between selenium intake and health in healthy individuals</td>
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<tr>
<td></td>
<td>• To establish the full range of selenium’s biochemical functions by further investigation of, for example:</td>
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<td></td>
<td>- the link between prostate cancer and selenoproteins</td>
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<td></td>
<td>- the role of selenoproteins in reproductive function</td>
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<td></td>
<td>- the novel protective functions of selenoprotein P</td>
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<td></td>
<td>- the biochemical roles of thioredoxin reductases and how they are related to selenium intake</td>
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<td></td>
<td>• To associate the biochemical or molecular function of selenium with an outcome that can be related to the maintenance of health, for example:</td>
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<tr>
<td></td>
<td>- the role of selenium in immune function, viral infectivity and virulence (e.g. HIV), and viral mutation rate</td>
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<td></td>
<td>- the anticancer mechanisms of a high selenium intake</td>
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<td></td>
<td>- the relationship between dietary selenium intake and thyroid function</td>
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<td></td>
<td>- the utilization and flux of selenium under stress conditions.</td>
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<tr>
<td>To develop accurate measures of bioavailability from foods</td>
<td>• To conduct further studies on bioavailability; in particular to investigate what determines the release of selenomethionine from body proteins and its availability to meet functional demands</td>
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<tr>
<td>(i) to measure the fraction of ingested nutrients which meets functional demands in target tissues</td>
<td>• To confirm whether the dietary factors shown to affect selenium metabolism in animals (e.g. vitamin A, C and E) also operate in humans</td>
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<td></td>
<td>• To obtain more information about the chemical forms of selenium present in foods in the UK, especially in yeast used in supplements, in order to make predictions about its bioavailability</td>
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<td>• To develop specific and sensitive functional markers of selenium status</td>
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<td>(ii) to develop functional markers of status for each micronutrient, or group of nutrients</td>
<td>• To relate functional markers of selenium status to biochemical markers of selenium intake</td>
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<td></td>
<td>• To develop simple, rapid and reliable assays for biochemical markers of selenium (e.g. ELISA method for determining phospholipid GSHPx activity)</td>
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<td>• To relate markers of selenium function to intakes prevalent in the UK to predict whether increasing intake from the diet or by supplementation would have any beneficial health benefits</td>
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<td>• To further investigate the link between selenium status and:</td>
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<td></td>
<td>- cancer morbidity/mortality</td>
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<td></td>
<td>- viral effects and virulence</td>
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<td></td>
<td>- changes in mood and cognitive function</td>
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<tr>
<td></td>
<td>- male and female fertility and reproductive function</td>
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<td></td>
<td>• To consider the relative requirements for selenium and vitamin E, since one may partially compensate for the other in antioxidant systems during deficiencies</td>
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<td></td>
<td>• To investigate the metabolic significance of possible adaptation to different selenium concentrations in the diet</td>
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<tr>
<td></td>
<td>• To obtain further information on selenium intakes of different population groups, such as neonates (breast-fed and formula-fed), premature infants, the elderly, and in pregnancy</td>
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<tr>
<td></td>
<td>• To carry out further research on individual variations in responses to selenium supplementation such as the effect of different dietary and genetic factors</td>
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<tr>
<td></td>
<td>• To investigate the effect of different eating patterns and lifestyles on selenium intake (i.e. is the fall in intake in the UK solely due to the reduced consumption of imported North American wheat?)</td>
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<tr>
<td>(iii) to use human intervention studies to determine dose-response relationships against tissue function</td>
<td>• To investigate the effect of seasonal and regional variations of selenium levels in foods on intake</td>
</tr>
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<td></td>
<td>(iv) to understand the nature and extent of inter-individual variations, so as to identify an optimal nutrient intake for the whole population</td>
</tr>
</tbody>
</table>

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38
Dietary Reference Values (1992)
The Nature and Risks of Obesity (1992)
Coronary Heart Disease I - The Wider Perspective (1992)
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