

**Nutrition Assessment  
Application A470 – Formulated Beverages**

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## Executive Summary

The purpose of the Nutrition Assessment is to determine the nutrition and health need for adding the 24 vitamins and minerals to formulated beverages as originally requested by the Applicant. Although the range of vitamins and minerals has been reduced at Final Assessment as a result of the applicant's revised application, this report provides the rationale for the decision making about the original 24 vitamins and minerals. This means that the outcomes described in this report may not be fully described in the body of the Final Assessment Report. In addition, further work has been undertaken in response to issues raised by submitters, particularly on the adverse health effects of consumption of acidified and sugars-containing beverages, and on bioavailability. These changes have been incorporated into the revised Nutrition Assessment at Final Assessment.

### Nutrition and Health Need

The Policy Guideline permits the voluntary addition of vitamins and minerals to food *where there is a need for increasing the intake of a vitamin or mineral in one or more population groups demonstrated by actual clinical or sub-clinical evidence of deficiency or by data indicating low levels of intake*. For an assessment of the 'nutrition and health need' of the requested vitamin and mineral additions, the first step of the nutrition assessment has therefore been to determine nutritional need, by assessing the extent of existing inadequate vitamin and mineral intakes, or alternatively the extent of vitamin and mineral deficiencies within Australia and New Zealand. If a vitamin or mineral was identified as having an inadequate or deficient population intake, then an existing nutritional need had been demonstrated and did not require further assessment in the context of 'nutrition and health need'.

The Policy Guideline also states that voluntary fortification can be permitted where there is *generally accepted scientific evidence that the fortification can deliver a health benefit*. This potential for a 'health benefit' was investigated for those vitamins and minerals that do not have an existing level of inadequacy or deficiency, as a second step in the assessment of 'nutrition and health need'.

The process used to assess the nutrition and health need for a vitamin or mineral is illustrated in Figure 1 below. Figure 1 shows the results of this process for each of the 24 requested vitamins and minerals. The results in Figure 1 were based on the following criteria at each step:

#### Step 1:

- Inadequate intakes were defined as the situation where 3% or more of the whole population or two sub-population groups have an intake of a vitamin or mineral at a level below the Estimated Average Requirement (EAR)<sup>1</sup>.
- Six vitamins and minerals could not be assessed on the basis of inadequacy as they had no EAR (beta-carotene, biotin, pantothenic acid, chromium, manganese) or because dietary intake data were not available for this assessment (molybdenum). In all cases of a nutritional need based on inadequacy, one of the subgroups with >3% of its intakes below the EAR covered ages representative of the target population for formulated beverages (20-39 years).

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<sup>1</sup> The EAR is a value representing the median requirement for a vitamin or mineral.

- A level of deficiency was established for a vitamin or mineral if there was scientific evidence to show that clinical or sub-clinical deficiency states were prevalent in Australian and New Zealand populations.

Step 2:

- The potential for a ‘health benefit’ was determined by criteria established by FSANZ in relation to the levels of generally accepted scientific evidence.

*Figure 1: Assessment of Nutrition and Health Need*

Vitamin / Mineral		Step 1	Step 2	Existence of a Nutrition and Health Need
		Nutritional Need	Health Benefit	
Group 1	Riboflavin	> 3% of population intakes were below the EAR,  OR  Evidence of deficiency existed	Assessed for the potential to deliver a health benefit  (none met FSANZ criteria for a ‘health benefit’)	<b>Identified as having a nutrition and health need</b>
	Folate			
	Vitamin B <sub>6</sub>			
	Vitamin D			
	Vitamin E			
	Calcium			
	Iodine			
	Iron			
	Magnesium			
	Selenium			
	Zinc			
Group 2	Vitamin A (retinol)	< 3% of population had intakes below the EAR,  AND  No evidence of deficiency  Unable to assess for inadequacy, AND No evidence of deficiency	Assessed for the potential to deliver a health benefit  (none met FSANZ criteria for a ‘health benefit’)	<b>No nutrition and health need identified</b>
	Thiamin			
	Niacin			
	Vitamin B <sub>12</sub>			
	Vitamin C			
	Copper			
	Phosphorus			
	Beta-carotene			
	Chromium			
	Biotin			
	Pantothenic acid			
	Manganese			
	Molybdenum			

Figure 1 shows that Group 1 met all criteria for demonstration of a nutrition and health need. Therefore, the vitamins and minerals with a nutrition and health need in support of their addition to formulated beverages are as follows:

Vitamins

- Riboflavin
- Folate
- Vitamin B<sub>6</sub>
- Vitamin D
- Vitamin E

Minerals

- Calcium
- Iodine
- Iron
- Magnesium
- Selenium
- Zinc

## **Nutrition-Related Health Risks – Overweight/Obesity and Dental Health**

In addition to assessments on nutritional need and health benefit, the Nutrition Assessment has identified the sugar content and acidity of formulated beverages as potential nutrition-related health risks. In order to assess the health risks associated with the consumption of formulated beverages, FSANZ has undertaken a process to first identify the nature and severity of the risks associated with sugars content and acidity of beverages generally, and then to determine whether such risks will increase following the introduction of formulated beverages. This process is outlined below, first for the sugar content of beverages in relation to overweight/obesity and dental caries, and second for beverage acidity and dental erosion.

‘Sugar-containing beverages’ are referred to in the scientific literature as including standard carbonated beverages, fruit juices and drinks, and cordials; but not milk-based beverages (Appendix 9 to Attachment 5). The content of total sugars from natural and added sources in the beverages considered in the literature therefore ranged between about 5-15 g /100 ml. The Nutrition Assessment report adopted the term ‘sugar-containing beverage’ to reflect the above definition of water-based beverages in the literature.

While conducting the assessment on sugar intakes and acidic beverages, FSANZ received comments from the Applicant, detailing ten separate articles critical of an association between sugar-containing beverage intakes and overweight/obesity. Of the ten articles provided by the Applicant, only four were considered suitable when compared to criteria used for the assessment (see Attachment 5 for more details). FSANZ also sought the assistance of an academic working in the field of obesity research to peer-review the assessment, to further ensure that the available evidence was reviewed in an objective manner.

Following assessment of the available literature, and subsequent peer-review, it was determined that an increase in sugar-containing beverage intakes was a risk factor for overweight and obesity. It was also determined that the sugar content of beverages represents a significant risk to dental health due to the positive association between sugar-containing beverage intake and dental caries. Therefore, a risk to public health could develop if the introduction of a formulated beverage category significantly increased population intakes of total sugars.

To assess whether these risks from consuming sugar-containing beverages were likely to arise in the Australian and New Zealand diets, FSANZ undertook dietary modelling at Final Assessment to determine if the consumption of sugar would change significantly with the introduction of formulated beverages.

The results of the modelling on sugar intakes show that the total substitution of all sugar-containing beverages by a formulated beverage category with an unweighted mean total sugars content of 5.5 g /100 ml (reflecting the mean of the current market) produces very little change in per capita total sugars intake. Only if all formulated beverages contained 7.5 g /100 ml (proposed maximum total sugar level) under the conservative condition of complete substitution of sugar-containing beverages would per capita total sugars intake modestly increase.

On the basis of these findings it was concluded that although sugar-containing beverages were identified as a risk factor for overweight and obesity, and dental health, it is unlikely that this potential risk will translate into actual adverse public health outcomes in relation to sugar intake and obesity, or in relation to sugars intake and dental caries with the introduction of formulated beverages.

The acidity of beverages was also assessed, and it is concluded that the consumption of acidic soft drinks and like beverages is probably associated with dental erosion, although it is recognised that the condition depends on a number of other contributing factors. However, exacerbation of current rates of dental erosion would occur only if there was a net increase in acidified non-alcoholic beverage consumption rather than substitution of the currently available products. Since water-type formulated beverage products are more likely to be acidified than their plain bottled water counterparts (which make up a 10% share of the 2005 beverage market), their consumption instead of these more neutral bottled waters may result in a net increase in acid beverages consumed and therefore pose a potential risk of increasing occurrence of dental erosion.

### **Bioavailability**

Several techniques have been developed to assess bioavailability ranging from *in vitro* methods to human balance studies and studies of impact on target body systems. However, controlled studies of fasting consumption of a single food examining the absorption or metabolic utilisation of nutrients are unlikely to provide an accurate assessment of the uptake and regulation within the body. This is because of different meal effects and the range of host-related modifiers that can vary gastrointestinal absorption in response to the internal environment.

Comparison of gastrointestinal absorption rates among vitamins and minerals – irrespective of whether naturally occurring or supplemental – shows wide variability with very few attaining complete intestinal absorption, and demonstrate that vitamins and minerals are not always fully bioavailable.

FSANZ is unaware of any studies that have investigated the bioavailability of vitamins and minerals from formulated beverages. Because the bioavailability of any one vitamin or mineral is likely to be variable, and dependent on several factors, it is therefore not possible to draw conclusions on the actual bioavailability of vitamins and minerals either naturally occurring or added to individual foods, including those in formulated beverages.

## 1. Introduction

The purpose of this assessment is to determine the nutritional and health need, and the health risk to Australian and New Zealand populations, associated with the addition of 24 vitamins and minerals to formulated beverages as requested by the Applicant. Although the range of vitamins and minerals has been reduced at Final Assessment as a result of the applicant's revised application, this report provides the rationale for the decision making about the original 24 vitamins and minerals. This means that the outcomes described in this report may not be fully described in the body of the Final Assessment Report.

FSANZ has conducted this nutrition assessment in accordance with its primary objectives as stated in the *Food Standards Australia New Zealand Act 1991* (the FSANZ Act), which are also reflected in the high order principles of the Policy Guideline 'Fortification of Food with Vitamins and Minerals' (the Policy Guideline):

- the protection of public health and safety;
- the provision of adequate information relating to food to enable consumers to make informed choices; and
- the prevention of misleading or deceptive conduct.

Additional guidance has been obtained from the Policy Guideline, which contains five specific order policy principles for voluntary fortification that are of relevance to population nutrition. These principles state that:

- 'The voluntary fortification of vitamins and minerals to food should be permitted only:
  - Where there is a need for increasing the intake of a vitamin or mineral in one or more population subgroups demonstrated by actual clinical or subclinical evidence or by data indicating low levels of intake.
  - Where there is generally accepted scientific evidence that an increase in the intake of a vitamin and/or a mineral can deliver a health benefit.'
- 'The permitted fortification has the potential to address the deficit or deliver the benefit to a population group that consumes the fortified food according to its reasonable intended use'.
- 'Permission to fortify should not promote consumption patterns inconsistent with the nutrition policies and guidelines of Australia and New Zealand'.
- 'Permission to fortify should not promote increased consumption of foods high in salt, sugar or fat'.
- 'The fortification of a food, and the amounts of fortificant in the food, should not mislead the consumer as to the nutritional quality of the fortified food'.

Although guidance has been sought from the specific order principles of the Policy Guideline, the outcomes of this assessment are primarily driven by the information found within the available scientific literature, and results from the Dietary Intake Assessment (see Attachment 7).

## **2. Assessing the Nutrition and Health Need Associated with Proposed Vitamin and Mineral Additions**

‘Nutrition and health need’ encompasses two concepts: i) nutritional need, referring to inadequate intakes or deficiency states; or ii) ‘health benefits’. The follow sections detail the scientific assessments performed by FSANZ as a means of assessing these two concepts in the context of Application A470.

### **2.1 Nutritional Need – Inadequate Intakes Associated with the Requested Vitamins and Minerals**

To determine the need for fortification, and its impact on population health, it is necessary to quantify the extent of inadequate population intakes of the relevant vitamin or mineral. To undertake this assessment three issues must be considered:

- the existence of a nutrient reference value<sup>2</sup> that can be used as a benchmark against intake data;
- how inadequate intakes are defined and measured against a nutrient reference value;
- the inadequate intakes of any specific population subgroup(s).

#### *2.1.1 Benchmark Nutrient Reference Value – the Estimated Average Requirement*

The estimated average requirement (EAR) is a value that represents the median requirement for the dietary intake of a particular nutrient in a given population group. EARs are commonly used by the United States (US), United Kingdom (UK) and Canada<sup>3</sup> to set other reference values. For example, the recommended dietary intake (RDI or its equivalent term) is set two standard deviations (97.5 percentile) above the EAR (United Kingdom Department of Health, 1993; United States Institute of Medicine, 2000a). Figure 2 below illustrates this relationship between the EAR and RDI.

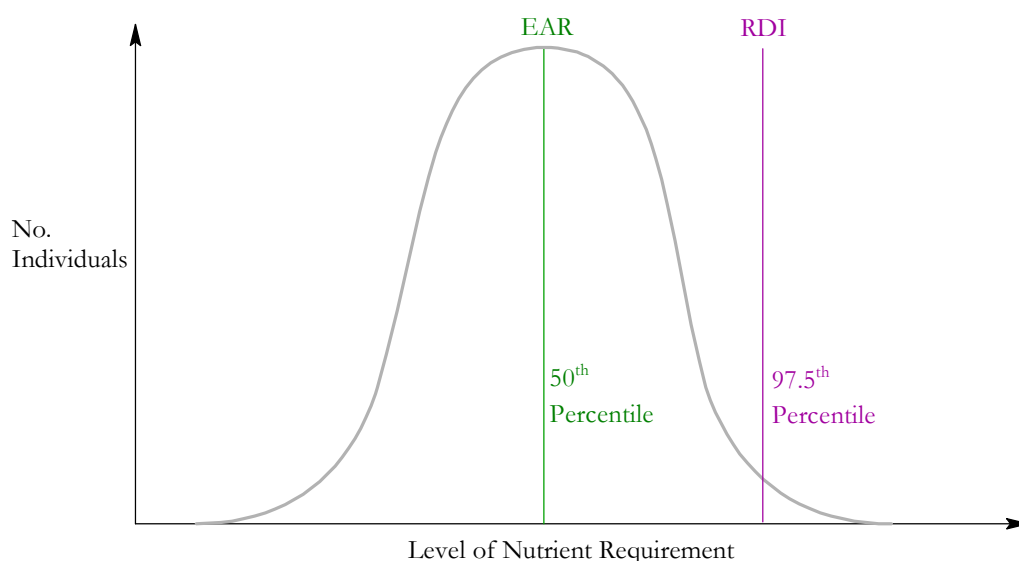
An EAR can also be used as a public health benchmark for comparing and evaluating nutrient intakes, and is useful for this purpose because it is established directly from evidence of nutrient requirements and applies specifically to large populations. The EAR has been assessed as having a high statistical probability of being representative for this purpose (United States Institute of Medicine, 2000a).

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<sup>2</sup> Nutrient reference values are figures set by official bodies (e.g. governments) for each nutrient that act as a measure of a population’s nutritional status.

<sup>3</sup> Canada has adopted the nutrient reference values for the US.

**Figure 2: Nutrient reference values across a distribution of nutrient requirements**



EARs have not been formally established for the Australian or New Zealand populations, although a review of Australian and New Zealand nutrient reference values is due for completion in late 2005, where it is anticipated EARs will be established. Therefore, overseas EARs were used for Application A470; if an overseas EAR did not exist for a vitamin or mineral, then the EAR was extrapolated from the RDI using the formula  $0.7 \times \text{RDI}$ , an approach that was used within the 1983 and 1985 Australian National Dietary Surveys (English *et al.*, 1987).

There are two sources of overseas EARs: the United States (US) Dietary Reference Intakes for vitamins and minerals (United States Institute of Medicine, 1997; 1998; 2000b; 2001) and the UK Dietary Reference Values (United Kingdom Department of Health, 1993). For a few vitamins and minerals the US EAR is equivalent to, or greater than the Australian and New Zealand RDIs. In this situation the US EAR loses its relativity to the RDI (as shown in Figure 1) when applied in the Australian and New Zealand context, and thus its suitability as a measure of the population's requirement for the relevant vitamin or mineral. Therefore, UK EARs are the preferred short-term benchmark for assessing nutritional inadequacy. US values have been used as an alternative if the UK has not set an EAR for a particular nutrient, and if no US value was available then the  $0.7 \times \text{RDI}$  formula has been used.

### 2.1.2 Criteria for Establishing an Inadequate Intake within the Population

Using the percentage of a population with intakes below the EAR as a measure of inadequate intakes is effective if the distribution of nutrient requirements is symmetrical around the EAR. For most vitamins and minerals this is the case, with the exception of iron; iron requirements are skewed due to higher requirements for women of childbearing age. Therefore, although this skewing is not expected to have a significant effect on assessments of iron, any outcomes for iron against the EAR have been treated with caution.

The United States Institute of Medicine has indicated that if any proportion of population intakes drop below the EAR, then the population can be said to have a level of inadequacy for the particular vitamin or mineral (United States Institute of Medicine, 2000a).



However, when applied to an actual assessment of intake data, a very small percentage of the population (i.e. 3% or less) with intakes below the EAR should be considered to represent an adequate population intake of the nutrient. This small percentage is a reflection of the inaccuracies that are inherent in population nutrient intake datasets. Therefore, only if more than 3% of the population has an intake below the EAR will the population as a whole be considered to have an inadequate intake of the relevant vitamin or mineral.

When assessing population intakes, two or more subgroups with greater than 3% of intakes below the EAR spread across a broad range of ages has been considered indicative of an inadequate population-wide intake of a vitamin or mineral. Particular attention has also been given to those age groups representative of the 20-39 year-old target consumer population for formulated beverages.

Population subgroups are based on those age groups allocated to the US or UK EARs, as the EARs have been established specifically for these age divisions. Some EARs may also differ across sex divisions for some nutrients, however FSANZ considers that sex groupings are too specific for a population-wide assessment of intakes.

### *2.1.3 Assessment of Individual Vitamins and Minerals Against the EAR.*

Eighteen vitamins and minerals have been assessed against their respective UK or US EARs as shown in Tables 1 and 2 respectively below. Full details on the statistical process for assessing against EARs can be found at Attachment 7 – Dietary Modelling Methodologies for Nutrient Intake Assessments.

The food consumption data used for the intake assessment were from the 1995 Australian National Nutrition Survey (NNS) and the 1997 New Zealand NNS. Both NNSs used a 24-hour food recall methodology. Approximately 10% percent of respondents from the Australian NNS and approximately 15% of people from the New Zealand NNS completed a second 24-hour recall. These second day data were used to adjust the majority of the vitamin and mineral intake estimates across two days, providing a better estimate of daily nutrient intakes across a longer period of time. For some vitamin and minerals, the second day adjustment could not be calculated (see Attachment 7 for details on these vitamins and minerals).

The vitamin and mineral concentrations used for formulated beverages in the dietary intake assessments are those requested in the Application document. Vitamin and mineral concentrations for all other foods were those from the 1995 Australian, 1997 New Zealand NNS, or analytical survey data.

Nutrient intakes have been assessed for inadequacy by estimating baseline intakes of nutrients and comparing these intakes to EARs. In order to determine whether consuming formulated beverages will address any inadequacy, estimated intakes of vitamins and minerals were calculated assuming that 5% of non-alcoholic beverages (excluding milks) will be replaced with formulated beverages. Vitamin and mineral intakes were then compared to the EAR.

Estimated intakes were calculated for various age groups, with age divisions allocated according to the particular type of EAR used for each vitamin and mineral. While the 1995 Australian NNS includes respondents aged 2 years and above, the 1997 New Zealand NNS only included respondents aged 15 years and above.

The results of the dietary intake assessment (Tables 1 and 2 below), demonstrate that Australian and New Zealand populations consume riboflavin, folate, vitamin B<sub>6</sub>, vitamin E, calcium, iodine, iron, magnesium, selenium and zinc at an inadequate level according to FSANZ's criteria for inadequacy. In each case of inadequacy, the 20-39 year-old target population of formulated beverages also has an inadequate level of intake (19-50 year-old group in Table 1, 19-30 and 31-50 year-old groups in Table 2, and 19-54 year-old group in Table 3).

**Table 1: Estimated Percentage of Respondents for Australian and New Zealand Population Groups With Vitamin and Mineral Intakes Below UK EARs (Results of 3% or more have been highlighted in bold text)**

<i>Nutrient</i>	<i>Modelling</i>	<i>Sub-category</i>	<i>2-3 yrs</i>	<i>4-6 yrs</i>	<i>7-10 yrs</i>	<i>11-14 yrs</i>	<i>15-18 yrs</i>	<i>19-50 yrs</i>	<i>51+ yrs</i>	<i>2+ yrs#</i>
Thiamin	EAR (mg)	Males	0.4	0.5	0.6	0.7	0.8	0.8	0.8	-
		Females	0.4	0.5	0.5	0.6	0.6	0.6	0.6	-
	% below EAR	Aust	0	0	0	0	<1	<1	1	<1
		NZ	-	-	-	-	<1	<1	4	2
Riboflavin	EAR (mg)	Males	0.5	0.6	0.8	1.0	1.0	1.0	1.0	-
		Females	0.5	0.6	0.8	0.9	0.9	0.9	0.9	-
	% below EAR	Aust	0	0	0	0	<b>5</b>	<b>3</b>	<b>5</b>	<b>3</b>
		NZ	-	-	-	-	2	1	<b>3</b>	2
Niacin	EAR (mg)	Males	6.7	9.4	10.8	12.2	15.2	14.0	14.0	-
		Females	6.4	8.5	9.6	10.1	11.6	10.7	10.7	-
	% below EAR	Aust	0	0	0	0	0	0	<1	<1
		NZ	-	-	-	-	0	0	<1	<1
Folate	EAR (µg)	Males	50	75	110	150	150	150	150	-
		Females	50	75	110	150	150	150	150	-
	% below EAR	Aust	0	0	<1	<b>3</b>	<b>4</b>	<b>3</b>	2	2
		NZ	-	-	-	-	<b>4</b>	<b>3</b>	<b>8</b>	<b>5</b>
Vitamin B <sub>12</sub>	EAR (µg)	Males	0.4	0.7	0.8	1.0	1.3	1.3	1.3	-
		Females	0.4	0.7	0.8	1.0	1.3	1.3	1.3	-
	% below EAR	Aust*	0	0	0	0	0	0	0	0
		NZ	-	-	-	-	0	0	0	0
Vitamin C	EAR (mg)	Males	20	20	20	22	25	25	25	-
		Females	20	20	20	22	25	25	25	-
	% below EAR	Aust	0	0	0	0	0	0	0	0
		NZ	-	-	-	-	0	0	0	0
Calcium	EAR (mg)	Males	275	350	425	750	750	525	525	-
		Females	275	350	425	625	625	525	525	-
	% below EAR	Aust	0	0	1	<b>25</b>	<b>30</b>	<b>15</b>	<b>25</b>	<b>20</b>
		NZ	-	-	-	-	<b>35</b>	<b>15</b>	<b>25</b>	<b>20</b>
Magnesium	EAR (mg)	Males	65	90	150	230	250	250	250	-
		Females	65	90	150	230	250	200	200	-
	% below EAR	Aust	0	0	<b>3</b>	<b>35</b>	<b>30</b>	<b>10</b>	<b>15</b>	<b>15</b>
		NZ	-	-	-	-	<b>20</b>	<b>5</b>	<b>20</b>	<b>10</b>
Phosphorus	EAR (mg)	Males	213	273	327	578	404	404	404	-
		Females	213	273	327	483	404	404	404	-
	% below EAR	Aust	0	0	0	<1	0	0	<1	<1
		NZ	-	-	-	-	0	0	0	0

\* Vitamin B<sub>12</sub> was not assessed in the 1995 Australian NNS. Therefore, vitamin B<sub>12</sub> concentrations in foods from the 1997 New Zealand NNS were used in the assessment of vitamin B<sub>12</sub> intakes for the Australian population (see Attachment 7 for more detail).

# 15 years and above for New Zealand.

- No intake data.

**Table 2: Estimated Percentage of Respondents for Australian and New Zealand Population Groups With Vitamin and Mineral Intakes Below US EARs (Results of 3% or more have been highlighted in bold text)**

<i>Nutrient</i>	<i>Modelling</i>	<i>Sub-category</i>	<i>2-3 yrs</i>	<i>4-8 yrs</i>	<i>9-13 yrs</i>	<i>14-18 yrs**</i>	<i>19-30 yrs</i>	<i>31-50 yrs</i>	<i>51-70 yrs</i>	<i>71+ yrs</i>	<i>2+ yrs#</i>
Vitamin A	EAR (µg)	Males	21 0	27 5	445	630	625	625	625	625	-
		Females	21 0	27 5	420	485	500	500	500	500	-
	% below EAR	Aust	0	0	0	<b>3</b>	2	0	0	0	<1
		NZ				0	0	0	0	0	0
Vitamin B <sub>6</sub>	EAR (mg)	Males	0.4	0.5	0.8	1.1	1.1	1.1	1.4	1.4	-
		Females	0.4	0.5	0.8	1.0	1.1	1.1	1.3	1.3	-
	% below EAR	Aust*	0	0	0	<b>10</b>	<b>15</b>	<b>25</b>	<b>45</b>	<b>60</b>	<b>25</b>
		NZ	-	-	-	0	0	<b>15</b>	<b>55</b>	<b>65</b>	<b>25</b>
Copper	EAR (µg)	Males	26 0	34 0	540	685	700	700	700	700	-
		Females	26 0	34 0	540	685	700	700	700	700	-
	% below EAR	Aust*	0	0	0	0	0	0	0	0	0
		NZ	-	-	-	<1	2	0	0	0	<1
Iron	EAR (mg)	Males	3.0	4.1	5.9	7.7	6.0	6.0	6.0	6.0	-
		Females	3.0	4.1	5.7	7.9	8.1	8.1	5.0	5.0	-
	% below EAR	Aust	0	0	2	<b>8</b>	<b>9</b>	<b>7</b>	<1	<b>3</b>	<b>5</b>
		NZ	-	-	-	<b>4</b>	<b>5</b>	1	<1	<1	2
Selenium	EAR (µg)	Males	17	23	35	45	45	45	45	45	-
		Females	17	23	35	45	45	45	45	45	-
	% below EAR	Aust*	<b>20</b>	<b>25</b>	<b>30</b>	<b>35</b>	<b>30</b>	<b>35</b>	<b>40</b>	<b>45</b>	<b>35</b>
		NZ	-	-	-	<b>50</b>	<b>45</b>	<b>15</b>	<b>60</b>	<b>75</b>	<b>40</b>
Zinc	EAR (mg)	Males	2.2	4.0	7.0	8.5	9.4	9.4	9.4	9.4	-
		Females	2.2	4.0	7.0	7.5	6.8	6.8	6.8	6.8	-
	% below EAR	Aust	0	0	<b>3</b>	<b>8</b>	<b>8</b>	<b>3</b>	<b>9</b>	<b>17</b>	<b>6</b>
		NZ	-	-	-	<b>5</b>	<b>4</b>	1	<b>13</b>	<b>18</b>	<b>7</b>

\* Vitamin B<sub>6</sub>, Copper, and Selenium intake data are available only for New Zealand (1997 NNS); the data for Australia has been adapted from the New Zealand NNS data for vitamin B<sub>6</sub> and copper, and derived from Australian survey data for selenium (see Attachment 7).

\*\* 15-18 years for New Zealand.

# 15 years and above for New Zealand.

- no intake data

**Table 3: Estimated Percentage of Respondents for Australian and New Zealand Population Groups With Vitamin and Mineral Intakes Below EAR (Derived by 0.7 x RDI) (Results of 3% or in bold text)**

Nutrient	Modelling	Sub-category	1-3 yrs	4-7 yrs	8-11 yrs	12-15 yrs**	16-18 yrs	19-54 yrs	55-64 yrs	65+ yrs	2+ yrs#
Vitamin E	EAR (mg α-tocopherol equivalents)	Males	3.5	4.2	5.6	7.4	7.7	7	7	7	-
		Females	3.5	4.2	5.6	6.3	5.6	4.9	4.9	4.9	-
	% below EAR	Aust	<1	<b>3</b>	2	<b>15</b>	<b>10</b>	<b>7</b>	<b>10</b>	<b>15</b>	<b>8</b>
		NZ	-	-	-	<b>4</b>	<b>9</b>	<b>3</b>	<b>3</b>	<b>3</b>	<b>3</b>

\* Vitamin E was not assessed in the 1995 Australian NNS. Therefore vitamin E concentrations in foods from the 1997 New Zealand NNS were used in the assessment of vitamin E intakes for the Australian population.

\*\* Only 15 year olds for New Zealand

# 15 years and above for New Zealand.

- no intake data

## 2.2. Nutritional Need – Evidence on Sub-clinical or Clinical Deficiencies

Nutritional need can also be determined outside of assessments on intake data, as inadequate population intakes can also express themselves through clinical indicators of deficiency.

A recent review of vitamin and mineral permissions in the *Australia New Zealand Food Standards Code* (the Code), Proposal P166 - Vitamins and Minerals in General Purpose Foods, identified vitamin D and iodine as having data showing an existing level of deficiency in Australia and New Zealand. The National Health and Medical Research Council (NHMRC) also identified vitamin D and iodine as the only two nutrients with an existing level of deficiency in Australia and New Zealand as part of its recent review of Nutrient Reference Values (NHMRC, 2005). Therefore, of the 24 vitamins and minerals proposed by the Applicant, FSANZ has focused its assessment on the prevalence of deficiency states in Australia and New Zealand to vitamin D and iodine.

### 2.2.1 Vitamin D

FSANZ commissioned an assessment (Nowson and Margerison, 2001) into the vitamin D status of Australians as part of Proposal P166 – Vitamins and Minerals. The vitamin D report gives a comprehensive assessment of the prevalence of vitamin D deficiencies in Australia. This report is still considered to be relevant today, and is also applicable to New Zealand given the similarities in climate, culture and food intakes.

The report by Nowson and Margerison (2001) details the following on vitamin D deficiency:

#### Elderly

For older persons living in the community the estimated prevalence of frank deficiency (FD) (serum 25-hydroxycholecalciferol <28 nmol/L) ranges from 17% to 22% of individuals (Inderjeeth *et al.*, 2000; Pasco *et al.*, 2001).

FD for elderly persons in residential care has been measured at 22% of residents (Flicker *et al.*, 2003), and at 45-67% for residents with limited mobility (Stein *et al.*, 1996; Inderjeeth *et al.*, 2000; Flicker *et al.*, 2003).

The rates of marginal deficiency (MD) (serum 25-hydroxycholecalciferol = 28-100 nmol/L) are considerably higher in the elderly at 58% of individuals in the community (Pasco *et al.*, 2001), and 53-76% of elderly persons in residential care (Stein *et al.*, 1996; Flicker *et al.*, 2003).

### Dark skinned pregnant women and their breast-fed infants

The majority of information on dark-skinned women and their infants in Australia is anecdotal. However, one published study (Grover and Morley, 2001), has indicated that 80% of pregnant dark-skinned, veiled women attending one antenatal clinic in a large teaching hospital had vitamin D levels <22 nmol/L (the lowest reference range value used within this study).

### Adolescents

An estimate of MD prevalence in adolescents puts the rate at 68% (Jones, 2001), and FD has been estimated at 10% (Jones *et al.*, 1999).

### General population

There is evidence that up to 8% of younger women (20-39 years) have FD at the end of winter and 33% have MD. The population group aged 20-80 years has also been estimated to have FD at 11% and MD at 43% during winter, and FD at 7% and MD at 30% for the whole year (Pasco *et al.*, 2001).

The information provided by Nowson and Margerison (2001) shows that there are several significant Australian population sub-groups that have vitamin D deficiency or are at risk of developing vitamin D deficiency.

### 2.2.2 Iodine

In the early 1990s it was reported that there was no evidence of iodine deficiency anywhere in Australia (Stanbury, 1996). In more recent years however, a downward trend in iodine status has been noted in both Australian and New Zealand populations (NHMRC, 2005).

Studies shown in Table 4 below indicate that iodine deficiency exists to various extents in both Australian and New Zealand population groups. In Australia, no national surveys have been undertaken to assess the iodine status of Australians, although national data collection in a National Iodine Nutrition Study is currently in progress. New Zealand has regularly monitored national iodine status because of the low iodine content of its soils. Monitoring of iodine status also occurs in Tasmania where iodised salt is now used in the majority of Tasmanian bread manufacture, however the data are currently unpublished.

Both the World Health Organization (WHO) and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) suggest that no more than 20 percent of a population should have a urinary iodine level less than 50 µg/L, and that a median urinary iodine of 100µg/L or greater is indicative of iodine sufficiency (ICCIDD, 2001).

Therefore, it is concluded from the studies of urinary iodine levels in Table 4 that a sizable proportion of the Australian and New Zealand populations are deficient in iodine to varying extents.

Table 4: Results from studies investigating iodine status of Australian and New Zealand populations

Author	Subjects	No.	% < 50 µg/L	% <100 µg/L	Median urinary iodine concentration
AUSTRALIA					
Gunton <i>et al.</i> (1999)	Pregnant women, Sydney	81	19.8	49.6	104 µg/L
	Postpartum women, Sydney	28	19.2	53.9	79 µg/L
	Patients with diabetes, Sydney	135	34.1	71.9	65 µg/L
	Volunteers, Sydney	19	26.3	73.7	64 µg/L
Guttikonda <i>et al.</i> (2003)	Children 5 -13 years, Central coast, NSW	301	14	69	82 µg/L
Li <i>et al.</i> (2001)	Children 6 -13 years, Sydney	94	13.8		84 µg/L
	Pregnant women from antenatal class, Sydney	101	20.6		88 µg/L
	Adult volunteers, medical staff, Sydney	86	17.8		88 µg/L
	Diabetes patients, Sydney	85	23.5		69 µg/L
McDonnell <i>et al.</i> (2003)	Males, 11-18 years, Melbourne	167	17	68	
	Females, 11-18 years, Melbourne	410	31	79	
	Total, Melbourne	577	27	76	
Hynes <i>et al.</i> (2004)	Children in 1998/1999 at baseline, Tasmania	170	13.5	77.6	76 µg/L
	The same children in 2000/2001, Tasmania	170	21.2	69.4	75 µg/L
Hamrosi <i>et al.</i> (2005)	Pregnant women – Caucasian, Melbourne	227	48.4		52 µg/L
	Pregnant women – Vietnamese, Melbourne	263	38.4		58 µg/L
	Pregnant women – Indian/Sri Lankan, Melbourne	262	40.8		61 µg/L
NEW ZEALAND					
Thomson <i>et al.</i> (1997)	Blood Donors, Dunedin and Waikato	333	57	92	Male 51 µg/L Female 42 µg/L
Skeaff <i>et al.</i> (2002)	Children 8 - 10 years, Dunedin and Wellington	282	35.0	79.7	66 µg/L
Thomson <i>et al.</i> (2001)	Men and women 18 - 49 years, Otago	233			Male 55 µg/L Female 52 µg/L
Ministry of Health (2003)	Children 5 -14 years, National	1796	28		66 µg/L (68 µg/L males, 62 µg/L females)
Skeaff <i>et al.</i> (2005)	Infants and toddlers 6-24 months, South Island	230	37	67.4	67 µg/L
	Breast fed infants and toddlers 6-24 months, South Island	43	51.2	83.7	44 µg/L
	Formula fed infants and toddlers 6-24 months, South Island	51	13.7	51.0	99 µg/L

### 2.3 Vitamins and Minerals not Assessed on Nutritional Need

It is not possible to determine the nutritional need of Australian and New Zealand intakes for all of the vitamins and minerals requested by the Applicant. Biotin, pantothenic acid,  $\beta$ -carotene, chromium, and manganese do not have an overseas EAR that can be used to assess their adequacy (or an RDI that can be used for a proxy calculation), nor do they have any other evidence on clinical indicators that can be used to assess any possible deficiency state. Molybdenum has an EAR, however there are extremely limited, unassessed food composition data on this mineral that does not allow for a robust intake assessment against its EAR. Therefore, FSANZ has determined that an inadequate level of intake cannot be determined for to these vitamins and minerals, as there is no available evidence to demonstrate such an outcome.

### 2.4 Assessing the Health Benefits from Increasing Individual Vitamin and Mineral Intakes

In addition to demonstrating a level of inadequacy or deficiency, the Policy Guideline also mentions that fortification can be permitted where there is generally accepted scientific evidence that an increase in the intake of a vitamin or mineral can deliver a health benefit.

As there is evidence that a number of vitamins and minerals are consumed at an inadequate or deficient level in Australia and New Zealand (see Sections 2.1 and 2.2 above), these vitamins and minerals can be considered eligible for addition to formulated beverages on the basis of a nutrition and health need. FSANZ has not assessed the potential to deliver a health benefit with an increased intake of these particular vitamins and minerals. Therefore, an assessment of health benefit has been undertaken on the balance (13) of the vitamins and minerals requested by the Applicant:

#### Vitamins

- vitamin A
- beta-carotene
- thiamin
- niacin
- vitamin B<sub>12</sub>
- Vitamin C
- biotin
- pantothenic acid

#### Minerals

- chromium
- copper
- manganese
- molybdenum
- phosphorus

#### 2.4.1 *Health Benefit in the Context of Fortification with Vitamins and Minerals*

There are two key elements to the concept of a ‘health benefit’ as stated in the Policy Guideline:

1. Generally accepted scientific evidence
2. An increase in the intake of a vitamin and/or mineral can deliver a health benefit



#### 2.4.1.1 Generally Accepted Scientific Evidence

From scrutiny of the orthodox scientific nutritional and medical literature, generally accepted scientific evidence has been collected according to documented search strategies designed to draw in the totality of evidence. The data were assessed, and conclusions drawn as to an overall level of evidence.

An acceptable level of evidence that acknowledges a health benefit is where the weight of the totality of that evidence – mainly from well-designed and controlled observational and/or experimental studies in humans – is generally supportive of an association between a defined intake of vitamin and mineral and beneficial health outcome.

#### 2.4.1.2 An Increase in the Intake of a Vitamin and/or Mineral can Deliver a Health Benefit

FSANZ considers the reference in the Policy Guideline to *an increase in the intake* is satisfied by a theoretical demonstration of changes in population intakes as they relate to possible new or amended permissions for voluntary addition of a vitamin or mineral to food.

It is accepted that increased intakes towards the RDI could deliver better nutrition for a population since the RDI, as a measure of nutritional adequacy, is a population recommendation that covers the nutritional needs of practically all healthy people. The potential delivery of nutritional benefits through voluntary fortification has been addressed through another component of the Policy Guideline, which refers to establishing nutritional need through assessment of dietary inadequacy or deficiency. Potentially increased intakes that traverse the EAR towards the RDI are anticipated to deliver better nutrition as a result of voluntary fortification. However, any nutritional benefits achieved through increases in intake from levels above the EAR towards the RDI are less certain and, as such, are not considered to constitute a separate ‘health benefit’ for the purposes of decision making.

Available evidence should therefore support a health benefit at intakes above the RDI but below an upper safe limit. By virtue of the definition of the RDI, such benefits are not likely to be nutritional in nature but related to other health benefits. Where an Australian/New Zealand RDI for nutritional adequacy has not yet been set, similar overseas values are used.

Health benefit is regarded as an increase in health status or reduction in chronic disease risk that is not nutritional in nature, however the term does not extend to pharmacological benefit or treatment of disease. Evidence of health benefit can be drawn from healthy populations as well as those at-risk or suffering diseases of public health significance. The selected list of diseases are those that contribute to more than 2% disability adjusted life years in the Australian and New Zealand burden of disease registers (Mathers *et al.*, 1999; Ministry of Health, 2001). These diseases include:

- Cardiovascular diseases;
- Cancer;
- Wound healing (injury);
- Bone disorders and bone maintenance;
- Diabetes;
- Gastrointestinal functioning / disorders;
- Chronic respiratory diseases; and
- Immune functioning / disorders.

Endpoints for health benefits are regarded as clinical endpoints as well as effects on physiological parameters (i.e. biomarkers of disease), but not biochemical changes or placebo effects.

In summary, the basis for determining the potential nutrition and health need for voluntary fortification of formulated beverages is based on either an assessment of nutritional need (with anticipated potential delivery of nutritional benefit) or evidence of other health benefit at intakes above the RDI for the populations and conditions described above. This is shown in the following figure where the vertical lines represent the two types of nutrient reference values.

**Figure 3: Schematic representation of evidence required to meet nutrition and health needs**

EAR	RDI	
Inadequate – nutritional need, anticipate nutritional benefit	Adequate	Other health benefit based on evidence at intakes > RDI

#### 2.4.2 Criteria Used to Assess the Evidence Base of a Vitamin or Minerals ‘Health Benefit’

The issues raised in Section 5.1 above have been applied to FSANZ’s assessment of health benefit. However, to finalise an assessment of health benefit, FSANZ has categorised all identified, relevant material into six levels of evidence. A summary of the main characteristics for each level is shown in Table 5 below.

**Table 5: Summary of the Categorisation of Evidence for a ‘Health Benefit’**

Level of Evidence	Association with a health outcome	Contradictory evidence	Human studies necessary	Minimum type of evidence	Source of vitamin and mineral intakes	Support from chemical, cellular or animal models
A	Insufficient evidence to establish an association					
0	Demonstrated lack of association					
1	Possible association with a high level of inconsistency in findings	Significant amount	No	Any		
2	Association with a moderate inconsistency in findings	Some	No	Any		
3	Association with little or no inconsistencies in findings	Little or none	Yes	Well-developed intervention or observational studies of suitable quality.	The identified health outcomes may occur with supplemental intake	

<b>Level of Evidence</b>	<b>Association with a health outcome</b>	<b>Contradictory evidence</b>	<b>Human studies necessary</b>	<b>Minimum type of evidence</b>	<b>Source of vitamin and mineral intakes</b>	<b>Support from chemical, cellular or animal models</b>
<b>4</b>	Causal relationship	Little or none	Yes	Well-developed intervention or observational studies of suitable quality.	The identified health outcomes must occur with intakes from food (i.e. not therapeutic doses)	Necessary

#### Level A Evidence

- The evidence base consists of a very limited number of studies, and therefore cannot be used to identify an association between the vitamin or mineral and a health outcome.

#### Level 0 Evidence

- Evidence exists that strongly confirms the absence of any health benefit associated with intakes of the vitamin or mineral above the RDI.
- The evidence base may also be a discontinued line of research.

#### Level 1 Evidence

- The evidence base suggests a possible relationship between the vitamin or mineral and a health outcome, but study results or outcomes may be inconsistent with each other or may reflect predominantly emerging evidence.
- There may be a significant number of contradictory findings within the evidence base.
- The evidence may be derived from any type of study: chemical, cellular or animal models; and/or experimental or observational studies.

#### Level 2 Evidence

- An association that is only moderately consistent between intakes of the vitamin or mineral beyond the RDI and the identified health outcomes. Alternatively, the evidence base may be insufficient to make a more definitive judgement, such as where available studies are of limited duration, have sample sizes of insufficient power, or have incomplete follow-up.
- There may be a proportion of studies with outcomes that contradict the association between the vitamin or mineral and the identified health outcomes.
- The evidence can be derived from any type of study: chemical, cellular or animal models; and/or experimental or observational studies.

### Level 3 Evidence

- An association that is not fully consistent between intakes of the vitamin or mineral beyond the RDI and the identified health outcomes. Alternatively, the evidence base may be insufficient to make a more definite judgement, such as where available studies are of limited duration, have sample sizes of insufficient power, or have incomplete follow-up.
- There is little or no evidence contradicting the association.
- The evidence base must include human studies.
- At a minimum, the evidence base contains either well-designed experimental or observational studies (including cohort studies and/or case-control studies as a minimum).

### Level 4 Evidence

- A consistent and causal relationship between intakes of the vitamin or mineral beyond the RDI and the identified health outcomes.
- There is little or no evidence contradicting the association.
- The evidence base must include human studies.
- The evidence base must show that vitamins and minerals provided in a food matrix can deliver the identified health outcomes (i.e. not just from supplemental intakes).
- At a minimum, the evidence base contains either well-designed experimental or observational studies (including cohort studies and/or case-control studies as a minimum).
- There must be chemical, cellular or animal model studies that support the findings of experimental and observational studies.

An increase in the intake of a vitamin or mineral is considered to have ‘generally accepted scientific evidence’ showing that it ‘can deliver a health benefit’ if the level of evidence is 3 or 4. The 3 and 4 levels are considered to demonstrate health benefit because these levels have little or no scientific material contradicting a positive health outcome.

The relevant scientific information on each of the 13 vitamins and minerals that require an assessment of their ability to deliver a health benefit has therefore been collated and categorised in accordance with the above measures.

#### *2.4.3 Health Benefit Literature Searches*

In acquiring scientific evidence on health benefits, the ‘PubMed’ and ‘Nutrition Abstracts and Reviews’ electronic databases were searched. The number of articles obtained through these literature searches is shown in Table 1 of the Appendix to this document.

If the search produced more than 130 results, then the original keywords were further refined to narrow the number of articles generated. The volume of material for beta-carotene and vitamin C was exceptionally large, and therefore PubMed was the only electronic database searched. In these cases, the draft NHMRC document ‘Nutrient Reference Values for Australia and New Zealand’ (NHMRC, 2005) was cross-referenced for additional material.

When considering any literature that used supplemental doses of a vitamin or mineral, the study was excluded if it did not assess the intake of an individual vitamin/mineral in an isolated dose; that is, the results from combination supplement doses (that contained the relevant vitamin/mineral) were not included in the assessment of health benefit.

#### 2.4.4 Assessment of Health Benefits

The full results of FSANZ’s assessments of health benefits can be found in Appendices 2-8 of this nutrition assessment report.

Of the vitamins and minerals that do not have an inadequate or deficient intake in Australia and New Zealand, none have been shown to have the potential to deliver a health benefit (evidence levels of 3 or 4). These vitamins and minerals have either an A, 0, 1 or 2 level of scientific evidence for their association with various health outcomes as shown in Table 6 below, a level that is too low to conclude that these vitamins and minerals have the potential to deliver a health benefit.

**Table 6: Levels of Evidence on Health Benefits**

Level of Evidence	Vitamins and Minerals Meeting the Evidence Level Category
A	Thiamin, niacin, biotin, pantothenic acid, copper, manganese, and molybdenum.
0	Vitamin B <sub>12</sub>
1	Vitamin C, β-carotene, phosphorus
2	Chromium
3	None
4	None

## 2.5 Outcomes of the Nutrition and Health Need Assessment

The Applicant has requested the addition of 24 vitamins and minerals to formulated beverages. Of these 24 vitamins and minerals the following assessments of nutrition and health need (inadequacy, deficiency and health benefit) have been made:

**Table 7: Assessment of Nutrition and Health Need**

<i>Vitamin or Mineral</i>	<i>Meets Inadequacy Criteria</i>	<i>Meets Deficiency Criteria</i>	<i>Meets Health Benefit Criteria</i>	<i>Assessed as Having a Nutrition and Health Need</i>
Vitamin A	No	No	No	
Beta-carotene	No	No	No	
Thiamin	No	No	No	
Riboflavin	✓			✓
Niacin	No	No	No	
Vitamin B <sub>6</sub>	✓			✓
Folate	✓			✓
Vitamin B <sub>12</sub>	No	No	No	
Biotin	No	No	No	
Pantothenic Acid	No	No	No	
Vitamin C	No	No	No	
Vitamin D	No	✓		✓
Vitamin E	✓			✓

<i>Vitamin or Mineral</i>	<i>Meets Inadequacy Criteria</i>	<i>Meets Deficiency Criteria</i>	<i>Meets Health Benefit Criteria</i>	<i>Assessed as Having a Nutrition and Health Need</i>
Calcium	✓			✓
Chromium	No	No	No	
Copper	No	No	No	
Iodine	N/A	✓		✓
Iron	✓			✓
Magnesium	✓			✓
Manganese	No	No	No	
Molybdenum	No	No	No	
Phosphorus	No	No	No	
Selenium	✓			✓
Zinc	✓			✓

N/A = not assessed.

### 3. The Potential for Formulated Beverage Fortification to Address Nutrition and Health Needs

The Policy Guideline mentions that in addition to demonstrating a nutrition and health need, a permitted fortification must have the *potential to address the deficit or deliver the benefit*.

As shown in Section 2 above, the ability to address a nutritional need is the only concern for formulated beverages, as there is no evidence to support a delivery of a health benefit from increases in the intakes of the vitamins and minerals proposed for addition to formulated beverages. Because any addressing of deficiency states requires monitoring of clinical indicators over time, the focus of this section has been on the ability to address inadequacy.

Therefore, to assess the ability to address an existing inadequacy, FSANZ has modelled the impact from formulated beverage fortification on the 9 vitamins and minerals identified in Section 2 as having an inadequate intake. If the percentage of respondents with intakes less than the EAR decreases, then the addition of that vitamin or mineral to formulated beverages can be said to have contributed to a correction in its inadequacy. Table 5 below summarises the results of this modelling process, showing the change in respondents with intakes less than the EAR as a range across various age groups.

Table 8: The Change in Percentage of Respondents with Intakes Less Than the EAR Following Formulated Beverage Fortification

<i>Nutrient</i>	<i>Range of Change (% Respondents with Intakes &lt; EAR)</i>	
	<i>Maximum Negative Change</i>	<i>Maximum Positive Change</i>
Riboflavin	-2	0
Vitamin B <sub>6</sub>	0	5 (change in one subgroup only)
Folate	0	0
Vitamin E	0	6
Calcium	0	5
Iron	-3	0
Magnesium	0	10
Selenium	-5	5
Zinc	-5	0

Table 8 shows that the addition of vitamins and minerals to formulated beverages has an inconsistent impact on the intakes of these nutrients, with some age groups in the population experiencing an improvement in intakes (a positive change) while others either have no change or a drop in intakes. This information indicates that formulated beverage fortification has a variable impact across the population, and that it is difficult to conclusively determine whether the fortification has the potential to be effective or not. Given that the proposed vitamin and mineral additions to formulated beverages are voluntary and subject to implementation by industry, this uncertainty in the effectiveness of formulated beverage fortification is reinforced further.

Therefore, although FSANZ recognises the intention behind the specific order principle on effectiveness stated in the Policy Guideline, this principle cannot be employed successfully to formulated beverages and is therefore excluded from further consideration in this nutrition assessment.

## **4. Nutrition-Related Health Risks**

The request to voluntarily fortify formulated beverages raises a number of nutritional issues. Formulated beverages may contain acids and sugars that could potential produce health risks in the context of Australian and New Zealand diets. Therefore, in order to assess the health risks associated with the consumption of formulated beverages, FSANZ has undertaken a process to first identify the nature and severity of the risks associated with sugars content and acidity of beverages generally, and then to determine whether such risks will increase following the introduction of formulated beverages. This process is outlined in the sections below, first for sugar contents of beverages in relation to overweight/obesity and dental caries, and second for beverage acidity and dental erosion.

### **4.1 Sugar-Containing Beverages and Overweight/Obesity**

There is a growing evidence base which indicates that unrestricted consumption of sugar-containing<sup>4</sup> beverages can lead to weight gain and the development of an overweight or obese status in both children and adults.

The purpose of this section is therefore to look at the association between consumption of sugar-containing beverages and overweight/obesity. In conducting this assessment, FSANZ recognises that sugar-containing beverages have not been identified as the sole contributor to overweight and obesity; these conditions are multifactorial in nature (Saris, 2003). Addressing one particular risk factor will not, by itself, eliminate the growing overweight and obesity problems facing Australia and New Zealand. There is however an indication that children receive between 7-15% of their energy from refined sugars, of which sugar-containing beverages are the largest contributor (Somerset, 2003). Therefore, an assessment of the association between sugar-containing beverages and overweight/obesity will better clarify a potential public health and safety risk associated with beverages.

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<sup>4</sup> 'Sugar-containing' in the context of this attachment refers to those products containing sucrose and fruit derived sugars (e.g. fructose).

Most literature reviews on sugar and obesity are not highly relevant for FSANZ's assessment, as they are directed more at the association between the overall dietary sugars intake and overweight/obesity, rather than specifically dealing with sugar-containing beverages (Hill and Prentice, 1995; Saris 2003).

However, two recently literature reviews have looked directly at the evidence on sugar-containing beverages and overweight/obesity. The Agencies for Nutrition Action concluded in its review (Agencies for Nutrition Action 2005) that there is extensive evidence showing that sugar-containing drinks contribute to weight gain in children (after accommodation for growth). The World Health Organization also classified the evidence base as showing a 'probable' level of association between sugar-containing beverages and weight gain (World Health Organization, 2003).

The findings of these literature reviews are significant in their own right, however the small number of literature reviews on sugar-containing beverages has persuaded FSANZ to conduct its own assessment directly from primary research material. FSANZ has also received comments from the Applicant, detailing ten separate articles in support of the view that there is no association between sugar-containing beverage intakes and overweight/obesity. To ensure an adequate assessment of this material from the Applicant, FSANZ has included the evidence in its review. Finally, FSANZ's assessment was peer-reviewed by a research fellow with extensive experience in the field of overweight and obesity management.

#### *4.1.1 Evidence on Sugar-Containing Beverages and Overweight/Obesity*

Primary research on sugar-containing beverages and overweight/obesity was obtained through a search strategy that included a search of both PubMed, and Nutrition Abstract and Review electronic databases, as well as an investigation of references cited in the two literature reviews mentioned above. Excluded from a final list of studies were articles with the following features:

- research that did not examine or report specifically on the association between sugar-containing beverages and weight (or similar anthropometry); and
- intervention studies, where the intervention measure was not designed to specifically address the intake of sugar-containing beverages.

From this search strategy, FSANZ has identified 20 studies that assess the relationship between sugar-containing beverage intakes and overweight/obesity; these studies are described in Appendix 9 of this Attachment. The 20 identified studies include nine cross-sectional, two case-control, eight prospective cohort, and one intervention study.

Within the 20 identified studies, 'sugar-containing beverages' can include regular carbonated beverages, fruit juices and drinks, and cordials; but not milk-based beverages. Not all studies looked at the consumption of these beverages though – some studies focused on one particular type of beverage only. Within the literature, the total sugars content of sugar-containing beverages ranged between approximately 5-15 g/100 ml. Also, the serving sizes attributed to beverage intakes were not consistently defined across studies, which adds a degree of uncertainty to interpretations made about the entire evidence base.



Associations between the intake of sugar-containing beverages and body weight were determined either by measuring changes in body mass index (BMI)<sup>5</sup>, or by classifying subjects into BMI-defined categories. For those studies using BMI-defined categories, the majority separated subjects into 'obese/overweight' and 'non-obese/normal weight' groups only. However, Welsh *et al.* (2005) and Melgar-Quinonez and Kaiser (2004) also added a third 'at risk of overweight' category, as a means of tracking trends across a spectrum of BMI categories.

Of the cross-sectional studies identified by FSANZ, four showed a significant ( $p < 0.05$ ) positive association between consumption of sugar-containing beverages and obesity in children (Troiano *et al.*, 2000; Giammattei *et al.*, 2003; Melgar-Quinonez and Kaiser, 2004; Ariza *et al.*, 2004), whereas four showed no association in children ( $p > 0.05$ ) (Bandini *et al.*, 1999; Forshee and Storey, 2003; Forshee *et al.*, 2004; Janssen *et al.*, 2005). One additional cross-sectional study by Lin *et al.* (2004) was identified, which assessed both adults (females) and children. Interestingly, Lin *et al.* (2004) found a significant positive association with adults, but no association for children.

Two case-control studies on children and adolescents showed significant positive associations between sugar-containing beverage intakes and those with an obese/overweight status (Tanasescu *et al.*, 2000; Gillis and Bar-Or, 2003).

The eight prospective cohort studies examined mostly children and adolescents, although Schulze *et al.* (2004) assessed adult females, and Kvaavik *et al.* (2005) tracked changes into adulthood. The eight studies also assessed changes over time periods of 1-18 years, with two years the most common length of time. Five of the prospective cohort studies showed a significant ( $p < 0.05$ ) association between increased sugar-containing beverage intakes over time and body weight change or overweight/obesity (Ludwig *et al.*, 2001; Berkey *et al.*, 2004; Schulze *et al.*, 2004; Phillips *et al.*, 2004; Welsh *et al.*, 2005). Three prospective cohort studies reported no significant association ( $p > 0.05$ ) over time (Newby *et al.*, 2004; Kvaavik *et al.*, 2005; Blum *et al.*, 2005).

One intervention study on primary school-aged children was identified (James *et al.*, 2004). This study used a cluster-randomised controlled design and produced a significant decrease in the sugar-containing beverage intake of intervention subjects compared to controls. A corresponding reduction in the prevalence of overweight and obesity was reported over 12 months ( $p < 0.05$ ).

#### 4.1.2 Assessment of the Evidence Base

##### 4.1.2.1 Assessment of Results

Results from cross-sectional studies are mixed, and show both positive associations ( $p < 0.05$ ) and no associations ( $p > 0.05$ ) between the intake of sugar-containing beverages and obesity. Increasing sample sizes did not favour either a significant positive association or no association with obesity.

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<sup>5</sup> The BMI is derived by dividing weight (kg) over height (m) squared. In adult populations this is a good estimate of the prevalence of overweight and obesity. In children however, weight and height can vary in relation to each other depending on the stage of growth. BMI comparisons across and between childhood ages therefore need to accommodate for this variation, usually through reference against BMI percentile distributions, or by use of established mathematical formulae.

Outcomes of case-control and prospective cohort studies were more definitive in their results than cross-sectional studies. The majority of these studies showed positive associations between sugar-containing beverages and overweight/obesity.

As longitudinal studies, the prospective cohort research also shows trends over time. Several trends were observed:

- High intakes of sugar-containing beverages result in significantly ( $p < 0.05$ ) greater subject numbers moving from a normal to an obese category (Ludwig *et al.*, 2001), and from a normal or 'at-risk' category into an obese category (Welsh *et al.*, 2005).
- An increase in sugar-containing beverage intake over time was associated with a significantly ( $p < 0.05$ ) greater level of weight gain (an increase in BMI, adjusted for growth in children) (Ludwig *et al.*, 2001; Berkey *et al.*, 2004; Schulze *et al.*, 2004; Phillips *et al.*, 2004); and
- Static intakes (either high or low) had no impact on BMI over time ( $p > 0.05$ ) (Schulze *et al.*, 2004).

The sole intervention study (James *et al.*, 2004) is a key piece of research, as the study was based on appropriate BMI percentile values using the latest growth references, and applied a small standard deviation in beverage intakes to give their results a high statistical power (90% at  $p < 0.05$ ). The good quality and high-level (intervention) design of the study effectively demonstrates that a successful reduction in the intake of sugar-containing beverages over time can reduce the prevalence of overweight and obesity.

#### 4.1.2.2 Assessment of Results in the Context of the Total Diet

The majority of the 20 identified studies restricted their research to sugar-containing beverages or total beverages<sup>6</sup> only. However, six studies (Tanasescu *et al.*, 2000; Gillis and Bar-Or 2003; Melgar-Quinonez and Kaiser 2004; Ariza *et al.*, 2004; Lin *et al.*, 2004; Janssen *et al.*, 2005) also assessed their data in the context of the entire diet, and therefore can be used for a comparison between sugar-containing beverages and other food and beverage categories.

Two of the total-diet studies (Tanasescu *et al.*, 2000; Gillis and Bar-Or 2003) showed a significant positive association between sugar-containing beverage intakes and the prevalence of overweight/obesity, as well as with high-energy snack food intake (e.g. potato chips, confectionery). Three other studies showed a significant positive association between intakes of sugar-containing beverages and the prevalence of overweight/obesity, yet did not identify any similar association for other food and beverage categories (Melgar-Quinonez and Kaiser 2004; Ariza *et al.*, 2004; Lin *et al.*, 2004). Two studies (Lin *et al.*, 2004; Janssen *et al.*, 2005) reported no association between intakes of sugar-containing beverages and body weight change (in children) or the prevalence of overweight/obesity, yet neither did they identify an association for any other category of food.

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<sup>6</sup> 'Total beverages' refers to all beverages including milk, juices, soft drinks, alcohol (if appropriate) and sports drinks.

#### 4.1.2.3 Quality of Identified Studies

Several studies have been identified as containing design issues:

- The body mass index (BMI) was measured by a number of childhood studies that reported no association with sugar-containing beverage consumption, yet these studies did not adjust the BMI for childhood growth, either by using growth percentiles or other benchmarks (Forshee and Storey 2003; Newby *et al.*, 2004; Lin *et al.*, 2004; Forshee *et al.*, 2004; Kvaavik *et al.*, 2005).
- Two cross-sectional studies, that reported a positive association with sugar-containing beverage consumption, failed to report details on their subjects that could have affected the study findings.
  - Troiano *et al.* (2000) did not include the actual statistics on weight change with beverage consumption, and instead provided a summarised result in their article.
  - Melgar-Quinonez and Kaiser (2004) did not make it clear whether ethnicity-based confounding variables were included in the adjustment model that showed an association between juice consumption and overweight/obesity. Giammattei *et al.* (2003) and Ariza *et al.* (2004) did, however, obtain similar positive associations and included ethnicity-based confounders in their adjustment models, indicating that the oversight of Melgar-Quinonez and Kaiser (2004) is unlikely to have had a significant impact on the study's outcomes.
- A number of the 20 identified studies reported a significant positive association with artificially sweetened beverages in addition to their findings on sugar-containing beverages (Ludwig *et al.*, 2001; Forshee and Storey 2003; Berkey *et al.*, 2004; Newby *et al.*, 2004; Kvaavik *et al.*, 2005; Blum *et al.*, 2005).
- Half of the 20 identified studies assessed carbonated soft drinks as the only type of sugar-containing beverage (Bandini *et al.*, 1999; Troiano *et al.*, 2000; Giammattei *et al.*, 2003; James *et al.*, 2004; Schulze *et al.*, 2004; Phillips *et al.*, 2004; Lin *et al.*, 2004; Forshee *et al.*, 2004; Kvaavik *et al.*, 2005; Janssen *et al.*, 2005).

Most of these design issues are of minor importance, however the absence of BMI growth adjustments in some childhood studies is highly relevant. A lack of accommodation for growth could have potentially contributed to a Type II Error, as the reported absence of an association may be due to the stage of a child subject's growth, instead of there been no influence on body weight or overweight/obesity status from sugar containing beverage intakes.

FSANZ also recognises that several authors (Fishbein, 2001; Henry and Warren, 2001; Murray and Kazman, 2005) have written letters into relevant journals, criticising two of the identified studies (Ludwig *et al.*, 2001; Schulze *et al.*, 2004) that support a positive association between sugar-containing beverage intake and overweight/obesity. Examination of the authors' replies to these letters shows that all of the criticisms raised were adequately rebutted.

### 4.1.3 Findings on the Relationship Between Sugar-Containing Beverages and Overweight/Obesity

The totality of evidence supports a positive association between sugar-containing beverage consumption and overweight/obesity. There are a small proportion of studies that show no association between sugar-containing beverage intake and overweight/obesity, however the collective weight of evidence on sugar-containing beverages favours a positive association. It is also noted that many of the studies showing no association were conducted on children, yet did not accommodate any change in body weight that may occur from normal growth patterns.

The greatest weight of evidence in support of a positive association comes from prospective cohort (longitudinal) studies, which show a relationship between increased sugar-containing beverage intake over time and an increased level of weight gain (above normal growth changes). Also, the school-based intervention study is significant, as it was of a high quality and showed a reduced prevalence of overweight/obesity with a decreased intake of sugar-containing beverages.

Examination of results in the context of the total diet produces conflicting outcomes, and none of the six total-diet studies employed a longitudinal or intervention design. Therefore, this evidence base is not strong enough to conclusively determine whether sugar-containing beverages have a greater potential to produce undesirable changes in population weight than other food and beverages categories. It is noted though, that none of the reviewed studies identified an association between consumption of other food and beverage categories and overweight/obesity, with the exception of high-energy snack foods.

The 20 studies examined by FSANZ do not identify a mechanism for an independent association between sugar-containing beverages and changes in weight or overweight/obesity status. However, other literature sources have theorised that the provision of sugar and energy in a liquid form is not detected physiologically as well as that in solid foods, and subsequent food intake is poorly adjusted by the body to account for the energy contribution made by beverages (Mattes, 1996). Another source (Lambert *et al.*, 2005) has also indicated that the current food choices of children are steered towards sugar-containing beverages, with such drinks being 20 times more popular than fresh fruit drinks and milk combined.

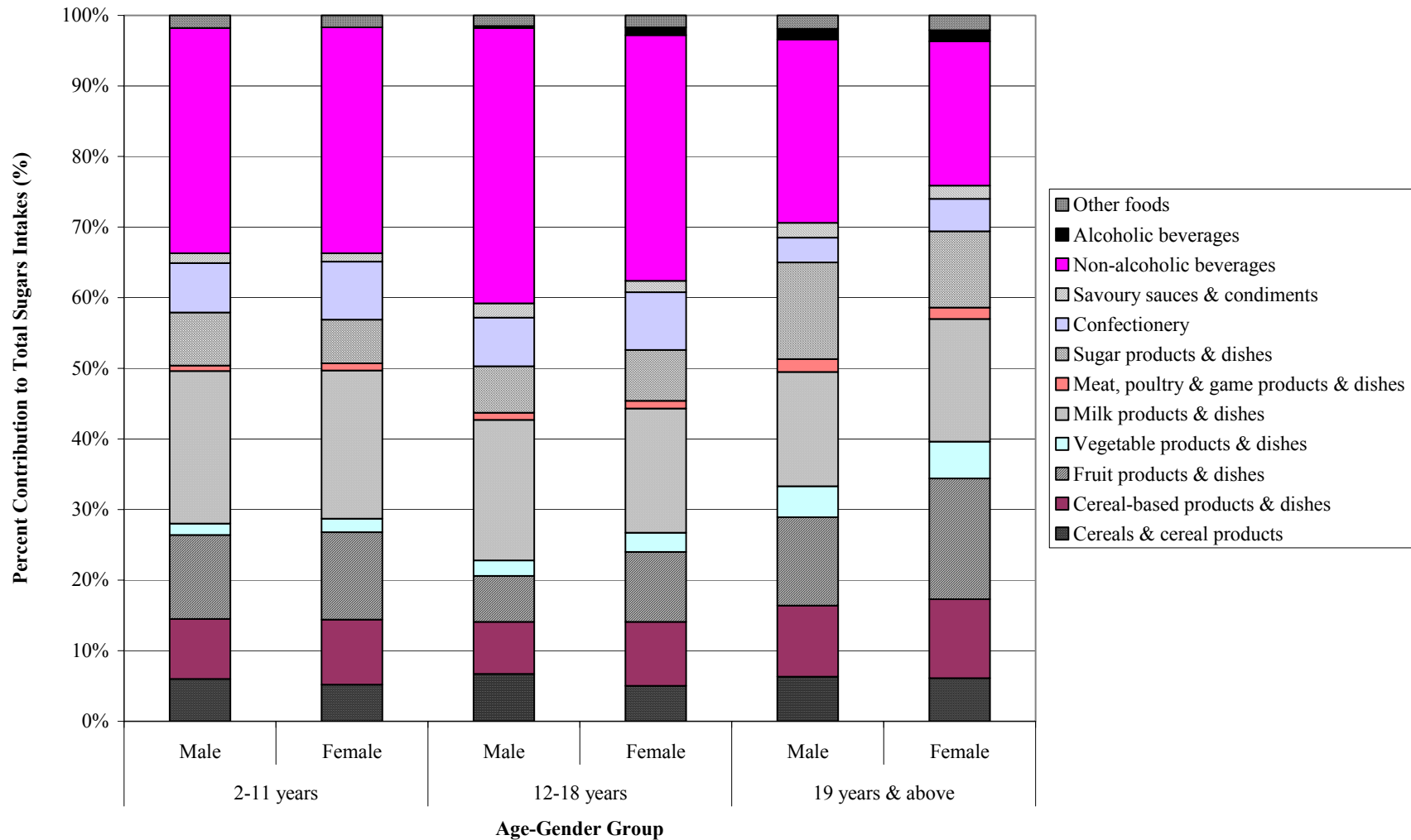
## 4.2 The Impact of Formulated Beverages on Population Sugars Intakes

### 4.2.1 Total sugars intake

The assessment of evidence in sections 4.2 and 4.3 indicates that the category of formulated beverages, which may include sugar-containing beverages, represents a potential health risk to Australian and New Zealand populations if the introduction of these products onto the market increased population total sugars intakes from the total diet. These risks are couched in terms of total sugars intake and thus energy intake for obesity, and total sugars intake for dental caries. At Draft Assessment, this potential health risk was considered sufficient justification for applying a compositional requirement of 7.5 g/100 ml sugars to formulated beverages. However, FSANZ has undertaken further assessment of the evidence at Final Assessment, including dietary modelling, to assess the impact on the intake of total sugars if a compositional requirement of 7.5 g/100 ml total sugars is applied.

In the 1995 Australian National Nutrition Survey (NNS), mean total sugars intakes ranged from 97 g/day to 212 g/day across a range of population groups (Table 9). Non-alcoholic beverages (including fruit and vegetable juices and drinks, soft drinks, flavoured mineral waters, electrolyte drinks and plain drinking water) contributed 20% – 39% of total sugars intakes, depending on the sub-population group (Table 10). The contribution of other food groups to the intake of total sugars is illustrated in Figure 4.

Figure 4: Contribution of different food groups to total sugars intake, as per the 1995 Australian National Nutrition Survey



Note: the food groups listed in the legend represent the order in which the food groups are depicted in the graph

**Table 9: Mean Total Sugars Intake for Sub-Populations of the 1995 NNS**

<b>Age Group</b>	<b>Gender</b>	<b>Mean Total Sugars Intake (g/person/day)</b>
2-3 years	Male	123.8
	Female	106.5
4-7 years	Male	133.1
	Female	124.2
8-11 years	Male	151.9
	Female	131.8
12-15 years	Male	181.1
	Female	137.5
16-18 years	Male	212.0
	Female	132.6
19 years & above	Male	133.5
	Female	97.0

Source: (McLennan and Podger, 1998)

**Table 10: Contribution of non-alcoholic beverages to total sugars intakes for the Australian population (1995 NNS)**

<b>Non-alcoholic beverages</b>	<b>Proportion of Total Sugars Intake from Non-Alcoholic Beverages (%)</b>					
	2-11 years		12-18 years		19 years and above	
	Male	Female	Male	Female	Male	Female
<b>Total</b>	<b>31.9</b>	<b>32.0</b>	<b>39.0</b>	<b>34.8</b>	<b>26.0</b>	<b>20.4</b>
Fruit and vegetables juices and drinks	22.2	23.9	18.4	18.5	10.1	10.4
Soft drinks, flavoured mineral waters and electrolyte drinks	9.8	8.1	20.6	16.2	15.5	9.3

Source: (McLennan and Podger, 1998)

It is known that beverage consumption patterns have changed markedly since 1995 with new products emerging on the market. Modelling was undertaken to assess whether substitution of selected non-alcoholic beverages by formulated beverages would increase total sugars intakes from those beverages only. Data from AC Nielsen ScanTrack data (Australian Beverages Council Ltd, 2005) for the Australian market in 2004 was used in the model. These data provided a more up-to-date estimate of beverage consumption patterns than the consumption data from the 1995 NNS. However, these data are on 'apparent' consumption only (mean consumption per capita based on total sales volumes), as they are not based on actual consumption amounts provided by individual dietary records (as is the case for NNS data). Since only Australian data were available, it was assumed that the New Zealand situation would be similar to Australia.

'Per capita' total sugars intakes from selected non-alcoholic beverages were calculated for Baseline and Scenario models using:

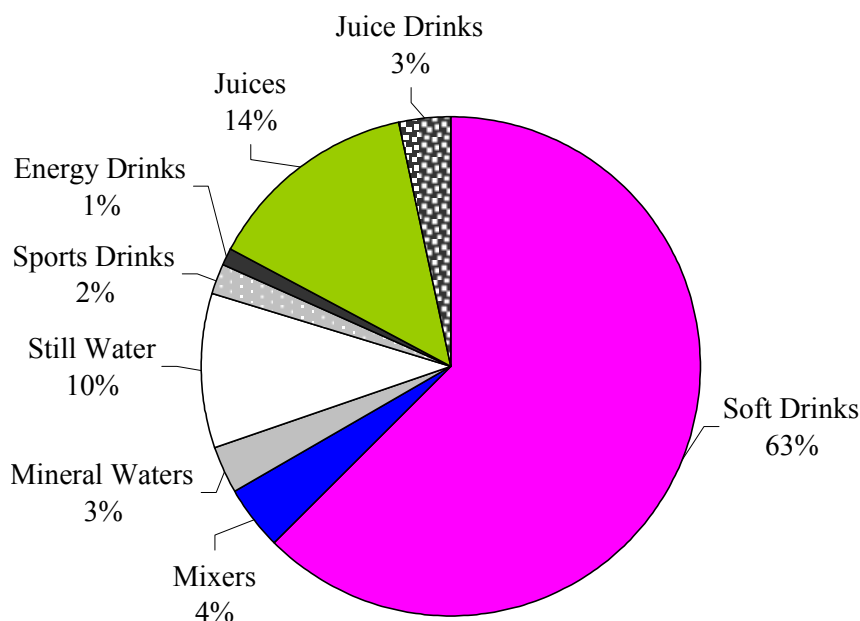
- the non-alcoholic beverages volumes from the AC Nielsen ScanTrack data (Australian Beverages Council Ltd, 2005);
- estimates of the size of the Australian population as at December 2004 (Australian Bureau of Statistics 2005); and
- weighted total sugars contents for each beverage type.

Total sugars intakes from other foods and beverages were not included in the calculation, as the NNS consumption data cannot be altered to take account of the updated market share data for non-alcoholic beverages.

The AC Nielsen ScanTrack data provided total volumes for different types of beverages in the non-alcoholic beverage market. The apparent consumption of each type of beverage (e.g. soft drink, energy drink, fruit drink) was calculated as a percentage of the total non-alcoholic beverage market (see Figure 5 below for further details). To enable comparison with the 1995 NNS data for total sugars intake, the data used in this assessment were for soft drinks, still water, energy drinks, mixers, mineral waters, sports drinks, juices and juice drinks. These beverages fit within the definition of ‘sugar-containing beverages’ used in sections 4.2 and 4.3 (includes standard carbonated beverages, fruit juices and drinks, and cordials, but not milk-based beverages) or fit within the category of ‘like products’. However, it was assumed that formulated beverages did not substitute for fruit juices so, although consumption of juices was included in the model, their sugars content remained the same in the Baseline and Scenario models.

At Baseline, all beverages were assigned a mean total sugars content derived from the food composition database for the 1995 NNS (AUSNUT 95) and weighted according to the proportion of intense sweetened beverages in each non-alcoholic beverage category (Table 10). Data on the proportion of unsweetened/intense sweetened products were derived from the AC Nielsen study (AC Nielson, 2004) and from the *Consumption of intense sweeteners in Australia and New Zealand – Roy Morgan Research Report* (Food Standards Australia New Zealand, 2003).

Figure 5: The 2004 non-alcoholic beverage market



Derived From: AC Nielsen ScanTrack (Australian Beverages Council Ltd, 2005)  
 Total Number of Litres: 2,294,847,000 litres/year (310 ml/capita/day)



Scenario models were conducted, assuming that 5% or 100% of fruit juice drinks, cordials, bottled waters, carbonated non-alcoholic beverages and sports drinks would be replaced by formulated beverages with total sugars contents of either 5.5 g/100 g or 7.5 g/100 g (Table 11). The 5% model was based on a predicted 5% penetration of formulated beverages into the current non-alcoholic beverage market, as derived from *Functional Soft Drinks – An International Perspective* (Leatherhead Food International, 2003). The 100% substitution model is a ‘worst case’ scenario where all drinks (except juices) are replaced by formulated beverages. In reality, the level of substitution is likely to be in the range from 5-100% but may vary for different drink categories and age groups. This uncertainty in the actual outcome is represented by the range of values presented. For the purposes of the dietary modelling it was assumed 100 ml of formulated beverages is equal to 100 g of formulated beverages.

Two total sugars levels in formulated beverages were included in the models:

1. 7.5 g total sugars/100 g formulated beverages, representing the total sugars limit proposed at Draft Assessment, equating to all products having the proposed maximum level; and
2. 5.5 g total sugars/100 g formulated beverages, representing a ‘free market’ model, being the arithmetic mean total sugars content of formulated beverages currently available on the market (but not weighted according to market share as specific data on the market share for all individual products on the market were not available), equating to all products having the proposed mean level.

**Table 11: Mean total sugars concentrations for selected non-alcoholic beverages, derived for use in dietary modelling**

Beverage Category	Total Sugars (g/100 g)			Proportion of Category Assumed to Be Intense Sweetened(%)
	Baseline	For 5.5 g/100 g substitution <sup>#</sup>	For 7.5 g/100 g substitution <sup>#</sup>	
Soft Drinks	6.5	5.5 - 6.5	7.5 - 6.6	35
Mixers	6.5	5.5 - 6.5	7.5 - 6.6	35
Mineral Waters	6.8	5.5 - 6.7	7.5 - 6.8	27
Still Water	0	5.5 - 0.3	7.5 - 0.4	100*
Sports Drinks	8.8	5.5 - 8.6	7.5 - 8.7	0
Energy Drinks	10.9	5.5 - 10.6	7.5 - 10.7	0
Juice Drinks	8.5	5.5 - 8.4	7.5 - 8.5	0
Juices	7.4	7.4	7.4	N/A

\* no added sugar

<sup>#</sup> the first number in the range represents the concentration used in 100% substitution modelling and the second number represents the concentration used in the 5% substitution modelling

#### 4.2.1.1 Impact on total sugars intake from non-alcoholic beverages

Changes in the estimated total sugars intakes between baseline the two mean formulated beverages total sugars content scenarios were calculated and are shown in Table 11.

A range of results is given for the scenarios based on whether 5% or 100% of non-alcoholic beverages are substituted with formulated beverages. The 100% substitution scenario is presented first in both Tables 11 and 12.

**Table 12: Estimated change in total sugars intakes from selected non-alcoholic beverages only between baseline and when formulated beverages are consumed**

Estimated intake of total sugars from non-alcoholic beverages (g/capita/day)			Change in intake of total sugars from non-alcoholic beverages (g/capita/day)		% change in intake of total sugars from non-alcoholic beverages	
Baseline	5.5 g total sugars/100 g scenario <sup>#</sup>	7.5 g total sugars/100 g scenario <sup>#</sup>	Baseline to 5.5g/100g <sup>#</sup>	Baseline to 7.5g/100g <sup>#</sup>	Baseline to 5.5g/100g <sup>#</sup>	Baseline to 7.5g/100g <sup>#</sup>
19.1	17.9 - 19.1	23.3 - 19.4	-1.1 to <0.1	4.2 – 0.3	-6 to <1	22 - 2

<sup>#</sup> the first number in the range represents the total sugars intake derived from 100% substitution modelling and the second number represents the total sugars intake derived from 5% substitution modelling

If the mean sugars level of 5.5 g/100 g in formulated beverages is maintained, the modelling suggests that there may be minimal change in total sugars intakes from non-alcoholic beverages (-1.1 to <0.1 g/day (4% decrease to <1% increase)). This assumes that the absence of weighting does not alter the mean sugars level currently used and the present range of total sugars in formulated beverages does not change. This model represents the consumer who selects a range of formulated beverages with varying total sugars contents and therefore over time consumes formulated beverages with a total sugars content equivalent to the mean. The ‘brand loyal’ consumer, who consumes formulated beverages with a higher total sugars content of around 10 g/100 g, will have a higher total sugars intake from non-alcoholic beverages if they replaced all of them with formulated beverages and vice versa for a brand loyal consumer who consumes formulated beverages with a total sugars level of less than 5.5 g/day.

When a total sugars limit of 7.5 g/100 g is imposed on formulated beverages, and assuming that all formulated beverages have this maximum level, the results indicate that there would be an increase in the total sugars intake from non-alcoholic beverages for formulated beverages consumers of 4.2 g/day (100% substitution) - 0.3 g/day (5% substitution) (22 - 2% increase from non-alcoholic beverages, depending on the level of substitution with formulated beverages).

In reality, it is likely that some products in the market would contain greater than 7.5g/100g. It is uncertain whether imposing a limit of 7.5 g/100 ml on the current market would reduce present per capita total sugars intakes, since this would depend on the resultant range of sugars contents in formulated beverages, the place of formulated beverages in the diet, and the beverages that consumers choose to substitute with formulated beverages. The implementation of a 7.5 g total sugars/100 ml maximum limit for formulated beverages may lead to a mean total sugars content for formulated beverages that is below the modelled ‘free market’ mean of 5.5 g/100 g. This assumes that there is minimal change to the total sugars contents of formulated beverages that currently meet the proposed limit. If the mean total sugars content of formulated beverages falls below 5.5 g/100 g, the total sugars intake from non-alcoholic beverages would be reduced more than that predicted by the 5.5 g/100 g model.

#### 4.2.1.2 Impact on total sugars intake from all foods

From the 1995 NNS, mean total sugars intakes ranged from 97 – 212 g /day. While the 1995 NNS total sugars data are not directly comparable to the total sugars data derived from the more recent apparent consumption data for non-alcoholic beverages, a –1.1 g to <0.1 g increase in total sugars intake from non-alcoholic beverages due to substitution with formulated beverages containing a mean total sugars content of 5.5 g/100 g would be indicative of a -1 – <1% overall increase in total sugars intake from the total diet, depending on the level of substitution with formulated beverages. Likewise, a 4.2 g – 0.3 g increase in total sugars intake from non-alcoholic beverages due to substitution with formulated beverages containing a maximum total sugars content of 7.5 g/100 g would be indicative of a <1 - 4% overall increase in total sugars intake from the total diet, depending on the level of substitution with formulated beverages.

#### *4.2.2 Summary of dietary modelling for total sugars*

The dietary modelling indicates a limited impact on total sugars intake from non-alcoholic beverages due to the introduction of formulated beverages, assuming they are substituted for like drinks, such as fruit juice drinks and bottled waters, and other non-alcoholic beverages. There is a degree of uncertainty in this modelling due to a lack of data on actual consumption of formulated beverages and likely consumer substitution behaviour, as is reflected in the allocation of a 5% to 100% range for likely formulated beverages substitution patterns.

In the current market, a 5% or 100% level of substitution of formulated beverages with a mean total sugars content of 5.5 g/100 g would result in minor reductions in total sugars intakes of up to 1 g (16 kJ) (up to 6% reduction in total sugars from non-alcoholic beverages or approximately 1% from the whole diet).

If a maximum limit were imposed and assuming that all formulated beverages have a maximum total sugars content of 7.5 g/100 g, a 5% or 100% level of substitution would result in increases in total sugars intakes of up to 4 g (54 kJ) (up to 22% increase in total sugars from non-alcoholic beverages or approximately 4% from the whole diet). However, it is likely that under the conditions of an imposed maximum level, some products in the market would contain less than 7.5 g/100 g thereby reducing the predicted increase of total sugars intake, the extent being dependant on the level of substitution, range of products available and consumer choice of beverages to substitutes.

### **4.3 Sugar, Acidity and Dental Health**

Diet can play a significant role in the development of dental problems, by increasing the exposure of teeth to an acidic environment. Dental caries is the progressive destruction of the teeth by acids that are generated by bacteria in the mouth. This condition differs from dental erosion, which involves the chemical etching and irreversible loss of dental hard tissue by exposure to non-bacterial acids (Moynihan and Petersen, 2004; British Nutrition Foundation 2005).

#### 4.3.1 Assessment of the Evidence Base on Dental Health

There is a well-established link between dental caries and sugar consumption. Dental caries is a multifactorial disease, influenced by tooth composition, exposure to fluoride and the type of bacteria in the mouth (Woodward and Walker, 1994). However, a regular and high intake of sugars from dietary sources remains one of several primary risk factors for the development of dental caries (Moynihan, 2002; World Health Organization, 2003). In particular, sugar-containing beverages are major contributors to this dietary risk factor (Levy *et al.*, 2003; Moynihan and Petersen 2004), and there is evidence that increased intakes of sugar-containing beverages (including juices) are associated with an increased risk of dental caries ( $p < 0.001$ ) (Marshall *et al.*, 2003).

Dental erosion has become a recent dental health issue, as its prevalence has increased over the last decade in developed nations. Emerging evidence based on observational studies has shown a strong association between acidic beverages – including the frequency of their consumption – and the development of dental erosion (Moynihan and Petersen 2004). The National Health and Medical Research Council notes that acidic drinks such as citrus-based and other juices, carbonated and uncarbonated drinks, sports drinks and herbal teas are likely to exacerbate dental erosion (NHMRC, 2003).

The World Health Organization has also reviewed the evidence on soft drinks and fruit juice, and classified the strength of evidence linking these beverages to dental erosion as ‘probable’ (World Health Organization, 2003). This evidence base includes in vitro exposure of enamel to soft drinks; animal studies involving exposure to soft drinks and fruit juices; human observational studies that show an association between dental erosion and fruit juice, soft drinks, and sports drinks; and human experimental studies which show that increased consumption of acidic beverages results in a lowering of the pH of oral fluids.

Although the evidence shows that acidic foods and beverages contribute to the development of erosion, the aetiology depends on many factors including the requirement for an individual to be predisposed to the development of the condition, either through non-dietary behaviours or physiological characteristics (Moss, 1998). Other factors that can contribute to the risk of developing dental erosion include:

- behavioural factors, such as the sipping of drinks during interrupted sleep, the use of medications that reduce the flow of saliva, and the use of chewable vitamin tablets; and
- biological factors, including saliva flow rate, oral buffering capacity, the composition of saliva, pellicle formation, tooth composition, dental and soft tissue anatomy (Australian Dental Association (2002; Lussi *et al.*, 2004).

FSANZ has been unable to identify any prevalence rates for dental erosion in Australia. One New Zealand study on children has been identified, which indicates that 82% of children may have some form of tooth wear (Ayers *et al.*, 2002). However, this figure may not represent the prevalence of dental erosion in the study population, as the authors did not distinguish between dental erosion and other forms of tooth wear (Mahoney and Kilpatrick, 2003).

European 1990-1995 data (predominantly the UK) show that 5-50% of their populations experience some degree of dental erosion, with a 25-30% prevalence rate being the most widely cited figure (Gandara and Truelove, 1999; Moynihan 2002).

Although these data do not indicate the degree of the erosion experienced by those with the condition or the extent of predisposing factors, they do show that the dental condition exists at substantial levels within European populations, and therefore at potentially significant levels in developed nations such as Australia and New Zealand (assuming comparable conditions).

#### 4.3.2 *Findings on Sugar, Acidity and Dental Health*

The consumption of sugar-containing beverages represents a significant risk for dental health due to the strong association between the intake of these beverages and dental caries. However, as shown in section 4.2 above, the intake of sugars in the diet is unlikely to increase as a result of the introduction of formulated beverages onto the market, and therefore formulated beverages are unlikely to contribute significantly to the development of dental caries in the population.

The acidity of soft drinks and fruit juice beverages does however, remain as a probable risk factor for dental erosion, although it is recognised that the condition depends on a number of other contributing factors.

#### **4.4 The Impact of Formulated Beverage Acidity on Dental Health**

FSANZ has not obtained evidence on the acidity (pH levels) of currently available formulated beverages. However, it is considered that formulated beverages will have a similar acidity to like products such as juices, fruit drinks, cordials, sports drinks, and carbonated beverages, due to the similar use of food acids in their manufacture. The pH levels of these products vary within an acidic range of 2.1 and 4.5 (Gandara and Truelove 1999; Mahoney and Kilpatrick 2003).

One type of product among formulated beverages whose acidity is likely to differ significantly from its unfortified counterpart is a water-type formulated beverage compared with bottled water. Bottled water products make up approximately 10% of the 2005 beverage market (see Figure 4 above), and generally have neutral (7.0) or slightly acidic (~6.5) pH levels (Ikem *et al.*, 2002).

Therefore, the risk from dental erosion associated with formulated beverages will depend the types of 'like' products that are replaced by these beverages. However, the consumption of water-type formulated beverages instead of more neutral bottled waters may result in a net increase in acidic beverages consumed, and their consumption could potentially increase the risk of dental erosion.

### **5. Bioavailability**

Bioavailability refers to the biological availability of a nutrient to the human body, and includes the metabolic use of vitamins and minerals as well as their intestinal absorption rates. Bioavailability can be influenced by many factors making it a highly variable attribute of vitamins and minerals. Because of this variability, a wide variety of research techniques have been applied to the measurement of bioavailability. These techniques include balance studies of the vitamin or mineral, changes in serum or urine vitamin/mineral concentrations (where intake is reflected by these changes), the use of isotopic tracers, the effect of the vitamin or mineral on target body systems, and *in vitro* assessments (Heaney, 2001).

## 5.1 The Variable Nature of Bioavailability

Despite the current research methods that have been developed, a large degree of uncertainty still remains with any findings on vitamin and mineral bioavailability, as there are a wide variety of modifying factors that can confound results from scientific studies. Even with advances in research methodology, current studies on bioavailability continue to be limited by their design, as they are all highly controlled experiments that do not reflect outcomes under actual human conditions.

There is a slight different range of modifying factors that can influence vitamin bioavailabilities versus mineral bioavailabilities, however a number of common modifying factors exist. Common modifying factors of bioavailability include the nutrient's release from the food matrix during digestion, physical interaction between other food/meal components during digestion, and the form of the nutrient. There are also a number of host-related modifiers, including the host's nutritional status, developmental state, gastrointestinal secretions, mucosal cell regulation, and gut microflora (Fairweather-Tait and Southon, 2004). Any assessment of vitamin and mineral bioavailability therefore must recognise that *in vitro* studies, and studies examining the fasting consumption of a single food, are unlikely to provide an accurate assessment of vitamin or mineral uptake and regulation within the body (Heaney 2001).

Two of the most heavily researched nutrients with respect to bioavailability are iron and calcium; these micronutrients illustrate how mineral bioavailability can be subject to confounding factors. With iron, it is more often the quality of the overall diet that determines the bioavailability than the addition of iron salts to individual foods (Fairweather-Tait and Teucher, 2002). In the case of calcium, balance and isotopic tracer studies have shown that age plays the most significant role in determining how much of the nutrient is absorbed, rather than its source or chemical form (United States Institute of Medicine, 1997).

Studies undertaken on calcium also illustrate that the modifiers of bioavailability cannot be readily predicted, especially in isolated experimental conditions. For example, when the various forms of calcium are compared to each other, *in vitro* studies indicate that forms of calcium (including dairy sources) have different bioavailabilities, yet assessments of the different forms on physiological parameters (e.g. bone mineral density) show that all types of calcium have approximately the same impact over time (Reid, 2005).

Vitamins have fewer issues surrounding their bioavailability than minerals. Water-soluble vitamins are rarely affected by the food matrix, and are subject more to the physiological state of the consumer, or the presence of inhibitors and enhancers within a meal (Finglas, 2004). Fat-soluble vitamins are also little affected by the food matrix, although they do require the use of micelle carriers during digestion to be effectively available to the body. Thus, factors that can impact on the efficiency of micelle carriers (such as a low level of fat within a meal) may also have a negative effect on the bioavailability of fat-soluble vitamins (Fairweather-Tait and Southon, 2004).

## 5.2 Intestinal Absorption of Specific Vitamins and Minerals

Investigations into the toxicity of vitamins and minerals by the UK Expert Group on Vitamins and Minerals (United Kingdom Department of Health, 1993) have yielded information on rates of absorption across the intestine (see Table 13 below).

Not all vitamins and minerals are listed in this table, as quantified absorption rates for some vitamins and minerals could not be obtained. The absorption rates encompass values for both natural and synthetic sources of the vitamins and minerals.

**Table 13: Absorption Rates of Various Vitamins and Minerals**

Vitamin / Mineral	Absorption (%)	Notes
Vitamin A (retinol)	~80	Absorption rate is dependent on concurrent fat intake.
Beta-carotene	10-90	Absorption rate is dependent on concurrent fat intake. Dispersal in a water medium facilitates absorption.
Folic Acid	50-100	The lower absorption values apply to naturally occurring forms of folic acid, while supplemental forms are more highly bioavailable.
Pantothenic Acid	50-100	Food sources are absorbed to a lesser extent than supplemental forms.
Vitamin B <sub>12</sub>	1.2-50	Vitamin B <sub>12</sub> is dose dependent; a maximum of 2 µg can only be absorbed from a dose/meal due to saturation of transport mechanisms. Lower doses have higher absorption rates.
Vitamin C	≤98%	Vitamin C is inversely dose/intake dependant; small doses have the highest absorption rates, while very large doses are poorly absorbed.
Vitamin E	<10-80	Vitamin E is inversely dose/intake dependent; small doses have the highest absorption rates, while very large doses are poorly absorbed.
Biotin	100	This value applies to supplemental biotin. Values for food derived biotin have not been identified.
Calcium	25-60	Food and supplemental sources of calcium do not differ in their rate of absorption. For all forms of calcium, the higher 60% absorption rate is found in young children, and decreases down to 25% by adulthood.
Chromium	0.5-2.0	
Copper	55-75	
Iodine	~97	
Iron	~15	This value applies to the whole diet (all sources). Iron absorption values fluctuate widely around this figure, and in the case of natural sources, haem iron is absorbed more readily than non-haem iron.
Magnesium	~50	This value applies to food sources of magnesium. This value can decrease depending on dietary fibre and protein intake. Supplemental forms of magnesium are not as well absorbed as food sources.
Molybdenum	40-50	This value applies to food sources of molybdenum. Values for supplemental molybdenum have not been identified.
Phosphorus	55-90	This value applies to all forms of phosphorus. Children absorb phosphorus more efficiently than adults.
Selenium	50-90	Food sources of selenium are absorbed at the higher end of this range. Supplemental sources are absorbed at the lower end of the range.
Zinc	15-60	This value applies to dietary sources of zinc. Values for supplemental zinc have not been identified. Values fluctuate widely depending on dietary factors, including concurrent copper intake.

Table 13 shows that there is no consistent pattern across the various vitamins and minerals; for some of these nutrients the form available in food is more readily absorbed, whereas for others the supplemental sources are more readily absorbed. Table 12 also shows that even under ideal conditions, regardless of its source, a vitamin or mineral is generally not fully absorbed and thus not fully bioavailable.

Although there is significant variation in vitamin and mineral bioavailabilities, this variation can be taken into account at a population diet level. Population health recommendations on vitamins and minerals such as current RDIs and the draft Nutrient Reference Values for Australia and New Zealand (NHMRC, 2005) already accommodate fluctuations in bioavailability across a national diet. Overseas population health recommendations (e.g. US and UK EARs) also accommodate bioavailability fluctuations.

Such accommodation makes the bioavailability from individual foods less relevant to population health, unless the vitamins and minerals in those foods are providing an important public health function (e.g. mandatory fortification), or act as the sole source of an individual's nutrition (e.g. infant formula products).

### **5.3 Bioavailability as it Relates to Formulated Beverages**

FSANZ is unaware of any studies that have investigated the bioavailability of vitamins and minerals from formulated beverages. Even so, as the bioavailability of any one vitamin or mineral is likely to be variable and dependent on several factors, it is not possible to draw definite conclusions on the actual bioavailability of vitamins and minerals added to individual foods, including formulated beverages.

### **5.4 Outcomes on Bioavailability**

The bioavailability of a vitamin or mineral intake relates to its biological availability to the human body through gastrointestinal absorption and metabolic use. A large number of modifiers influence bioavailability including the nutrient's release from the food matrix during digestion, physical interaction between other food/meal components during digestion, and the form of the nutrient, the host's nutritional status, developmental state, gastrointestinal secretions, mucosal cell regulation, and gut microflora.

Several techniques have been developed to assess bioavailability ranging from *in vitro* methods to human balance studies and studies of impact on target body systems. However, controlled studies of fasting consumption of a single food examining the absorption or metabolic utilisation of nutrients are necessarily limited in their conclusions and unlikely to provide an accurate assessment of the uptake and regulation within the body. This is because of different meal effects and the range of host-related modifiers that can vary gastrointestinal absorption in response to the body's internal environment.

Comparison of gastrointestinal absorption rates among vitamins and minerals – irrespective of whether naturally occurring or supplemental – shows wide variability with very few vitamins and minerals attaining complete intestinal absorption. Differences in bioavailability have been generally accounted for in setting nutritional reference values based on the national diet.

Therefore, as the actual bioavailability of any one vitamin or mineral is dependant on a wide range of factors, it is not possible to draw definite conclusions on the bioavailability as it applies to any individual food product, including formulated beverages. It is, however, expected that the vitamins and minerals in formulated beverages are bioavailable to varying extents.



## 6. Overall Conclusion

There is no nutrition and health need for a number of the requested vitamin and mineral additions to formulated beverages. This nutrition assessment does not support the addition of the following vitamins and minerals to formulated beverages on the basis of nutritional or other health needs:

### Vitamins

- Vitamin A
- $\beta$ -carotene
- Thiamin
- Niacin
- Vitamin B<sub>12</sub>
- Vitamin C
- Biotin
- Pantothenic Acid

### Minerals

- Chromium
- Copper
- Manganese
- Molybdenum
- Phosphorus

However, the following 11 vitamins and minerals do have a nutrition and health need in support of their addition to formulated beverages, by virtue of an existing inadequate intake or evidence of deficiency within the community:

### Vitamins

- Riboflavin
- Folate
- Vitamin B<sub>6</sub>
- Vitamin D
- Vitamin E

### Minerals

- Calcium
- Iodine
- Iron
- Magnesium
- Selenium
- Zinc

Although the above vitamins and minerals have a nutrition and health need supporting their addition to formulated beverages, this outcome does not mean that these additions are also safe. Safety considerations for vitamin and mineral additions have been assessed separately from nutritional need within the Draft Assessment Report for Application A470 (see Attachment 6).

A potential risk was identified between sugar-containing beverage intakes and overweight/obesity and dental caries, and between consumption of acidified beverages and dental erosion.

However, the impact depends entirely on the pattern of consumption of this product group. Under conditions of substitution with like products, introduction of formulated beverages into the market is unlikely to further adversely affect public health in relation to sugars intake and obesity, or in relation to sugars intake and dental caries. This is also the case where similarly acidified beverages are substituted. However because water-type formulated beverages are more commonly acidified than bottled waters, substitution of bottled water by formulated beverages may increase the risk of dental erosion.

FSANZ is unaware of any studies that have investigated the bioavailability of vitamins and minerals from formulated beverages. As the actual bioavailability of any one vitamin or mineral is dependant on a wide range of factors, it is not possible to draw definite conclusions on the bioavailability of vitamins and minerals either naturally occurring or added to individual foods, including those in formulated beverages. It is, however, expected that the vitamins and minerals in formulated beverages are bioavailable to varying extents.

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## Appendix 1

### Electronic Literature Search on Health Benefits (Number of Articles Identified)

Keywords	Vitamin A		$\beta$ -carotene	Thiamin		Niacin		Vitamin B <sub>12</sub>		Vitamin C
	PubMed	Nutrition Abstracts & Reviews	PubMed	PubMed	Nutrition Abstracts & Reviews	PubMed	Nutrition Abstracts & Reviews	PubMed	Nutrition Abstracts & Reviews	PubMed
[Vitamin/Mineral]	33604	3	6811	10751	1568	3136	837	9663	1510	29579
‘[Vitamin/Mineral]’ AND bone	1493	-	63	77	13	32	14	356	34	204
‘[Vitamin/Mineral]’ AND intake AND bone	73	-	-	-	-	-	-	13	-	40
‘[Vitamin/Mineral]’ AND cancer	8177	-	1952	259	32	127	38	506	74	1174
‘[Vitamin/Mineral]’ AND intake AND cancer	455	-	599	33	-	31	-	-	-	462
‘[Vitamin/Mineral]’ AND intake AND ‘cancer prevention’	132	-	81	-	-	-	-	-	-	40
‘[Vitamin/Mineral]’ AND intake AND ‘cancer risk’	121	-	128	-	-	-	-	-	-	125
‘[Vitamin/Mineral]’ AND chronic disease	233	-	73	98	2	8	2	103	7	130
‘[Vitamin/Mineral]’ AND intake AND chronic disease	34	-	-	-	-	-	-	-	-	-
‘[Vitamin/Mineral]’ AND cardiovascular disease	718	-	626	466	12	466	16	503	77	937
‘[Vitamin/Mineral]’ AND intake AND ‘cardiovascular disease’	71	-	71	38	-	21	-	59	-	80
‘[Vitamin/Mineral]’ AND intake AND ‘heart disease’	43	-	95	-	-	-	-	16	37	74
‘[Vitamin/Mineral]’ AND gastrointestinal	270	-	69	57	11	48	6	155	30	132
‘[Vitamin/Mineral]’ AND intake AND gastrointestinal	36	-	-	-	-	-	-	14	-	23
‘[Vitamin/Mineral]’ AND homocysteine	-	-	-	-	-	-	-	106	130	-
‘[Vitamin/Mineral]’ AND immune system	1941	-	338	173	3	55	2	416	8	524
‘[Vitamin/Mineral]’ AND intake AND immune system	64	-	49	7	-	-	-	14	-	63
‘[Vitamin/Mineral]’ AND osteoporosis	85	-	15	12	5	5	0	-	-	46

Keywords	Vitamin A		$\beta$ -carotene	Thiamin		Niacin		Vitamin B <sub>12</sub>		Vitamin C
	PubMed	Nutrition Abstracts & Reviews	PubMed	PubMed	Nutrition Abstracts & Reviews	PubMed	Nutrition Abstracts & Reviews	PubMed	Nutrition Abstracts & Reviews	PubMed
'[Vitamin/Mineral]' AND wound	498	-	82	83	1	15	0	47	1	170
'[Vitamin/Mineral]' AND intake AND wound	26	-	-	-	-	-	-	-	-	23
Total of shaded areas	685	3	726	405	79	215	78	417	400	644
Screening of article titles	201	0	141	37	15	18	2	50	61	141

Keywords	Biotin		Pantothenic Acid		Chromium		Copper	
	PubMed	Nutrition Abstracts & Reviews	PubMed	Nutrition Abstracts & Reviews	PubMed	Nutrition Abstracts & Reviews	PubMed	Nutrition Abstracts & Reviews
[Vitamin/Mineral]	17914	424	2686	220	20328	940	51224	4345
‘[Vitamin/Mineral]’ AND bone	499	4	19	1	1430	19	862	125
‘[Vitamin/Mineral]’ AND intake AND bone	2	-	-	-	11	-	82	-
‘[Vitamin/Mineral]’ AND cancer	3283	13	41	1	799	25	1163	117
‘[Vitamin/Mineral]’ AND intake AND cancer	5	-	-	-	18	-	39	-
‘[Vitamin/Mineral]’ AND ‘chronic disease’	104	0	12	0	113	0	344	8
‘[Vitamin/Mineral]’ AND intake AND ‘chronic disease’	-	-	-	-	-	-	13	-
‘[Vitamin/Mineral]’ AND cardiovascular disease	486	2	57	2	29	0	111	39
‘[Vitamin/Mineral]’ AND intake AND ‘cardiovascular disease’	1	-	-	-	-	-	-	-
‘[Vitamin/Mineral]’ AND intake AND ‘heart disease’	-	-	-	-	66	0	-	-
‘[Vitamin/Mineral]’ AND diabetes	-	-	-	-	362	92	-	-
‘[Vitamin/Mineral]’ AND intake AND diabetes	-	-	-	-	31	-	-	-
‘[Vitamin/Mineral]’ AND gastrointestinal	116	3	33	1	36	0	295	61
‘[Vitamin/Mineral]’ AND intake AND gastrointestinal	-	-	-	-	-	-	21	-
‘[Vitamin/Mineral]’ AND immune system	1632	7	39	1	3918	6	1751	39
‘[Vitamin/Mineral]’ AND intake AND immune system	4	-	-	-	7	-	61	-
‘[Vitamin/Mineral]’ AND osteoporosis	3	0	1	0	36	0	85	27
‘[Vitamin/Mineral]’ AND intake AND osteoporosis	-	-	-	-	-	-	-	-
‘[Vitamin/Mineral]’ AND wound	128	0	59	1	461	0	230	10
‘[Vitamin/Mineral]’ AND intake AND wound	-	-	-	-	3	-	-	-
Total of shaded areas	363	29	261	6	252	142	406	300
Screening of article titles	0	0	4	5	20	29	46	35

Keywords	Manganese		Molybdenum		Phosphorus	
	PubMed	Nutrition Abstracts & Reviews	PubMed	Nutrition Abstracts & Reviews	PubMed	Nutrition Abstracts & Reviews
[Vitamin/Mineral]	21916	1562	5896	306	53681	3231
‘[Vitamin/Mineral]’ AND bone	350	42	196	7	6030	486
‘[Vitamin/Mineral]’ AND intake AND bone	39	-	3	-	560	19
‘[Vitamin/Mineral]’ AND intake AND ‘bone health’	-	-	-	-	40	0
‘[Vitamin/Mineral]’ AND intake AND ‘bone status’	-	-	-	-	71	0
‘[Vitamin/Mineral]’ AND cancer	1140	25	237	10	3934	49
‘[Vitamin/Mineral]’ AND intake AND cancer	10	-	10	-	55	-
‘[Vitamin/Mineral]’ AND ‘chronic disease’	130	2	15	1	297	3
‘[Vitamin/Mineral]’ AND intake AND ‘chronic disease’	-	-	-	-	11	-
‘[Vitamin/Mineral]’ AND cardiovascular disease	451	0	51	3	1897	10
‘[Vitamin/Mineral]’ AND intake AND ‘cardiovascular disease’	12	-	-	-	63	-
‘[Vitamin/Mineral]’ AND intake AND ‘heart disease’	3	0	16	3	-	-
‘[Vitamin/Mineral]’ AND gastrointestinal	61	14	24	6	360	35
‘[Vitamin/Mineral]’ AND intake AND gastrointestinal			-	-	52	-
‘[Vitamin/Mineral]’ AND immune system	813	4	120	2	1669	5
‘[Vitamin/Mineral]’ AND intake AND immune system	9	-	-	-	8	-
‘[Vitamin/Mineral]’ AND osteoporosis	19	13	4	0	923	97
‘[Vitamin/Mineral]’ AND intake AND osteoporosis			-	-	115	-
‘[Vitamin/Mineral]’ AND wound	128	1	55	1	730	1
‘[Vitamin/Mineral]’ AND intake AND wound	2	-	-	-	28	-
Total of shaded areas	285	101	298	33	443	219
Screening of article titles	4	3	9	0	32	8



### Assessment of Health Benefit: Chromium

The searches conducted on the PubMed and Nutrition Abstract and Reviews databases yielded a total of 49 eligible studies on chromium. The abstracts of these articles were further reviewed to ensure that the subject matter, not just the title, was relevant to this assessment. In assessing the subject matter, articles were excluded if they used serum chromium as an indicator of chromium status. Serum chromium is very close to the detection limits of current analytical techniques, and cannot be accurately measured by these methods (United States Institute of Medicine, 2001). The available evidence was therefore reduced to 23 articles once duplicate material was eliminated. A detailed summary of these articles is provided in Tables A2-1 to A2-3 below. Of these 23 articles, 7 assessed both coronary heart disease (CHD) and diabetes endpoints.

Ten articles included an assessment of CHD endpoints following increased chromium intake, of which eight were intervention trials. There was no consistent set of findings across the evidence base on chromium intakes above the recommended level<sup>7</sup> and CHD, with two beneficial and four null studies identified. The other four studies report disparate results between various subgroups of their study populations, or between different CHD endpoints.

The greatest volume of scientific material on chromium related to diabetes related outcomes, with a total of 19 studies identified. The majority of these studies were intervention trials investigating the use of chromium supplements, with only one observation study that assessed chromium status via nail chromium concentrations. This evidence base predominantly indicated an inverse association between supplemental chromium use (at intakes above the recommended level), however the studies often varied in how this outcome was obtained. Three studies reported significant decreases in serum insulin levels with increased chromium intakes even though there was no concurrent change in serum glucose or HbA1c levels over time. Two other studies indicated that increased intakes of chromium well above the recommended level, rather than moderately increased above, were capable of producing significant benefits for diabetes/glucose metabolism. However, even with this variation in findings, there was also a moderate level of evidence (seven studies) showing no significant relationship between increased chromium intake and diabetes/glucose metabolism.

Five remaining articles, mostly observational studies, were identified that examined the relationship between cancer (3 studies) or weight management (2 studies). None of these studies indicated any definitive benefit with increased chromium intakes.

A strong evidence base exists indicating that increased chromium intakes have a beneficial influence on diabetes and blood glucose management, although the exact relationship has yet to be fully described within the current evidence base. Despite these strong positive findings, a moderately strong level of information also contradicts an association between chromium and improved diabetic/glucose management.

**Chromium is Assigned an Evidence Level of 2**

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<sup>7</sup> The recommended intake for chromium used in the assessment of health benefits has been assigned the value of 35 µg/day, the AI for males as proposed by the NHMRC in their draft NRVs (NHMRC, 2005).

Table A2-1: Identified Studies on Chromium and Coronary Heart Disease

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Abraham <i>et al.</i> (1992)	Not reported	Biomarkers of CHD – cholesterol, HDL and triglyceride levels	Randomised controlled trial	7-16 months	Patients with atherosclerosis aged 42-83 years	Chromium supplementation	38	250 mg chromium chloride	<ul style="list-style-type: none"> <li>Chromium supplementation significantly increased serum chromium levels (<math>p &lt; 0.05</math>).</li> <li>There was no significant (<math>p &gt; 0.05</math>) difference in serum triglycerides and cholesterol levels between the two groups.</li> <li>There was a significant increase (<math>p &lt; 0.005</math>) in serum HDL levels.</li> </ul>
						Placebo treatment	38	-	
Anderson <i>et al.</i> (1997)	Double-blinded	Biomarkers of CHD – serum cholesterol, HDL and triglycerides	Randomised controlled trial	4 months	Persons with Type II diabetes aged 35-65 years.	High chromium supplementation	60	500 µg/day chromium picolinate	<ul style="list-style-type: none"> <li>500 µg/day chromium supplementation significantly (<math>p &lt; 0.02</math>) decreased serum cholesterol levels compared to the placebo group.</li> <li>There was no significant (<math>p &gt; 0.05</math>) impact of chromium supplementation on other measured study endpoints.</li> </ul>
						Low chromium supplementation	60	100 µg/day chromium picolinate	
						Placebo	60	-	
Bahijiri <i>et al.</i> (2000)	Double-blinded	Biomarker of CHD – serum cholesterol, HDL and triglyceride levels.	Randomised controlled crossover trial	8 weeks for each treatment alternating with 8	Persons with Type II diabetes aged 36-68 years.	Treatment 1 - chromium supplementation	78	200 µg/day chromium chloride	<ul style="list-style-type: none"> <li>Both chromium supplementations significantly (<math>p &lt; 0.001</math>) decreased serum triglyceride levels and</li> </ul>

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
				week placebo washout		Treatment 2 – Brewer's yeast	78	23.2 µg/day chromium	significantly (p<0.001) increased serum HDL levels. <ul style="list-style-type: none"> <li>There was no significant (p&gt;0.05) impact of chromium supplementation on serum cholesterol.</li> </ul>
Offenbacher and Pi-Sunyer (1980)	Single-blinded	Biomarkers of CHD – serum cholesterol and triglyceride levels.	Randomised controlled trial	8 weeks	Persons (mean age 78 years)	Chromium supplementation via Brewer's yeast	12	11 µg/day chromium	Chromium supplementation significantly (p>0.05) decreased serum cholesterol and triglyceride levels compared to the placebo group.
						Placebo (Torula yeast)	12	-	
Offenbacher <i>et al.</i> (1985)	Single-blinded	Biomarkers of CHD – serum cholesterol and triglyceride levels.	Randomised controlled trial	10 weeks	Persons aged 63-86 years	Chromium supplementation	8	200 µg/day chromic chloride	There was no association between chromium supplementation and serum cholesterol and triglyceride levels.
						Chromium supplementation via Brewer's yeast	8	5 µg/day chromium	
						Placebo (Torula yeast)	7	-	
Pasman <i>et al.</i> (1997)	Double-blinded	Biomarkers of CHD – serum cholesterol, LDL, and HDL levels.	Randomised controlled trial	16 months	Females with BMI>30, mean age = 35 years	Diet + 50 g carbohydrate + chromium supplement	13	200 µg/day chromium picolinate	There was no significant (p>0.05) difference in serum lipid levels between the three groups over time.
						Diet + 50 g carbohydrate	11	-	
						Placebo (Diet only)	9	-	

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Rabinovitz <i>et al.</i> (2004)	Single-blinded	Biomarkers of CHD – serum cholesterol, LDL, HDL and triglyceride levels.	Randomised controlled trial	21 days	Persons with Type II diabetes	Chromium supplementation	39	200 µg/day chromium picolinate	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.02</math>) inverse association between chromium supplementation and serum cholesterol levels.</li> <li>• However, there was no significant (<math>p &gt; 0.05</math>) association between chromium supplementation and HDL, LDL or serum triglyceride levels.</li> </ul>
						Placebo	39	-	
Tang <i>et al.</i> (2003)	n/a	Clinical – CHD with aged hypertension (compared to chromium status as measured by hair and fingernail concentrations)	Case-control	Single timepoint	Persons (mean age = 68 years)	Cases of CHD	99	n/a	Chromium concentrations of hair and fingernails were significantly ( $p < 0.05$ ) reduced in cases compared to controls.
						Controls	95	n/a	
Thomas and Gropper (1996)	Double-blinded	Biomarkers of CHD – serum cholesterol, LDL, HDL and triglyceride levels.	Crossover study	8 weeks for each treatment	Persons (mean age = 45 years)	Treatment 1 - chromium supplementation	8	200 µg/day niacin-bound chromium	There was no significant ( $p > 0.05$ ) association between chromium supplementation and serum cholesterol, HDL, LDL or triglyceride levels when compared to controls.
						Treatment 2 – placebo	5	-	
Uusitupa <i>et al.</i> (1992)	?	Biomarkers of CHD – serum cholesterol, HDL and triglyceride levels.	Randomised controlled trial	6 months	Persons with impaired glucose tolerance, aged 65-74 years	Supplementation with chromium-rich yeast	13	160 µg/day chromium	There was no (significant?) association between chromium supplementation and serum cholesterol, HDL or triglyceride levels when compared to the placebo treatment.
						Placebo	13	-	

**Table A2-2: Identified Studies on the Chromium and Diabetes / Glucose Metabolism**

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Abraham <i>et al.</i> (1992)	Not reported	Biomarkers of diabetes – serum glucose levels	Randomised controlled trial	7-16 months	Patients with atherosclerosis aged 42-83 years	Chromium supplementation	38	250 mg chromium chloride	<ul style="list-style-type: none"> <li>Chromium supplementation significantly increased serum chromium levels (p&lt;0.05).</li> <li>There was no significant (p&gt;0.05) difference in serum glucose levels between the two groups.</li> </ul>
						Placebo treatment	38	-	
Anderson <i>et al.</i> (1997)	Double-blinded	Biomarkers of diabetes – fasting serum glucose and HbA1c levels	Randomised controlled trial	4 months	Persons with Type II diabetes aged 35-65 years.	High chromium supplementation	60	500 µg/day chromium picolinate	<ul style="list-style-type: none"> <li>500 µg/day chromium supplementation significantly (p&lt;0.0001) decreased serum glucose, insulin and HbA1c levels compared to the placebo group.</li> <li>100 µg/day chromium supplementation significantly (p&lt;0.0001) decreased serum insulin levels, however had no significant (p&gt;0.05) impact on serum glucose or HbA1c</li> </ul>
						Low chromium supplementation	60	100 µg/day chromium picolinate	
						Placebo	60	-	
Anderson <i>et al.</i> (2001)	Double-blinded	Biomarkers of diabetes – fasting serum glucose, insulin and HbA1c levels	Randomised controlled trial	6 months	Persons with Type II diabetes aged <65 years.	Chromium supplementation	27	400 µg/day chromium pidolate	There was no significant (p<0.05) difference in serum glucose, insulin or HbA1c levels between the two study groups.
						Placebo	29	-	

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Bahijiri <i>et al.</i> (2000)	Double-blinded	Biomarker of diabetes – fasting serum glucose and 2 hr glucose.	Randomised controlled crossover trial	8 weeks for each treatment alternating with 8 week placebo washout	Persons with Type II diabetes aged 36-68 years.	Treatment 1 - chromium supplementation	78	200 µg/day chromium chloride	Both chromium supplementations significantly decreased (p<0.001) decreased serum glucose levels.
						Treatment 2 – Brewer's yeast	78	23.2 µg/day chromium	
Cefalu <i>et al.</i> (1999)	Double-blinded	Biomarkers of diabetes – serum glucose and insulin levels (measured over 2 and 24 hours following glucose tolerance test), and HbA1c.	Randomised controlled trial	8 months	Persons at risk of diabetes aged 42-53 years.	Chromium supplementation	15	1000 µg/day chromium picolinate	<ul style="list-style-type: none"> <li>Chromium supplementation significantly (p&lt;0.005) decreased the insulin response to the glucose tolerance test compared to the placebo.</li> <li>Chromium supplementation had no significant (p&gt;0.05) effect on glucose or HbA1c levels.</li> </ul>
						Placebo	14	-	
Cheng <i>et al.</i> (1999)	n/a	Biomarkers of diabetes – fasting and postprandial serum glucose levels	Single administration (follow-up to Anderson <i>et al.</i> 1997)	10 months	Persons with Type II diabetes aged 35-65 years.	Chromium supplementation	833	500 µg/day chromium picolinate	Chromium supplementation significantly (p<0.05) decreased serum glucose levels compared to the initial readings of the follow-up period.
Ghosh <i>et al.</i> (2002)	Double-blinded	Biomarkers of diabetes – fasting serum glucose, insulin and HbA1c levels.	Randomised controlled cross-over study	12 weeks for each treatment with a 4 week washout	Patients with Type II diabetes (mean age =53 years)	Treatment 1 - chromium supplementation	50	400 µg/day chromium picolinate	There was a significantly inverse association between chromium supplementation and fasting serum glucose (p<0.001), insulin (p<0.05) and HbA1c (p<0.05) levels.
						Treatment 2 – placebo	50	-	

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Grant <i>et al.</i> (1997)	Double-blinded	Biomarkers of diabetes – fasting serum insulin levels (following a glucose tolerance test)	Randomised controlled trial	9 weeks	Obese females	Chromium supplementation	10	200 µg/day chromium picolinate	<ul style="list-style-type: none"> <li>• There was no significant (<math>p&gt;0.05</math>) difference between the study groups for serum glucose or HbA1c measurements.</li> <li>• There was a significant (<math>p&lt;0.05</math>) inverse association between chromium supplementation and serum insulin levels.</li> </ul>
						Chromium supplementation	10	200 µg/day niacin-bound chromium	
						Placebo	23	-	
Joseph <i>et al.</i> (1999)	Double-blinded	Biomarkers of diabetes – fasting serum glucose and insulin levels.	Randomised controlled trail	12 weeks	Persons with BMI >25 (mean age = 62 years)	Chromium supplementation	17	900 µg/day chromium picolinate	There was no significant ( $p>0.05$ ) association between chromium supplementation and serum glucose and insulin levels.
						Placebo	15	-	
Jovanovic <i>et al.</i> (1999)	Double-blinded	Biomarkers of diabetes – fasting serum glucose, insulin and HbA1c levels.	Randomised controlled trial	8 weeks	Females with gestational diabetes (20-24 months pregnant) aged 25-43 years.	High chromium supplementation	10	8 µg/kg bw/day chromium picolinate	<ul style="list-style-type: none"> <li>• Both chromium supplement groups had significantly (<math>p&lt;0.05</math>) lower serum glucose and insulin levels compared to the placebo group.</li> <li>• Compared to the placebo group, HbA1c levels were significantly decreased (<math>p&lt;0.05</math>) in the high chromium supplementation group only.</li> </ul>
						Low chromium supplementation	10	4 µg/kg bw/day chromium picolinate	
						Placebo	10	-	

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Offenbacher and Pi-Sunyer (1980)	Single-blinded	Biomarkers of diabetes – fasting serum glucose and insulin levels.	Randomised controlled trial	8 weeks	Persons (mean age 78 years)	Chromium supplementation via Brewer's yeast	12	11 µg/day chromium	Chromium supplementation significantly ( $p<0.05$ ) decreased serum glucose and insulin levels compared to the placebo group.
						Placebo (Torula yeast)	12	-	
Offenbacher <i>et al.</i> (1985)	Not reported	Biomarkers of diabetes – fasting serum glucose and insulin levels.	Randomised controlled trial	10 weeks	Persons aged 63-93 years	Chromium supplementation	8	200 µg/day chromic chloride	There was no association between chromium supplementation and serum glucose or insulin levels.
						Chromium supplementation via Brewer's yeast	8	5 µg/day chromium	
						Placebo (Torula yeast)	7	-	
Pasman <i>et al.</i> (1997)	Double-blinded	Biomarkers of diabetes – fasting serum glucose and insulin levels.	Randomised controlled trial	16 months	Females with BMI>30, mean age = 35 years	Diet + 50 g carbohydrate + chromium supplement	13	200 µg/day chromium picolinate	Serum blood glucose and insulin levels did not significantly ( $p>0.05$ ) differ between the three groups over time.
						Diet + 50 g carbohydrate	11	-	
						Placebo (Diet only)	9	-	



Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Rabinovitz <i>et al.</i> (2004)	Single-blinded	Biomarkers of diabetes – fasting serum glucose, insulin and HbA1c levels.	Randomised controlled trial	21 days	Persons with Type II diabetes	Chromium supplementation	39	200 µg/day chromium picolinate	<ul style="list-style-type: none"> <li>• There was a significant (p&lt;0.01) inverse association between chromium supplementation and serum glucose and HbA1c levels.</li> <li>• There was no significant (p&gt;0.05) association between chromium supplementation and serum insulin levels.</li> </ul>
						Placebo	39	-	
Rajpathak <i>et al.</i> (2004)	n/a	Clinical – incidence of diabetes (compared to chromium status as measured by toenail concentrations)	Case-control	7 years	Males aged 40-75 years	Cases of diabetes	688	n/a	<ul style="list-style-type: none"> <li>• There was a significant (p&lt;0.01) inverse association between chromium status and the incidence of diabetes in combination with CVD.</li> <li>• However, there was no significant (p&gt;0.05) association between chromium status and diabetes incidence alone.</li> </ul>
						Cases of diabetes and CVD	198	n/a	
						Age matched healthy controls	361	n/a	
Thomas and Gropper (1996)	Double-blinded	Biomarkers of diabetes – serum glucose and insulin levels as measured by a glucose tolerance test.	Crossover study	8 weeks for each treatment	Persons (mean age = 45 years)	Treatment 1 - chromium supplementation	8	200 µg/day niacin-bound chromium	There was no significant (p>0.05) association between chromium supplementation and serum glucose or insulin when compared to controls.
						Treatment 2 – placebo	5	-	

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Trow <i>et al.</i> (2000)	Not blinded	Biomarkers of diabetes – serum glucose and insulin levels as measured by a glucose tolerance test.	Crossover study	4 weeks placebo then 8 weeks treatment	Persons with Type II diabetes	Habitual diet + chromium supplementation	12	100 µg/day chromium	There was no significant (p>0.05) association between chromium supplementation and serum glucose or insulin when compared to the non-treatment period.
						Habitual diet only	12	-	
Urberg and Zemel (1987)	Not reported	Biomarkers of diabetes – serum glucose levels as measured by a glucose tolerance test.	Randomised controlled trial	28 days	Persons	Chromium supplementation	5	200 µg/day chromium	<ul style="list-style-type: none"> <li>• There was a significant (p&lt;0.05) decrease in serum glucose over time with chromium + niacin supplementation.</li> <li>• There was no significant (p&gt;0.05) change in glucose levels over time with chromium or niacin supplementation alone.</li> </ul>
						Niacin supplementation	5	100 mg/day nicotinic acid	
						Chromium + niacin supplementation	6	200 µg/day chromium + 100 mg/day nicotinic acid	
Uusitupa <i>et al.</i> (1992)	Double-blinded	Biomarkers of diabetes – serum glucose and insulin levels (as measured by a glucose tolerance test), and HbA1c levels.	Randomised controlled trial	6 months	Persons with impaired glucose tolerance, aged 65-74 years	Supplementation with chromium-rich yeast	13	160 µg/day chromium	There was no association between chromium supplementation and serum glucose, insulin or HbA1c levels when compared to the placebo treatment.
						Placebo	13	-	

**Table A2-3: Identified Studies on Cancer and Obesity Outcomes from Increased Chromium Intakes**

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Crawford <i>et al.</i> (1999)	Double-blinded	Clinical – weight and fat mass (fat measured via bioimpedence)	Randomised controlled cross-over study	2 months on each treatment	Females with BMI>25	Treatment 1 – chromium supplementation	20	600 µg/day niacin-bound chromium	There was no significant (p>0.05) decrease in weight as a result of chromium supplementation, however there was a significant (p<0.05) loss of fat mass following supplementation.
						Treatment 2 – placebo	20	-	
Garland <i>et al.</i> (1996)	n/a	Clinical – breast cancer (compared to chromium status as measured by toenail concentrations)	Case-control (subset of the Nurses’ Health Study Cohort)	4 years	Females aged 30-55 years	Cases of breast cancer	433	n/a	<ul style="list-style-type: none"> <li>• There was no significant (p&gt;0.05) association between chromium status and breast cancer risk amongst the total cohort.</li> <li>• There was, however a significant (p&lt;0.05) inverse association between chromium status and breast cancer risk in pre-menopausal women.</li> <li>• The OR between the lowest (&lt;0.52 µg/g) and highest (&gt;2.37 µg/g) toenail concentrations of premenopausal women was 0.47.</li> </ul>
						Matched controls	433	n/a	
Kilic <i>et al.</i> (2004)	n/a	Clinical – breast cancer (compared to chromium status as measured by hair concentrations)	Case-control	4 years	Females (mean age = 54 years)	Cases of breast cancer	26	n/a	There was a significant (p<0.05) <u>positive</u> association between chromium status and breast cancer incidence.
						Matched controls	27	n/a	
Pasman <i>et al.</i> (1997)	Double-blinded	Clinical – weight (BMI)	Randomised controlled trial	16 months	Females with BMI>30, mean age	Diet + 50 g carbohydrate + chromium supplement	13	200 µg/day chromium picolinate	Chromium supplementation had no significant (p>0.05) impact on the weight of subjects.

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
					= 35 years	Diet + 50 g carbohydrate	11	-	
						Placebo (Diet only)	9	-	
Rogers <i>et al.</i> (1993)	n/a	Clinical – laryngeal, oesophageal, oral cancers (compared to chromium status as measured by toenail concentrations)	Case-control	4 years	Persons aged 20-74 years	Cases of cancer	507	n/a	There was no association between chromium status and cancer incidence.
						Controls	434	n/a	

### Assessment of Health Benefit: Vitamin A

A total of 201 articles were identified on the health benefits associated with vitamin A intake. A review of abstracts further refined the number of articles. The abstracts of these articles were further reviewed to ensure that the subject matter, not just the title, was relevant to this assessment.

When conducting the review of abstracts, it was noted that many of the articles referred to vitamin A and not retinol ( $\beta$ -carotene has been assessed separately in Section 5.5 below). Therefore, those articles' abstracts that made reference to retinol *per se* were only considered. As a check, four studies where the abstract made reference to vitamin A and had a strong study design (Feskanich *et al.*, 2003; Cho *et al.*, 2003; Lim *et al.*, 2004; Steck-Scott *et al.*, 2004) were selected and the full paper sourced. Of these four papers, three referred to retinol within the text (Feskanich *et al.*, 2003; Cho *et al.*, 2003; Lim *et al.*, 2004), one did not (Steck-Scott *et al.*, 2004).

The abstracts were also assessed to determine if serum retinol had been used as an indicator of vitamin A status of subjects. These articles were excluded, as serum retinol levels do not necessarily reflect retinol intake, and may be influenced by other dietary factors such as the intake of protein, energy or zinc (United States Institute of Medicine, 2001).

Following a review of abstracts, the available evidence was reduced to 16 articles once duplicate material was eliminated. The details of these articles are provided in Tables A3-1 to A3-3 below.

Twelve studies investigated retinol in relation to various cancers, showing that the relationship between retinol intake and cancer varies depending on the type of cancer. An inverse association between retinol intake and cancer risk was found several of the 12 studies. These inverse associations were based on linear trends comparing retinol intake with cancer, usually as ascertained by a semi quantitative food frequency questionnaire. Four cancer studies showed no statistically significant relationship between retinol intake and breast cancer. Two studies used biochemical indices to ascertain retinol status (breast tissue and plasma retinol), neither showing a relationship between retinol intake and a health outcome.

Two of the twelve cancer studies investigated melanoma endpoints, and showed an inverse relationship between retinol intake and incidence of melanoma. An inverse association between retinol intakes was observed for lung and colon cancer in one study. Of two studies investigating prostate cancer, one showed an association between retinol intake and cancer incidence, the other did not. Single studies investigating ovarian and head/neck cancer did not show an association between retinol and cancer incidence.

The literature search revealed three studies investigating the relationship between vitamin A and bone health. One study investigated retinol intakes separate from total vitamin A intakes. This study investigated the relationship between retinol intake and bone mineral density and the relationship between retinol intake and fracture risk. Retinol intake was associated negatively with bone mineral density, and an increased intake was associated with increased risk of hip fracture. The remaining two studies investigated retinol as a component of vitamin A.

One showed an inverse relationship between retinol intake from food and supplements and hip fracture, and the other did not show any association between retinol and the risk of fracture.

There was only one other study outside of cancer and bone health investigations. This paper examined the effect of retinol intake on cataracts, and did not show a significant association.

The evidence base on vitamin A indicates that there may be a beneficial outcome for cancer risk, primarily melanomas. However there is also a strong level of evidence that supports the null hypothesis for cancer, as well as for other health-related endpoints.

**Vitamin A is assigned an evidence level of 1**

**Table A3-1: Identified Studies on Vitamin A (Retinol) and Cancer**

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Results
Bertone <i>et al.</i> (2001)	Clinical – ovarian cancer (Food frequency questionnaire to quantify typical consumption of retinol 5 years prior to diagnosis)	Retrospective population based case control	4 years	Women	Cases of ovarian cancer	327	Intake of retinol was unrelated to risk of ovarian cancer
					Controls	3129	
Bohlke <i>et al.</i> (1999)	Clinical – histologically confirmed breast cancer (compared to retinol intake as ascertained by food frequency questionnaire)	Case control study	Not reported	Women	Cases of breast cancer	820	In postmenopausal women there was no association between retinol intake and risk of breast cancer.
					Controls	1548	
Bosetti <i>et al.</i> (2004)	Clinical -Prostrate cancer (compared with retinol intake as ascertained by food frequency questionnaire)	Case control	9 years	Males <75 years of age	Cases of prostrate cancer	1294	<ul style="list-style-type: none"> <li>The risk of prostrate cancer was inversely associated with retinol intakes.</li> <li>The odds ratio (OR) for highest vs. lowest quintiles of intake was 0.79.</li> </ul>
					Controls	1451	
Cho <i>et al.</i> (2003)	Clinical – Breast Cancer (compared to retinol intake as ascertained by food frequency questionnaire)	Prospective cohort	8 years follow up	Women – 26-46 years at beginning of study (Nurses study)	Cases of breast cancer	714	<ul style="list-style-type: none"> <li>There was an inverse relationship between retinol intake and breast cancer, however this association was not statistically significant (<math>p&gt;0.05</math>).</li> <li>The relative risk (RR) between the highest quintile of intake compared to lowest was 0.80.</li> </ul>
					Cohort	90 655	
Copper <i>et al.</i> (1999)	Clinical – measurement of plasma retinol in head and neck cancer patients	Case control	Not reported	Persons	Cases of head/neck cancer	25	There was no difference found in plasma retinol between cases and controls
					Controls	26	

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Results
Feskanich <i>et al.</i> (2003)	Clinical – melanoma (compared to dietary and supplemental retinol intake as measured by food frequency questionnaire).	Prospective cohort	4 years	Women in Nurses health study I and II	Cases of melanoma	414	<ul style="list-style-type: none"> <li>• There was a significantly (<math>p&lt;0.01</math>) inverse association between retinol intake from foods and supplements and melanoma incidence</li> <li>• The RR between the lowest (400 mg) and highest (<math>&gt;1800</math> mg) retinol intake was 0.39.</li> </ul>
					Cohort	162000	
Fontham <i>et al.</i> (1988)	Clinical – lung cancer (compared to retinol intake as ascertained by semi quantitative food frequency questionnaire)	Case-control	3 years	Persons	Cases of lung cancer	1253	<ul style="list-style-type: none"> <li>• There was a significant (<math>p&lt;0.05</math>) inverse association between retinol intake and adenocarcinoma risk. This risk was more pronounced amongst black subjects.</li> <li>• The OR for this association was 0.64.</li> </ul>
					Controls without history of cancer	1274	
Ghadirian <i>et al.</i> (1997)	Clinical – colon carcinoma (compared to retinol intake as ascertained by food frequency questionnaire).	Case control	4 years	Persons	Cases of colon carcinoma	402	<ul style="list-style-type: none"> <li>• There was a significant (<math>p&lt;0.05</math>) inverse association between dietary retinol intake and colon cancer risk</li> <li>• The OR for this association was 0.069</li> </ul>
					Controls	682	
Giovannucci <i>et al.</i> (1995)	Clinical - prostate cancer (compared to retinol intake as ascertained by food frequency questionnaire)	Prospective cohort	6 years	Men	Cases of prostate cancer	812	No consistent association was observed for dietary retinol and risk of prostate cancer
					Cohort	47894	
Kushi <i>et al.</i> (1996a)	Clinical – breast cancer (compared to retinol intake as ascertained by food frequency questionnaire)	Prospective cohort	8 years	Postmenopausal women IOWA	Cases of breast cancer	879	There was no relation between retinol intakes and breast cancer incidence.
					Cohort	34387	
Naldi <i>et al.</i> (2004)	Clinical - Patients with histologically confirmed cutaneous malignant melanoma (compared with dietary vitamin A intake)	Case control	2 years	Men and women	Cases of melanoma	542	<ul style="list-style-type: none"> <li>• There was a significant (<math>p&lt;0.05</math>) inverse relationship between retinol intake and melanoma risk.</li> <li>• Adjusted OR for this association = 0.57.</li> </ul>
					Controls	538	



Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Results
Zhu <i>et al.</i> . (1995)	Clinical – breast cancer (compared to vitamin A concentration in breast adipose tissue, and dietary vitamin A intake – method of analysis not reported).	Clinical case control	Not reported	Women	Cases of breast cancer	36	<ul style="list-style-type: none"> <li>• Vitamin A concentration of breast adipose tissue was no different between the two groups.</li> <li>• Vitamin A intake was not statistically (<math>p&gt;0.05</math>) different between cases and controls.</li> <li>• Vitamin A concentration of breast adipose tissue had a significant (<math>p&lt;0.05</math>) correlation with dietary intake in breast cancer cases only.</li> </ul>
					Controls with benign breast disease	45	

**Table A3-2: Identified Studies on Vitamin A and Bone Health**

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Results
Feskanich <i>et al.</i> (2002)	Clinical – hip fracture (compared with intake of retinol as estimated from diet records and food frequency questionnaire).	Prospective Cohort	18 year follow up	Women, nurses study	Cases of hip fracture	603	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.01</math>) positive association between total vitamin A intake and the incidence of hip fracture. This increased risk was attributable primarily to retinol.</li> <li>• The RR between the lowest (<math>&lt; 500</math> <math>\mu\text{g/day}</math>) and highest (<math>&gt; 2000</math> <math>\text{mg/day}</math>) quintiles of retinol intake was 1.89.</li> </ul>
					Cohort	72 337	
Lim <i>et al.</i> (2004)	Clinical - bone mineral density and hip fracture (compared with intake of retinol as estimated from diet records and food frequency questionnaire).	Prospective Cohort	9.5 years	Post - menopausal women (IOWA women's health study)	Cases of hip fracture	6502	There was no significant ( $p > 0.05$ ) dose response relationship between retinol intake and hip fracture risk.
					Cohort	34 703	
Melhus <i>et al.</i> (1998)	Clinical - bone mineral density and hip fracture (compared with intake of retinol as estimated from diet records and food frequency questionnaire).	Cross sectional	5.5 years	Women	Women 28-74 years	175	Retinol intake was negatively associated with bone mineral density
		Nested case control	5.5 years	Women	Cases of hip fracture	247	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.01</math>) association between retinol intake and hip fracture risk.</li> <li>• For every 1 mg increase in retinol intake risk for hip fracture increased by 68%.</li> </ul>
					Controls	873	

**Table A3-3: Identified Studies on Other Health Outcomes Associated with Increased Vitamin A (Retinol) Intake**

<b>Study</b>	<b>Study Endpoint Type</b>	<b>Study Design</b>	<b>Length of Study</b>	<b>Subjects</b>	<b>Subject Grouping</b>	<b>Subject number</b>	<b>Results</b>
Chasan-Taber <i>et al.</i> (1999)	Clinical – cases who had cataracts extracted (compared to food frequency questionnaire).	Prospective cohort	12 years	77466 female nurses aged 30-55 years	Cases of cataracts	1471	Retinol intake was not significantly ( $p>0.05$ ) associated with cataract formation.

### Assessment of Health Benefit: $\beta$ -carotene

A review of abstracts refined the 141  $\beta$ -carotene articles identified from the PubMed and NHMRC sources. This process ensured that the subject matter was relevant to this assessment. In assessing the subject matter, articles that assessed changes in serum  $\beta$ -carotene against health outcomes were included, as there is evidence showing that serum  $\beta$ -carotene is reflective of a change in dietary  $\beta$ -carotene intake (United States Institute of Medicine, 2000b).

The available evidence used to assess  $\beta$ -carotene was reduced to 72 articles. A detailed summary of these articles is provided in Tables A4-2 to A4-3 below.

Eighteen articles were identified that examined the association between  $\beta$ -carotene intakes above the RDI (i.e. the vitamin A RDI expressed as retinol equivalents) and CHD. There was a clear division in the articles relating to CHD, with ten articles reporting a significant inverse association between CHD endpoints and  $\beta$ -carotene intakes, and eight articles that showed no significant association between CHD endpoints and  $\beta$ -carotene intakes.

The greatest number of articles (50) on  $\beta$ -carotene related to the association between its intake above the RDI and cancer. The majority of these articles (31) showed no significant association between cancer endpoints and  $\beta$ -carotene intakes. Nineteen articles showed a significant inverse relationship between cancer endpoints and  $\beta$ -carotene intakes. Six of the 50 cancer articles were intervention studies, of which only two showed an inverse relationship between increased  $\beta$ -carotene intakes and cancer risk.

There were four articles that reported on other health outcomes, including bone health, respiratory diseases, and the common cold. None of these articles indicated a significant beneficial health effect with  $\beta$ -carotene intakes above the RDI.

Although there is information to indicate that a beneficial association may exist between  $\beta$ -carotene intakes and CHD / cancer, the high volume of contradictory evidence shows that this association is most likely a weak one.

**$\beta$ -carotene is assigned an evidence level of 1**

Table A4-1: Identified Studies on  $\beta$ -Carotene and Coronary Heart Disease (CHD)

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Asherio <i>et al.</i> (1999)	n/a	Clinical – ischaemic and haemorrhagic stroke (compared to $\beta$ -carotene intake as measured by food frequency questionnaire).	Cohort	8 years	40-75 year males without CVD or diabetes	Total Stroke	328	n/a	There was no significant difference in the incidence of stroke ( $p < 0.05$ ) between highest and lowest quintiles of $\beta$ -carotene intake.
						Ischaemic stroke	210	n/a	
						Haemorrhagic stroke	70	n/a	
Bolton-Smith <i>et al.</i> (1992)	n/a	Clinical – diagnosed and undiagnosed CHD (compared to $\beta$ -carotene intake as measured by food frequency questionnaire).	Cross sectional study	10 years	Adult persons	Diagnosed CHD males	369	n/a	<ul style="list-style-type: none"> <li>• CHD risk was significantly (<math>p &lt; 0.05</math>) lower between the highest and lowest quintiles of <math>\beta</math>-carotene intake for undiagnosed males.</li> <li>• There was no significant (<math>p &gt; 0.05</math>) difference in the risk of CHD between the highest and lowest quintiles of <math>\beta</math>-carotene intake for undiagnosed female or diagnosed CHD subjects.</li> </ul>
						Diagnosed CHD females	235	n/a	
						Undiagnosed CHD males	659	n/a	
						Undiagnosed CHD females	795	n/a	
						Healthy male controls	3720	n/a	
						Healthy female controls	3749	n/a	
Daviglus <i>et al.</i> (1997)	n/a	Clinical – cases of stroke (compared to $\beta$ -carotene intake)	Cohort	46 years	Middle-aged males	Cases of stroke	222	n/a	<ul style="list-style-type: none"> <li>• There was no significant (<math>p &gt; 0.05</math>) association between <math>\beta</math>-carotene intakes and the risk of stroke.</li> <li>• Adjusted RR between the highest and lowest intake of <math>\beta</math>-carotene was 0.84.</li> </ul>

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
de Lorgeril <i>et al.</i> (2001)	n/a	Biomarkers of congestive heart failure – peak exercise oxygen consumption, and left ventricular ejection function (compared to $\beta$ -carotene intake)	Case-control	Not reported	Persons	Cases of congestive heart failure	21	n/a	<ul style="list-style-type: none"> <li>• Serum <math>\beta</math>-carotene was inversely associated with the two biomarkers endpoints (<math>p &lt; 0.05</math>).</li> <li>• There was no significant (<math>p &gt; 0.05</math>) association between dietary <math>\beta</math>-carotene and the study endpoints.</li> </ul>
						Age and gender matched controls	21	n/a	
Do <i>et al.</i> (2003)	n/a	Clinical – breast cancer (compared to $\beta$ -carotene intake as measured by food frequency questionnaire)	Case-control	2 years	Females aged 20-69 years	Cases of breast cancer	224	n/a	The intake of $\beta$ -carotene was inversely, but not significantly ( $p > 0.05$ ) associated with breast cancer.
						Age matched controls	299	n/a	
Genkinger <i>et al.</i> (2004)	n/a	Clinical – mortality from cancer, CHD and all causes (compared to $\beta$ -carotene intake as measured by a food frequency questionnaire)	Cohort	15 years	6151 persons	Cases of cancer	307	n/a	$\beta$ -carotene intakes had no significant ( $p > 0.05$ ) impact on the mortality from CHD.

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Hak <i>et al.</i> (2003)	Double - blinded	Clinical – MI incidence (compared to $\beta$ -carotene intake as measured by food frequency questionnaire)	Randomised clinical trial	5 years	Male physicians aged 40-84	$\beta$ -carotene supplement intake	531	50 mg/day	<ul style="list-style-type: none"> <li>• There was no significant (<math>p&gt;0.05</math>) difference in the incidence of MI between the two study groups.</li> <li>• There was no significant (<math>p&gt;0.05</math>) association between <math>\beta</math>-carotene intake and the risk of MI.</li> </ul>
						Placebo intake	531	-	
Hak <i>et al.</i> (2004)	n/a	Clinical – stroke (compared to serum $\beta$ -carotene levels)	Case-control	13 years	Male physicians aged 45-70 years	Cases of stroke	297	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p&gt;0.05</math>) inverse association between serum <math>\beta</math>-carotene levels and the risk of stroke.</li> <li>• The OR between the lowest and highest <math>\beta</math>-carotene intakes was 0.62.</li> </ul>
						Age matched controls	297	n/a	
Hirvonen <i>et al.</i> (2000)	n/a	Clinical – stroke events (compared to $\beta$ -carotene intake measured by a food frequency questionnaire)	Cohort	6.1 years	Male smokers	Cerebral infarction cases	736	n/a	<ul style="list-style-type: none"> <li>• The risk of cerebral infarction was significantly (<math>p&lt;0.001</math>) reduced with increasing dietary <math>\beta</math>-carotene intake.</li> <li>• The RR of cerebral infarction between 1<sup>st</sup> (0.81 mg/day) and 4<sup>th</sup> (3.69 mg/day) quintiles of dietary <math>\beta</math>-carotene intake was 0.74.</li> <li>• Dietary <math>\beta</math>-carotene intake was not significantly associated (<math>p&gt;0.05</math>) with intracerebral haemorrhage or subarachnoid haemorrhage.</li> </ul>
						Subarachnoid haemorrhage cases	83	n/a	
						Intracerebral haemorrhage cases	95	n/a	

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Klipstein-Grobusch <i>et al.</i> (1999)	n/a	Clinical – myocardial infarction (MI) (compared to $\beta$ -carotene intake measured by food frequency questionnaire)	Cohort	4 years	4802 persons aged $\geq 55$ years	Cases of MI	173	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.02</math>) inverse association between <math>\beta</math>-carotene intake and the risk of MI.</li> <li>• The OR between the lowest (<math>&lt; 1.13</math> mg/day) and highest (<math>&gt; 1.57</math> mg/day) intakes of <math>\beta</math>-carotene was 0.55.</li> </ul>
Kardinaal <i>et al.</i> (1995)	n/a	Clinical – acute MI (compared to serum $\beta$ -carotene)	Case-control	2 years	Males aged $< 70$ years	Cases of acute MI	674	n/a	Tissue $\beta$ -carotene levels were significantly ( $p < 0.05$ ) lower in cases compared to controls.
						Age matched controls	725	n/a	
Klipstein-Grobusch <i>et al.</i> (2001)	n/a	Clinical – peripheral arterial disease incidence (compared to dietary $\beta$ -carotene intake measured by a food frequency questionnaire)	Cohort	4 years	4367 persons aged $\geq 55$ years	Female cases of peripheral arterial disease	370	n/a	$\beta$ -carotene intakes were not significantly ( $p > 0.05$ ) associated with the risk of peripheral arterial disease.
						Male cases of peripheral arterial disease	204	n/a	
Osganian <i>et al.</i> (2003b)	n/a	Clinical – coronary artery disease including fatal and non-fatal MI (compared to $\beta$ -carotene intake measured by food frequency questionnaire)	Cohort	10 years	73286 females aged 30-55 years	Cases of coronary artery disease	998	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.05</math>) inverse association between <math>\beta</math>-carotene intake and the risk of coronary artery disease.</li> <li>• The OR between the lowest (1.72 mg/day) and highest (7.64 mg/day) intakes of <math>\beta</math>-carotene was 0.74.</li> </ul>
Rapola <i>et al.</i> (1997)	Double-blind	Clinical – non-fatal MI and fatal CHD	Randomised controlled trial	5.3 years	Male smokers	$\beta$ -carotene supplement intake group	461	20 mg/day	There was no significant ( $p < 0.05$ ) difference in the incidence of non-fatal MI or fatal CHD between the



Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
	g					Placebo intake group	438	-	two groups.
Singh <i>et al.</i> (1994)	n/a	Clinical – incident of coronary artery disease (compared to $\beta$ -carotene intake as measured by a 7-day food recall)	Cross-sectional study	Not reported	Persons aged 26-65 years	Total population	152	n/a	$\beta$ -carotene intakes were significantly ( $p < 0.01$ ) lower in individuals with coronary artery disease compared to those without CHD risk factors.
Singh <i>et al.</i> (1995)	n/a	Clinical – coronary artery disease (compared to $\beta$ -carotene intake)	Cross-sectional study	Not reported	Persons aged 50-84 years	Total population	72	n/a	$\beta$ -carotene intakes were significantly ( $p > 0.05$ ) lower in individuals with coronary artery disease compared to those without.
Tavani <i>et al.</i> (1997)	n/a	Clinical – non-fatal acute MI (compared to $\beta$ -carotene intake)	Case-control	9 years	Females	Cases of non-fatal acute MI	433	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.01</math>) inverse association between <math>\beta</math>-carotene intake and the risk of acute MI.</li> <li>• The OR between the lowest and highest intakes of <math>\beta</math>-carotene was 0.5.</li> </ul>
						Controls	869	n/a	
van Poppel <i>et al.</i> (1994)	Double - blinded	Biomarkers of CHD – total cholesterol, HDL, apolipoproteins A-I and B-100 and (a)	Randomised controlled trial	14 weeks	Male smokers	$\beta$ -carotene supplement intake	25	20 mg/day	There was no significant ( $p > 0.05$ ) difference in the study parameters between the two study groups.
						Placebo intake	25	-	

**Table A4-2: Identified Studies on  $\beta$ -Carotene and Cancer**

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Adzersen <i>et al.</i> (2003)	n/a	Clinical – primary breast cancer (compared to $\beta$ -carotene intake)	Case-control	2 years	Females	Cases of primary breast cancer	310	n/a	<ul style="list-style-type: none"> <li>• There was no significant (<math>p&gt;0.05</math>) association between <math>\beta</math>-carotene intake and breast cancer risk.</li> <li>• The OR between the lowest and highest <math>\beta</math>-carotene intakes was 0.46.</li> </ul>
						Controls without dietary or endocrine conditions	353	n/a	
Albanes <i>et al.</i> (1996)	?	Clinical – lung cancer incidence	Randomised controlled trial	5-8 years	Male smokers aged 50-69 years	$\beta$ -carotene supplement intake	?	20 mg/day	<ul style="list-style-type: none"> <li>• There was a significant (<math>p&lt;0.05</math>) increase in the incidence of lung cancer for the <math>\beta</math>-carotene supplement group compared to the placebo group.</li> <li>• The RR for <math>\beta</math>-carotene supplementation was 1.16.</li> </ul>
						Placebo intake	?	-	
Albanes <i>et al.</i> (2000)	Double-blinded	Clinical – colorectal cancer incidence	Randomised controlled trial (sub-set of ATBC trial)	8 years	Male smokers aged 50-69 years	$\beta$ -carotene supplement intake	7280	20 mg/day	<ul style="list-style-type: none"> <li>• <math>\beta</math>-carotene supplementation had no significant impact on the incidence between the two study groups (<math>p&gt;0.05</math>).</li> </ul>
						Placebo intake	7280	-	

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
ATBC Prevention Study Group (1994)	Double-blinded	Clinical – lung cancer and other cancers	Randomised controlled trial	8 years	Male smokers aged 50-69 years	Synthetic $\beta$ -carotene supplement intake	7280	20 mg/day	<ul style="list-style-type: none"> <li>The <math>\beta</math>-carotene supplement group had a significantly (<math>p &lt; 0.01</math>) <u>higher</u> incidence of lung cancer compared to the placebo group.</li> <li>Prostate cancer incidence was increased in the <math>\beta</math>-carotene supplement group, however the significance was not reported.</li> </ul>
						Placebo intake	7280	-	
Bertone <i>et al.</i> (2001)	n/a	Clinical – ovarian cancer (compared to dietary and supplemental $\beta$ -carotene intake as measured by food frequency questionnaire)	Case-control	3 years	Females	Cases of ovarian cancer	327	n/a	There was no significant ( $p < 0.05$ ) difference in the risk of ovarian cancer between highest and lowest quintiles of $\beta$ -carotene intake.
						Controls	3129	n/a	
Bohlke <i>et al.</i> (1999)	n/a	Clinical – breast cancer (compared to vitamin C intake measured by food frequency questionnaire)	Case-control	Not reported	Adult females	Breast cancer cases	820	n/a	<ul style="list-style-type: none"> <li>There was no association between <math>\beta</math>-carotene intake and breast cancer for post-menopausal women.</li> <li>There was an inverse association between <math>\beta</math>-carotene intake and breast cancer for pre-menopausal women.</li> </ul>
						Healthy controls	1548	n/a	

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results																													
Candelora <i>et al.</i> (1992)	n/a	Clinical – lung cancer (compared to $\beta$ -carotene intake as measured by food frequency questionnaire)	Case-control	3 years	Female non-smokers	Cases of lung cancer	124	n/a	<ul style="list-style-type: none"> <li>• There was no significant (<math>p&gt;0.05</math>) inverse association between <math>\beta</math>-carotene intake and lung cancer.</li> <li>• The OR between the lowest and highest <math>\beta</math>-carotene intakes was 0.4.</li> </ul>																													
						Controls	263	n/a		Ching <i>et al.</i> (2002)	n/a	Clinical – breast cancer (compared to serum $\beta$ -carotene levels)	Case-control	2 years	Females aged 30-84 years	Cases of breast cancer	341	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p&lt;0.02</math>) inverse association between serum <math>\beta</math>-carotene levels and breast cancer.</li> <li>• The adjusted OR between the lowest (<math>\leq 0.4 \mu\text{mol/L}</math>) and highest (<math>\geq 1.1 \mu\text{mol/L}</math>) quartiles of serum <math>\beta</math>-carotene was 0.47.</li> </ul>	Age matched controls	151	n/a	Cramer <i>et al.</i> (2001)	n/a	Clinical – ovarian cancer (compared to $\beta$ -carotene intake as measured by food frequency questionnaire)	Case-control	5 years	Females	Cases of ovarian cancer	549	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p&lt;0.05</math>) inverse association between <math>\beta</math>-carotene intake and ovarian cancer.</li> <li>• The adjusted OR between the lowest (<math>\leq 2.3 \text{ mg/day}</math>) and highest (<math>&gt;7.2 \text{ mg/day}</math>) quintiles of intake was 0.58</li> </ul>	Controls	516	n/a	Daviglus <i>et al.</i> (1996)	n/a	Clinical – cases of prostate cancer (compared to $\beta$ -carotene intake)
Ching <i>et al.</i> (2002)	n/a	Clinical – breast cancer (compared to serum $\beta$ -carotene levels)	Case-control	2 years	Females aged 30-84 years	Cases of breast cancer	341	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p&lt;0.02</math>) inverse association between serum <math>\beta</math>-carotene levels and breast cancer.</li> <li>• The adjusted OR between the lowest (<math>\leq 0.4 \mu\text{mol/L}</math>) and highest (<math>\geq 1.1 \mu\text{mol/L}</math>) quartiles of serum <math>\beta</math>-carotene was 0.47.</li> </ul>																													
						Age matched controls	151	n/a		Cramer <i>et al.</i> (2001)	n/a	Clinical – ovarian cancer (compared to $\beta$ -carotene intake as measured by food frequency questionnaire)	Case-control	5 years	Females	Cases of ovarian cancer	549	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p&lt;0.05</math>) inverse association between <math>\beta</math>-carotene intake and ovarian cancer.</li> <li>• The adjusted OR between the lowest (<math>\leq 2.3 \text{ mg/day}</math>) and highest (<math>&gt;7.2 \text{ mg/day}</math>) quintiles of intake was 0.58</li> </ul>	Controls	516	n/a	Daviglus <i>et al.</i> (1996)	n/a	Clinical – cases of prostate cancer (compared to $\beta$ -carotene intake)	Cohort	30 years	Middle-aged males	Cases of prostate cancer	132	n/a	<ul style="list-style-type: none"> <li>• No significant (<math>p&gt;0.05</math>) association between the intake of <math>\beta</math>-carotene and the risk of prostate cancer.</li> <li>• Relative risks (RR) between the lowest and highest intake of <math>\beta</math>-carotene was 1.27.</li> </ul>						
Cramer <i>et al.</i> (2001)	n/a	Clinical – ovarian cancer (compared to $\beta$ -carotene intake as measured by food frequency questionnaire)	Case-control	5 years	Females	Cases of ovarian cancer	549	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p&lt;0.05</math>) inverse association between <math>\beta</math>-carotene intake and ovarian cancer.</li> <li>• The adjusted OR between the lowest (<math>\leq 2.3 \text{ mg/day}</math>) and highest (<math>&gt;7.2 \text{ mg/day}</math>) quintiles of intake was 0.58</li> </ul>																													
						Controls	516	n/a		Daviglus <i>et al.</i> (1996)	n/a	Clinical – cases of prostate cancer (compared to $\beta$ -carotene intake)	Cohort	30 years	Middle-aged males	Cases of prostate cancer	132	n/a	<ul style="list-style-type: none"> <li>• No significant (<math>p&gt;0.05</math>) association between the intake of <math>\beta</math>-carotene and the risk of prostate cancer.</li> <li>• Relative risks (RR) between the lowest and highest intake of <math>\beta</math>-carotene was 1.27.</li> </ul>																			
Daviglus <i>et al.</i> (1996)	n/a	Clinical – cases of prostate cancer (compared to $\beta$ -carotene intake)	Cohort	30 years	Middle-aged males	Cases of prostate cancer	132	n/a	<ul style="list-style-type: none"> <li>• No significant (<math>p&gt;0.05</math>) association between the intake of <math>\beta</math>-carotene and the risk of prostate cancer.</li> <li>• Relative risks (RR) between the lowest and highest intake of <math>\beta</math>-carotene was 1.27.</li> </ul>																													

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Franceschi <i>et al.</i> (1999)	n/a	Clinical – colorectal cancer (compared to dietary $\beta$ -carotene intake as measured by food frequency questionnaire)	Case-control	4 years	Persons with a median age of 62 years	Cases of colorectal cancer	1953	n/a	There was an inverse association between $\beta$ -carotene intake and the risk of colorectal cancer.
						Controls	4154	n/a	
Genkinger <i>et al.</i> (2004)	n/a	Clinical – mortality from cancer, CHD and all causes (compared to $\beta$ -carotene intake as measured by food frequency questionnaire)	Cohort	15 years	6151 persons	Cases of cancer	307	n/a	$\beta$ -carotene intakes had no significant ( $p>0.05$ ) impact on the mortality from cancer.
Giovannucci <i>et al.</i> (1995)	n/a	Clinical – prostate cancer (compared to $\beta$ -carotene intake as measured by food frequency questionnaire)	Cohort	6 years	47894 males	Cases of prostate cancer	812	n/a	There was no association between $\beta$ -carotene intake and the risk of prostate cancer.
Green <i>et al.</i> (1999)	Double-blinded	Clinical – skin cancer	Randomised clinical trial	4.5 years	Persons	$\beta$ -carotene supplement intake	405	n/a	There was no significant ( $p>0.05$ ) difference in the rate of skin cancer between the two study groups.
						Placebo intake	405	n/a	
Greenberg <i>et al.</i> (1990)	Double-blinded	Clinical – skin cancer	Randomised controlled trial	5 years	Persons with non-melanoma skin cancer	$\beta$ -carotene supplement intake	903	50 mg/day	There was no significant ( $p>0.05$ ) difference between the two groups in the incidence and prevalence of skin cancer.
						Placebo intake	902	-	
Greenberg <i>et al.</i> (1994)	Double-blinded	Clinical – incidence of new colon cancer polyps	Randomised controlled trial	4 years	Persons with history of colon cancer	$\beta$ -carotene supplement intake	184	25 mg/day	There was no significant ( $p>0.05$ ) difference in the incidence of colon cancer between the two study groups.
						Placebo intake	187	-	

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results																													
Hansson <i>et al.</i> (1994)	n/a	Clinical – gastric cancer (compared to dietary and supplementary $\beta$ -carotene intake)	Case-control	20 years	Persons	Cases of gastric cancer	338	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.01</math>) inverse association between <math>\beta</math>-carotene intake and the risk of gastric cancer.</li> <li>• The OR between the lowest (0.8 mg/day) and highest (4.3 mg/day) quartile of intake was 0.52.</li> </ul>																													
						Controls	679	n/a		Holmberg <i>et al.</i> (1994)	n/a	Clinical – breast cancer (compared to $\beta$ -carotene intake)	Case-control	3 years	Females	Cases of breast cancer	265	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.05</math>) inverse association between <math>\beta</math>-carotene intake and the risk of breast cancer.</li> <li>• The OR between the lowest (2.7-3.9 mg/day) and highest (&gt;5.3 mg/day) tertiles of intake was 0.6.</li> </ul>	Age matched controls	432	n/a	Jain <i>et al.</i> (2000)	n/a	Clinical – endometrial cancer (compared to $\beta$ -carotene intake as measured by food frequency questionnaire)	Cohort	5 years	56837 females	Cases of endometrial cancer	221	n/a	There was no significant ( $p > 0.05$ ) association between endometrial cancer and $\beta$ -carotene intake.	Kaaks <i>et al.</i> (Kaaks <i>et al.</i> , 1998)	n/a	Clinical – gastrointestinal cancers (compared to $\beta$ -carotene intake as measured by a diet history)	Case-control	4 years	Persons aged 35-74 years
Holmberg <i>et al.</i> (1994)	n/a	Clinical – breast cancer (compared to $\beta$ -carotene intake)	Case-control	3 years	Females	Cases of breast cancer	265	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.05</math>) inverse association between <math>\beta</math>-carotene intake and the risk of breast cancer.</li> <li>• The OR between the lowest (2.7-3.9 mg/day) and highest (&gt;5.3 mg/day) tertiles of intake was 0.6.</li> </ul>																													
						Age matched controls	432	n/a		Jain <i>et al.</i> (2000)	n/a	Clinical – endometrial cancer (compared to $\beta$ -carotene intake as measured by food frequency questionnaire)	Cohort	5 years	56837 females	Cases of endometrial cancer	221	n/a	There was no significant ( $p > 0.05$ ) association between endometrial cancer and $\beta$ -carotene intake.	Kaaks <i>et al.</i> (Kaaks <i>et al.</i> , 1998)	n/a	Clinical – gastrointestinal cancers (compared to $\beta$ -carotene intake as measured by a diet history)	Case-control	4 years	Persons aged 35-74 years	Cases of gastrointestinal cancer	201	n/a	<ul style="list-style-type: none"> <li>• There was a significantly (<math>p &lt; 0.001</math>) inverse association between <math>\beta</math>-carotene intake and the risk of gastrointestinal cancer.</li> <li>• The OR between the lowest and highest quartile of intake was 0.5.</li> </ul>	Controls	2851	n/a						
Jain <i>et al.</i> (2000)	n/a	Clinical – endometrial cancer (compared to $\beta$ -carotene intake as measured by food frequency questionnaire)	Cohort	5 years	56837 females	Cases of endometrial cancer	221	n/a	There was no significant ( $p > 0.05$ ) association between endometrial cancer and $\beta$ -carotene intake.																													
Kaaks <i>et al.</i> (Kaaks <i>et al.</i> , 1998)	n/a	Clinical – gastrointestinal cancers (compared to $\beta$ -carotene intake as measured by a diet history)	Case-control	4 years	Persons aged 35-74 years	Cases of gastrointestinal cancer	201	n/a	<ul style="list-style-type: none"> <li>• There was a significantly (<math>p &lt; 0.001</math>) inverse association between <math>\beta</math>-carotene intake and the risk of gastrointestinal cancer.</li> <li>• The OR between the lowest and highest quartile of intake was 0.5.</li> </ul>																													
						Controls	2851	n/a																														

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Le Marchand <i>et al.</i> (1993)	n/a	Clinical – lung cancer (compared to $\beta$ -carotene intake as measured by diet history)	Case-control	2 years	Persons	Cases of lung cancer	332	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.01</math>) inverse association between the intake of <math>\beta</math>-carotene and the risk of lung cancer.</li> <li>• The OR between the lowest and highest quartiles of intake was 0.5 and 0.3 for males and females respectively.</li> </ul>
						Age matched controls	865	n/a	
McCann <i>et al.</i> (2001)	n/a	Clinical – ovarian cancer (compared to $\beta$ -carotene intake as measured by food frequency questionnaire)	Case-control	12 years	Females aged 20-87 years	Cases of ovarian cancer	496	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.05</math>) inverse association between the intake of <math>\beta</math>-carotene and the risk of ovarian cancer.</li> <li>• The OR between the lowest and highest intakes was 0.68.</li> </ul>
						Controls	1425	n/a	
Männistö <i>et al.</i> (2004)	n/a	Clinical – lung cancer (compared to $\beta$ -carotene intake as measured by food frequency questionnaire)	Pooled cohort	7-16 years	399765 Persons	Cases of lung cancer	3155	n/a	<ul style="list-style-type: none"> <li>• When adjusted for age, <math>\beta</math>-carotene intake was inversely associated with the risk for lung cancer (<math>p &lt; 0.05</math>).</li> <li>• When controlling for other confounding variables, the inverse association was insignificant (<math>p &gt; 0.05</math>).</li> <li>• The OR between the lowest and highest intakes was 0.98.</li> </ul>

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Mayne <i>et al.</i> (1994)	n/a	Clinical – lung cancer (compared to $\beta$ -carotene intake as measured by diet history)	Case-control	3 years	Persons	Cases of lung cancer	413	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.05</math>) inverse association between the intake of dietary <math>\beta</math>-carotene and the risk of lung cancer.</li> <li>• The OR between the lowest and highest <math>\beta</math>-carotene intakes was 0.7.</li> </ul>
						Age and gender matched controls	413	n/a	
Michaud <i>et al.</i> (2000)	n/a	Clinical – lung cancer (compared to $\beta$ -carotene intake as measured by food frequency questionnaire)	Control	10 years	51529 males aged 40-75 years	Cases of lung cancer	275	n/a	Adjusted $\beta$ -carotene intakes had no significant ( $p > 0.05$ ) association with the risk of lung cancer in either males or females.
				14 years	121700 females aged 30-55 years	Cases of lung cancer	519	n/a	
Michaud <i>et al.</i> (2002)	n/a	Clinical – bladder cancer (compared to $\beta$ -carotene intake as measured by food frequency questionnaire)	Cohort	11 years	27111 male smokers aged 50-69 years	Cases of bladder cancer	344	n/a	There was no significant ( $p > 0.05$ ) association between $\beta$ -carotene intake and the risk of bladder cancer.
Murtaugh <i>et al.</i> (2004)	n/a	Clinical – rectal cancer (compared to $\beta$ -carotene intake as measured by food diet history)	Case-control	4 years	Persons aged 30-79 years	Cases of rectal cancer	952	n/a	There was no significant ( $p > 0.05$ ) association between $\beta$ -carotene intake and the risk of rectal cancer.
						Age and gender matched controls	1205	n/a	



Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Negri <i>et al.</i> (1996)	n/a	Clinical – breast cancer (compared to $\beta$ -carotene intake as measured by food frequency questionnaire)	Case-control	3 years	Females	Cases of histologically confirmed breast cancer	2569	n/a	<ul style="list-style-type: none"> <li>• There was an inverse association between the intake of dietary <math>\beta</math>-carotene and the risk of breast cancer.</li> <li>• The OR between the lowest and highest <math>\beta</math>-carotene intakes was 0.84.</li> </ul>
						Controls with no history of cancer	2588	n/a	
Nkondjock and Ghadirian (2004)	n/a	Clinical – breast cancer (compared to $\beta$ -carotene intake as measured by food frequency questionnaire)	Case-control	4 years	Females aged 35-79 years	Cases of breast cancer	414	n/a	There was no significant ( $p>0.05$ ) association between adjusted $\beta$ -carotene intake and the risk of breast cancer.
						Age matched controls	668	n/a	
Norrish <i>et al.</i> (2000)	n/a	Clinical – prostate cancer (compared to $\beta$ -carotene intake)	Case-control	2 years	Males	Cases of prostate cancer	317	n/a	There was no significant ( $p>0.05$ ) association between $\beta$ -carotene intake and the risk of prostate cancer.
						Controls	480	n/a	
Nyberg <i>et al.</i> (1998)	n/a	Clinical – lung cancer (compared to $\beta$ -carotene intake)	Case-control	6 years	Persons aged > 30 years	Cases of lung cancer	124	n/a	<ul style="list-style-type: none"> <li>• There was a significantly (<math>p&lt;0.05</math>) inverse association between <math>\beta</math>-carotene intake and the risk of lung cancer.</li> <li>• The OR between the lowest and highest quintiles of intake was 0.47.</li> </ul>
						Controls	235	n/a	
Ocke <i>et al.</i> (1997)	n/a	Clinical – lung cancer (compared to vitamin C intake as measured by diet history)	Cohort	19 years	561 males	Cases of lung cancer	54	n/a	There was no significant ( $p>0.05$ ) association between $\beta$ -carotene intake and the risk of lung cancer.

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Ohno <i>et al.</i> (1988)	n/a	Clinical – prostate cancer (compared to $\beta$ -carotene intake as measured by food frequency questionnaire)	Case-control	3 years	Males	Cases of prostate cancer	100	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.01</math>) inverse association between the intake of dietary <math>\beta</math>-carotene and the risk of prostate cancer.</li> <li>• The RR between the lowest and highest <math>\beta</math>-carotene intakes was 0.48.</li> </ul>
						Controls	100	n/a	
Rohan <i>et al.</i> (2002)	n/a	Clinical – lung cancer (compared to $\beta$ -carotene intake as measured by food frequency questionnaire)	Case-control	5 years	Females	Cases of lung cancer	155	n/a	There was no significant ( $p > 0.05$ ) association between $\beta$ -carotene intake and lung cancer.
						Controls	5361	n/a	
Schuurman <i>et al.</i> (2002)	n/a	Clinical – prostate cancer (compared to $\beta$ -carotene intake as measured by food frequency questionnaire)	Cohort	6.3 years	58279 males aged 55-69 years	Cases of prostate cancer	642	n/a	There was no significant ( $p > 0.05$ ) association between $\beta$ -carotene intake and the risk of prostate cancer.
Shibata <i>et al.</i> (1992)	n/a	Clinical – cancer incidence (compared to $\beta$ -carotene intake)	Cohort	8 years	11580 persons	Cases of cancer	1335	n/a	There was no significant ( $p > 0.05$ ) association between $\beta$ -carotene intake and cancer incidence.
Slattery <i>et al.</i> (1990)	n/a	Clinical – cervical cancer (compared to $\beta$ -carotene intake)	Case-control	3 years	Females	Cases of cervical cancer	266	n/a	There was no significant ( $p > 0.05$ ) association between the intake of dietary $\beta$ -carotene and the risk of cervical cancer.
						Age matched controls	408	n/a	

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results																			
Stefani <i>et al.</i> (1999)	n/a	Clinical – lung cancer (compared to $\beta$ -carotene intake)	Case-control	4 years	Persons aged 30-89 years	Cases of lung cancer	541	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.001</math>) inverse association between the adjusted intake of dietary <math>\beta</math>-carotene and the risk of lung cancer.</li> <li>• The RR between the lowest (<math>&lt; 1.94</math> mg/day) and highest (<math>&gt; 5.86</math> mg/day) quartiles of <math>\beta</math>-carotene intake was 0.3.</li> </ul>																			
						Controls	540	n/a		Tavani <i>et al.</i> (1994)	n/a	Clinical – oesophageal cancer (compared to dietary $\beta$ -carotene intake as measured by food frequency questionnaire)	Case-control	8 years	Persons	Histologically confirmed cases of oesophageal cancer)	316	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.05</math>) inverse association between the adjusted intake of <math>\beta</math>-carotene and the risk of oesophageal cancer.</li> <li>• The RR between cases and controls was 0.4.</li> </ul>	Controls	230	n/a	Tavani <i>et al.</i> (1999)	n/a	Clinical – breast cancer (compared to dietary $\beta$ -carotene intake as measured by food frequency questionnaire)	Case-control	11 years	Females
Tavani <i>et al.</i> (1994)	n/a	Clinical – oesophageal cancer (compared to dietary $\beta$ -carotene intake as measured by food frequency questionnaire)	Case-control	8 years	Persons	Histologically confirmed cases of oesophageal cancer)	316	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.05</math>) inverse association between the adjusted intake of <math>\beta</math>-carotene and the risk of oesophageal cancer.</li> <li>• The RR between cases and controls was 0.4.</li> </ul>																			
						Controls	230	n/a		Tavani <i>et al.</i> (1999)	n/a	Clinical – breast cancer (compared to dietary $\beta$ -carotene intake as measured by food frequency questionnaire)	Case-control	11 years	Females	Cases of histologically confirmed breast cancer	579	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.01</math>) inverse association between the adjusted intake of <math>\beta</math>-carotene and the risk of breast cancer.</li> <li>• The RR between the lowest (32 IU/day) and highest (240 IU/day) quintiles of intake was 0.5.</li> </ul>	Controls	668	n/a						
Tavani <i>et al.</i> (1999)	n/a	Clinical – breast cancer (compared to dietary $\beta$ -carotene intake as measured by food frequency questionnaire)	Case-control	11 years	Females	Cases of histologically confirmed breast cancer	579	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.01</math>) inverse association between the adjusted intake of <math>\beta</math>-carotene and the risk of breast cancer.</li> <li>• The RR between the lowest (32 IU/day) and highest (240 IU/day) quintiles of intake was 0.5.</li> </ul>																			
						Controls	668	n/a																				

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Terry <i>et al.</i> (2002)	n/a	Clinical – colorectal cancer (compared to $\beta$ -carotene intake as measured by food frequency questionnaire)	Case-control	3 years	Females	Cases of colorectal cancer	295	n/a	There was no significant ( $p>0.05$ ) association between $\beta$ -carotene intakes and the risk of colorectal cancer.
						Controls	5334	n/a	
Varis <i>et al.</i> (1998)	Double-blinded	Clinical – gastric cancer	Randomised controlled trial (subset of the ATBC trial)	5.1 years	Males aged 50-69 years with gastritis	$\beta$ -carotene supplement intake	7282	20 mg/day	There was no significant ( $p>0.05$ ) difference in the incidence of gastric cancer between the two study groups.
						Placebo intake	7287	-	
Verhoeven <i>et al.</i> (1997)	n/a	Clinical – breast cancer (compared to $\beta$ -carotene intake)	Cohort	4.3 years	62573 females aged 55-69 years	Cases of breast cancer	650	n/a	There was no significant ( $p>0.05$ ) association between $\beta$ -carotene intake and the risk of breast cancer.
Voorrips <i>et al.</i> (2000)	n/a	Clinical – lung cancer (compared to dietary and supplemental $\beta$ -carotene intake as measured by food frequency questionnaire)	Cohort	6.3 years	58279 males aged 55-69 years	Cases of lung cancer	939	n/a	There was no significant ( $p>0.05$ ) association between $\beta$ -carotene intake and the risk of lung cancer.
West <i>et al.</i> (1989)	n/a	Clinical – colon cancer (compared to dietary $\beta$ -carotene intake as measured by food frequency questionnaire)	Case-control	4 years	Persons	Cases of colon cancer	231	n/a	<ul style="list-style-type: none"> <li>• There was an inverse association between the adjusted intake of <math>\beta</math>-carotene and the risk of colon cancer.</li> <li>• The RR between the lowest and highest <math>\beta</math>-carotene intake was 0.5.</li> </ul>
						Controls	391	n/a	

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
West <i>et al.</i> (1991)	n/a	Clinical – prostate cancer (compared to $\beta$ -carotene intake as measured by a food frequency questionnaire)	Case-control	2 years	Males	Cases of prostate cancer	358	n/a	There was no significant ( $p>0.05$ ) association between $\beta$ -carotene intake and the risk of prostate cancer.
						Controls	679	n/a	
Wright <i>et al.</i> (2003)	n/a	Clinical – lung cancer (compared to $\beta$ -carotene intake as measured by a food frequency questionnaire)	Case-control	3 years	Females	Cases of lung cancer	587	n/a	There was no significant ( $p>0.05$ ) inverse association between the intake of $\beta$ -carotene and the risk of lung cancer.
						Age matched controls	624	n/a	
Wu <i>et al.</i> (2004)	n/a	Clinical – prostate cancer (compared to dietary $\beta$ -carotene intake as measured by a food frequency questionnaire)	Case-control	12 years	Males aged 40-75 years	Cases of prostate cancer	450	n/a	There was no significant ( $p>0.05$ ) association between $\beta$ -carotene intake and the risk of prostate cancer.
						Age matched controls	450	n/a	
Zhang <i>et al.</i> (1999)	n/a	Clinical – breast cancer (compared to dietary and supplemental $\beta$ -carotene intake as measured by food frequency questionnaire)	Cohort	14 years	83234 females aged 30-55 years	Cases of breast cancer	2697	n/a	<ul style="list-style-type: none"> <li>Adjusted <math>\beta</math>-carotene intakes were inversely (<math>p&lt;0.05</math>) associated with the risk of breast cancer in pre-menopausal women.</li> <li>The RR between the lowest and highest <math>\beta</math>-carotene intakes of pre-menopausal women was 0.84.</li> <li>There was an inverse, but non-significant (<math>p&gt;0.05</math>) association between supplemental and dietary <math>\beta</math>-carotene intake and the risk of breast cancer in post-menopausal women.</li> </ul>

**Table A4-3: Identified Studies on  $\beta$ -Carotene and Other Health Outcomes**

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Grievink <i>et al.</i> (2000)	n/a	Clinical – chronic respiratory symptoms (compared to serum $\beta$ -carotene levels)	Case-control	1 year	Non-smoker Persons	Cases of chronic respiratory illness	491	n/a	There was no association between serum $\beta$ -carotene levels and the symptoms of chronic respiratory illness.
						Controls	496	n/a	
Hemila <i>et al.</i> (2002)	n/a	Clinical – incidence of the common cold (compared to supplemental and dietary $\beta$ -carotene intake)	Cohort	4 years	Male smokers	Total cohort	21796	n/a	Neither dietary nor supplemental $\beta$ -carotene had an association with the incidence of the common cold.
Rautalahti <i>et al.</i> (1997)	n/a	Clinical – symptoms of chronic obstructive pulmonary disease	Randomised controlled trial	5.3 years	Male smokers	$\beta$ -carotene supplement intake group	461	20 mg/day	There was no significant ( $p < 0.05$ ) difference in the symptoms of chronic obstructive pulmonary disease between the two study groups.
						Placebo intake group	438	-	
Wattanapen paiboon <i>et al.</i> (2003)	n/a	Biomarker of bone metabolism – bone mineral content and BMD (compared to dietary $\beta$ -carotene intake as measured by food frequency questionnaire)	Cross-population study	12 months	Persons aged $\geq 25$ years	Males	69	n/a	There was no significant ( $p > 0.05$ ) association between $\beta$ -carotene intake and bone mineral content or density.
						Pre-menopausal females	46	n/a	
						Post-menopausal females	90	n/a	

### Assessment of Health Benefit: Vitamin C

The 141 articles on vitamin C identified from the PubMed and NHMRC sources were further reviewed on the bases of their abstract summary to ensure that the subject matter was relevant to this assessment. In assessing the subject matter, articles were excluded if they used serum vitamin C levels as an indicator of vitamin C status. The body caps serum vitamin C concentrations at intakes above 80 mg/day; increases in dietary intakes beyond this level will not be detected by changes in serum vitamin C levels (United States Institute of Medicine, 2000b)

The available evidence was therefore reduced to 61 articles. A detailed summary of these articles is provided in Tables A5-1 to A5-5 below.

Of the 61 articles obtained, 24 were related to the association between vitamin C intake and CHD. Only one intervention study on CHD (Tofler *et al.*, 2000) was found. This study showed an inverse relationship between supplemental vitamin C intake and total serum cholesterol, however there was no significant association with other CHD risk biomarkers.

There is little consistency in the results across the remaining 23 observational (case-control and cohort) CHD studies. Seven studies reported no significant association between vitamin C and CHD risk, and two even show an increased risk in CHD with increased vitamin C intakes. Fifteen studies (including a meta-analysis) report significant decreases in the risk of cardiovascular disease with increased vitamin C intake, however only six studies show this relationship throughout all of their study parameters. The other nine studies report disparate results between various subgroups of their study populations, of different CHD endpoints, or with supplemental versus dietary intakes of vitamin C. Of the eight studies that accommodate supplemental vitamin C intakes in their methodologies, there is support from the results for both an inverse association with CHD risk as well as the null hypothesis.

Twenty-five studies were obtained that assessed the impact of vitamin C intake on the risk of cancer. All of these studies were of either case-control or cohort design.

Unlike studies investigating CHD, the studies on cancer were more definitive in their results, with only three studies reporting differing outcomes amongst their study parameters. However, while a substantial number (13) of studies showed an inverse relationship between vitamin C intake and cancer risk, there was an equally strong level of support for the null hypothesis (9 studies). Five studies that included supplemental vitamin C intake in their analyses also showed conflicting results.

The effect of vitamin C intake on bone mineral density (BMD) was assessed in four studies. The results of these studies show a weak relationship between vitamin C intake and improvements in BMD. Two studies showed an increase in BMD in certain part of the body, but not consistently throughout, while one study reported an inverse relationship between vitamin C and BMD only where the calcium intake of subjects was less than 500 mg/day.

Five studies have investigated other health outcomes in respect to vitamin C intake, including cataract formation, the common cold and gastritis. The evidence showed some benefits from vitamin C intakes, however there were also a number that reported no significant association between vitamin C and a health outcome.

A significant proportion of the evidence base on vitamin C shows that increased intakes above the RDI have an association with improved health outcomes. However there is a high number of well-designed studies that do not support these findings. In many of the studies conducted on vitamin C, the results are not consistent throughout the study parameters, with health benefits occurring in certain circumstances or for certain groups, and not in others. Overall, there is a high degree of inconsistency in the evidence base on vitamin C.

**Vitamin C is assigned an evidence level of 1**



**Table A5-1: Identified Studies on Vitamin C and Coronary Heart Disease**

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Asherio <i>et al.</i> (1999)	n/a	Clinical – ischaemic and haemorrhagic stroke (compared to dietary and supplemental vitamin C intake measured by food frequency questionnaire).	Cohort	8 years	40-75 year males without CVD or diabetes	Total Stroke	328	n/a	There was no significant difference (p<0.05) between highest and lowest quintiles of vitamin C intake.
						Ischaemic stroke	210	n/a	
						Haemorrhagic stroke	70	n/a	
Bolton-Smith <i>et al.</i> (1992)	n/a	Clinical – diagnosed and undiagnosed CHD (compared to dietary vitamin C intake as measured by food frequency questionnaire).	Cross sectional study	10 years	Adult persons aged 40-59 years	Diagnosed CHD males	369	n/a	<ul style="list-style-type: none"> <li>• CHD risk was significantly (p&lt;0.05) lower between the highest and lowest quintiles of vitamin C intake for undiagnosed males.</li> <li>• There was no significant (p&gt;0.05) difference in the risk of CHD between the highest and lowest quintiles of vitamin C intake for undiagnosed female or diagnosed CHD subjects.</li> </ul>
						Diagnosed CHD females	235	n/a	
						Undiagnosed CHD males	659	n/a	
						Undiagnosed CHD females	795	n/a	
						Healthy male controls	3720	n/a	
						Healthy female controls	3749	n/a	
Davignus <i>et al.</i> (1997)	n/a	Clinical – cases of stroke (compared to dietary vitamin C intake as measured by diet history)	Cohort	46 years	Males aged 40-55 years	Cases of stroke	222	n/a	<ul style="list-style-type: none"> <li>• There was no significant (p&gt;0.05) association between vitamin C intakes and the risk of stroke.</li> <li>• The RR between the highest and lowest vitamin C intake was 0.71.</li> </ul>

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
de Lorgeril <i>et al.</i> (2001)	n/a	Biomarkers of congestive heart failure – peak exercise oxygen consumption, and left ventricular ejection function (compared to vitamin C intake)	Case-control	Not reported	Persons	Cases of congestive heart failure	21	n/a	There was no significant ( $p>0.05$ ) association between dietary vitamin C intake and changes in study endpoints.
						Age and gender matched controls	21	n/a	
Enstrom <i>et al.</i> (1986)	n/a	Clinical – mortality from CVD and all causes (compared to dietary + supplemental vitamin C intake as measured by food frequency questionnaire)	Cohort	10 years	3119 persons aged >16 years	Death from all causes	276	n/a	There was no significant association ( $p>0.05$ ) between vitamin C intake and mortality from CVD or all causes.
						Death from CVD	102	n/a	
Enstrom <i>et al.</i> (1992)	n/a	Clinical – mortality from CVD and all causes (compared to supplemental and dietary vitamin C intake as measured by food frequency questionnaire)	Cohort	10 years	Persons aged 25-74 years	Death from all causes	1809	n/a	<ul style="list-style-type: none"> <li>Vitamin C intake was associated with a significantly (<math>p&lt;0.05</math>) decreased standard mortality ratio (SMR) for all causes.</li> <li>Vitamin C intake was associated with a decreased SMR for CVD, however its statistical significance was not reported.</li> </ul>
						Death from CVD	929	n/a	
Gale <i>et al.</i> (1995)	n/a	Clinical – mortality from stroke and CHD (compared to vitamin C intake measured by a 1-week food diary in years 1 and 2 of study)	Cohort	20 years	Elderly (65+ years) persons without a history of CVD	All subjects	730	n/a	<ul style="list-style-type: none"> <li>Adjusted RR between highest (45 mg/day) and lowest tertile (28 mg/day) of vitamin C was 0.5 (<math>p&lt;0.003</math>).</li> <li>Vitamin C was positively associated with an intake of other macro and micronutrients.</li> </ul>
						Total deaths	643	n/a	
						Mortality from stroke	124	n/a	

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Hirvonen <i>et al.</i> (2000)	n/a	Clinical – stroke events (compared to dietary vitamin C intake measured by a food frequency questionnaire)	Cohort (subset of the ATBC trial)	6.1 years	Male smokers aged 50-69 years	Cerebral infarction cases	736	n/a	<ul style="list-style-type: none"> <li>The RR of stroke as intracerebral haemorrhage between the 1<sup>st</sup> (52 mg/day) and 4<sup>th</sup> (141 mg/day) quintiles of dietary vitamin C intake was 0.39 (p&lt;0.05).</li> <li>Dietary vitamin C intake was not significantly associated (p&gt;0.05) with cerebral infarction or subarachnoid haemorrhage.</li> </ul>
						Subarachnoid haemorrhage cases	83	n/a	
						Intracerebral haemorrhage cases	95	n/a	
Klipstein-Grobusch <i>et al.</i> (1999)	n/a	Clinical – myocardial infarction (MI) (compared to dietary vitamin C intake measured by food frequency questionnaire)	Cohort	4 years	4802 persons aged ≥ 55 years	Cases of MI	173	n/a	There was no significant association between vitamin C intake and the risk of myocardial infarction.
Klipstein-Grobusch <i>et al.</i> (2001)	n/a	Clinical – peripheral arterial disease incidence (compared to dietary vitamin C intake measured by a food frequency questionnaire)	Cohort	4 years	4367 persons aged ≥ 55 years	Female cases of peripheral arterial disease	370	n/a	<ul style="list-style-type: none"> <li>There was a significant (p&lt;0.01) inverse association between vitamin C intake and peripheral arterial disease in women. The RR between highest and lowest quartile of intake = 0.64.</li> <li>There was no significant (p&gt;0.05) association for males.</li> </ul>
						Male cases of peripheral arterial disease	204	n/a	
Knekt <i>et al.</i> (1994)	n/a	Clinical – CHD mortality (compared to vitamin C intake as measured by 1 yr diet history)	Cohort	6 years	5133 persons aged 30-69 years	Female CHD deaths	47	n/a	There was an association between vitamin C intakes and CHD mortality.
						Male CHD deaths	148	n/a	

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Kritchevsky <i>et al.</i> (1995)	n/a	Biomarker of CHD – arterial wall thickness (compared to dietary vitamin C intake as measured by food frequency questionnaire)	Cohort	11 years	11307 persons	Female CHD cases	210	n/a	There was no significant association between vitamin C intake and arterial wall thickness ( $p>0.05$ ).
						Male CHD cases	416	n/a	
Kushi <i>et al.</i> (1996b)	n/a	Clinical – CHD mortality (compared to dietary and supplemental vitamin C intake as measured by food frequency questionnaire)	Cohort	6 years	34486 post-menopausal females	CHD deaths	242	n/a	<ul style="list-style-type: none"> <li>• There was a positive association between increasing vitamin C intake and CHD mortality (<math>p&lt;0.05</math>).</li> <li>• The RR between the lowest (<math>\leq 112</math> mg/day) and highest (<math>\geq 391</math> mg/day) vitamin C intakes was 1.08 and 1.49 for CHD mortality respectively.</li> </ul>
Lee <i>et al.</i> (2004)	n/a	Clinical – CHD, coronary artery disease and stroke (compared to dietary and supplemental vitamin C intake measured by food frequency questionnaire)	Cohort	9 years	41836 post-menopausal women aged 55-69 years	1 <sup>st</sup> quintile (vitamin C intake = 85 mg/day)	315	n/a	<ul style="list-style-type: none"> <li>• There was a significant positive association between vitamin C intake and CHD (<math>p&lt;0.01</math>), coronary artery disease (<math>p&lt;0.01</math>) and stroke incidence (<math>p&lt;0.05</math>).</li> <li>• The adjusted RR between highest and lowest quintile of intake was 1.84, 1.91 and 2.57 for CHD, coronary artery disease and stroke respectively.</li> </ul>
						2 <sup>nd</sup> quintile (vitamin C intake = 139 mg/day)	413	n/a	
						3 <sup>rd</sup> quintile (vitamin C intake = 189 mg/day)	433	n/a	
						4 <sup>th</sup> quintile (vitamin C intake = 279 mg/day)	413	n/a	
						5 <sup>th</sup> quintile (vitamin C intake = 667 mg/day)	349	n/a	

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Leng <i>et al.</i> (1994)	n/a	Clinical – peripheral arterial disease (compared to vitamin C intake as measured by food frequency questionnaire)	Cohort	Single time point	1592 persons aged 55-74 years	Cases of peripheral arterial disease	153	n/a	There was a significant difference in vitamin C intake between cases and controls (p<0.05).
						Healthy controls	122	n/a	
Mayer-Davis <i>et al.</i> (1997)	n/a	Biomarkers of CVD – serum HDL, LDL, and triglycerides (compared to diet and supplemental vitamin C intake as measured by food frequency questionnaire and diet history)	Cross-sectional (Study 1) and Cohort (study 2)	Study 1 = 1 year and Study 2 = 4 years	Type II Diabetics aged 40-69 years	Study 1	520	n/a	There was no significant association (p>0.05) in either study between vitamin C and serum levels of HDL, LDL or triglycerides.
						Study 2	422	n/a	
Nam <i>et al.</i> (2003)	n/a	Clinical – non-fatal ischaemic heart disease (compared to dietary vitamin C intake as measured by food frequency questionnaire)	Retrospective case-control	1 year	Persons	Persons with MI or coronary artery disease	108	n/a	<ul style="list-style-type: none"> <li>• Vitamin C intake was significantly (p&lt;0.05) associated with non-fatal ischaemic heart disease incidence.</li> <li>• The OR between the lowest (&lt;141.8 mg/day) and highest (≥220.2 mg/day) tertiles of vitamin C intake was 0.34.</li> </ul>
						Aged-matched controls	142	n/a	
Okamoto (2002)	n/a	Biomarkers of CHD – serum lipids (compared with dietary vitamin C intake as measured by food frequency questionnaire)	Cross-sectional	2 months	Elderly persons (mean age of 65 years)	Total cohort	680	n/a	<ul style="list-style-type: none"> <li>• Adjusted vitamin C intake had a significant (p&lt;0.01) <u>inverse</u> association with serum LDL and apolipoprotein B.</li> <li>• Adjusted vitamin C intake had a significant <u>positive</u> association with serum HDL (p&lt;0.05) and apolipoprotein A1 (p&lt;0.01).</li> </ul>

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Osganian <i>et al.</i> (2003a)	n/a	Clinical – non-fatal MI and fatal CHD (compared to dietary and supplemental vitamin C intake as assessed by food frequency questionnaire)	Cohort	16 years	85118 females aged 30-55 years	CHD cases	1356	n/a	<ul style="list-style-type: none"> <li>Adjusted total vitamin C intake had a significant (<math>p &lt; 0.001</math>) inverse association with CHD risk.</li> <li>The RR between the lowest (70 mg/day) and highest (704 mg/day) quintiles of vitamin C intake = 0.7.</li> <li>Vitamin C supplement use &gt;400 mg/day or &gt;2 years was associated with a reduced CHD risk compared to no use (RR = 0.72).</li> </ul>
Rimm <i>et al.</i> (1993)	n/a	Clinical – fatal and non-fatal CHD events (compared to supplemental + dietary vitamin C intake as measured by food frequency questionnaire)	Cohort	4 years	39910 males aged 40-75 years	CHD cases	607	n/a	Neither dietary nor supplemental vitamin C intake was not significantly associated with CHD events ( $p > 0.05$ ).
Sahyoun <i>et al.</i> (1996)	n/a	Clinical – mortality from heart disease (compared to dietary and supplemental vitamin C intake as measured by a 3-day food record)	Case-control	12 years	747 persons aged 60-101 years	Mortality from heart disease	725	n/a	<ul style="list-style-type: none"> <li>Adjusted total vitamin C intake had an inverse association with mortality from heart disease, however this result was not significant (<math>p &gt; 0.05</math>).</li> <li>The RR between the lowest and highest vitamin C intakes was 0.38.</li> </ul>

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Todd <i>et al.</i> (1995)	n/a	Clinical – CHD (compared to dietary vitamin C intake as measured by a food frequency questionnaire)	Cohort	2 years	10359 persons aged 40-59 years	Cases of diagnosed CHD	625	n/a	<ul style="list-style-type: none"> <li>Adjusted total vitamin C intake had a significantly (<math>p &lt; 0.01</math>) inverse association with CHD in males.</li> <li>There was a significant (<math>p &lt; 0.01</math>) <u>positive</u> association between total vitamin C intake and CHD in females.</li> </ul>
						Cases of undiagnosed CHD	1497	n/a	
						Age and gender matched controls	7618	n/a	
Tofler <i>et al.</i> (2000)	Double-blinded	Biomarkers of CHD – serum lipids, platelet adhesion, tissue plasminogen activator antigen, plasminogen activator inhibitor, fibrinogen, plasma viscosity, and non-Willebrand factor.	Randomised controlled crossover study	6 weeks for each intake with a placebo washout period of 4 weeks	Healthy males aged 30-65 years	Vitamin C supplement intake	18	2 g/day	<ul style="list-style-type: none"> <li>There was a significant decrease in total cholesterol (<math>p &lt; 0.01</math>), and a significant increase in HDL (<math>p &lt; 0.05</math>) with vitamin C intake</li> <li>There was no significant (<math>p &gt; 0.05</math>) association between vitamin C intake and the other biomarkers.</li> </ul>
						Placebo intake	18	-	

**Table A5-2: Identified Study on Vitamin C and CHD (Meta-Analysis)**

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results	
Knekt <i>et al.</i> (2004)	n/a	Clinical – incidence of all major CHD events and CHD mortality (compared to vitamin C intake as measured either by a food frequency questionnaire or by a diet history, and 4 studies also assessed supplemental vitamin C intake).	Meta-analysis of 9 cohort studies	Barefoot <i>et al.</i> (1995)	11 years	1824 persons	Female CHD cases	37	n/a	<ul style="list-style-type: none"> <li>Adjusted dietary vitamin C intake was not significantly (<math>p&gt;0.05</math>) related to CHD incidence. The RR between lowest (45 mg/day) and highest (152 mg/day) quintiles of intake was 1.23.</li> <li>Supplemental vitamin C intake up to 700 mg/day significantly reduced CHD incidence compared to no intake (RR = 0.87, <math>p&lt;0.02</math>).</li> <li>There was no significant impact of vitamin C supplement intake on CHD mortality.</li> <li>There was no significant (<math>p&gt;0.05</math>) heterogeneity between the vitamin C results of the 9 cohorts.</li> </ul>
							Male CHD cases	82	n/a	
				Knekt <i>et al.</i> (1994)	6 years	5133 persons aged 30-69 years	Female CHD deaths	47	n/a	
							Male CHD deaths	148	n/a	
				Kritchevsky <i>et al.</i> (1995)	11 years	11307 persons	Female CHD cases	210	n/a	
							Male CHD cases	416	n/a	
				Kushi <i>et al.</i> (1996a)	6 years	34486 post-menopausal females	CHD deaths	242	n/a	
				MONICA investigators (1988)	6 years	9364 persons	Female CHD cases	22	n/a	
							Male CHD cases	162	n/a	
				Pietnen <i>et al.</i> (1996)	8 years	4739 males	CHD cases	413	n/a	
Rimm <i>et al.</i> (1993)	4 years	39910 males aged 40-75 years	CHD cases	607	n/a					
Stampfer <i>et al.</i> (1993) part 1	6 years	48639 females	CHD cases	375	n/a					
Stampfer <i>et al.</i> (1993) part 2	6 years	21450 females	CHD cases	412	n/a					



**Table A5-3: Identified Studies on Vitamin C and Cancer**

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject Group Number	Dose	Results
Bandera <i>et al.</i> (1997)	Clinical – lung cancer (compared to dietary and supplemental vitamin C intake as measured by food frequency questionnaire)	Cohort	7 years	32689 males	Males with lung cancer	395	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.01</math>) inverse association and vitamin C intake and lung cancer in males.</li> <li>• Vitamin C intake had no association (<math>p &gt; 0.05</math>) with lung cancer incidence in females.</li> </ul>
				25279 females	Females with lung cancer	130	n/a	
Bohlke <i>et al.</i> (1999)	Clinical – breast cancer (compared to dietary vitamin C intake measured by food frequency questionnaire)	Case-control	3 years	Females (mean age = 56 years)	Breast cancer cases	820	n/a	<ul style="list-style-type: none"> <li>• There was no significant (<math>p &gt; 0.05</math>) association between vitamin C intake and breast cancer for post-menopausal women.</li> <li>• There was an inverse but non-significant (<math>p &lt; 0.05</math>) association between vitamin C intake and breast cancer for pre-menopausal women.</li> <li>• The OR between the lowest (&lt;143 mg/day) and highest (&gt;343 mg/day) intake of vitamin C by pre-menopausal women was 0.45.</li> </ul>
					Healthy controls	1548	n/a	
Bueno de Mesquita <i>et al.</i> (1991)	Clinical – pancreatic cancer (compared to dietary vitamin C as measured by food frequency questionnaire)	Retrospective case-control	4 years	Persons aged 35-79 years	Cases of pancreatic cancer	164	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.05</math>) inverse association between adjusted vitamin C intake and pancreatic cancer incidence in women but not men.</li> <li>• The OR between the lowest and highest quintiles of vitamin C intake was 0.75</li> </ul>
					Age and gender matched controls	480	n/a	

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject Group Number	Dose	Results
Daviglus <i>et al.</i> (1996)	Clinical – cases of prostate cancer (compared to dietary vitamin C intake as measured by diet history)	Cohort	30 years	2107 Males aged 40-55 years	Cases of prostate cancer	132	n/a	<ul style="list-style-type: none"> <li>• There was no significant (<math>p&gt;0.05</math>) association between vitamin C intake and the risk of prostate cancer.</li> <li>• Relative risk (RR) between the lowest (<math>\leq 74</math> mg/day) and highest (<math>&gt;121</math> mg/day) intake of vitamin C was 1.27.</li> </ul>
Fontham <i>et al.</i> (1988)	Clinical – lung cancer (compared to dietary vitamin C intake as measured by food frequency questionnaire)	Case-control	3 years	Persons	Cases of lung cancer	1253	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p&lt;0.001</math>) inverse association between adjusted vitamin C intake and lung cancer incidence.</li> <li>• The OR between lowest and highest tertile of vitamin C intake = 0.67.</li> </ul>
					Controls without history of cancer	1274	n/a	
Freudenheim <i>et al.</i> (1990)	Clinical – rectal cancer (compared to dietary vitamin C intake as measured by diet history)	Case-control	8 years	Persons aged $\geq 40$ years	Cases of rectal cancer	145	n/a	There was an inverse association between vitamin C intake and rectal cancer incidence, however this result was not significant ( $p>0.05$ ).
					Aged and gender matched controls	277	n/a	
Ghadirian <i>et al.</i> (1991)	Clinical – pancreatic cancer (compared to vitamin C intake as measured by food frequency questionnaire)	Case-control	4 years	Persons	Cases of pancreatic cancer	179	n/a	There was an inverse association between vitamin C intake and pancreatic cancer, however this result was not significant.
					Age and gender matched controls	179	n/a	

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject Group Number	Dose	Results															
Howe <i>et al.</i> (1990)	Clinical – breast cancer (compared to vitamin C intake as measured by food frequency questionnaire)	Pooled results of 12 case-control studies	1-5 years	Post-menopausal females	Cases of breast cancer	4427	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.05</math>) inverse association between vitamin C intake and breast cancer for post-menopausal but not pre-menopausal women.</li> <li>• The RR between the lowest (59 mg/day) and highest (305 mg./day) quintile of intake = 0.82.</li> </ul>															
					Controls	6095	n/a		Howe <i>et al.</i> (1992)	Clinical – pancreatic cancer (compared to dietary vitamin C intake as measured by diet history)	Case-control (in five different international locations)	2 years	Persons aged 28-87 years	Cases of pancreatic cancer	802	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.001</math>) inverse association between vitamin C intake and pancreatic cancer.</li> <li>• The RR between lowest (<math>\leq 72</math> mg/day) and highest (<math>\geq 195</math> mg/day) quintile of intake = 0.41.</li> </ul>	Controls without a history of cancer	1669	n/a	Knekt <i>et al.</i> (1991)	Clinical – lung cancer (compared to dietary vitamin C intake as measured by a diet history)	Cohort
Howe <i>et al.</i> (1992)	Clinical – pancreatic cancer (compared to dietary vitamin C intake as measured by diet history)	Case-control (in five different international locations)	2 years	Persons aged 28-87 years	Cases of pancreatic cancer	802	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.001</math>) inverse association between vitamin C intake and pancreatic cancer.</li> <li>• The RR between lowest (<math>\leq 72</math> mg/day) and highest (<math>\geq 195</math> mg/day) quintile of intake = 0.41.</li> </ul>															
					Controls without a history of cancer	1669	n/a		Knekt <i>et al.</i> (1991)	Clinical – lung cancer (compared to dietary vitamin C intake as measured by a diet history)	Cohort	20 years	4538 males aged 20-69 years	Cases of lung cancer	117	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.01</math>) inverse association between vitamin C intake and lung cancer.</li> <li>• The RR between highest and lowest tertile of intake = 0.3.</li> </ul>						
Knekt <i>et al.</i> (1991)	Clinical – lung cancer (compared to dietary vitamin C intake as measured by a diet history)	Cohort	20 years	4538 males aged 20-69 years	Cases of lung cancer	117	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.01</math>) inverse association between vitamin C intake and lung cancer.</li> <li>• The RR between highest and lowest tertile of intake = 0.3.</li> </ul>															

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject Group Number	Dose	Results
Kristal <i>et al.</i> (1999)	Clinical – prostate cancer (compared to vitamin C supplement use determined by a food frequency and supplement questionnaire)	Retrospective case-control	2 years prior to baseline	667 males – prostate cancer cases, aged 40-64 years	No supplement use	62.3% of cases	n/a	<ul style="list-style-type: none"> <li>• There was an inverse but insignificant (<math>p&gt;0.05</math>) association between vitamin C supplement intake and prostate cancer incidence.</li> <li>• The adjusted OR between highest and lowest categories of intake was 0.77.</li> </ul>
					<1/ week	6.2% of cases	n/a	
					1-6/week	10.6% of cases	n/a	
					$\geq 7$ /week	20.9% of cases	n/a	
				666 healthy male controls, aged 40-64 years	No supplement use	58.7 of cases	n/a	
					<1/ week	7.7 of cases	n/a	
					1-6/week	11.7 of cases	n/a	
					$\geq 7$ /week	21.9 of cases	n/a	
Kushi <i>et al.</i> (1996a)	Clinical – breast cancer (compared to dietary and supplemental vitamin C intake as measured by food frequency questionnaire)	Cohort	6 years	34387 post-menopausal women aged 55-69 years	Case of breast cancer	879	n/a	There was no significant ( $p>0.05$ ) inverse association between either dietary or supplemental vitamin C intake and breast cancer.
					La Vecchia <i>et al.</i> (1997)	Clinical – histologically confirmed colorectal cancer (compared to dietary vitamin C as measured by food frequency questionnaire)	Case-control	
Healthy controls (no history of cancer)	4154	n/a						

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject Group Number	Dose	Results
Levi <i>et al.</i> (2000)	Clinical – histologically confirmed colorectal cancer (compared to dietary vitamin C intake as measured by a food frequency questionnaire)	Case-control	5 years	Persons aged 27-74 years	Cases of colorectal cancer	223	n/a	<ul style="list-style-type: none"> <li>• Vitamin C intake was inversely associated with the risk of colorectal cancer (<math>p &lt; 0.01</math>).</li> <li>• The OR between the lowest (<math>\leq 65</math> mg/day) and highest (<math>\geq 186</math> mg/day) tertile of intake was 0.45.</li> </ul>
					Controls without diet-related illness	491	n/a	
Negri <i>et al.</i> (1996)	Clinical – breast cancer (compared to dietary vitamin C intake as measured by food frequency questionnaire)	Case-control	3 years	Females aged 23-74 years	Cases of histologically confirmed breast cancer	2569	n/a	There was no significant ( $p > 0.05$ ) difference in vitamin C intake between cases and controls.
					Controls with no history of cancer	2588	n/a	
Ocke <i>et al.</i> (1997)	Clinical – lung cancer (compared to dietary and supplemental vitamin C intake as measured by diet history)	Cohort	19 years	561 males	Cases of lung cancer	54	n/a	There was no significant ( $p > 0.05$ ) association between vitamin C intake and the risk of lung cancer.
Satia-Abouta <i>et al.</i> (2003)	Clinical – colon cancer (compared to dietary and supplement vitamin C intake as measured by food frequency questionnaire)	Retrospective case-control	1 year	Persons aged 40-80 years	Cases of histologically confirmed colon cancer	613	n/a	<ul style="list-style-type: none"> <li>• Adjusted total vitamin C intake (including supplements) had a significant (<math>p &lt; 0.05</math>) inverse association with the incidence of colon cancer.</li> <li>• The OR between the lowest (59 mg/day) and highest (644 mg/day) vitamin C intakes was 0.5.</li> </ul>
					Aged matched controls	996	n/a	

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject Group Number	Dose	Results
Shibata <i>et al.</i> (1992)	Clinical – cancer incidence (compared to supplemental and dietary vitamin C intake as measured by food frequency questionnaire)	Cohort	8 years	11580 persons	Cases of cancer	1335	n/a	<ul style="list-style-type: none"> <li>Adjusted dietary vitamin C intake had no significant (<math>p &lt; 0.05</math>) association with the incidence of cancer.</li> <li>There was a significant (<math>p &lt; 0.05</math>) inverse association between supplemental vitamin C intake and the risk of bladder cancer in men, and breast cancer in women.</li> </ul>
Stefani <i>et al.</i> (1999)	Clinical – lung cancer (compared to dietary vitamin C intake as measured by food frequency questionnaire)	Case-control	4 years	Persons aged 30-89 years	Cases of lung cancer	541	n/a	Adjusted total vitamin C intake had no significant ( $p > 0.05$ ) association with the risk of lung cancer.
					Controls	540	n/a	
Verhoeven <i>et al.</i> (1997)	Clinical – breast cancer (compared to supplemental and dietary vitamin C intake as measured by food frequency questionnaire)	Cohort	4.3 years	62573 females aged 55-69 years	Cases of breast cancer	650	n/a	There was no significant ( $p > 0.05$ ) association between vitamin C intakes and the risk of breast cancer.

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject Group Number	Dose	Results
Voorrips <i>et al.</i> (2000)	Clinical – lung cancer (compared to dietary and supplemental vitamin C intake as measured by food frequency questionnaire)	Cohort	6.3 years	58279 males aged 55-69 years	Cases of lung cancer	939	n/a	<ul style="list-style-type: none"> <li>• Dietary vitamin C intake was inversely associated with the incidence of lung cancer (<math>p &lt; 0.05</math>).</li> <li>• The RR between the lowest (51 mg/day) and highest (138 mg/day) dietary vitamin C quintiles was 0.77.</li> <li>• Supplemental vitamin C intake was not significantly (<math>p &gt; 0.05</math>) associated with lung cancer incidence.</li> </ul>
Wassertheil-Smoller <i>et al.</i> (1981)	Clinical – cervical cancer identified by pap smear (compared to supplemental and dietary vitamin C intake as measured by 3-day food recall)	Case-control	Single timepoint	Females aged 15-75 years	Cases of cervical cancer	87	n/a	Vitamin C intake had a significant ( $p < 0.05$ ) inverse association with the incidence of cervical cancer.
					Age matched controls	82	n/a	
Yong <i>et al.</i> (1997)	Clinical – lung cancer (compared to dietary and supplemental vitamin C intake as measured by a 24-hour recall)	Cohort	19 years	3968 males and 6100 females aged 25-74 years	Cases of lung cancer	248	n/a	<ul style="list-style-type: none"> <li>• Dietary vitamin C intake was inversely associated with the incidence of lung cancer (<math>p &lt; 0.01</math>).</li> <li>• The RR between the lowest (<math>&lt; 23</math> mg/day) and highest (<math>&gt; 113</math> mg/day) dietary vitamin C quintiles was 0.66.</li> </ul>

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject Group Number	Dose	Results
Zatonski <i>et al.</i> (1991)	Clinical – pancreatic cancer (compared to dietary vitamin C intake as measured by diet history)	Case-control	3 years	Persons (mean age = 60 years)	Cases of pancreatic cancer	110	n/a	<ul style="list-style-type: none"> <li>• Vitamin C intake was inversely associated with the risk of pancreatic cancer (<math>p &lt; 0.01</math>).</li> <li>• The RR between the lowest (<math>\leq 83</math> mg/day) and highest (<math>\geq 135</math> mg/day) quartile of vitamin C intakes was 0.37.</li> </ul>
					Age matched controls	195	n/a	
Zeegers <i>et al.</i> (2001)	Clinical – bladder cancer (compared to dietary and supplemental vitamin C intake as measured by food frequency questionnaire)	Case-control	6.3 years	120852 persons aged 55-69 years	Cases of bladder cancer	569	n/a	<ul style="list-style-type: none"> <li>• Adjusted total vitamin C intake had an inverse association with the incidence of bladder cancer, however this result was not significant (<math>p &gt; 0.05</math>).</li> <li>• Supplemental vitamin C intake was not associated with bladder cancer, although the statistical significance of this result was not reported.</li> </ul>
					Controls without history of cancer	3123	n/a	
Zhang <i>et al.</i> (1999)	Clinical – breast cancer (compared to dietary and supplemental vitamin C intake as measured by food frequency questionnaire)	Cohort	14 years	83234 females aged 30-55 years	Cases of breast cancer	2697	n/a	There was no significant ( $p > 0.05$ ) association between supplemental or dietary vitamin C intake and the risk of breast cancer.



**Table A5-4: Identified Studies on Vitamin C and Bone and Osteoporosis**

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Results
Hall and Greendale (1998)	Biomarker of bone disorders – bone mineral density (BMD)	Cohort	1 year	45-64 post-menopausal females	Total cohort	775	<ul style="list-style-type: none"> <li>• Each adjusted vitamin C intake of 100 mg/day increment = 0.017 g/cm<sup>2</sup> increase in neck and hip BMD (p&lt;0.005).</li> <li>• The significant BMD increases were not observed with calcium intakes &gt;500 mg.</li> <li>• There was no significant association (p&gt;0.05) between vitamin C intake and spine BMD.</li> </ul>
Leville <i>et al.</i> (1997)	Biomarker of bone disorders – bone mineral density (BMD) (compared to supplemental and dietary vitamin C intake as measured by food frequency questionnaire)	Retrospective cross-sectional study	1 year	1892 females aged 55-80 years	Total study population		<ul style="list-style-type: none"> <li>• There was no significant (p&gt;0.05) association between vitamin C intake and BMD.</li> <li>• Women with supplement use ≥ 10 years had a significantly (p&lt;0.05) higher BMD than those with use &lt; 10 years.</li> </ul>
Morton <i>et al.</i> (2001)	Biomarker of bone disorders – bone mineral density (BMD) (compared to supplemental vitamin C intake)	Cross-sectional	3 years	994 post-menopausal females	Daily users of vitamin C supplements	277	<ul style="list-style-type: none"> <li>• Regular Vitamin C supplement users had significantly (p&lt;0.02) higher neck and hip BMD compared to non-users.</li> <li>• Supplement use was not significantly associated with spine BMD (p&gt;0.05).</li> <li>• There was a significant linear trend in vitamin C supplement use and ultradistal BMD (p&lt;0.04), but not at other bone sites.</li> </ul>
					Non-users of vitamin C supplements	717	
Wang <i>et al.</i> (1997)	Biomarker of bone disorders – bone mineral density (BMD) (compared to supplemental and dietary vitamin C intake as measured by food frequency questionnaire)	Cross-sectional	1 year	Post-menopausal females aged 59-84 years	Total cohort	125	Vitamin C intake was positively associated with neck BMD (p<0.05), but not with spinal BMD.

**Table A5-5: Identified Studies on Vitamin C and Other Health Outcomes**

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Hankinson <i>et al.</i> (1992)	n/a	Clinical – incidence of cataract extraction (compared to dietary and supplemental vitamin C intake as measured by food frequency questionnaire)	Cohort	8 years	Females 45-67 years from 50828 cohort	Cases of cataract extraction	493	Supplement intake per day was not specified	<ul style="list-style-type: none"> <li>• Dietary vitamin C was not associated with the risk of cataract extraction.</li> <li>• RR of cataracts was 0.5 for women using vitamin C supplements for more than 10 years (p&lt;0.05), however this effect became insignificant (p&gt;0.05) when the RR was adjusted for confounding factors.</li> </ul>
Hemila <i>et al.</i> (2002)	n/a	Clinical – incidence of the common cold (compared to dietary vitamin C intake as measured by food frequency questionnaire)	Cohort (subset of the ATBC trial)	4 years	Male smokers aged 50-69 years	Placebo arm of study	4990	n/a	Dietary vitamin C had no association with incidence of the common cold.
Sasazuki <i>et al.</i> (2003)	Double-blinding	Biomarker of gastritis – serum pepsinogen and <i>H.pylori</i> (serum antibodies)	Pseudorandomised controlled trial	5 years	Males diagnosed with chronic gastritis	Supplement group 1	144	50 mg/day vitamin C	<ul style="list-style-type: none"> <li>• In both groups, the <i>H.pylori</i> count significantly decreased over the study (p&lt;0.05), however there was no difference between groups (p&gt;0.05).</li> <li>• Serum pepsinogen status significantly decreased over the study period (p&lt;0.001), however there was no significant difference between groups.</li> </ul>
						Supplement group 2	161	500 mg/day vitamin C	

### Assessment of Health Benefit: Phosphorus

Forty articles on phosphorus were identified from the literature search of electronic databases, and their abstracts were further reviewed to ensure that the subject matter was relevant to this assessment. In assessing the subject matter, articles that assessed changes in serum phosphorus against health outcomes were included, as there is evidence showing that serum phosphorus is reflective of a change in dietary phosphorus intake (United States Institute of Medicine, 1997)

The available evidence was reduced to 16 articles. A detailed summary of these articles is provided in Tables A6-1 to A6-3 below.

Ten studies have looked into possible effects of high/supplemented phosphorus intakes (above the RDI) on bone health and/or osteoporosis. The majority (8) of these studies found no significant association between phosphorus intake and bone status, and some even reported a negative association between an increased phosphorus intake and bone mineral density (BMD). From this limited evidence, it would appear that increased phosphorus intakes either have no effect on bone health, or even may cause adverse health effects.

Four studies investigated phosphorus intakes in relation to cancer. Three of these studies indicated that increased phosphorus intakes were inversely associated with cancer risk. However, the small evidence base on cancer does not allow for the conclusive establishment of association between phosphorus and cancer. The results of these four studies also varied depending on the different types of cancers investigated.

Two studies, both conducted in the 1980s, investigated phosphorus intake and blood pressure. One study indicated an inverse association, while the other supported the null hypothesis.

Therefore, the evidence base on phosphorus provides only a tentative link to improved health outcomes. A large volume of contradictory evidence also exists, which confounds any association of phosphorus intake with improved health outcomes.

**Phosphorus is Assigned an Evidence Level of 1**

**Table A6-1: Identified Studies on Phosphorus and Bone Metabolism**

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dosage	Results
Bizik <i>et al.</i> (1996)	Clinical – parathyroid hormone levels, bone resorption markers (urinary deoxypyridinoline), urinary ammonia, urea and total N	Cohort	20 days	7 men aged 22-31 years old, average weight 70 kgs	Single group	7	Diet to day 10 with 800 mg phosphorus, 1200 mg calcium,, Days 10-20 with 1600 mg/day dietary P.	High P intake was not found to promote bone resorption if the Ca:P ratio is <1:1.5
ChoonHie <i>et al.</i> (2004)	Clinical - Bone Mineral Density (BMD) as measured by dual energy x-ray absorptiometry.	Cross sectional	Single time point – collection of baseline data on bone health	Korean males of various age groups.	Elementary school children	80	n/a	Increased phosphorus intakes were positively related to BMD in all age groups.
					High school students	83	n/a	
					Adults 25 – 35 years old	87	n/a	
					Adults 60+ years old	98	n/a	
Goldsmith <i>et al.</i> (1976)	Clinical – bone density parameters.	Cross sectional	Not reported	Post-menopausal women with osteoporosis	Single group	7	Diet supplemented with phosphorus (inorganic phosphate)	<ul style="list-style-type: none"> <li>• Bone forming surface decreased and bone resorbing surface increased in all patients.</li> <li>• Bone resorbing surface was highly correlated with total phosphorus intake.</li> </ul>

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dosage	Results
Grimm <i>et al.</i> (2001)	Clinical – biochemical markers for bone status, bone-related hormones, markers of bone resorption and parameters of renal function (collectively: serum PTH, serum osteocalcin, creatine in urinary pyridinoline, creatine in pyridinoline deoxypyridinoline, urinary microalbumin) and digestive responses.	Crossover	14 weeks	Women aged 20-30 years old from a German university.	Control period	10	Diet with 1700 mg P and 1500 mg Ca/day (4 weeks)	<ul style="list-style-type: none"> <li>There were no significant changes in bone-related hormones, markers of bone re-absorption or parameters of renal function.</li> <li>Phosphorus supplementation caused intestinal distress, soft faeces or mild diarrhoea</li> </ul>
					Treatment period		Diet with 3008 mg P and 1995 mg Ca/day (6 weeks)	
					Control period		Diet – as for above (4 weeks)	
Hoppe <i>et al.</i> (2000)	Clinical – whole body bone measurements	Cross-sectional	Single time point	10 year old healthy children from Denmark	Single group	105	n/a	<ul style="list-style-type: none"> <li>Bone area (size-adjusted) was negatively associated with phosphorus intakes.</li> <li>Mean intake of phosphorus was 3.3g, which is above the RDI for this age group (1250 mg/day).</li> </ul>
Mendez <i>et al.</i> (2002)	Clinical – bone density measures.	Cross sectional	Single time point	Women aged 45 – 63 years old in northern Mexico.	Single group.	45	n/a	Dietary intake phosphorus had no significant ( $p<0.05$ ) relation to bone density.
Metz <i>et al.</i> (1993)	Clinical – radial bone measurements	Cross-sectional	Not reported	24-28 year old Caucasian women	Single group	38	n/a	Phosphorus intake was negatively associated with radial bone measurements ( $p<0.05$ ).
SeIn <i>et al.</i> (2003)	Clinical - osteoporosis	Case-control	Not reported	Korean premenopausal women	Case - osteoporotic	78	n/a	Serum levels of phosphorus and calcium showed significant ( $p<0.001$ ) negative correlations with lumbar spine bone mineral density.
					Control – non-osteoporotic	78	n/a	

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dosage	Results
Whybro <i>et al.</i> (1998)	Biomarkers of bone metabolism – bone turnover and calcium homeostasis markers.	Study 1 - Randomised controlled cross-over trial.	1 week	Healthy volunteers 19-32 years old.	Single group, standard diet with 800 mg P/day	10	Supplemented with 1000 mg elemental P	There was no significant change in serum phosphate, osteocalcin or intact parathyrin.
		Study 2 Randomised controlled trial.	1 week	Men aged 19-38 years	Diet only	12	-	There was no significant change in serum phosphate, intact parathyrin or urinary deoxyypyridinoline.
					Diet+ low P	12	1000 mg/day elemental P	
					Diet + moderate P	12	1500 mg/day elemental P	
					Diet + high P	12	2000 mg/day elemental P	

**Table A6-2: Identified Studies on Phosphorus and Cancer**

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Results
Chan <i>et al.</i> (2000)	Clinical – prostate cancer cases (compared to dietary phosphorus intake as measured by a food-use questionnaire)	Cohort (initially surveyed for another reason)	8 years	Finish male smokers, (originally recruited in a randomised trial study)	Cases – prostate cancer	184	There was an inverse association between phosphorus intakes and cancer risk independent of calcium intakes.
Launoy <i>et al.</i> (1998)	Clinical – squamous cell cancer of the oesophagus	Case-control	3 years	Males in 3 regions of France.	Cases	208	After adjustment of results for drinking and smoking, phosphorus intakes were found to have an independent protective factor against cancer incidence.
					Controls	399	
Negri <i>et al.</i> (2000)	Clinical – oral cancers	Case-control	5.5 years	Patients admitted to major teaching and general hospitals in Italy and Switzerland.	Histologically confirmed oral cancer cases	754	<ul style="list-style-type: none"> <li>• There was an inverse association between phosphorus intake and pharyngeal cancer risk.</li> <li>• The adjusted OR for this relationship was 0.88.</li> </ul>
					Controls with no history of cancer	1775	
SooWon <i>et al.</i> (2003)	Clinical – stomach cancer	Case-control	Not reported	People in the Korean Republic	Case patients recently diagnosed with stomach cancer	102	Phosphorus intake was significantly ( $p>0.05$ ) higher amongst cases compared to controls.
					Controls people without gastrointestinal diseases	105	

**Table A6-3: Identified Studies on Phosphorus and Cardiovascular Disease**

<b>Study</b>	<b>Study Endpoint Type</b>	<b>Study Design</b>	<b>Length of Study</b>	<b>Subjects</b>	<b>Subject Grouping</b>	<b>Subject number</b>	<b>Results</b>
Gruchow <i>et al.</i> (1985)	Clinical - systolic blood pressure	Cross sectional – (subset of Health and Nutrition Examination Survey	n/a	Persons	n/a	n/a	Increased phosphorus intakes were positively associated with systolic blood pressure.
Joffres <i>et al.</i> (1987)	Clinical – blood pressure	Cross-sectional	n/a	Men with no history of cardiovascular disease or treated hypertension	Single group assessed by 24 hour recall	615	Phosphorus intakes were inversely associated with blood pressure.



**Assessment of Health Benefit: Vitamin B<sub>12</sub>**

From the 111 vitamin B<sub>12</sub> articles identified, a review of their abstracts refined the final number of articles to 28. This process was used to ensure that the subject matter, not just the title, was relevant to this assessment. In assessing the subject matter of abstracts, articles that assessed changes in serum vitamin B<sub>12</sub> against health outcomes were included, as there is evidence showing that serum vitamin B<sub>12</sub> is reflective of a change in dietary vitamin B<sub>12</sub> intake (United States Institute of Medicine, 1998). The details of the 28 articles are provided in Tables A7-1 to A7-3 below.

Of the 28 identified articles, 18 were related to coronary heart disease outcomes, either as clinical endpoints or as changes in serum homocysteine levels. The majority of the 18 articles (13) showed no significant association between CHD endpoints and vitamin B<sub>12</sub> intakes beyond the RDI. There were only 2 articles in that showed a significant inverse association.

Seven articles were identified that examined the association between vitamin B<sub>12</sub> intake above the RDI and cancer endpoints. The majority of these articles (5) also indicated no significant association between cancer endpoints and vitamin B<sub>12</sub> intakes.

The three remaining articles assessed bone metabolism and gastrointestinal endpoints. The two studies on bone metabolism showed no significant association between vitamin B<sub>12</sub> intakes above the RDI and bone disorders. The sole gastrointestinal article also showed no significant association between vitamin B<sub>12</sub> intakes and gastrointestinal infections. With the small numbers of articles on bone metabolism and gastrointestinal functioning, these lines of research can be considered as new and emerging.

For CHD and cancer, the evidence base provides strong support for the null hypothesis. Therefore, on the basis of available evidence, increased intakes of vitamin B<sub>12</sub> are considered to have no appreciative health benefit.

<b>Vitamin B<sub>12</sub> is assigned an evidence level of 0</b>
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**Table A7-1: Identified Studies on Vitamin B<sub>12</sub> and Coronary Heart Disease**

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Appel <i>et al.</i> (2000)	Double-blinded	Biomarker of CHD – serum tHcy (compared to serum vitamin B <sub>12</sub> levels)	Randomised controlled trial	3 week adaptation, 8 week study period	Persons aged ≥ 22 years	Control diet	39	n/a	An increase in vitamin B <sub>12</sub> intake as a result of the intervention diets was not significantly (p>0.05) associated with tHcy.
						Diet = control with high intake of fruit and vegetables	41	n/a	
						Diet = low fat, high in fruit, vegetables and dairy	38	n/a	
de Bree <i>et al.</i> (2001)	n/a	Biomarker of CHD – serum homocysteine (tHcy) (compared to dietary and supplemental vitamin B <sub>12</sub> intake as measured by food frequency questionnaire)	Cross-sectional	3 years	Persons aged 20-65 years	Males	1275	n/a	<ul style="list-style-type: none"> <li>• There was a significant (p&lt;0.001) inverse association between vitamin B<sub>12</sub> intakes of both males and females and serum tHcy levels.</li> <li>• However, this result became statistically non-significant (p&gt;0.05) when adjusted for confounding variables.</li> </ul>
						Females	1160	n/a	
de Bree <i>et al.</i> (2003)	n/a	Clinical – CHD mortality (compared to serum vitamin B <sub>12</sub> levels)	Case-control	10.3 years	Persons aged 20-59 years	Deaths from CHD	102	n/a	There was no significant (p>0.05) association between serum vitamin B <sub>12</sub> levels and the risk of CHD mortality.
						Controls	630	n/a	

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
He <i>et al.</i> (2004)	n/a	Clinical – incidence of ischaemic and haemorrhagic stroke (compared to dietary B <sub>12</sub> intake as measured by food frequency questionnaire)	Cohort	14 years	43732 males aged 40-75 years	Cases of ischaemic stroke	455	n/a	<ul style="list-style-type: none"> <li>• There was a significant (p=0.05) inverse association between vitamin B<sub>12</sub> intakes and the risk of ischaemic stroke.</li> <li>• The RR between the lowest (5 µg/day) and highest (29 µg/day) intake of vitamin B<sub>12</sub> was 0.73 for ischaemic stroke.</li> <li>• There was no significant (p&gt;0.05) association between vitamin B<sub>12</sub> intakes and the risk of haemorrhagic stroke.</li> </ul>
						Cases of haemorrhagic stroke	125	n/a	
Huerta <i>et al.</i> (2004)	n/a	Biomarker of CHD – serum tHcy (compared to dietary vitamin B <sub>12</sub> intake as measured by food frequency questionnaire)	Cross-sectional	Not reported	Elderly persons	Total cohort	140	n/a	There was no significant association between serum tHcy and vitamin B <sub>12</sub> intake.
Hung <i>et al.</i> (2003)	n/a	Clinical – fatal CHD and CVD (compared to serum vitamin B <sub>12</sub> levels)	Cohort	29 years	Persons aged 20-90 years	Male deaths from CHD or CVD	213	n/a	There was no significant (p>0.05) association between vitamin B <sub>12</sub> levels and CHD/CVD mortality.
						Female deaths from CHD or CVD	159	n/a	
Jacques and Chylack, Jr. (1991)	n/a	Biomarker of CHD – serum tHcy (compared to dietary vitamin B <sub>12</sub> intake as measured by food frequency questionnaire, and to serum vitamin B <sub>12</sub> levels)	Cross-sectional	20 years	Persons aged 30-59 years	Total cohort	5135	n/a	<ul style="list-style-type: none"> <li>• There was a significant (p&lt;0.001) inverse association between adjusted plasma vitamin B<sub>12</sub> and tHcy.</li> <li>• Adjusted dietary vitamin B<sub>12</sub> intake was not significantly (p&gt;0.05) associated with serum tHcy.</li> </ul>

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Kelly <i>et al.</i> (2003)	n/a	Clinical – incidence of stroke (compared to serum vitamin B <sub>12</sub> levels).	Case-control	2 years	Persons (mean age = 68 years)	Cases of stroke	180	n/a	There was no significant (p>0.05) association between serum vitamin B <sub>12</sub> levels and the risk of stroke.
						Age matched controls	147	n/a	
Leowattana <i>et al.</i> (2000)	n/a	Clinical – incidence of CAD (compared to serum vitamin B <sub>12</sub> levels)	Cross-sectional	1 year	Persons (mean age = 58-60 years)	Cases of CAD	178	n/a	There was no significant (p>0.05) association between serum vitamin B <sub>12</sub> levels and CAD risk.
						Age matched healthy controls	178	n/a	
Medrano <i>et al.</i> (2000)	n/a	Clinical – mortality from CVD (compared to dietary vitamin B <sub>12</sub> intake as measured by a 7-day food record)	Cohort	4 years	21155 persons	Cases of CVD deaths	Not reported	n/a	There was no significant (p>0.05) association between vitamin B <sub>12</sub> intake and the risk of mortality from CVD.
Mennen <i>et al.</i> (2002)	n/a	Biomarker of CHD – serum tHcy (compared to dietary vitamin B <sub>12</sub> intake as measured by 24-hour diet record, and serum vitamin B <sub>12</sub> levels)	Cross-sectional	8 years	Persons aged 35-60 years	Total cohort	2070	n/a	<ul style="list-style-type: none"> <li>Adjusted serum vitamin B<sub>12</sub> was not significantly (p&gt;0.05) associated with tHcy.</li> <li>Dietary vitamin B<sub>12</sub> intake was not significantly (p&gt;0.05) associated with tHcy.</li> </ul>
Merchant <i>et al.</i> (2003)	n/a	Clinical – peripheral arterial disease (compared to dietary vitamin B <sub>12</sub> intake as measured by food frequency questionnaire)	Cohort	12 years	46036 males aged 40-75 years	Cases of peripheral arterial disease	308	n/a	<ul style="list-style-type: none"> <li>There was no significant (p&gt;0.05) association between vitamin B<sub>12</sub> intake and the risk of peripheral arterial disease.</li> <li>The RR of peripheral arterial disease from the lowest (5 µg/day) to the highest (22 µg/day) intake of vitamin B<sub>12</sub> was 0.74.</li> </ul>

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Ortega <i>et al.</i> (2002)	n/a	Biomarker of CHD – serum tHcy (compared to compared to dietary vitamin B <sub>12</sub> intake as measured by 7-day food record)	Cross-sectional	Not reported	Persons aged >65 years	Total cohort	130	n/a	There was no significant (p<0.05) difference in tHcy between subjects with lower than recommended vitamin B <sub>12</sub> intakes and those with intakes above this levels.
Pancharunit i <i>et al.</i> (1994)	n/a	Clinical – early onset coronary artery disease (compared to serum vitamin B <sub>12</sub> levels)	Case-control	3 years	Males aged 30-50 years	Cases of coronary artery disease	101	n/a	There was no significant (p>0.05) difference in the mean serum vitamin B <sub>12</sub> levels between cases and controls.
						Age matched controls	108	n/a	
Shimakawa <i>et al.</i> (1997)	n/a	Biomarker of CHD – serum tHcy (compared to dietary and supplemental vitamin B <sub>12</sub> intake as measured by food frequency questionnaire)	Case-control	3 years	Persons aged 45-64 years	Cases of carotid artery atherosclerosis	322	n/a	There was a significant (p<0.01) inverse association between vitamin B <sub>12</sub> intake and serum tHcy.
						Controls without atherosclerosis	318	n/a	
Siri <i>et al.</i> (1998)	n/a	Clinical – coronary atherosclerosis (compared to serum vitamin B <sub>12</sub> levels)	Case-control	2 years	Persons aged 25-65 years	Cases of atherosclerosis	131	n/a	There was no significant (p>0.05) association between serum vitamin B <sub>12</sub> levels and the risk of coronary atherosclerosis.
						Coronary referent controls	88	n/a	
Vrentzos <i>et al.</i> (2004)	n/a	Clinical – IHD (compared to dietary vitamin B <sub>12</sub> intake as measured by a 3-day food record, and serum vitamin B <sub>12</sub> levels)	Case-control	2 years	Persons aged 33-77 years	Cases of IHD	152	n/a	<ul style="list-style-type: none"> <li>• Cases had significantly higher intakes of vitamin B<sub>12</sub> (p&lt;0.05), and significantly higher serum vitamin B<sub>12</sub> levels (p&lt;0.01) than controls.</li> <li>• There was, however, no significant (p&gt;0.05) linear trend between vitamin B<sub>12</sub> intakes, serum vitamin B<sub>12</sub> levels, and the risk of IHD.</li> </ul>
						Age and gender matched controls	152	n/a	

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Waldmann <i>et al.</i> (2004)	n/a	Biomarker of CHD – serum tHcy (compared to serum vitamin B <sub>12</sub> levels)	Cross-sectional	Not reported	Vegans aged 20-82 years	Total cohort	131	n/a	There was a significant (p<0.001) inverse association between serum vitamin B <sub>12</sub> and tHcy levels when controlled for veganism.
Wasilewska <i>et al.</i> (2003)	n/a	Clinical – cardiac problems requiring surgery (compared to serum vitamin B <sub>12</sub> levels)	Case-control	Not reported	Persons aged 24-80 years	Cases of cardiac surgery	55	n/a	There was no significant (p>0.05) difference in serum vitamin B <sub>12</sub> levels between cases and controls
						Health controls	38	n/a	

**Table A7-2: Identified Studies on Vitamin B<sub>12</sub> and Cancer**

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject Group Number	Results
Alberg <i>et al.</i> (2000)	Clinical – cervical cancer (compared to serum vitamin B <sub>12</sub> levels)	Case-control	15 years	Females aged >18 years	Cases of cervical cancer	39	There was no significant (p>0.05) association between vitamin B <sub>12</sub> intake and the risk from cervical cancer.
					Age matched controls	39	
Goodman <i>et al.</i> (2000)	Biomarkers of cervical cancer – squamous intraepithelial lesions (SIL) and atypical squamous cells (compared to serum vitamin B <sub>12</sub> levels)	Case-control	4 years	Females	Cases of SIL	185	There was no significant (p>0.05) association between serum vitamin B <sub>12</sub> levels and the risk of developing SIL or atypical squamous cell pap smear results.
					Cases of atypical squamous cells	147	
					Controls with normal pap smear	191	
Harnack <i>et al.</i> (2002)	Clinical – colorectal cancer (compared to vitamin B <sub>12</sub> intake as measured by food frequency questionnaire)	Cohort	13 years	Females aged 55-69 years	Cases of colonic cancer	598	There was no significant (p>0.05) association between vitamin B <sub>12</sub> intakes and the risk of colorectal cancer.
					Cases of rectal cancer	123	

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject Group Number	Results																								
Hartman <i>et al.</i> (2001)	Clinical – lung cancer (compared to serum vitamin B <sub>12</sub> levels)	Case-control (subset of the ATBC trial)	8 years	Male smokers aged 50-69 years	Cases of lung cancer	300	<ul style="list-style-type: none"> <li>• There was no significant (<math>p&gt;0.05</math>) association between serum vitamin B<sub>12</sub> levels and the risk of lung cancer.</li> <li>• The OR between the lowest (<math>\leq 345</math> pg/mL) and highest (<math>&gt;580</math> pg/mL) serum vitamin B<sub>12</sub> levels and lung cancer risk was 1.41</li> </ul>																								
					Controls	300		Hernandez <i>et al.</i> (2003)	Biomarkers of cervical cancer – premalignant cervical lesions (compared to dietary and supplemental vitamin B <sub>12</sub> intake as measured by food frequency questionnaire)	Case-control	4 years	Females aged >18 years	Cases with premalignant lesions	214	<ul style="list-style-type: none"> <li>• There was a significant (<math>p&lt;0.05</math>) inverse association between supplemental vitamin B<sub>12</sub> intake and the risk of developing premalignant lesions.</li> <li>• Dietary and total vitamin B<sub>12</sub> intake was not significantly (<math>p&gt;0.05</math>) associated with the risk of developing cervical cancer.</li> </ul>	Controls	271	Vlajinac <i>et al.</i> (1997)	Clinical – prostate cancer (compared to dietary and supplemental vitamin B <sub>12</sub> intake as measured by food frequency questionnaire)	Case-control	4 years	Males (mean age = 71 years)	Cases of histologically confirmed prostate cancer	101	<ul style="list-style-type: none"> <li>• There was a significant (<math>p&lt;0.05</math>) <u>positive</u> association between vitamin B<sub>12</sub> intake and the risk of prostate cancer.</li> <li>• The OR between the lowest and highest intakes was 2.02.</li> </ul>	Age matched controls	202	Zhang <i>et al.</i> (2003)	Clinical – breast cancer (compared to serum vitamin B <sub>12</sub> levels)	Case-control	14 years
Hernandez <i>et al.</i> (2003)	Biomarkers of cervical cancer – premalignant cervical lesions (compared to dietary and supplemental vitamin B <sub>12</sub> intake as measured by food frequency questionnaire)	Case-control	4 years	Females aged >18 years	Cases with premalignant lesions	214	<ul style="list-style-type: none"> <li>• There was a significant (<math>p&lt;0.05</math>) inverse association between supplemental vitamin B<sub>12</sub> intake and the risk of developing premalignant lesions.</li> <li>• Dietary and total vitamin B<sub>12</sub> intake was not significantly (<math>p&gt;0.05</math>) associated with the risk of developing cervical cancer.</li> </ul>																								
					Controls	271		Vlajinac <i>et al.</i> (1997)	Clinical – prostate cancer (compared to dietary and supplemental vitamin B <sub>12</sub> intake as measured by food frequency questionnaire)	Case-control	4 years	Males (mean age = 71 years)	Cases of histologically confirmed prostate cancer	101	<ul style="list-style-type: none"> <li>• There was a significant (<math>p&lt;0.05</math>) <u>positive</u> association between vitamin B<sub>12</sub> intake and the risk of prostate cancer.</li> <li>• The OR between the lowest and highest intakes was 2.02.</li> </ul>	Age matched controls	202	Zhang <i>et al.</i> (2003)	Clinical – breast cancer (compared to serum vitamin B <sub>12</sub> levels)	Case-control	14 years	Females aged 30-55 years	Cases of breast cancer	735	There was no significant ( $p>0.05$ ) association between serum vitamin B <sub>12</sub> levels and the risk of breast cancer.	Age matched controls	735				
Vlajinac <i>et al.</i> (1997)	Clinical – prostate cancer (compared to dietary and supplemental vitamin B <sub>12</sub> intake as measured by food frequency questionnaire)	Case-control	4 years	Males (mean age = 71 years)	Cases of histologically confirmed prostate cancer	101	<ul style="list-style-type: none"> <li>• There was a significant (<math>p&lt;0.05</math>) <u>positive</u> association between vitamin B<sub>12</sub> intake and the risk of prostate cancer.</li> <li>• The OR between the lowest and highest intakes was 2.02.</li> </ul>																								
					Age matched controls	202		Zhang <i>et al.</i> (2003)	Clinical – breast cancer (compared to serum vitamin B <sub>12</sub> levels)	Case-control	14 years	Females aged 30-55 years	Cases of breast cancer	735	There was no significant ( $p>0.05$ ) association between serum vitamin B <sub>12</sub> levels and the risk of breast cancer.	Age matched controls	735														
Zhang <i>et al.</i> (2003)	Clinical – breast cancer (compared to serum vitamin B <sub>12</sub> levels)	Case-control	14 years	Females aged 30-55 years	Cases of breast cancer	735	There was no significant ( $p>0.05$ ) association between serum vitamin B <sub>12</sub> levels and the risk of breast cancer.																								
					Age matched controls	735																									

**Table A7-3: Identified Studies on Vitamin B<sub>12</sub> and Other Health Outcomes**

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Results
Cagnacci <i>et al.</i> (2003)	Clinical – osteoporosis and osteopenia (compared to serum vitamin B <sub>12</sub> )	Case-control	1 year	Post-menopausal females (mean age = 53 years)	Cases of osteoporosis	28	There was no significant (p>0.05) difference in BMD between cases and controls when stratified on serum vitamin B <sub>12</sub> levels.
					Cases of osteopenia	61	
					Healthy controls	72	
Shuval-Sudai <i>et al.</i> (2003)	Biomarker of gastrointestinal infection – <i>H. pylori</i> IgG antibodies (compared to serum vitamin B <sub>12</sub> levels)	Cohort	Single timepoint	Persons	Subjects with seropositive result for <i>H. pylori</i> IgG antibodies	133	There was no significant (p>0.05) inverse association between serum vitamin B <sub>12</sub> and <i>H.pylori</i> infection.
Tucker <i>et al.</i> (2005)	Biomarker of bone disorders –BMD (compared to serum vitamin B <sub>12</sub> )	Cross-sectional	5 years	Persons aged 30-87 years	Total cohort	3532	<ul style="list-style-type: none"> <li>• Hip BMD was significantly greater (p&lt;0.01) with vitamin B<sub>12</sub> levels &gt;259 pM in males, and spine BMD at levels &gt;185 pM in females. However, this significance was non-linear.</li> <li>• Spine BMD and hip BMD in males and females respectively were non-significantly associated with vitamin B<sub>12</sub> levels (p&gt;0.05).</li> </ul>



### **Assessment of Health Benefit: Thiamin, Niacin, Biotin, Pantothenic acid, Copper, Manganese, and Molybdenum**

Following a review of the abstracts on for thiamin, niacin, biotin, pantothenic acid, copper, manganese, and molybdenum, the number of articles identified from the PubMed and NHMRC sources was reduced to a small number for each vitamin and mineral:

- Thiamin: 7 articles
- Niacin: 2 articles
- Biotin: 0 articles
- Pantothenic Acid: 0
- Copper: 4 articles
- Manganese: 1 article
- Molybdenum: 1 article

The evidence on thiamin, niacin, biotin, pantothenic acid, copper, manganese, and molybdenum is contained in Tables A8-1 to A8-6.

For each of these vitamins and minerals, the evidence base is too small to conclusively establish a relationship between their increased intake and the delivery of a health benefit. It has therefore been determined that there is an absence of evidence on the potential for thiamin, niacin, biotin, pantothenic acid, copper, manganese, molybdenum and phosphorus to deliver a health benefit.

**Thiamin, Niacin, Biotin, Pantothenic Acid, Copper, Manganese and Molybdenum are assigned an Evidence Level of 'A'**

**Table A8-1: Identified Studies on the Thiamin and Cancer**

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Bidoli <i>et al.</i> (2003)	Clinical - cancer of the larynx (compared to dietary thiamin intake as measured by food frequency questionnaire).	Case-control	8 years	Persons	Patients with incident cancer of larynx.	527	n/a	<ul style="list-style-type: none"> <li>• Significant (<math>p &lt; 0.05</math>) inverse relations emerged between laryngeal cancer and thiamin intake</li> <li>• The OR between the lowest and highest thiamin intakes was 0.4.</li> </ul>
					Patients with acute, non-neoplastic diseases	1297	n/a	
D'Avanzo <i>et al.</i> (1997)	Clinical – thyroid cancer	Case-control	6 years	Population of Northern Italy.	Histologically confirmed thyroid cancer cases.	399	n/a	There was no significant association between thiamin intake and the risk of thyroid cancer.
					Controls without cancer	617	n/a	
Hernandez <i>et al.</i> (2003)	Clinical – squamous intraepithelial lesions of the cervix (SIL) (compared to dietary and supplemental thiamin intake as measured by food intake survey).	Case-control	4 years	Multi-ethnic women identified from clinics in Oahu, Hawaii	High or low grade SIL	214	n/a	Thiamin from food displayed an inverse, dose-responsive association with high-grade SIL.
					Controls	271	n/a	
Marshall <i>et al.</i> (1992); HaengShi <i>et al.</i> , 2001)	Clinical – oral cancer	Case-control	Not reported	Population of Western New York	Cases of oral cancer	290	n/a	Thiamin was associated with a decreased risk of oral cancer.
					Age and gender matched controls	290	n/a	

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Negri <i>et al.</i> (1996)	Clinical – oral cancers (compared to dietary thiamin intake as measured by food frequency questionnaire).	Case-control	5.5 years	Patients admitted to major teaching and general hospitals in Italy and Switzerland.	Incident, histologically confirmed oral cancers	754	n/a	<ul style="list-style-type: none"> <li>• There was an inverse association between the intake of dietary thiamin and the risk of oral cancer</li> <li>• The OR between the lowest and highest thiamin intakes was 0.82.</li> </ul>
					Patients with no history of cancer admitted to hospitals with acute, non-neoplastic diseases.	1775	n/a	
Slattery <i>et al.</i> (1997)	Clinical – colon cancer (dietary thiamin intake as measured by an administered questionnaire).	Case-control	Not reported	Population of Northern California, Utah and the ‘Twin Cities’ area of Minnesota.	Cases – colon cancer	1993	n/a	Thiamin intake was inversely associated with the risk of colon cancer.
					Controls	2410	n/a	

**Table A8-2: Identified Studies on the Thiamin and Other Health Outcomes**

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
HaengShi <i>et al.</i> (2001)	Serum biomarkers of bone metabolism – fasting serum osteocalcin, calcium, phosphorous, estradiol, free testosterone (compared to thiamin intake as measured by a 24-hour recall over 3 days).	Cross-sectional	n/a	Postmenopausal women aged 50-77 years.	n/a	56	n/a	There was a statistically significant ( $p>0.05$ ) association between serum calcium and high intakes of thiamin.

**Table A8-3: Identified Studies on the Health Outcomes of Increased Niacin Intakes**

Study		Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dosage	Results
Sasaki and Yanagibori (2001)	Biomarker of bone health – BMD (compared to – niacin intake as measured by diet history)	Cross-sectional	2 years	Japanese women 29-60 years	pre menopausal	243	n/a	<ul style="list-style-type: none"> <li>Increased niacin intakes were significantly (<math>p &lt; 0.05</math>) and positively associated with BMD in premenopausal women.</li> <li>There was no significant (<math>p &gt; 0.05</math>) association between niacin intake and BMD for postmenopausal women.</li> </ul>
					post menopausal	137	n/a	
Morris <i>et al.</i> (2004)	Clinical – incidence of Alzheimer’s disease (compared to niacin intake as measured by food frequency questionnaire).	Cohort	Average 3.9 years	6158 persons > 65 years	Cases of Alzheimer’s disease	815	n/a	<ul style="list-style-type: none"> <li>Adjusted total niacin intake, including intake from food and supplements, was significantly (<math>p &lt; 0.05</math>) and inversely associated with the incidence of Alzheimer’s disease.</li> <li>Dietary niacin intake alone also had a significantly (<math>p &lt; 0.01</math>) inverse association with Alzheimer’s disease.</li> </ul>

**Table A8-4: Identified Studies on the Health Outcomes of Increased Copper Intakes**

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dosage	Results
Cashman <i>et al.</i> (2001)	Double-blind	Biomarkers of bone metabolism – serum osteocalcin, urinary creatinine, urinary pyridinoline.	Placebo-controlled, crossover	Treatment over 4 weeks, with a 3-week washout period.	Healthy females	High Cu supp.	16	6 mg copper sulphate	There was no significant difference ( $p > 0.05$ ) between study groups on biomarkers
						Low Cu supp.	16	3 mg copper sulphate	
						Placebo	16	-	

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dosage	Results
Cunzhi <i>et al.</i> (2003)	n/a	Study 1: Clinical – cervical cancer and uterine myoma (compared to tissue copper levels)	Paired Comparison	Single timepoint	Females aged 30-65 years with cervical or uterine cancer	Cancerous tissue samples from subjects	70	n/a	<ul style="list-style-type: none"> <li>• Copper levels were significantly (<math>p &lt; 0.05</math>) higher in cervical cancer tissue samples than non-lesion tissue samples.</li> <li>• There was no significant (<math>p &gt; 0.05</math>) difference in copper levels between uterine and non-lesion tissues.</li> </ul>
						Non-lesion tissue samples from subjects	70	n/a	
		Study 2: Clinical – cervical cancer and uterine myoma (compared to serum copper levels)	Case-control	Single timepoint	Females aged 30-65 years.	Cases of cervical cancer	100	n/a	<ul style="list-style-type: none"> <li>• The serum copper levels of cervical cancer subjects were significantly (<math>p &lt; 0.001</math>) higher than those of healthy subjects.</li> <li>• There was no significant (<math>p &gt; 0.05</math>) difference in the serum copper levels of uterine cases and controls.</li> </ul>
						Cases of uterine cancer	100	n/a	
Healthy controls	100					n/a			
Jones <i>et al.</i> (1997)	Not reported	Biomarkers of CHD – serum cholesterol, serum lipoprotein (a), VLDL lag time, and LDL oxidation.	Placebo-controlled, crossover	Treatment over 4 weeks	Adult males with elevated cholesterol	Copper supplement	20	2 mg/day of Cu	Cu supplementation had no significant impact ( $p > 0.05$ ) on any of the study's biomarker parameters.
						Placebo	20	-	
Sennese <i>et al.</i> (2004)	n/a	Clinical – colorectal cancer (comparison with dietary copper intake as measured by food frequency questionnaire)	Case-control	5 years	Persons aged 30-79 years	Colorectal cases	171	n/a	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.01</math>) inverse association between copper intakes and the risk of colorectal cancer.</li> <li>• The OR between the lowest and highest quartiles of copper intake was 2.4.</li> </ul>
						Healthy controls	309	n/a	

**Table A8-5: Identified Study on Manganese and Cancer**

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Results
Cunzhi <i>et al.</i> (2003)	Study 1: Clinical – cervical cancer and uterine myoma (compared to tissue manganese levels)	Paired Comparison	Single timepoint	Females aged 30-65 years with cervical or uterine cancer	Cancerous tissue samples from subjects	70	<ul style="list-style-type: none"> <li>• Manganese levels were significantly (<math>p &lt; 0.05</math>) lower in cervical cancer tissue samples than non-lesion tissue samples.</li> <li>• There was no significant (<math>p &gt; 0.05</math>) difference in manganese levels between uterine and non-lesion tissues.</li> </ul>
					Non-lesion tissue samples from subjects	70	
	Study 2: Clinical – cervical cancer and uterine myoma (compared to serum manganese levels)	Case-control	Single timepoint	Females aged 30-65 years.	Cases of cervical cancer	100	The serum manganese levels of both case groups were significantly ( $p < 0.001$ ) higher than those of healthy subjects.
					Cases of uterine cancer	100	
Healthy controls					100		

**Table A8-6: Identified Study on Molybdenum and Cancer**

Study	Study Endpoint Type	Study Design	Study Duration	Subjects	Subject Grouping	Subject number	Results
Nakadaira <i>et al.</i> (1995)	Clinical – cancer mortality (compared with levels of molybdenum in soils of 19 agricultural based areas in Japan).	Prospective cohort	10 years	Japanese residence of 19 areas within the Niigata province	Cancer mortality	Not reported	<ul style="list-style-type: none"> <li>• There was a significant (<math>p &lt; 0.05</math>) inverse correlation between molybdenum levels and female mortality from rectal cancer.</li> <li>• There was also a significant (<math>p &lt; 0.01</math>) positive correlation between molybdenum soil levels and female mortality from pancreatic cancer.</li> </ul>

### Studies on the Intake of Sugar-Containing Beverages and Overweight/Obesity

**Table 9-1: Cross-Sectional Studies on Sugar-Containing Beverages and Overweight/Obesity**

Study	Study Endpoint Type	Study Design	Study Duration	Subjects	Subject Grouping	Subject number	Results
<b>No Association (p&gt;0.05)</b>							
Bandini <i>et al.</i> (1999)	BMI compared to soft drink intake (as measured by 14 day food record).	Cross-sectional	Single timepoint	43 adolescents	Obese adolescents (BMI $\geq$ 30)	21	Consumption of soft drinks was not significantly (p>0.05) different between the two groups.
					Non-obese adolescents (BMI <30)	22	
Forshee <i>et al.</i> (2004)	BMI compared to soft drink intake (as measured by food frequency questionnaire and 24-hour recall)	Cross-sectional (from NHANES III data)	Single timepoints collected over a four year period	Children aged 12-16 years	Males	1141	There was no significant (p>0.05) positive association between weight and the intake of soft-drinks.
					Females	1075	
Forshee and Storey (2003)	BMI compared to the intake of different beverages (as measured by food frequency questionnaire)	Cross-sectional	Single timepoint	Children aged 6-19 years	Males	1689	<ul style="list-style-type: none"> <li>• Diet soft drinks were positively associated (p&lt;0.05) with increased BMI.</li> <li>• There was no significant association between weight and other beverages.</li> </ul>
					Females	1624	
Janssen <i>et al.</i> (2005)	BMI compared to soft drink intake (measured by food frequency questionnaire)	Cross-sectional (data from Health Behaviour in School-aged Children study)	Single timepoint collected over two years	Children aged 10-16 years	Total cohort	137593	There was no significant (p>0.05) positive association between overweight subjects (BMI above an internationally defined cut-point for children) and the intake of soft-drinks.

Study	Study Endpoint Type	Study Design	Study Duration	Subjects	Subject Grouping	Subject number	Results
<b>Positive Association (p&lt;0.05)</b>							
Ariza <i>et al.</i> (2004)	BMI compared to sugar-containing beverage intake (as measured by food frequency questionnaire).	Cross-sectional	Single timepoint	250 Hispanic children aged 5-6 years	Overweight (BMI $\geq 95^{\text{th}}$ percentile)	58	When the two groups were compared, a significantly (p=0.03) greater number of overweight children consumed sugar-containing beverages.
					Non-overweight (BMI < 95 <sup>th</sup> percentile)	192	
Giammattei <i>et al.</i> (2003)	BMI compared to soft drink intake (as measured by food frequency questionnaire).	Cross-sectional	Single timepoint	319 children aged 11-14 years	<3 serves sugar-containing beverages/day	270	There was a significant (p=0.006) greater prevalence of obesity ( $\geq 85^{\text{th}}$ BMI percentile) amongst those consuming $\geq 3$ serves/day compared with those consuming <3 serves/day.
					$\geq 3$ serves sugar-containing beverages/day	49	
Lin <i>et al.</i> (2004)	BMI compared to soft drink and juice intake (as measured by food frequency questionnaire).	Cross-sectional	Single timepoint	Adult women and school aged children	Adult women	2419	<ul style="list-style-type: none"> <li>• There was no significant (p&gt;0.05) association between sugar-containing beverage intake and BMI (unadjusted) in children.</li> <li>• Sugar-containing beverages were significantly (p&lt;0.01) positively associated with BMI in high income earning adult women.</li> </ul>
					Children	1651	
Melgar-Qinonez and Kaiser (2004)	BMI compared fruit juice intake (% energy intake as measured by food frequency questionnaire).	Cross-sectional	Single-timepoint	204 Hispanic children (mean age = 4.4 years)	Overweight (BMI $\geq 95^{\text{th}}$ percentile)	48	There was a significant difference in the percentage of energy intake from juice between non-overweight children and overweight subjects (p=0.04), and between non-overweight children and those at risk of overweight (p=0.03).
					Risk of overweight (BMI $\geq 85^{\text{th}}$ percentile)	88	
Troiano <i>et al.</i> (2000)	BMI compared to soft drink and fruit juice intake (as measured by 24 hour recall).	Cross-sectional	Single-timepoint	Children aged 2-19 years	Total cohort	10371	When stratified by overweight status ( $\geq 95^{\text{th}}$ BMI percentile), there was a positive association with soft drink intake. The classification and numbers of overweight children were not reported.



**Table 9-2: Case-Control Studies on Sugar-Containing Beverages and Overweight/Obesity**

Study	Study Endpoint Type	Study Design	Study Duration	Subjects	Subject Grouping	Subject number	Results
Gillis <i>et al.</i> (2003)	BMI compared to sugar-containing beverage intake (as measured by diet history, 24-hour recall, and food frequency questionnaire).	Case-control	Single-timepoint (collected over 1 year)	Children aged 4-16 years	Obese children (BMI $\geq 95^{\text{th}}$ percentile)	91	<ul style="list-style-type: none"> <li>There was a significantly (<math>p &lt; 0.02</math>) greater intake of sugar-containing beverages between the two groups.</li> <li>When carbonated soft drinks were excluded from the sugar-containing beverage category, the difference was more significant (<math>p &lt; 0.002</math>).</li> </ul>
					Non-obese children (BMI $< 95^{\text{th}}$ percentile)	90	
Tanasescu <i>et al.</i> (2000)	BMI compared to soft drink and fruit juice intake (as measured by 24 hour recall).	Case-control	Single-timepoint	Hispanic children aged 7-11 years	Obese (BMI $\geq 85^{\text{th}}$ percentile)	29	<ul style="list-style-type: none"> <li>There was a significant difference (<math>p = 0.01</math>) in fruit juice intake between obese and non-obese children, but not for soft-drinks (<math>p &gt; 0.05</math>).</li> <li>The OR between the two groups was 4.02 for fruit juice.</li> </ul>
					Non-obese (BMI $< 85^{\text{th}}$ percentile)	24	

**Table 9-3: Prospective Cohort Studies on Sugar-Containing Beverages and Overweight/Obesity**

Study	Study Endpoint Type	Study Design	Study Duration	Subjects	Subject Grouping	Subject number	Results
<b>No Association (<math>p &gt; 0.05</math>)</b>							
Blum <i>et al.</i> (2005)	BMI compared to sugar-containing beverage intake (as measured by 24-hour recall)	Prospective cohort	2 years	Children aged 8-12 years	Normal weight (BMI z-score $< 1.0$ )	164	<ul style="list-style-type: none"> <li>There was no difference (<math>p &gt; 0.05</math>) over time between the overweight and normal weight groups with the intake of sugar-containing beverages.</li> <li>Weight gain or loss was not significantly associated (<math>p &gt; 0.05</math>) over time with the intake of sugar-containing beverages.</li> </ul>
					Overweight (BMI z-score $\geq 1.0$ )	48	
					Gained weight (Normal to overweight)	11	
					Lost weight (Overweight to normal weight)	6	

Study	Study Endpoint Type	Study Design	Study Duration	Subjects	Subject Grouping	Subject number	Results
Kvaavik <i>et al.</i> (2005)	BMI compared to soft drink intake (as measured by food frequency questionnaire).	Prospective cohort	18 years	423 Children (mean age = 14.6 females, and 14.7 males)	High soft drink intake ( $\geq 3$ serves/week)	61	There was no significant ( $p > 0.05$ ) association between soft drink intake and the numbers of overweight (BMI $> 25$ ) and obesity (BMI $> 30$ ).
					Low soft drink intake ( $< 3$ serves/week)	194	
					Change in soft drink intake over study period	116	
Newby <i>et al.</i> (2004)	BMI compared to beverage intake, including sugar-containing beverages (as measured by food frequency questionnaire).	Prospective cohort	1 year	Children aged 2-5 years	Total cohort	1345	There was no significant ( $p > 0.05$ ) association between sugar-containing beverage intakes and changes in BMI (unadjusted for growth).
<b>Positive Association (<math>p &lt; 0.05</math>)</b>							
Berkey <i>et al.</i> (2004)	BMI compared to the intake of beverages with added sugar (as measured by food frequency questionnaire).	Prospective cohort (offspring data from the Nurses' Health Study)	2 years	16711 children aged 9-14 years	Males	7770	<ul style="list-style-type: none"> <li>For males, there was a significant (<math>p = 0.038</math>) positive association between the intake of sugar-added beverages and growth-adjusted BMI.</li> <li>No significant (<math>p &gt; 0.05</math>) association was found for females.</li> <li>Increases in male sugar-added beverage intake over time were also proportional to changes in growth-adjusted BMI over time (<math>p &lt; 0.01</math>).</li> <li>No significant (<math>p &gt; 0.05</math>) association was found between intakes of fruit juice and growth-adjusted BMI percentiles of males and females.</li> </ul>
					Females	8941	

Study	Study Endpoint Type	Study Design	Study Duration	Subjects	Subject Grouping	Subject number	Results
Ludwig <i>et al.</i> (2001)	BMI compared to sugar-containing beverage intake (as measured by food frequency questionnaire).	Prospective cohort	2 years	Children (mean age 11.7 years)	Obese at baseline ( $\geq 85^{\text{th}}$ BMI percentile)	150	<ul style="list-style-type: none"> <li>There was a significant (<math>p=0.02</math>) positive association between adjusted sugar-containing beverage intake and the incidence of obesity.</li> <li>The OR for obesity incidence between the lowest and highest intake of sugar-containing beverages was 1.44.</li> <li>Increased sugar-containing beverage intake was positively associated (<math>p=0.03</math>) with growth-adjusted BMI.</li> </ul>
					Non-obese at baseline (BMI $< 85^{\text{th}}$ BMI percentile)	152	
Phillips <i>et al.</i> (2004)	BMI compared to soft drink intake (as measured by food frequency questionnaire).	Prospective cohort	4 years	Premenstrual females aged 8-12 years	Total cohort	196	<ul style="list-style-type: none"> <li>There was a significant (<math>p&lt;0.01</math>) positive association between adjusted soft drink intake and BMI z-scores (adjusted for growth).</li> <li>There was a <math>0.17 \text{ kg/m}^2</math> difference in the mean BMI z-score between the lowest (<math>&lt;0.74\%</math> energy intake) and highest (<math>\geq 3.2\%</math> energy intake) quartiles of soft drink intake.</li> </ul>
Schulze <i>et al.</i> (2004)	BMI compared to dietary patterns, including soft drink consumption (as measured by food frequency questionnaire).	Prospective cohort (data from the Nurses' Health Study)	8 years	Adult females, aged 24-44 years, and free of diabetes.	Low soft drink intake ( $\leq 1/\text{wk}$ )	38737	A change from a low to a high soft drink intake over the study period was significantly ( $p<0.001$ ) associated with an increase in BMI over other intakes of sugar-containing beverages.
					High soft drink intake ( $\leq 1/\text{wk}$ )	2366	
					Change from low to high	1007	
					Change from high to low	1020	

Study	Study Endpoint Type	Study Design	Study Duration	Subjects	Subject Grouping	Subject number	Results
Welsh <i>et al.</i> (2005)	BMI compared to sugar-containing beverage intake (as measured by food frequency questionnaire).	Prospective cohort	1 year	10904 Children aged 2-3 years	Normal or underweight (BMI <85 <sup>th</sup> percentile)	8828	<ul style="list-style-type: none"> <li>High sugar-containing beverage intakes (&gt;1 serve/day) were significantly (p&lt;0.05) associated with the development into an overweight category for subjects in the 'at risk group'.</li> <li>High intakes were associated with significantly (p&lt;0.05) more subjects in the overweight group remaining overweight.</li> <li>No significant (p&gt;0.05) association was found for 'normal/underweight'.</li> <li>The adjusted OR between the low and high intakes was 2.0 and 2.2 for the 'at risk' and overweight groups respectively.</li> </ul>
					At risk of overweight (85 <sup>th</sup> – <95 <sup>th</sup> percentiles)	1579	
					Overweight (≥ 95 <sup>th</sup> percentile)	1097	

**Table 9-4: Intervention Studies on Sugar-Containing Beverages and Overweight/Obesity**

Study	Study Endpoint Type	Study Design	Study Duration	Subjects	Subject Grouping	Subject number	Results
James <i>et al.</i> (2004)	BMI compared to soft drink intake (as measured by 3 day food record).	Cluster randomised controlled trial	1 year	Children aged 7 – 11 years	Intervention group (received education on reducing soft-drink intake)	325	<ul style="list-style-type: none"> <li>The intervention resulted in a significant (p=0.02) decrease in the carbonated soft drink intake of intervention group compared to the control group.</li> <li>There was a significantly (p&lt;0.05) lower number of overweight (&gt;91<sup>st</sup> BMI percentile) subjects in the control group compared to the intervention group at follow-up.</li> </ul>
					Control group	319	