Attachment 5

Nutrition Assessment
Application A470 – Formulated Beverages

CONTENTS

Executive Summary

The purpose of the nutrition assessment is to determine the nutrition and health need for adding the requested 24 vitamins and minerals to FB, and to examine the nutrition-related health risks to the broader Australian and New Zealand populations. The overarching approach to the nutrition assessment has been to consider FSANZ's statutory objectives as stated in section 10 of the FSANZ Act, and to have regard to the Ministerial Policy Guideline 'Fortification of Food with Vitamins and Minerals' (the Policy Guideline).

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)[1]. 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 was not available for this assessment (molybdenum).
- 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.

[1] The EAR is a value representing the median requirement for a vitamin or mineral.

Figure 1: Assessment of Nutrition and Health Need

Vitamin / Mineral		Step 1 Nutritional Need	Step 2 Health Benefit	Existence of a Nutrition and Health Need
Group 1	Riboflavin Folate Vitamin B_6 Vitamin D Vitamin E Calcium Iodine Iron Magnesium Selenium Zinc	> 3% of population intakes were below the EAR, OR Evidence of deficiency existed	→	**Identified as having a nutrition and health need**
Group 2	Vitamin A (retinol) Thiamin Niacin Vitamin B_{12} Vitamin C Copper Phosphorus	< 3% of population had intakes below the EAR, AND No evidence of deficiency	Assessed for the potential to deliver a health benefit (none met FSANZ criteria for a 'health benefit')	→ **No nutrition and health need identified**
	Beta-carotene Chromium Biotin Pantothenic acid Manganese Molybdenum	Unable to assess for inadequacy, AND No evidence of deficiency		

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 FB are as follows:

Vitamins	Minerals
Riboflavin	Calcium
Folate	Iodine
Vitamin B_6	Iron
Vitamin D	Magnesium
Vitamin E	Selenium
	Zinc

As a final component of the nutrition assessment, FSANZ reviewed the energy and sugars content of FB and their potential impact on the overall diet. A potential risk was identified, that intakes of sugar-containing beverages (including those with a natural sugar content) would increase as a result of FB expanding the beverage sector of the market. There is evidence to show that consumption of standard sugar-containing beverages (e.g. soft-drinks) can significantly increase the overall intake of energy within the diet and thus contribute to weight gain. Therefore, a potentially higher beverage intake resulting from approval of Application A470 will likely increase the intake of sugars and energy in the Australian and New Zealand populations, and is potential health risk.

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 (FB) as requested by the Applicant.

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[2] 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

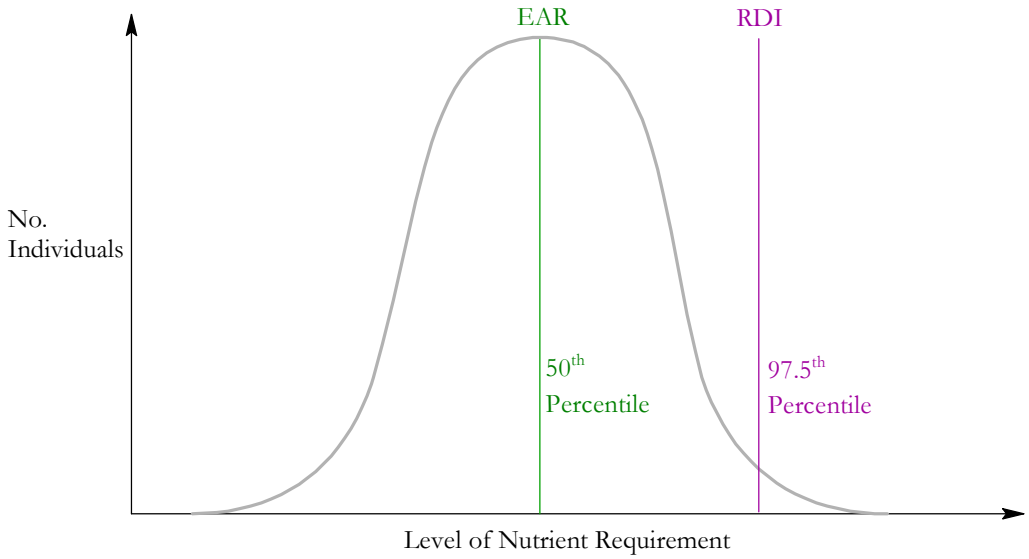
The estimated average requirement (EAR) is a value that represents the median requirement for the dietary intake of a particular nutrient in a given population group. EARs are commonly used by the United States (US), United Kingdom (UK) and Canada[3] to set other reference values. For example, the recommended 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 1 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).

[2] 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.

[3] 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 will primarily be used for Application A470; if an overseas EAR does not exist for a vitamin or mineral, then the EAR will be extrapolated from the RDI using the formula 0.7 x 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 United Kingdom (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 is available then the 0.7 x RDI formula has been used.

2.1.2 Criteria for Establishing an Inadequate Intake within the Population

The use of percentages below the EAR as a measure of an 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 FB.

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 to be calculated (see Attachment 7 for details on these vitamins and minerals).

The vitamin and mineral concentrations used for FB 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.

The nutrients have been assessed for inadequacy by estimating baseline intakes of nutrients and comparing these intakes to EARs. In order to determine whether consuming FB 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 FB. 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_6, 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 FB 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)

Nutrient	*Modelling*	*Sub-category*	*2-3 yrs*	*4-6 yrs*	*7-10 yrs*	*11-14 yrs*	*15-18 yrs*	*19-50 yrs*	*51+ yrs*	*2+ yrs#*
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	**5**	**3**	**5**	**3**
		NZ	-	-	-	-	2	1	**3**	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	**3**	**4**	**3**	2	2
		NZ	-	-	-	-	**4**	**3**	**8**	**5**
Vitamin B_{12}	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	**25**	**30**	**15**	**25**	**20**
		NZ	-	-	-	-	**35**	**15**	**25**	**20**
Magnesium	EAR (mg)	Males	65	90	150	230	250	250	250	-
		Females	65	90	150	230	250	200	200	-
	% below EAR	Aust	0	0	**3**	**35**	**30**	**10**	**15**	**15**
		NZ	-	-	-	-	**20**	**5**	**20**	**10**
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_{12} was not assessed in the 1995 Australian NNS. Therefore, vitamin B_{12} concentrations in foods from the 1997 New Zealand NNS were used in the assessment of vitamin B_{12} 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)

Nutrient	*Modelling*	*Sub-category*	*2-3 yrs*	*4-8 yrs*	*9-13 yrs*	*14-18 yrs***	*19-30 yrs*	*31-50 yrs*	*51-70 yrs*	*71+ yrs*	*2+ yrs#*
Vitamin A	EAR (µg)	Males	210	275	445	630	625	625	625	625	-
		Females	210	275	420	485	500	500	500	500	-
	% below EAR	Aust	0	0	0	**3**	2	0	0	0	<1
		NZ				0	0	0	0	0	0
Vitamin B_6	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	**10**	**15**	**25**	**45**	**60**	**25**
		NZ	-	-	-	0	0	**15**	**55**	**65**	**25**
Copper	EAR (µg)	Males	260	340	540	685	700	700	700	700	-
		Females	260	340	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	**8**	**9**	**7**	<1	**3**	**5**
		NZ	-	-	-	**4**	**5**	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*	**20**	**25**	**30**	**35**	**30**	**35**	**40**	**45**	**35**
		NZ	-	-	-	**50**	**45**	**15**	**60**	**75**	**40**
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	**3**	**8**	**8**	**3**	**9**	**17**	**6**
		NZ	-	-	-	**5**	**4**	1	**13**	**18**	**7**

* Vitamin B_6, 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_6 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	**3**	2	**15**	**10**	**7**	**10**	**15**	**8**
		NZ	-	-	-	**4**	**9**	**3**	**3**	**3**	**3**

* 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	Urinary Iodine Concentration			
		No.	% < 50 μg/L	% <100 μg/L	Median Value (μg/L)
AUSTRALIA					
Gunton *et al.* (1999)	Pregnant women	81	19.8	49.6	
	Postpartum women	28	19.2	53.9	
	Patients with diabetes	135	34.1	71.9	
	Volunteers	19	26.3	73.7	
Guttikonda *et al.* (2003)	Children 5 -13 years	301	14	69	82
Li *et al.* (2001)	Children 6 -13 years	94	13.8		84
	Pregnant women from antenatal class	101	20.6		88
	Adult volunteers, medical staff	86	18		88
	Diabetes patients	85	23		69
McDonnell *et al.* (2003)	Children 11-18 years: Male	167	17	69	
	Children 11-18 years: Female	410	31	79	
	Total	577	27	76	
NEW ZEALAND					
Thomson *et al.* (1997)	Blood Donors	333	57	92	Male: 51 Female: 42
Skeaff *et al.* (2002)	Children 8 - 10 years	282	31.4	79.7	66
Thomson *et al.* (2001)	Men and women 18 - 49 years	233			59 ±33
Ministry of Health (2003)	Children 5 -14 years		28		All: 66 Male: 68 Female: 62

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, β-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.

Vitamin D does not have an overseas EAR that can be used, however there is evidence relating to vitamin D deficiency within Australia and New Zealand. This information has been reviewed in Section 2.2.1 above. Vitamin E also has no EAR, however a proxy derivation of the EAR from its RDI was undertaken as outlined in Section 2.1.1 above.

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 FB 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	Minerals
vitamin A	chromium
beta-carotene	copper
thiamin	manganese
niacin	molybdenum
vitamin B_{12}	phosphorus
Vitamin C	
biotin	
pantothenic acid	

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 was 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 on vitamin and mineral fortification.

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 or similar value 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 FB 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		

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*
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	
4	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 the vitamin/mineral alone; 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 for the Proposed Vitamin and Mineral Additions

Level of Evidence	*Vitamins and Minerals Meeting the Evidence Level Category*
A	Thiamin, niacin, biotin, pantothenic acid, copper, manganese, and molybdenum.
0	Vitamin B_{12}
1	Vitamin C, β-carotene, phosphorus
2	Chromium
3	None
4	None

2.5 Summary of the Nutrition and Health Need Assessment

The Applicant has requested the addition of 24 vitamins and minerals to FB. 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

Vitamin or Mineral	*Meets Inadequacy Criteria*	*Meets Deficiency Criteria*	*Meets Health Benefit Criteria*	*Assessed as Having a Nutrition and Health Need*
Vitamin A	No	No	No	
Beta-carotene	No	No	No	
Thiamin	No	No	No	
Riboflavin	✓			✓
Niacin	No	No	No	
Vitamin B_6	✓			✓
Folate	✓			✓
Vitamin B_{12}	No	No	No	
Biotin	No	No	No	
Pantothenic Acid	No	No	No	
Vitamin C	No	No	No	
Vitamin D	No	✓		✓
Vitamin E	✓			✓
Calcium	✓			✓

Vitamin or Mineral	*Meets Inadequacy Criteria*	*Meets Deficiency Criteria*	*Meets Health Benefit Criteria*	*Assessed as Having a Nutrition and Health Need*
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 FB, 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 FB. 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 FB 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 FB 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 of 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

Nutrient	*Range of Change (% Respondents with Intakes < EAR)*	
	Maximum Negative Change	*Maximum Positive Change*
Riboflavin	-2	0
Vitamin B_6	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 FB 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 FB 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 FB are voluntary and subject to implementation by industry, this uncertainty in the effectiveness of FB 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 FB and is therefore excluded from further consideration in this nutrition assessment.

4. Nutrition-Related Health Risks

The request to voluntarily fortify FB raises a number of nutritional issues that are broader than the assessment of nutrition and health needs. There are issues in this Application that represent potential health risks, namely whether the introduction of FB beverages into the Australian market will impact on wider dietary trends (in both Australia and New Zealand), and whether FB are an appropriate food vehicle for voluntary vitamin and mineral fortification.

The identification and prevention / mitigation of these health risks is reflected in both the Section 10 objectives of the FSANZ Act 1991 on the protection of public health and safety, and the prevention of misleading and deceptive conduct.

4.1 Nutritional Impact from the Macronutrient Profile of Formulated Beverages

4.1.1 Impact on Macronutrient Intakes from Beverage Substitution

One approach FSANZ has taken to determining the impact from the macronutrient profile of FB has been to examine the composition of FB currently available in Australia and New Zealand and the implications for beverage substitution.

The 2005 Australian and New Zealand stock-takes of beverages identified a total of 27 different FB, with 20 of the 27 FB on the Australian market and 10 of the 27 on the New Zealand market. This is in comparison to the eleven different FB identified in the 2003 Australia and New Zealand Food-Type Dietary Supplements Product Surveys (Food Technical Services, 2003; Food Concepts & Design Ltd, 2003). The ingredients of these products ranged from beverages with less than 2% fruit juice and no added sugars to beverages with greater than 5% fruit juice and added sugars.

The 2005 stock-take data shows that the energy and macronutrient composition per 100 ml varied between the beverages. The water-based beverages containing less than 2% fruit juice and 'no added sugar' had less than 2 kJ/100 ml and 0% sugars. The beverages containing 2-5% fruit juice and added sugar had approximately 38-94 kJ/100 ml and 2.2-5.4% sugars. Those beverages containing greater than 5% fruit juice and added sugar had approximately 171-196 kJ/100 ml and 9.7-11.3% sugars. The protein and fat contents of all FB surveyed were less than 1 g/100 ml.

The Applicant proposes that FB will replace some soft drink sales. For comparison, a standard lemonade soft drink contains 174 kJ and 10.8 g/100 ml of sugars, and thus has 1044 kJ and 64.8 g of sugars per 600 ml (the Applicant has requested a reference quantity of 600 ml for FB). These amounts are comparable to those found in FB made with greater than 5% fruit juice and added sugar.

4.1.2 Overall Dietary Impacts from the Macronutrient Profile of Formulated Beverages

FSANZ has also investigated the possible impact on the entire diet from the macronutrient profile of FB. Given that sugars are likely to be the only significant macronutrient in FB, the focus of this investigation has been on the impact for population intakes of energy and sugars.

There is evidence to show that consumption of standard sugar-containing beverages (including those with natural sources of sugar), whether FB or otherwise, can significantly increase the overall intake of energy within the diet and thus contribute to weight gain (Krebs-Smith, 2001; Ludwig *et al*., 2001; Somerset, 2003; Berkey *et al*., 2004; James *et al*., 2004). The majority of this evidence is based on epidemiological correlations between sugar-containing beverage consumption and weight gain. However, Krebs-Smith (2001) has also demonstrated that it is the contribution of additional sugar to the diet from sugar-containing beverages that is the contributor to increases in energy intakes.

Should FB increase the volume of sugar-based beverages consumed in the diet, either by substituting for other beverages with smaller serving sizes, or by expanding the overall consumption of these beverages as a whole, then an adverse impact on population health may result. This scenario is a real nutrition-related health risk, as the main driver for adding vitamins and minerals to FB is to increase the product's nutritional attractiveness and thus marketability, potentially above other existing beverage products. Although not all FB will contain high levels of sugars, products of this type are currently contained within the scope of the Applicant's request. It is therefore possible that an increased nutritional profile for FB will increase the intake of sugar-containing beverages across the population.

This nutrition assessment cannot fully determine the impact on energy or sugar intakes from FB permissions, as the impact would be dependent on the future in-roads that FB make into the Australian market, and the changes that an emerging Australian FB market may have on the current New Zealand FB market. However, the potential for an increase in energy intakes within Australian and New Zealand diets from proposed FB permissions (via increased sugar-containing beverage consumption) is still recognised as a potential health risk.

4.1.3 Conclusion

The substitution of other beverages by FB, as a process itself, will not have any significant adverse impacts on macronutrient intakes, as the macronutrient composition of these products is comparable to other non-fortified beverages. There is an additional concern, however, that the addition of vitamins and minerals to FB will provide additional motivation for consumers to purchase these beverages, and that this nutritional attractiveness will expand the beverage market, including the market for sugar-containing beverages. As such, there may be a health risk from the introduction of FB into the market, through increases in energy intakes resulting from increased sugar-containing beverage consumption.

4.2 Suitability of Formulated Beverages for Voluntary Fortification – The Influence on Bioavailability

Bioavailability refers to the biological availability of a nutrient to the human body. This property 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).

4.2.1 Bioavailability Issues Specific to Various Vitamins and Minerals

Two of the most heavily researched nutrients in respect to bioavailability are iron and calcium, and are thus perhaps two of the best examples of mineral bioavailability. These two examples show that regardless of their source, minerals cannot be fully absorbed by the intestine even during ideal conditions (Turnlund, 1991). For example, balance and isotopic tracer studies have shown that maximum of 60% of ingested calcium can be absorbed during infancy, and this figure decreases with increasing age down to approximately 25% (excepting calcium uptake during pregnancy) (United States Institute of Medicine, 1997).

Additionally, any limitations in mineral bioavailability are unlikely to be due to the use of synthetic forms of these nutrients. In the case of iron, it is more often the quality of the overall diet that determines the bioavailability of consumed iron than the addition of iron salts to individual foods (Fairweather-Tait and Teucher, 2002). Recker *et al.* (1988) has also shown, through the use of isotopic tracers, that the use of a calcium salt in food (such as calcium carbonate) is as bioavailable as the form of calcium found in milk.

Compared to minerals, vitamins have fewer issues surrounding their bioavailability. 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 affected little 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).

4.2.2 The Variable Nature of Bioavailability

Current research has developed methods to account for the variable nature of vitamin and mineral bioavailability. However, a large degree of uncertainty still remains with any findings on vitamin and minerals bioavailability, as there are a wide variety of modifying factors that can confound results from scientific studies.

Confounding modifiers of bioavailability include the nutrient's release from the food matrix during digestion, physical interaction between other food 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).

A major influence on bioavailability is also the interaction between foods within a meal. 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).

4.2.3 Conclusion

Due to the large number of modifiers influencing bioavailability, especially those that may confound scientific research into this area, FSANZ cannot fully assess the bioavailability of vitamin and mineral additions to FB.

FSANZ has reviewed the scientific literature on bioavailability for both vitamins and minerals (Section 4.2.1 above), however the uncertainty surrounding bioavailability studies means that a limited picture can only be formed. From this limited assessment, it can be determined that the addition of vitamins and minerals to FB is likely to be comparable to the bioavailability obtained from other food sources of these nutrients. For this reason, the Applicant's request to use vitamin and mineral chemical forms that are permitted for other generally consumed foods (i.e. the permitted forms listed in the Schedule of Standard 1.1.1 of the Code) is appropriate for the proposed addition of vitamins and minerals to FB.

5. Conclusion

There is no nutrition and health need for a number of the proposed vitamin and mineral additions to FB. The addition of the following vitamins and minerals to FB is not supported by the findings of this nutrition assessment:

Vitamins	Minerals
☐ Vitamin A	☐ Chromium
☐ β-carotene	☐ Copper
☐ Thiamin	☐ Manganese
☐ Niacin	☐ Molybdenum
☐ Vitamin B_{12}	☐ Phosphorus
☐ Vitamin C	
☐ Biotin	
☐ Pantothenic Acid	

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

Vitamins	Minerals
☐ Riboflavin	☐ Calcium
☐ Folate	☐ Iodine
☐ Vitamin B_6	☐ Iron
☐ Vitamin D	☐ Magnesium
☐ Vitamin E	☐ Selenium
	☐ Zinc.

Although the above vitamins and minerals have a nutrition and health need supporting their addition to FB, 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).

Finally, in the context of the overall diet, there is the possibility that beverage intakes will increase as a result of FB expanding this sector of the market. A potential risk was identified, that intakes of sugar-containing beverages (including those with a natural sugar content) would increase as a result of FB expanding the beverage sector of the market. Therefore, a potentially higher beverage intake resulting from approval of Application A470 will likely increase the intake of sugars and energy in the Australian and New Zealand populations, and is potential health risk.

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Appendix 1

Electronic Literature Search on Health Benefits (number of articles identified)

Keywords	Vitamin A		β-carotene	Thiamin		Niacin		Vitamin B_{12}		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
"[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

Appendix 2

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[4] 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

[4] 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 *et al.* (1992)	Not reported	Biomarkers of CHD – cholesterol, HDL and triglyceride levels	Randomised controlled trial	7-16 months	Patients with athero-sclerosis aged 42-83 years	Chromium supplementation	38	250 mg chromium chloride	- Chromium supplementation significantly increased serum chromium levels ($p<0.05$). - There was no significant ($p>0.05$) difference in serum triglycerides and cholesterol levels between the two groups . - There was a significant increase ($p<0.005$) in serum HDL levels.
						Placebo treatment	38	-	
Anderson *et al.* (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	- 500 µg/day chromium supplementation significantly ($p<0.02$) decreased serum cholesterol levels compared to the placebo group. - There was no significant ($p>0.05$) impact of chromium supplementation on other measured study endpoints.
						Low chromium supplementation	60	100 µg/day chromium picolinate	
						Placebo	60	-	
Bahijiri *et al.* (2000)	Double-blinded	Biomarker of CHD – serum cholesterol, HDL and triglyceride levels.	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 ($p<0.001$) decreased serum triglyceride levels and significantly ($p<0.001$) increased serum HDL levels. - There was no significant ($p>0.05$) impact of chromium supplementation on serum cholesterol.
						Treatment 2 – Brewer's yeast	78	23.2 µg/day chromium	

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 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 *et al.* (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 *et al.* (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	-	
Rabinovitz *et al.* (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	- There was a significant ($p<0.02$) inverse association between chromium supplementation and serum cholesterol levels. - However, there was no significant ($p>0.05$) association between chromium supplementation and HDL, LDL or serum triglyceride levels.
						Placebo	39	-	

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Tang *et al.* (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 *et al.* (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 *et al.* (1992)	Not reported	Biomarkers of diabetes – serum glucose levels	Randomised controlled trial	7-16 months	Patients with athero-sclerosis aged 42-83 years	Chromium supplementation	38	250 mg chromium chloride	- Chromium supplementation significantly increased serum chromium levels ($p<0.05$). - There was no significant ($p>0.05$) difference in serum glucose levels between the two groups.
						Placebo treatment	38	-	
Anderson *et al.* (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	- 500 µg/day chromium supplementation significantly ($p<0.0001$) decreased serum glucose, insulin and HbA1c levels compared to the placebo group. - 100 µg/day chromium supplementation significantly ($p<0.0001$) decreased serum insulin levels, however had no significant ($p>0.05$) impact on serum glucose or HbA1c
						Low chromium supplementation	60	100 µg/day chromium picolinate	
						Placebo	60	-	
Anderson *et al.* (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	-	
Bahijiri *et al.* (2000)	Double-blinded	Biomarker of diabetes – fasting serum glucose and 2hr glucose.	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	Both chromium supplementations significantly decreased ($p<0.001$) decreased serum glucose levels.

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	
Cefalu *et al.* (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	- Chromium supplementation significantly ($p<0.005$) decreased the insulin response to the glucose tolerance test compared to the placebo. - Chromium supplementation had no significant ($p>0.05$) effect on glucose or HbA1c levels.
						Placebo	14	-	
Cheng *et al.* (1999)	n/a	Biomarkers of diabetes – fasting and postprandial serum glucose levels	Single administration (follow-up to Anderson *et al.* 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 *et al.* (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	-	

Grant *et al.* (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	- There was no significant ($p>0.05$) difference between the study groups for serum glucose or HbA1c measurements. - There was a significant ($p<0.05$) inverse association between chromium supplementation and serum insulin levels.
						Chromium supplementation	10	200 µg/day niacin-bound chromium	
						Placebo	23	-	
Joseph *et al.* (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 *et al.* (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	- Both chromium supplement groups had significantly ($p<0.05$) lower serum glucose and insulin levels compared to the placebo group. - Compared to the placebo group, HbA1c levels were significantly decreased ($p<0.05$) in the high chromium supplementation group only.
						Low chromium supplementation	10	4 µg/kg bw/day chromium picolinate	
						Placebo	10	-	
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 *et al.* (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 *et al.* (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	-	
Rabinovitz *et al.* (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	- There was a significant ($p<0.01$) inverse association between chromium supplementation and serum glucose and HbA1c levels. - There was no significant ($p>0.05$) association between chromium supplementation and serum insulin levels.
						Placebo	39	-	

Rajpathak *et al.* (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	- There was a significant ($p<0.01$) inverse association between chromium status and the incidence of diabetes in combination with CVD. - However, there was no significant ($p>0.05$) association between chromium status and diabetes incidence alone.
						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	-	
Trow *et al.* (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	- There was a significant ($p<0.05$) decrease in serum glucose over time with chromium + niacin supplementation. - There was no significant ($p>0.05$) change in glucose levels over time with chromium or niacin supplementation alone.
						Niacin supplementation	5	100 mg/day nicotinic acid	
						Chromium + niacin supplementation	6	200 µg/day chromium + 100 mg/day nicotinic acid	
Uusitupa *et al.* (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 *et al.* (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 *et al.* (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	- There was no significant ($p>0.05$) association between chromium status and breast cancer risk amongst the total cohort. - There was, however a significant ($p<0.05$) inverse association between chromium status and breast cancer risk in pre-menopausal women. - The OR between the lowest (<0.52 µg/g) and highest (>2.37 µg/g) toenail concentrations of premenopasual women was 0.47.
						Matched controls	433	n/a	
Kilic *et al.* (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 ($p<0.05$) positive association between chromium status and breast cancer incidence.
						Matched controls	27	n/a	

Pasman *et al.* (1997)	Double-blinded	Clinical – weight (BMI)	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	Chromium supplementation had no significant ($p>0.05$) impact on the weight of subjects.
						Diet + 50 g carbohydrate	11	-	
						Placebo (Diet only)	9	-	
Rogers *et al.* (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	

Appendix 3

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 (β-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 prostrate 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 *et al.* (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 *et al.* (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 *et al.* (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	- The risk of prostrate cancer was inversely associated with retinol intakes. - The odds ratio (OR) for highest vs. lowest quintiles of intake was 0.79.
					Controls	1451	
Cho *et al.* (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	- There was an inverse relationship between retinol intake and breast cancer, however this association was not statistically significant ($p>0.05$). - The relative risk (RR) between the highest quintile of intake compared to lowest was 0.80.
					Cohort	90 655	
Copper *et al.* (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	
Feskanich *et al.* (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	- There was a significantly ($p<0.01$) inverse association between retinol intake from foods and supplements and melanoma incidence - The RR between the lowest (400 mg) and highest (>1800 mg) retinol intake was 0.39.
					Cohort	162000	

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Results
Fontham *et al.* (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	- There was a significant ($p<0.05$) inverse association between retinol intake and adenocarcinoma risk. This risk was more pronounced amongst black subjects. - The OR for this association was 0.64.
					Controls without history of cancer	1274	
Ghadirian *et al.* (1997)	Clinical – colon carcinoma (compared to retinol intake as ascertained by food frequency questionnaire).	Case control	4 years	Persons	Cases of colon carcinoma	402	- There was a significant ($p<0.05$) inverse association between dietary retinol intake and colon cancer risk - The OR for this association was 0.069
					Controls	682	
Giovannucci *et al.* (1995)	Clinical - prostrate cancer (compared to retinol intake as ascertained by food frequency questionnaire)	Prospective cohort	6 years	Men	Cases of prostrate cancer	812	No consistent association was observed for dietary retinol and risk of prostrate cancer
					Cohort	47894	
Kushi *et al.* (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 *et al.* (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	- There was a significant ($p<0.05$) inverse relationship between retinol intake and melanoma risk. - Adjusted OR for this association = 0.57.
					Controls	538	
Zhu *et al.* (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	- Vitamin A concentration of breast adipose tissue was no different between the two groups. - Vitamin A intake was not statistically ($p>0.05$) different between cases and controls. - Vitamin A concentration of breast adipose tissue had a significant ($p<0.05$) correlation with dietary intake in breast cancer cases only.
					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 *et al.* (2002)	Clinical – hip facture (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	- There was a significant ($p<0.01$) positive association between total vitamin A intake and the incidence of hip fracture. This increased risk was attributable primarily to retinol. - The RR between the lowest (<500 µg/day) and highest (>2000 mg/day) quintiles of retinol intake was 1.89.
					Cohort	72 337	
Lim *et al.* (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 *et al.* (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	- There was a significant ($p<0.01$) association between retinol intake and hip fracture risk. - For every 1 mg increase in retinol intake risk for hip fracture increased by 68%.
					Controls	873	

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

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Results
Chasan-Taber *et al.* (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.

Appendix 4

Assessment of Health Benefit: β-carotene

A review of abstracts refined the 141 β-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 β-carotene against health outcomes were included, as there is evidence showing that serum β-carotene is reflective of a change in dietary β-carotene intake (United States Institute of Medicine, 2000b).

The available evidence used to assess β-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 β-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 β-carotene intakes, and eight articles that showed no significant association between CHD endpoints and β-carotene intakes.

The greatest number of articles (50) on β-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 β-carotene intakes. Nineteen articles showed a significant inverse relationship between cancer endpoints and β-carotene intakes. Six of the 50 cancer articles were intervention studies, of which only two showed an inverse relationship between increased β-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 β-carotene intakes above the RDI.

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

β-carotene is assigned an evidence level of 1

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

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Asherio *et al.* (1999)	n/a	Clinical – ischaemic and haemorrhagic stroke (compared to β-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 β-carotene intake.
						Ischaemic stroke	210	n/a	
						Haemorrhagic stroke	70	n/a	
Bolton-Smith *et al.* (1992)	n/a	Clinical – diagnosed and undiagnosed CHD (compared to β-carotene intake as measured by food frequency questionnaire).	Cross sectional study	10 years	Adult persons	Diagnosed CHD males	369	n/a	- CHD risk was significantly ($p<0.05$) lower between the highest and lowest quintiles of β-carotene intake for undiagnosed males. - There was no significant ($p>0.05$) difference in the risk of CHD between the highest and lowest quintiles of β-carotene intake for undiagnosed female or diagnosed CHD subjects.
						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 *et al.* (1997)	n/a	Clinical – cases of stroke (compared to β-carotene intake)	Cohort	46 years	Middle-aged males	Cases of stroke	222	n/a	- There was no significant ($p>0.05$) association between β-carotene intakes and the risk of stroke. - Adjusted RR between the highest and lowest intake of β-carotene was 0.84.

de Lorgeril *et al.* (2001)	n/a	Biomarkers of congestive heart failure – peak exercise oxygen consumption, and left ventricular ejection function (compared to β-carotene intake)	Case-control	Not reported	Persons	Cases of congestive heart failure	21	n/a	- Serum β-carotene was inversely associated with the two biomarkers endpoints ($p<0.05$). - There was no significant ($p>0.05$) association between dietary β-carotene and the study endpoints.
						Age and gender matched controls	21	n/a	
Do *et al.* (2003)	n/a	Clinical – breast cancer (compared to β-carotene intake as measured by food frequency questionnaire)	Case-control	2 years	Females aged 20-69 years	Cases if breast cancer	224	n/a	The intake of β-carotene was inversely, but not significantly ($p>0.05$) associated with breast cancer.
						Age matched controls	299	n/a	
Genkinger *et al.* (2004)	n/a	Clinical – mortality from cancer, CHD and all causes (compared to β-carotene intake as measured by a food frequency questionnaire)	Cohort	15 years	6151 persons	Cases of cancer	307	n/a	β-carotene intakes had no significant ($p>0.05$) impact on the mortality from CHD.
Hak *et al.* (2003)	Double - blinded	Clinical – MI incidence (compared to β-carotene intake as measured by food frequency questionnaire)	Randomised clinical trial	5 years	Male physicians aged 40-84	β-carotene supplement intake	531	50 mg/day	- There was no significant ($p>0.05$) difference in the incidence of Mi between the two study groups. - There was no significant ($p>0.05$) association between β-carotene intake and the risk of MI.
						Placebo intake	531	-	

Hak *et al.* (2004)	n/a	Clinical – stroke (compared to serum β-carotene levels)	Case-control	13 years	Male physicians aged 45-70 years	Cases of stroke	297	n/a	- There was a significant ($p>0.05$) inverse association between serum β-carotene levels and the risk of stroke. - The OR between the lowest and highest β-carotene intakes was 0.62.
						Age matched controls	297	n/a	
Hirvonen *et al.* (2000)	n/a	Clinical – stroke events (compared to β-carotene intake measured by a food frequency questionnaire)	Cohort	6.1 years	Male smokers	Cerebral infarction cases	736	n/a	- The risk of cerebral infarction was significantly ($p<0.001$) reduced with increasing dietary β-carotene intake. - The RR of cerebral infarction between 1st (0.81 mg/day) and 4th (3.69 mg/day) quintiles of dietary β-carotene intake was 0.74. - Dietary β-carotene intake was not significantly associated ($p>0.05$) with intracerebral haemorrhage or subarachinoid haemorrhage.
						Subarachinoid haemorrhage cases	83	n/a	
						Intracerebral haemorrhage cases	95	n/a	
Klipstein-Grobusch *et al.* (1999)	n/a	Clinical – myocardial infarction (MI) (compared to β-carotene intake measured by food frequency questionnaire)	Cohort	4 years	4802 persons aged ≥ 55 years	Cases of MI	173	n/a	- There was a significant ($p<0.02$) inverse association between β-carotene intake and the risk of MI. - The OR between the lowest (<1.13 mg/day) and highest (>1.57 mg/day) intakes of β-carotene was 0.55.
Kardinaal *et al.* (1995)	n/a	Clinical – acute MI (compared to serum β-carotene)	Case-control	2 years	Males aged < 70 years	Cases of acute MI	674	n/a	Tissue β-carotene levels were significantly ($p<0.05$) lower in cases compared to controls.
						Age matched controls	725	n/a	

Klipstein-Grobusch *et al.* (2001)	n/a	Clinical – peripheral arterial disease incidence (compared to dietary β-carotene intake measured by a food frequency questionnaire)	Cohort	4 years	4367 persons aged ≥ 55 years	Female cases of peripheral arterial disease	370	n/a	β-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 *et al.* (2003b)	n/a	Clinical – coronary artery disease including fatal and non-fatal MI (compared to β-carotene intake measured by food frequency questionnaire)	Cohort	10 years	73286 females aged 30-55 years	Cases of coronary artery disease	998	n/a	- There was a significant ($p<0.05$) inverse association between β-carotene intake and the risk of coronary artery disease. - The OR between the lowest (1.72 mg/day) and highest (7.64 mg/day) intakes of β-carotene was 0.74.
Rapola *et al.* (1997)	Double-blinding	Clinical – non-fatal MI and fatal CHD	Randomised controlled trial	5.3 years	Male smokers	β-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 two groups.
						Placebo intake group	438	-	
Singh *et al.* (1994)	n/a	Clinical – incident of coronary artery disease (compared to β-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	β-carotene intakes were significantly ($p<0.01$) lower in individuals with coronary artery disease compared to those without CHD risk factors.
Singh *et al.* (1995)	n/a	Clinical – coronary artery disease (compared to β-carotene intake)	Cross-sectional study	Not reported	Persons aged 50-84 years	Total population	72	n/a	β-carotene intakes were significantly ($p>0.05$) lower in individuals with coronary artery disease compared to those without.

Tavani *et al.* (1997)	n/a	Clinical – non-fatal acute MI (compared to β-carotene intake)	Case-control	9 years	Females	Cases of non-fatal acute MI	433	n/a	- There was a significant ($p<0.01$) inverse association between β-carotene intake and the risk of acute MI. - The OR between the lowest and highest intakes of β-carotene was 0.5.
						Controls	869	n/a	
van Poppel *et al.* (1994)	Double - blinded	Biomarkers of CHD – total cholesterol, HDL, apolipoproteins A-I and B-100 and (a)	Randomised controlled trial	14 weeks	Male smokers	β-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 β-Carotene and Cancer

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Adzersen *et al.* (2003)	n/a	Clinical – primary breast cancer (compared to β-carotene intake)	Case-control	2 years	Females	Cases of primary breast cancer	310	n/a	- There was no significant ($p>0.05$) association between β-carotene intake and breast cancer risk. - The OR between the lowest and highest β-carotene intakes was 0.46.
						Controls without dietary or endocrine conditions	353	n/a	
Albanes *et al.* (1996)	?	Clinical – lung cancer incidence	Randomised controlled trial	5-8 years	Male smokers aged 50-69 years	β-carotene supplement intake	?	20 mg/day	- There was a significant ($p<0.05$) increase in the incidence of lung cancer for the β-carotene supplement group compared to the placebo group. - The RR for β-carotene supplementation was 1.16.
						Placebo intake	?	-	
Albanes *et al.* (2000)	Double-blinded	Clinical – colorectal cancer incidence	Randomised controlled trial (sub-set of ATBC trial)	8 years	Male smokers aged 50-69 years	β-carotene supplement intake	7280	20 mg/day	β-carotene supplementation had no significant impact on the incidence between the two study groups ($p>0.05$).
						Placebo intake	7280	-	
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 β-carotene supplement intake	7280	20 mg/day	- The β-carotene supplement group had a significantly ($p<0.01$) higher incidence of lung cancer compared to the placebo group. - Prostate cancer incidence was increased in the β-carotene supplement group, however the significance was not reported.
						Placebo intake	7280	-	

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Bertone *et al.* (2001)	n/a	Clinical – ovarian cancer (compared to dietary and supplemental β-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 β-carotene intake.
						Controls	3129	n/a	
Bohlke *et al.* (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	- There was no association between β-carotene intake and breast cancer for post-menopausal women. - There was an inverse association between β-carotene intake and breast cancer for pre-menopausal women.
						Healthy controls	1548	n/a	
Candelora *et al.* (1992)	n/a	Clinical – lung cancer (compared to β-carotene intake as measured by food frequency questionnaire)	Case-control	3 years	Female non-smokers	Cases of lung cancer	124	n/a	- There was no significant ($p>0.05$) inverse association between β-carotene intake and lung cancer. - The OR between the lowest and highest β-carotene intakes was 0.4.
						Controls	263	n/a	
Ching *et al.* (2002)	n/a	Clinical – breast cancer (compared to serum β-carotene levels)	Case-control	2 years	Females aged 30-84 years	Cases of breast cancer	341	n/a	- There was a significant ($p<0.02$) inverse association between serum β-carotene levels and breast cancer. - The adjusted OR between the lowest ($\leq$0.4 μmol/L) and highest ($\geq$1.1 μmol/L) quartiles of serum β-carotene was 0.47.
						Age matched controls	151	n/a	

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Cramer *et al.* (2001)	n/a	Clinical – ovarian cancer (compared to β-carotene intake as measured by food frequency questionnaire)	Case-control	5 years	Females	Cases of ovarian cancer	549	n/a	- There was a significant ($p<0.05$) inverse association between β-carotene intake and ovarian cancer. - The adjusted OR between the lowest (≤2.3 mg/day) and highest (>7.2 mg/day) quintiles of intake was 0.58
						Controls	516	n/a	
Daviglus *et al.* (1996)	n/a	Clinical – cases of prostate cancer (compared to β-carotene intake)	Cohort	30 years	Middle-aged males	Cases of prostate cancer	132	n/a	- No significant ($p>0.05$) association between the intake of β-carotene and the risk of prostate cancer. - Relative risks (RR) between the lowest and highest intake of β-carotene was 1.27.
Franceschi *et al.* (1999)	n/a	Clinical – colorectal cancer (compared to dietary β-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 β-carotene intake and the risk of colorectal cancer.
						Controls	4154	n/a	
Genkinger *et al.* (2004)	n/a	Clinical – mortality from cancer, CHD and all causes (compared to β-carotene intake as measured by food frequency questionnaire)	Cohort	15 years	6151 persons	Cases of cancer	307	n/a	β-carotene intakes had no significant ($p>0.05$) impact on the mortality from cancer.
Giovannucci *et al.* (1995)	n/a	Clinical – prostate cancer (compared to β-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 β-carotene intake and the risk of prostate cancer.

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Green *et al.* (1999)	Double-blinded	Clinical – skin cancer	Randomised clinical trial	4.5 years	Persons	β-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 *et al.* (1990)	Double-blinded	Clinical – skin cancer	Randomised controlled trial	5 years	Persons with non-melanoma skin cancer	β-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 *et al.* (1994)	Double-blinded	Clinical – incidence of new colon cancer polyps	Randomised controlled trial	4 years	Persons with history of colon cancer	β-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	-	
Hansson *et al.* (1994)	n/a	Clinical – gastric cancer (compared to dietary and supplementary β-carotene intake)	Case-control	20 years	Persons	Cases of gastric cancer	338	n/a	- There was a significant ($p<0.01$) inverse association between β-carotene intake and the risk of gastric cancer. - The OR between the lowest (0.8 mg/day) and highest (4.3 mg/day) quartile of intake was 0.52.
						Controls	679	n/a	
Holmberg *et al.* (1994)	n/a	Clinical – breast cancer (compared to β-carotene intake)	Case-control	3 years	Females	Cases of breast cancer	265	n/a	- There was a significant ($p<0.05$) inverse association between β-carotene intake and the risk of breast cancer. - The OR between the lowest (2.7-3.9 mg/day) and highest (>5.3 mg/day) tertiles of intake was 0.6.
						Age matched controls	432	n/a	

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Jain *et al.* (2000)	n/a	Clinical – endometrial cancer (compared to β-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 β-carotene intake.
Kaaks *et al.* (Kaaks *et al*., 1998)	n/a	Clinical – gastrointestinal cancers (compared to β-carotene intake as measured by a diet history)	Case-control	4 years	Persons aged 35-74 years	Cases of gastrointestinal cancer	201	n/a	- There was a significantly ($p<0.001$) inverse association between β-carotene intake and the risk of gastrointestinal cancer. - The OR between the lowest and highest quartile of intake was 0.5.
						Controls	2851	n/a	
Le Marchand *et al.* (1993)	n/a	Clinical – lung cancer (compared to β-carotene intake as measured by diet history)	Case-control	2 years	Persons	Cases of lung cancer	332	n/a	- There was a significant ($p<0.01$) inverse association between the intake of β-carotene and the risk of lung cancer. - The OR between the lowest and highest quartiles of intake was 0.5 and 0.3 for males and females respectively.
						Age matched controls	865	n/a	

McCann *et al.* (2001)	n/a	Clinical – ovarian cancer (compared to β-carotene intake as measured by food frequency questionnaire)	Case-control	12 years	Females aged 20-87 years	Cases of ovarian cancer	496	n/a	- There was a significant ($p<0.05$) inverse association between the intake of β-carotene and the risk of ovarian cancer. - The OR between the lowest and highest intakes was 0.68.
						Controls	1425	n/a	
Männisto *et al.* (2004)	n/a	Clinical – lung cancer (compared to β-carotene intake as measured by food frequency questionnaire)	Pooled cohort	7-16 years	399765 Persons	Cases of lung cancer	3155	n/a	- When adjusted for age, β-carotene intake was inversely associated with the risk for lung cancer ($p<0.05$). - When controlling for other confounding variables, the inverse association was insignificant ($p>0.05$). - The OR between the lowest and highest intakes was 0.98.
Mayne *et al.* (1994)	n/a	Clinical – lung cancer (compared to β-carotene intake as measured by diet history)	Case-control	3 years	Persons	Cases of lung cancer	413	n/a	- There was a significant ($p<0.05$) inverse association between the intake of dietary β-carotene and the risk of lung cancer. - The OR between the lowest and highest β-carotene intakes was 0.7.
						Age and gender matched controls	413	n/a	
Michaud *et al.* (2000)	n/a	Clinical – lung cancer (compared to β-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 β-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 *et al.* (2002)	n/a	Clinical – bladder cancer (compared to β-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 β-carotene intake and the risk of bladder cancer.
Murtaugh *et al.* (2004)	n/a	Clinical – rectal cancer (compared to β-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 β-carotene intake and the risk of rectal cancer.
						Age and gender matched controls	1205	n/a	
Negri *et al.* (1996)	n/a	Clinical – breast cancer (compared to β-carotene intake as measured by food frequency questionnaire)	Case-control	3 years	Females	Cases of histologically confirmed breast cancer	2569	n/a	- There was an inverse association between the intake of dietary β-carotene and the risk of breast cancer. - The OR between the lowest and highest β-carotene intakes was 0.84.
						Controls with no history of cancer	2588	n/a	
Nkondjock and Ghadirian (2004)	n/a	Clinical – breast cancer (compared to β-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 β-carotene intake and the risk of breast cancer.
						Age matched controls	668	n/a	
Norrish *et al.* (2000)	n/a	Clinical – prostate cancer (compared to β-carotene intake)	Case-control	2 years	Males	Cases of prostate cancer	317	n/a	There was no significant ($p>0.05$) association between β-carotene intake and the risk of prostate cancer.
						Controls	480	n/a	

Nyberg *et al.* (1998)	n/a	Clinical – lung cancer (compared to β-carotene intake)	Case-control	6 years	Persons aged > 30 years	Cases of lung cancer	124	n/a	- There was a significantly ($p<0.05$) inverse association between β-carotene intake and the risk of lung cancer. - The OR between the lowest and highest quintiles of intake was 0.47.
						Controls	235	n/a	
Ocke *et al.* (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 β-carotene intake and the risk of lung cancer.
Ohno *et al.* (1988)	n/a	Clinical – prostate cancer (compared to β-carotene intake as measured by food frequency questionnaire)	Case-control	3 years	Males	Cases of prostate cancer	100	n/a	- There was a significant ($p<0.01$) inverse association between the intake of dietary β-carotene and the risk of prostate cancer. - The RR between the lowest and highest β-carotene intakes was 0.48.
						Controls	100	n/a	
Rohan *et al.* (2002)	n/a	Clinical – lung cancer (compared to β-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 β-carotene intake and lung cancer.
						Controls	5361	n/a	
Schuurman *et al.* (2002)	n/a	Clinical – prostate cancer (compared to β-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 β-carotene intake and the risk of prostate cancer.

Shibata *et al.* (1992)	n/a	Clinical – cancer incidence (compared to β-carotene intake)	Cohort	8 years	11580 persons	Cases of cancer	1335	n/a	There was no significant ($p>0.05$) association between β-carotene intake and cancer incidence.
Slattery *et al.* (1990)	n/a	Clinical – cervical cancer (compared to β-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 β-carotene and the risk of cervical cancer.
						Age matched controls	408	n/a	
Stefani *et al.* (1999)	n/a	Clinical – lung cancer (compared to β-carotene intake)	Case-control	4 years	Persons aged 30-89 years	Cases of lung cancer	541	n/a	- There was a significant ($p<0.001$) inverse association between the adjusted intake of dietary β-carotene and the risk of lung cancer. - The RR between the lowest (<1.94 mg/day) and highest (>5.86 mg/day) quartiles of β-carotene intake was 0.3.
						Controls	540	n/a	
Tavani *et al.* (1994)	n/a	Clinical – oesophageal cancer (compared to dietary β-carotene intake as measured by food frequency questionnaire)	Case-control	8 years	Persons	Histologically confirmed cases of oesophageal cancer)	316	n/a	- There was a significant ($p<0.05$) inverse association between the adjusted intake of β-carotene and the risk of oesophageal cancer. - The RR between cases and controls was 0.4.
						Controls	230	n/a	

Tavani *et al.* (1999)	n/a	Clinical – breast cancer (compared to dietary β-carotene intake as measured by food frequency questionnaire)	Case-control	11 years	Females	Cases of histologically confirmed breast cancer	579	n/a	- There was a significant ($p<0.01$) inverse association between the adjusted intake of β-carotene and the risk of breast cancer. - The RR between the lowest (32 IU/day) and highest (240 IU/day) quintiles of intake was 0.5.
						Controls	668	n/a	
Terry *et al.* (2002)	n/a	Clinical – colorectal cancer (compared to β-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 β-carotene intakes and the risk of colorectal cancer.
						Controls	5334	n/a	
Varis *et al.* (1998)	Double - blinded	Clinical – gastric cancer	Randomised controlled trail (subset of the ATBC trial)	5.1 years	Males aged 50-69 years with gastritis	β-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 *et al.* (1997)	n/a	Clinical – breast cancer (compared to β-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 β-carotene intake and the risk of breast cancer.
Voorrips *et al.* (2000)	n/a	Clinical – lung cancer (compared to dietary and supplemental β-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 β-carotene intake and the risk of lung cancer.

West *et al.* (1989)	n/a	Clinical – colon cancer (compared to dietary β-carotene intake as measured by food frequency questionnaire)	Case-control	4 years	Persons	Cases of colon cancer	231	n/a	- There was an inverse association between the adjusted intake of β-carotene and the risk of colon cancer. - The RR between the lowest and highest β-carotene intake was 0.5.
						Controls	391	n/a	
West *et al.* (1991)	n/a	Clinical – prostate cancer (compared to β-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 β-carotene intake and the risk of prostate cancer.
						Controls	679	n/a	
Wright *et al.* (2003)	n/a	Clinical – lung cancer (compared to β-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 β-carotene and the risk of lung cancer.
						Age matched controls	624	n/a	
Wu *et al.* (2004)	n/a	Clinical – prostate cancer (compared to dietary β-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 β-carotene intake and the risk of prostate cancer.
						Age matched controls	450	n/a	

Zhang *et al.* (1999)	n/a	Clinical – breast cancer (compared to dietary and supplemental β-carotene intake as measured by food frequency questionnaire)	Cohort	14 years	83234 females aged 30-55 years	Cases of breast cancer	2697	n/a	- Adjusted β-carotene intakes were inversely ($p<0.05$) associated with the risk of breast cancer in pre-menopausal women. - The RR between the lowest and highest β-carotene intakes of pre-menopausal women was 0.84. - There was an inverse, but non-significant ($p>0.05$) association between supplemental and dietary β-carotene intake and the risk of breast cancer in post-menopausal women.

Table A4-3: Identified Studies on β-Carotene and Other Health Outcomes

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

Appendix 5

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 *et al.* (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 *et al.* (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	- CHD risk was significantly ($p<0.05$) lower between the highest and lowest quintiles of vitamin C intake for undiagnosed males. - There was no significant ($p>0.05$) difference in the risk of CHD between the highest and lowest quintiles of vitamin C intake for undiagnosed female or diagnosed CHD subjects.
						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 *et al.* (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	- There was no significant ($p>0.05$) association between vitamin C intakes and the risk of stroke. - The RR between the highest and lowest vitamin C intake was 0.71.

de Lorgeril *et al.* (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 *et al.* (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 *et al.* (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	- Vitamin C intake was associated with a significantly ($p<0.05$) decreased standard mortality ratio (SMR) for all causes. - Vitamin C intake was associated with a decreased SMR for CVD, however its statistical significance was not reported.
						Death from CVD	929	n/a	
Gale *et al.* (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	- Adjusted RR between highest (45 mg/day) and lowest tertile (28 mg/day) of vitamin C was 0.5 ($p<0.003$). - Vitamin C was positively associated with an intake of other macro and micronutrients.
						Total deaths	643	n/a	
						Mortality from stroke	124	n/a	

Hirvonen *et al.* (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	- The RR of stroke as intracerebral haemorrhage between the 1st (52 mg/day) and 4th (141 mg/day) quintiles of dietary vitamin C intake was 0.39 ($p<0.05$). - Dietary vitamin C intake was not significantly associated ($p>0.05$) with cerebral infarction or subarachinoid haemorrhage.
						Subarachinoid haemorrhage cases	83	n/a	
						Intracerebral haemorrhage cases	95	n/a	
Klipstein-Grobusch *et al.* (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 *et al.* (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	- There was a significant ($p<0.01$) inverse association between vitamin C intake and peripheral arterial disease in women. The RR between highest and lowest quartile of intake = 0.64. - There was no significant ($p>0.05$) association for males.
						Male cases of peripheral arterial disease	204	n/a	
Knekt *et al.* (1994)	n/a	Clinical – CHD mortality (compared to vitamin C intake as measured by 1yr 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	

Kritchevsky *et al.* (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 *et al.* (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	- There was a positive association between increasing vitamin C intake and CHD mortality ($p<0.05$). - The RR between the lowest ($\leq$112 mg/day) and highest ($\geq$391 mg/day) vitamin C intakes was 1.08 and 1.49 for CHD mortality respectively.
Lee *et al.* (2004)	n/a	Clinical – CHD, coronary artery disease and stroke (compared to dietary and supplemental vitamin C intake measured by food frequency questionnaire)	Cohort	9 years	41836 post-menopausal women aged 55-69 years	1st quintile (vitamin C intake = 85 mg/day)	315	n/a	- There was a significant positive association between vitamin C intake and CHD ($p<0.01$), coronary artery disease ($p<0.01$) and stroke incidence ($p<0.05$). - 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.
						2nd quintile (vitamin C intake = 139 mg/day)	413	n/a	
						3rd quintile (vitamin C intake = 189 mg/day)	433	n/a	
						4th quintile (vitamin C intake = 279 mg/day)	413	n/a	
						5th quintile (vitamin C intake = 667 mg/day)	349	n/a	

Leng *et al.* (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 *et al.* (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 *et al.* (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	- Vitamin C intake was significantly ($p<0.05$) associated with non-fatal ischaemic heart disease incidence. - The OR between the lowest (<141.8 mg/day) and highest (≥220.2 mg/day) tertiles of vitamin C intake was 0.34.
						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	- Adjusted vitamin C intake had a significant ($p<0.01$) inverse association with serum LDL and apolipoprotein B. - Adjusted vitamin C intake had a significant positive association with serum HDL ($p<0.05$) and apolipoprotein A1 ($p<0.01$).

Osganian *et al.* (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	- Adjusted total vitamin C intake had a significant ($p<0.001$) inverse association with CHD risk. - The RR between the lowest (70 mg/day) and highest (704 mg/day) quintiles of vitamin C intake =0.7. - Vitamin C supplement use >400 mg/day or >2 years was associated with a reduced CHD risk compared to no use (RR = 0.72).
Rimm *et al.* (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 *et al.* (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	- Adjusted total vitamin C intake had an inverse association with mortality from heart disease, however this result was not significant ($p>0.05$). - The RR between the lowest and highest vitamin C intakes was 0.38.

Todd *et al.* (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	- Adjusted total vitamin C intake had a significantly ($p<0.01$) inverse association with CHD in males. - There was a significant ($p<0.01$) positive association between total vitamin C intake and CHD in females.
						Cases of undiagnosed CHD	1497	n/a	
						Age and gender matched controls	7618	n/a	
Tofler *et al.* (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 wash out period of 4 weeks	Healthy males aged 30-65 years	Vitamin C supplement intake	18	2 g/day	- There was a significant decrease in total cholesterol ($p<0.01$), and a significant increase in HDL ($p<0.05$) with vitamin C intake - There was no significant ($p>0.05$) association between vitamin C intake and the other biomarkers.
						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 *et al.* (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 *et al.* (1995)	11 years	1824 persons	Female CHD cases	37	n/a	- Adjusted dietary vitamin C intake was not significantly ($p>0.05$) related to CHD incidence. The RR between lowest (45 mg/day) and highest (152 mg/day) quintiles of intake was 1.23. - Supplemental vitamin C intake up to 700mg/day significantly reduced CHD incidence compared to no intake (RR = 0.87, $p<0.02$). - There was no significant impact of vitamin C supplement intake on CHD mortality. - There was no significant ($p>0.05$) heterogeneity between the vitamin C results of the 9 cohorts.
							Male CHD cases	82	n/a	
				Knekt *et al.* (1994)	6 years	5133 persons aged 30-69 years	Female CHD deaths	47	n/a	
							Male CHD deaths	148	n/a	
				Kritchevsky *et al.* (1995)	11 years	11307 persons	Female CHD cases	210	n/a	
							Male CHD cases	416	n/a	
				Kushi *et al.* (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 *et al.* (1996)	8 years	4739 males	CHD cases	413	n/a	
				Rimm *et al.* (1993)	4 years	39910 males aged 40-75 years	CHD cases	607	n/a	
				Stampfer *et al.* (1993) part 1	6 years	48639 females	CHD cases	375	n/a	
				Stampfer *et al.* (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 *et al.* (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	- There was a significant ($p<0.01$) inverse association and vitamin C intake and lung cancer in males. - Vitamin C intake had no association ($p>0.05$) with lung cancer incidence in females.
				25279 females	Females with lung cancer	130	n/a	
Bohlke *et al.* (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	- There was no significant ($p>0.05$) association between vitamin C intake and breast cancer for post-menopausal women. - There was an inverse but non-significant ($p<0.05$) association between vitamin C intake and breast cancer for pre-menopausal women. - The OR between the lowest (<143 mg/day) and highest (>343 mg/day) intake of vitamin C by pre-menopausal women was 0.45.
					Healthy controls	1548	n/a	
Bueno de Mesquita *et al.* (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	- There was a significant ($p<0.05$) inverse association between adjusted vitamin C intake and pancreatic cancer incidence in women but not men. - The OR between the lowest and highest quintiles of vitamin C intake was 0.75
					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 *et al.* (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	- There was no significant ($p>0.05$) association between vitamin C intake and the risk of prostate cancer. - Relative risk (RR) between the lowest ($\leq$74 mg/day) and highest (>121 mg/day) intake of vitamin C was 1.27.
Fontham *et al.* (1988)	Clinical – lung cancer (compared to dietary vitamin C intake as measured by food frequency questionnaire)	Case-control	3 years	Persons	Cases of lung cancer	1253	n/a	- There was a significant ($p<0.001$) inverse association between adjusted vitamin C intake and lung cancer incidence. - The OR between lowest and highest tertile of vitamin C intake = 0.67.
					Controls without history of cancer	1274	n/a	
Freudenheim *et al.* (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 *et al.* (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 *et al.* (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	- There was a significant ($p<0.05$) inverse association between vitamin C intake and breast cancer for post-menopausal but not pre-menopausal women. - The RR between the lowest (59 mg/day) and highest (305 mg./day) quintile of intake = 0.82.
					Controls	6095	n/a	
Howe *et al.* (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	- There was a significant ($p<0.001$) inverse association between vitamin C intake and pancreatic cancer. - The RR between lowest ($\leq$72 mg/day) and highest ($\geq$195 mg/day) quintile of intake = 0.41.
					Controls without a history of cancer	1669	n/a	
Knekt *et al.* (1991)	Clinical – lung cancer (compared to dietary vitamin C intake as measured by a diet history)	Cohort	20 years	4538 males aged 20-69 years	Cases of lung cancer	117	n/a	- There was a significant ($p<0.01$) inverse association between vitamin C intake and lung cancer. - The RR between highest and lowest tertile of intake = 0.3.

Kristal *et al.* (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	- There was an inverse but insignificant ($p>0.05$) association between vitamin C supplement intake and prostate cancer incidence. - The adjusted OR between highest and lowest categories of intake was 0.77.
					<1/ week	6.2% of cases	n/a	
					1-6/week	10.6% of cases	n/a	
					≥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	
					≥7/week	21.9 of cases	n/a	
Kushi *et al.* (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 *et al.* (1997)	Clinical – histologically confirmed colorectal cancer (compared to dietary vitamin C as measured by food frequency questionnaire)	Case-control	4 years	Persons aged 23-74 years	Cases of colorectal cancer	1953	n/a	- There was a significant ($p<0.01$) inverse association between vitamin C intake and colorectal cancer. - The OR between highest and lowest quintile of intake = 0.73.
					Healthy controls (no history of cancer)	4154	n/a	

Levi *et al.* (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	- Vitamin C intake was inversely associated with the risk of colorectal cancer ($p<0.01$). - The OR between the lowest ($\leq$65 mg/day) and highest ($\geq$186 mg/day) tertile of intake was 0.45.
					Controls without diet-related illness	491	n/a	
Negri *et al.* (1996)	Clinical – breast cancer (compared to dietary vitamin C intake as measured by food frequency questionnaire)	Case-control	3 years	Females aged 23-74 years	Cases of histologically confirmed breast cancer	2569	n/a	There was no significant ($p>0.05$) difference in vitamin C intake between cases and controls.
					Controls with no history of cancer	2588	n/a	
Ocke *et al.* (1997)	Clinical – lung cancer (compared to dietary and supplemental vitamin C intake as measured by diet history)	Cohort	19 years	561 males	Cases of lung cancer	54	n/a	There was no significant ($p>0.05$) association between vitamin C intake and the risk of lung cancer.
Satia-Abouta *et al.* (2003)	Clinical – colon cancer (compared to dietary and supplement vitamin C intake as measured by food frequency questionnaire)	Retrospective case-control	1 year	Persons aged 40-80 years	Cases of histologically confirmed colon cancer	613	n/a	- Adjusted total vitamin C intake (including supplements) had a significant ($p<0.05$) inverse association with the incidence of colon cancer. - The OR between the lowest (59 mg/day) and highest (644 mg/day) vitamin C intakes was 0.5.
					Aged matched controls	996	n/a	

Shibata *et al.* (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	- Adjusted dietary vitamin C intake had no significant ($p<0.05$) association with the incidence of cancer. - There was a significant ($p<0.05$) inverse association between supplemental vitamin C intake and the risk of bladder cancer in men, and breast cancer in women.
Stefani *et al.* (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 *et al.* (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.
Voorrips *et al.* (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	- Dietary vitamin C intake was inversely associated with the incidence of lung cancer ($p<0.05$). - The RR between the lowest (51 mg/day) and highest (138 mg/day) dietary vitamin C quintiles was 0.77. - Supplemental vitamin C intake was not significantly ($p>0.05$) associated with lung cancer incidence.

Wassertheil-Smoller *et al.* (1981)	Clinical – cervial 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 *et al.* (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	- Dietary vitamin C intake was inversely associated with the incidence of lung cancer ($p<0.01$). - The RR between the lowest (<23 mg/day) and highest (>113 mg/day) dietary vitamin C quintiles was 0.66.
Zatonski *et al.* (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	- Vitamin C intake was inversely associated with the risk of pancreatic cancer ($p<0.01$). - The RR between the lowest (≤83 mg/day) and highest (≥135 mg/day) quartile of vitamin C intakes was 0.37.
					Age matched controls	195	n/a	
Zeegers *et al.* (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	- Adjusted total vitamin C intake had an inverse association with the incidence of bladder cancer, however this result was not significant ($p>0.05$). - Supplemental vitamin C intake was not associated with bladder cancer, although the statistical significance of this result was not reported.
					Controls without history of cancer	3123	n/a	

Zhang *et al.* (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	- Each adjusted vitamin C intake of 100 mg/day increment = 0.017 g/cm^2 increase in neck and hip BMD ($p<0.005$). - The significant BMD increases were not observed with calcium intakes >500mg. - There was no significant association ($p>0.05$) between vitamin C intake and spine BMD.
Leville *et al.* (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		- There was no significant ($p>0.05$) association between vitamin C intake and BMD. - Women with supplement use $\geq$ 10 years had a significantly ($p<0.05$) higher BMD than those with use < 10 years.
Morton *et al.* (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	- Regular Vitamin C supplement users had significantly ($p<0.02$) higher neck and hip BMD compared to non-users. - Supplement use was not significantly associated with spine BMD ($p>0.05$). - There was a significant linear trend in vitamin C supplement use and ultradistal BMD ($p<0.04$), but not at other bone sites.
					Non-users of vitamin C supplements	717	

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Results
Wang *et al.* (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 *et al.* (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	- Dietary vitamin C was not associated with the risk of cataract extraction. - RR of cataracts was 0.5 for women using vitamin C supplements for more than 10 years ($p<0.05$), however this effect became insignificant ($p>0.05$) when the RR was adjusted for confounding factors.
Hemila *et al.* (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 *et al.* (2003)	Double-blinding	Biomarker of gastritis – serum pepsinogen and *H.pylori* (serum antibodies)	Pseudorandomised controlled trial	5 years	Males diagnosed with chronic gastritis	Supplement group 1	144	50 mg/day vitamin C	- In both groups, the *H.pylori* count significantly decreased over the study ($p<0.05$), however there was no difference between groups ($p>0.05$). - Serum pepsinogen status significantly decreased over the study period ($p<0.001$), however there was no significant difference between groups.
						Supplement group 2	161	500 mg/day vitamin C	

Appendix 6

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 *et al.* (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 800mg phosphorus, 1200mg calcium,, Days 10-20 with 1600mg/day dietary P.	High P intake was not found to promote bone resorption if the Ca:P ratio is <1:1.5
ChoonHie *et al.* (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 *et al.* (1976)	Clinical – bone density parameters.	Cross sectional	Not reported	Post-menopausal women with osteoporosis	Single group	7	Diet supplemented with phosphorus (inorganic phosphate)	- Bone forming surface decreased and bone resorbing surface increased in all patients. - Bone resorbing surface was highly correlated with total phosphorus intake.

Grimm *et al.* (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 Treatment period Control period	10	Diet with 1700mg P and 1500mg Ca/day (4 weeks) Diet with 3008mg P and 1995mg Ca/day (6 weeks) Diet – as for above (4 weeks	- There were no significant changes in bone-related hormones, markers of bone re-absorption or parameters of renal function. - Phosphorus supplementation caused intestinal distress, soft faeces or mild diarrhoea
Hoppe *et al.* (2000)	Clinical – whole body bone measurements	Cross-sectional	Single time point	10 year old healthy children from Denmark	Single group	105	n/a	- Bone area (size-adjusted) was negatively associated with phosphorus intakes. - Mean intake of phosphorus was 3.3g, which is above the RDI for this age group (1250mg/day).
Mendez *et al.* (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 *et al.* (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 *et al.* (2003)	Clinical - osteoporosis	Case-control	Not reported	Korean premenopausal women	Case - osteoporotic Control – non-osteoporotic	78 78	n/a n/a	Serum levels of phosphorus and calcium showed significant ($p<0.001$) negative correlations with lumbar spine bone mineral density.

Whybro *et al.* (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 800mg P/day	10	Supplemented with 1000mg elemental P	There was no significant change in serum phosphate, osteocalcin or intact parathryin.
		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 deoxypyridinoline.
					Diet+ low P	12	1000mg/day elemental P	
					Diet + moderate P	12	1500mg/day elemental P	
					Diet + high P	12	2000mg/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 *et al.* (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 *et al.* (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 *et al.* (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	- There was an inverse association between phosphorus intake and pharyngeal cancer risk. - The adjusted OR for this relationship was 0.88.
					Controls with no history of cancer	1775	

SooWon *et al.* (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 dieases	105	

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

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Results
Gruchow *et al.* (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 *et al.* (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.

Appendix 7

Assessment of Health Benefit: Vitamin B_{12}

From the 111 vitamin B_{12} 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_{12} against health outcomes were included, as there is evidence showing that serum vitamin B_{12} is reflective of a change in dietary vitamin B_{12} 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_{12} 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_{12} intake above the RDI and cancer endpoints. The majority of these articles (5) also indicated no significant association between cancer endpoints and vitamin B_{12} intakes.

The three remaining articles assessed bone metabolism and gastrointestinal endpoints. The two studies on bone metabolism showed no significant association between vitamin B_{12} intakes above the RDI and bone disorders. The sole gastrointestinal article also showed no significant association between vitamin B_{12} 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_{12} are considered to have no appreciative health benefit.

Vitamin B_{12} is assigned an evidence level of 0

Table A7-1: Identified Studies on Vitamin B_{12} and Coronary Heart Disease

Study	Blinding	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Dose	Results
Appel *et al.* (2000)	Double-blinded	Biomarker of CHD – serum tHcy (compared to serum vitamin B_{12} 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_{12} 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 *et al.* (2001)	n/a	Biomarker of CHD – serum homocysteine (tHcy) (compared to dietary and supplemental vitamin B_{12} intake as measured by food frequency questionnaire)	Cross-sectional	3 years	Persons aged 20-65 years	Males	1275	n/a	- There was a significant ($p<0.001$) inverse association between vitamin B_{12} intakes of both males and females and serum tHcy levels. - However, this result became statistically non-significant ($p>0.05$) when adjusted for confounding variables.
						Females	1160	n/a	
de Bree *et al.* (2003)	n/a	Clinical – CHD mortality (compared to serum vitamin B_{12} 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_{12} levels and the risk of CHD mortality.
						Controls	630	n/a	

He *et al.* (2004)	n/a	Clinical – incidence of ischaemic and haemorrhagic stroke (compared to dietary B_{12} intake as measured by food frequency questionnaire)	Cohort	14 years	43732 males aged 40-75 years	Cases of ischaemic stroke	455	n/a	- There was a significant (p=0.05) inverse association between vitamin B_{12} intakes and the risk of ischaemic stroke. - The RR between the lowest (5 µg/day) and highest (29 µg/day) intake of vitamin B_{12} was 0.73 for ischaemic stroke. - There was no significant (p>0.05) association between vitamin B_{12} intakes and the risk of haemorrhagic stroke.
						Cases of haemorrhagic stroke	125	n/a	
Huerta *et al.* (2004)	n/a	Biomarker of CHD – serum tHcy (compared to dietary vitamin B_{12} 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_{12} intake.
Hung *et al.* (2003)	n/a	Clinical – fatal CHD and CVD (compared to serum vitamin B_{12} 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_{12} 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_{12} intake as measured by food frequency questionnaire, and to serum vitamin B_{12} levels)	Cross-sectional	20 years	Persons aged 30-59 years	Total cohort	5135	n/a	- There was a significant (p<0.0001) inverse association between adjusted plasma vitamin B_{12} and tHcy. - Adjusted dietary vitamin B_{12} intake was not significantly (p>0.05) associated with serum tHcy.
Kelly *et al.* (2003)	n/a	Clinical – incidence of stroke (compared to serum vitamin B_{12} 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_{12} levels and the risk of stroke.
						Age matched controls	147	n/a	

Leowattana *et al.* (2000)	n/a	Clinical – incidence of CAD (compared to serum vitamin B_{12} 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_{12} levels and CAD risk.
						Age matched healthy controls	178	n/a	
Medrano *et al.* (2000)	n/a	Clinical – mortality from CVD (compared to dietary vitamin B_{12} 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_{12} intake and the risk of mortality from CVD.
Mennen *et al.* (2002)	n/a	Biomarker of CHD – serum tHcy (compared to dietary vitamin B_{12} intake as measured by 24-hour diet record, and serum vitamin B_{12} levels)	Cross-sectional	8 years	Persons aged 35-60 years	Total cohort	2070	n/a	- Adjusted serum vitamin B_{12} was not significantly ($p>0.05$) associated with tHcy. - Dietary vitamin B_{12} intake was not significantly ($p>0.05$) associated with tHcy.
Merchant *et al.* (2003)	n/a	Clinical – peripheral arterial disease (compared to dietary vitamin B_{12} intake as measured by food frequency questionnaire)	Cohort	12 years	46036 males aged 40-75 years	Cases of peripheral arterial disease	308	n/a	- There was no significant ($p>0.05$) association between vitamin B_{12} intake and the risk of peripheral arterial disease. - The RR of peripheral arterial disease from the lowest (5 μg/day) to the highest (22 μg/day) intake of vitamin B_{12} was 0.74.
Ortega *et al.* (2002)	n/a	Biomarker of CHD – serum tHcy (compared to compared to dietary vitamin B_{12} 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_{12} intakes and those with intakes above this levels.
Pancharuniti *et al.* (1994)	n/a	Clinical – early onset coronary artery disease (compared to serum vitamin B_{12} 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_{12} levels between cases and controls.
						Age matched controls	108	n/a	

Shimakawa *et al.* (1997)	n/a	Biomarker of CHD – serum tHcy (compared to dietary and supplemental vitamin B_{12} 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 B12 intake and serum tHcy.
						Controls without atherosclerosis	318	n/a	
Siri *et al.* (1998)	n/a	Clinical – coronary atherosclerosis (compared to serum vitamin B_{12} 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_{12} levels and the risk of coronary atherosclerosis.
						Coronary referent controls	88	n/a	
Vrentzos *et al.* (2004)	n/a	Clinical – IHD (compared to dietary vitamin B_{12} intake as measured by a 3-day food record, and serum vitamin B_{12} levels)	Case-control	2 years	Persons aged 33-77 years	Cases of IHD	152	n/a	- Cases had significantly higher intakes of vitamin B_{12} ($p<0.05$), and significantly higher serum vitamin B_{12} levels ($p<0.01$) than controls. - There was, however, no significant ($p>0.05$) linear trend between vitamin B_{12} intakes, serum vitamin B_{12} levels, and the risk of IHD.
						Age and gender matched controls	152	n/a	
Waldmann *et al.* (2004)	n/a	Biomarker of CHD – serum tHcy (compared to serum vitamin B_{12} levels)	Cross-sectional	Not treported	Vegans aged 20-82 years	Total cohort	131	n/a	There was a significant ($p<0.001$) inverse association between serum vitamin B_{12} and tHcy levels when controlled for veganism.
Wasilewska *et al.* (2003)	n/a	Clinical – cardiac problems requiring surgery (compared to serum vitamin B_{12} 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_{12} levels between cases and controls
						Health controls	38	n/a	

Table A7-2: Identified Studies on Vitamin B_{12} and Cancer

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject Group Number	Results
Alberg *et al.* (2000)	Clinical – cervical cancer (compared to serum vitamin B_{12} 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_{12} intake and the risk from cervical cancer.
					Age matched controls	39	
Goodman *et al.* (2000)	Biomarkers of cervical cancer – squamous intraepithelial lesions (SIL) and atypical squamous cells (compared to serum vitamin B_{12} levels)	Case-control	4 years	Females	Cases of SIL	185	There was no significant ($p>0.05$) association between serum vitamin B_{12} levels and the risk of developing SIL or atypical squamous cell pap smear results.
					Cases of atypical squamous cels	147	
					Controls with normal pap smear	191	
Harnack *et al.* (2002)	Clinical – colorectal cancer (compared to vitamin B_{12} 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_{12} intakes and the risk of colorectal cancer.
					Cases of rectal cancer	123	
Hartman *et al.* (2001)	Clinical – lung cancer (compared to serum vitamin B_{12} levels)	Case-control (subset of the ATBC trial)	8 years	Male smokers aged 50-69 years	Cases of lung cancer	300	- There was no significant ($p>0.05$) association between serum vitamin B_{12} levels and the risk of lung cancer. - The OR between the lowest ($\leq$345 pg/mL) and highest (>580 pg/mL) serum vitamin B_{12} levels and lung cancer risk was 1.41
					Controls	300	
Hernandez *et al.* (2003)	Biomarkers of cervical cancer – premalignant cervical lesions (compared to dietary and supplemental vitamin B_{12} intake as measured by food frequency questionnaire)	Case-control	4 years	Females aged >18 years	Cases with premalignant lesions	214	- There was a significant ($p<0.05$) inverse association between supplemental vitamin B_{12} intake and the risk of developing premalignant lesions. - Dietary and total vitamin B_{12} intake was not significantly ($p>0.05$) associated with the risk of developing cervical cancer.
					Controls	271	

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject Group Number	Results
Vlajinac *et al.* (1997)	Clinical – prostate cancer (compared to dietary and supplemental vitamin B_{12} intake as measured by food frequency questionnaire)	Case-control	4 years	Males (mean age = 71 years)	Cases of histologically confirmed prostate cancer	101	- There was a significant ($p<0.05$) positive association between vitamin B_{12} intake and the risk of prostate cancer. - The OR between the lowest and highest intakes was 2.02.
					Age matched controls	202	
Zhang *et al.* (2003)	Clinical – breast cancer (compared to serum vitamin B_{12} 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_{12} levels and the risk of breast cancer.
					Age matched controls	735	

Table A7-3: Identified Studies on Vitamin B_{12} and Other Health Outcomes

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Results
Cagnacci *et al.* (2003)	Clinical – osteoporosis and osteopenia (compared to serum vitamin B_{12})	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_{12} levels.
					Cases of osteopenia	61	
					Healthy controls	72	
Shuval-Sudai *et al.* (2003)	Biomarker of gastrointestinal infection – *H.pylori* IgG antibodies (compared to serum vitamin B_{12} levels)	Cohort	Single timepoint	Persons	Subjects with seropositive result for *H.pylori* IgG antibodies	133	There was no significant ($p>0.05$) inverse association between serum vitamin B_{12} and *H.pylori* infection.

Study	Study Endpoint Type	Study Design	Length of Study	Subjects	Subject Grouping	Subject number	Results
Tucker *et al.* (2005)	Biomarker of bone disorders – BMD (compared to serum vitamin B_{12})	Cross-sectional	5 years	Persons aged 30-87 years	Total cohort	3532	- Hip BMD was significantly greater ($p<0.01$) with vitamin B_{12} levels >259 pM in males, and spine BMD at levels >185 pM in females. However, this significance was non-linear. - Spine BMD and hip BMD in males and females respectively were non-significantly associated with vitamin B_{12} levels ($p>0.05$).

Appendix 8

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:

- Thaimin: 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 *et al.* (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	- Significant ($p<0.05$) inverse relations emerged between laryngeal cancer and thiamin intake - The OR between the lowest and highest thiamin intakes was 0.4.
					Patients with acute, non-neoplastic diseases	1297	n/a	
D'Avanzo *et al.* (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 *et al.* (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 *et al.* (1992; HaengShi *et al*., 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	

Negri *et al.* (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	- There was an inverse association between the intake of dietary thiamin and the risk of oral cancer - The OR between the lowest and highest thiamin intakes was 0.82.
					Patients with no history of cancer admitted to hospitals with acute, non-neoplastic diseases.	1775	n/a	
Slattery *et al.* (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 *et al.* (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	- Increased niacin intakes were significantly ($p<0.05$) and positively associated with BMD in premenopausal women. - There was no significant ($p>0.05$) association between niacin intake and BMD for postmenopausal women.
					post menopausal	137	n/a	
Morris *et al.* (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	- Adjusted total niacin intake, including intake from food and supplements, was significantly ($p<0.05$) and inversely associated with the incidence of Alzheimer's disease. - Dietary niacin intake alone also had a significantly ($p<0.01$) inverse association with Alzheimer's disease.

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 *et al.* (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	-	

Cunzhi *et al.* (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	- Copper levels were significantly ($p<0.05$) higher in cervical cancer tissue samples than non-lesion tissue samples. - There was no significant ($p>0.05$) difference in copper levels between uterine and non-lesion tissues.
						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	- The serum copper levels of cervical cancer subjects were significantly ($p<0.001$) higher than those of healthy subjects. - There was no significant ($p>0.05$) difference in the serum copper levels of uterine cases and controls.
						Cases of uterine cancer	100	n/a	
						Healthy controls	100	n/a	
Jones *et al.* (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 *et al.* (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	- There was a significant ($p<0.01$) inverse association between copper intakes and the risk of colorectal cancer. - The OR between the lowest and highest quartiles of copper intake was 2.4.
						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 *et al.* (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	- Manganese levels were significantly ($p<0.05$) lower in cervical cancer tissue samples than non-lesion tissue samples. - There was no significant ($p>0.05$) difference in manganese levels between uterine and non-lesion tissues.
					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 *et al.* (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	- There was a significant ($p<0.05$) inverse correlation between molybdenum levels and female mortality from rectal cancer. - There was also a significant ($p<0.01$) positive correlation between molybdenum soil levels and female mortality from pancreatic cancer.