11 • Cobalamin (Vitamin B12)

11.1 Introduction

Cobalamin, also known as Vitamin B12, is a water-soluble vitamin that exists in several forms and contains the mineral cobalt. Cobalamin refers to a group of cobalt-containing compounds (corrinoids) that contains the sugar ribose, phosphate, and a base (5, 6-dimethyl benzimidazole) attached to the corrin ring. Cyanocobalamin is a common synthetic form of the cobalamin that is produced by chemically modifying bacterial hydroxocobalamin and used for addition to food and food supplements and drugs. In the body, cyanocobalamin is converted into the human physiological forms methylcobalamin and 5'-deoxyadenosylcobalamin, the forms of cobalamin that are active in human metabolism.

11.2 Functions

Cobalamin is required for proper red blood cell formation, neurological function, and DNA synthesis (IOM, 1998). Cobalamin plays essential roles in folate metabolism and acts as a cofactor for two enzymes, namely L-methylmalonyl-CoA mutase and methionine synthase.

L-methylmalonyl-CoA mutase requires 5'-deoxyadenosylcobalamin as a cofactor to catalyse the conversion of L-methylmalonyl-CoA to succinyl-CoA which then enters the citric acid cycle. Succinyl-CoA plays a major role in the production of energy from lipids and proteins and is also required for the synthesis of haemoglobin, the oxygen-carrying pigment in red blood cells (Shane, 2000).

Methylcobalamin is required for the function of the folate-dependent enzyme, methionine synthase. Methionine synthase is required for the synthesis of the methionine and tetrahydrofolate from homocysteine (IOM, 1998). Methionine, in turn, is required for the synthesis of S-adenosylmethionine (SAM), a methyl donor for almost 100 different substrates, including DNA, RNA, hormones, proteins, and lipids as well as detoxification reactions (Shane, 2000). Without adequate supplies of cobalamin and folate, the synthesis of methionine and its derivative SAM is disrupted, with profound effects on normal cellular function. Without methionine, myelin and neurotransmitters (serotonin, dopamine, acetylcholine and norepinephrine) cannot be produced that are needed for neurological development, maintenance and functions. Furthermore, inadequate function of methionine synthase can lead to an accumulation of homocysteine, an amino acid that is related to many neurodegenerative diseases that lead to brain damage and cognitive disturbances. Thus, the synthesis of methionine prevents the accumulation of homocysteine in the brain (de Jager, 2014).

11.3 Metabolism

Normally, cobalamin is attached to a protein either for transport or storage. In the stomach, hydrochloric acid and pepsin are secreted to degrade the cobalamin from protein (IOM, 1998). The released cobalamin then binds to another protein, R protein secreted by the salivary glands and the gastric mucosa and transports it through the stomach and into the small intestine. The stomach cells also produce a protein called intrinsic factor (IF), a glycoprotein secreted by the stomach's parietal cells which travel to the small intestine.

In the small intestine, the vitamin 12, bound to IF interacts with the protein receptor known as cubilin-IF receptor when it is transported from the duodenum to the ileum. Another protein, amnionless, facilitates the attachment of cubilin to the ileal cell membrane. The binding of the vitamin B12-IF complex to the cubilin receptor is important in order for the vitamin to be absorbed. Cobalamin is then released and degraded in lysosomes. Cobalamin is finally metabolised to its methyl and deoxyadenosyl- derivatives.

In plasma, cobalamin is bound to the cobalamin-binding proteins transcobalamin (TC) and haptocorrin. TC combines with cobalamin at the ileal cell to form holotranscobalamin (holoTC) and rapidly delivers cobalamin to tissues. The liver takes up approximately 50 percent of the cobalamin, and the remainder is transported to other tissues. The highest cobalamin losses occur through the faeces. Sources of faecal cobalamin include unabsorbed cobalamin from food or bile, desquamated cells, gastric and intestinal secretions and cobalamin synthesized by bacteria in the colon. There are no known interactions of cobalamin with other nutrients with regards to absorption or excretion.

11.4 Sources

Cobalamin is found only in animal foods. Unlike other B vitamins, cobalamin is not a normal constituent of plant foods except for certain algae. Cobalamin is not supplied by commonly eaten plant foods unless they have been exposed to bacterial action that has produced cobalamin; contaminated with soil, insects, or other substances that contain cobalamin; yogurt, tempeh, miso, kimchi, and pickles are all examples of foods sometimes made with the lactic acid bacteria that can produce vitamin B12. Examples of cobalamin content of some foods are shown in Table 11.1.

Table 11.1 Cobalamin (Vitamin B12) content of foods

Food	µg/100g
Rice, noodle, bread, cereals and cereals products and tubers	
Fortified cereals	20.0
Fish, poultry and meat	
Clams, cooked	98.9
Liver (lamb), cooked	85.7
Liver (beef) cooked	83.1
Liver (veal), cooked	72.5
Oysters, cooked	28.8
Mussels, cooked	24.0
Liver (chicken, pork), cooked	21.1
Mackerel, cooked	19.0
Tuna, bluefin, raw or cooked	10.9
Salmon, cooked	3.2
Beef	2.6
Shrimp, cooked	1.7
Pork	1.2
Egg	0.9
Duck or chicken, cooked	0.3
Milk and milk products	
Tofu	2.4
Parmesan	2.3
Mozzarella	0.9
Cheddar	0.8
Yougurt Plain (regular, low fat)	0.8
Milk, Semi-skim/skim	0.5
Milk, Whole	0.4
Others	
Seaweed	2.3
Tempeh	0.1

Source: USDA nutrient database (2012)

11.5 Deficiencies

Megaloblastic anaemia is the most frequent clinical expression of cobalamin deficiency, which affects red blood cells and all other blood cells. Most of the cobalamin deficiency occurs due to cobalamin malabsorption, rather than inadequate dietary intake. The deficiency results in 1) an autoimmune condition called pernicious anemia and 2) food-bound cobalamin malabsorption syndrome. Impairment of cobalamin absorption can cause megaloblastic anaemia and neurologic disorders in deficient individuals. Both conditions have been associated with a chronic inflammatory disease of the stomach known as atrophic gastritis. Atrophic gastritis is associated with the presence of autoantibodies directed towards stomach cells and infection by the bacteria, Helicobacter pylori (H. pylori) that damage stomach cells that make intrinsic factor, a substance the body needs to absorb B12 (Lahner, Persechino and Annibale, 2012). Insufficient dietary intake is rare in adults living in developed countries but is more often reported in vegans.

The clinical signs of deficiency include fatigue, weakness, constipation, loss of appetite, and weight loss (Kapadia, 1995). Apart from that, neurological changes can also occur in the individual with cobalamin deficiency such as numbness and tingling in the hands and feet, difficulty walking, memory loss, disorientation, and dementia (IOM, 1998). In an infant, failure to thrive, movement disorders, developmental delays, and megaloblastic anemia are signs of a cobalamin deficiency (Monsen and Ueland, 2003).

Cobalamin status is assessed via serum or plasma cobalamin levels. The plasma cobalamin levels of adults with cobalamin deficiency are approximately (120-180 picomol/L) (IOM, 1998). Another reliable indicator of cobalamin status is elevated methylmalonic acid (MMA) levels (values >0.4 micromol/L) in blood and urine, resulting from impaired metabolic cobalamin activity with no specific clinical symptoms (Andrès *et al.,* 2007). This indicator can detect a metabolic change that is highly specific to cobalamin deficiency.

In 1950s, cobalamin was found to be a major contributing factor to anaemia in pregnancy amongst Malaysians (Tasker, Richardson and Llewellyn, 1956; Tasker, 1958). The Institute for Medical Research (IMR) embarked on a series of two periods of five-year interval (1987/88 and 1992/93) intensive studies into the cause of the cobalamin deficiency anaemia from hospitals all over Malaysia (Roshidah and Khalid, 1994). The IMR researchers reported that there was increase in cobalamin deficiency anaemia over the five-year interval from 2.6% to 8.2% with most Indians having a prevalence of about 49%, indicating the need to improve cobalamin intake in this group. The problem seems to have been observed in individuals consuming vegetarian diets too since cobalamin is found only in animal products (Roshidah and Khalid, 1994). In a more recent study, Khor *et al.* (2011) reported adequate concentrations of serum cobalamin among 7-12 primary school children in Kuala Lumpur.

11.6 Factors affecting requirements

Strict vegetarians and vegans are at greater risk of developing cobalamin deficiency than lacto-ovo vegetarians since natural food sources of cobalamin are limited to animal foods (IOM, 1998).

In the general elderly population, plasma cobalamin tends to decrease and concentration of serum methylmalonic acid (MMA) tends to increase resulting in a decline in cobalamin status. Factors that may contribute to these changes include a decrease in gastric acidity and the presence of atrophic gastritis and bacterial overgrowth accompanied by food-bound cobalamin malabsorption. Older adults with atrophic gastritis are unable to absorb the vitamin B12 due to progressive reduction of the inability of the parietal cells to secrete hydrochloric acid. It has also been suggested that the decreased hydrochloric acid levels might also increase the growth of normal intestinal bacteria in the stomach and intestine that use vitamin B12, further reducing the amount of vitamin B12 available to the body. Despite the absence of this acid in preventing the release of protein-bound vitamin B12, it would not interfere with the absorption of free vitamin B12 found in fortified foods or supplements. As a result, the IOM recommends that adults older than 50 years obtain most of their cobalamin from vitamin supplements or fortified foods (e.g., fortified cereals) to prevent cobalamin deficiency (IOM, 1998). However, some elderly patients with atrophic gastritis require doses much higher than the RDA to avoid subclinical deficiency.

11.7 Setting requirements and recommended intake

There were no recommendations for vitamin K in the previous version of Malaysian RNI (2005). The main references used by the Technical Sub-Committee (TSC) on Vitamins, cobalamin were the reports from the IOM (1998), WHO/FAO (2004) and the EFSA (2015). The rationale and approaches taken by these consultations were considered. There are no known local studies on cobalamin requirements of communities that the Technical Sub-Committee (TSC) on Vitamins could use as a reference when considering RNI for the vitamin. Previous studies of the biochemical status of cobalamin among Malaysians were published over 6 decades ago and recent studies are rare.

The Food and Nutrition Board of the National Academy of Sciences (NAS) Institute of Medicine derived the recommended dietary allowances based on their review on the evidence of intake, status and health for all age groups and during pregnancy and lactation using serum or plasma vitamin B12 and MMA as biomarkers of cobalamin status. From this review, the consultation group derives the calculations of an Estimated Average Requirement (EAR). Recommended dietary allowances were estimated to be the EARs plus 2 standard deviations (SDs). WHO/FAO (2004) consultation agreed to adopt the approach of the IOM (1998) for deriving its recommended nutrient intake of cobalamin.

In the European Food Safety Authority (EFSA) 2015 consultation report, the Panel agreed that the most suitable way to derive Dietary Reference Values (DRV) for cobalamin is a combination of biomarkers of cobalamin status i.e. serum cobalamin, holoTC, MMA and plasma total homocysteine (tHcy) (EFSA, 2015). Based on the literature, the Panel considered that

serum concentrations of holoTC and cobalamin within the reference ranges for healthy adults, together with MMA and plasma tHcy concentrations below cut-off values for cobalamin insufficiency and hyperhomocysteineaemia are indicative of an adequate cobalamin status. In fact, in the IOM (1998) report, the use of holoTC and MMA as biomarkers was highlighted as the high-priority recommendations for future studies. This recommendation was adopted by EFSA (2015).

The TSC is in general agreement with the comprehensive approach of the EFSA (2015) report and decided to adopt the values proposed by this organisation. The proposed values for the RNI (2017) for Malaysia are given in bold in the following paragraphs according to age groups and summarised in Appendix 11.1

Infants

In determining cobalamin requirement, EFSA (2015) recommendation was based on the estimation of adequate intake (AI) since there is limited number of studies using an accurate method to estimate the breast milk concentration of cobalamin (EFSA, 2015). Due to uncertainties in estimating breastmilk cobalamin concentration used for upward extrapolation from the cobalamin intake in exclusively breast-fed infants aged 0-6 months, and considering the use of scaling down approach from adults as a basis, an intake consistent with biomarker data, an AI for cobalamin for infants aged 7-11 months at 1.5µg/day was set. The recommendation in term of adequate intake (AI) for infant aged 0-6 months was made using the proportion based on recommended value of 0-6 months in IOM and WHO/FAO, that is 20% lower than 7-12 months recommendation, thus an AI for cobalamin for infants aged 0-6 months was set at 1.2 µg/day.

RNI for infants

0 - 5 months 1.2 µg/day
6 - 11 months 1.5 µg/day

Children and Adolescents

The same recommendation in term of adequate intake (AI) was made for the intake of cobalamin in children and adolescents by the EFSA (2015) since there are insufficient data to derive an Average Requirement (AR) (EFSA, 2015). AIs were derived from the unrounded AIs for adults after adjustment on the basis of differences in reference body weight, and then rounded to the closest 0.5.

RNI for children

1 - 3 years	**1.5 µg/day**
4 - 6 years	**1.5 µg/day**
7- 9 years	**2.5 µg/day**

RNI for adolescents

10 - 12 years	**3.5 µg/day**
13 - 18 years	**4.0 µg/day**

Adults and elderly

The same recommendations were made for the intakes of adults by the EFSA (2015). The EFSA Panel decided to use a combination of cobalamin biomarkers of status to derive DRVs for cobalamin for adults. However, there are uncertainties with respect to cut-off values for cobalamin insufficiency of these indicators and limited data available to determine an AR.

In the absence of the required information, the cobalamin recommendation was made for the adults by the EFSA Panel based on consistent evidence from observational and intervention studies. The studies showed that intake of cobalamin at 4µg/day and greater is associated with serum concentrations of holoTC and cobalamin within the reference ranges derived from healthy subjects, together with MMA and tHcy concentrations below the cut-off values for adults that indicates an adequate cobalamin status. Therefore, the EFSA (2015) Panel sets an AI for cobalamin at 4µg/day for adults based on data on different biomarkers of cobalamin status and in consideration of observed intakes. The recommended intake for older adults is the same as those for adults.

RNI for adults

19 - 65 years	**4.0 µg/day**

RNI for elderly

> 65 years	**4.0 µg/day**

Pregnancy and Lactation

The EFSA Panel suggested that 0.2 µg/day of cobalamin is transferred to the foetus and absorption of 40%. An additional requirement of 0.5µg/day of cobalamin to the AI for non-pregnant women was felt to be adequate. This addition results in an AI of 4.5µg/day for pregnant women.

An AI for lactating women is based on the cobalamin intake that is required to compensate for the amount of cobalamin secreted in breast milk. It is estimated that a mean milk transfer of 0.8L/day in exclusively breastfeeding women during the first six months of lactation would secrete breast milk with 0.4µg cobalamin/ day. Taking into account 40% absorption, an extra amount of 1.0µg/day cobalamin is required to balance the secretion in milk. Therefore, an AI of 5µ/day is recommended for lactating women.

RNI for

Pregnancy	**4.5 µg/day**
Lactation	**5.0 µg/day**

Discussion on revised RNI for Malaysia

There were no recommendations for cobalamin in the previous version of the Malaysian RNI. The proposed recommended intakes for the revised RNI for Malaysia 2017 are adopted from the latest report by EFSA (2015). These proposed recommended intakes are higher than the recommendations by IOM (1998) and WHO/FAO (2004) across all age groups by approximately 50%. As previously mentioned in Section 15.7, the use of additional biomarkers by EFSA 2015 to derive the values is highlighted and this probably contributes to the differences in values of recommendations by IOM (1998) and WHO/FAO (2004) (refer Appendix 11.1).

11.8 Toxicity and tolerable intake levels

No toxic or adverse effects have been associated with large intakes of cobalamin from food or supplements in healthy people. Doses as high as 2mg/day by mouth or 1 mg monthly by intramuscular (IM) injection have been used to treat pernicious anaemia without significant side effects. When high doses of cobalamin are given orally, only a small percentage can be absorbed, which may explain the low toxicity (Carmel, 2008). Because of the low toxicity of cobalamin, no tolerable upper intake level (UL) has been set by the US Food and Nutrition Board.

11.9 Research recommendations

The following priority areas of research are recommended:

- Determination of cobalamin status and extent of deficiency especially among vegan.
- Identification of more sensitive and specific biochemical measures of cobalamin status.
- The contribution of fermented vegetable foods to cobalamin status of vegan communities.

11.10 References

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Appendix 11.1 Comparison of recommended intakes for Cobalamin (Vitamin B12): RNI Malaysia (2017), AI and RDA (IOM, 1998), RNI (WHO/FAO, 2004) and AI (EFSA, 2015)

Malaysia (2017)		IOM (1998)		WHO/FAO 2004 (2004)		EFSA (2015)	
Age group	**RNI (µg/day)**	**Age group**	**AI (µg/day)**	**Age group**	**RNI (µg/day)**	**Age group**	**AI (µg/day)**
Infants (boys)		**Infants**		**Infants**		**Infants**	
0 - 5 months	1.2	0 - 6 months	0.4	0 - 6 months	0.4		
6 - 11 months	1.5	7 - 12 months	0.5	7 - 12 months	0.7	7 - 11 months	1.5
Infants (girls)							
0 - 5 months	1.2						
6 - 11 months	1.5						
			RDA (µg/day)				
Children (boys)		**Children (boys)**		**Children (boys)**		**Children**	
1 - 3 years	1.5	1 - 3 years	0.9	1 - 3 years	0.9	1 - 3 years	1.5
4 - 6 years	1.5	4 - 8 years	1.2	4 - 6 years	1.2	4 - 6 years	1.5
7 - 9 years	2.5			7 - 9 years	1.8	7 - 10 years	2.5
Children (girls)		**Children (girls)**		**Children (girls)**			
1 - 3 years	1.5	1 - 3 years	0.9	1 - 3 years	0.9		
4 - 6 years	1.5	4 - 8 years	1.2	4 - 6 years	1.2		
7 - 9 years	2.5			7 - 9 years	1.8		
Adolescent (Boys)		**Adolescent (Boys)**		**Adolescent (Boys)**		**Adolescent**	
10 - 12 years	3.5	9 - 13 years	1.8	10 - 18 years	2.4	11 - 14 years	3.5
		14 - 18 years	2.4				
13 - 14 years	4					15 - 17 years	4
15 years	4						
16 - 18 years	4						

Malaysia (2017)		IOM (1998)		WHO/FAO 2004 (2004)		EFSA (2015)	
Age group	**RNI (µg/day)**	**Age group**	**AI (µg/day)**	**Age group**	**RNI (µg/day)**	**Age group**	**AI (µg/day)**
Adolescent (Girls)		**Adolescent (Girls)**					
10 - 12 years	3.5	9 - 13 years	1.8				
13 - 14 years	4	14 - 18 years	2.4				
15 years	4						
16 - 18 years	4						
Men		**Men**		**Adults**		**Adults**	
19 - 29 years	4	19 - 30 years	2.4	19 - 65 years	2.4	>18 years	4
30 - 50 years	4	31 - 50 years	2.4	>6.5 years	2.4		
51 - 59 years	4	51 - 70 years	2				
60 - 65 years	4	>70 years	2				
>65 years	4						
Women		**Women**					
19 - 29 years	4	19 - 30 years	2.4				
30 - 50 years	4	31 - 50 years	2.4				
51 - 59 years	4	51 - 70 years	2.4				
60 - 65 years	4	>70 years	2.4				
>65 years	4						
Pregnancy	4.5	**Pregnancy**	2.6	**Pregnancy**	2.6	**Pregnancy**	4.5
Lactation	5	**Lactation**	2.8	**Lactation**	2.8	**Lactation**	5

14 • Vitamin D

14.1 Introduction

Vitamin D or calciferol is a fat-soluble vitamin. It can exist in 2 isoforms which is D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D2 is mostly human-made and added to foods. Vitamin D3 is synthesized in the skin from 7-dehydrocholesterol. The vitamin D3 synthesis can be activated with the exposure of bare skin to sunlight. Vitamin D3 can also be obtained from the diet via the intake of animal-based food. Both D2 and D3 are synthesised commercially and found in fortified foods and dietary supplements. Vitamin D3 is reported to have higher stability in blood compared to vitamin D2 due to the higher ability of binding protein towards vitamin D3.

The D2 and D3 forms differ only in their side chain structure of the chemical compound. The differences do not affect metabolism/activation and both forms function as prohormones. When activated, the D2 and D3 forms have been reported to exhibit identical responses in the body. It was reported that the specific potency related to the ability to cure vitamin D-deficiency rickets is the same between both isoforms (Jones, Strugnell, & DeLUCA, 1998; Jurutka *et al.,* 2001).

14.2 Functions

The dominant function of Vitamin D in its hormonal/active form (calcitriol or 1,25-dihydroxyvitamin D) is with the skeletal system.The main biological function is to maintain normal blood levels of calcium and phosphorus. These minerals are important for the normal mineralization process of the bone (Holick, 1996). Vitamin D also regulates the transcription of a number of vitamin D-dependent genes coding for calcium transporting proteins and bone matrix proteins. Furthermore, the elevation of plasma calcium to normal levels is also required for the functioning of the neuromuscular junction as well as vasodilatation, nerve transmission, and hormonal secretion.

It is noteworthy that the vitamin D receptor (VDR) is present in the nucleus of many tissues that are not involved in the regulation of calcium and phosphate metabolism. For example, the VDR has been clearly described in epidermal keratinocytes, in activated T cells of the immune system, in antigen-presenting cells, in macrophages and monocytes, and in cytotoxic T cells.

Hence, with the discovery of VDR on non-skeletal tissue systems, a large number of research has been focused at the non-skeletal chronic disease outcomes such as diabetes, cancer, cardiovascular disease and metabolic syndrome. However, after extensive and comprehensive review of literature, the Institute of Medicine (IOM, 2011) concluded that the causality was inconsistent and inconclusive and there was insufficient evidence on the non-skeletal chronic disease outcomes to serve as a basis for the development of Dietary Reference Intake (DRI) of vitamin D. Holick *et al.* (2011) performed a meta-analysis and made a scientific statement stating that although many observational studies have identified links of vitamin D with several chronic diseases, but these have neither been evaluated nor replicated in randomised controlled trials and in any cohort studies.

14.3 Metabolism

Vitamin D maintains serum calcium levels by three different mechanisms. The first mechanism, which does not require parathyroid hormone (PTH), is the well-established role of vitamin D in stimulating intestinal calcium absorption throughout the entire length of the intestine, with its greatest activity in the duodenum and jejunum. In the second mechanism, vitamin D plays an essential role in the mobilisation of calcium from bone, a process requiring PTH (Garabedian *et al.,* 1972; Lips, 2006). It induces the formation and activation of the osteoclast to function in the mobilisation of calcium from bone. In the third mechanism, vitamin D together with PTH stimulates the renal distal tubule reabsorption of calcium, ensuring retention of calcium by the kidney when calcium is needed (Sutton & Lazarus, 1976; Yamamoto *et al.,* 1984). Through the VDR, vitamin D suppresses parathyroid gene expression and parathyroid cell proliferation, providing important feedback loops that reinforce the direct action of increased serum calcium levels (Silver *et al.,* 1986; Slatopolsky *et al.,* 1984).

14.4 Sources

Dietary vitamin D can be obtained from three sources, namely natural food, fortified food and supplements. There are a few naturally occurring food sources of vitamin D which includes fatty fish (salmon, tuna, sardine, herring, mackerel), cod liver oil and egg yolk (USDA, 2016). Meat, poultry and vegetables are generally poor sources of the vitamin. Dairy products are fair sources of vitamin D. Other possible sources of vitamin D are from fortified foods which are made available on a voluntary basis by manufacturers. Commercially, vitamin D is fortified in cereals, bread, butter and yoghurt. Beverages such as milk and soy milk are also fortified with vitamin D. In Malaysia, the Malaysian Food Regulation permits the addition of vitamin D according to different categories of foods (MOH, 1985). Currently, voluntary vitamin D fortification of milk powder for children and adults are being carried out by manufacturers. The intake of foods fortified with vitamin D can increase vitamin D in the diet.

In recent years, vitamin D dietary supplements either combined only with calcium or with multivitamin/ multi-mineral formulations have become more common and have been more frequently consumed. Generally, the form of vitamin D used in supplement products can be either from vitamin D2 or vitamin D3 compound. However, the industry is switching from vitamin D2 to D3. Some manufacturers are also found to produce vitamin D with higher concentration. Traditionally, many marketed dietary supplements contain 400 IU (10 ug) per daily dose (IOM, 2011). Direct sunlight exposure to the skin is also a good source to achieve optimum level of vitamin D. Vitamin D content of foods is given in Table 14.1.

Table 14.1. Vitamin D content of foods

Food	Vitamin D µg/100g
Poultry, Meat, Fish	
Fish, salmon, pink	10.9
Fish, mackerel, cooked	7.3
Fish, sardines, cooked	4.8
Egg, whole	2.0
Beef, liver	1.2
Fish, catfish, farmed	0.2
Beef, Meat	0.1
Chicken, Meat	0.1
Lamb, meat	0.1
Dairy	
Milk, cow fortified, low fat	1.3
Yogurt, fortified, low fat	1.2
Cheese, cheddar	1.0
Vegetables	
Mushroom, oyster	0.7
Potatoes, mashed	0.3

Source: USDA, (2016) - 1 ug = 40 IU

14.5 Deficiencies

Vitamin D deficiency is manifested as rickets in children and as osteomalacia in adults. Lack of the vitamin in adults may also contribute to the development of osteoporosis. Higher prevalence of vitamin D deficiency has been found among females compared to males (Moy & Bulgiba, 2011). Infants are the group most at risk of deficiency in vitamin D simply because of their high rate of skeletal growth. Although at birth, vitamin D is acquired in utero, the stores will only be sufficient for the first month of life. In temperate countries, infants born in the autumn months are especially at risk because they spend the first six months of their life indoors. Therefore, they have less opportunity to synthesise vitamin D in their skin during this period.

In the elderly, clinical research studies have suggested age related decline in many key steps of vitamin D action (Holick, 1994). This included rate of skin synthesis, rate of hydroxylation leading to activation to the hormonal form, and response of target tissues (bone) as well as reduced skin exposure. Some studies have indicated that there appears to be vitamin deficiency in a subset of elderly population across the globe (Chapuy, Meunier, & Feldman, 1997). Kok-Yong *et al.* (2016) reported the prevalence of osteoporosis among elderly in Kuala Lumpur as 10.6% in males and 8.0% in females, respectively. A few groups have found that moderate increases in vitamin D intakes (10 to 20 µg/day) reduce the rate of bone loss and

fractures (Chapuy *et al.,* 1997; Dawson-Hughes *et al.,* 1991). These results were used as evidence by IOM (2011) to recommend an increase in vitamin D intakes for the elderly to a value (10-15 (g/day) that is able to maintain normal vitamin D levels.

Since early year 2000, there has been a significant increase in research publications related to vitamin D in Malaysia. Currently, data on several life stages show high prevalence of vitamin D deficiency among adults and children in Malaysia. Appendix 14.1 shows the summary of vitamin D research findings in Malaysia. It is noteworthy that several different cut-off values were used by the respective researchers. Furthermore, varied methodologies were used thus possibly increasing the variability in findings. The cut-off values and laboratory methods in detecting serum vitamin D has been a popular topic of debate among researchers. Perhaps, these have been translated into the weak clinical evidence on non-skeletal system defect even with the presence of vitamin D insufficiency or deficiency in several population studies.

14.6 Factors affecting vitamin D requirements

Technically, individuals living near the equator (sunny regions) could achieve optimum 25OHD in serum from the activation of sun light on the skin. However, this is not the case as majority of individuals such as housewives office and sedentary persons spend most of their day indoor. Other situations that will result in reduced sunlight exposure include the use of sunscreen and cultural clothing cover-up. Darker skin also reduces skin synthesis of pre-vitamin D in response to sunlight exposure. Darker-skinned people may require longer sunlight exposure than light-skinned people. It is noteworthy that all the groups above do not require vitamin D in excess of the RNI because recommendation has been set with the assumption of minimal sunlight exposure.

Across all age groups, obese individuals were also found to have lower serum vitamin D level compared to individuals with normal weight. One of the main reasons could be due to the sequestration of the fat-soluble vitamin D into adipose tissue. However, the IOM (2011) did not recommend higher requirement of vitamin D among this group due to lack of conclusive and beneficial evidence Elderly person's poor diet and low outdoor activities plus poor health condition may also lead to higher requirement for vitamin D among this vulnerable age group. Highest requirement across age group is set by IOM (2011) for elderly person.

The latitude, monsoon season and time of day can affect vitamin D synthesis.The ultraviolet rays that promote vitamin D synthesis are blocked by heavy clouds, smoke or smog. Hence, the change of atmospheric environment should be monitored with caution.

Best foods to obtain vitamin D from the diet are from animal source such as salmon, tuna, sardine, herring, mackerel, liver and egg yolk. These foods are not consumed by vegetarians. Possible plant-based food source for vitamin D is from mushroom. Hence, individuals practicing vegetarianism should try to achieve optimum activation of serum vitamin D from sunlight, from vitamin D fortified foods and possibly supplements.

14.7 Setting requirements and recommended intake of vitamin D

Vitamin A is an existing vitamin in the Malaysian RNI 2005. In making the recommendation for vitamin D intake then, there was no local data on vitamin D requirements that could be used by the Technical Sub Committee (TSC) on vitamin. The RNI Malaysia (2005) referred to the WHO/FAO (2004) consultation report as well as the IOM (1997) DRI recommendations. These organisations had made the same recommended intakes for the vitamin. The rationale and steps taken in setting the requirements and the levels recommended by these organisations were considered. The TSC on Vitamins agreed to adapt the WHO/FAO (2004) values as the RNI for Malaysia 2005.

In preparing for the 2017 review of the RNI for vitamin D, the TSC on vitamins sourced for recent recommendations of the vitamin by international research organisations. It was noted that WHO/FAO has not updated their 2004 recommendations. There were no other new published reports on vitamin D recommendations except by IOM (2011). It was also noted that the European Food and Safety Authority produced a scientific opinion draft on DRI for Vitamin D (EFSA, unpublished) which recommends similar RNI as IOM (2011). Thus, the TSC referred only to the IOM (2011) DRI recommendations as it has the latest published recommendations on Vitamin D. The rationale and steps taken in setting the requirements and the levels recommended by IOM (2011) and available reports on vitamin D status of communities in Malaysia were considered. The TSC on vitamins agreed to adapt the IOM (2011) values as the revised RNI for Malaysia, given in bold in the following paragraphs according to age group and summarised in Appendix 14.2.

The IOM (2011) considered minimal sun exposure in deriving the DRI. This condition is not different with the sun exposure situation in Malaysia even with the availability of sunlight almost throughout the year. This is mainly due to sunlight avoidance practice related to the heat of sunlight among Malaysian. This is evident from a local study which found minimal sunlight exposure and high sun light avoidance practice among Malaysians (Moy & Bulgiba, 2011). Occupation also plays an important roles as a study compared vitamin D level between indoor and outdoor workers (Hamid Jan & Norliyana, 2016) indicating higher serum vitamin D level among outdoor workers compared to indoor workers. Holicks (2002) reported that the best time for sunlight activation of vitamin D is during the noon as the UVB radiation is at peak. In countries near the equator like Malaysia, this is also the time when the heat is at the highest level. Hence, this could be the main reason for sun avoidance practice among majority of Malaysians.

A local study has shown that with minimum surface exposure (face and hand) to sunlight for 30 minutes, 2 times per week at 11am could increase 40% of serum vitamin D (Hamid Jan & Norliyana, 2016). However, caution should be made by individuals who have sensitive skin to heat from sunlight as it may cause skin irritation. The abovementioned study also reported similar effect among participants who took 50,000 IU (1250 ug) (1 vitamin D per week for 3 months. Indicating, alternative source compared to sunlight.

Infants

Data are not sufficient to establish an Estimated Average Requirement (EAR) for infants less than 1 year of age, and therefore an AI has been developed for vitamin D recommendation for this age group. The AI for the 0 to 6 months and 7 to 12 months life stage groups is set at 10 (g of vitamin D per day by IOM (2011). There are no data to suggest that older infants would benefit from higher intakes. There are differences in the volume of milk or formula intake during this 12-month period, with newborns taking in less than older infants. The AI of 10 µg/day, therefore, represents an overall intake for the first year of life, and may vary across the life stages; it also assumes early introduction of a supplement for breast-fed babies. In the case of exclusive formula feeding, there is an assumption of a gradual increase in intake from 800 to 1,000 mL/day during infancy, which for most standard formulas provides about 10 µg /day.

Human milk from vitamin D deficient mother has been shown to contain low amounts of vitamin D (Jan Mohamed *et al.,* 2014). Thus, for the above reasons and assuming that infants are not getting any vitamin D from sunlight, IOM (2011) recommended an intake of at least 10 µg/day for infants 0-6 months. Similarly, for infants 7-12 months, it has been observed that in the absence of any sunlight exposure, an intake of 10 (g/day will result in most of the infants with serum 25(OH)D above 50 nmol/L.

RNI for infants

0 - 6 months	**10 µg/day**
7 - 12 months	**10 µg/day**

Children and adolescents

For children and adolescents, ensuring normal, healthy bone accretion is the main criteria to the DRI values. The requirement distribution developed using serum vitamin D concentrations and the intakes estimated to achieve such concentrations are the basis for the reference values by IOM (2011).

For very young children in this life stage group, currently no data are available to link vitamin D nutriture directly to measures related to bone health outcomes. The Agency for Healthcare Research and Quality based in University of Ottawa (AHRQ-Ottawa) conducted a systematic evidence-based review to examine the relationship between vitamin D and rickets in children 0 to 5 years of age. AHRQ-Ottawa found no studies that evaluated bone mineral content (BMC) and bone mineral density (BMD), or fractures in comparison with measures of vitamin D intake (Cranney *et al.,* 2007).

However, AHRQ-Ottawa found that there was fair evidence that circulating vitamin D levels are associated with a positive change in BMD and BMC in studies in older children and adolescents. Serum 25OHD concentrations of 40 to 50 nmol/L would ideally coincide with bone health benefits such as positive effects on BMC and BMD. A study conducted by Viljakainen et al. (2006) reported that vitamin D intakes of 200 IU/day (5 ug/day) and 400 IU/day (10 ug/day) in adolescent girls were associated with positive BMC measures at serum vitamin D levels of 50 nmol/L and above.

The IOM (2011) refers to several research evidences that indicate an intake of vitamin D of 10 µg/day achieves serum concentrations of 40 nmol/L, and this intake is therefore set as the EAR for persons 1 to 3 years, 4 to 8 years, 9 to 13 years, and 14 to 18 years of age. As this requirement distribution appears to be normally distributed, the assumption of another 30 percent to cover nearly all the population (i.e., 97.5 percent) is appropriate and consistent with a serum vitamin D level of approximately 50 nmol/L as the target for an RDA value. Based on the same analysis relating serum vitamin D levels to intake, and with the assumption of minimal sun exposure, an intake of 15 µg/day is set as the RNI. These reference values assume minimal sun exposure.

RNI for children

1 - 3 years	**15 µg/day**
4 - 6 years	**15 µg/day**
7 - 9 years	**15 µg /day**

RNI for adolescents

Boys 10 - 18 years	**15 µg/day**
Girls 10 - 18 years	**15 µg/day**

Adults

Bone maintenance is the focus for adult stage. The requirement distribution based on serum vitamin D concentrations and the intakes estimated to achieve such concentrations are the basis for the reference values.

Data relating bone health outcomes to vitamin D intake are generally limited for adults 19 to 50 years of ages. Although bone mass measures are, of course, studied in this population, consideration of the dose-response relationship between vitamin D and bone health are not usually included in such studies. In fact, there are no randomized trials in this age group, and whatever data available come from association studies. The results are inconsistent, in part because the confounding inherent in observational studies.

The IOM (2011) recommendation is considered based on the relationship between serum vitamin D levels and calcium absorption, in which serum vitamin D levels of between 30 and 50 nmol/L were consistent with maximal calcium absorption. Based on these considerations as well as the intake versus serum response analysis described above, an RNI of 15 µg/day are established for adults 19 to 65 years of age. These RNI values assume minimal sun exposure.

RNI for adults

Men	**19 - 50 years**	**15 µg/day**
Women	**19 - 50 years**	**15 µg/day**

RNI for adults

Men	**19 - 50 years**	**15 µg/day**
Women	**19 - 50 years**	**15 µg/day**

RNI for adults

Men	**51 - 65 years**	**15 µg/day**
Women	**51 - 65 years**	**15 µg/day**

Elderly

For elderly group, the reduction in fracture risk is the most important indicator of interest, not only because of the actual event, but also because of the high mortality and morbidity associated with fractures. Changes such as impaired renal function, less efficient synthesis of vitamin D in skin, lower endogenous production of active vitamin D, increased PTH as well as age-related changes in body composition affect the daily requirement of vitamin D. Moreover, a sizeable proportion of this population can be categorised as frail compared with other age groups, and the concerns for bone health are increased.

Findings from a large longitudinal study (n = 2,686) carried out by Trivedi, Doll, & Khaw, 2003 was used by IOM (2011) as reference for developing RNI for elderly. Furthermore, upon reviewing available data, IOM (2011) felt that evidence is strong that the elderly are at high risk for vitamin D deficiency, which causes secondary hyperparathyroidism and osteomalacia and exacerbates osteoporosis, resulting in increased risk of skeletal fractures. Based on the available literature and uncertainty due to the elderly physiological changes, a higher value of 20 µg/day was felt prudent for individuals over 70 years of age with limited sun exposure and stores. The TSC on Vitamins agreed to adjust the elderly age starting at 65 years instead of 70 to standardize with other nutrients presented in the updated RNI of Malaysia. It is suggested that the additional 5 ug/day for the lower age group is not expected to have any safety concern.

RNI for elderly

Men	**> 65 years**	**20 µg/day**
Women	**> 65 years**	**20 µg/day**

Pregnancy and Lactation

The EAR for non-pregnant women and adolescents is appropriate for pregnant women and adolescents based on the AHRQ-Ottawa's finding of insufficient evidence on the association of serum vitamin D level with maternal BMD during pregnancy. Furthermore, there is no evidence that the vitamin D requirements of pregnant women differ from those of non-pregnant women. Hence, the RNI values for pregnant women and non-pregnant women are applicable, providing an RDA of 15 µg/day for each group.

The EAR for non-lactating women and adolescents is appropriate for lactating women and adolescents based on evidence from RCTs (Basile *et al.,* 2006; Hollis & Wagner, 2004; Saadi *et al.,* 2007; Wagner *et al.,* 2006). Furthermore, there is no evidence that lactating women require higher serum vitamin D levels than non-lactating women. Hence, the RNI values for lactating women and non-lactating women are applicable, providing an RDA of 15 µg/day for each group.

RNI for

Pregnancy	**15 µg/day**
Lactation	**15 µg/day**

Discussions on revised RNI for Malaysia

There is a one- to two-fold increase in the RNI 2017 compared to RNI 2005. This is due to the reference document that is used in this review which is the IOM 2011. This more recent IOM report reflects comprehensive evidence-based reviews and latest literature searchers which was prepared by experts in vitamin D. Based on the detailed analysis, the IOM 2011 panel suggested higher recommendation as compared to its previous report (IOM 1997) which was referred by the RNI 2005 Technical Sub Committee on vitamin.

Numerous studies conducted by various investigators in different part of Malaysia (Appendix 14.1) have reported high prevalence of Vitamin D deficiency and insufficiency. These findings also lend support for increasing RNI for vitamin D in this country. It is noteworthy that this higher recommendation is based on the assumption of minimal sunlight exposure. Thus, this recommendation is applicable to people in Malaysia as even with abundance of sunlight, high sunlight avoidance practices is found to be very prominent. Furthermore, there are limited choices of food with high level of vitamin D available to Malaysia.

14.8 Tolerable upper intake levels

Serum 25(OH)D is a useful indicator of vitamin D status, both under normal conditions and in the context of hypervitaminosis D. The latter is characterised by a considerable increase in plasma 25(OH)D concentration to a level of approximately 160 to 500 ng/ml. Because changes in circulating levels of 1,25(OH)2D are generally small and unreliable, the elevated levels of 25(OH)D are considered the indicator of toxicity. Serum levels of 25(OH)D have diagnostic value, particularly in distinguishing the hypercalcemia due to hypervitaminosis D

from that due to other causes, such as hyperparathyroidism, thyrotoxicosis, humoral hypercalcemia of malignancy and lymphoma (Alshahrani & Aljohani, 2013).

To determine the Tolerable Upper Intake (UL), the IOM (2011) committee considered the emerging evidence of a U-shaped relationship for all-cause mortality, cardiovascular disease, vascular calcification, pancreatic cancer, falls, frailty and fractures, which indicates increased risk at low and high levels and lowest risk at moderate levels of vitamin D. The UL for ages 9 years and older is 100 ug/day with lower value for infants and young children. The UL was derived from the acute possible toxicity from vitamin D of 250 ug/day which is also supported as NOAEL (no observed adverse event concentration). It is adjusted for uncertainty based on chronic disease outcomes and all-cause mortality as well as emerging concerns about risks at serum vitamin D levels more than 50 ng/mL (125 nmol/L). It is noteworthy that acute toxicity is not the appropriate basis for a UL that is intended to reflect long-term chronic intake and to be used for public health (Ross *et al.,* 2011).

The tolerable upper intake for vitamin D for various age groups as proposed by IOM (2011) is given in Table 14.2.

Table 14.2. Tolerable Upper Intake (UL) levels of vitamin D for various age groups

Age groups	ug/day of vitamin D
Infants (0-6 months)	25
Infants (6-12 months)	37.5
Children, 1-13 years	100
Adolescence > 14-18 years	100
Adults > 18	100
Pregnant women	100
Lactating women	100

Source: IOM (2011)

14.9 Research recommendations

- Addition of vitamin D in the Malaysian Food Composition Database as this would encourage more local research on dietary intake of vitamin D.
- Comprehensive nationwide vitamin D status study.
- Rigorous large scale RCT to test the effects of vitamin D on nonskeletal outcomes.
- Investigating the possible variations of biological effect of vitamin D on time and duration of sun exposure, adiposity, ethnicity and genetic factor
- Research on cut-off with skeletal system and chronic disease outcomes.

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Appendix 14.1: Prevalence of Vitamin D status

Author, year	Study Population	Study Location	Participants, n	25 Hydroxyvitamin D (nmol/l)			Cut-off reference used
				% Sufficient [cut off]	% Insufficient [cut off]	% Deficient [cut off]	
Suriah *et al.,* (2004)	Healthy postmenopausal women (50 - 65 years)	Kuala Lumpur	Malay, 101 Chinese, 173	26.7 87.8 [50 – 100 nmol/L]	71.3 12.2 [25 – 50 nmol/L]	2.0 - [<25 nmol/L]	(Washburn, Smith, Jette, & Janney, 1993)
Green *et al.,* (2008)	Nonpregnant women (18 - 40 years)	Kuala Lumpur	Malay, 133 Chinese, 123 Indian, 122	- - -	74 38 68 [< 50.0 nmol/l]	- - 1.0 [< 17.5 nmol/l]	Not mentioned
Khor *et al.,* (2011)	Primary school children (7 - 12 years)	Kuala Lumpur	Total, 402 Boys, 180 Girls, 222	27.6 33.9 22.5 [> 50.0 nmol/l]	37.1 37.8 36.5 [37.5 – 50.0 nmol/l]	35.3 28.3 41.0 [≤ 37.5 nmol/l]	(Rovner & O'Brien, 2008)
Moy & Bulgiba, (2011)	Malay employees (35 years above)	Kuala Lumpur	Total, 380 Male, 158 Female, 222	32.1 - - [> 50.0 nmol/l]	67.9 41.1 86.9 [< 50.0 nmol/l]	- - -	(Zittermann & Gummert, 2010)
Nurbazlin *et al.,* (2013)	Urban and rural adult women	Kuala Lumpur. Negeri Sembilan	Total, 400 Urban, 107 Rural, 293	69.5 18.7 88.1 [≥ 50.0 nmol/l]	18.5 37.4 11.6 [30– 50.0 nmol/l]	12.0 43.9 0.3 [< 30 nmol/l]	IOM (2011)
Jan Mohamed, Rowan, Fong, and Loy (2014)	Malay pregnant women (19-40 years)	USM Hospital & Kubang Kerian Health Clinic, Kelantan.	2nd Trimester 3rd Trimester	5.9 22.5 [≥ 75 nmol/l]	34.3 40.2 [50 - 75 nmol/l]	59.8 37.3 [< 50nmol/l]	(Dawodu & Tsang, 2012)

Author, year	Study Population	Study Location	Participants, n	25 Hydroxyvitamin D (nmol/l)			Cut-off reference used
				% Sufficient [cut off]	% Insufficient [cut off]	% Deficient [cut off]	
Chin, Ima-Nirwana, Ibrahim, Mohamed, and Wan Ngah (2014)	Chinese and Malay adult men (20 years and above)	Klang Valley	Chinese, 233 Malay, 150 Total, 383	84.5 66.0 77.3 [≥ 50.0 nmol/l]	15.5 32.7 85.0 [30– 50.0 nmol/l]	0 1.33 1.92 [< 30 nmol/l]	IOM (2011)
Hamid Jan & Norliyana (2016)	Malay workers	Kelantan	Outdoor workers, 119 Indoor workers, 118	100 45.8 [≥ 50.0 nmol/l]	0 35.6 [30–50.0 nmol/l]	0 18.6 [< 30 nmol/l]	IOM (2011)
Al-Sadat *et al.* (2016)	Adolescents (13 years)	Klang Valley and Perak	Urban, 723 Rural, 638	1.4 14.3 [> 50.0 nmol/l]	9.8 18.2 [37.5 – 50.0 nmol/l]	86.3 67.2 [≤ 37.5 nmol/l]	(Misra, Pacaud, Petryk, Collett-Solberg, & Kappy, 2008)
Bee Koon *et al.* (2016)	Children (0.5-12 years)	Malaysia	Urban Rural	27.5 30.1 [50 – 100 nmol/L]	40.1 38.5 [25 – 50 nmol/L]	4.9 2.7 [<25 nmol/L]	Not mentioned

Appendix 14.2. Comparison of recommended intake for Vitamin D: RNI Malaysia (2017), RNI Malaysia (2005), and IOM (2011)

Malaysia (2017)		Malaysia (2005)		IOM (2011)	
Age group	**RNI (µg/day)**	**Age group**	**RNI (µg/day)**	**Age group**	**RNI (µg/day)**
Infants		**Infants**		**Infants**	
0 - 6 months	10	0 - 5 months	5	0 - 6 months	10
7 - 12 months	10	6 - 12 months	5	7 - 12 months	10
Children		**Children**		**Children**	
1 - 3 years	15	1 - 3 years	5	1 - 3 years	15
4 - 6 years	15	4 - 6 years	5	4 - 8 years	15
7 - 9 years	15	7 - 9 years	5		
Boys		**Boys**		**Boys**	
10 - 18 years	15	10 - 18 years	5	9 - 13 years	15
		-		14 - 18 years	15
		-			
Girls		**Girls**		**Girls**	
10 - 18 years	15	10 - 18 years	5	9 - 13 years	15
	-			14 - 18 years	15
	-				-
Men		**Men**		**Men**	
19 - 50 years	15	19 - 65 years	5	19 - 30 years	15
51 - 65 years	15	51 - 65 years	10	31 - 50 years	15
> 65 years	20	> 65 years	15	51 - 70 years	15
				> 70 years	20

Malaysia (2017)		Malaysia (2005)		IOM (2011)	
Age group	**RNI (µg/day)**	**Age group**	**RNI (µg/day)**	**Age group**	**RNI (µg/day)**
Women		**Women**		**Women**	
19 - 50 years	15	19 - 65 years	5	19 - 30 years	15
51 - 65 years	15	51 - 65 years	10	31 - 50 years	15
> 65 years	20	> 65 years	15	51 - 70 years	15
				> 70 years	20
Pregnancy		**Pregnancy**		**Pregnancy**	
	15		5	14 - 18 years	15
				19 - 50 years	15
Lactation		**Lactation**		**Lactation**	
	15		5	14 - 18 years	15
				19 - 50 years	15

Notes:1 mg = 40 IU