

# 11 Vitamin A

## 11.1 Introduction

Vitamin A (retinol) is required by humans for the normal functioning of the visual system. Retinol is transported to ocular tissue and to the retina of the eye by intracellular binding and transport protein in which it plays an important part in the formation of rhodopsin, an important visual pigment, particularly for dim-light vision. All-trans retinol is converted to retinaldehyde, isomerised to the 11-cis form and bound to opsin to form rhodopsin. When there is insufficient amount of retinol available, rhodopsin synthesis is affected and night blindness may result. The condition can, however, also be due to a lack of other nutrients which are critical to the regeneration of rhodopsin such as protein and zinc.

The second main function of vitamin A is in the maintenance of growth and epithelial cellular integrity and immune function in the body. Thus, in vitamin A deficiency, the number of goblet cells are reduced in epithelial tissues, resulting in a reduction in mucous secretions with their antimicrobial components. Cells lining protective tissue surfaces flatten and accumulate keratin because they fail to regenerate and differentiate. All these changes result in diminished resistance to invasion by potentially pathogenic organisms. The immune system is also adversely affected by direct interference with production of some types of protective secretion and cells. As these changes in internal epithelial tissues occur, the external reflections of such changes are seen in the classical eye changes in xerophthalmia and xerosis.

## 11.2 Deficiencies

Ocular manifestations of vitamin A deficiency (VAD), termed “xerophthalmia” or “dry eye” has been recognised for a long time. The most frequently encountered of these signs is night blindness, which is the earliest manifestation of xerophthalmia. In VAD, the time required to regenerate rhodopsin is prolonged, thereby delaying adaptation time to dark environments. Night-blind young children tend to stumble when going from bright to dimly-lit areas and they tend to remain inactive at dusk and at night. No field-applicable objective tool is currently available for measuring night blindness. There is also no clearly defined blood retinol level that is associated with the occurrence of the symptom.

The other eye changes have been well documented in a WHO field guide for the classification of xerophthalmia (Sommer, 1995).

There are several biochemical methods for estimating sub-clinical vitamin A status, including breast milk retinol and serum retinol levels, as well as percent relative dose response and modified relative dose response methods. These indicators are less specific to VAD than clinical eye signs and less sensitive for measuring sub-clinical vitamin A status. The biochemical indicator of choice for population assessment is the distribution of serum levels of retinol. The prevalence of values below 0.70  $\mu\text{mol/l}$  is the

recommended population cut-off for pre-school children to indicate risk of inadequate vitamin A status and above 1.05  $\mu\text{mol/l}$  to indicate an adequate status.

Prior to the 1950s, vitamin A deficiency in Malaysia was reported to be an important sight-threatening disorder, affecting mainly young children on unbalanced diet, amongst lower socio-economic segments of the population. Vitamin A intake was generally low, with little or no retinol and most of it from the provitamins. Even then, the amount of vegetables and fruits consumed were generally low (Tee, 1993).

No exact estimates of the magnitude of the problem in the country are presently available. However, as seen from reports in the literature, the problem appears to be confined to certain groups, mainly in the rural areas, and does not pose a major health hazard nationwide. The problem appears to have lessened over the years, judging from reports up to the 1990s. There are probably very few cases of children with eye signs past the conjunctival xerosis and with serum vitamin A < 10  $\mu\text{g/dl}$  (Tee, 1993). In a nation-wide study of 439 children under 5 years conducted by the Ministry of Health (MOH, 2000), only 3.9% of the children were found to have vitamin A deficiency (serum retinol < 0.7  $\mu\text{mol/l}$ ). A study among 350 rural elderly Malays also showed that there was no sub-clinical vitamin A deficiency (Suzana *et al.*, 1999). On the other hand, a study of the problem amongst undernourished preschool children included in the nutrition rehabilitation programme in Sabah showed that some 30% of these children had marginal sub-clinical vitamin A deficiency (serum retinol < 30  $\mu\text{g/dl}$ ) (Tee *et al.*, 1997). It should thus be recognised that although the vitamin A deficiency problem is small in the country, the problem can be serious amongst malnourished children.

### 11.3 Food sources

Preformed vitamin A (retinol) is found almost exclusively in animal products. The vitamin A content of several commonly consumed foods as obtained from the Malaysian nutrient composition database (Tee *et al.*, 1997) are summarised below.

Liver from various animals are extremely rich sources of retinol, containing up to as much as 9,000  $\mu\text{g}$  and 16,000  $\mu\text{g}$  per 100 g of ox liver and chicken liver respectively. Meat of these animals, on the other hand, are generally only medium sources, with levels generally around 30  $\mu\text{g}/100$  g of meat, chicken, duck or mutton. Whole egg is a very good source of vitamin A, with an estimated content of 350  $\mu\text{g}/100$  g. Most of this vitamin is in the egg yolk, a 100 g of which contains about 570  $\mu\text{g}$  retinol.

Commercial ready-to-drink milk, eg UHT milk and fresh milk contains about 30  $\mu\text{g}$  retinol per 100 ml. The vitamin is high in full cream milk powder, containing about 400  $\mu\text{g}/100$  g and when prepared according to instructions for consumption, the vitamin A content should be around 100  $\mu\text{g}/100$  ml, depending on the brand in the market. Fish in general are not particularly good sources of vitamin A, as only a few species contain the vitamin at a concentration of 20- 30  $\mu\text{g}/100$  g.

Carotenoids, especially  $\alpha$ - and  $\beta$ -carotene which are potential provitamin A precursors that can be converted into retinol, are present in plant products, especially green leafy vegetables, red palm oil and yellow and orange fruits. Carotenoids are biologically less available than retinol but they are generally more affordable than animal foods. Thus carotenoids provide most of the vitamin A activity in the diets of lower socio-economic segments of the populations.

#### 11.4 Factors affecting requirements

Dietary fat plays an important role in the absorption of ingested vitamin A. Dietary vitamin A is digested in mixed micelles and absorbed with fat. There are indications that increasing the level of fat in a low fat diet can improve retinol and carotene absorption. Particularly for optimal carotenoid absorption, dietary fat must be consumed alongside these provitamin A compounds.

The matrix of the food affects the ability of carotenoids to be released from food and therefore affects intestinal absorption. For example, the rise in serum  $\beta$ -carotene concentration has been observed to be significantly less when individuals consumed carrots than when they received the same amount of the vitamin of  $\beta$ -carotene supplement. The processing of food also greatly affects the absorption of carotenoids. For instance, the absorption of carotene from sliced carrots was much lower than from homogenised carrot. Cooking of carrot and spinach also greatly improved absorption.

Malabsorption of vitamin A can occur with diarrhea and intestinal infections such as in gastroenteritis and respiratory infections. Malabsorption of the vitamin is also associated with intestinal parasitism.

#### *Units of expression and conversion factors*

In blood, tissues and human milk, vitamin A levels are conventionally expressed in mg/dl or mmol/l all-trans retinol. Most of the circulating vitamin A is retinol whereas in most tissues, secretions and other animal food sources it exists mainly as retinyl esters.

To express the vitamin A activity of carotenoids in diets on a common basis, FAO/WHO introduced the concept of retinol equivalent (RE) and established the following relationship among food sources of vitamin A:

1 $\mu$ g retinol	= 1 RE
1 $\mu$ g $\beta$ -carotene	= 0.167 $\mu$ g RE
1 $\mu$ g other pro-vitamin A carotenoids	= 0.084 $\mu$ g RE

In recent years, there has been renewed interest in examining bioavailability factors by using more quantitative stable isotope techniques. Available data are

inconsistent but in general suggests a revision towards lower bioavailability estimates. Until more definitive data become available, the conversion factors above are to be used.

It has been strongly recommended that weight or molar units replace the use of IU to decrease confusion and overcome limitations in the non-equivalence of the IU values for retinol and beta-carotenes. The conversion factors to be used are as follows:

1 IU retinol	= 0.3 µg retinol
1 IU β-carotene	= 0.6 µg β-carotene
1 IU retinol	= 3 IU β-carotene

### **11.5 Setting requirements and recommended intakes of vitamin A**

There is hardly any local data on vitamin A requirements that the Technical Sub-Committee (TSC) on Vitamins could use for arriving at RNI for the vitamin. The TSC therefore referred to the FAO/WHO (2002) consultation report and the IOM (2001) DRI recommendations. The rationale and steps taken in setting requirements and the levels recommended by these organisations as well as available reports of vitamin A status of communities in the country were considered. The TSC on Vitamins decided to adapt the FAO/WHO (2002) values as the revised RNI for Malaysia, given in bold in the following paragraphs according to age groups and summarised in Appendix 11.1.

The FAO/WHO international expert consultation had used the term “safe level of intake” as it was felt that the values arrived at do not strictly correspond to the definition of a recommended nutrient intake. These safe levels of intake are basically the same as those in the 1988 FAO/WHO Expert Consultation (FAO/WHO, 1988).

The safe level of intake for an individual is defined as the average continuing intake of vitamin A required to enable adequate growth and permit other vitamin A-dependent functions to take place as well as to maintain an acceptable total body reserve of the vitamin. This reserve helps offset periods of low intake or increased need resulting from infections and other stresses.

#### ***Infants***

No functional criteria of vitamin A status have been demonstrated that reflect response to dietary intake in infants. Thus recommended intakes of vitamin A are based on an adequate intake that reflects a calculated mean vitamin A intake of infants principally fed human milk.

During the first 6 months of life, exclusive breast-feeding is known to provide sufficient vitamin A to maintain health, permit normal growth and maintain sufficient stores in the liver. The safe level of intake for infants up to 6 months of age is calculated

based on observations of breast-fed infants in generally healthy communities. The average breast milk consumption is about 750 ml/day. The average concentration of vitamin A in human milk is about 1.75  $\mu\text{mol/l}$  (range, 0.70-2.45  $\mu\text{mol/l}$ ). Thus mean daily intake would then be about 375  $\mu\text{g RE}$ , which is taken as the recommended safe level.

For the second half of infancy, human milk intake averages 650 ml which would provide 325  $\mu\text{g}$  vitamin A daily. In order to reduce risk to death from 6 months onwards, especially in endemic vitamin A-deficient populations, the recommended safe intake is increased to 400  $\mu\text{g}$ .

#### **RNI for infants**

<b>0 - 5 months</b>	<b>375 <math>\mu\text{g RE/day}</math></b>
<b>6 - 11 months</b>	<b>400 <math>\mu\text{g RE/day}</math></b>

#### ***Children and adolescents***

For older children, the recommended intakes were estimated from those derived from infancy, i.e. 39  $\mu\text{g RE/kg}$  body weight/day. Providing for allowances for storage requirements and variability, the safe intake for children 1-9 years was estimated to range from 400-500  $\mu\text{g}$  per day. The safe intake for adolescents was stepped up from that for children.

#### **RNI for children**

<b>1 - 3 years</b>	<b>400 <math>\mu\text{g RE/day}</math></b>
<b>4 - 6 years</b>	<b>450 <math>\mu\text{g RE/day}</math></b>
<b>7 - 9 years</b>	<b>500 <math>\mu\text{g RE/day}</math></b>

#### **RNI for adolescents**

<b>Boys 10 - 18 years</b>	<b>600 <math>\mu\text{g RE/day}</math></b>
<b>Girls 10 - 18 years</b>	<b>600 <math>\mu\text{g RE/day}</math></b>

#### ***Adults and elderly***

Estimates for the recommended safe intakes for adults are also obtained from those derived from late infancy, i.e. 9.3  $\mu\text{g/kg}$  body weight/day. The levels recommended are essentially the same as those made during the 1988 consultation as the group felt that there were no new published studies to indicate a need to revise the assumptions previously made. The safe intakes recommended are said to be consistent with the per capita vitamin A content in the food supply of countries that show adequate vitamin A status in all sectors of the population.

The FAO/WHO consultation felt that there was no indication that the vitamin A requirement of healthy elderly individuals differed from those of other adults. It should however be borne in mind that the elderly are more commonly affected by several disease conditions that impede vitamin A absorption, storage, and transport which hence affected their requirements for the vitamin.

**RNI for adults**

<b>Men</b>	<b>19 – 65 years</b>	<b>600 µg RE/day</b>
<b>Women</b>	<b>19 – 65 years</b>	<b>600 µg RE/day</b>

**RNI for elderly**

<b>Men</b>	<b>&gt; 65 years</b>	<b>600 µg RE/day</b>
<b>Women</b>	<b>&gt; 65 years</b>	<b>600 µg RE/day</b>

***Pregnancy and lactation***

During pregnancy, additional vitamin A is needed for the growth and maintenance of the foetus for providing a limited reserve in the foetal liver and for maternal tissue growth. There are no reliable figures available for the specific vitamin A requirements for these processes. Recognising that a large portion of the world's population of pregnant women live under conditions of deprivation, the FAO/WHO expert consultation recommended that the safe level for women be raised by 300 µg, bringing it to 800 µg RE per day. The Consultation also pointed out that women who are or who might become pregnant should carefully limit their total daily vitamin A intake to a maximum of 3,000 µg RE to minimise risk of foetal toxicity.

If the amounts of vitamin A recommended for infants are supplied by human milk, mothers should absorb at least as much in their diets to replace maternal losses. Thus, an amount of 350 µg was recommended to be added to the safe intake for women, bringing the total during lactation to 850 µg RE.

**RNI for**

<b>Pregnancy</b>	<b>800 µg RE</b>
<b>Lactation</b>	<b>850 µg RE</b>

***Discussions on revised RNI for Malaysia***

The proposed RNI values for vitamin A for Malaysia, adapted from FAO/WHO (2002), are also the same as those adopted by the Working Group for the Harmonisation of RDAs in SEAsia (2002). Appendix 11.1 provides a summary of these revised RNI, compared with the previous Malaysian RDI of 1975, the FAO/WHO (2002) recommendations and the values recommended by IOM (2001).

The levels for young children are similar to the recommendations of IOM (2001). These revised values for young children are higher than the previous Malaysian RDI (Teoh, 1975). This is deemed justifiable as there is still considerable sub-clinical vitamin A deficiency amongst young children in the lower socio-economic segments of the community as shown by a study of the vitamin A status among children below 5 years in Sabah (Tee *et al.*, 1997). For adolescents, adults and lactating women, the revised values are lower than the previous RDI. The revised RNI for adolescents, adults and lactating women are lower than the IOM (2001) values, which the TSC felt were unnecessarily high.

The previous Malaysian RDI of 1975 for vitamin A for adults and lactating women are felt to be too high. With the absence of reported cases of xerophthalmia, it is felt that the vitamin A requirement could be lower. Furthermore, with improvement in socio-economic status in the last 30 years, a higher percentage of intakes of vitamin A would be from animal sources as compared to the past, where it was derived mostly from plant sources. IOM (2001) values recommended for adults are higher than those recommended by FAO/WHO, probably due to the large body size of Americans.

## 11.6 Toxicity and tolerable upper intake levels

Being a fat-soluble vitamin, retinol can be stored in the human body, primarily in the liver. Thus long term regular consumption of large amounts of the ascorbic acid can result in toxic symptoms. These symptoms are varied and non-specific and include central nervous system effects, liver damage, bone abnormalities and joint pain, alopecia, headaches and vomiting and skin desquamation. Rarely does toxicity occur from ingesting food sources of preformed vitamin A. When this occurs, it usually results from very frequent consumption of liver products (FAO/WHO, 2002). Acute toxicity is characterised by nausea, vomiting, headache, increased cerebrospinal fluid pressure, vertigo, blurred vision, muscular incoordination and bulging frontal in infants (IOM, 2001).

Infants, including newborns, administered single doses equivalent to 15,000 and 30,000 mg retinol in oil generally show no adverse symptoms. Daily prophylactic or therapeutic doses should not exceed 900 µg. Most children 1-6 years of age tolerate single oral doses of 60,000 µg vitamin in oil at intervals of 4-6 months without adverse symptoms.

When taken by women at early stages of gestation at daily levels of more than 7500 µg, foetal anomalies and poor reproductive outcomes have been reported. Women who are pregnant or might become pregnant should avoid taking excessive amounts of vitamin A. The WHO expert group recommended that daily intakes in excess of 3,000 µg or weekly intakes in excess of 7,500 µg should not be taken at any period during gestation.

The Tolerable Upper Intake Level (UL) is the highest level of daily vitamin A intake that is likely to pose no risk of adverse health effects in almost all individuals. Members of the general population should be advised not to routinely exceed the UL. For the purposes of deriving a UL, three primary adverse effects of chronic vitamin A intake are: reduced bone mineral density, teratogenicity and liver abnormalities. The ULs recommended by IOM (2001) are slightly different from those of FAO/WHO and are as given in Table 11.1.

**Table 11.1 Tolerable Upper Intake (UL) levels of vitamin A for various age groups**

<b>Age groups</b>	<b>µg/day of preformed vitamin A</b>
Infants	600
Children	
1-3 years	600
4-8 years	900
9-13 years	1,700
Adolescents, 14-18 years	2,800
Women, ≥ 19 years	3,000
Men, ≥19 years	3,000
Pregnant women	2,800
Lactating women	2,800

Source: IOM (2001)

### **11.7 Research recommendations**

The following priority areas of research are recommended:

- Data on dietary intake of vitamin A among different community groups, particularly children and women, both in terms of amounts of vitamin A and carotene-rich foods as well as the amounts of retinol consumed
- Content of vitamin A and carotenoids in a variety of foods available in the market to improve the food composition tables
- Vitamin A status of pre-schoolers using biochemical indicators amongst communities of lower socio-economic status
- Studies on health benefits of carotenoids, eg lycopene, zeaxanthin in local fruits and vegetables/ ulam.
- Bioavailability and effect of processing on bioavailability of vitamin A and provitamin A compounds.



## 11.8 References

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**Appendix 11.1 Comparison of recommended intake for vitamin A: RDI Malaysia (1975), RNI Malaysia (2005), “safe intake” of FAO/WHO (2002) and RDA of IOM (2001)**

Malaysia (1975)		Malaysia (2005)		FAO/WHO (2002)		IOM (2001)	
Age groups	RDI (µgRE/day)	Age groups	RNI (µg RE/day)	Age groups	Safe intake (µg RE/day)	Age groups	AI (µg RE/day)
Infants		Infants		Infants		Infants	
< 1 year	300	0 – 5 months	375	0 – 6 months	375	0 – 6 months	400
		6 – 11 months	400	7 – 11 months	400	7 – 12 months	500
							<b>RDA (µgRE/day)</b>
Children		Children		Children		Children	
1 – 3 years	250	1 – 3 years	400	1 – 3 years	400	1 – 3 years	300
4 – 6 years	300	4 – 6 years	450	4 – 6 years	450	4 – 8 years	400
7 – 9 years	400	7 – 9 years	500	7 – 9 years	500		
Boys		Boys		Boys		Boys	
10 – 12 years	575	10 – 18 years	600	10 – 18 years	600	9 – 13 years	600
13 – 15 years	725					14 – 18 years	900
16 – 19 years	750						
Girls		Girls		Girls		Girls	
10 – 12 years	575	10 – 18 years	600	10 – 18 years	600	9 – 13 years	600
13 – 15 years	725					14 – 18 years	700
16 – 19 years	750						
Men		Men		Men		Men	
20 – 39 years	750	19 – 65 years	600	19 – 65 years	600	19 – 30 years	900
40 – 49 years	750	> 65 years	600	> 65 years	600	31 – 50 years	900
50 – 59 years	750					51 – 70 years	900
≥ 60 years	750					>70 years	900
Women		Women		Women		Women	
20 – 39 years	750	19 – 65 years	500	19 – 65 years	500	19 – 30 years	700
40 – 49 years	750	> 65 years	600	> 65 years	600	31 – 50 years	700
50 – 59 years	750					51 – 70 years	700
≥ 60 years	750					> 70 years	700
Pregnancy		Pregnancy		Pregnancy		Pregnancy	
1 <sup>st</sup> trimester	750		800		800	14 – 18 years	750
2 <sup>nd</sup> trimester	750					19 – 30 years	770
3 <sup>rd</sup> trimester	750					31 – 50 years	770
Lactation		Lactation		Lactation		Lactation	
1 <sup>st</sup> 6 months	1,200		850		850	14 – 18 years	1,200
2 <sup>nd</sup> 6 months	750					19 – 30 years	1,300
						31 – 50 years	1,300