15 Iron

15.1 Introduction

Iron represents approximately 35 and 45 mg/kg of body weight in adult women and men, respectively. Functionally important forms of iron in the body exist in four major classes (IOM, 2001):

1. Iron containing heme proteins (hemoglobin, myoglobin and cytochromes) - important for oxygen transport and storage as well as electron transport.
2. Iron sulphur enzymes (flavoproteins, heme-flavoproteins) involved primarily in energy metabolism.
3. Iron storage and transport proteins (transferrin, lactoferrin, ferritin and hemosiderin) participating in iron uptake, transport and storage in the body.
4. Other iron-containing or activated enzymes (sulphur, nonheme enzymes)

Iron also plays important roles in cellular processes such as the synthesis of DNA, RNA and proteins; electron transport; cellular respiration; cell proliferation and differentiation; and regulation of gene expression. It plays a crucial role in maintaining cellular iron homeostasis by regulating gene expression at the post-transcriptional level. Iron homeostasis is critical for normal brain function, especially in learning and memory.

15.2 Food sources

There are two types of iron in foods - haem iron and non-haem iron. Haem iron is derived primarily from the haemoglobin and myoglobin of flesh foods such as meats, fish, and poultry. About 40 percent of iron from meat, fish, and poultry is in the haem form while the rest is nonheme iron. Non-haem iron is found in plant foods such as breads, cereals, dark leafy vegetables (such as spinach, fern shoots, *kangkung*), legumes and eggs. Examples of food sources of iron are given in Table 15.1.

Table 15.1 Food sources of iron

Food	Iron (mg/100g)
Chickpea	6.9
Fried soya bean curd	7.3
Fern Shoots (*pucuk paku*)	4.8
Bitter gourd	6.1
Spinach	5.0
Kangkung	5.2
Lean beef meat	2.2
Chicken	2.8
Egg	2.4
Anchovy, whole	5.3
Fresh cockles	13.2
Kuih-teow	3.4
Wholemeal bread	3.2

Source: Tee *et al*. (1997)

15.3 Deficiencies

Important subclinical and clinical consequences of iron deficiency are impaired physical work performance, developmental delay, cognitive impairment, and adverse pregnancy outcomes (IOM, 2001). The bulk of experimental and epidemiological evidence in humans suggests that functional consequences of iron deficiency (related both to anemia and tissue iron concentration) occur only when iron deficiency is of a severity sufficient to cause a measurable decrease in hemoglobin concentration.

Iron deficiency has been shown to impair work performance. Haas and Brownlie (2001) reviewed 29 studies and explained two separate mechanisms whereby iron deficiency can affect productivity. The first is through a reduction in tissue oxidative capacity, which can affect endurance and efficiency, and is related to iron deficiency not necessarily accompanied by anemia. Work output can also be brought about by a decrease in hemoglobin concentration. The authors suggested interventions for not only those showing signs of iron deficiency anaemia, but also those having iron deficiency without anaemia.

There is evidence of an association between iron deficiency anaemia and impaired performance in tests of mental and motor function in childhood. Less is known about the actual mechanism involved, and which part of the brain is affected. Reversibility of cognition in children has been observed when iron was given and anaemia was corrected. Nonetheless, longitudinal studies consistently indicate that children anaemic in infancy continue to have poorer cognition, school achievement and more behavioral problems in middle childhood (Grantham-Mcgregor & Ani, 2001).

Iron deficiency anaemia is a significant problem for pregnant mothers in developing countries (IOM, 2001). Increased perinatal maternal mortality is associated with anemia in women when the anemia is severe (hemoglobin < 40 g/l). However, even moderate anemia (hemoglobin < 80 g/l) has been associated with a two-fold risk of maternal death. The mechanisms associated with higher mortality of anemic women are not well understood. Heart failure, hemorrhage, and infection have been identified as possible causes

Several large epidemiological studies have demonstrated that maternal anaemia is associated with premature delivery, low birth weight and increased perinatal infant mortality. High haemoglobin concentrations at the time of delivery are also associated with adverse pregnancy outcomes, such as the newborn infant being small for gestational age. Therefore, there is a U-shaped relationship between haemoglobin concentrations and prematurity, low birth weight and foetal death, the risk being increased for haemoglobin concentration below 90 g/l, or above 130 g/l. The etiological factors are different however at each end of the spectrum. Iron deficiency limits the expansion of the maternal erythrocyte cell mass while elevated haemoglobin levels decrease plasma volume that is associated with maternal hypertension and eclampsia. Maternal iron deficiency anaemia may also limit the infant's iron status although infants appear to meet their iron needs at the expense of the mother.

The World Health Organization estimated that about 40% of the world's population (more than 2 billion individuals) suffers from anaemia (WHO, 2000). The groups with the highest prevalence are: pregnant women and the elderly, about 50%; infants and children of 1-2 years, 48%; school children, 40%; non-pregnant women, 35%; adolescents, 30-55%; and preschool children, 25% (Allen & Gillespie, 2001). WHO suggested the classification of anaemia of public health significance according to the prevalence rate, namely <15% as "low", 15-40% as "medium" and >40% as "high".

Various studies in the country have shown that iron deficiency anaemia remains a significant problem. A survey in 1999-2000 by Ministry of Health Malaysia supported by UNICEF reported 18.3% and 20.8% of boys and girls below 5 years old respectively to be anaemic (hemoglobin concentration < 11 g/dl) (Khor, 2002). A study carried out in Peninsular Malaysia reported prevalence of 22% anemia in children aged 7-12 years of both sexes, 25% among female subjects aged 18 to under 60 years and 23% in elderly of both sexes (Tee *et al*., 1998). Subjects studied comprised various community groups, namely fishing, rice-growing, rubber, coconut and estates. The prevalence of anemia among rural elderly Malays was also found to be quite high by Shahar et al. (1999), approximately a third of the men and women were anaemic (Hb <12 g/dl for men; <13 g/dL for women). Rural pregnant women have also shown high prevalence of anaemia (Somboonsook *et al*., 1995). In a study on adolescents from a rural community in Sabah, 20% of the subjects were anaemic (Foo *et al*., 2004). Remote interior communities in Sarawak also showed a high prevalence of anaemia among men >40 years, among adolescents, young women, as well as elderly females > 61 years old (Sagin *et al*., 2002).

15.4 Factors affecting iron requirement

Iron status of subject

The body iron stores regulator plays an important part in regulating iron absorption in accordance with the body’s needs, increasing absorption when stores are low and decreasing when they are high. During the development of a negative iron balance (when absorption is smaller than losses), iron stores are first depleted (serum ferritin is lowered), which is successively associated with a continuous increase in dietary iron absorption. When iron stores are depleted there will be a concomitant reduction in the concentration of Hb. This reduction is also associated with an increase in iron absorption ((Hallberg & Hulthen, 2000).

Amount of dietary haem iron and potentially available non-haem iron (adjustment for fortification iron and contamination iron)

Dietary haem iron is better absorbed because haem is soluble at the pH of the small intestine. For example, the average absorption of haem iron from meat-containing meals is about 25 percent. Haem iron uptake by absorptive enterocytes is not influenced by the dietary constituents that adversely affect the absorption of inorganic iron. However, haem iron can be degraded and converted to non-haem iron if foods are cooked at a high temperature for too long. Non-haem iron compound used for the fortification of foods will only be partially available for absorption. Once iron is dissolved, its absorption from fortificants and food contaminants is influenced by the same factors as the iron native to the food substance.

Balance between enhancing and inhibiting factors

Several dietary factors have been identified which positively or negatively influenced the absorption of the dietary iron (Hallberg & Hulthen, 2000). The absorption of nonheme iron from a meal depends upon the net effect of factors enhancing iron absorption (ascorbic acid and organic acids; meat, chicken, fish and other seafood; fermented vegetables, fermented soy sauces) and factors inhibiting iron absorption (phytates and inositol phosphates; iron-binding polyphenols; calcium; soy proteins and vegetable proteins) (FAO/WHO, 2002).

Bioavailability

The bioavailability of iron in western-type diet is 14 to 16% in borderline iron deficient subjects (Hallberg & Rossander-Hulthen, 1991). Diets that contain smaller portions of meat and fish, high phytates and some vegetarian meals each week was found to have iron bioavailability of 12%. Reducing the meat and fish intake further will reduce the iron bioavailability to about 10%. In the absence of meat and fish and with a high intake of phytate, polyphenols and vitamin C, the bioavailability of iron is about 5%. Table 15.2 shows examples of diets with different iron bioavailability. Common Malaysian diets have iron bioavailability of about 4 to 12% (Ismail *et al.*, 2001).

The amount of dietary iron absorbed is mainly determined by the amount of body stores of iron and by the properties of the diet (iron content and bioavailability). The absorption of haem iron varies from about 40 percent during iron deficiency to about 10 percent during iron repletion (Hallberg, Hulthen & Gramatkovski, 1997). On the other hand, the absorption of non-haem iron differs depending on the presence of other dietary components and physiological conditions. Examples of several types of diets and their iron bioavailability are given in Table 15.2. It is important then to adjust absorbed iron requirements according to different types of diets especially in vulnerable groups. Table 15.3 shows data of iron absorption in women of 55 kg body weight with no iron stores.

The FAO/WHO (2002) recommended developing countries to adopt the 5% and 10% bioavailability level and in population consuming more Western-type diets (mainly depending on meat intake), the two levels of 12% and 15% would be adequate..

Table 15.2 Examples of diet with different iron bioavailability

Type of diet	Bioavailability µg/kg/day
Preagricultural ancestors Plant/animal subsistence: 65/35	
Very high meat and ascorbic acid	150
Very high meat in 2 main meals daily and high ascorbic acid (theoretical)	75
High meat/fish in 2 main meals daily	66.7
Moderate meat/fish in 2 main meals daily	53.2
Moderate meat/fish in 2 main meals daily, low phytate and calcium	42.3
Meat/fish in 60% of 2 main meals daily, high phytate and calcium	31.4
Lower meat intake, high phytate. Often one main meal	25
Meat/fish negligible, high phytate. High tannin, low ascorbic acid	15

Source: FAO/WHO (2002)

Table 15.3 Translation of bioavailability expressed as amount of iron absorbed into percent absorbed for two levels of iron intake

Bioavailability, µg/kg/day	Absorption as mg Fe at no iron stores in women of 55 kg body weight	Bioavailability %	
		15 mg	**17 mg**
150	8.25	55.0	48.8
75	4.13	27.5	24.4
66.7	3.67	24.5	21.8
53.2	2.93	19.5	17
42.3	2.32	15.5	13.5
31.4	1.73	11.5	10
25	1.38	9.2	8.2
15	0.83	5.5	4.7

Source: FAO/WHO (2002)

15.5 Setting requirements and recommended intakes of iron

The recommended nutrient intake (RNI) for iron for Malaysia is based on the FAO/WHO (2002) recommendations. The various physiological requirements (basal iron losses, iron for growth and menstrual iron losses) taken by both FAO/WHO (2002) (Table 15.4) and IOM (2001) in setting the requirement were considered. Beside the physiological requirements, the amount of iron in food and its bioavailability in different diets were also taken into consideration. Taking into consideration available local reports on iron intake of communities and the magnitude of the iron deficiency problem in the country, the Technical Sub-Committee on Minerals decided to adopt two iron bioavailability levels of FAO/WHO (2002) - 10% and 15%. The RNIs for iron for Malaysia are given in bold in the following paragraphs according to age groups and summarised in Appendix 15.1.

Table 15.4 Iron intakes required for growth, median basal iron, menstrual losses in women and total absolute iron requirements for adolescents

Age/Sex	Growth needs mg/day	Basal loss mg/day	Menstruation mg/day	Absorbed iron required, mg/day (95th percentile)
Boys: 10 - 14 years	0.55	0.62	-	1.46
15 - 18 years	0.60	0.90	-	1.88
Girls: 10 - 14 years*	0.55	0.65	-	1.40
10 - 14 years	0.55	0.65	0.48	3.27
15 - 18 years	0.35	0.79	0.48	3.10

* Non-menstruating

Source: FAO/WHO (2002)

Infants (0-5 months)

Infants ages 0-5 months have a considerable endowment of iron (80 mg/kg) from the mother and possess a high haemoglobin concentration. Iron requirements during the first 4-6 months of life of full-term infants can be met by iron provided through breast milk as the total body iron of infants at birth and 4 months of age remain essentially the same. Infants born prematurely or with low birth weight should receive additional iron from other dietary sources after two months from birth.

Thus, for 0-5 months old infants, there will be no recommended iron intakes as neonatal stores are adequate to meet iron requirement during this age period, and breast feeding is fully encouraged (FAO/WHO, 2002)

Infants (6-11 months)

Infants aged 6-11 months have an increase in body iron need due to increase in basal iron losses, growth and the decrease in iron store from birth. In addition to breast milk, iron needs must be met from foods. Total iron requirements is calculated by taking into consideration basal iron losses (about 0.17 mg/day) and iron required for growth (0.55 mg/day) which lead to total iron required of 0.93 mg/day (95th percentile)

(FAO/WHO, 2002). During this period, the infant should be introduced to complementary foods.

	% Bioavailability	
	10	**15**
RNI for infants, mg/day		
6 - 11 months	**9**	**6**

Children

The mean increase of weight from age 2 till onset of puberty is averaged 2.5-2.75 kg/year (Bothwell *et al.,* 1979) which is equivalent to iron requirement for growth of 0.3 mg/day. Basal iron losses range from 0.2 to 0.4 mg/day. The total iron required (95th percentile) for the age ranges 1-3, 4-6 and 7-9 years old are 0.58 mg/day, 0.63 mg/day and 0.89 mg/day respectively. It is assumed that children by the second half of their second year of life would have started to eat with the families.

	% Bioavailability	
	10	**15**
RNI for children, mg/day		
1 - 3 years	**6**	**4**
4 - 6 years	**6**	**4**
7 - 9 years	**9**	**6**

Adolescents

The major physiological event occurring in this age group is puberty. The associated physiological processes that have major impacts on iron requirements are growth spurt in both sexes, menarche in girls and major increases in haemoglobin concentrations in boys. Due to differences in requirements, the recommendations are specified separately for boys and girls.

At low bioavailability levels of 5 and 10%, iron needs (especially for female adolescent) are exceedingly high and would be difficult to be met by the usual plant-based diets of Malaysians. Thus, it is important that dietary advice on choice of diets be made or iron supplementation be recommended.

		% Bioavailability	
		10	**15**
RNI adolescents, mg/day			
Boys	**10 - 14 years**	**15**	**10**
	15 - 18 years	**19**	**12**

		% Bioavailability 10	15
RNI adolescents, mg/day			
Girls	**10 - 14 years***	**14**	**9**
	10 - 14 years	**33**	**22**
	15 - 18 years	**31**	**21**

**non-menstruating*

Adults

In men and menopause women, basal iron loss is the only component used to estimate total needs for absorbed iron, which amounts to about 1.37 mg/day and 1.13 mg/day respectively (95th percentile). For menstruating women, the needs derived from basal iron loss (0.87 mg/day) and menstrual loss (1.90 mg/day) giving a total requirement of 2.94 mg/day (95th percentile). Based on the habitual diets of Malaysian adult, it is difficult for a menstruating women to achieve the RNI for 5% bioavailability.

		% Bioavailability 10	15
RNI adults, mg/day			
Men	**19 years and above**	**14**	**9**
Women	**19 years and above**		
	Premenopause	**29**	**20**
	Postmenopause	**11**	**8**

Pregnancy

The components used to estimate requirement for absorbed iron include basal losses, iron deposited in foetus and related tissues, and iron utilized in expansion of haemoglobin mass. According to FAO/WHO (2002), the needs for iron at first trimester remain at the level of replacing basal iron loss since there is no menstrual loss. However, during the second and third trimester, iron needs increase tremendously and generally beyond that can be adequately supplied by diets and therefore no recommendation are made. Iron supplementation (about 100 mg) is therefore recommended for pregnant women.

Lactation

For lactation women, iron is secreted in breast milk. Adding this value of 0.3 mg/day to the basal loss of 0.87 mg/day, it is estimated that the iron requirements for lactating women to be about 1.1 mg/day (FAO/WHO, 2002). The Malaysian RNI also assumes that menstruation may resume after 6 months of exclusive breast feeding. Thus, lactating women with menstruation may have a higher iron requirement.

	% Bioavailability	
	10	**15**
RNI for lactation, mg/day		
0 - 3 months	**15**	**10**
4 - 6 months	**15**	**10**
7 - 12 months	**15**	**10**
7 - 12 months*	**32**	**21**

** For lactating women with menstruation*

Discussions on revised RNI for Malaysia

The revised RNI for Malaysia for iron proposes two bioavailability levels namely, 10% and 15% based on the considerations explained in FAO/WHO (2002). It is believed that, while 15% bioavalability approximates the usual level of iron intake among the middle and higher income categories, there is a need to include a lower bioavailability level (10%) for others such as vegetarians and the poor.

A comparison of the revised RNI for Malaysia with the previous Malaysian RDI, the recommended intakes of FAO/WHO and those of IOM (2001) are given in Appendix 15.1. The values recommended by IOM (2001) are generally lower than those of FAO/WHO (2002) because the former are based on a higher bioavailability level, presumably higher than 15%. Highlighted below are some differences between the Malaysian RNI values and those in the previous Malaysian RDI (Teoh, 1975), which was based on 10% iron bioavailability:

(i). In Teoh (1975), there was no recommendation for iron for infants, perhaps based on the assumption that infants have sufficient store to last through one year of age. However, in the Malaysian RNI, such an assumption is made for 0-5 months only, after which 6 to 9 mg iron/day is recommended for 6-11 months depending on the bioavailability level considered.

(ii). For children 1-6 years, the revised RNIs are lower than the 10 mg/day recommended in Teoh (1975). For older children 7-9 years, the decrease is marginal.

(iii). For adolescents, the situation is reversed. The revised RNIs for both boys and girls of all age groups are higher than the previous RDI. The increase ranged from 6-50%. This trend continued for the adult men and women.

(iv). As for pregnancy, both the previous RDI and the current Malaysian RNI do not include any recommendations, as iron requirement during period is difficult to be met from diet only, and supplementation becomes necessary.

(v). Unlike in Teoh (1975) that did not include iron recommendation for lactation, the Malaysian RNI has 10 to 15 mg/day depending on the bioavailability level. The Malaysian RNI has also included iron recommendation for lactating women who have resumed menstruation.

15.6 Toxicity and tolerable upper intake levels

Iron in excess may lead to health problems. The deleterious effects of excess iron is related to its ability to generate reactive oxygen species via the Fenton reaction (McCord, 1998). The net effects are DNA damage, impaired synthesis of proteins, membrane lipids and carbohydrates, induction of proteases and altered cell proliferation. Excess free iron can react directly with unsaturated fatty acids and induce lipid hydroperoxidases to form alkoxyl and/or peroxyl radicals which in turn, impair severely cellular integrity leading to cell death. This destructive potential of iron has led to the suggestion that excess iron might play a role in the multi-step processes of carcinogenesis, pathogenesis of atherosclerosis, or neurodegerative disorders such as Parkinson's or Alzheimer's diseases (Connor *et al*., 1992).

Gastrointestinal side effects were selected as the critical adverse effects on which to base the UL for iron. Although gastrointestinal distress is not a serious side effect when compared with possible risk for vascular disease and cancer, the other side effects considered did not permit the determination of UL (IOM, 2001). Based on this, the upper tolerable level is set at 45 mg/day for adolescents and adults. For children, due to lack of data, the median intake of iron given supplement was used and the level of 40 mg/day for infants and children was adopted.

Tolerable upper intake levels (UL)

Infants and children (0 - 9 years)	**40 mg/day**
Adolescents and adults (10 years and above)	**45 mg/day**

15.7 Research recommendations

The following priority areas of research are recommended:

- Periodic assessment of the iron status of vulnerable groups such as young children, women of reproductive ages and elderly especially in poor communities.
- Studies on iron bioavailability of mixed diets among various ethnic, socioeconomic and vegetarian groups.
- Intervention studies to determine the efficiency and efficacy of long-term supplementation of iron among women.
- Content of phytate and iron-binding polyphenols in foods.

15.8 References

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Appendix 15.1 Comparison of recommended intake for iron: RDI Malaysia (1975), RNI Malaysia (2005), RNI of FAO/WHO (2002), and RDA of IOM (2001)

Malaysia (1975)		Malaysia (2005)			FAO/WHO (2002)					IOM (2001)	
Age groups	RDI (mg/day)	Age groups	RNI (mg/day) % Bioavailability 10	15	Age groups	RNI (mg/day) % Bioavailability 5	10	12	15	Age groups	RDA (mg/day)
Infants		Infants			Infants					Infants	
< 1 year	none	0 – 5 months	*a*	*a*	0 – 6 months	a	a	a	a	0 – 6 months	0.27[f]
		6 – 12 months	9	6	7 – 12 months	19	9	8	6	7 – 12 months	11
Children		Children			Children					Children	
1 – 3 years	10	1 – 3 years	6	4	1 – 3 years	13	6	5	4	1 – 3 years	7
4 – 6 years	10	4 – 6 years	6	4	4 – 6 years	13	6	5	4	4 – 8 years	10
7 – 9 years	10	7 – 9 years	9	6	7 – 9 years	18	9	7	6		
Boys		Boys			Boys					Boys	
10 – 12 years	10	10 – 14 years	15	10	10 – 14 years	29	15	12	10	9 – 13 years	8
13 – 15 years	18	15 – 18 years	19	12	15 – 18 years	38	19	16	12	14 – 18 years	11
16 – 19 years	18										
Girls		Girls			Girls					Girls	
10 – 12 years	10	10 – 14 years[b]	14	9	10 – 14 years[b]	28	14	12	9	9 – 13 years	8
13 – 15 years	24	10 – 14 years	33	22	10 – 14 years	65	33	28	22	14 – 18 years	15
16 – 19 years	28	15 – 18 years	31	21	15 – 18 years	62	31	26	21		
Men		Men			Men					Men	
20 – 39 years	9	19 – 65 years	14	9	19 – 65 years	27	14	11	9	19 – 30 years	8
40 – 49 years	9	>65 years	14	9	> 65 years	27	14	11	9	31 – 50 years	8
50 – 59 years	9									51 – 70 years	8
≥ 60 years	9									>70 years	8
Women		Women			Women					Women	
20 – 39 years	28	19 – 50 years[c]	29	20	19 – 50 years[c]	59	29	24	20	19 – 30 years	18
40 – 49 years	28	51 – 65 years[d]	11	8	51 – 65 years[d]	23	11	9	8	31 – 50 years	18
50 – 59 years	9	>65 years	11	8	> 65 years	23	11	9	8	51 – 70 years	8
≥ 60 years	9									>70 years	8
Pregnancy		Pregnancy			Pregnancy					Pregnancy	
1st trimester	*g*	1st trimester	*e*	*e*	1st trimester	*e*	*e*	*e*	*e*	14 – 18 years	27
2nd trimester	*g*	2nd trimester	*e*	*e*	2nd trimester	*e*	*e*	*e*	*e*	19 – 30 years	27
3rd trimester	*g*	3rd trimester	*e*	*e*	3rd trimester	*e*	*e*	*e*	*e*	31 – 50 years	27
Lactation		Lactation			Lactation					Lactation	
1st 6 months	*g*	0 – 3 months	15	10	0 – 3 months	30	15	13	10	14 – 18 years	10
2nd 6 months	*g*	4 – 6 months	15	10	4 – 6 months	30	15	13	10	19 – 30 years	9
		7 – 12 months	15	10	7 – 12 months	30	15	13	10	31 – 50 years	9
		7 – 12 months[h]	32	21							

a - Neonatal iron stores are sufficient to meet the iron requirement for the first six months in full term infants. Premature infants and low birth weight infants require additional iron.
b - Non-menstruating adolescents
c - Pre-menopausal
d - Menopausal
e - It is recommended that iron supplements in tablet form be given to all pregnant women because of the difficulties in correctly evaluating iron status in pregnancy. In the non-anaemic pregnant woman, daily supplements of 100 mg of iron (e.g., as ferrous sulphate) given during the second half of pregnancy are adequate. In anaemic women higher doses are usually required.
f - Average intake
g - If adequate stores of iron have been built up throughout life, recommended intake for pregnant and lactating women would be the same as that for nonpregnant women. Iron stores of majority of women are however inadequate and would thus require nondietary supplements of iron
h - Lactating women with menstruation