

# Iron

## Introduction

Scientists have known since the seventeenth century that iron was present in the blood, but definitive evidence that inorganic iron could be used in the synthesis of hemoglobin was obtained only some seventy years ago (Fairbanks 1999). In addition, iron is an essential component of the myoglobin in muscle, cytochromes, and other enzymes, including the antioxidant enzyme catalase (Yip and Dallman 1996).

Dietary iron occurs in three major forms: ferrous iron ( $\text{Fe}^{2+}$ ), ferric iron ( $\text{Fe}^{3+}$ ), and heme iron ( $\text{Fe}^{2+}$  chelated into a complex organic compound to complete the heme structure, which occurs in hemoglobin, myoglobin, and certain enzymes). Ferrous iron and ferric iron may be present as part of, or attached to, many different inorganic or organic compounds: the oxide of iron, or complexed with amino acids, citric acid, vitamin C, transferrin, ferritin, and iron-cytochrome reductase (“Iron and iron deficiency” 1998).

Iron deficiency may result from inadequate amounts of dietary iron, depressed or inhibited absorption, or blood loss. Protracted deficiency can lead to a characteristic anemia (microcytic or hypochromic). In more recent studies, iron deficiency has been linked to decreased work performance, altered behavior, decreased intellectual performance, disturbed body temperature regulation, decreased immune function, and decreased resistance to infection (Yip and Dallman 1996; Lynch, 2011).

## Bioavailability

The amount of iron in the body is regulated principally by intestinal absorption, transport, storage (mainly in the liver), mobilization, and loss (such as during menstruation) (Yip and Dallman 1996; Fairbanks 1999; Tandara and Salamunic 2012; Collings et al. 2013). In general, the bioavailability of ferrous iron ( $\text{Fe}^{2+}$ ) is somewhat higher than that of ferric iron ( $\text{Fe}^{3+}$ ), and more soluble salts have higher bioavailability than less soluble ones. Heme iron ( $\text{Fe}^{2+}$ , but bound

with the heme molecule unbound from hemoglobin and myoglobin) is more efficiently absorbed than nonheme iron, and heme iron absorption is not limited by the iron absorption control mechanism of the intestine. Depending on the amounts of meats and related products consumed, this extremely efficient absorption of heme iron presents significant problems in identifying the amount of nonheme iron salts that can be considered safe.

In general, ferrous iron, especially the more soluble compounds such as ferrous citrate or ferrous ascorbate, is more easily absorbed than the ferric compounds, which must be reduced from  $\text{Fe}^{3+}$  to  $\text{Fe}^{2+}$  before they can be absorbed. Vitamin C is especially effective in enhancing iron absorption not only because it forms soluble complexes with iron but also because it is effective in reducing the ferric form to the ferrous form.

Assuming that ferrous iron is presented to the intestinal mucosa cells, the amount of iron absorbed is regulated by the body's stores of iron—the more stored, the less absorbed. Specifically, the proteins ferritin and transferrin facilitate and regulate iron absorption. Some 4 to 10 percent of dietary nonheme iron is usually absorbed, depending on the specific chemical forms, other dietary components such as vitamin C and amino acids and inhibitors such as phytic acid, and the body stores of iron. Also, low amounts of stomach acid allow the pH of the gastric contents to go up, and  $\text{Fe}^{2+}$  can be precipitated as the very insoluble compound ferrous hydroxide. This increase in gastric pH also occurs as a result of regular, heavy use of antacid drugs.

The amount of nonheme iron is strongly regulated by the intestinal mucosa (ferritin and then transferrin) to help assure that the total body amount of iron is within an acceptable range. In brief, nonheme iron absorption is strongly regulated.

In contrast, heme iron absorption is not strongly regulated: it is usually on the order of 20 to 25 percent of the heme iron ingested, regardless of the body load of iron. Heme iron is absorbed from meat more efficiently than dietary inorganic iron and in a different manner. Thus, iron deficiency is less frequent in countries where meat constitutes a significant part of the diet. Proteolytic digestion of myoglobin, hemoglobin, and cytochromes results in the release of heme,

which is maintained in a soluble form by globin protein degradation products so that it remains available for absorption. Chelators that either diminish or enhance the absorption of inorganic iron have little effect on the absorption of heme iron. Heme enters the small intestinal absorptive cell as an intact metalloporphyrin.

These differences in iron absorption present difficulties that have yet to be significantly addressed by the scientific, policy, and regulatory communities.

### **Safety Considerations**

Almost all supplemental or fortification iron is in the form of one or another ferrous compound. The safety of these amounts depends not only on the body load of iron and the specific chemical form but also on the amount of heme consumed (principally in animal-based foods such as meats, fish, and poultry). A few heme supplements are available in the U.S. If heme consumption is high, the tolerance for nonheme iron in supplements or fortified foods should be lowered. Few experiments have been conducted to describe and quantify this relationship.

Consequently, policy and regulatory decisions must be made with very incomplete evidence. Because numerous clinical trials have been conducted with various levels of supplemental nonheme iron over short to intermediate periods, some evidence is available that the common dietary variations in heme iron consumption are not great enough to have major effects on the safety of the supplemental nonheme iron. Because of the absences of appropriate quantitative data, it is necessary to assume some average intake of heme that does not vary greatly enough to have public safety impacts—for most people.

For chronic, habitual intake by individuals who do not have any genetic defects that increase iron absorption or retention, iron has shown no adverse effects at levels several times the RDA of 8 mg for men and 18 mg for young women (Institute of Medicine [IOM] 2001). Loss of iron during menstruation accounts for most or all of the difference between the male and female RDAs.

Chronic iron overload has resulted from several conditions or circumstances, including hereditary hemochromatosis, alcoholic liver disease, and excessive intake of dietary iron, especially from home-brewed alcoholic beverages (Fairbanks 1999). Long-term daily ingestions of iron from some home-brewed alcoholic beverages may exceed 100 mg per day. This level of chronic iron intake, at least in combination with chronically high alcohol intake, can lead to Bantu siderosis, a liver disease first discovered in Africa that involves excessive storage of iron and subsequent diseases of the liver and other organs.

Hereditary hemochromatosis, a genetic disorder of iron uptake and storage, has a homozygous frequency of less than 3 to 4 per 1,000 in populations of European extraction (Yip and Dallman 1996). This condition may lead to excessive iron storage even at intake levels recommended for most of the population. There is no clear evidence that carriers for the gene (heterozygous condition) have any increased risk of excessive iron uptake and storage, but such an effect, if any, must be very small compared with the effect in those who are homozygous.

### ***Heart Disease***

Select studies on high plasma ferritin levels (Sullivan 1981; Salonen et al. 1992) led some scientists to suggest that dietary iron might be linked to an increased risk of heart disease. This relationship has been contradicted by subsequent evidence and evaluation (Aronow 1993; Baer et al. 1994; Liao et al. 1994; Morrison et al. 1994; Moore et al. 1995; Sempos et al. 1996; Franco et al. 1998; Nasser et al. 1998; Danesh and Appleby 1999; Kaldara-Papatheodorou et al. 2010; Avni et al. 2012) indicating that there is, in fact, no causal relationship. Although some follow-up studies in Europe and Japan support the concept that dietary iron may increase the risk of heart disease (Roest et al. 1999; Tuomainen et al. 1999; Zhang, Iso, et al. 2012), the preponderance of evidence and expert opinion suggests that there is no significant risk (IOM 2001; Expert Group on Vitamins and Minerals [EVM] 2003; European Food Safety Authority [EFSA] 2004).

For prolonged but not chronic use, such as in pregnancy, daily supplements of up to 60 mg are routinely and safely consumed. In other adults, the 95th percentile of supplemental intake is

reported as 54 mg for men and 67 mg for women (Stewart et al. 1985). Many high-potency multivitamin and multimineral dietary supplements contain 27 mg of iron. No adverse effects have been attributed to this intake level.

### ***Colonic Cancer***

The hypothetical basis on which dietary iron might increase the risk of colonic cancer involves several factors: the catalytic oxidative effects of iron, the procarcinogenic effects of oxidative stress, the association of elevated plasma ferritin values with risk of colonic adenomatous polyps, and the progression of polyps to colonic cancer (Nelson 1992; Tseng et al. 1996). While there is strong evidence for most steps in this mechanistic or associative chain, it does not follow that increases in dietary iron necessarily lead to an increased risk of colonic cancer (Zhang, Giovannucci, et al. 2011).

Dietary iron is absorbed with an efficiency that ranges from as low as 1 or 2 percent (from diets high in inhibitors such as phytic acid) to as high as 30 percent (in pregnant women or those who are iron deficient) (Fairbanks 1999). The mucosal control of iron applies only to nonheme forms, making heme iron absorption usually much more efficient than that of nonheme iron. Regardless of the various absorption factors, however, most ingested iron is not absorbed, giving it the potential to produce oxidative effects in the colonic contents during intestinal transit. The oxidative influences of unabsorbed iron in the intestine may possibly increase the risk of cancer, but this has not been confirmed.

### ***Acute Iron Poisoning in Children***

Acute iron poisoning has occurred in children under three years of age who have accidentally consumed massive amount of iron salts in the form of high-potency (usually 60 or 65 mg), single-nutrient iron supplements (Food and Drug Administration [FDA] 1995), which are usually recommended for prenatal use. The quantities of iron involved in these cases exceed 900 mg in a single ingestion. Such levels of iron override the intestinal regulatory mechanisms and lead to greatly increased plasma levels of iron. No severe adverse effects other than mild gastrointestinal

symptoms, however, have been reported in association with acute ingestion of any of the many children's multivitamins that contain iron (most with 27 mg or less iron). The adverse effects that may result from acute ingestion of large amounts of iron have no bearing on the safety of appropriately used iron supplements (Chang and Rangan 2011).

## **Official Reviews**

After a comprehensive review and analysis, the key organizational bodies concerned with vitamin and mineral issues ( the IOM, the EVM, and EFSA have found no credible evidence that high iron intake causes any increased risk of cardiovascular disease or cancer in healthy adults (IOM 2001; EVM 2003; EFSA 2004).

**IOM (2001).** The IOM review identified, based on the clinical evidence by Frykman and coworkers (1994), a significant but low frequency of adverse gastrointestinal effects (constipation and irritation) after administration of iron fumarate, a soluble iron salt, in amounts of 60 mg or more of supplemental iron. Thus, the IOM recommended a supplemental iron LOAEL of 60 mg. To this value, it added the 10 to 11 mg per day dietary iron intake used in the Frykman study (Frykman et al. 1994), setting a total intake LOAEL at 70 mg. Because of the low frequency of the adverse effects and patients' ability to notice and correct for them, the IOM selected a relatively small UF of 1.5 to derive a UL of 45 mg for adults.

**EVM (2003).** The UK's EVM concluded that the evidence was insufficient to set an SUL value for iron. Instead, it set a guidance level based on some clinical reports of gastrointestinal effects from doses of soluble iron salts containing iron levels as low as 50 mg. The guidance level was calculated by applying a standard default UF of 3 to the low end of the range of doses causing gastrointestinal effect. That is, the guidance level is 50 mg divided by 3, or 17 mg per day. This value is much lower than the IOM value and contrasts with the EFSA conclusion that the data are simply insufficient to reach any conclusion.

**EFSA (2004).** EFSA reviewed and evaluated iron safety but concluded that the data were not sufficient to identify a UL value.

## CRN Recommendations

A substantial body of evidence supports a NOAEL value for longer-term iron supplementation of 18 to 65 mg per day (with little data on intermediate values) for ferrous and ferric compounds. The data of Frykman and coworkers (1994) indicate a low frequency of mild gastrointestinal effects that are not pathological and are self-limiting due to consumer awareness. This frequency of mild effects represents a nuisance rather than a hazard, and 60 mg of iron qualifies as a supplemental NOAEL if the product label makes the consumer aware of the potential gastrointestinal effects. The large database supporting this conclusion and the complete absence of similar effects at lower supplemental levels, at least when the iron is not taken on an empty stomach, make it reasonable to apply a UF of 1.0. Thus, the CRN ULS for iron is 60 mg per day. It would be appropriate to have a label statement that iron-containing supplements should be taken with food. Note that these recommendations are for ferrous or ferric compounds, not heme iron.

## Quantitative Summary for Iron

CRN UL, supplemental intake	60 mg/day
IOM UL, total intake	45 mg/day
EFSA UL, total intake	Not determined
EC supplement maximum	Not determined
EVM, guidance level, supplemental intake	17 mg/day

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