

Iron

Function

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 sixty 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).

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. In recent studies, iron deficiency has been linked to decreased work performance, altered behavior and intellectual performance, disturbed body temperature regulation, and decreased immune function and resistance to infection (Yip and Dallman 1996).

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) (Fairbanks 1999; Yip and Dallman 1996). In general, the bioavailability of ferrous iron (Fe^{2+}) is somewhat higher than that of ferric iron (Fe^{3+}), and more soluble salts have higher bioavailability than less soluble ones. Heme iron (Fe^{2+} bound in the heme molecule of hemoglobin and myoglobin) is more efficiently absorbed than non-heme iron, and heme iron absorption is not limited by the control mechanism of the intestine.

Safety Evidence

For chronic, habitual intake by persons who do not have any genetic defects increasing 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 (Food and Nutrition Board 2001). Loss of iron during menstruation accounts for the difference between the male and female RDA.

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, and this level of chronic iron intake, at least in combination with chronically high alcohol intake, can lead to Bantu siderosis, a liver disease that involves excessive storage of iron.

Hereditary hemochromatosis, a genetic disorder of iron uptake and storage, has a homozygous frequency of 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, and the effect, if any, must be small compared with the effect in those who are homozygous.

Iron and 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 (Danesh and Appleby 1999; Franco et al. 1998; Nasser et al. 1998; Sempos et al. 1996; Liao et al. 1994; Aronow 1993; Moore et al. 1995; Baer et al. 1994; Morrison et al. 1994) indicating that there is, in fact, no causal relationship. Although a couple of follow-up studies in Europe support the concept that dietary iron may increase the risk of heart disease (Tuomainen et al. 1999; Roest et al. 1999), the preponderance of evidence suggesting otherwise indicates that there is no such risk (Food and Nutrition Board 2001).

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 intake is a reported 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. Adverse effects have not been attributed to any of these intake levels.

Iron and 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.

Dietary iron is absorbed with an efficiency that ranges from as low as 1 or 2 percent to as high as 30 percent, depending on the chemical form of iron ingested, the presence of dietary promoters or inhibitors, and the body's iron status (Fairbanks 1999). The mucosal control of iron applies only to non-heme forms, making heme iron absorption more efficient than that of non-heme 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. Hypothetically, 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 a massive amount of iron salts in the form of high-potency (usually 60 or 65 mg) single-nutrient iron supplements (Food and Drug Administration 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. The adverse effects that may result from accidental acute ingestion of large amounts of iron have no bearing on the safety of appropriately used iron supplements.

Published Official Reviews of Iron Safety

After a comprehensive review and analysis, FNB found no credible evidence that high iron intake caused any increased risk of cardiovascular disease or cancer in healthy adults (Food and Nutrition Board 2001). The FNB was able to identify, based on clinical evidence (Frykman et al.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, FNB identified 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, setting a total intake LOAEL at 70 mg. Because of the low frequency and self-limiting nature (due to subject awareness and correction) of the adverse effects, FNB selected a relatively small UF of 1.5 to derive a UL of 45 mg for adults.

The UK EVM concluded that the evidence was insufficient to set an SUL value for iron (Expert Group on Vitamins and Minerals 2003). Instead, it set a GL based on some clinical reports of gastrointestinal effects from doses of soluble iron salts containing iron levels as low as 50 mg. The GL was calculated by applying a default UF of 3 to the low end of the range of doses causing gastrointestinal effect. That is, the GL is 50 mg divided by 3, or 17 mg per day.

CRN ULS for Iron

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). The data of Frykman and coworkers 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.

Comparison of Safety Values for Iron

CRN ULS	60 mg (full stomach)
US FNB UL	45 mg (empty stomach)
EC SCF UL	Not reviewed (as of May 2004)
EC supplement maximum	Not established (as of May 2004)
UK EVM GL, supplement	17 mg

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From: **Vitamin and Mineral Safety 2nd Edition** ~ by John N. Hathcock, Ph.D.
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