Iron
Dietary Supplement Fact Sheet

Introduction
Iron is a mineral that is naturally present in many foods, added to some food products, and available as a dietary supplement. Iron is an essential component of hemoglobin, an erythrocyte protein that transfers oxygen from the lungs to the tissues [1]. As a component of myoglobin, a protein that provides oxygen to muscles, iron supports metabolism [2]. Iron is also necessary for growth, development, normal cellular functioning, and synthesis of some hormones and connective tissue [3].

Dietary iron has two main forms: heme and nonheme [1]. Plants and iron-fortified foods contain nonheme iron only; whereas meat, seafood, and poultry contain both heme and nonheme iron [2]. Heme iron, which is formed when iron combines with protoporphyrin IX, contributes about 10% to 16% of total iron intake in Western populations [3–5].

Most of the 3 to 4 grams of elemental iron in adults is in hemoglobin [2]. Much of the remaining iron is stored in the form of ferritin or hemosiderin (a degradation product of ferritin) in the liver, spleen, and bone marrow or is located in myoglobin in muscle tissue [1,5]. Humans typically lose only small amounts of iron in urine, feces, the gastrointestinal tract, and skin. Losses are greater in menstruating women because of blood loss. Hepcidin, a circulating peptide hormone, is the key regulator of both iron absorption and the distribution of iron throughout the body, including in plasma [1,2,6].

Many different measures of iron status are available, and different measures are useful at different stages of iron depletion. Measures of serum ferritin can be used to identify iron depletion at an early stage [7]. A reduced rate of delivery of stored and absorbed iron to meet cellular iron requirements represents a more advanced stage of iron depletion, which is associated with reduced serum iron, reticuloocyte hemoglobin, and percentage transferrin saturation and with higher total iron binding capacity, red cell zinc protoporphyrin, and serum transferrin receptor concentration. The last stage of iron deficiency, characterized by iron-deficiency anemia (IDA), occurs when blood hemoglobin concentrations, hematocrit (the proportion of red blood cells in blood by volume), mean corpuscular volume, and mean cell hemoglobin are low [2,8]. Hemoglobin and hematocrit tests are the most commonly used measures to screen patients for iron deficiency, even though they are neither sensitive nor specific [5,9]. Hemoglobin concentrations lower than 13 g/dL in men and 12 g/dL in women indicate the presence of IDA [5]. Normal hematocrit values, which are generally three times higher than hemoglobin levels, are approximately 41% to 50% in males and 36% to 44% in females [10].

Recommended Intakes
Intake recommendations for iron and other nutrients are provided in the Dietary Reference Intakes (DRIs) developed by the Food and Nutrition Board (FNB) at the Institute of Medicine (IOM) of the National Academies (formerly National Academy of Sciences) [5]. DRI is the general term for a set of reference values used for planning and assessing nutrient intakes of healthy people. These values, which vary by age and gender, include:

- Recommended Dietary Allowance (RDA): average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%-98%) healthy individuals.
- Adequate Intake (AI): established when evidence is insufficient to develop an RDA; intake at this level is assumed to ensure nutritional adequacy.
- Estimated Average Requirement (EAR): average daily level of intake estimated to meet the requirements of 50% of healthy individuals. It is usually used to assess the adequacy of nutrient intakes in population groups but not individuals.
- Tolerable Upper Intake Level (UL): maximum daily intake unlikely to cause adverse health effects.

Table 1 lists the current adult RDA for nonvegetarians. The RDAs for vegetarians are 1.6 times higher than for people who eat meat. This is because
Table 1 lists the current RDAs for iron. The RDAs for vegetarians are 1.8 times higher than for people who eat meat. This is because heme iron from meat is more bioavailable than nonheme iron from plant-based foods, and meat, poultry, and seafood increase the absorption of nonheme iron [5].

For infants from birth to 6 months, the FNB established an AI for iron that is equivalent to the mean intake of iron in healthy, breastfed infants.

Table 1: Recommended Dietary Allowances (RDAs) for Iron [5]

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
<th>Pregnancy</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 6 months</td>
<td>0.27 mg*</td>
<td>0.27 mg*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7–12 months</td>
<td>11 mg</td>
<td>11 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3 years</td>
<td>7 mg</td>
<td>7 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4–6 years</td>
<td>10 mg</td>
<td>10 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9–13 years</td>
<td>8 mg</td>
<td>8 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14–18 years</td>
<td>11 mg</td>
<td>15 mg</td>
<td>27 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>19–50 years</td>
<td>8 mg</td>
<td>10 mg</td>
<td>27 mg</td>
<td>9 mg</td>
</tr>
<tr>
<td>51+ years</td>
<td>8 mg</td>
<td>8 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adequate Intake (AI)

Sources of Iron

Food

The richest sources of heme iron in the diet include lean meat and seafood [11]. Dietary sources of nonheme iron include nuts, beans, vegetables, and fortified grain products. In the United States, about half of dietary iron comes from bread, cereal, and other grain products [2,3,9]. Breast milk contains highly bioavailable iron but in amounts that are not sufficient to meet the needs of infants older than 4 to 6 months [2,12].

In the United States, Canada, and many other countries, wheat and other flours are fortified with iron [13,14]. Infant formulas are fortified with 12 mg iron per liter [12].

Heme iron has higher bioavailability than nonheme iron, and other dietary components have less effect on the bioavailability of heme than nonheme iron [3,4]. The bioavailability of iron is approximately 14% to 18% from mixed diets that include substantial amounts of meat, seafood, and vitamin C (ascorbic acid, which enhances the bioavailability of nonheme iron) and 6% to 12% from vegetarian diets [2,4]. In addition to ascorbic acid, meat, poultry, and seafood can enhance nonheme iron absorption, whereas phytate (present in grains and beans) and certain polyphenols in some non-animal foods (such as cereals and legumes) have the opposite effect [4]. Unlike other inhibitors of iron absorption, calcium might reduce the bioavailability of both nonheme and heme iron. However, the effects of enhancers and inhibitors of iron absorption are attenuated by a typical mixed western diet, so they have little effect on most people’s iron status.

Several food sources of iron are listed in Table 2. Some plant-based foods that are good sources of iron, such as spinach, have low iron bioavailability because they contain iron-absorption inhibitors, such as polyphenols [15,16].

Table 2: Selected Food Sources of Iron [17]

<table>
<thead>
<tr>
<th>Food</th>
<th>Milligrams per serving</th>
<th>Percent DV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakfast cereals, fortified with 100% of the DV for iron, 1 serving</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>Oysters, raw, cooked with moist heat, 3 ounces</td>
<td>8</td>
<td>44</td>
</tr>
<tr>
<td>White beans, canned, 1 cup</td>
<td>8</td>
<td>44</td>
</tr>
<tr>
<td>Chocolate, dark, 45%–69% cacao solids, 3 ounces</td>
<td>7</td>
<td>39</td>
</tr>
<tr>
<td>Beef liver, pan fried, 3 ounces</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>Lentils, boiled and drained, ½ cup</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Spinach, boiled and drained, ½ cup</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Tofu, firm, ¼ cup</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Kidney beans, canned, ½ cup</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Sardines, Atlantic, canned in oil, drained solids with bone, 3 ounces</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Chickpeas, boiled and drained, ½ cup</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Tomatoes, canned, stewed, ¼ cup</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Beef, braised bottom round, trimmed to 1/8&quot; fat, 3 ounces</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Potato, baked, flesh and skin, 1 medium potato</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Cashew nuts, oil roasted, 1 ounce (15 nuts)</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Green peas, boiled, ¾ cup</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Chicken, roasted, meat and skin, 3 ounces</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Rice, white, long grain, enriched, parboiled, drained, ¼ cup</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Bread, whole wheat, 1 slice</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Bread, white, 1 slice</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Raisins, seedless, ¼ cup</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>
Table 2: Selected Food Sources of Iron [17]

<table>
<thead>
<tr>
<th>Food</th>
<th>Milligrams per serving</th>
<th>Percent DV*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spaghetti, whole wheat, cooked, 1 cup</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Tuna, light, canned in water, 3 ounces</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Turkey, roasted, breast meat and skin, 3 ounces</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Nuts, pistachio, dry roasted, 1 ounce (40 nuts)</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Broccoli, boiled and drained, ½ cup</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Egg, hard boiled, 1 large</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Rice, brown, long or medium grain, cooked, 1 cup</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Cheese, cheddar, 1½ ounces</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cantaloupe, diced, ½ cup</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mushrooms, white, sliced and stir-fried, ½ cup</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cheese, cottage, 2% milk-fat, ½ cup</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Milk, 1 cup</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* DV = Daily Value. DVs were developed by the U.S. Food and Drug Administration (FDA) to help consumers compare the nutrient contents of products within the context of a total diet. The DV for iron is 18 mg for adults and children age 4 and older. Foods providing 20% or more of the DV are considered to be high sources of a nutrient.

The U.S. Department of Agriculture’s (USDA’s) Nutrient Database Web site [17] lists the nutrient content of many foods and provides a comprehensive list of foods containing iron arranged by nutrient content and by food name.

Dietary supplements

Iron is available in many dietary supplements. Multivitamin/multimineral supplements with iron, especially those designed for women, typically provide 18 mg iron (100% of the DV). Multivitamin/multimineral supplements for men or seniors frequently contain less or no iron. Iron-only supplements usually deliver more than the DV, with many providing 65 mg iron (360% of the DV).

Frequently used forms of iron in supplements include ferrous and ferric iron salts, such as ferrous sulfate, ferrous gluconate, ferric citrate, and ferric sulfate [9,18]. Because of its higher solubility, ferrous iron in dietary supplements is more bioavailable than ferric iron [3]. High doses of supplemental iron (45 mg/day or more) may cause gastrointestinal side effects, such as nausea and constipation [9]. Other forms of supplemental iron, such as heme iron polypeptides, carboxyl iron, iron amino-acid chelates, and polysaccharide-iron complexes, might have fewer gastrointestinal side effects than ferrous or ferric salts [18].

The different forms of iron in supplements contain varying amounts of elemental iron. For example, ferrous fumarate is 33% elemental iron by weight, whereas ferrous sulfate is 20% and ferrous gluconate is 12% elemental iron [18]. Fortunately, elemental iron is listed in the Supplement Facts panel, so consumers do not need to calculate the amount of iron supplied by various forms of iron supplements.

Approximately 14% to 18% of Americans use a supplement containing iron [19,20]. Rates of use of supplements containing iron vary by age and gender, ranging from 5% of children aged 12 to 19 years to 60% of women who are lactating and 72% of pregnant women [19,21].

Calcium might interfere with the absorption of iron, although this effect has not been definitively established [4,22]. For this reason, some experts suggest that people take individual calcium and iron supplements at different times of the day [23].

Iron Intakes and Status

People in the United States usually obtain adequate amounts of iron from their diets, but infants, young children, teenaged girls, pregnant women, and premenopausal women are at risk of obtaining insufficient amounts [19,24-26]. The average daily iron intake from foods is 11.5–13.7 mg/day in children aged 2–11 years, 15.1 mg/day in children and teens aged 12–19 years, and 22.9–15.1 mg/day in men and 12.6–13.5 mg/day in women older than 19 [19]. The average daily iron intake from foods and supplements is 13.7–15.1 mg/day in children aged 2–11 years, 16.3 mg/day in children, and 16–18.5 mg/day in women older than 19. The median dietary iron intake in pregnant women is 14.7 mg/day [5].

Rates of iron deficiency vary by race and other sociodemographic factors. Six percent of white and black toddlers aged 1 to 3 years in the United States are iron deficient (defined as at least two abnormal results for the child's age and gender on transferrin saturation, free erythrocyte protoporphyrin, and/or serum ferritin tests), compared with 12% of Hispanic toddlers [27]. Deficiency (including IDA) is more common among children and adolescents in food-insecure households than in food-secure households [27,28]. Among pregnant women, deficiency based on depleted iron stores is more common in Mexican American (23.6%) and non-Hispanic black women (29.6%) than in non-Hispanic white women (13.9%) [29].

Some groups are at risk of obtaining excess iron. Individuals with hereditary hemochromatosis, which predisposes them to absorb excessive amounts of dietary iron, have an increased risk of iron overload [30]. One study suggests that elderly people are more likely to have chronic positive iron balance and elevated total body iron than iron deficiency. Among 1,106 elderly white adults aged 67 to 96 years in the Framingham Heart Study, 13% had high iron stores (serum ferritin levels higher than 300 mcg/L in men and 200 mcg/L in women), of which only 1% was due to chronic disease [31]. The authors did not assess genotypes, so they could not determine whether these results were due to hemochromatosis [31].

Iron Deficiency
Isolated iron deficiency is uncommon in the United States. Because iron deficiency is associated with poor diet, malabsorptive disorders, and blood loss, people with iron deficiency usually have other nutrient deficiencies [2]. The World Health Organization (WHO) estimates that approximately half of the 1.62 billion cases of anemia worldwide are due to iron deficiency [32]. In developing countries, iron deficiency often results from enteropathies and blood loss associated with gastrointestinal parasites [2].

Iron depletion and iron deficiency progresses through several stages [8]:

1. Mild deficiency or storage iron depletion: Serum ferritin concentrations and levels of iron in bone marrow decrease.
2. Marginal deficiency, mild functional deficiency, or iron-deficient erythropoiesis (erythrocyte production): Iron stores are depleted, iron supply to erythropoietic cells and transferrin saturation decline, but hemoglobin levels are usually within the normal range. In addition, plasma iron levels decline and plasma transferrin concentrations (measured by plasma total iron-binding capacity) rise, resulting in decreased transferrin saturation. Serum transferrin receptor concentrations also increase.
3. IDA: Iron stores are exhausted; hematocrit and levels of hemoglobin decline; and the resulting microcytic, hypochromic anemia is characterized by small red blood cells with low hemoglobin concentrations.

IDA is defined as a hemoglobin level that is lower than two standard deviations from the mean distribution in a healthy population of the same gender and age living at the same altitude [33]. At sea level, hemoglobin concentrations lower than 11 to 12 g/dL in children younger than 12, 12 g/dL in adolescents and women, and 13 g/dL in men indicate the presence of IDA [2]. In 2002, the WHO characterized IDA as one of the 10 leading risk factors for disease around the world [34]. Although iron deficiency is the most common cause of anemia, deficiencies of other micronutrients (such as folate and vitamin B12) and other factors (such as chronic infection and inflammation) can cause different forms of anemia or contribute to their severity.

The functional deficits associated with anemia include gastrointestinal disturbances and impaired cognitive function, immune function, exercise or work performance, and body temperature regulation [35]. In infants and children, IDA can result in psychomotor and cognitive abnormalities that, without treatment, can lead to learning difficulties [2,35]. Some evidence indicates that the effects of deficiencies early in life persist through adulthood [2]. Because iron deficiency is often accompanied by deficiencies of other nutrients, the signs and symptoms of iron deficiency can be difficult to isolate [2].

Groups at Risk of Iron Inadequacy

The following groups are among those most likely to have inadequate intakes of iron.

**Pregnant women**

During pregnancy, plasma volume and red cell mass expand due to dramatic increases in maternal red blood cell production [2]. As a result of this expansion and to meet the needs of the fetus and placenta, the amount of iron that women need increases during pregnancy. Iron deficiency during pregnancy increases the risk of maternal and infant mortality, premature birth, and low birthweight [33].

**Infants and young children**

Infants—especially those born preterm or with low birthweight or whose mothers have iron deficiency—are at risk of iron deficiency because of their high iron requirements due to their rapid growth [25,36]. Full-term infants usually have sufficient iron stores and need little if any iron from external sources until they are 4 to 6 months old [2]. However, full-term infants have a risk of becoming iron deficient at 6 to 9 months unless they obtain adequate amounts of solid foods that are rich in bioavailable iron or iron-fortified formula.

**Women with heavy menstrual bleeding**

Women of reproductive age who have menorrhagia, or abnormally heavy bleeding during menstruation, are at increased risk of iron deficiency. At least 10% of menstruating women are believed to have menorrhagia, but the percentage varies widely depending on the diagnostic criteria used [37-39]. Women with menorrhagia lose significantly more iron per menstrual cycle on average than women with normal menstrual bleeding [40]. Limited evidence suggests that menorrhagia might be responsible for about 33% to 41% of cases of IDA in women of reproductive age [41,42].

**Frequent blood donors**

Frequent blood donors have an increased risk of iron deficiency [5]. In the United States, adults may donate blood as often as every 8 weeks, which can deplete iron stores. About 25%–35% of regular blood donors develop iron deficiency [43]. In a study of 2,425 blood donors, men who had given at least three and women who had given at least two whole-blood donations in the previous year were more than five times as likely to have depleted iron stores as first-time donors [44]. A clinical trial of iron supplementation found that of 216 adults who had donated a unit of blood within the past 3–6 days, those randomized to take an iron supplement (37.5 mg/day elemental iron from ferrous gluconate) for 24 weeks recovered their lost hemoglobin and iron in less than half the time of those not given the supplement [43]. Without iron supplementation, two-thirds of the donors had not recovered the iron they lost, even after 24 weeks.

**People with cancer**

Up to 60% of patients with colon cancer have iron deficiency at diagnosis, probably due to chronic blood loss [45]. The prevalence of iron deficiency in patients with other types of cancer ranges from 29% to 48%. The main causes of iron deficiency in people with cancer are anemia of chronic disease (discussed in the Iron and Health section below) and chemotherapy-induced anemia. However, chronic blood loss and deficiencies of other nutrients (due, for example, to cancer-induced anorexia) can exacerbate iron deficiency in this population.

**People who have gastrointestinal disorders or have had gastrointestinal surgery**

People with certain gastrointestinal disorders (such as celiac disease, ulcerative colitis, and Crohn’s disease) or who have undergone certain gastrointestinal surgical procedures (such as gastrectomy or intestinal resection) have an increased risk of iron deficiency because their disorder or surgery reduces dietary restrictions or results in iron malabsorption or blood loss in the gastrointestinal tract [46,48]. The combination of low iron intake and malabsorption increases the risk of iron deficiency in these patients.
surgery requires dietary restrictions or results in iron malabsorption or blood loss in the gastrointestinal tract [24, 49]. The combination of low iron intake and high iron loss can lead to a negative iron balance, reduced production of hemoglobin, or microcytic, hypochromic anemia [49].

**People with heart failure**

Approximately 60% of patients with chronic heart failure have iron deficiency and 17% have IDA, which might be associated with a higher risk of death in this population [50, 51]. Potential causes of iron deficiency in people with heart failure include poor nutrition, malabsorption, defective mobilization of iron stores, cardiac cachexia, and use of aspirin and oral anticoagulants, which might result in the loss of some blood in the gastrointestinal tract [52].

**Iron and Health**

This section focuses on the role of iron in IDA in pregnant women, infants, and toddlers, as well as in anemia of chronic disease.

**IDA in pregnant women**

Insufficient iron intakes during pregnancy increase a woman’s risk of IDA [53-56]. Low intakes also increase her infant’s risk of low birthweight, premature birth, low iron stores, and impaired cognitive and behavioral development.

An analysis of 1999–2006 data from the National Health and Nutrition Examination Survey (NHANES) found that 18% of pregnant women in the United States had iron deficiency [29]. Rates of deficiency were 6.9% among women in the first trimester, 14.3% in the second trimester, and 29.7% in the third trimester.

Randomized controlled trials have shown that iron supplementation can prevent IDA in pregnant women and related adverse consequences in their infants [57-58]. A Cochrane review showed that daily supplementation with 45–90 mg iron reduced the risk of anemia in pregnant women at term by 70% and of iron deficiency at term by 57% [59]. In the same review, use of daily iron supplements was associated with an 8.4% risk of having a low-birthweight newborn compared to 10.2% with no supplementation. In addition, mean birthweight was 3.1 g higher for infants whose mothers took daily iron supplements during pregnancy compared with the infants of mothers who did not take iron.

Guidelines on iron supplementation during pregnancy vary, but many recommend some form of iron supplementation to prevent IDA:

- The American College of Obstetricians and Gynecologists (ACOG) states that good and consistent evidence shows that iron supplementation decreases the prevalence of maternal anemia at delivery [59]. However, it acknowledges that only limited or inconsistent evidence shows that IDA during pregnancy is associated with a higher risk of low birthweight, preterm birth, or perinatal mortality. ACOG recommends screening all pregnant women for anemia and treating those with IDA (which it defines as hemoglobin levels less than 11% in the first and second trimesters and less than 12% in the second trimester) with supplemental iron in addition to prenatal vitamins [59].
- The Centers for Disease Control and Prevention (CDC) recommends that all pregnant women, at their first prenatal visit, begin taking an oral, low dose (50 mg/day) supplement of iron and be screened for IDA [9]. Women with IDA (which it defines as a hemoglobin concentration less than 9 g/dL or a hematocrit level less than 27%) should be treated with an oral dose of 60-120 mg/day of iron.
- In contrast, the U.S. Preventive Services Task Force (USPSTF) has concluded that the current evidence is insufficient to recommend for or against testing for IDA in pregnant women and routinely supplementing them with iron to prevent adverse maternal health and birth outcomes [58]. They note, however, that their recommendation does not apply to pregnant women who are malnourished, have symptoms of iron deficiency anemia, or those with special hemoglobin conditions or nutritional needs that increase iron requirements.

The IOM notes that because the median intake of dietary iron by pregnant women is well below the EAR, pregnant women need iron supplementation [9]. The Dietary Guidelines for Americans advise that women who are pregnant take an iron supplement when recommended by an obstetrician or other health-care provider [11]. It adds that low intakes of iron are a public health concern for pregnant women.

**IDA in infants and toddlers**

Approximately 12% of infants aged 6 to 11 months in the United States have inadequate iron intakes, and 8% of toddlers have iron deficiency [27, 51]. The prevalence of IDA in U.S. toddlers aged 12 to 35 months ranges from 0.9% to 4.4% depending on race or ethnicity and socioeconomic status [12]. Full-term infants typically have adequate iron stores for approximately the first 4 to 6 months, but the risk of iron deficiency in low-birthweight and preterm infants begins at birth because of their low iron stores.

IDA in infancy can lead to adverse cognitive and psychological effects, including delayed attention and social withdrawal; some of these effects might be irreversible [2, 12]. In addition, IDA is associated with higher lead concentrations in the blood (although the cause of this is not fully understood), which can increase the risk of neurotoxicity [12].

A Cochrane review of 26 studies in 2,726 preterm and low-birthweight infants found that enteral iron supplementation (at least 1 mg/kg/day) reduces the risk of iron deficiency, but the long-term effects of supplementation on neurodevelopmental outcomes and growth is not clear [62]. Another Cochrane review of 8 trials in 3,746 children younger than 2 in low-income countries showed that home fortification of semi-solid foods with micronutrient powders containing 12.5 mg to 30 mg elemental iron as ferrous fumarate and 4 to 14 other micronutrients for 2 to 12 months reduced rates of anemia by 31% and of iron deficiency by 51% compared with no intervention or placebo but had no effect on any growth measurements [53].

Guidelines vary on dietary iron intakes and possible supplementation to ensure adequate iron status and to prevent or treat IDA in infants and young children:

- The CDC recommends that infants less than 12 months of age who are not exclusively or primarily breastfed drink iron-fortified infant formula [9]. Breastfed infants who were born preterm or with a low birthweight should receive 2.4 mg/kg/day of iron drops (to a maximum of 15 mg/day) from ages 1-12 months. Breastfed infants who receive insufficient iron (less than 1 mg/kg/day) from supplementary foods by age 6 months should receive 1 mg/kg/day of iron drops. The CDC also recommends that infants and preschool children at high risk for IDA (e.g., children from...
low-income families and migrant children) be screened between ages 9-12 months, 6 months later, and annually from ages 2-5 years. Treatment for IDA begins with 3 mg/kg/day of iron drops given between meals. (See reference 9 for additional advice from the CDC.)

- The American Academy of Pediatrics recommends 1 mg/kg/day iron supplementation for exclusively or primarily breastfed full-term infants from age 4 months until the infants begin eating iron-containing complementary foods, such as iron-fortified cereals [12]. Standard infant formulas containing 10 to 12 mg/L iron can meet the iron needs of infants for the first year of life. The Academy recommends 2 mg/kg/day iron supplementation for preterm infants aged 1 to 12 months who are fed breast milk.

- The WHO recommends universal supplementation with 2 mg/kg/day of iron in children aged 6 to 23 months whose diet does not include foods fortified with iron or who live in regions (such as developing countries) where anemia prevalence is higher than 40% [53].

- In a recommendation statement issued in 2015, the USPSTF concluded that the available evidence is insufficient to recommend for or against routine screening for IDA in children ages 6 to 24 months who live in the United States and who are asymptomatic for IDA [54]. It added that this recommendation does not apply to severely malnourished children or children who were born prematurely or with low birthweight. Earlier, in 2006, the USPSTF stated that while insufficient evidence to recommend routine iron supplementation in asymptomatic infants at average risk of IDA, it did recommend routine iron supplements for children aged 6 to 12 months who are at increased risk of IDA (e.g., those who were premature or low birthweight) [65]. The USPSTF’s 2015 statement notes that its current recommendation is limited to screening because the widespread use of iron-fortified foods in the United States (including infant formulas and cereals) would likely limit the impact of iron supplementation prescribed by physicians [64].

Some studies have suggested that iron supplementation in young children living in areas where malaria is endemic could increase their risk of malaria [66,67]. However, a Cochrane review of 33 trials in 13,114 children showed that intermittent supplementation does not appear to have this effect [68]. The WHO therefore recommends 6-month supplementation cycles as follows: children aged 24 to 69 months should receive 25 mg iron and those aged 6 to 12 years should receive 45 mg every week for 3 months, followed by 3 months of no supplementation [66]. The WHO recommends providing these supplements in malaria-endemic areas in conjunction with measures to prevent, diagnose, and treat malaria.

**Anemia of chronic disease**

Certain inflammatory, infectious, and neoplastic diseases (such as rheumatoid arthritis, inflammatory bowel disease, and hematologic malignancies) can cause anemia of chronic disease, also known as anemia of inflammation [2,69]. Anemia of chronic disease is the second most common type of anemia after IDA [70]. In people with anemia of chronic disease, inflammatory cytokines upregulate the hormone hepcidin. As a result, iron homeostasis is disrupted and iron is diverted from the circulation to storage sites, limiting the amount of iron available for erythropoiesis.

Anemia of chronic disease is usually mild to moderate (hemoglobin levels 8 to 9.5 g/dL) and is associated with low counts of erythrocytes and decreased erythropoiesis [69]. The condition can be difficult to diagnose because, although low serum ferritin levels indicate iron deficiency, these levels tend to be higher in patients with infection or inflammation [71].

The clinical implications of iron deficiency in people with chronic diseases are not clear. Even mild anemia of chronic disease is associated with an increased risk of hospitalization and mortality in elderly people [72]. Two prospective observational studies found that iron deficiency in patients with objectively measured heart failure was associated with an increased risk of heart transplantation and death, and this association was independent of other well-established prognostic factors for poor outcomes, including anemia [73,74]. However, an analysis of NHANES data on 574 adults with self-reported heart failure found no association between iron deficiency and all-cause or cardiovascular mortality [51].

The main therapy for anemia of chronic disease is treatment of the underlying disease [70]. But when such treatment is not possible, iron supplementation and/or erythropoiesis-stimulating agents (ESAs) are sometimes used. The use of iron supplements—whether oral, intravenous, or parenteral—in this setting is controversial because they might increase the risk of infection and cardiovascular events and could cause tissue damage [70].

Only a few small studies have evaluated the benefits of oral iron supplementation alone or in combination with ESAs to treat anemia of chronic disease. For example, a prospective observational study in 132 patients with anemia and chronic kidney disease who were not on dialysis or ESAs found that oral supplements (150 mg/day elemental iron from ferrous sulfate twice daily) for 1 year resulted in a decline in hemoglobin of only 0.13 g/dL compared with 0.46 g/dL in the placebo group [75]. A randomized trial of oral iron supplements (equivalent to 200 mg/day elemental iron, form of iron not specified) taken with an ESA once weekly in 100 patients with cancer-related anemia resulted in a mean increase of 2.4 g/dL hemoglobin after 24 weeks compared with oral supplements only [76]. Iron administered parenterally increases hemoglobin levels to a greater extent and is associated with fewer side effects than oral iron supplementation in patients with anemia of chronic disease [77].

**Health Risks from Excessive Iron**

Adults with normal intestinal function have very little risk of iron overload from dietary sources of iron [2]. However, acute intakes of more than 20 mg/kg iron from supplements or medicines can lead to gastric upset, constipation, nausea, abdominal pain, vomiting, and faintness, especially if food is not taken at the same time [2,5]. Taking supplements containing 25 mg elemental iron or more can also reduce zinc absorption and plasma zinc concentrations [5,78,79]. In severe cases (e.g., one-time ingestions of 60 mg/kg), overdoses of iron can lead to multisystem organ failure, coma, convulsions, and even death [18,80].


In 1997, the FDA began requiring oral supplements containing more than 30 mg elemental iron per dose to be sold in single-dose packaging with strong warning labels. At the same time, many manufacturers voluntarily replaced the sugar coating on iron tablets with film coatings. Between 1996 and 2002, only one child death due to ingesting an iron-containing tablet was reported [16]. As a result of a court decision, the FDA removed its single-
dose packaging requirement for iron supplements in 2003 [81]. FDA currently requires that iron-containing dietary supplements sold in solid form (e.g., tablets or capsules but not powders) carry the following label statement: "WARNING: Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately" [82]. In addition, since 1978, the Consumer Product Safety Commission has required manufacturers to package dietary supplements containing 250 mg or more elemental iron per container in child-resistant bottles or packaging to prevent accidental poisoning [83, 84].

Hemochromatosis, a disease caused by a mutation in the hemochromatosis (HFE) gene, is associated with an excessive buildup of iron in the body [3, 30-65]. About 1 in 10 whites carry the most common HFE mutation (C282Y), but only 4.4 whites per 1,000 are homozygous for the mutation and have hemochromatosis [86]. The condition is much less common in other ethnic groups. Without treatment by periodic chelation or phlebotomy, people with hereditary hemochromatosis typically develop signs of iron toxicity by their 30s [3]. These effects can include liver cirrhosis, hepatocellular carcinoma, heart disease, and impaired pancreatic function. The American Association for the Study of Liver Diseases recommends that treatment for hemochromatosis include the avoidance of iron and vitamin C supplements [30].

The FDA has established ULs for iron from food and supplements based on the amounts of iron that are associated with gastrointestinal effects following supplemental intakes of iron salts (see Table 3). The ULs apply to healthy infants, children, and adults. Physicians sometimes prescribe intakes higher than the UL, such as when people with IDA need higher doses to replenish their iron stores [5].

**Table 3: Tolerable Upper Intake Levels (ULs) for Iron [9]**

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
<th>Pregnancy</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 6 months</td>
<td>40 mg</td>
<td>40 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-12 months</td>
<td>40 mg</td>
<td>40 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 years</td>
<td>40 mg</td>
<td>40 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-8 years</td>
<td>40 mg</td>
<td>40 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-13 years</td>
<td>40 mg</td>
<td>40 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14-18 years</td>
<td>45 mg</td>
<td>45 mg</td>
<td>45 mg</td>
<td>45 mg</td>
</tr>
<tr>
<td>19+ years</td>
<td>45 mg</td>
<td>45 mg</td>
<td>45 mg</td>
<td>45 mg</td>
</tr>
</tbody>
</table>

* Breast milk, formula, and food should be the only sources of iron for infants.

**Interactions with Medications**

Iron can interact with certain medications, and some medications can have an adverse effect on iron levels. A few examples are provided below. Individuals taking these and other medications on a regular basis should discuss their iron status with their health care providers.

**Levodopa**

Some evidence indicates that in healthy people, iron supplements reduce the absorption of levodopa (found in Sinemet® and Stalevo®), used to treat Parkinson’s disease and restless leg syndrome, possibly through chelation [87-89]. In the United States, the labels for levodopa warn that iron-containing dietary supplements might reduce the amount of levodopa available to the body and, thus, diminish its clinical effectiveness [90, 91].

**Levothyroxine**

Levothyroxine (Levothroid®, Levoxyl®, Synthroid®, Tirosint®, and Unithroid®) is used to treat hypothyroidism, goiter, and thyroid cancer. The simultaneous ingestion of iron and levothyroxine can result in clinically significant reductions in levothyroxine efficacy in some patients [92]. The labels for some of these products [93, 94] warn that iron supplements can reduce the absorption of levothyroxine tablets and advise against administering levothyroxine within 4 hours of iron supplements.

**Proton pump inhibitors**

Gastric acid plays an important role in the absorption of nonheme iron from the diet. Because proton pump inhibitors, such as lansoprazole (Prevacid®) and omeprazole (Prilosec®), reduce the acidity of stomach contents, they can reduce iron absorption [3]. Treatment with proton pump inhibitors for up to 10 years is not associated with iron depletion or anemia in people with normal iron stores [95]. But patients with iron deficiency taking proton pump inhibitors can have suboptimal responses to iron supplementation [96].

**Iron and Healthful Diets**

The federal government’s 2015-2020 Dietary Guidelines for Americans notes that “Nutritional needs should be met primarily from foods. … Foods in nutrient-dense forms contain essential vitamins and minerals and also dietary fiber and other naturally occurring substances that may have positive health effects. In some cases, fortified foods and dietary supplements may be useful in providing one or more nutrients that otherwise may be consumed in less-than-recommended amounts.”

For more information about building a healthy diet, refer to the Dietary Guidelines for Americans® and the U.S. Department of Agriculture’s MyPlate®.

The Dietary Guidelines for Americans describes a healthy eating pattern as one that:

- Includes a variety of vegetables, fruits, whole grains, fat-free or low-fat milk and milk products, and oils.
  
  Many ready-to-eat breakfast cereals are fortified with iron, and some fruits and vegetables contain iron.

- Includes a variety of protein foods, including seafood, lean meats and poultry, eggs, legumes (beans and peas), nuts, seeds, and soy products.
Oysters and beef liver have high amounts of iron. Beef, cashews, chickpeas, and sardines are good sources of iron. Chicken, tuna, and eggs contain iron.

- Limits saturated and trans fats, added sugars, and sodium.
- Stays within your daily calorie needs.

References

82. Code of Federal Regulations, Title 21 (Food and Drugs). Section 101.17 (Food labeling warning, notice, and safe handling statements).

Disclaimer

This fact sheet by the Office of Dietary Supplements provides information that should not take the place of medical advice. We encourage you to talk to your healthcare providers (doctor, registered diettian, pharmacist, etc.) about your interest in, questions about, or use of dietary supplements and what may be best for your overall health. Any mention in this publication of a specific brand name is not an endorsement of the product.

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