Iron

Common Acronyms

CNS	Chinese Nutrition Society
CRN	Council for Responsible Nutrition
DRI	dietary reference intake
EC SCF	European Commission Scientific Committee on Food
EFSA	European Food Safety Authority
EVM	Expert Group on Vitamins and Minerals
ICMR-NIN	Indian Council of Medical Research - National Institute of Nutrition
IOM	Institute of Medicine
IU	international unit
KNS	Korean Nutrition Society
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
NIH	National Institute of Health
NOEL	no observed effect level
NOAEL	no observed adverse effect level
RCT	randomized clinical trial
SUL	safe upper level
UF	uncertainty factor
UL	tolerable upper intake level

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 in 1928 (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; Wessling-Resnick 2016).

Dietary iron occurs in three major forms: ferrous iron (Fe^{2+}), ferric iron (Fe^{3+}), and heme iron

Published by Council for Responsible Nutrition (CRN), Washington, D.C.

(Fe^{2+} chelated into a complex organic compound to complete the heme structure, which occurs in hemoglobin, myoglobin, and certain enzymes). Dietary heme iron (e.g., iron bound to hemoproteins such as hemoglobin or myoglobin) only occurs naturally, mostly as proteins from animal tissues. Common iron sources present in foods include ferric citrate, ferric phosphate, ferric oxalate, ferric phytate, and ferric hydroxide. Various forms of iron are sold as dietary supplements, including ferrous bisglycinate, ferrous fumarate, ferrous sulfate, and ferrous carbonate (EFSA 2024; Wessling-Resnick 2016).

Iron deficiency may result from inadequate amounts of dietary iron, depressed or inhibited iron absorption, or blood loss. Protracted deficiency can lead to a characteristic anemia (microcytic or hypochromic). Additionally, 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; Wessling-Resnick 2016).

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 (Fe^{2+}) is somewhat higher than that of ferric iron (Fe^{3+}), and more soluble salts (e.g., ferrous citrate or ferrous ascorbate) have higher bioavailability than less soluble forms. Similarly, ferrous iron, especially from more soluble compounds, is more easily absorbed than the ferric compounds, which must be reduced from Fe^{3+} to Fe^{2+} before they can be absorbed. 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. 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.

Safety Considerations

Almost all supplemental or fortification iron is in the form of a ferrous compound, such as ferrous sulfate, ferrous gluconate, etc. (Wessling-Resnick, 2016).[1] 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 iron consumed by an individual (from animal-based foods such as meats, fish, and poultry). However, few experiments have been conducted to describe and quantify this relationship between exposure to heme and nonheme iron forms. For chronic, habitual intake by individuals who do not have any genetic defects that increase iron absorption or retention, iron has shown no serious adverse effects or *true hazards* (as defined by CRN's methodology) at levels several times the RDA of 8 mg for men, 18 mg for premenopausal women, and 27 mg during pregnancy (IOM 2001). Loss of iron during menstruation accounts for most or all of the difference between the male and female RDAs. For prolonged but not chronic use, such as in pregnancy, daily supplements of up to 60 mg are routinely and safely consumed.

A large volume of human intervention studies published since the 3rd edition were identified with potential relevance to this update (approximately 350). Given that the EFSA Panel (2024) conducted a comprehensive review of available studies and did not identify any outcomes sufficient for deriving an UL value for iron other than incidence of black stool (determined to be non-adverse; see Gastrointestinal Effects and Black Stool), the date of the EFSA's comprehensive literature search used to support its evaluation (i.e., 2022) was selected as the publication date for CRN's screening approach. Therefore, while titles and abstracts of identified studies were screened, only studies published between 2022 and 2025 were reviewed in detail for the purposes of this update. Approximately 50 human clinical trials published starting in 2022 were identified that met the inclusion criteria for the current update. A full literature review is outside the scope of this chapter; however, an overview of the information reviewed is summarized below.

Numerous studies were identified in populations without any form of documented iron

[1] A few heme supplements are available in the U.S. (NIH 2024).

deficiency (e.g., anemia) at supplemental levels ranging from 20-65 mg elemental iron per day. Four studies in healthy, non-pregnant individuals administered 60-65 mg elemental iron per day (Lorinczova et al. 2022; Finlayson-Trick et al. 2023; Friling et al. 2022; Pei et al. 2023). Lorinczova et al. (2022) observed the presence of black stool at the 65 mg per day dose during the six-week study but reported no significant difference between the iron group and the placebo group. Finlayson-Trick et al. (2023) performed a secondary analysis of data from a double-blind randomized study in healthy, non-pregnant women that were administered 0, 18, or 60 mg elemental iron per day. Gastrointestinal events such as diarrhea were observed at the baseline measurement and after 12 weeks of supplementation of iron in this study. Friling et al. (2022) followed healthy premenopausal women consuming 60 mg elemental iron per day for two 14-day periods and reported no serious or significant adverse events. Pei et al. (2023) analyzed data from a previous randomized, placebo-controlled trial in which 356 non-pregnant women received 60 mg elemental iron with or without other micronutrients for 12-weeks and had complete hemoglobin data (e.g., at baseline and after 12 weeks).[2] No serious adverse effects were reported in any study; the primary side effects reported were gastrointestinal in nature, which are considered *nuisance effects* as defined by CRN's methodology (discussed more below).

Three studies tested iron intervention levels ranging from 20-80 mg elemental iron per day, administered for 3-28 weeks, in healthy pregnant women without documented iron deficiencies (Díaz-Torres et al. 2024; Milman et al. 2024; Stanworth et al. 2024). Díaz-Torres et al. (2024) did not report adverse events associated with iron supplementation, while Milman et al. (2024) observed "favorable gastrointestinal side effect profiles" at 25 mg elemental iron per day dose compared to gastrointestinal side effects, including black stool, at doses of 40-50 mg/elemental iron per day. Stanworth et al. (2024) observed side effects that were also reported at baseline and were considered to "overlap with normal pregnancy symptoms," with the exception of black stool observations at the 40 mg elemental iron per day dose. However, the relevance of these studies to the general population is limited, given that the requirement for and utilization of iron is significantly increased during pregnancy due to maternal blood volume expansion and

[2] Of the 356, 60.7% were determined to be anemic at baseline. However, the remaining 141 women represent a healthy population.

increased iron utilization in the placenta and fetus (IOM 2001; Wessling-Resnick 2016). Therefore, these studies in pregnant women were determined not to be sufficient for deriving an UL for iron for the general adult population.

Other studies conducted with higher iron intervention levels were also reviewed as part of this update. All such studies were conducted in iron-deficient populations and reported no serious adverse effects. Typically, higher doses of iron are used in the prevention or treatment of iron-deficient conditions under medical supervision (EFSA 2024). Numerous studies were identified administering doses of 100-150 mg elemental iron per day for 4-12 weeks to iron-deficient populations; none reported serious adverse effects (e.g., Hansen et al. 2023; Awomolo et la. 2023; Chawla et al. 202; von Siebenthal et al. 2023; Dhanush et al. 2024). An additional five studies administered doses greater than 150 mg per day for 2.5-16 weeks, reporting only gastrointestinal effects in iron-deficient patients (Zhang et al. 2024; Wang et al. 2022; Talboom et al. 2023; Jongkraijakra et al. 2023; Chang et al. 2023). As treatment of iron deficient (i.e., anemic) patients typically occurs under medical supervision, these studies were determined not to be appropriate as the basis for UL derivation for the general population. Studies conducted at similar (higher) iron intervention levels in individuals without iron deficiency were not identified in this update.

Iron Overload and Liver Toxicity

Chronic iron overload has resulted from several conditions or circumstances, including hereditary hemochromatosis (i.e., individuals with impaired downregulation of iron absorption), alcoholic liver disease, and excessive intake of dietary iron, especially from home-brewed alcoholic beverages (EFSA 2024; Fairbanks 1999). Long-term daily ingestion of iron from some home-brewed alcoholic beverages may exceed 100 mg iron per day (Fairbanks 1999). Systemic iron overload can cause accumulation of iron in organs such as the liver, leading to liver cirrhosis, liver failure, and hepatocellular carcinoma. Studies have suggested there is a genetic polymorphism associated with hemochromatosis (typically an amino acid mutation, C282Y), though this hypothesis has not been fully elucidated (EFSA 2024; Gangaidzo & Gordeuk 1995; Kew 2014; Kew & Asare 2007; Oh & Moon 2019). 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; EFSA 2024). This condition may lead to excessive iron storage even at intake levels recommended for most of the population. Patients with hereditary hemochromatosis have an increased risk of diabetes mellitus, loss of insulin secretory capacity and/or development of insulin resistance, arthritis, and cardiomyopathy (EFSA 2024).

The EFSA (2024) Panel stated that there is evidence that excess dietary iron intake may also lead to liver toxicity or iron overload syndrome in individuals without iron metabolism disorders, citing case reports with intake levels ranging from 100 to 1,000 mg elemental iron per day for 15 years or longer. However, most studies were in individuals with iron intakes greater than 300 mg per day or included co-exposure to large amounts of alcohol. One study reviewed demonstrated that consumption of a fermented beverage led to dietary iron overload with a median iron intake of 138 mg iron /day; however, consumption of this fermented beverage also included a median intake of 96 g alcohol per day (EFSA 2024; MacPhail et al. 1999). Bell et al. (2000) examined case reports that associated iron overload syndrome in C282Y-mutation negative patients with consumption of iron supplements, typically over a duration of 5 to 50 years. While most cases did not report the concentration of iron consumed in this study, one patient reported consumption of 300 mg elemental iron per day for 20 years (EFSA 2024; Bell et al. 2000). Another publication discussed three case reports in C282Y-mutation negative patients with iron overload syndrome who consumed elemental iron at 100-220 mg iron/day over 15 to 61 years (EFSA 2024; Barton et al. 2006). Additional case reports in C282Y-mutation negative patients also observed iron overload syndrome associated with elemental iron consumption ranging from 325-1000 mg/day for the duration range of 15-30 years (EFSA 2024; Lands and Isang 2017; Green et al. 1989).

Gastrointestinal Effects and Black Stool

Iron supplementation has been reported in some studies to be associated with gastrointestinal side effects, such as gastrointestinal irritation, nausea, vomiting, diarrhea, or constipation (EFSA 2024; Wessling-Resnick 2016). Darker stools have also been reported with iron supplementation. These

gastrointestinal effects were used by the IOM (2001) and EVM (2003) as the basis for setting guidance values for iron supplementation based on the Frykman et al. (1994) study, which was designed specifically to assess side effects of iron. In this controlled, double blind, parallel-designed study, individuals donating blood were administered either 60 mg elemental iron per day (as ferrous fumarate) or 2.4 mg elemental iron per day (as heme iron from porcine blood) plus 16 mg elemental iron per day (as ferrous fumarate) for two out of three consecutive months; "all participants randomly received a placebo during one of the last two periods." The percentages of participants experiencing adverse gastrointestinal effects when taking the iron, heme + iron, or placebo were: nausea: 6%, 8%, and 4%; epigastric pain: 19%, 6%, and 10%; obstipation: 35%, 14%, and 20%; diarrhea: 37%, 26%, and 14%; and total (mean): 25%, 14%, and 14%, respectively. Of these findings, only the results for obstipation ($p<0.05$) and total ($p<0.01$) in the nonheme group were found by the study authors to be statistically significantly different (higher) than other groups. Other examples of studies reporting gastrointestinal effects associated with iron include those administering high doses of ferric citrate up to 1,260 mg elemental iron per day in chronic kidney disease patients with iron deficiency (Pergola et al. 2020; Womack et al. 2020) and/or hyperphosphatemia[3] (Lee et al. 2015; Ito et al. 2021). Of note, these higher dose studies did not report any serious adverse effects.

However, a recent opinion from the EFSA (2024) based on systematic review of available data concluded that observations of adverse gastrointestinal effects were variable with no evident dose-response relationship. The dose of iron administered in most studies ranged from 10 to 222 mg elemental iron per day (EFSA 2024). The Panel noted that the variability in the occurrence of gastrointestinal adverse effects could be due to the daily dose being divided into multiple doses, differences in the study population (e.g., blood donors, pregnant women, and non-pregnant adults), form of iron used, or the "characteristics of the individuals taking the supplements." EFSA concluded that the available data were not sufficient to further investigate these "hypotheses" (EFSA 2024).

The same EFSA (2024) assessment identified a dose-response association between iron

[3] Ferric citrate hydrate was used as a phosphate binder in these studies.

supplementation and the occurrence of black stool. The Panel discussed three RCTs that reported black stool following intervention with 50-80 mg elemental iron per day; noting no increases in incidence of black stool (as compared to baseline levels) at iron supplemental doses between 20-25 mg elemental iron per day (Milman et al. 2006; Milman et al 2014; Makrides et al 2003). The EFSA Panel stated that it does not consider incidence of black stool to be an "adverse event," but rather "a conservative endpoint among the chain of undesirable events that may lead to systemic iron overload and iron toxicity" (as described above in Liver Toxicity). The presence of black stool "reflects the large amount of unabsorbed iron in the gut" and was considered an indicator of an established dose-response for iron. Since the EFSA's conclusion, the recent literature search conducted as part of CRN's updated assessment identified six publications that discussed observations of either black stool, discolored feces, or dark stool upon supplementation with iron. Several studies observed black stool or dark stool at elemental iron doses of 25-198 mg per day (Friling et al. 2022; Milman et al. 2024; Lorinczova et al. 2022; Howaldt et al. 2022; Talboom et al. 2023; Stanworth et al. 2024). These studies included healthy populations and those with iron deficiency and/or other disease state (i.e., colorectal cancer or inflammatory bowel disease), as well as pregnant and non-pregnant individuals.

Heart Disease and Colonic Cancer

The 3rd edition of this book discussed two potential outcomes of interest, which have been more recently assessed and determined not to be relevant to the derivation of an UL for iron.

First, select studies on high plasma ferritin levels (Sullivan 1981; Salonen et al. 1992) previously 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 demonstrating no association (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). 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 et al. 2012), authoritative reviews of available data have concluded there to be no increased risk (IOM 2001; EVM 2003; EFSA

2024). The EFSA Panel briefly summarized the available data on cardiovascular disease and mortality and concluded that these cannot be used to set an UL for iron according to its process.

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 is not conclusive that increases in dietary iron necessarily lead to an increased risk of colonic cancer (Zhang et al. 2011). As noted by the IOM (2001), the "evidence for a relationship between dietary iron intake and cancer in the general population is inconclusive." In addition, the EFSA (2024) Panel reviewed available data on cancer incidence, including colon cancer, and concluded that "although positive associations have been observed between heme iron and certain types of cancers, the available evidence does not allow disentangling a causal contribution of heme iron from that of other risk factors associated with 'high' red meat intake" (EFSA 2024).

Official Reviews

IOM (2001). The IOM review identified, based on the clinical evidence by Frykman and colleagues (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, the IOM 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 iron for adults. The IOM stated that the UL is not meant to apply to individuals being treated with iron "under close medical supervision."

EVM (2003). The UK's EVM concluded that the evidence was insufficient to set an SUL value for iron. Instead, the EVM set a guidance level based on some clinical reports of gastrointestinal

effects (i.e., nausea, vomiting, and epigastric pain) from doses of soluble iron salts containing iron levels as low as 50 mg, including the Frykman et al. (1994) study. 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, which equates to 17 mg per day. This value is much lower than the IOM (2001) value and the recent EFSA (2024) "safe level" value.

EFSA (2024). The 2004 EFSA review concluded that the iron safety data were not sufficient to identify a UL value. An updated 2024 EFSA review was conducted, in which the Panel determined that "systemic iron overload leads to organ toxicity, but no UL could be established" due to lack of adequate data to "characterize a dose-response relationship or identify a reference point for iron toxicity." The EFSA Panel acknowledged there is a dose-response associated with iron intake levels and the observation of black stools, which were linked to large amounts of unabsorbed iron in the gut. According to the Panel, supplemental iron intakes of 20-25 mg elemental iron per day did not lead to black stools, whereas studies with iron intakes at 50 mg per day or greater reported incidences of black stools. The EFSA recognized the dose gap from 20 to 50 mg iron per day, explaining that the dose leading to gastrointestinal effects may depend on the form of iron used for supplementation and characteristics of the individuals. Currently, the available data were determined by the Panel to be insufficient to investigate this dose gap.[4] The presence of black stools was used to set a "safe level of supplemental intake". The EFSA concluded that "black stools are not considered an adverse effect;" however, they are indicative of "the presence of a large amount of unabsorbed iron in the gastrointestinal tract." The Panel set a "safe level" of 40 mg iron per day for the total consumption of iron from diet (15 mg per day for mean background intake) and supplements (25 mg per day), which is "not expected to lead to adverse effects in the general adult population." As noted by the Panel, "The safe levels of intake proposed by the Panel do not apply to individuals who receive iron under medical supervision."

Of note, the EFSA Panel also conducted reviews of several outcomes previously associated with iron intake. Following its systematic review, the Panel concluded that the data were insufficient

[4] All gastrointestinal effects, including incidence of black stool, are considered *nuisance effects* as defined by CRN's methodology and were therefore not further assessed as part of this update.

to "conclude a positive relationship" between iron consumption and risk of Type 2 or gestational diabetes, and insufficient to further investigate the hypothesis related to gastrointestinal effects. As discussed in Safety Considerations, the Panel determined that the available data on liver toxicity, colon cancer, and cardiovascular disease risk or mortality cannot be used to set an UL for iron.

Chinese Nutrition Society (CNS 2023). An UL value for iron of 42 mg per day in adults was set by the CNS.

Indian Council of Medical Research - National Institute of Nutrition (ICMR-NIN 2020). Based on gastrointestinal side effects observed in studies above 60 mg per day, and noting the absence of studies with iron doses less than 60 mg per day, the ICMR-NIN (2020) identified an UL value of 40 mg per day for adults and 45 mg per day for pregnant and lactating women, to be consistent with IOM (2001). The ICMR-NIN added, "It is estimated that an additional requirement of about 900 - 1000 mg of iron is needed during pregnancy, which cannot be met from diet. Considering this and the severity of anemia, iron supplementation much above the TUL (60-200 mg) is recommended by WHO and Ministry of Health and Family Welfare, Gol. However, these are given for a short period and monitored by health workers."

Korean Nutrition Society (KNS 2020). The KNS published its general approach to evaluating data for setting DRI values. Based on this approach, an UL of 45 mg iron per day was derived for adults.

CRN Recommendations

The goal of the current update to CRN's supplemental UL for iron was to determine whether more recent human clinical data are available that might impact the conclusions published in the 3rd edition, which derived a supplemental UL value of 60 mg iron per day for adults. While not all human clinical trials are specifically designed to evaluate adverse effects, no new trials were identified following CRN's updated methodology that reported any serious adverse effects (i.e., liver toxicity or liver iron overload) associated with iron intervention in healthy volunteers, as well

as most trials in unhealthy populations. As with any assessment in which not all available data are reviewed, inherent uncertainties with the risk assessment and selection of the UL are recognized.

CRN's safety methodology for deriving a supplemental intake UL prioritizes data from human studies, when available. The table below summarizes the key human clinical studies considered in deriving an updated UL for supplemental intakes by CRN according to its principal points of departure for risk assessment (as described in CRN's Methods chapter). Fifty-three human clinical trials, published starting in 2022, were identified that met the inclusion criteria for the current update (as described in the Methods chapter). A full literature review is outside the scope of this chapter; therefore, only studies identified in the updated search with the highest iron intake levels (approximately 60 mg per day) and in individuals without iron-related deficiencies, and therefore pertinent to assessing a revised UL based on CRN's methodology, are presented.

Key Studies Considered for the CRN UL for Iron in Adults

Reference	Study Design	Participant Description	No. of Subjects	Dose(s) (mg/day)[a]	Duration	NOAEL (mg/day)
Key studies from 3rd edition						
Frykman et al. 1994	Double blind, controlled, parallel group, crossover study	Healthy blood donors	97	60 (as ferrous fumarate), 2.4 heme iron + 16 (as ferrous fumarate)	2 months total[b]	60
Key studies identified in update						
Lorinczova et al. 2022	Double blind, placebo-controlled, randomized	Healthy	155	0, 18, 65 (as ferrous sulphate)	6 weeks	65
Finlayson-Trick et al. 2023[c]	Double blind, randomized, controlled	Healthy, non-pregnant females	480	0, 18, 60 (as ferrous sulfate or ferrous bisglycinate)	12 weeks	60
Friling et al. 2022	Double-blind, 2-way crossover, randomized, comparator-controlled	Healthy premenopausal females	51	60 (as microencapsulated ferric saccharate or ferric saccharate)	Two 2-week periods	60
Pei et al. 2023[c]	Placebo-controlled, randomized	Healthy, non-pregnant females	141[d]	60	12 weeks	60

[a] Presented as mg elemental iron
[b] "The study was divided into three consecutive periods of 1 month each. All participants received a placebo during one of the last two periods."
[c] Secondary analysis of the respective clinical trial
[d] Total study population was 356; however, 215 were found to be anemic at study baseline.

As summarized in the Official Reviews section, UL values derived previously by the IOM (2001), the EVM (2003), and EFSA (2024) were based on gastrointestinal side effects and/or the occurrence of black stool observed in studies at lower doses of iron. These outcomes are considered *nuisance effects* and not *true hazards* according to CRN's methodology; therefore, they were not selected as the basis for CRN's supplemental UL for iron. The EFSA (2024) also reviewed data on systemic iron overload that have been reported to be associated with liver toxicity. While the Panel summarized the limited studies investigating systemic iron overload in individuals (with and without iron metabolism disorders related to genetic polymorphisms) receiving iron at dose ranges of 100 to 1000 mg per day, no dose-response relationship associated with these observations was identified. Therefore, the EFSA concluded that these data could not be used alone for setting an UL for iron based on liver toxicity. Nevertheless, these data were taken into consideration as part of CRN's assessment.

Available data demonstrate no serious adverse effects associated with the supplementation of elemental iron at 60-65 mg per day for 4-12 weeks in healthy (i.e., those without documented iron deficiency disorders), non-pregnant populations (Lorinczova et al. 2022; Finlayson-Trick et al. 2023; Friling et al. 2022; Pei et al. 2023; Frykman et al. 1994). Therefore, 60 mg per day is maintained as the NOAEL for iron for adults following the CRN process. As described in CRN's Methods, if the supplemental intake dose-response relationship is identified from the strongest data and assessed conservatively, no additional uncertainty factor is needed (that is, the implicit UF is 1.0). Consistent with CRN's methodology, an UF of 1 is applied to yield an UL of 60 mg per day for adults for supplemental iron.[5,6]

Factors such as individual diet (i.e., amount of heme consumed), body load of iron, and health status, as well as form of iron, have been shown to affect bioavailability of iron. The CRN supplemental UL value is based on studies in healthy, non-pregnant populations and using various forms of iron. As described herein, studies have been conducted in which pregnant individuals and populations with iron-related deficiency disorders received supplemental iron at

[5] These recommendations are for ferrous or ferric compounds, not heme iron.
[6] Based on the information reviewed, it would be appropriate to have a label statement that iron-containing supplements should be taken with food to reduce potential gastrointestinal effects.

levels higher than 60-65 mg per day without serious adverse effects. Iron intervention at levels equal to or greater than the CRN UL are sometimes used for the prevention or treatment of iron deficiencies (i.e., anemia), including during pregnancy; however, individuals should discuss the need for additional iron supplementation that may be needed during pregnancy or for other medical conditions with their healthcare provider.

Quantitative Summary for Iron in Healthy Adults

CRN (2025) UL, supplemental intake	60 mg/day[a,b]
IOM (2001) UL, total intake	45 mg/day[b]
EFSA (2024) "safe level", total intake	40 mg/day (including 25 mg/day supplemental)[b]
EVM (2003), guidance level, supplemental intake	17 mg/day
CNS (2023), total intake	42 mg/day
ICMR-NIN (2020), total intake	45 mg/day[c]
KNS (2020), total intake	45 mg/day

[a] These recommendations are for ferrous or ferric compounds, not heme iron.
[b] Not applicable to individuals under medical supervision (CRN 2025; IOM 2002; EFSA 2024)
[c] Iron "supplementation much above the TUL (60-200 mg) is recommended" during pregnancy (FSAAI 2018).

References

Aronow WS. 1993. Serum ferritin is not a risk factor for coronary artery disease in men and women aged ≥ 62 years. *Am J Cardiol.* 72:347–378.

Avni T, Leibovici L, Gafter-Gvili A. 2012. Iron supplementation for the treatment of chronic heart failure and iron deficiency: systematic review and meta-analysis. *Eur J Heart Fail.* 4:423–429.

Awomolo AM, McWhirter A, Sadler LC, Coppola LM, Hill MG. 2023. Intravenous infusions of ferumoxytol compared to oral ferrous sulfate for the treatment of anemia in pregnancy: a randomized controlled trial. *Am J Obstet Gynecol.* 5(9):101064.

Baer DM, Tekawa IS, Hurley LB. 1994. Iron stores are not associated with acute myocardial infarction. *Circulation* 89:2915–2918.

Barton JC, Lee PL, West C, Bottomley SS. 2006. Iron overload and prolonged ingestion of iron supplements: Clinical features and mutation analysis of hemochromatosis- associated genes in four cases. *Am J Hematol*. 81:760–767.

Bell H, Berg JP, Undlien DE, Distante S, Raknerud N, Heier HE, Try K, Thomassen Y, Haug E, Raha-Chowdhury R, Thorsby E. 2000. The clinical expression of hemochromatosis in Oslo, Norway - excessive oral iron intake may lead to secondary hemochromatosis even in HFE C282Y mutation negative subjects. *Scand J Gastroenterol*. 35:1301–1307.

Chang A, Rugivarodom M, Pungpipattrakul N, Akarapatima K, Suwanno K, Rattanasupar A, Ovartlarnporn B, Prachayakul V. 2023. Role of oral iron supplementation for anemia secondary to acute nonvariceal upper gastrointestinal bleeding: a randomized controlled trial. *J Gastroenterol Hepatol.* 38(8):1283-1291.

Chawla S, Singh A, Jhamb D, Anupama CH. 2022. A randomised controlled trial to compare injection ferric carboxymaltose and oral iron in treating iron deficiency anemia during pregnancy. *J Obstet Gynecolo India*. 72(6):492-496.

Chinese Nutrition Society (CNS). 2023. Dietary Reference Intakes for China, A summary Report. People's Medical Publishing House.

Collings R, Harvey LJ, Hooper L, et al. 2013. The absorption of iron from whole diets: a systematic review. *Am J Clin Nutr.* 98:65–81.

Danesh J, Appleby P. 1999. Coronary heart disease and iron status: meta-analyses of prospective studies. *Circulation.* 99:852–854.

Dhanush M, Vinod KV, Manivannan P, Adole PS, Govindan D. 2024. Daily Versus Alternate Day Oral Iron Replacement for Women with Iron Deficiency Anaemia: A Randomized Controlled Trial. *Indian J Hematol Blood Transfus*. 1-7.

Díaz-Torres S, Díaz-López A, Arija V. 2024. Effect of prenatal iron supplementation adapted to hemoglobin levels in early pregnancy on fetal and neonatal growth—ECLIPSES Study. *Nutrients.* 16(3):437.

European Food Safety Authority (EFSA). 2004. Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission Related to the Tolerable Upper Intake Level of Iron. *EFSA J*. 125:1–34.

European Food Safety Authority (EFSA). 2024. Scientific opinion on the tolerable upper intake level for iron. *EFSA J*. 22(6):e8819.

Expert Group on Vitamins and Minerals (EVM). 2003. *Safe Upper Levels for Vitamins and Minerals*. London: Food Standards Agency Publications.

Fairbanks VF. 1999. Iron in medicine and nutrition. In: Shils ME, Olson JA, Shike M, Ross CA, eds. *Modern Nutrition in Health and Disease.* 9th ed. Philadelphia: Lea and Febiger; 193–221.

Finlayson-Trick E, Nearing J, Fischer JA, Ma Y, Wang S, Krouen H, Goldfarb DM, Karakochuk CD. 2023. The effect of oral iron supplementation on gut microbial composition: a secondary analysis of a double-blind, randomized controlled trial among Cambodian women of reproductive age. *Microbiol Spectr*. 11(3):05273-22.

Food and Drug Administration. 1995. Iron-containing supplements and drugs: label warning statements and unit-dose packaging requirements. *Federal Register.* 60:8989–8993.

Franco RF, Zago MA, Trip MD, et al. 1998. Prevalence of hereditary haemochromatosis in premature atherosclerotic vascular disease. *Br J Haematol.* 102:1172–1175.

Friling M, García-Muñoz AM, Perrinjaquet-Moccetti T, Victoria-Montesinos D, Pérez-Piñero S, Abellán-Ruiz MS, Luque-Rubia AJ, García-Guillén AI, Cánovas F, Ivanir E. 2022. Tolerability of oral supplementation with microencapsulated ferric saccharate compared to ferrous sulphate in healthy premenopausal woman: a crossover, randomized, double-blind clinical trial. *Int J Mol Sci*. 23(20):12282.

Frykman E, Bystrom M, Jansson U, Edberg A, Hansen T. 1994. Side effects of iron supplements in blood donors: superior tolerance of heme iron. *J Lad Clin Med.* 123:561–564.

Gangaidzo IT, Gordeuk VR. 1995. Hepatocellular carcinoma and African iron overload. *Gut*. 37:727–730.

Green P, Eviatar JM, Sirota P, Avidor I. 1989. Secondary hemochromatosis due to prolonged iron ingestion. *Isr J med Sci*. 25:199–201.

Hansen R, Sommer VM, Pinborg A, Krebs L, Thomsen LL, Moos T, Holm C, 2023. Intravenous

ferric derisomaltose versus oral iron for persistent iron deficient pregnant women: a randomised controlled trial. *Arch Gynecol Obstet.* 308(4): 1165-1173.

Howaldt S, Domènech E, Martinez N, Schmidt C, Bokemeyer B. 2022. Long-term effectiveness of oral ferric maltol vs intravenous ferric carboxymaltose for the treatment of iron-deficiency anemia in patients with inflammatory bowel disease: a randomized controlled noninferiority trial. *Inflamm Bowel Dis*. 28(3):373-384.

Indian Council of Medical Research - National Institute of Nutrition (ICMR-NIN). 2020. *ICMR-NIN Expert Group on Nutrient Requirement for Indians, Recommended Dietary Allowances (RDA) and Estimated Average Requirements (EAR).*

Institute of Medicine (IOM). 2001. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc.* Washington, DC: National Academy Press.

Ito K, Yokoyama K, Nakayama M, Fukagawa M, Hirakata H. 2021. Association of fibroblast growth factor 23 and α-klotho in hemodialysis patients during administration of ferric citrate hydrate: post hoc analysis of ASTRIO study. *BMC Nephrol*. 22:1-12.

Jongkraijakra S, Doungngern T, Sripakdee W, Lekhakula A. 2023. A randomized controlled trial of thrice-weekly versus thrice-daily oral ferrous fumarate treatment in adult patients with iron-deficiency anemia. *Ann Hematol*. 102(6):1333-1340.

Kaldara-Papatheodorou EE, Terrovitis JV, Nanas JN. 2010. Anemia in heart failure: should we supplement iron in patients with chronic heart failure? *Pol Arch Med Wewn*. 120(9):354–360.

Kew MC. 2014. Hepatic iron overload and hepatocellular carcinoma. *Liver Cancer*. 3:31–40.

Kew MC, Asare GA. 2007. Dietary iron overload in the African and hepatocellular carcinoma. *Liver Int*. 27:735–741.

Korean Nutrition Society (KNS). 2020. Ministry of Health and Welfare (KR). The Korean Nutrition Society. *Dietary Reference Intakes for Koreans*. Sejong: Ministry of Health and Welfare.

Lands R, Isang E. 2017. Secondary hemochromatosis due to chronic oral iron supplementation.

Case rep hematol. 2494167.

Lee CT, Wu IW, Chiang SS, Peng YS, Shu KH, Wu MJ, Wu MS. 2015. Effect of oral ferric citrate on serum phosphorus in hemodialysis patients: multicenter, randomized, double-blind, placebo-controlled study. *J Nephrol*. 28:105-113.

Liao Y, Cooper RS, McGee DL. 1994. Iron status and coronary heart disease: negative findings from the NHANES I epidemiological follow-up study. *Am J Epidemiol.* 139:704–712.

Lorinczova HT, Begum G, Temouri L, Renshaw D, Zariwala MG. 2022. Co-administration of iron and bioavailable curcumin reduces levels of systemic markers of inflammation and oxidative stress in a placebo-controlled randomised study. *Nutrients*. 14(3):712.

Lynch, S. 2011. Why nutritional iron deficiency persists as a worldwide problem. *J Nutr*. 141:763S–768S.

MacPhail AP, Mandishona EM, Bloom PD, Paterson AC, Rouault TA, Gordeuk VR. 1999. Measurements of iron status and survival in African iron overload. *S Afr Med J*. 89:966–972.

Makrides M, Crowther CA, Gibson RA, Gibson RS, Skeaff CM. 2003. Efficacy and tolerability of low- dose iron supplements during pregnancy: A randomized controlled trial. *Am J Clin Nutr*. 78:145–153.

Milman N, Byg KE, Bergholt T, Eriksen L. 2006. Side effects of oral iron prophylaxis in pregnancy–myth or reality? *Acta Haematol*. 115:53–57.

Milman N, Jønsson L, Dyre P, Pedersen PL, Larsen LG. 2014. Ferrous bisglycinate 25 mg iron is as effective as ferrous sulfate 50 mg iron in the prophylaxis of iron deficiency and anemia during pregnancy in a randomized trial. *J Perinat Med*. 42:197–206.

Milman NT, Bergholt T. 2024. Low-Dose Prophylactic Oral Iron Supplementation (Ferrous Fumarate, Ferrous Bisglycinate, and Ferrous Sulphate) in Pregnancy Is Not Associated With Clinically Significant Gastrointestinal Complaints: Results From Two Randomized Studies. *J Pregnancy*. 2024(1):1716798.

Moore M, Folson AR, Barnes RW, Eckfeldt JH. 1995. No association between serum ferritin and asymptomatic carotid atherosclerosis: The Atherosclerosis Risk in Communities (ARIC) Study.

Am J Epidemiol. 141:719–723.

Morrison HI, Semenciw RM, Mao Y, Wigle DT. 1994. Serum iron and risk of fatal acute myocardial infarction. *Epidemiology.* 5:243–246.

Nasser BA, Zayed EM, Title LM, et al. 1998. Relation of HFE gene mutations, high iron stores and early onset coronary artery disease. *Can J Cardiol.* 14:215–220.

NIH (National Institute of Health). 2024. Iron- Fact Sheet for Health Professionals web page. https://ods.od.nih.gov/factsheets/Iron-HealthProfessional/

Nelson, RL. 1992. Dietary iron and colorectal cancer risk. *Free Radical Biology and Medicine.* 12:16–8.

Oh CK, Moon Y. 2019. Dietary and sentinel factors leading to hemochromatosis. *Nutr*. 11(5):1047.

Pei LX, Kroeun H, Karakochuk CD. 2023. Reticulocyte haemoglobin equivalent (RET-He) as an early marker of responsiveness to oral iron supplementation. *J Clin Pathol*. 76(6):407-412.

Pergola P, Belo D, Crawford P, Moustafa M, Vargo D, Luo W, Goldfarb-Rumyantezev A. 2020. Different Ferric Citrate Dose Regimens in the Treatment of Iron Deficiency Anaemia in Patients with Non-dialysis Depending CKD: The COMPASS Trial. *Nephrol Dial Transplant*. 35(Supplement_3), pp.gfaa139-SO050.

Roest M, van der Schouw YT, de Valk B, et al. 1999. Heterozygosity for hereditary hemochromatosis gene is associated with cardiovascular death in women. *Circulation.* 100:1268–1273.

Salonen JT, Nyyssonen K, Korpela H, Tuomilehto J, Seppanen R, Salonen R. 1992. High stored iron levels are associated with excess risk of myocardial infarction in eastern Finnish men. *Circulation.* 86:803–811.

Sempos CT, Looker AC, Gillum RF. 1996. Iron and heart disease: the epidemiologic data. *Nutr Rev.* 54:73–84.

Stanworth SJ, Churchill D, Sweity S, Holmes T, Hudson C, Brown R, Lax SJ, Murray J, Spiby

H, Roy N, Farmer A. 2024. The impact of different doses of oral iron supplementation during pregnancy: a pilot randomized trial. *Blood Adv*. 8(21):5683-5694.

Sullivan JL. 1981. Iron and sex difference in heart disease risk. *Lancet.* 1:1293–1294.

Talboom K, Borstlap WA, Roodbeen SX, Bruns ER, Buskens CJ, Hompes R, Tytgat KM, Tuynman JB, Consten EC, Heuff G, Kuiper T. 2023. Ferric carboxymaltose infusion versus oral iron supplementation for preoperative iron deficiency anaemia in patients with colorectal cancer (FIT): a multicentre, open-label, randomised, controlled trial. *Lancet Haematol*. 10(4):e250-e260.

Tandara L, Salamunic I. 2012. Iron metabolism: current facts and future directions. *Biochem Med* (Zagreb). 22:311–328.

Tseng M, Murray SC, Kupper LL, Sandler RS. 1996. Micronutrients and the risk of colorectal adenomas. *Am J Epidemiol.* 144:1005–1014.

Tuomainen TP, Kontula K, Nyyssonsen K, Lakka TA, Helio T, Salonen JT. 1999. Increased risk of acute myocardial infarction in carriers of the hemochromatosis gene Cys282Tyr mutation: a prospective cohort study in men in eastern Finland. *Circulation.* 100:1274–1279.

von Siebenthal HK, Gessler S, Vallelian F, Steinwendner J, Kuenzi UM, Moretti D, Zimmermann MB, Stoffel NU. 2023. Alternate day versus consecutive day oral iron supplementation in iron-depleted women: a randomized double-blind placebo-controlled study. *EClinicalMedicine*. 65.

Wang YF, Deng Y, Zhang SY, Liu D, Luo B, Wang X, Deng M, Ma RL, Sun AJ. 2022. Efficacy and Mechanism of Buxue Yimu Pills on Gynecological Anemia: A Combination of Clinical and Network Pharmacology Study. *Chin J Integr Med*. 28(12):1072-1080.

Wessling-Resnick M. 2016. Iron webpage. Linus Pauling Institute website. https://lpi.oregonstate.edu/mic/minerals/iron. (Updated April 2016; reviewed May 2016).

Womack R, Berru F, Panwar B, Gutiérrez OM. 2020. Effect of ferric citrate versus ferrous sulfate on iron and phosphate parameters in patients with iron deficiency and CKD: a randomized trial. *Clin J Am Soc Nephrol*. 15(9):1251-1258.

Yip R, Dallman PR. 1996. Iron. In: Ziegler EE, Filer LJ, eds. Present Knowledge of Nutrition.

7th ed. Washington, DC: ILSI Press; 277–292.

Zhang Q, Wang H, Zhang YM, Li XL, Shen YY, Wei N, Zou K, Su WX, Dai HP, Wu DP, Liu LM. 2024. Comparison of the efficacy and safety between high-dose intravenous iron and oral iron in treating iron deficiency anemia: a multicenter, prospective, open-label, randomized controlled study. *Zhonghua Xue Ye Xue Za Zhi*. 45(12):1113-1118.

Updated July 2025

Zhang X, Giovannucci EL, Smith-Warner SA, et al. 2011. A prospective study of intakes of zinc and heme iron and colorectal cancer risk in men and women. *Cancer Causes Control.* 22:1627–1637.

Zhang W, Iso H, Ohira T, et al. 2012. Associations of dietary iron intake with mortality from cardiovascular disease: the JACC study. J Epidemiol. 22:484–493.