

Risk Assessment

Iron

General information

Chemistry

Iron, a transition metal, is ubiquitous in biological systems. In solid form the element exists free, or in iron-containing compounds. In aqueous solution, it exists in one of two oxidation states, Fe^{2+} , the ferrous form, and Fe^{3+} , the ferric form. Iron has a particularly high redox potential in solution. Within this risk assessment, the word iron refers to ionic iron, except where specific iron compounds are mentioned.

Natural occurrence

Iron is found in certain minerals, and in nearly all soils and in mineral waters

Occurrence in food, food supplements and medicines

Dietary sources rich in iron include liver, meat, beans, nuts, dried fruits, poultry, fish, whole grains or enriched cereals, soybean flour and most dark green leafy vegetables. Iron in foods occurs in two main forms: haem and non-haem. The major sources of haem iron in the diet are haemoglobin and myoglobin from meat, poultry and fish. Non-haem iron consists mainly of iron salts, derived from plant and dairy products. Most of the non-haem iron present as foods is in the ferric form.

Fortification of food with iron is common in developing countries, where deficiency of the element is widespread. In the UK there is mandatory fortification of white and brown flour at a level not less than 16.5 mg iron/kg flour. Many breakfast cereals are fortified on a voluntary basis; levels vary but are typically within the range of 70 to 120 mg/kg.

Inorganic dietary iron supplements are generally available as ferrous salts (chloride, fumarate, gluconate, glycerophosphate, succinate, sulphate), which are more readily absorbed than ferric salts. Ferrous sulphate and succinate are the most commonly available.

Other sources of exposure

Water is a potential source of iron. The limit in UK water supplies is 0.2 mg/L.

Recommended amounts

Estimated average daily iron requirements in the UK are 8.7 and 6.7 mg for males aged 11-18 and 19+ years, respectively (COMA, 1991). For women in the 11-50 years age group the estimated average daily iron requirement is 11.4 mg, whilst that for postmenopausal (50+ years) women is 6.7 mg. Estimated average daily requirements for children are 1.3 mg (0-3 months), 3.3 mg (4-6 months), 6.0 mg (7-12 months), 5.3 mg (1-3 years), 4.7 mg (4-6 years) and 6.7 mg (7-10 years). It has been estimated that the total

amounts of iron required for a full gestation is 680 mg. Existing body iron stores should provide this requirement, assuming adequate iron stores at conception, cessation of menstruation and increased intestinal absorption throughout gestation.

Analysis of tissue levels and iron status

A number of haematological and biochemical tests may be used to characterise iron nutritional status. Serum ferritin, serum iron concentration, total iron binding capacity (TIBC) and transferrin saturation (Fe/TIBC) indicate the level of iron supply to the tissues. Transferrin receptors are expressed on cell surfaces in proportion to the cells requirement for iron. As functional iron depletion occurs, more transferrin receptors appear on the cell surfaces. The concentration of cleaved extracellular domains, or soluble serum transferrin receptors, rises in parallel. Elevated serum ferritin and transferrin saturation are useful as indicators of iron overload. In healthy subjects, an accurate determination of iron status can be made using combined measures of serum ferritin, transferrin saturation and erythrocyte protoporphyrin.

Brief overview of non-nutritional beneficial effects

No relevant data have been identified.

Function

The majority of functional iron within the body is present in haem proteins, such as haemoglobin, myoglobin and cytochromes, which are involved in oxygen transport or mitochondrial electron transfer. Many other enzymes also contain or require iron for their biological function.

Total body iron averages approximately 3800 mg in men and 2300 mg in women. Approximately one third of body iron in men and one eighth in women is in the form of storage iron. Iron is stored mainly in the liver within the iron storage proteins, ferritin and haemosiderin. Small amounts of ferritin are also present in the plasma, although there are a number of differences from tissue ferritin and plasma has a low iron content, even in iron-overloaded individuals.

Many of the key biological functions of iron in living systems rely on the high redox potential, enabling rapid conversion between the Fe^{2+} and Fe^{3+} forms. The redox potential is, however, also potentially harmful in terms of the capacity for oxidative damage to cellular components such as fatty acids, proteins and nucleic acids. However, iron within the body (whether it is being stored, transported or as a component of various catalytic pathways) is normally bound to carrier proteins and/or molecules with antioxidant properties, which minimise the capacity of the free ion to cause oxidative stress.

Deficiency

Iron deficiency generally develops slowly, and may not be clinically apparent until iron stores are exhausted and the supply of iron to the tissues is compromised, resulting in iron-deficiency anaemia. Groups that are vulnerable to iron deficiency include: infants over 6 months, toddlers, adolescents and pregnant women (due to high requirements); older people and people consuming foods high in iron absorption inhibitors (due to poor absorption); menstruating women or individuals with pathological blood loss (due to high blood losses).

Interactions

Interactions may occur between iron and other metals close to iron in the periodic table, such as copper, manganese, zinc and chromium. Studies in rats have shown that iron supplementation impairs the absorption of zinc, and this has raised concerns that iron supplements may have adverse effects on zinc nutrition in humans. However, the magnitude of such an effect is less apparent in human studies than in rats. In general, calcium inhibits the absorption of iron. This may be relevant in consumption of iron supplements with milk or calcium-rich foods.

Absorption and bioavailability

Modulation of absorption of iron from the gastrointestinal tract is the primary mechanism for regulation of body iron levels. The amount of iron absorbed from the diet can vary widely and depends on body iron stores and physiological requirement (generally, the rate of erythrocyte production).

Absorption of haem and non-haem iron involves different mechanisms. In general haem iron uptake, which is via a specific haem receptor, occurs approximately 2- to 3-fold more extensively than that of non-haem iron and is largely independent of other dietary components. The mechanism by which non-haem iron enters intestinal mucosal cells is not clearly established, although there appear to be separate mechanisms for the uptake of ferrous and ferric iron. Uptake of non-haem iron depends initially on a low pH to effect solubilisation. Iron chelators, such as ascorbic acid, increase absorption by maintaining iron in solution. In the absence of chelators, ferric iron is generally less well absorbed than ferrous iron, due to its low solubility at higher pH. Dietary supplements are mostly inorganic salts. Iron supplements are also available in the form of the iron protein complex, ferritin, but poor absorption is reported.

Iron absorption from a diverse diet has been estimated to be approximately 15%. Women and children generally have lower iron stores than men, and thus absorb a greater percentage of the amount ingested. This is particularly pronounced during pregnancy with absorption of dietary iron increasing throughout gestation. Conversely, absorption is lower in postmenopausal women, in whom iron stores are generally high.

Distribution and metabolism

Iron is transported by the plasma transport protein, transferrin. In healthy adults approximately one-third of the total iron binding capacity is saturated. In conditions of iron overload or atransferrinaemia, non-protein-associated iron may also be detected in the plasma. Turnover of the total plasma iron pool (approximately 3 mg) is more than 10-fold every day. Approximately 80% of iron leaving the plasma is delivered to erythroid bone marrow. Iron in circulating erythrocytes is returned to plasma transferrin by means of reticuloendothelial cell phagocytosis.

Iron uptake by cells (other than during absorption from the intestinal lumen) occurs via binding of transferrin to the transferrin receptor, which is subsequently internalised within an endocytic vesicle. Recent studies have identified a number of novel proteins which are also likely to be involved in iron transport into and within cells, although the function of these proteins in iron transport has yet to be determined.

Excretion

Little of the absorbed iron is excreted. Very small losses occur in the faeces, by desquamation of gastrointestinal cells, in haemoglobin and bile, and via the urine. Substantial iron loss can occur through loss of blood. Average, total daily iron losses for healthy adults are 1.0 mg for men and 1.3 mg for premenopausal women (assuming an average blood loss of 30 – 40 mL per menstrual cycle). Daily iron losses for children have not been measured directly but are estimated as 0.2 and 0.5 mg for infants and children aged 6 – 11 years, respectively.

Toxicity

Human data

Acute and sub-chronic toxicity

Most cases of acute iron poisoning occur in children, due to accidental ingestion of iron supplements intended for adults. The acute toxic dose of iron in infants is considered to be approximately 20 mg/kg bw, associated with gastrointestinal irritation, whilst systemic effects do not generally occur at doses < 60 mg/kg bw. The lethal dose in children is approximately 200 – 300 mg/kg bw. Iron poisoning in adults is rare. Individual case reports suggest that a dose of approximately 100 g (approximately 1400 mg/kg bw) iron is lethal, although survival may occur with treatment.

High doses of iron supplements are frequently associated with gastrointestinal effects, especially constipation, but also with nausea, diarrhoea and vomiting. The severity and occurrence of the effect depends upon the formulation of the supplement and the amount of iron released in the stomach.

Severe gastrointestinal damage has been described following iron overdose. Reports of mucosal injury resulting from iron tablet ingestion at therapeutic levels are rare. Very few systematic studies of the potential of therapeutic doses of iron to cause or promote gastric or oesophageal ulceration have been conducted. The limited data available suggest that tissue damage due to iron tablets can be demonstrated histopathologically. It is unclear whether therapeutic doses of iron are likely to initiate gastrointestinal damage.

Chronic toxicity and carcinogenicity

Chronic iron overload may result from parenteral administration (as therapeutic iron or blood transfusions). Increased oral iron intake does not generally result in significant iron overload unless the iron is in a highly bioavailable form or there is an accompanying genetic defect, or increased demand (e.g. anaemia), causing increased iron absorption. 'Generalised iron overload' has been arbitrarily defined as an excess total body iron of more than 5 g in adults, and 'severe iron overload' as an excess of 10 g or more, associated with iron-induced tissue damage, including cirrhosis of the liver and impaired heart and endocrine function. The term haemochromatosis, previously used to describe massive iron overload associated with iron-induced tissue damage, is now usually restricted to the primary, genetically-determined disturbance of iron metabolism, hereditary haemochromatosis (HHC), an autosomal recessive disorder, associated with homozygosity for a specific mutation (Cys282Tyr) of the HLA-linked, *HFE* gene. The overall prevalence of HHC in Caucasian populations is approximately 1/250 with an estimated carrier frequency of approximately 0.1. The disorder is characterised by unregulated dietary

iron absorption, excess to bodily requirement, leading to accumulation of excess iron in the parenchymal cells of the major organs of the body, primarily the liver, pancreas and heart. This results in irreversible tissue damage, with clinical disease (cirrhosis and hepatocellular carcinoma, diabetes and heart failure) being manifested in middle age. Heterozygotes for HHC may show mildly increased signs of iron storage, but significant iron loading does not occur in the absence of other disorders related to excess iron-loading.

Secondary iron overload is defined as a quantitative increase in total body iron that is not the result of a genetically determined increase in iron absorption. The iron originates from either parenteral administration and/or increased absorption. Parenteral iron is initially cleared by the macrophages of the reticuloendothelial system, whilst iron absorbed from the gut may be taken up directly by hepatocytes. Pathology is most severe when there is both parenteral administration and increased absorption, as often occurs, for example, in the chronic inherited anaemia syndromes, β -thalassaemia and sideroblastic anaemia. In such cases iron chelation therapy is required to prevent the development of severe pathology and early death.

Many epidemiological studies have found associations between markers of high body iron status and increased risk of either cardiovascular disease or cancer in the general population. Interpretation of such studies is difficult because the biochemical indices used to assess body iron status may have been altered by the existence of chronic disease. The results of epidemiological studies suggesting that individuals heterozygous for HHC show increased risk of chronic disease, particularly cardiovascular disease, are also controversial.

Iron supplementation is common during pregnancy, generally during the 2nd and 3rd trimesters (at levels up to approximately 200 mg/day), with no reports of adverse effects other than gastrointestinal irritation. The relatively small number of reports that are available suggest that acute iron overdose during pregnancy is not associated with substantially increased foetal iron levels.

Supplementation studies

A large number of studies involving oral iron supplementation have been reported. Analysis of all reports was not possible, but was limited to those identified by database search as randomised, controlled trials. Many of these studies were carried out with the aim to improve iron status in population groups who were known or likely to be at risk of iron deficiency, such as pre-school children, juveniles, adolescent girls and pregnant and non-pregnant women, often in developing countries where such deficiency is common. Apart from gastrointestinal side effects, such studies have generally not addressed issues of potential adverse effects associated with oral iron supplementation.

Supplementary doses of 100-200 mg iron/day and above have been associated with nausea, vomiting and epigastric pain (Ganzoni *et al.*, 1974; Hallberg *et al.*, 1966b; Reddaiah *et al.* 1989). Other studies have reported a range of gastrointestinal effects, including diarrhoea, nausea, vomiting, constipation and epigastric pain, following supplementary doses of between 50 and 220 mg/day (Hallberg *et al.*, 1966a; Lokken and Birkland, 1970; Blot *et al.*, 1981; Brock *et al.*, 1985; Coplin *et al.*, 1991; Liguori, 1993; Frykman *et al.*, 1994). However, such effects were variable and appeared to vary depending on the formulation of the iron supplement given, with fewer adverse effects reported by subjects given supplementary iron as chelated iron or haem iron than by subjects given ferrous sulphate.

Several studies have suggested that excess iron intake could result in decreased serum zinc levels. Decreased maternal serum zinc concentrations were reported following iron supplementation at doses

of more than 60 mg/day during pregnancy (Breskin *et al.*, 1983; Hambidge *et al.*, 1983, 1987) and Dawson *et al.* (1989) reported that daily supplementation of pregnant women with 18 mg iron, in combination with a multivitamin supplement (on average from 13 weeks of gestation to term), resulted in a significant decrease in serum zinc level in the third trimester, compared with women who were given an equivalent multivitamin supplement without iron. Conversely, Sheldon *et al.* (1985) reported that supplementation with 480 mg/day ferrous fumarate (160 mg/day elemental iron), from the first or second trimester of pregnancy to term, had no effect on maternal serum zinc concentrations. As plasma zinc levels are not considered to be a good index of body zinc status the significance of these findings is unclear.

One study found an association between supplementation with ferrous sulphate (equivalent to 60 mg elemental iron/day) during pregnancy and reduced birth weight in women who were carriers for the sickle cell anaemia genotype (Menendez *et al.*, 1995).

Animal data

Acute toxicity

Oral lethal doses of 675 and 1230 mg/kg bw were reported for ferrous sulphate and phospholipid-microencapsulated ferrous sulphate, respectively, in Swiss strain mice. An acute oral LD₅₀ value of 2800 mg/kg bw (560 mg/kg bw iron) was reported for ferrous bisglycinate chelate (Ferrochel) in Sprague-Dawley rats.

Sub-acute, sub-chronic and chronic toxicity

Loading with high doses of carbonyl iron, a form of iron with higher bioavailability than other forms, has been used most to assess the effects of dietary iron overload in experimental animals. Chronic, high-dose supplementation in rats and mice results in rapid hepatic iron deposition, with a pattern similar to that seen in human HHC, and associated with cellular changes but not, in the majority of studies, with the development of fibrosis or cirrhosis. The main targets, in addition to the liver, were the heart, pancreas and the spleen.

A number of genetic mouse models have also been developed to mimic dietary iron overload in humans. The haemochromatosis (*HFE* -/-) gene-knockout mouse exhibits a pattern of iron overload similar to that seen in human HHC, and develops even greater levels of iron overload in association with high-dose dietary iron supplementation. These mice may, thus, provide a good model for future studies of iron overload in humans with HHC.

Reproductive and developmental toxicity

A multigeneration study in rats showed no adverse effects of 20 mg/kg bw/week maternal iron supplementation (by intramuscular injection, but not during pregnancy) on the numbers of offspring produced or their growth weights, with no significant evidence of excess iron transfer across the placenta. A study of maternal iron poisoning in an ovine model also showed that extremely elevated maternal serum iron concentrations were not accompanied by corresponding increases in foetal serum iron levels.

One study showed that iron gluconate was teratogenic after intraperitoneal administration to pregnant mice on the 8th and 9th days of gestation, the most pronounced defect being exencephaly.

Carcinogenicity and genotoxicity

A number of studies have shown that supplementary iron added to the diet enhances the development of neoplasia in animals that produce spontaneous tumours, are inoculated with tumour cells, or are exposed to chemical carcinogens. However, high-level (1200 – 1500 mg/kg bw/day) dietary carbonyl-iron supplementation had no effect on the initiation or promotion of hepatocarcinoma in the Solt-Farber model of hepatocarcinogenesis in rats. There appear to have been relatively few studies carried out to assess the effects of dietary iron overload, in the absence of chemical carcinogens, on tumourigenesis in experimental animals. Supplementation of the diet with 80 mg/kg bw/day iron in mice fed a high-fat diet was associated with increased mitotic and labelling indices in colonic crypts, but low-level dietary iron supplementation in rats (approximately 5.1 mg/kg bw/day iron, for 5 days) was associated with a significantly increased frequency of colonic crypt cell mitoses. Supplementation of BALB/cJ mice with levels of carbonyl-iron up to 4,500 mg/kg bw/day, for periods of up to 12 months, was not associated with the development of hepatic fibrosis or hepatocellular carcinoma, although there was evidence of nuclear changes in hepatocytes in the animals receiving the highest dose supplement for 12 months.

The majority of ferric and ferrous iron salts that have been assessed, and also carbonyl iron, have produced negative results in gene mutation assays, but were positive for viral-enhanced cell transformation in Syrian hamster embryo cells, *in vitro*, or in a mouse lymphoma assay.

Mechanisms of toxicity

In the presence of available cellular reductants, iron may act as a catalyst in the initiation of free radical-mediated reactions. The resultant oxyradicals or lipid hydroperoxides have the potential to damage a variety of cellular structures, including lipids in organelle membranes, nucleic acids, proteins, and carbohydrates, which could result in the disruption of numerous cellular functions. However, the relationship of such effects to the progressive fibrosis associated with chronic iron overload in humans is currently unclear.

Dose response characterisation

Although there are many studies on iron in humans, there is no relevant information on the dose response because the studies are correcting deficiency and frequently only test one dose level. With regards to gastrointestinal effects in iron-replete subjects, the form of the iron affects the findings and therefore it is hard to compare doses.

The animal database is too limited to draw any conclusions regarding dose response.

Vulnerable groups

Individuals with pre-existing gastrointestinal tract disease or chronic hepatitis, have been shown to be vulnerable to the toxic effects of iron.

Genetic variations

Several inherited diseases, for example, hereditary haemochromatosis (HHC), are associated with increased iron absorption. Hereditary anaemias, such as thalassaemia or sideroblastic anaemia, frequently require treatment by repeated blood transfusions, which may result in iron overload and toxicity.

Studies of particular importance to the risk assessment

(For full review see <http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers> or the enclosed CD)

Blot et al., 1981

In this study 132 pregnant women were given 105 mg iron (form not stated) plus 500 mg ascorbic acid, with or without 350 mg folic acid for 90 days. 14 % of subjects reported severe gastrointestinal effects (diarrhoea or constipation) and 16% minor effects. There was no difference in incidence between the groups, but there was no placebo group.

Brock et al., 1985

The tolerability of supplemental iron delivered from a wax-matrix tablet of ferrous sulphate was compared to that from a conventional ferrous sulphate tablet in a single blind, parallel group study. Both tablets delivered 50 mg of iron. The incidence of adverse gastrointestinal effects was significantly greater amongst subjects taking the conventional tablets, than amongst those taking the wax-matrix preparation. Of those taking the wax-matrix formulation only 19% experienced a severe or moderate adverse effect (306 reports), compared to 50% (1021 reports) of those taking the conventional tablets.

Coplin et al., 1991

The tolerability of supplemental iron (50 mg iron) in the chelated form of bis-glycino iron was compared with that of ferrous sulphate in a randomised double-blind cross-over trial. Of the 38 participants, 37% experienced moderate to severe adverse gastrointestinal effects whilst taking ferrous sulphate, compared to 21% who experienced similar side effects whilst taking the chelate formulation.

Frykman et al., 1994

In a controlled double-blind cross-over trial, haem and non-haem iron were administered to 100 healthy volunteers for periods of 1 month each. Groups of participants were given one of two different iron preparations: Group 1: two tablets of 1.2 mg haem iron from porcine blood, plus 8 mg non-haem iron as iron fumarate. Group 2: one tablet of 60 mg iron as iron fumarate. The study was divided into three consecutive periods of one month each and all participants received a placebo for one of the last two periods. Participants assessed side effects by keeping individual symptom diaries, a multiple-choice questionnaire was used for daily evaluation with listing of effects known to be related to iron therapy. The number of reports of obstipation and the total side effects, were significantly higher for the non-haem iron treatment, than for the haem iron or placebo. Constipation was reported in 35% and all gastrointestinal side effects were reported by 25% of participants during the non-haem iron phase of the trial. The effects reported for the haem iron treatment were indistinguishable from the placebo.

Liguori, 1993

In a prospective, controlled, double-blind, two-placebo controlled, multicentre trial the tolerability of ironproteinsuccinylate (ITF 282) was compared with a ferrous sulphate controlled release tablet. 1095 patients were randomised to receive either two ITF 282 tablets per day (60 mg iron per tablet) or one controlled release ferrous sulphate tablet per day, containing 105 mg iron, both treatments lasted 60 days. The general tolerability was reported to be favourable with both treatments, but significantly more favourable with ITF 282. With ITF 282, 63 patients (11.5%) complained of 69 adverse reactions (25 heartburn, 19 constipation, 25 abdominal pain), compared with 141 adverse events (33 heartburn, 31 epigastric pain, 23 constipation, 32 abdominal pain, 8 skin rash, 14 nausea) reported by 127 (26.5%) of those taking ferrous sulphate.

Lokken and Birkelan, 1979

In a randomised, double-blind crossover study, 19 young women received a dose of 120 mg/day (2 x 60) iron as ferrous fumarate or placebo for 2 periods of 8 weeks. Seven participants experienced gastrointestinal discomfort, 2 while taking placebo.

Exposure assessment

Total exposure/intake:

Food	Mean: 12 mg /day 97.5th percentile: 24 mg/day (from 1986/87 NDNS)
Water	0.4 mg/day (assuming 2 L/day at UK limit of 0.2 mg/L)
Supplements	20 mg/day (up to 60 mg/day for particular conditions, e.g. pregnancy) (Annex 4)

Estimated maximum intake: $24 + 0.4 + 20 \text{ mg} = 44 \text{ mg/day}$

Risk assessment

In humans acute iron poisoning is associated with severe gastrointestinal damage which may include haemorrhagic gastroenteritis. Blood and other fluid loss may lead to shock and coma. In some cases, apparent recovery may take place, possibly due to a latency period during which the iron is distributed throughout the body. Systemic iron toxicity is characterised by multi-system damage, principally in the liver, metabolic acidosis, coagulopathies and cardiovascular collapse. Acute poisoning is relatively unusual in adults, the lethal dose being approximately 100 g, but is more common in children.

Iron overload as a result of dietary intake is unusual in the normal population and only a handful of case reports exist describing this phenomenon. This may be due to the reduction in iron absorption that occurs as exposure increases.

Individuals with conditions such as hereditary haemochromatosis (HHC) are particularly vulnerable to iron overload, which occurs as a result of enhanced uptake. In subjects heterozygous for the condition, a small increase in iron storage may occur. It has been suggested that heterozygous subjects (up to 1% of the population) may have an increased risk of cardiovascular disease but this remains controversial. Similarly, the suggestion that high iron status may be associated with other chronic conditions remains unresolved.

Studies in rodents suggest a pattern of iron overload comparable with that seen in haemochromatosis, with cellular changes but not with fibrosis occurring. Reproductive studies in rodents have shown no significant evidence of iron transfer across the placenta. This is supported by a study in an ovine model where maternal iron poisoning did not result in increases in foetal serum iron levels. However one study reports that iron gluconate is teratogenic, causing exencephaly in mice following administration on the 8th and 9th days of gestation.

ESTABLISHMENT OF GUIDANCE LEVEL

Overall, there are insufficient appropriate data to establish a Safe Upper Level for iron. Many supplementation studies have been conducted, generally in iron-deficient groups and none of them are applicable to the population as a whole. For iron-replete individuals in non-developing countries, the most common side effects reported are gastrointestinal in nature, usually constipation but nausea, vomiting and epigastric pain have also been reported. These effects are reported to follow supplement doses of between 50 and 220 mg iron/day, the frequency increasing at higher dose levels. The severity and occurrence of effects depends on the formulation of the supplement (Coplin *et al.*, 1991; Liguori, 1993). A number of studies have examined the effects of different iron formulations.

For guidance purposes, a supplemental intake of approximately 17 mg/day (equivalent to 0.28 mg/kg bw/day for a 60 kg adult) would not be expected to produce adverse effects in the majority of people. This is derived by dividing the lower end of the range found to have an effect by an uncertainty factor of 3 to allow for extrapolation from a LOAEL to a NOAEL. This is based on data referring to ferrous iron (Fe II), which is the form of iron used in supplements currently available in this country. No additional uncertainty factor is needed for inter-individual variation because the assessment is based on studies on large numbers of people. A safe upper level for total iron has not been estimated, as gastrointestinal effects are associated with iron in supplements rather than in foods.

The guidance value of 17 mg/day calculated above, does not apply to the small proportion of the population who have increased susceptibility to iron overload, via a mechanism of unregulated (increased) absorption from the diet, associated with the homozygous haemochromatosis genotype (estimated prevalence, approximately 0.4% in Caucasian populations). It is not possible to give quantitative information on the difference in susceptibility between this group and normal subjects.

It should be recognised that many of the available studies do not look at side effects in detail and information on the long-term implications of iron supplementation on iron status and storage is lacking.

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