Iron – toxicological and nutritional aspects in the body

Đokić[1], M., N. Bilandžić[1]

review

Summary

Iron is the most common transitional metal on Earth and it is essential for many life forms. On the other hand, iron and its compounds are present as atmospheric pollution, which can cause harmful effects in humans, animals and materials. Living organisms have been forced to adopt an efficient system for iron transport and a mechanism for its storage in order to maintain the balance between the harmful and beneficial effects of iron. The distribution of iron in the human body is regulated by a complex mechanism that maintains homeostasis. During childhood, pregnancy or blood loss, the need for iron increases, as does its adsorption. Iron is absorbed throughout the entire digestive system and is best assimilated from heme (80% soluble iron in meat) and physiologically binds with specific proteins, forming reversible compounds of iron and protein, i.e. protein complexes. Iron participates in various metabolic processes in the body, including oxygen transport, DNA synthesis and electron transport. Iron metabolic disorders are among the most common illnesses in people, and include a broad spectrum of diseases with various clinical manifestations, from anaemia to neurodegenerative diseases. Acute iron poisoning is almost always the result of ingestion of iron enriched medicines, and occurs most commonly in children. Chronic iron poisoning is a more frequent problem among adults. Iron is a catalyser in the reaction that creates hydroxyl radicals from hydrogen peroxide and increases oxidation stress, which ultimately increases the concentration of free iron. This process can lead to damage to the lipid membranes and ultimately to the liver, kidney and spleen. Iron deficiency in the diet increases the mechanism of intestinal iron absorption from the body's stores, and reserves are spent faster than iron is absorbed from food, which can lead to its deficiency in the body. Iron deficiency is still an endemic issue in certain areas around the world. Contemporary procedures to enrich food with iron today also consider the potential risk of interaction between micronutrients that can influence the absorption and bioavailability of iron.

Key words: *iron, toxicokinetics of iron, diet*

Introduction

Iron is the most common transitional metal on Earth and is important for many life forms and, with rare exceptions, essential for the survival of all organisms. It is considered essential as it is an integral part of all cell processes, including breathing, redox processes, energy metabolism, DNA synthesis and gene regulation (Andrews, 1998). Despite the widespread distribution and abundance of iron in the biosphere, organisms can be subject to iron deficiencies or overload, which can even have fatal consequences.

In nature, iron appears in two oxidation states, as iron(II) and iron(III), i.e. in the form of the ions Fe^{2+} and Fe^{3+}. Bivalent iron salts, such as ferrous sulphate ($FeSO_4$) are green in colour and readily water soluble, while trivalent iron salts are red or brown in colour and near insoluble (Raos, 2008). The great differences in the redox potential of Fe^{2+} and Fe^{3+} contribute to the role of iron as an important biological metal. Therefore, the role of iron is limited by its poor solubility and its preference to participate in reactions that create free radicals (Miethke & Marahiel, 2007).

Living organisms have been forced to adopt an efficient way to transport iron and to create a mechanism for its storage in order to maintain a balance between the harmful and useful effects of iron. For example, bacteria and fungi create natural compounds called siderophores that serve to transport iron from the environment into the cell (Neilands, 1995). In plants, there are two forms of iron transport from the soil, reduction and chelation (Briat, 2005).

In animals, iron is primarily taken up through the diet, and as such has either good or limited bioavailability, depending on the source. Iron from red meats is well resorbed, while plant based iron is poorly absorbed due to the presence of phosphates and polyphenols that inhibit resorption and create insoluble complexes (Crichton & Ward, 2003).

Iron in the environment

In monitoring the geochemical cycle important for the emergence of the Earth and in comparison of

[1] **Maja Đokić, BSc**; **Nina Bilandžić, PhD**, Scientific Advisor, Laboratory for residue determination, Department for Veterinary Public Health, Croatian Veterinary Institute, Zagreb

the cycling of oxygen, dissolved iron and sulphides in the atmosphere and ocean, it was established that the iron cycle is greater than the oxygen and sulphide cycles. Due to the insolubility of iron oxides and sulphides, it is believed that dissolved iron is quite abundant in the atmosphere and oceans, while oxygen and sulphur are rarely present (Walker & Briamblecombe, 1985). With oxidation of iron with oxygen, insoluble Fe(III) is formed and loses its bioavailability. However, with the creation of chelates of Fe(III), iron is again available and therefore control of its potential toxicity in food is enabled as the non-toxic water soluble protein ferritin (Crichton & Pierre, 2001).

Iron and iron compounds are present as atmospheric pollutants that can cause detrimental effects in humans, animals and materials. Iron and its oxides cause benign siderosis. With iron oxides, high concentrations of carcinogenic compounds and sulphur dioxide are transported deep into the lungs. Analysis of the air in urban settlements has shown average iron concentrations of about 1.6 μg/m^3 and the main sources of airborne iron are iron and steel industrial plants (Smith et al., 1998). Iron pollution can be reduced by using equipment that controls the size of particles emitted into the environment (Sullivan, 1969).

The effects of iron chloride and oxides have been tested in China, in the area of the Tongchuan mines, using thermogravimetric analysers (Liu et al., 2001). The results showed that all iron compounds used in the process, above all $FeCl_3$, $FeCl_2$ and Fe_2O_3, can influence the emissions of SO_2 and NO, though via different mechanisms. For example, $FeCl_3$ has the role of a catalyser and absorber during the transfer of sulphur from coal into SO_2 and in the transition of nitrogen from coal into NO (Liu et al., 2001, 2002).

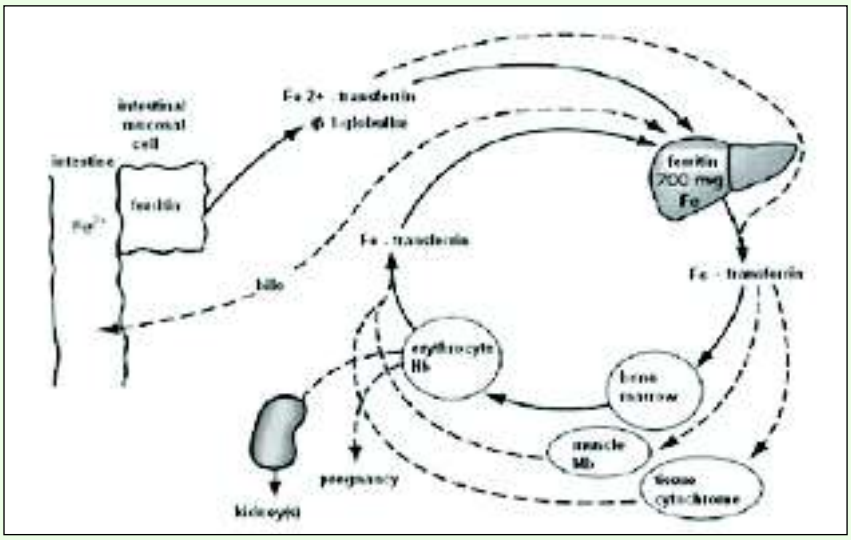

Figure 1 **Transport of iron in the body**

Iron is the main component of soil, and its concentrations in soil are largely influenced by industrial processes. More than 45% of the total global population currently lives in urban areas, and by 2030, that figure will reach 60% (United Nations, 2001). Various levels of iron concentrations in soil have been found in urban areas (Yang et al., 2001). Soil is most often controlled by determination of the content of lead, zinc, copper and nickel, and lead most often appears in combination with iron oxides.

In surface waters, 61 to 2680 mg/kg of iron is present (Vuori, 1995). Some studies have shown that due to agricultural activities and the increased use of groundwater, the level of ground water in the Netherlands has been significantly reduced (Smolders & Roelofs, 1995). As a result, in order to compensate for this decreased water, alkaline waters from rivers such as the Rhine, which are rich in sulphates and poor in iron are being used. This further enhances alkalinity in the soil and the breakdown of organic sediments. Increased sulphate reduction leads to the settling of iron sulphides and creates an alkaline environment in which the concentration of phosphates and ammonia compounds increases. The release of these compounds into the water layer causes internal eutrophication and a drop in iron levels, while sulphides accumulate in the water to toxic concentrations (Smolders & Roelofs, 1995).

Iron can have direct and indirect effects on the ecosystem (Vuori, 1995). Under the influence of the mining industry, increased reforestation, the production of peat and drainage of waters from agricultural lands, the iron load has been increased in many ecosystems. The impacts of iron on aquatic organisms and their habitats is primarily indirect, though in some habitats it can be direct due to the inflow of iron rich waters, particularly in the winter months. Iron hydroxide and humus with a layer of deposited iron indirectly impact aquatic organisms, hindering their normal metabolism and osmoregulation by influencing the structure and quality of habitats and food resources. Both direct and indirect impacts of iron pollution cause a reduction of species diversity, and reduce the abundance of periphyton, invertebrates and fish (Vuori, 1995).

The bioaccumulation of iron in the organs and tissues of the freshwater crab *Potamonautes warreni* was monitored in three aquatic ecosystems

with metal pollution (Steenkamp et al., 1993). The concentration of iron in the water and sediments differed and were associated with environmental influences. The highest iron concentrations were detected in the gills, indicating that this organ is the primary site for iron adsorption from aquatic media. Though the iron concentration in organs and tissues of crabs was not dependent on the season or gender, it was discovered that there is an inverse relationship between crab size and its capacity for iron bioaccumulation.

It is known that plants have the ability to accumulate various chemical compounds, including metals. This process primarily depends on the plant species and the concentration of certain metals in the soil. In the hilly region of south central Norway, different concentrations of iron, copper, molybdenum, zinc, selenium and manganese were found. The mean values and ranges of these concentrations were determined in different native plant species and were (mg/kg dry matter): Fe: 208, 15–2245; Cu: 6.0, 0.9–27.2; Mo: 0.25, 0.01–3.57; Zn: 77, 8–320; Se: 0.05, 0.01–0.32; Mn: 338, 31–3784. The quantity of individual elements showed large differences between and within plant groups. Furthermore, large differences were found between the peripheral parts of two lichen species, with high concentrations of Fe and Al in the lichen *Xanthoria* and Cd and Zn in the lichen *Parmelia* (Nimis et al., 2001).

Toxicokinetics of iron

The distribution of iron in the human body is regulated by a complex mechanism that maintains homeostasis. Humans have a relatively weak ability to excrete iron ions, and so homeostasis is achieved by regulating the resorption of iron in the small intestine. From 2 to 15% of iron is absorbed in the gastrointestinal tract, while the elimination of absorbed iron is only 0.01% per day. The bioavailability of dietary iron, the quality of stored iron and the development rate of erythrocytes all affect the absorption of iron. Vitamin C stimulates resorption and is important in the production of haemoglobin. Dietary inhibitors to the absorption of non-heme iron are oxalic acid, tannins, polyphenols and calcium-carbonate based supplements (Mahan & Escott-Stump, 2008).

During childhood, pregnancy or due to blood loss, the need for iron and its adsorption increase. Iron is absorbed throughout the entire digestive tract, and the most iron is absorbed in the duodenum, while absorption is progressively reduced in the distal segments of the intestines. Considering that there is no adequate way of extracting excess iron via standard physiological paths (kidneys, lungs, skin), absorption from the duodenum is considered to be the primary homeostatic regulator of the iron content in the body. Namely, with reduced absorption, the accumulation of iron in the body is prevented, while in some species, when haemolysis or large blood loss occurs, absorption is increased (Gamulin et al., 2011).

Dietary iron is primarily trivalent (ferric iron). In the acidic medium of the stomach (hydrochloric acid), ferric acid is reduced to ferrous iron. In addition to hydrochloric acid, the stomach mucosa cells also produce the protein gastroferrin, which binds iron and enables better absorption. Iron is best absorbed from heme (80% soluble iron in meat), and physiologically binds to specific proteins, creating reversible iron and protein complexes (Hoffbrand, 1986).

In the intestinal lumen, iron takes over the protein apoferritin from the intestinal mucosa and transports it to the protein plasma transferrin (siderofilin) which transports it further to all cells (Figure 1). In compound with specific proteins, haemoglobin, myoglobin, ferritin, haemosiderin and various enzymes are formed. The turnover of iron depends on the quantity of specific apoproteins in the body. The largest share of iron in the circulation of plasma and extracellular fluid is bound to the specific protein transferrin. Constant competition for free iron ions takes place between the transferrin and other proteins that can bind iron. Transferrin is a β1-globulin that is produced in the liver and has a molecular weight of 75,000. After the Fe^{2+} ions are released into the plasma, they are oxidised in the presence of ferroxidase, which is, in fact ceruloplasmin (Boggen et al., 2000).

In normal dietary conditions, adults usually have about 45 mg (women) or 55 mg (men) iron per kilogram of body weight, i.e. a total of 3 to 5 g of iron in the body. The total quantity of iron in the body is primarily in the form of haemoglobin (60–70%), followed by myoglobin, cytochrome and other enzymes with iron (10%), while 20–30% is bound to ferritin and haemosiderin. The extracellular transport protein, transferrin, accounts for only 0.1–0.2% of the total iron in the body (Fontecave & Pierre, 1993). The excess iron is excreted, while a certain amount remains in the intestines, bile, urine and a small amount may be present in sweat, nails and hair. The total iron excreted is about 0.5 mg per day. In excessive exposure to iron or iron overload, the synthesis of ferritin is increased in the parenchymal liver cells. At that point, the ability of the liver to synthesize ferritin exceeds the ability of the lysosomes to excrete iron. The lysosomes transform ferritin into haemosiderin, which then remain *in situ*. The production of haemosiderin from ferritin is still inadequately studied, though it is believed that it includes denaturation of the apoferritin molecule. In increasing the in-

take of iron, the concentration of ferritin reaches its maximum and a large amount of iron is found in the haemosiderin. Therefore, both ferritin and haemosiderin are reservoirs and have a protected role, as they maintain the intracellular iron in bound form (Gurzau et al., 2003).

Impacts of iron on health

Iron participates in various metabolic processes in the body, including oxygen transport, DNA synthesis and electron transfer. Iron concentrations in tissues should be well regulated, as increased quantities lead to tissue damage as a result of the creation of free radicals. Iron metabolism disorders are among the most common illnesses in humans, and include a wide spectrum of diseases with various clinical manifestations, from anaemia to neurodegenerative diseases. Familiarity with iron regulation at the molecular level is critical for identifying the cause of disease and to ensure setting the proper diagnosis and course of treatment (NRC, 1979; Adamama-Moraitou et al., 2001; Evans & Halliwel, 2001; Kuvibidila et al., 2001; Lieu et al., 2001).

Iron has the capacity to receive and give electrons, making it a physiologically important component of the cytochrome and oxygen binding molecules. However, iron is also biochemically hazardous, as it acts as a catalyser in the reaction to convert hydrogen peroxide to free radicals that damage the cell membrane, proteins and DNA, and ultimately tissue, according to the reaction:

$$Fe^{2+} + H_2O_2 + H^+ \rightarrow Fe^{3+} + H_2O + HO^-$$

In healthy organisms, this reaction is weakened as there is an insufficient amount of free iron that could serve as a catalyser. In the pathological state, the metabolism of iron and superoxide interact mutually, as each can increase the toxicity of the other. Iron overload can increase the detrimental effects of hyperproduction of superoxide in a wide range of inflammatory states of the organism, both acute and chronic. Furthermore, chronic oxidative stress can modulate the intake and storage of iron, and lead to self-sustainable and increasing cytotoxicity and mutagenic effects.

Table 1 **Iron content in different foodstuffs**

Foodstuffs	mg Fe / 100 g foodstuff
shells, canned	26,4
ready to eat cereals	6-70.3
oysters, wild, cooked	11,33
organ meats, liver	5.78-10.89
soybeans cooked	3.67
lentils cooked	2.75
spinach cooked from fresh	2.67
beef (bottom round)	3.44
sardines, canned in oil	2.75
chickpeas cooked	2
duck, meat only, roasted	2.56
lamb cooked	2.56
shrimp canned	2.5
tomato paste	3.33

Deferoxamin is a free iron chelator used in clinical practice to remove excess iron. This is a large molecule with a short half-life (about 20 minutes), which results in the need for its long-term use, and the daily dose can vary between 2 and 10 g/day (Emerit et al., 2001).

Iron overload can be divided according to the intake path of iron into the body, or according to the predominant tissue in which it has accumulated. Iron intake can be either enteral or parenteral, or through the placenta during pregnancy. The varying distribution of iron in the parenchial and reticuloendothelial system induces the pathogenic mechanism of iron accumulation, and has an important influence on organ damage and prognosis for the patient.

The diagnosis of iron overload can be given based on clinical data, high saturation of transferring and/or values of ferritin. However, increased levels of ferritin are not always associated with iron overload, but can be symptoms of other disorders, such as inflammation or neoplasia. A liver biopsy and determining the distribution of iron within the organ is still the most useful way to diagnose iron overload. Determination of a mutation of the *HFE* gene (C282Y and H63D) is an important method of proving the presence of iron overload (Piperno, 1998).

Iron toxicity

The quantity of iron in the organism is primarily regulated by absorption, and there is no physiological mechanism that could eliminate excesses. Regulation is specific, i.e. the type of diet, quantity of iron in the diet and lifestyle influence the absorption of iron. In the past, nutritional programmes based on iron-enriched foods were very widespread due to the serious lack of iron in many areas worldwide. Today, we also know that a large number of people without symptoms carry the *HFE* gene, and have the potential to accumulate excess iron in the body during their life. In increasing the intake of iron, regulation via homeostatic mechanisms is not sufficient

Table 2 **Display of vegetable and animal foodstuffs abundant with iron**

Foodstuffs abundant with iron	Nonheme foodstuffs with abundant iron
oysters	wheat
liver	millet
red meat (especially beef)	oats
poultry (dark red meat)	beans
tuna	soybeans
salmon	peas
iron fortified cereals	almonds
dried beans	brazil nuts
whole grains	prunes
eggs (especially egg yolks)	raisins
dried fruits	broccoli
lamb	spinach
pork	asparagus
shellfish	kale

to prevent its accumulation. Excess iron in the body can have various toxicological effects, and can impact the liver, heart, pancreas or lungs and lead to various health problems, such as diabetes mellitus, pancreatic hypertrophy or hormonal irregularities. For that reason, it is very important to set an early diagnosis of iron oversaturation and to implement the appropriate therapy (Fujiwara, 1989; Anderson, 1993; Hershko et al., 1993; Gutterridge et al., 2001; Kang, 2001).

Acute iron poisoning is usually always the consequence of ingestion of iron enriched medication, and occurs most often in children. Chronic iron poisoning is a common problem among adults. Excess iron ingested in pharmaceutical products can cause poisoning, while therapeutic doses can cause gastrointestinal problems. A chronic excess of iron in primary and secondary haemochromatosis can lead to liver fibrosis, diabetes and heart failure (Bassett, 2001; Hash, 2001; Schumann, 2001).

There are three fundamental ways in which iron is accumulated in the body: idiopathic haemochromatosis, excess dietary iron or blood transfusion. It has been established that patients with increased ferritin levels and normal transferrin levels suffer more often from liver steatosis (Fargion et al., 2001).

Iron is a catalyser in the reaction creating hydroxyl radicals from hydrogen peroxide, and thereby increases oxidative stress, which ultimately increases the concentration of free iron. This process can lead to damage of the lipid membranes and ultimately to organ damage, including liver, kidney and spleen (Heys & Dormandy, 1981; Hultcrantz et al., 1984; Houglum et al., 1990). Lipid peroxidation can cause dysfunction of lysosomes and mitochondria or cirrhosis (Bassett et al., 1986; Myers et al., 1991; Tecator et al., 1995).

In line with this, various epidemiological studies and observations have indicated that high iron reserves represent a serious threat to health, as this increases the risk of atherosclerosis and myocardial infarction. Clinical and epidemiological studies indicate that increased oxidative stress can also cause DNA damage, activate carcinogenesis and accelerate the appearance of tumour cells (Fargion et al., 2001).

Dietary iron

Though it is not scientifically proven, the data indicate that it is not recommended to take iron outside of one's physiological requirements but that to avoid symptoms of iron deficiency, it is necessary to meet the recommended daily allowances.

When iron is insufficiently represented in food, a homeostatic mechanism increases intestinal absorption of iron from bodily stores. In that case, stores are more quickly spent than iron can be absorbed from food, which can lead to a deficiency in the body. Iron deficiency is still endemically present in certain areas around the world. Therefore, in those areas, the consumption of iron enriched foods is recommended to prevent the appearance of anaemia. In the past few decades, attempts to supply dietary iron have primarily been limited to preventing iron deficiencies during growth and during pregnancy (Schumann, 2001). A high daily intake of iron, for example among the population of sub-Saharan Africa, who consume 50 to 100 mg per day through homemade beer, caused the appearance of cirrhosis and diabetes (Gurzau et al., 2003).

Research in the area of iron absorption from food confirmed the relationship between the bioavailability, loss and storage of iron (Hallberg, 2001). It was established that an iron deficiency is associated with age, and appears after one's 20s, which explains earlier controversial findings. In enriching food with iron, it is also necessary to consider the potential risk of interactions between micronutrients that can influence absorption and bioavailability. At the level of essential needs, the majority of micronutrients are absorbed via specific mechanisms that are not sensitive to mutual interactions. However, in intake in aquatic solutions and in high concentrations, competition occurs between elements of similar characteristics and the result is an unregulated intake process. A nega-

tive influence of iron supplements has been established on the state of zinc and copper, and of zinc supplements on the state of iron and copper. However, no negative influence of calcium was found on iron absorption in the long-term use of calcium supplements. Ascorbic acid is known to have a strong potential for stimulating iron absorption and its supplementation in food improves iron status, especially in the population consuming a vegetarian diet.

Numerous studies on iron contents (Table 1) in various types of foods have enabled the consumption of a balanced diet, which can prevent the appearance of iron deficiencies, or acute or chronic excesses of iron (Mahan & Escott-Stump, 2008).

Interest in iron is also increased by the fact that a part of the world's population does not consume meat or meat products, which according to many, can cause a lack of essential elements, such as zinc and iron. It is believed that in addition to a low intake of meat and increased intake of legumes and cereals, the absorption of zinc and iron are decreased (Hunt, 2003). Cereals and legumes often contain a high amount of inhibitors to mineral absorption, such as phytates and polyphenols, which inhibit zinc and/or non-heme iron, and creating insoluble complexes in the intestines. Therefore the bioavailability of these micronutrients from these foods is often poor (Gibson, 1994).

Deficiencies of this micronutrient represent an important health care problem in developing countries, influencing the growth, development and memory in children (Appel et al., 2001). It is generally known that iron rich foods are those of animal origin, while those of plant origin are rich in non-heme iron (Table 2; Mahan & Escott-Stump, 2008).

Table 3 **Iron content in different meat**

Meat	mg Fe/100 g
Turkey, all classes, giblets, cooked	7,71
Chicken, broilers , giblets, cooked	7,04
A liver sausage, pork	11,20
Duck, domesticated, meat only, cooked, roasted	2,70
Beef stew, canned entree	2,48
Beef, variety meats and by-products, liver, cooked, pan-fried	6,16
Turkey, all classes, neck, meat only, cooked	2,30
Beef, chuck, separable lean only, cooked	3,68
Beef, round, steak, separable lean only, cooked	2,87
Lamb, domestic, shoulder, separable lean only, cooked	2,71
Chicken, liver, all classes, cooked	11,63
Chicken, canned, meat only, with broth	1,58
Beef, ground, 85% lean meat / 15% fat,cooked	2,60
Lamb, domestic, shank , separable lean,only, cooked	2,12
Beef, corned beef, canned	2,08
Chicken, broilers , breast, meat and skin, cooked	1,25
Lamb, domestic, loin, separable lean only,	2,00

Animal proteins in the pork, veal, beef, lamb and chicken meat stimulate the resorption of iron. Compounds responsible for better absorption, usually called meat factors, are not known, though specific animal acids or dipeptides that arise from decomposition in the digestive system can increase iron resorption (Mahan & Escott-Stump, 2008). Animal organs such as liver, kidney and heart, and lean meats and poultry are the best sources of iron (Table 3; Anonymous, 2012).

In the Republic of Croatia, the Ordinance on food additives stimulates the daily intake of vitamins and minerals intended for health adults, and the maximum permitted intake of iron is 30 mg, while the recommended daily intake is 14 mg (Anonymous, 2011a). Also, the Ordinance on the maximum permitted quantities of certain contaminants in food (Official Gazette 154/2008), until the adoption of the Ordinance on amendments to the Ordinance on the maximum permitted quantities of certain contaminants in food (Anonymous, 2011b), prescribes the maximum permitted quantity of iron in certain foods as: 1.5 mg/kg for oils and fats of vegetable and animal origin, margarine and margarine spreads; 5.0 mg/kg for unrefined oils, fats and fish oils; 20 mg/kg for honey; 30 mg/kg for fish products in metal packaging. The Ordinance on foods for infants and small children and processed cereal based foods for infants and small children (Official Gazette 74/08) prescribes the minimum and maximum permitted quantity of iron in first and transitional foods, and the highest permitted quantity of iron in processed cereal-based foods and products ready for use in the form that they appear on the market.

Literature

Adamama-Aoraitou, A., T. Rallis, A. Papasteriadis, N. Roubies, A. Kaldrimidis (2001): Iron, zinc, and copper concentration in serum, various organs and hair of dogs with experimentally induced exocrine pancreatic insufficiency. Dig. Dis. Sci.46 (7), 1444–1457.

Anderson, B. D. (1993): Pediatric iron poisoning. ASHP Midyear Clinical Meeting, p. 23.

Andrews, S. C. (1998): Iron storage in bacteria. Adv. Microbiol. Physiol. 40, 281–351.

Anonymous (2008): Ordinance on food for infants and small children and processed cereal-based foods for infants and small children

(Official Gazette 74/08).

Anonymous (2008): Ordinance on the maximum permitted quantities of certain contaminants in food (Official Gazette 154/08).

Anonymous (2011a): Ordinance on food additives (Official Gazette 46/11).

Anonymous (2011b): Ordinance on amendments to the Ordinance on the maximum permitted quantities of certain contaminants in food (Official Gazette 78/11).

Anonymous (2012): USDA Nutrient Data Laboratory U.S. Department of Agriculture, Agricultural Research Service. 2011. USDA National Nutrient Database for Standard Reference, Release 24. Nutrient Data Laboratory Home Page http://www.ars.usda.gov/nutrientdata, accessed 6 March 2012.

Appel, M. J., C. F Kuper, R. A. Woutersen (2001): Disposition, accumulation and toxicity of iron fed as iron(II)sulfate or as sodium iron EDTA in rats. Food Chem. Toxicol. 39, 261-269.

Bassett, M. L., J. W. Halliday, L. W. Powell (1986): Value of hepatic measurements in early hemochromatosis and determination of the critical iron level associated with fibrosis. Hepatology 6, 24–29.

Bassett, M. L. (2001): Haemochromatosis: iron still matters. Int. Med. J. 31 (4), 237–242.

Boggen, D. L., A. K. Duggan, G. J. Dover, M. H. Wilson (2000): Screening for iron deficiency anemia by dietary history in a high risk population. Pediatrics 105(6), 1254-1259.

Briat, J. F. (2005): Cellular and whole organism aspects of iron transport and storage in plants, in: M.J. Tamás, E. Martinoia (Eds.), Molecular Biology of Metal Homeostasis and Detoxification, Topics in Current Genetics, vol. 14, Springer-Verlag, Berlin Heidelberg, p. 193–213.

Crichton, R. R., J. L. Pierre (2001): Old iron, young copper: from Mars to Venus. Biometals 14 (2), 99–112.

Crichton, R. R., R. J. Ward (2003): An overview of iron metabolism: molecular and cellular criteria for the selection of iron chelators. Curr. Med. Chem. 10, 997–1004.

Emerit, J., C. Beaumont, F. Trivin (2001): Iron metabolism, free radicals, and oxidative injury. Biomed. Pharmacother. 55 (6), 333–339.

Evans, P., B. Halliwell (2001): Micronutrients: oxidant/antioxidant status. Br. J. Nutr. 85, S67–S74.

Fargion, S., M. Mattioli, A. L. Frananzani, M. Sampietro, D. Tavazzi, M. Focianti, E. Taioli, L. Valenti, G. Fiorelli (2001): Hyperferritinemia, iron overload, and multiple metabolic alterations identify patients at risk for nonalcoholic steatohepatitis. Am. J. Gastroenterol. 96 (8), 2448–2455.

Fontecave, M., J. L. Pierre (1993): Iron. Biochimie 75, 767–773.

Fujiwara, K. (1989): Studies of iron metabolism of the lung: Part 1.Influence of inhaled iron on iron metabolism of an experimental welder's lung. Okayama Igakkai Zasshi 01 (7–8), 723–732.

Gamulin, S., M. Marušić, Z. Kovač (2011): Patofiziologija. Medicinska naklada, Zagreb.

Gibson, R. S. (1994): Zinc nutrition in developing countries. Nutr. Res. Rev. 7, 151–173.

Gurzau, E. S., C. Neagu, A. E. Gurzau (2003): Essential metals—case study on iron. Ecotoxicol. Environ. Saf. 56, 190–200.

Gutterridge, J. M., G. J. Quinlan, T. W. Evans (2001): The iron paradox of heart and lungs and its implications for a lung injury. Free Radic. Res. 34 (5), 439–443.

Hallberg, L. (2001): Perspectives on nutritional iron deficiency. Annu. Rev. Nutr. 21, 1–21.

Hash, R. B. (2001): Hereditary hemochromatosis. J. Am. Board Fam. Pract. 14 (4), 266–273.

Hershko, C., G. Link, M. Tzahor, A. Pinson (1993): The role of iron and iron chelators in anthracycline cardiotoxicity. Leuk. Lymphoma 11 (3–4), 207–214.

Heys, A. D., T. L. Dormandy (1981): Lipid peroxidation in iron-overloaded spleens. Clin. Sci. 60, 295–301.

Houglum, K., M. Filip, J. L. Witztum, M. Chojkier (1990): Malondialdehyde and 4-hydroxynonenal protein adducts in plasma and liver of rats with iron overload. J. Clin. Investig. 86, 1991–1998.

Hultcrantz, J., L. E Ericsson, T. Hirth (1984): Levels of malondialdehyde production in rat liver following loading and unloading of iron. Virch. Arch. 45, 139–146.

Hoffbrand, V. (1986): Iron deficiency anaemia u Postgraduate Haematology, ed. A. V. Hoffbrand, S. M. Lewis, William Heinemann Medical Books LTD, London.

Hunt, J. R. (2003): Bioavailability of iron, zinc, and other trace minerals from vegetarian diets. Am. J. Clin. Nutr. 78 Suppl, 633S–639S.

Kang, J. O. (2001): Chronic iron overload and toxicity: clinical chemistry perspectives. Clin. Lab. Sci.14 (3), 209–219.

Kuvibidila, S. R., C. Porretta, B. S. Baliga (2001): Iron deficiency alters the progression of mitogen-treated mur splenic lymphocytes through the cell cycle. J. Nutr. 131 (7), 2028–2033.

Lieu, P. T., M. Heiskala, P. A. Peterson, Y. Yang (2001): The roles of iron in health and disease. Mol. Asp. Med. 22 (1–2), 1–87.

Liu, Y., D. Che, S. Hui, T. Xu (2001): The effects of iron compounds on SO_2 and NO emissions in coal combustion process. Environ. Sci. 22(2), 25–30.

Liu, Y., D. Che, S. Hui, T. Xu (2002): Catalytic reduction of SO_2 during combustion of typical Chinese coals. Fuel Process. Technol. 79, 157–169.

Mahan, L. K., S. Escott-Stump (2008): Krause's Food and Nutrition Therapy. Saunders Elsevier. Appendix 54. 1299.

Myers, B. M., F. G. Prendergast, R. Holman, S. M. Kuntz, N. F. Larusso (1991): Alterations in the structure, physicochemical properties, and pH of hepatocyte lysosomes in experimental iron overload. J. Clin. Investig. 88, 1207–1215

Miethke, M., M. Marahiel (2007): Siderophore-based iron acquisition and pathogen control. Microbiol. Mol. Biol. Rev. 71 (2007) 413–451.

Neilands, J. B. (1995): Siderophores: structure and function of microbial iron transport compounds. J. Biol. Chem. 270, 26723–26726.

Nimis, P. L., S. Andreussi, E. Pittao (2001): The performance of two lichen species as bioaccumulators of metals. Sci. Total. Environ. 275 (1–3), 43–51.

NRC (1979)**:** Iron, TA: Medical and Biologic Effects of Environmental Pollutants. National Research Council, Washington, DC.

Piperno, A. (1998): Classification and diagnosis of iron overload. Haematologica 83 (5), 447–455.

Raos, N. (2008): Metali života metali smrti, Školska knjiga, Zagreb.

Smith, K. R., J. M. Veranth, J. S. Lighty, A. E. Aust (1998): Mobilization of iron from coal fly ash was dependent upon the particle size and the source of coal. Chem. Res. Toxicol. 11 (12), 1494–1500.

Smolders, A., J. G. M. Roelofs (1995): Internal eutrophication, iron limitation and sulphide accumulation due to the inlet of river Rhine water in peaty shallow waters in the

Eisen – toxikologische und nutritive Aspekte im Organismus

Zusammenfassung

Eisen ist das meist vertretene Übergangsmetall auf der Erde, grundlegend für viele Lebensformen. Andererseits kann das Eisen und dessen Zusammensetzungen als Verschmutzer der Atmosphäre verschiedene Schaden an Menschen, Tieren und Materialen verursachen. Lebende Organismen sind gezwungen, sich eine wirkungsvolle Transportweise von Eisen und dessen Lagerung anzueignen, um das Gleichgewicht zwischen den schädlichen und nützlichen Wirkungen von Eisen zu erzielen. Die Verteilung von Eisen im Menschenkörper ist durch einen komplexen Mechanismus reguliert, wodurch die Homeostase aufrecht erhalten wird. Während der Kindheit, der Schwangerschaft oder des Blutverlustes wird der Bedarf an Eisen größer, gleichzeitig auch die Adsorption. Das Eisen wird im gesamten Verdauungssystem absorbiert. Es wird am besten aus „hem" (heme iron) (80 % auflösbares Eisen im Fleisch) absorbiert, physiologisch an spezifische Proteine gebunden, dabei reversibile Verbindungen von Eisen und Proteinen, bzw. Proteinkomplexe bildend. Das Eisen nimmt an verschiedenen metabolischen Prozessen im Organismus teil, einschließend die Übertragung von Sauerstoff, DNA Synthese und die Übertragung von Elektronen. Die Störungen des Eisenmetabolismus gehören zu den häufigsten Erkrankungen bei Menschen, sie umfassen ein breites Spektrum von Krankheiten mit verschiedenen klinischen Manifestationen, von Anämie bis zu den neurodegenerativen Krankheiten. Akute Eisenvergiftungen sind immer die Folgen der Ingestion von Arzeneien angereichert mit Eisen, besonders häufig bei Kindern. Die chronische Eisenvergiftung ist ein häufiges Problem bei Erwachsenen. Das Eisen ist der Katalysator bei Reaktion der Entstehung von Hydroxilradikalen aus Wasserstoffperoxid, vergrößert der Oxidationsstress, der endlich die Konzentration von freiem Eisen vergrößert. Dieser Prozess kann zur Beschädigung der Lipidomembranen führen, dann endlich zur Beschädigung der Organe: Leber, Nieren und Milz. Die ungenügende Anwesenheit von Eisen in Nahrung vergrößert den Mechanismus der Darmabsorbtion von Eisen aus körperlicher Lagerung, so werden die Reserven schneller verbraucht, als das Eisen aus der Nahrung absorbiert wird, was zu Mangel von Eisen im ganzen Organismus führen kann. Mangel an Eisen ist immer noch in einigen Erdgebieten endemisch anwesend. Zeitgenössische Verfahren der Anreicherung und Verstärkung der Nahrung mit Eisen stellen heutzutage das potentielle Risiko der Interaktion zwischen Mikronutrienten dar, was die Absorption und Biozugänglichkeit von Eisen beeinflussen kann.

Schlüsselwörter: *Eisen, Toxikokinetik von Eisen, Nahrung*

Ferro – posizioni tossicologiche e nutritive nell'organismo

Sommario

Il ferro è il più abbondante metallo all'interno della Terra, ed è mportante per molte forme di vita. Dall'altra parte, il ferro e i suoi composti sono presenti come contaminanti nell'atmosfera e possono causare gli effetti dannosi sull'uomo, gli animali e gli materiali in generale. Gli organismi viventi sono costretti di addottare il modo efficace di trasporto del ferro e il suo meccanismo di immagazinamento per mantenere l'equilibrio tra gli effetti utili e quelli dannosi del ferro. La distribuzione del ferro nel corpo umano è regolata dal meccanismo complessivo con il quale si mantiene l'omeostasi. Durante l'infanzia, gravidanza o perdita del sangue cresce la necessità del ferro, e al contempo il suo assorbimento. Il ferro viene assorbito per tutto il sistema metabolico e si assimila ottimamente dall'emo (l'80% del ferro solubile nella carne) e si connette fisiologicamente con le proteine specifiche creando quelle reversibili, i composti di ferro e e proteine, cioè i complessi proteici. Il ferro fa parte di vari processi metabolici nell'organismo, trasporto di ossigeno, sintesi del DNA e trasporto di elettroni inclusi. Le disordini metabolici del ferro appartengono alle più frequenti malattie umane e fanno una vasta gamma di malattie con varie manifestazioni cliniche, dall'anemia alle malattie neurodegenerative. L'intossicazione acuta col ferro di solito è la conseguenza d'ingestione di farmaci e succede spesso ai bambini. L'intossicazione cronica col ferro è un problema che succede spesso agli adulti. Il ferro è catalizzatore nella reazione di formazione di radicali idrossili dal perossido di idrogeno e fa aumentare lo stress ossidativo che alla fin fine fa aumentare la concentrazione del ferro libero. Questo processo può danneggiare le membrane lipidiche e nella fase successiva fare un danno serio sugli organi seguenti: fegato, reni e milza. La carenza del ferro negli alimentari fa crescere il meccanismo di assorbimento intestinale del ferro dagli depositi del corpo e questi depositi si consumano più velocemente che il ferro viene assorbito dagli alimenti, e perciò è possibile la sua mancanza nell'organismo. La mancanza del ferro nell'organismo è ancora presente nel modo endemicamente presente in alcune parti della Terra. I procedimenti moderni che aggiungono l'alimentazione col ferro oggi osservano il probabile rischio di interazione tra i micronutrienti stessi che può avere influsso sull'assorbimento e la biodisponibilità del ferro.

Parole chiave: *ferro, tossicocinetica, alimenti*

Netherlands. Arch. Hydrobiol. 133 (3), 349–365.

Sullivan, R. J. (1969): Preliminary air pollution survey of iron and its compounds. Natl. Air Pollut. Control Admin. Publ. 69, 1–100.

Schumann, K. (2001): Safety aspects of iron in food. Ann. Nutr. Metab. 45 (3), 91–101.

Steenkamp, V. E., H. H. Du Preez, H. J. Schoonbee, A. J. B. Wild, M. M. Bester (1993): Bioaccumulation of iron in the freshwater crab (*Potamonautes warreni*) from three industrial, mine and sewage polluted freshwater ecosystems in the Transvaal. Water S.A. (Pretoria) 9 (4), 281–290.

Tector, A. J., J. K. Olynyk, R. S. Britton, C. G. Janney, R. O'Neill, B. R. Bacon (1995): Hepatic mitochondrial oxidative metabolism and lipid peroxidation in iron-loaded rats fed ethanol. J. Labor. Clin. Med. 126, 597–602.

United Nations (2001): The State of World Population 2001. United Nations Publications, New York.

Vuori, K.-M. (1995): Direct and indirect effects of iron on river ecosystems. Ann. Zoologici. Fennici. 32 (3), 317–329.

Walker, J. C., P. Brimblecombe (1985): Iron and sulfur in the pre-biologic ocean. Precambrian Res. 28, 205–222.

Yang, Y., E. Paterson, C. Campbell (2001): Accumulation of heavy metals in urban soils and impacts on microorganisms. Huan Jing Ke Xue 22 (3), 44–48.

Submitted: February 16, 2012
Accepted: March 8, 2012