

# Chromium as an essential nutrient: a review

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**ABSTRACT:** Chromium (Cr) has been studied since the end of the 19<sup>th</sup> century, when carcinogenic effects of hexavalent Cr were discovered. Essentiality of trivalent Cr was demonstrated in 1959; Cr<sup>3+</sup> has been studied in humans and laboratory animals since the 1970s and it is only since the 1990s that Cr has been studied as an essential element in livestock animals with the same intensity. Trivalent chromium is essential to normal carbohydrate, lipid and protein metabolism. Chromium is biologically active as part of an oligopeptide – chromodulin – potentiating the effect of insulin by facilitating insulin binding to receptors at the cell surface. With chromium acting as a cofactor of insulin, Cr activity in the organism is parallel to insulin functions. Cr absorption is low, ranging between 0.4 and 2.0% for inorganic compounds while the availability of organic Cr is more than 10 times higher. Absorbed Cr circulates in blood bound to the  $\beta$ -globulin plasma fraction and is transported to tissues bound to transferrin. Absorbed Cr is excreted primarily in urine, by glomerular filtration; a small amount is excreted through perspiration, bile and in milk. The demand for Cr has been growing as a result of factors commonly referred to as stressors, especially during different forms of nutritional, metabolic and physical strain. This review describes Cr metabolism, the different biological functions of Cr and symptoms of Cr deficiency.

**Keywords:** microelements; metabolism; blood; insulin; cortisol

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## 1. Introduction

Elemental chromium (Cr) was discovered in crocoite ( $\text{PbCrO}_4$ ) by Vaquelin in 1798 (Barceloux, 1999). Carcinogenic effects of hexavalent Cr were discovered towards the end of the 19<sup>th</sup> century, when nose tumours in workers handling chromium pigments in Scotland were described (Cohen et al., 1993). In the 1930s, case studies focusing on lung cancer incidence in workers handling Cr were published and lung cancer was recognised as an occupational disease in these workers in Germany during 1936 (Teleky, 1936). Since then, Cr has been studied especially as a mineral with toxic effect on the organism.

The fact that Cr is an essential mineral was first demonstrated by Schwarz and Mertz (1959) in rats and the essentiality of Cr was demonstrated in humans in 1977 (Jeejebhoy et al., 1977). In the years to follow, papers on Cr in human nutrition in all kinds of clinical and stress situations were published (Anderson et al., 1982, 1988), the main focus being on the association between Cr and diabetes mellitus, for type 2 diabetes (Rabinowitz et al., 1983). A number of animal trials were performed as well (Abraham et al., 1982a,b; Schrauzer et al., 1986). It was as late as in the 1990s that Cr also started to be studied intensively as an essential mineral in livestock animals (cattle, sheep, horses, pigs and poultry).

## 2. Chemical properties of chromium

Chromium is the 21<sup>st</sup> most abundant mineral in the crust of the earth; the average Cr concentration in US soils is around 40 mg/kg (Barnhart, 1997). The results of research focusing on the content of risk elements in farm land throughout the Czech Republic in 1991–1994 have been published by Mazanec (1996). The results by regions are presented in Table 1.

Although chromium (relative atomic mass 51.996 g) may theoretically occur in all oxidation states from –2 to +6, it is most often found in 0, +2, +3 and +6. Elemental chromium (0) is not naturally present in the earth crust and is biologically inert. Almost all naturally found Cr is trivalent while hexavalent Cr is mostly of industrial origin. Most Cr compounds are halides, oxides or sulphides.

**Divalent chromium** ( $\text{Cr}^{2+}$ ) is a strong reductant; the form is readily oxidised when in contact with

Table 1. Cr content on farm land in the Czech Republic (Mazanec, 1996)

Region	Cr content (mg/kg of soil)
Central Bohemia	6.20
South Bohemia	7.50
West Bohemia	7.43
North Bohemia	4.16
East Bohemia	4.90
South Moravia	5.96
North Moravia	5.23

air, producing  $\text{Cr}^{3+}$ . This explains why divalent Cr is not available in biological systems.

**Hexavalent chromium** ( $\text{Cr}^{6+}$ ) is the second most stable form and a strong oxidising agent, especially in acidic media. Hexavalent chromium is bound to oxygen as chromate ( $\text{CrO}_4^{2-}$ ) or dichromate ( $\text{Cr}_2\text{O}_7^{2-}$ ) with a strong oxidative capacity. This form of Cr crosses biological membranes easily, reacting with protein components and nucleic acids inside the cell while being deoxygenated to  $\text{Cr}^{3+}$ . The reaction with genetic matter provides for the carcinogenic properties of  $\text{Cr}^{6+}$ .

**Trivalent chromium** ( $\text{Cr}^{3+}$ ) is the most stable oxidation state in which Cr is found in living organisms. It does not have the capacity to cross cell membranes easily (Mertz, 1992) and has a low reactivity, which is the most significant biological feature distinguishing it from  $\text{Cr}^{6+}$ . Trivalent Cr forms a number of coordination complexes, hexadentate ligands being the basic form. Some forms of  $\text{Cr}^{3+}$  (e.g.  $\text{Cr}_2\text{O}_3$ ) are, thanks to their low reactivity and absorption from the gastrointestinal system, used as markers in the study of digestion processes (Furnival et al., 1990a,b).

## 3. Metabolism of chromium

### 3.1. Absorption

Chromium may be present in diets in the form of inorganic compounds or organic complexes. Elemental Cr is not absorbed and has no nutritional value (Ducros, 1992). Hexavalent Cr reaches humans and animals primarily by inhalation or due to industrial contamination.  $\text{Cr}^{6+}$  compounds dissolve better than  $\text{Cr}^{3+}$  compounds and are absorbed

better than  $\text{Cr}^{3+}$  compounds when supplemented directly to the intestine. This is documented by isotope experiments, which have revealed that the content of  $^{51}\text{Cr}$  in blood is three to five times higher when the isotope is supplemented as  $\text{Cr}^{6+}$  (Mackenzie et al., 1959). If, however, Cr is supplemented orally, most  $\text{Cr}^{6+}$  seems to be reduced to  $\text{Cr}^{3+}$  before reaching the site of absorption in the small intestine (Doisy et al., 1976).

The main path for  $\text{Cr}^{3+}$  to get into the organism is through the digestive system. The most active absorption site in rats is the jejunum; absorption is less efficient in the ileum and the duodenum (Chen et al., 1973). The mechanism of Cr intestinal absorption is not fully known yet. Some papers give evidence of passive diffusion (Stoecker, 1999b). Absorption of inorganic  $\text{Cr}^{3+}$  is indirectly proportional to dietary content. In people supplemented with 10  $\mu\text{g}$  of Cr daily only 2% of Cr was absorbed (Anderson and Kozlowski, 1985). The percentage of Cr absorbed from diet decreases until it reaches 40  $\mu\text{g}/\text{day}$  after which the absorption stabilises at 0.5% (Anderson and Kozlowski, 1985; Bunker et al., 1984). The daily absorption of Cr is relatively stable at the daily intake of 40–240  $\mu\text{g}/\text{day}$ . Cr absorption is generally low, ranging between 0.4 and 2.0%. Lyons (1994) claims that the bioavailability of inorganic Cr is < 3% while organic Cr is over ten times more available.

The causes of the low bioavailability of inorganic Cr are numerous and they are likely to be in connection with the formation of non-soluble Cr oxides, Cr binding to natural chelate-forming compounds in fodders, interference with ion forms of other minerals (Zn, Fe, V) (Borel and Anderson, 1984), also the slow conversion of inorganic Cr to the bioactive form (Ranhotra and Gelroth, 1986) and a suboptimal amount of niacin (Urberg and Gemel, 1987). Cr absorption from food is enhanced by the presence of amino acids, the ascorbic acid, high carbohydrate, oxalate and aspirin levels in the diet, while phytates and antacids (natrium hydrogen carbonate, magnesium hydroxide) reduce Cr concentrations in blood and tissues (Hunt and Stoecker, 1996).

### 3.2. Transport

Absorbed Cr circulates in blood bound to the  $\beta$ -globulin plasma fraction and is transported to tissues bound to transferrin or other complexes

at the physiological concentration. Transferrin receptors are insulin-sensitive; an increase of this hormone in blood stimulates the transport of transferrin receptors from the vesicles inside cells to the plasmatic membrane (Kandror, 1999). Receptors on the cell surface bind chromium-saturated transferrin, which is partly subject to endocytosis accompanied by Cr release at the acidic pH of the newly formed vesicles. Chromium released from the multiple transferrin molecules is sequestered by apochromodulin to produce chromium-loaded chromodulin (Vincent, 2000).

Chromium from blood is relatively quickly absorbed by bones, accumulating also in the spleen, liver and kidneys (Stoecker, 1999a).

### 3.3. Excretion

Absorbed Cr is excreted primarily in urine by glomerular filtration, or bound to a low-molecular organic transporter (Ducros, 1992). A small amount is nevertheless eliminated in hair, perspiration and bile. It is claimed that the average amount of Cr excreted in human urine is 0.22  $\mu\text{g}/\text{day}$  (Borel and Anderson, 1984), the average daily intake being 62–85  $\mu\text{g}/\text{day}$ , (which is consistent with) the relatively low absorption rate (approx. 0.5%). The minimum excretion of Cr is through milk, as a human study has shown, in which the supplemented isotope  $^{53}\text{Cr}$  was detected in blood, but not in milk (Mohamedshah et al., 1998). Van Bruwaene et al. (1984) monitored Cr metabolism in lactating cows. Within 102 days after the intravenous application of  $^{51}\text{Cr}$ , 63% of the chromium was excreted in urine, about 18% in excrement and only 3.6% in milk.

Cr excretion, especially by the urinary system, may increase 10 to 300 times in stressful situations or due to a diet rich in carbohydrates. The different factors impacting on the urinary excretion of Cr in humans have been studied by a number of authors. A review of the different factors as proposed by Anderson (1997a) is presented in Table 2.

This review suggests in which situations the demand for chromium increases and when its content in the diet needs to be increased. Urinary excretion of Cr also heavily depends on the form of Cr supplementation. Juturu et al. (2003) studied excretion of different Cr forms in urine using rats after a one-off dose of 1 000 mg/kg. Administration of Cr-oxide led to Cr concentrations in urine < 0.2 mg/l, while

Table 2. A review of different factors with an influence on urinary excretion of Cr in humans according to Anderson (1997a)

Stress factor	Cr in urine ( $\mu\text{g}/\text{day}$ )	Reference
Basal state (no stress)	$0.16 \pm 0.02$	Anderson et al. (1982, 1983)
Acute stress	$0.30 \pm 0.07$	Anderson et al. (1982)
Chronic stress	$0.09 \pm 0.01$	Anderson et al. (1988)
Diet rich in carbohydrates	$0.28 \pm 0.01$	Kozlowski et al. (1986)
Lactation	$0.37 \pm 0.02$	Anderson et al. (1993)
Physical trauma	$10.80 \pm 2.10$	Borel et al. (1984)

administration of chromium chloride and chromium acetate led to the concentrations 174 mg/l and 93 mg/l of urine, respectively.

Monitoring the amount of Cr excreted in urine is used for monitoring Cr stress (Minoia and Cavalleri, 1988), but the very short elimination half time of Cr in urine, shorter than 2 days, represents a certain limitation (Paustenbach et al., 1997). Kumpulainen et al. (1983) regard the 24-hour excretion of Cr in urine as a good indicator of the daily Cr intake. The above review however suggests that when assessing the amount of Cr excreted in urine, all factors that may affect urinary excretion of Cr must be considered.

### 3.4. Chromium concentration in blood

Methods for adequate analysis of Cr in biological material have not been developed until recently. This is why there has been relatively little data on Cr content in different body tissues and fluids. The blood concentrations of Cr reported in literature have come down with the gradual improvement of instrumentation. Levels of chromium ranging between 1 and 40  $\mu\text{g}/\text{l}$  had been claimed until 1978 (Veillon and Patterson, 1999). 1978 was a turning point of a kind since electrothermic atomic absorption spectrophotometry started to be used, making Cr content analysis more accurate, which got reflected in the lower Cr concentrations detected in biological samples. Christensen et al. (1993) claim that the concentrations are 0.035–0.04  $\mu\text{g}/\text{l}$  and 0.120–0.34  $\mu\text{g}/\text{l}$  for the blood serum of a healthy population and full blood, respectively. There is a greater difference between full blood and blood serum according to Schermaier et al. (1985), who

reported 0.058–0.388  $\mu\text{g}/\text{l}$  of Cr in the blood serum of a healthy population and 0.120–0.673  $\mu\text{g}/\text{l}$  of Cr in full blood. Anderson et al. (1985) have found the basal serum concentration of Cr in adults to be  $0.13 \pm 0.02 \mu\text{g}/\text{l}$ , followed by a significant increase to  $0.38 \pm 0.02 \mu\text{g}/\text{l}$  after 3 months of Cr supplementation, but despite this, they do not regard serum concentrations of Cr as a good indicator of the Cr nutritional status.

Concentrations of Cr in the blood of cattle with respect to the Cr content in pasture plants in a region characterised by an increased Cr stress level have been studied by Sahin et al. (1996). Cr blood levels detected in this trial ranged from 9 to 92  $\mu\text{g}/\text{l}$ , depending on the Cr content in the plants. Pechova et al. (2002a) found the Cr blood concentrations in dairy cows during the peripartur period to be 3–5  $\mu\text{g}/\text{l}$  while supplementation with 10 mg Cr per animal/day had no effect on the Cr concentrations in blood.

The concentration of Cr in full blood is approximately 2–3 times higher than the Cr concentration in plasma (Wood et al., 1990). Plasmatic Cr concentrations reflect the exposure to both  $\text{Cr}^{3+}$  and  $\text{Cr}^{6+}$  while intracellular concentration reflects the exposure to  $\text{Cr}^{6+}$ , this is because only  $\text{Cr}^{6+}$  has the capacity to penetrate into erythrocytes (Minoia and Cavalleri, 1988). The low concentration of Cr in erythrocytes also testifies to the fact that the  $\text{Cr}^{6+}$  concentration has not significantly surpassed the reduction capability of blood plasma for  $\text{Cr}^{6+}$  (Barceloux, 1999).

In the light of recent research results, determination of the Cr concentration in blood does not seem to provide a good indicator of the Cr supplementation status and therefore, cannot be used for the diagnosis of Cr deficiency in the organism.

### 3.5. Chromium concentration in tissues

The total amount of Cr in the human body ranges between 0.4 and 6 mg. The Cr reserve relative to the body weight is higher in newborn children compared with adults (Dubois and Belleville, 1991).

Trivalent Cr tends to accumulate in epidermal tissues (hair etc.) and in bones, liver, kidney, spleen, lungs and the large intestine. Accumulation in other tissues, especially muscles, seems to be strictly limited or non-existent (Wallach, 1985). The hypothesis has been confirmed by Anderson et al. (1997), who supplemented pigs weighing between 30 and 60 kg with 0.3 mg/kg Cr. Cr supplementation led to increased Cr levels in the kidneys (1.1 vs. 2.3 µg/kg) and in the liver (5.9 vs. 8.8 µg/kg), but Cr content in muscle tissue did not exceed 1.5 µg/kg disregarding the supplementation. Lindemann et al. (2004) measured the content of Cr in sows after supplementing different amounts of Cr picolinate (0, 200, 600 and 1 000 µg/kg Cr as-fed basis). The concentrations of Cr were measured in the adrenal gland (18.4, 20.0, 34.0 and 48.4 µg/kg), the kidneys (35.8, 56.4, 132.6 and 176.0 µg/kg) and in the liver (22.8, 37.4, 87.6 and 92.2 µg/kg). Jamal et al. (1991) monitored the Cr concentration in different organs of maturing chickens after a 3-week supplementation of  $K_2CrO_4$ , the doses being 100, 1 000 and 5 000 µg per kg of dry matter. Cr tended to accumulate in the liver, kidneys, pancreas and spleen rather than in blood, muscles, heart and lungs. A very small amount of Cr was detected in the brain.

Ellen et al. (1989) monitored renal Cr concentrations in cattle from different regions of the Netherlands. In most samples, the concentrations did not reach 10 µg/kg, the detection limit of the method applied.

Frank et al. (2000b) found the average Cr concentrations in experimentally induced Cr deficiency compared with controls to be 11 vs. 10 µg/kg in the kidney, 5.5 vs. 4.6 µg/kg in the liver and 90 vs. 145 µg/kg in the ribs.

## 4. Biological functions of chromium

### 4.1. The assumed mechanism for the action of chromium

Older research (Schwarz and Mertz, 1957, 1959) associated Cr activity in animal organisms with a

substance called the glucose tolerance factor (GTF), whose active substance is Cr. Further research into the GTF however revealed that GTF activity does not correlate with Cr content (Simonoff et al., 1992). According to the latest research, GTF activity is not dependent on a unique Cr compound and the complexation of Cr by yeast is more likely simple ligand substitution by components in the growth medium. Attention has thus recently turned to chromodulin and it has been proposed that GTF is merely a decomposition product of this true biologically active form of chromium. In the 1980s, Wada et al. (1983) reported they had isolated a chromium-binding oligopeptide called the low-molecular-weight chromium binding substance – LMWCr or chromodulin. The molecular weight of the oligopeptide is ~ 1 500 Da and it is formed by 4 types of amino-acid residues (glycine, cysteine, glutamate and aspartate). Despite its low molecular weight, it binds 4 equivalents of chromic ions in a complex of four nuclei. This oligopeptide has been isolated and purified from rabbit liver (Yamamoto et al., 1987), pig kidney (Sumrall and Vincent, 1997), cattle kidney (Davis and Vincent, 1997b) and colostrum (Yamamoto et al., 1983), dog liver (Wada et al., 1983) and isolated from mouse and rat kidneys (Yamamoto et al., 1983). Chromodulin is present in mammals; no paper dealing with isolation of this oligopeptide in other animal species has been published yet.

The assumed mechanism for the action of chromodulin has been described by Vincent (2000). Increased glucose concentration leads to the fast release of insulin into blood. Insulin binds to an external  $\alpha$  subunit of the transmembrane protein insulin receptor, causing its conformation change. The receptor autophosphorylates tyrosine residues on the internal portion of its  $\beta$  subunit, turning the receptor into an active kinase. Chromodulin is stored in its apo-form (apochromodulin) in the cytosol (Yamamoto et al., 1989) and the nucleus of insulin-sensitive cells. Increases in plasma insulin concentrations have been found to result in a movement of chromium from the blood to insulin-dependent cells (Morris et al., 1993). Due to the high Cr ion binding constant of apochromodulin ( $K \approx 1\,021$ ) (Sun et al., 2000), four  $Cr^{3+}$  are bound upon the entry of Cr into the cell, producing holochromodulin (i.e.  $Cr_4$ -chromodulin). The newly formed compound is bound to insulin-stimulated receptors, helps maintain their active conformation and enhances insulin signalling. When the level of insulin in blood decreases and receptor signalling must be interrupted,

chromodulin is eliminated from the cells. The high Cr-binding constant suggests that Cr might not be released from chromodulin to regenerate the apo form as formation of the apo-oligopeptide from holochromodulin requires chelating agent activity at a low pH and increased the temperature, this is not possible if physiological conditions are to be preserved (Davis and Vincent, 1997a). Loss of chromodulin from cells is consistent with increased Cr concentration in urine following the intake of carbohydrates (Anderson et al., 1982); chromodulin seems to be the main form of Cr<sup>3+</sup> presence in urine.

## 4.2. The role of chromium in the metabolism

### 4.2.1. Metabolism of carbohydrates

The association between Cr and carbohydrate metabolism has been demonstrated by trials involved with results in people fed parenteral nutrition. Jeejebhoy et al. (1977) have published the results of a trial on women kept at parenteral nutrition for 5 years. The patients developed symptoms of diabetes together with a significant glucose intolerance and loss of weight. Insulin therapy was not efficient and it was only after supplementation of 250 µg of Cr that the state of the patients started to improve and further insulin therapy became redundant. Also, syndromes similar to diabetes mellitus, which improved significantly after Cr supplementation, have been described showing an association between reduced sensitivity of peripheral tissues to insulin and Cr deficiency (Anderson et al., 1996). Improved glucose tolerance was however not observed in all trials. The lack of Cr deficiency or some other etiological factors may provide an explanation. A number of human studies (Anderson, 2000; Tuzcu et al., 2004), studies on pigs (Wenk et al., 1995), horses (Pagan et al., 1995; Ott and Kivipelto, 1999), cattle (Subiyatno et al., 1996) and rats (Kim et al., 2004) have confirmed the possibility of influencing glucose tolerance and insulin resistance by Cr supplementation.

Supplementation of Cr and insulin to animal tissues in *in vitro* experiments has led to increased glucose oxidation, resulting in CO<sub>2</sub> + H<sub>2</sub>O formation, increased glycogenesis and conversion of glucose to lipids, all this was in combination with increased glucose utilisation (Anderson, 1997b).

### 4.2.2. Metabolism of lipids

Numerous studies show evidence that Cr is essential for lipid metabolism and reducing the risk of atherogenesis. For example, rats and rabbits fed on a Cr-deficient diet had increased total cholesterol and aortal lipid concentrations and showed increased plaque formation (Abraham et al., 1982a,b). Cr supplementation has decreased the total cholesterol in their blood. An increase of HDL-cholesterol (Riales and Albrink, 1981) and a decrease in total cholesterol, LDL-cholesterol and triacylglycerols (Lefavi et al., 1993) have been observed in humans after Cr supplementation. These results are in agreement with other research (Lifschitz et al., 1980; Mossop, 1983). On the other hand, Cr supplementation was not proven to have any effect in other human trials (Anderson et al., 1983; Rabinowitz et al., 1983; Offenbacher et al., 1985; Potter et al., 1985; Uusitupa et al., 1992). These ambiguous results concerning the response of blood lipids and lipoproteins to Cr supplementation may be due to differences in the Cr supplementation of different individuals. Similarly, these studies mostly ignored other main dietary factors directly impacting upon the lipid metabolism. McNamara and Valdez (2005) studied the action of chromium propionate on lipogenesis and lipolysis in adipose tissues in Holstein dairy cows from 21 days *prepartum* to 35 days *post partum*. Chromium increased the net synthesis of fat in the adipose tissue and decreased the net release. This might be acting through linkage of chromodulin with the insulin receptor and the increased glucose flux into the adipocyte.

### 4.2.3. Metabolism of proteins

It is assumed that the activity of Cr is mediated by the anabolic action of insulin, but other mechanisms cannot be ruled out. Evans and Bowman (1992) have demonstrated increased amino acid and glucose uptake by skeletal muscles of rats that had been incubated with Cr-picolinate. This alteration in uptake of nutrients was associated with the alteration of insulin parameters and is Cr-dependent. These observations may explain the effect of glucose tolerance as well as the increase in the percent of skeletal muscle reported by some researchers. The potential improvement of amino acid uptake by muscle cells is beneficial to the total protein

deposition. Roginski and Mertz (1969) claim that Cr supplementation intensifies the incorporation of amino acids into heart proteins and amino acid uptake by tissues in rats.

#### 4.2.4. Metabolism of nucleic acids

Trivalent Cr seems to be involved in the structure and expression of genetic information in animals. The binding of Cr to nucleic acids is stronger than in other metal ions (Okada et al., 1982). Chromium protects RNA from heat denaturation. It is also clear that Cr is concentrated in cell nuclei. Cr has increased *in vitro* RNA synthesis in mice (Okada et al., 1983); this supports the hypothesis that Cr has an effect on gene functions. Chromium participates in gene expression by binding to chromatin, causing an increase in initiation loci and consequently, an increase in RNA synthesis. This increase is due to the induction of protein bound in the nucleus and nuclear chromatin activation (Okada et al., 1989).

#### 4.2.5. Metabolism of mineral substances

There are relatively few papers on the effect of Cr supplementation on the metabolism of other mineral substances. The relation between Cr and Fe has been investigated most since both these minerals are transported as transferrin-bound. At low Fe saturation, Cr and Fe bind preferentially to different binding sites. When, however, the Fe concentration is higher, the two minerals compete for the same binding sites. This seems to be the reason why a lower Cr retention has been identified in patients suffering from hemochromatosis than in healthy subjects or patients with a Fe deficiency (Sargeant et al., 1979). Evidence that Cr may impair Fe metabolism has been published by Ani and Mostaghie (1992). Fe homeostasis alteration has been reported by other authors too, the most significant alteration being detected in association with Cr-picolinate supplementation (Lukaski et al., 1996). Alteration of Fe metabolism in association with Cr supplementation has also been reported by Anderson et al. (1996), decreased tissue Fe concentrations was detected in response to Cr supplementation.

Mineral metabolism in experimentally induced Cr deficiency, using goats, has been explored in detail by Frank et al. (2000a,b) on the basis of deter-

mining Al, Ca, Cd, Co, Cr, Cu, Fe, Mg, Mn, Mo, Ni, P, Pb, Se, Sr, V and Zn concentrations in the liver, kidneys, ribs and blood plasma. They detected a renal Cu concentration 43% lower compared with controls and conversely, higher Al, Co and V concentrations in the kidneys and liver. The authors attribute the increased concentrations of these minerals to a decreased Cr concentration causing subsequent freeing of binding sites on the transferrin, competed for by the individual minerals. A decreased loss of some microelements (Zn, Fe, Cu and Mn) during stress after Cr supplementation to mice has been reported by Schrauzer et al. (1986). Interaction between Cr and Cu was studied by Stahlhut et al. (2006b), Cr supplementation had no effect on the liver or plasma Cu concentrations in cows, although, supplemental Cr resulted in higher plasma Cu concentrations in calves on Day 279. Similarly Pechova et al. (2002b) have detected higher plasmatic Cu concentrations in response to Cr supplementation in fattening bulls. Interactions between Cr, Ca and Mg have been reported by Moonsie-Shageer and Mowat (1993), who found Cr supplementation to be associated with Ca and Mg concentration increases on Day 7 of the trial.

### 4.3. Hormonal regulation

#### 4.3.1. Cortisol

A number of studies confirm the association between Cr and the metabolism during increased physiological, pathological and nutritional stress. Cr demand in humans and animals increases during periods of higher stress – e.g. fatigue, trauma, gestation and different forms of nutritional (high-carbohydrate diet), metabolic, physical, and emotional stress as well as environmental effects (Anderson, 1994). Under stressor influence, secretion of the cortisol increases, acting as an insulin antagonist through increasing blood glucose concentration and reduction of glucose utilisation by peripheral tissues. Increased blood glucose levels stimulate the mobilisation of the Cr reserve, Cr being then irreversibly excreted in urine (Borel et al., 1984; Mertz, 1992). Cr excretion in urine is enhanced by all stress-inducing factors (Mowat, 1994).

A number of authors confirm decreased sensitivity to stress in Cr supplemented animals through a reduced concentration of cortisol in blood (Chang and Mowat, 1992; Moonsie-Shageer and Mowat,

1993; Mowat et al., 1993; Pechova et al., 2002c). Nevertheless, serum cortisol concentrations in dairy cows after parturition showed an inconsistent increase in Cr supplemented animals (Burton et al., 1995; Yang et al., 1996; Pechova 2002a), which suggests that the association between Cr and cortisol may be less straightforward than originally assumed.

Al-Saiady et al. (2004) found that adding chelated chromium to the diet of dairy cows under heat stress improved milk yield and feed intake without affecting milk components, but no decrease in sensitivity of animals to cold stress has been detected (Sano et al., 1999; 2000a,b).

#### 4.3.2. Insulin

Chromium has an improving effect on insulin binding and increases the number of insulin receptors on the cell surface and sensitivity of pancreatic  $\beta$ -cells together with an overall increase of insulin-sensitivity (Anderson, 1997b). Chromium acts as a cofactor for insulin and therefore, Cr activity in the organism is parallel to insulin functions. Despite enhancing insulin activity, chromium cannot substitute insulin. In the presence of organic Cr a lower insulin level is sufficient to achieve a similar biological response (Mertz, 1993). The results reported by Striffler et al. (1999), who have detected increased insulin secretions in Cr-deficient rats during response to an increased concentration of glucose in the blood, testify to this. Stahlhut et al. (2006a) found 10–45 min after glucose administration lower serum insulin concentration in serum in chromium picolinate supplemented cows versus control group. Schachter et al. (2001) studied the effect of Cr supplementation to the diet of diabetic dogs treated with insulin. No positive or negative effect on the dogs under examination was found at doses of 20–60  $\mu\text{g}/\text{kg}$ .

#### 4.4. Reproduction

The mechanism of effect of Cr on reproduction functions has not been known. One of the theories (Lindemann, 1996) assumes reproduction can be affected by changing sensitivity to insulin. Most attention has been devoted to studying the effect of Cr on reproduction in pigs. Cr supplementation to sows during the reproduction cycle has had a posi-

tive effect on the size of the litter at birth as well as the weight at weaning (Lindemann et al., 1995a,b). In contrast to that, Campbell (1998) has found no effect on the number of piglets per litter or the number of piglets weaned when supplementing 200  $\mu\text{g}/\text{kg}$  of Cr, but Cr supplementation did have a positive effect on the per cent of pregnant sows (79% vs. 92%). The effect of doses of Cr (0, 200, 600, 1 000 ppb as-fed basis) was studied in cooperative study involving 353 litters from three stations (Lindemann et al. 2004). Supplemental Cr picolinate increased the number of pigs born live per litter (9.49, 9.82, 10.94, and 10.07) but decreased individual birth weight of total pigs born (1.61, 1.57, 1.47, and 1.56 kg). Garcia et al. (1997) have studied the effect of Cr-picolinate supplementation on sensitivity of tissues to insulin, ovulation rate, and progesterone and oxytocin secretion. Although Cr supplementation has had a positive effect on sensitivity of tissues to insulin (reduced insulin: glucose ratio), the ovulation rate and progesterone concentration remained unchanged. The issues of reproduction in relation to Cr supplementation in cattle have been devoted relatively little attention. Despite this, a positive effect of Cr supplementation on the insemination index, interval and service period has been established (Bonomi et al., 1997; Pechova et al., 2003) as well as a reduced incidence of endometritis and placental retention (Chang et al., 1996; Villalobos et al., 1997). Bryan et al. (2004) studied the effect of supplementing 6.25 mg/day of Cr from Cr methionine on lactation and reproduction in intensively grazed cattle. Greater percentages of supplemented cows were observed to be anestrus by dairy personnel (45.5 vs. 32.0%). However, Cr supplementation tended to increase the percentage of cows pregnant in the first 28 day of the mating season (50.0 vs. 39.2%).

Most authors have studied the effect of Cr on reproduction functions in female animals. In a unique study, Anderson and Polansky (1981) have explored the effect of Cr deficiency on male rats. They found that male rats fed a diet containing < 100  $\mu\text{g}/\text{kg}$  had by 50% less sperm cells and fertility lower by 25%.

#### 4.5. Growth and body composition

The effect of Cr supplementation on the intensity of growth has been studied especially in pigs and cattle. In cattle, a positive effect of Cr supplementen-



tation on weight gain has been recorded by Chang and Mowat (1992), Moonis-Shageer and Mowat (1993) and Kegley et al. (1997) while Bunting et al. (1994), Mathison and Engstrom (1995) and Swanson et al. (2000) have found no positive effect. Despite the fact that the results have been ambiguous, most authors agree that Cr supplementation during periods of increased stress has a positive effect on weight gain. At longer intervals after increased stress (sale, moving or transport) no positive effect of Cr supplementation on growth intensity has been found.

The above results have also been confirmed by experimental results on pigs. Page et al. (1993) have found an increase in weight gain when supplementing Cr 0.05 and 0.2 mg/kg, but a decrease when supplementing 0.1 mg/kg of the feeding ration. Other studies (Mooney and Cromwell, 1995, 1997) have confirmed the positive effect of supplementing 0.2 mg/kg of Cr on weight growth, but not on nutrient conversion. Conversely, supplementation of 0–0.8 mg/kg Cr has led to a decreasing linear trend regarding fodder intake as well as weight gain with growing Cr doses (Page et al., 1993). Other studies have reported no weight gain increase when Cr supplementation was lower than 0.25 mg/kg (Amoikon et al., 1995; Boleman et al., 1995; Lindemann et al., 1995b). A similar new study (Lien et al. 2005) with chromium propionate (0.2 mg/kg) in weanling pigs 4 weeks old, during nine weeks of the experiment, indicated that Cr had no effect on growth performance even if *Escherichia coli* lipopolysaccharide was used as a stress-inducing agent.

A number of authors have studied the effect of Cr supplementation on the composition of the carcass, especially from the perspective of fat and muscle content, but these results are not equivocal. Page et al. (1993), Lindemann et al. (1995b) and Mooney and Cromwell (1995) report an increased proportion of muscle tissue in response to Cr supplementation. On the other hand, Ward et al. (1995) have not observed any effect of Cr supplementation on the composition of a pig carcass. Likewise, Crow and Newcomb (1997) and Crow et al. (1997) did not find Cr-picolinate to have any effect of muscle and fat proportion. A detailed study on pigs has been undertaken by Mooney and Cromwell (1997), who administered Cr in the picolinate and chloride form on a long-term basis. Cr supplementation did not have any significant effect on back fat of weight gain, but Cr picolinate supplementation did increase the muscle content

by 5.4% while the fat content decreased by 8.2%. Waylan et al. (2003) have identified no effect of Cr-nicotinate supplementation on sensory properties (colour and sensory), *musculus longissimus dorsi* or bacon characteristics.

In cattle, no positive effect of Cr supplementation on the composition of the carcass has been identified (Mathison and Engstrom, 1995; Pehrson and Danielsson, 1997; Danielsson and Pehrson, 1998). In sheep (Gardner et al., 1998), Cr supplementation has had no effect on growth, weight or glycogen content in muscle, but it did reduce the subcutaneous fat layer.

In humans, Cr is recommended as a tool for weight reduction and reduction of fat content in the body. Pitler et al. (2003) published results of a meta-analysis whose aim was to assess the evidence of the effect of chromium picolinate for reducing body weight. They suggest a relatively small effect of chromium picolinate compared with the placebo for reducing body weight.

#### 4.6. Immune function

A number of authors have been involved in the study investigating effects of Cr supplementation on the immune function. Although Cr is believed to have different kinds of inborn, humoral and cellular immunomodulatory effects, the underlying mechanism of intercellular and intracellular action remains unknown. The immune function may be affected in association with insulin and/or cortisol activity, but it can just as well be mediated by production regulation of certain cytokines (Borgs and Mallard, 1998).

Results of trials focused on the effect of Cr supplementation on parameters characterising the immune function in cattle may be summed up as follows: cows supplemented with Cr from 6 weeks before parturition until 16 weeks after parturition showed a much stronger blastogenic response when stimulated with concavalin A (ConA) (Burton et al., 1993). Conversely, Cr-supplemented cows vaccinated with ovalbumin showed a weaker ovalbumin-stimulated blastogenic response of peripheral blood mononuclear cells (PBMC) compared with unsupplemented cows (Burton et al., 1993). Supplementation of blood serum, collected from Cr-supplemented cows, to the PBMC culture of unsupplemented cows has increased lymphocyte blastogenesis after ConA stimulation (Burton et

al., 1995). The same effect has been observed when Cr was directly supplemented to a PBMC culture from unsupplemented cows (Chang et al., 1996). PBMC cultures from supplemented cows after *in vitro* ConA stimulation have led to lower interleukin (IL)-2 levels, interferon (IFN)- $\gamma$  levels and tumour necrosis factor (TNF)- $\alpha$  levels (Burton et al., 1996). Antibody production in response to the antigenic stimulus showed differences depending on the antigen type. Supplemented cows had a stronger antigenic response after ovalbumin application, but not to human erythrocytes (Burton et al., 1993). Chromium did not have any impact on antibody response to combined vaccination with commercial preparations against infectious bovine rhinotracheitis (IBR) parainfluenza type 3 (PI-3), bovine respiratory syncytial virus (BRSV) or *Pasteurella haemolytica*, but did increase the antibody titre against bovine viral diarrhoea (BVD) (Burton et al., 1993). Nevertheless, Cr supplementation did increase the production of antibodies against IBR (Burton et al., 1994) and tetanus toxoid (Faldyna et al., 2003) in other studies. Lien et al. (2005) studied the immune response in weaning pigs with a supplementation of chromium propionate (0.2 mg/kg). Pigs supplemented with Cr had higher antibody titres specific for sheep red blood cells and total serum globulin. A challenge with *Escherichia coli* lipopolysaccharide (0.1 mg/kg BW) was used in this experiment as stress-inducing agent. This challenge increased in the white blood cells of the Cr group and higher IgG and gamma-globulin was also exhibited.

## 5. Chromium deficiency

Papers dealing with the experimental study of Cr deficiency are relatively scarce and most of the existing ones quote results of experiments on laboratory animals. Anderson (1994) has summed up the results of a number of trials on humans, rats, mice and other animal species in a review of physiological and biochemical symptoms of Cr deficiency that we present in Table 3. Frank et al. (2000a,b) have studied experimentally induced Cr deficiency in goats. The population with a Cr deficiency showed higher weight gains ( $31.1 \pm 11.7$  vs.  $20.0 \pm 7.3$  kg) for the period of monitoring (84 weeks) compared with the control group. The authors explain this unexpected effect by the possibility that Cr deficiency has impaired glucose tolerance and increased insulin

release subsequently leading to hyperinsulinemia. Cr deficiency has also led to an increase in haematological parameters (haemoglobin, haematocrit, erythrocytes, leucocytes and mean erythrocyte volume); increased total protein concentrations and hyperinsulinemia were observed compared with the group of controls as well.

## 6. Chromium toxicity

Cr toxicity is associated mainly with hexavalent chromium, while trivalent Cr is believed to be a highly safe mineral. Hexavalent Cr is more soluble than trivalent Cr and at least five times as toxic (Barceloux, 1999). The safety limit for Cr<sup>3+</sup> is approximately 1:10 000. Cr<sup>3+</sup> toxicity is in fact lower than the toxicity of all other essential elements such as Cu, I, Zn, Mn and especially Se (Lindemann, 1996).

The toxicity of Cr<sup>6+</sup> compounds is most probably based on an oxidative DNA impairment (Cohen et al., 1993). The details of Cr<sup>6+</sup> toxic activity are however not known. It is assumed that genotoxicity may be due to a transient form (Cr<sup>5+</sup>) of intracellular origin formed by the reduction of Cr<sup>6+</sup> to Cr<sup>3+</sup> (Stearns et al., 1995). Extracellular reduction of Cr<sup>6+</sup> to Cr<sup>3+</sup> is regarded as a protective reaction (De Flora et al., 1989). The main protection mechanism against Cr<sup>6+</sup> activity in the lungs and the stomach is the reduction of Cr<sup>6+</sup> to Cr<sup>3+</sup> by an NADPH-dependent mechanism involving ascorbate. Animal trials show that glutathione plays an important role in Cr<sup>6+</sup> reduction in erythrocytes, also showing certain reduction activity in the lungs (Suzuki and Fukuda, 1990).

Cr intoxication is characterised by pathological-anatomical changes in the lungs, kidneys and liver. The lungs are affected with hyperaemia, erosion and an inflammatory change in the respiratory system mucosa developing after Cr inhalation. With Cr<sup>6+</sup> compounds sensitising the lungs, a bronchial spasm or even an anaphylactic reaction may develop. Chronic exposure to Cr has been observed to cause nose septum perforation (Lee et al., 2002) and small cell cancer of the lung tissue has been reported. Acute intoxication with Cr<sup>6+</sup> leads to acute renal tubular necrosis characterised by significant interstitial change and subsequent renal failure (Ellis et al., 1982; Saryan and Reedy, 1988). Renal glomeruli usually remain intact. The hepatic parenchyma develops necrosis only at very high Cr<sup>6+</sup> doses.

Table 3. Symptoms of Cr deficiency (Anderson, 1994)

Function	Species
Glucose intolerance	humans, rats, mice, monkeys, Guinea pigs
Increased circulating insulin	humans, rats, pigs
Glycosuria	humans, rats
Hunger hyperglycemia	humans, rats, mice
Growth disorders	humans, rats, mice, turkeys
Hypoglycaemia	humans
Increased serum cholesterol and triacylglycerols	humans, rats, mice, cattle, pigs
Increased incidence of aortal plaques	rabbits, rats, mice
Increased surface of aortal plaques of the inner surface	rabbits
Neuropathy	humans
Encephalopathy	humans
Corneal lesions	rats, monkeys
Increased intraocular pressure	humans
Reduced fertility and number of sperm cells	rats
Diminished longevity	rats, mice
Reduced insulin binding	humans
Reduced number of insulin receptors	humans
Reduced muscle proportion	humans, pigs, rats
Increased proportion of body fat	humans, pigs
Reduced humoral immune response	cattle
Increased morbidity	cattle

## 7. Conclusions

This brief review of research results for chromium as an essential element shows that chromium is an important microelement essential for normal carbohydrate, lipid and protein metabolism. On the other hand, there are many unanswered questions concerning chromium supplementation and even a paper challenging the essentiality of chromium has recently been published (Stearns, 2000).

In human nutrition, chromium is used as a nutritional supplement recommended in impaired carbohydrate metabolism characterised by reduced glucose tolerance and impaired insulin action, for weight reduction and last but not least as a prevention for the formation of atherosclerotic plaques in blood vessels. In contrast to that, supplementation of livestock animal diets with chromium has currently been banned in EU countries. The cause

seems to be due to the results of research into chromium supplementation in feeding rations fed to livestock animals being ambiguous. The positive effects associated with the use of chromium as a nutritional supplement include the reduction of animal sensitivity to negative environmental impacts, enhanced growth, increased proportion of muscle compared with fat, improved reproduction function, support of the immune function etc. Literary data show that a positive effect of chromium supplementation in feeding rations has been demonstrated in only 40–50% of experiments, depending on the animal category and the effect of chromium supplementation monitored. In other experiments, no positive effect of chromium supplementation has been identified. Chromium has the benefit of high safety, verified by the fact that the experiments revealed no negative effect of trivalent chromium on the animals' health status. The ambiguous results of

research into Cr as a feeding supplement seem to be due to a lack of methodology for Cr deficiency diagnostics, which would enable targeted Cr supplementation on Cr-deficient farms only. Further research should focus primarily on the possibilities of Cr deficiency identification and on determining a daily requirement of chromium in different species and categories of livestock animals.

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