Chapter 5
Chromium in Health and Longevity

Ruslana Iskra and Halyna Antonyak

Abstract 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(III) can help enhance the role of insulin, the critical hormone that controls blood sugar and helps bring glucose into cells where it's used for bodily energy. Chromium deficiency has been suggested to lead to symptoms associated with adult-onset diabetes and cardiovascular disease, and these supplements have recently found potential as therapeutic agents in the treatment of adultonset diabetes. Cr(VI) is one of the few carcinogenic metals that directly reacts with DNA, forming adducts, and inducing mutations. The results of a wide range of studies indicate that the CpG1 methylation level of p16 could be used as a biomarker of epigenetic effect caused by Cr(VI) treatment, which can enhance cell damage by regulating its expression or affecting some transcription factors to combine with their DNA strand sites. In addition, it is difficult to distinguish between the effects caused by chromium(VI) and those caused by chromium(III) since chromium(VI) is rapidly reduced to chromium(III) after penetration of biological membranes and in the gastric environment. In addition to its role in glucose and lipid metabolism, chromium also functions as an antioxidant. Chromium(III) protects organism from oxidative stress associated with reactive oxygen species. These ROS extremely reactive chemical molecules, are considered toxic to produce oxidative damage to various cellular components which causes cellular dysfunction that accompanies aging process. The antiaging effect of chromium is undoubtedly related to the effect of chromium on insulin action. Chromium in a utilizable form, like dietary restriction, prevents hyperglycemia, hyperinsulinemia, protein glycation and extends life span. Because the body's ability to control blood glucose is critical

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to many life functions, a consequence of Cr supplementation can be improved health and reproductive outcomes as well as improved survival rate or life span.

Keywords Chromium(III) · Absorption · Biological function · Metabolism Toxicity · Diabetes mellitus · Mortality · Life span

5.1 Introduction

Chromium is a naturally occurring element found in animals, plants, rocks, and soil and in volcanic dust and gases. Chromium has oxidation states (or "valence states") ranging from chromium(-II) to chromium(VI). Chromium compounds are stable in the trivalent (III) state and occur in nature in this state in ores, such as ferrochromite. The hexavalent (VI) form is the second-most stable state. However, chromium(VI) rarely occurs naturally, but is usually produced from anthropogenic sources (EPA 1984).

Chromium levels in soil vary according to area and the degree of contamination from anthropogenic chromium sources. Chromium(VI) in soil can be rapidly reduced to chromium(III) by organic matter.

Cr(VI) is a strong oxidant—in the form of chromates and dichromates it penetrates biological membranes and reacts with cell contents, proteins or nucleic acids, while being reduced to Cr(III).

In contrast, Cr(III) is the most stable form in biological systems (Cohen et al. 1993; Losi et al. 1994) it does not penetrate biological membranes easily, and it appears that the transport of specific chromium compounds is strictly regulated by the organism. Cr(III) ion has a strong tendency to form coordination compounds with a very slow reaction rate (Mertz 1992).

That slow rate suggests that chromium would exert a structural function rather than an active site in an enzyme, which may explain that no chromium-containing enzymes have been identified (Mertz 1992).

5.2 Chromium Absorption, Blood Transport and Excretion

The total amount of Cr in the human body ranges between 0.4 and 6 mg. Daily intake strongly depends upon feed levels, and is usually approximately 15–200 μg, but may be as high as 1 mg.

Chromium is present in the diet both as the inorganic form and organic complexes. The rate of absorption of inorganic Cr is low, from 0.4–3%, and is a function of daily dose supplied. According to Anderson (1987) ingestion of daily dose of 10 μg, up to 2% is absorbed, while at the dose of 40 μg, absorption decreases to 0.5%, and at the higher doses, it remains constant at 0.4%. The absorption of Cr from CrCl3 and acetate (Mertz 1975) is approx. 0.5%, and approx. 40% for chromium

trisacetylacetonate in rats (Anderson 1987). Chromium chloride, chromium pinacolinate and chromium polynicotinate are the most common supplemental sources available. Although absorption of chromium picolinate is lower than 4%, it is still significantly greater than that of chromium chloride (Mertz 1975). There is also a report claiming that niacin-bound chromium was 672% better absorbed than chromium chloride and 311% better than chromium picolinate (Krejpcio 2001; Madhavi et al. 2013).

The absorption of Cr is facilitated by certain amino acids, such as histidine, which chelates Cr and prevents the precipitation of Cr at the basic pH in the small intestine (Mertz 1969; Mertz and Roginski 1971). Nicotnic acid and ascorbic acid are required for Cr absorption and act in synergy with this element. Ascorbic acid has been reported to enhance chromium transport or absorption in animals (Dowling et al. 1990) and humans (Mertz and Roginski 1971).

Compared with simple sugars such as glucose, fructose and sucrose, starch increased tissue chromium in mice (Dowling et al. 1990). Metals can form complexes or compete with Cr and modify its absorption. For example: Zn, V and Fe supplementation decreased the absorption of Cr (Chen et al. 1973). On the other hand, absorption of 51Cr was elevated in Zn-deficient rats and was reduced by zinc supplementation (Hahn and Evans 1975). Phytates significantly decrease the absorption of Cr in the intestines of rats, whereas oxalate act inversely (Chen et al. 1973).

Chromium is absorbed in the intestinal mucosa. In rats the middle section of the small intestine was the most active segment for Cr absorption, followed by the illeum and duodenum (Chen et al. 1973). In humans, the site of absorption also includes the jejunum (Doisy et al. 1976). The mechanism responsible for the intestinal absorption of Cr is not known.

Absorbed Cr circulates in blood bound to the β-globulin plasma fraction and is transported to tissues bound to transferrin or other complexes at the physiological concentration.

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 placenta is the organ with the highest chromium amounts.

The Cr reserve relative to the body weight is higher in newborn children compared with adults (Dubois and Belleville 1991). The concentration of Cr in the lungs, aorta, heart and spleen decreases during the first months of life, whereas the liver and kidneys maintain their neonatal level up to the age of 10 years.

Absorbed Cr is excreted principally in the urine, and in small quantities in the hair, sweat and bile. The major route of elimination after absorption is faecal. Urinary excretion is the major route of elimination of Cr from the body, is a good reflection of the ingestion, but not necessarily of body status (Anderson et al. 1983).

5.3 Biological Function of Chromium

The biological function of chromium is not fully known yet. It is postulated that chromium interacts with the thyroid metabolism in humans. Binding of Cr(III) with nucleic acids has been found to stimulate the DNA-dependant RNA synthesis (Mertz 1992). The third interaction of Cr(III) is with the hormone insulin and its receptors. This suggests that Cr(III) acts with insulin on the first step in the metabolism of sugar entry into the cell, and facilitates the interaction of insulin with its receptor on the cell surface.

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; Lindemann et al. 2009). 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 ~1500 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; Fig. 5.1). Increased glucose concentration leads to the fast release of insulin into blood. Insulin binds to an external α subunit of the transmembrane protein insulin receptor, causing its conformation change. The receptor autophosphorylates tyrosine residues on the internal portion of its β 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 insulinsensitive 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. 1993a, b). Due to the high Cr ion binding constant of apochromodulin ($K \approx 1021$) (Sun et al. 2000), four Cr^{3+} are bound upon the entry of Cr into the cell, producing holochromodium (i.e. Cr4-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

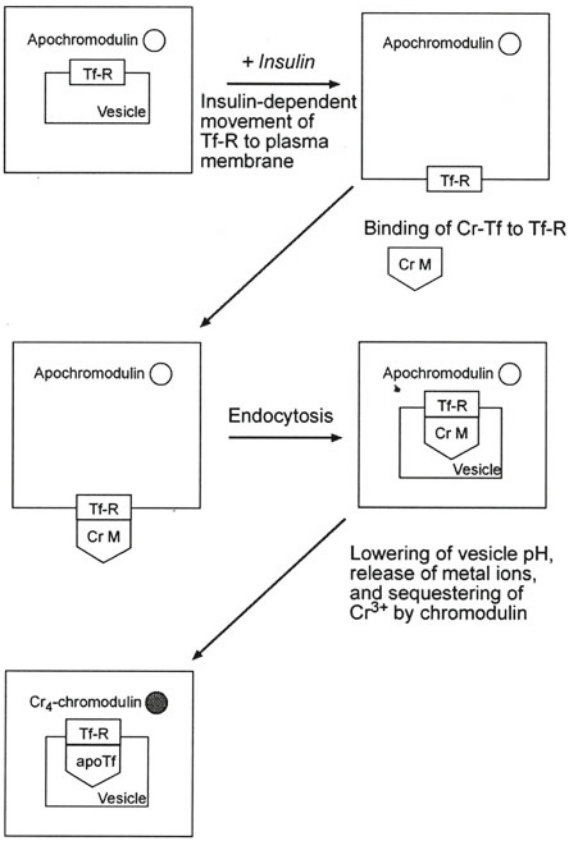

Fig. 5.1 Proposed mechanism for the movement of chromium from the blood to LMWCr (Vincent 2000, 2007). Cr—chromic ion; M—metal ion; Tf—transferrin; Tf-R—Tf receptor

the apo-oligopepetide 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; Lindemann et al. 2009); chromodulin seems to be the main form of Cr^{3+} presence in urine.

5.4 The Role of Chromium in the Metabolism

5.4.1 Metabolism of Carbohydrates

The association between Cr and carbohydrate metabolism has been demonstrated by trials involved with results in people fed parenteral nutrition. Jeejeebhoy 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). The current study aimed to examine the associations of plasma chromium levels with T2DM and pre-diabetes mellitus (pre-DM) demonstrated an inverse association between plasma chromium concentrations and T2DM and pre-diabetes in a Chinese population (Chen et al. 2017). 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 2000a; 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; Bunting et al. 1994) 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 $CO_2 + H_2O$ formation, increased glycogenesis and conversion of glucose to lipids, all this was in combination with increased glucose utilisation (Anderson 1997). We have established that the action of chromium chloride and organic compounds of chromium content of glucose goes down and rises activity of hexokinase and lactate dehydrogenase (Iskra 2011; Iskra et al. 2014).

5.4.2 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. 1982; Pechova and Pavlata 2007). 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.

It was established that the addition of chromium (250 mcg/kg) level in the ration of piglets leads to the decline of cholesterol content in blood plasma (Iskra 2010; Iskra et al. 2014).

Niacin, or vitamin B3, tends to reinforce chromium's beneficial effects, especially on the lipid profile, both raise levels of "good" HDL while lowering "bad" LDL and triglyceride levels (McKenney 2004).

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.

5.4.3 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 (Pechova and Pavlata 2007). 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.

It was established that the addition of chromium (250 μg/kg) level in the ration of piglets leads to increase of protein content in blood plasma (Iskra 2010; Iskra et al. 2014).

5.4.4 Chromium and Body Composition

Another effect of chromium supplementation that could be a result of its potentiation of insulin sensitivity is the redistribution of body fat, protein and water. The mechanism of this regulatory action of Cr is not known.

It has been proposed that the positive effect of chromium picolinate on body composition is through its ability to improve insulin use, thereby reducing fat deposition and improving entry of glucose and amino acids into muscle cells.

Chromium has been reported to increase lean body mass in people who exercise, such as football players, however, some follow-up studies have not supported these observations (Anderson 2000b). However, the role of chromium in the regulation of lean body mass, percentage body fat, and weight reduction is still controversial because a significant number of studies do not support the effect of chromium on body composition.

5.4.5 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).

5.4.6 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. Cr is bound to transferrin that possesses two binding sites: A and B with different affinities for Fe as a function of pH. At low Fe saturation, Cr and Fe bind preferentially to different binding sites. It has been shown that Cr binds exclusively to site B. When, however, the Fe concentration is higher, the two minerals compete for the same binding sites. Thus, there is antagonism between Cr and Fe competing for this carrier (Sayato et al. 1980).

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 Moshtaghie (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. (2006), 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. (2002) 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.

5.5 Chromium and Lipid Peroxidation

In addition to its role in glucose and lipid metabolism, chromium also functions as an antioxidant. Recent studies have shown that chromium protects rats from oxidative stress associated with exposure to CCl_4. Also chromium protects against lipid peroxidation in isolated rat hepatocites (Vincent 2007; Anderson 2000a), and decreases the effects of free radicals in people with type 2 diabetes (Roussel and Zouari 1998).

We found that the action of chromium compounds decreases products of lipid peroxidation and increase of activity of the antioxidant system enzymes in blood of rats (Iskra 2011; Iskra et al. 2014). Addition of chromium citrate in a quantity of 25 μg Cr/kg body resulted to the decreased content of the MDA, activity of superoxide dismutase, but increased activity of catalase, glutathione peroxidase, glutathione reductase and the content of reduced glutathione compared to their levels in animals from group II with an experimental diabetes (Iskra and Slivinska 2015).

Chromium(III) protects organism from oxidative stress associated with reactive oxygen species.

Based on free radical theory by Harman (1956), free radicals, which are reactive oxygen species (ROS) produced in metabolic pathways, may play a critical role in aging. These ROS extremely reactive chemical molecules, are considered toxic to produce oxidative damage to various cellular components which causes cellular dysfunction that accompanies aging process. The mitochondrial respiration defined as the main source of ROS, which primarily produce cumulative damage to lipids, proteins and mitochondrial DNA and lead to cellular aging (Hoopes 2002; Piotrowska and Bartnik 2014).

However, recent workers in this and in related fields are exploring the view that superoxide radical and reactive oxygen species exert beneficial effects. Thus, such ROS are viewed as involved in cellular regulation by acting as (redox) signals, and their harmful effects are seen mostly as a result of compromised signaling, rather than due to direct damage to sensitive targets. According to some followers of this view, ROS such as hydrogen peroxide and superoxide are not just causative agents of aging but may also be agents that increase the life span by acting, for example, as prosurvival signals (Liochev 2013).

One of the controversies surrounding the use of Cr(III)-containing nutritional supplements concerns the proposed roles of such supplements as antioxidants that reduce the diabetes-related oxidative stress (Cheng et al. 2004; Vinson et al. 2002;

Peng et al. 2014), or pro-oxidants that promote the oxidative stress through the formation of ROS (Petit et al. 2005).

The dual action of Cr(III) as an antioxidant or a pro-oxidant, can be explained based on the redox reactions The reactions of Cr(III) complexes with lipid peroxides are probably responsible for the abilities of these compounds to reduce the levels of lipid peroxidation (Cheng et al. 2004; Vinson et al. 2002), but these reactions produce other strong oxidants such as Cr(V) species. These species, as well as the peroxyl (ROO·) radicals formed in the redox cycling reactions of certain Cr(III) complexes, are probably responsible for the increases in the oxidative stress markers caused by Cr(III) administration (Medeiros et al. 2003; Petit et al. 2005). Thus, Cr(III) complexes used as nutritional supplements are involved in a delicate balance between the oxidation and the reduction reactions in blood plasma, as shown most clearly by a change from a mild antioxidant effect of a prolonged treatment with Cr(III) in type II diabetic patients to a mild pro-oxidant effect of the same treatment protocol in healthy individuals (Cheng et al. 2004).

5.6 Epigenetic and Toxicological Effects of Chromium

Cr(VI) compounds induce human respiratory cancers and increase the risk of other types of human cancers (Costa and Klein 2006). Chronic poisoning by chromium compounds has been observed at the work place, by direct contact with skin and mucus membrane, or inhalation of dusts or aerosols (Ducros 1992). Because Cr is a potent sensitizer, external contacts with chromates and dichromates can induce allergic eczema in some people (Taton 1993). Reports from the chromate production industry have identified Cr(VI) as a potential carcinogen (Katz and Salem 1994).

The International Agency for Research on Cancer (IARC) has determined that chromium(VI) compounds are carcinogenic to humans. The National Toxicology Program 11th Report on Carcinogens classifies chromium(VI) compounds as known to be human carcinogens.

In laboratory animals, chromium(VI) compounds have been shown to cause tumors to the stomach, intestinal tract, and lung (Wilbur et al. 2012). Acute inhalation LC50 values in rats for several chromium(VI) compounds (sodium chromate, sodium dichromate, potassium dichromate, and ammonium dichromate) ranged from 29 to 45 mg chromium(VI)/m^3 for females and from 33 to 82 mg chromium(VI)/m^3 for males (Gad et al. 1986). Female rats were more sensitive than males to the lethal effects of most chromium(VI) compounds except sodium chromate, which was equally toxic in both sexes. Signs of toxicity included respiratory distress, irritation, and body weight depression (Gad et al. 1986).

Cr intoxication is characterised by pathologicalanatomical changes in the kidneys and liver. Acute intoxication with Cr^{6+} 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^{6+} doses.

The reaction with genetic material is the basis for the carcinogenicity of some Cr(VI) salts. Cr(VI) is one of the few carcinogenic metals that directly reacts with DNA, forming adducts, and inducing mutations (Zhitkovich et al. 1996). There are a number of studies demonstrating that Cr(VI) carcinogenesis involves gene silencing and other epigenetic effects (Sun et al. 2009; Salnikow and Zhitkovich 2008). Cr(VI) has been shown to prevent the expression of inducible genes in cells by crosslinking a histone deacetylase to inducible promoters (Wei et al. 2004). The presence of this deacetylating enzyme, which removes acetyl groups from lysines in histone tails, keeps the nucleosome condensed, thereby preventing transcription factors from binding and activating gene expression (Wei et al. 2004). In order for cells to survive chronic Cr(VI) treatment, they must adapt and evade apoptosis. The loss of apoptotic activity is often accompanied by a loss of mismatch repair, since the two processes are tightly linked. Consistent with the latter, chronic exposure of cells to Cr(VI) or tumors induced by this agent in humans are often missing mismatch DNA repair capacity (Takahashi et al. 2005; Peterson-Roth et al. 2005; Reynolds and Zhitkovich 2007).

Cr(VI) exposure leads to silencing of MLH1, a component of mismatch repair, via a decreased mRNA expression resulting from enhanced H3K9 dimethylation of its promoter (Sun et al. 2009). In human lung cancers induced by Cr(VI) exposure, silencing of *MLH1* as well as tumor suppressor *p16* was correlated with DNA methylation of their promoters (Takahashi et al. 2005; Kondo et al. 2006; Ali et al. 2011).

The results of a wide range of studies indicate that the CpG1 methylation level of p16 could be used as a biomarker of epigenetic effect caused by Cr(VI) treatment, which can enhance cell damage by regulating its expression or affecting some transcription factors to combine with their DNA strand sites (Hu et al. 2016a, b).

In spite of considerable research effort, the epigenetic mechanisms of Cr(VI)-induced carcinogenesis remain largely unknown.

Nupr1 (nuclear protein 1) is a small, highly basic, and unfolded protein with molecular weight of 8800 daltons and is induced by a variety of stressors. Studies in animal models have suggested that Nupr1 is a key factor in the development of lung and pancreatic cancers, with little known about the underlying molecular mechanisms (Chen et al. 2016). Nupr1 mRNA is strongly induced by a variety of stressors such as lipopolysaccharides (Jiang et al. 1999), CCl_4 (Taieb et al. 2005), starvation (Zinke et al. 2002), cell cycle arrest and many others. Overexpression of Nupr1 has been implicated in a number of cancers. Nupr1 enhances the expression of at least two major epithelial-mesenchymal transition (EMT)-related genes, namely MMP9 and MMP13 metalloproteases (Goruppi et al. 2007). Downregulation of H4K16ac is likely a mechanism whereby Nupr1 promotes cancer development. Recent study has demonstrated that Nupr1 overexpression inhibits acetylation of lysine 16 of histone H4 (H4K16ac) (Gironella et al. 2009) and the histone acetyltransferase MOF (Kat8, Myst 1), which specifically acetylates H4K16 (Smith et al. 2005). The loss of H4K16ac and MOF correlate with increased genome instability, which is considered an important step in cancer development (Taipale et al. 2005; Li et al. 2010; Gupta et al. 2008). The loss of H4K16ac is found in a number of

tumors, including lung cancer and considered as a 'hallmark' of human cancer (Van Den Broeck et al. 2008; Song et al. 2012; Fraga et al. 2005). Cr(VI) exposure leads to increase in the level of Nupr1 in human bronchial epithelial BEAS2B cells and the loss of H4K16ac. Cr(VI)-induced reduction of H4K16ac appears to be caused by the induction of Nupr1, since overexpression of Nupr1 decreases the levels of H4K16ac, while knockdown of Nupr1 by siRNA greatly compromised the loss of H4K16ac following Cr(VI) exposure (Bollati et al. 2010). Importantly, overexpression of Nupr1 induces anchorage-independent cell growth and knockdown of Nupr1 expression prevents Cr(VI)-induced cell transformation. Together, downregulation of H4K16 acetylation through inducing Nupr1 expression might represent a new mechanism for Cr(VI) carcinogenesis.

Based upon these findings, it is conceivable that an epigenetic modification of gene expression patterns may be a key element of the developmental and carcinogenic outcomes of exposure to chromium (Schnekenburger et al. 2007)

It is thought that Cr(VI) is carcinogenic while Cr(III) has such a low toxicity that delaterious effects from excessive intake of this form do not occur readily (Barceloux 1999). It becomes toxic only at extremally high amounts. For example, cats tolerate 1000 μg Cr(III)/day and rats 100 μg Cr(III)/kg b.w. Chromium(III) compounds have a relatively low order of toxicity when ingested. Animal and human studies suggest that long-term supplemental intakes of 200 μg/day, and short-term intakes (several months) between 200 and 1000 μg/day are safe.

The safety limit for Cr^{3+} is approximately 1:10 000. Cr^{3+} 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^{6+} compounds is most probably based on an oxidative DNA impairment (Cohen et al. 1993). The details of Cr^{6+} toxic activity are however not known.

It is assumed that genotoxicity may be due to a transient form (Cr^{5+}) of intracellular origin formed by the reduction of Cr^{6+} to Cr^{3+} (Stearns et al. 1995). Extracellular reduction of Cr^{6+} to Cr^{3+} is regarded as a protective reaction (De Flora et al. 1989).

In addition, it is difficult to distinguish between the effects caused by chromium(VI) and those caused by chromium(III) since chromium(VI) is rapidly reduced to chromium(III) after penetration of biological membranes and in the gastric environment (Petrilli et al. 1986; Samitz 1970). The first defense against chromium(VI) after oral exposure is the reduction of chromium(VI) to chromium(III) in the gastric environment where gastric juice (De Flora et al. 1987) and ascorbate (Samitz 1970) play important roles by an NADPH-dependent mechanism.

However, whereas chromium(VI) can readily be transported into cells, chromium(III) is much less able to cross cell membranes (Hu et al. 2016a, b). Reduction of chromium(VI) in the red blood cell occurs by the action of glutathione. Since the red blood cell membrane is permeable to chromium(VI) but not chromium(III), the chromium(III) formed by reduction of chromium(VI) by glutathione is essentially trapped within the red blood cell (Devoy et al. 2016). Eventually the diffusion of chromium(VI), the reduction to chromium(III), and complexing to nucleic acids and proteins within the cell will cause the concentration equilibrium to change so that more chromium(VI) is diffused through the membrane. Thus, there is a physi-

ological drag so that increased diffusion results in greater chromium concentrations in the cell (Aaseth et al. 1982). It appears that the rate of uptake of chromium(VI) by red blood cells may not exceed the rate at which they reduce chromium(VI) to chromium(III) (Corbett et al. 1998).

The evaluation of toxicity of Cr^{3+} supplements has revolved around questions of genotoxicity, mutagenicity, and cancer for several reasons. First, carcinogenic Cr^{6+} is metabolized to Cr^{3+} in the body, and Cr^{3+} may be one of the ultimate species that interacts with DNA in Cr^{6+}-induced cancers. Second, the chemistry and bioavailability of Cr^{3+} is altered by its coordinating ligands (Zhitkovich 2005).

Chromium(III) nutritional supplements are widely consumed for their purported antidiabetic activities. Research results strongly support the hypothesis that the antidiabetic activity of Cr(III) and the carcinogenicity of Cr(VI) compounds arise from similar mechanisms involving highly reactive Cr(VI) and Cr(V) intermediates (Wu et al. 2016).

However, chromium is the same as any other mineral element in that the dose is the poison. The question that remains to be determined is the concentration at which the various forms of orally ingested chromium become of toxic concern because homeostatic mechanisms are unable to prevent chromium accumulation in high enough quantity in cells that will allow chemical reactions that can cause non-repairable damage to occur.

It thus seems plausible that, under an oxidative-stress situation that might compromise life before reproduction is attained, the balance between dedicating resources to prolong lifespan or to reproduction be shifted toward the lifespan side. This hypothesis has recently received some scientific support by the discovery of what is known as the hormetic effect, according to which low doses of either toxic substances may provoke a protective effect, sometimes resulting in a lifespan prolongation rather than in the expected lifespan shortening. The underlying principle might be an action–reaction mechanism by which the biochemical defences unchained by the stress situation exceed the insults produced by it (overcompensation).

Chromium(VI) and other heavy metals have recently been reported to show a relatively low toxicity, as well as a hormetic effect, in long-term viability of fish (Perez-Benito 2006; Johnson and Radhakrishnan 2015).

Since redox processes play a crucial role in living organisms, and are thought to unchain a cascade of reactions leading to senescence and other degenerative diseases in aerobes, the effect of moderate oxidants on their lifespan is a topic of some interest.

5.7 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 5.1. Frank et al. (2000a, b) have

Table 5.1 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

studied experimentally induced Cr deficiency in goats. The population with a Cr deficiency showed higher weight gains (31.1 ± 11.7 vs. 20.0 ± 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.

5.8 Dietary Chromium Intake and Recommendations

Trivalent chromium, the form found in foods and nutrient supplements, is considered one of the safest nutrients (NRC 1989). The Environmental Protection Agency has established a reference dose, defined as "an estimate of a daily exposure to humans, including sensitive subgroups, that is likely to be without an appreciable risk of delaterious side effects over a lifetime, that is 350 times the National Research Council's upper limit of the "safe and adequate range".

Table 5.2 Dietary Cr intakes in various countries (Kumpulainen 1992)

Mean Cr intake (μg/d)	Country	Type of diet
62	Germany	Self-selected
62–89	USA	Formulated to meet US dietary requirements
31	Finland	Self-selected
56	Canada	Self-selected
24.5	UK	Self-selected
28	USA	Self-selected
49	Turkey	Self-selected
50	Switzerland	Mixed institutional
50	Sweden	Average market basket
85	Brazil	Average market basket
75	Iran	Self-selected
60	Italy	Self-selected
60	Spain	Self-selected
105	Sudan	Self-selected

Recent studies obtained as part of the Trace Elements in Food Research Programme of the FAO European Research Network on Trace Elements (FAO 1989) demonstrated that the Cr content in animal foodstuffs such as meat, poultry and fish is low providing 2 μg Cr (Anderson et al. 1992). Most dairy products are also low in Cr and provide <0.6 μg/serving. Whole wheat and wheat flour contain 5–10 μg of Cr/kg (Anderson et al. 1992). Pulses, seeds and dark chocolate may contain more chromium than most other foods (Jorhem and Sundstrom 1993). Certain species such as black pepper contain high concentrations of Cr (Anderson et al. 1992). Some brands of beer contain significant amounts of $C\Gamma$, some of which presumably comes from the brewing containers (Anderson and Bryden 1983). According to Mertz et al. (1974) the best known chromium complex is the glucose tolerance factor, found in brewer's yeast.

Most of the average daily dietary Cr intake estimates representing various populations living in 14 different countries ranges between 30 and 60 μg. WHO (1996) estimates that the daily minimum population mean intake likely to meet normal requirements for chromium might be approximately 33 μg/person.

Kumpulainen (1992) compared the average dietary Cr in various countries (Table 5.2). It is thought that dietary chromium intake in the USA and other developed countries is sub-optimal and is 50–60% of the minimum US suggested safe and adequate daily intake of 50 μg (Anderson et al. 2003).

The Estimated Safe and Adequate Daily Dietary Intake (ESADDI) of Cr as proved by the Food and Nutrition Board of the US National Academy of Science in 1989. For adults and adolescents that range was 50–200 mcg (NRC 1989). In 2001, DRIs for chromium were established. The research base was insufficient to establish RDAs,

Table 5.3 Adequate intakes (AIs) for chromium (RDI 2001)

Age	Infants and children (μg/day)	Males (μg/day)	Females (μg/day)	Pregnancy (μg/day)	Lactation (μg/day)
0–6 months	0.2				
7–12 months	5.5				
1–3 years	11				
4–8 years	15				
9–13 years		25	21		
14–18 years		35	24	29	44
19–50 years		35	25	30	45
>50 years		30	20		

so AIs were developed based on average intakes of chromium from food as found in several studies (DRI 2001). Chromium AIs are provided in Table 5.3.

Adult women in the United States consume about 23–29 μg of chromium per day from food, which meets their AIs unless they're pregnant or lactating. In contrast, adult men average 39–54 μg per day, which exceeds their AIs. Recently, a new daily adequate intake (AI) has been set at 35 μg/day for males and 25 μg/day for females (DRI 2001), which more accurately reflects normal dietary intakes. Because pregnancy and lactation are known to deplete chromium stores, taking 30 μg daily is recommended for pregnant women, and women who are breastfeeding should take at least 45 μg daily.

The average amount of chromium in the breast milk of healthy, well-nourished mothers is 0.24 μg per quart, so infants exclusively fed breast milk obtain about 0.2 μg (based on an estimated consumption of 0.82 quarts per day) (DRI 2001). Infant formula provides about 0.5 μg of chromium per quart (Cocho et al. 1973). No studies have compared how well infants absorb and utilize chromium from human milk and formula (DRI 2001; Stoecker 2001).

It is believed that intense exercise and traumatic injury also increase the body's demand for chromium (Anderson et al. 1997).

Other health care professionals recommend more chromium to help with blood sugar control, especially for people with existing cases of mild or serious insulin-resistance or diabetes.

Dr. Anderson postulates that doses well above these recommended minimum levels may be necessary to treat chronic diseases. Citing a study conducted in China, he notes that patients there received up to 1000 μg of chromium per day, a dose that proved "highly effective" in relieving many of the symptoms of type II diabetes (Anderson 1997, 1998).

5.9 Diabetes Mellitus and Chromium

Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period. Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced. In the form of this disease known as maturity-onset diabetes, the pancreas often continues to secrete normal amounts of insulin, but this insulin is ineffective in preventing the symptoms of diabetes which includes heperglycemia, impaired carbohydrate metabolism, glycosuria and decreased insulin sensitivity (Press and Geller 1990).

Diabetes in particular has been growing at the particularly high rate and is now one of the world's most common long term health conditions.

It is estimated that 415 million people are living with diabetes in the world, which is estimated to be 1 in 11 of the world's adult population. 46% of people with diabetes are undiagnosed. The figure is expected to rise to 642 million people living with diabetes worldwide by 2040.

The International Diabetes Federation (IDF) currently states that the top 5 countries with the highest amount of people with diabetes are as follows:

China: 109 million
India: 69 million
USA: 29 million
Brazil: 14 million
Russian Federation: 12 million

According to the 2013 IDF in Europe, diabetes is estimated to affect 56.3 million adults aged between 20 and 79—8.5% of the adult population. Even more worryingly, this figure is set to increase: by 2035, it is estimated that nearly 70 million people will be living with diabetes in Europe, driving regional prevalence to beyond 10%.

For the 45–74 year-old age group, the prevalence is higher among men, while for those above 75 years, the rate is higher among women.

In several European countries, diabetes and its complications have caused the greatest increase of deaths over the past 20 years. Diabetes is ranked among the leading causes of cardiovascular disease, blindness, renal failure and lower limb amputation. About 75% of people with diabetes die of cardiovascular events—the number one cause of death in Europe. People with type 2 diabetes have a 2–4 times higher risk of coronary heart disease than the overall population.

Of great concern is that children and adolescents are also now developing type 2 diabetes, largely due to the high levels of obesity in these age groups. Estimates suggest that 1 in 5 children in Europe is overweight and that each year 400,000 children become overweight.

In the late 1950s Schwarz and Mertz (1959) first demonstrated that the dietary-induced impairment of glucose tolerance in rats could be reversed by the administration of trivalent chromium compounds. Since then, the possible beneficial role of Cr(III) in carbohydrate, protein and fat metabolism has been extensively studied in

various experimental systems (Wrobel et al. 1999). Experiments carried out so far in humans can be classified into 3 groups: studies in long-term parenteral nutrition, administration of high glucose doses, supplementation with various compounds of Cr(III) (Wrobel et al. 1999).

Also in parenteral nutritional studies chromium deficiency cases were observed and glucose tolerance was reversed by daily Cr(III) supplementation (Jeejeebhoy et al. 1977). Further experiments carried out at constant or elevated glucose concentration in plasma, showed an inverse relationship between plasma insulin and plasma chromium (Morris et al. 1993a, b).

Anderson et al. (1991) studied the effect of Cr(III) supplementation in healthy subjects, in patients with type 2 diatetes and/or lipemia. The results indicated that Cr(III) is in some way required for insulin action improving blood glucose, insulin and lipid indices.

Glucose intolerance, related to insufficient dietary chromium is a widespread health problem. On the other hand, improved chromium nutrition leads to improved sugar metabolism in hypoglycemics, hyperclycemics and diabetics (Anderson 1989; Shinde Urmila et al. 2004). Absorption of chromium from the gut and its urinary excretion are significantly higher in insulin-requiring diabetes than in healthy subjects. Chromium maintains normal glucose tolerance primarily by regulating insulin action. In the presence of chromium, much lower amounts of insulin are required (Anderson 1989). It is important to keep insulin at low levels to prevent secondary signs of diabetes. There is very strong evidence that insufficient dietary chromium leads to impaired glucose tolerance that can be alleviated by supplemental chromium.

Fasting glucose, circulation insulin, insulin binding, circulatory glucagon, and β-cell sensitivity improve with increasing chromium status (Jeejeebhoy et al. 1977). Response to chromium is related to degree of glucose intolerance. Subjects with hypoglycemia, hyperglycemia and maturity-onset diabetes have shown to respond to supplemental chromium, while subjects with normal glucose tolerance with no signs of marginal chromium deficiency do not respond to supplementation with chromium.

The prevalence of type 2 diabetes and impaired glucose tolerance (IGT) increases with aging (Chang and Halter 2003).

Insulin secretion (both first and second phase) normally decreases at a rate of 0.7% per year with aging; this decrease in β-cell function is accelerated about two-fold in people with impaired glucose tolerance—first phase to a greater extent than second phase. Finally, aging per se has no effect on insulin sensitivity independent of changes in body composition (Szoke et al. 2008).

Chromium status decline with age. Recent, well-controlled, double-blind studies reported that the glucose tolerance of the elderly subjects given supplemental chromium improved. However, if subjects were eating well-balanced diets with a mean Cr intake more than 37 μg Cr/d, glucose tolerance was unchanged.

Urberg and Zemmel (1987) showed that fasting glucose and glucose tolerance of elders also improved following daily supplementation with 200 μg Cr as $CrCl_3$ together with 100 μg of nicotinic acid, but not with Cr alone (Anderson 1989). Cefalu

(1998) demonstrated that chromium picolinate appears to increase insulin sensitivity in moderately obese, nondiabetic subjects.

The number of in-dividuals with impaired glucose tolerance is alarmingly high. Metabolic syndrome, also known as Syndrome X, is a combination of medical conditions characterized by abnormal glucose metabolism, elevated insulin levels, excess weight and abdominal fat distribution, disturbances of normally healthy lipid levels, and high blood pressure—all of which are associated with the subsequent development of type II diabetes and cardiovascular disease.

While diabetes and cardiovascular disease are well-recognized threats to overall health, some researchers believe that elevated blood sugar—even absent these other conditions—contributes directly to aging. By interacting with proteins and nucleic acids, excess glucose molecules wreak havoc with tissue elasticity and normal function (Turkoski 2004). Thus, controlling blood sugar may actually put the brakes on the aging process, and should be an essential component of any life-extension strategy.

5.10 Effects of Chromium on Life Span

Some of the original studies from the 1960s (Schroeder et al. 1963; Schroeder 1968) were life-term studies with mice and rats given 5 ppm Cr from Cr acetate (an organic form of trivalent Cr) in drinking water showed increased growth over unsupplemented controls for both males and females and decreased mortality of males. In a study of controlled stress, the percentage of rats surviving was greater for the Cr-supplemented group (Mertz and Roginski 1969). Evans and Meyer (1992) fed three groups of rats 1 ppm Cr from either Cr chloride, Cr nicotinate, or CrPic. The authors followed plasma glucose and glycated hemoglobin throughout the study. After 41 months of supplementation, all rats fed the supplemental Cr from Cr chloride or Cr nicotinate had died while 80% of the rats fed CrPic remained alive; median life span for the first two groups of rats was 33 months (a fairly normal life span for laboratory rats) while median life span for the rats supplemented with CrPic was 45 months (Evans and Meyer 1994).

A series of studies with broilers provides clear evidence of an effect of Cr on mortality. The first two studies (Hossain et al. 1998) were conducted in Brazil using a high Cr-yeast and the latter three studies (Kim et al. 1996a, b, 1997) in Korea using CrPic.

Mortality rate was significantly lower for Poultry, that were supplemented with 150 PPb Cr^{+3}—yeast from 1 to 56 days of age. This reduction in mortality rate could be due to the role of Cr^{+3}—yeast in improving birds health and increase immune response which result in reducing heat stress (Hossain et al. 1998).

Several points can be made from the studies. First, when mortality is low (and presumably the cumulative stress from crowding, disease challenge, heat, etc. is low) there is less of a response to supplemental Cr but when mortality (and presumably

stress load) is high then the response to Cr can be quite large. A second point to be made is that the response is clearly dose dependent.

A question that naturally arises is whether there are potential Cr effects on mortality in reproducing sows. It would seem from our understanding of nutrient responses that the potential for a response would be greatest in those situations where there was the greatest departure from normal performance, i.e. when performance was most compromised. The same concept would exist with regard to potential mortality benefits in sows. One of the earliest studies reported does illustrate very clearly the potential benefit of Cr supplementation on some of these parameters. A large study (Campbell 1996) from Australia involving over 800 sows wherein supplementation of 200 ppb Cr from CrPic resulted in a highly significant improvement in farrowing rate (from 79.0 to 92.4%; $p < 0.001$). Numerical reductions of more than 60% in abortions, natural sow deaths, and sows that returned to estrus and were rebred were also observed with the supplementation. Every aspect of reproductive health that was recorded was benefited by supplementation. Of particular note should be the reduction in mortality—a response consistent with the broiler observations.

Numerical improvements in mortality were also observed in the study of Hagen et al. (2000). The reduction in mortality was greater in first litter sows and sows older than three parities (both of which had mortality substantially greater than that of the second and third parity sows). In this study, there were also improvements in litter size and wean to first service interval. The improvements in litter size were seen for sows of all parities and the improvements in wean to first service interval were most pronounced in first parity females (when the interval was greater than that of older sows). These effects have much statistical strength given the size of the study; this study utilized 48,000 sows that farrowed almost 100,000 litters for almost 1,000,000 pigs.

Because the body's ability to control blood glucose is critical to many life functions, a consequence of Cr supplementation can be improved health and reproductive outcomes as well as improved survival rate or life span.

Cerami (1985) first suggested that elevated blood glucose levels may decrease survival by accelerating the process known as protein glycation. Later, Masoro et al. (1992) demonstrated that food restriction in rats resulted in decreased serum glucose concentrations with a concomitant decrease in glycation of hemoglobin.

The results demonstrate that chromium in a utilizable form, like dietary restriction, prevents hyperglycemia, hyperinsulinemia, protein glycation and extends life span. An increase in life span of rodents resulting from chromium supplementation has been noted previously (Mertz and Roginski 1969; Schroeder 1968). Additions of CrO_3 to the drinking water increased the survival of rats compared to unsupplemented controls. A significant increase in the mean age of the tenth-percentile survivors was observed when male rats fed a chromium deficient diet were supplemented with chromium acetate in the drinking water (5 μg Cr^{+3}/ml). In addition, the survival of male mice fed a chromium deficient diet was significantly increased when the mice were supplemented with chromium acetate in the drinking water (5 μg Cr^{+3}/ml).

The antiaging effect of chromium is undoubtedly related to the effect of chromium on insulin action, since several investigations with cell cultures, animals and human,

provide evidence that chromium increases insulin sensitivity. Investigators discovered that the symptoms of diabetes which developed during long-term parenteral nutrition could be prevented by the addition of chromium to the intravenous solution (Jeejeebhoy et al. 1977; Freund et al. 1979). When either swine or heifer calves were fed chromium picolinate in the diet, increased plasma glucose clearance rates were accompanied by decreased plasma insulin levels (Evock-Clover et al. 1993).

Evans and Bowman (1992) and Evans and Pouchnik (1993) discovered that insulin internalization was markedly increased in rat muscle cells cultured in a medium that contained chromium picolinate and the increased internalization rate was accompanied by a marked increase in the uptake of both glucose and leucine. The effect was specific for chromium picolinate since neither zinc picolinate nor any other form of chromium tested was effective.

Schroeder et al. (1963) established the fact that chromium deficiency leads to increased mortality while other results prove that the form in which chromium is ingested also influences the aging process. Chromium picolinate is a neutral, lipophilic complex while chromium nicotinate is a charged complex (Evans and Pouchnik 1993). Chromium chloride of course dissociates into the ionic components. Absorption experiments demonstrate that the charged forms of chromium are not readily absorbed when mixed with the diet and tests of biological function indicate that chromium nicotinate and chromium chloride are either unstable in physiological media or are simply not utilized by cells (Mertz and Roginski 1969; Evans and Meyer 1992; Evans and Pouchnik 1993).

Glucose is the preferred carbon and energy source in prokaryotes, unicellular eukaryotes, and metazoans. However, excess of glucose has been associated with several diseases, including diabetes and the less understood process of aging. On the contrary, limiting glucose (i.e., calorie restriction) slows aging and age-related diseases in most species. Understanding the mechanism by which glucose limits life span is therefore important for any attempt to control aging and age-related diseases. The pro-aging effect of glucose signaling on life span correlated with an increase in reactive oxygen species and a decrease in oxidative stress resistance and respiration rate (Roux et al. 2009).

Thus, when adequate quantities of chromium are ingested in a form that can be absorbed and utilized inside the body, insulin resistance and the subsequent hyperinsulinemia which occurs can be prevented. Because hyperinsulinemia has been associated with long term deleterious effects (Reaven 1988), we suggest that chromium, like dietary restriction, increases longevity by preventing development of symptoms associated with insulin resistance.

5.11 Conclusions

Trivalent chromium is essential to normal carbohydrate, lipid and protein metabolism. Chromium is an essential micronutrient which is required for the normal functioning of insulin and regulation of blood sugar levels. It acts as a vital

antioxidant for maintaining insulin homeostasis. Cr(III) supplementation may be therapeutic or useful as an adjunct treatment for some cases of type 2 diabetes or other disorders caused by insulin insensitivity.

Cr(VI) is a strong oxidant—in the form of chromates and dichromates it penetrates biological membranes and reacts with cell contents, proteins or nucleic acids, while being reduced to Cr(III). Research results strongly support the hypothesis that the antidiabetic activity of Cr(III) and the carcinogenicity of Cr(VI) compounds arise from similar mechanisms involving highly reactive Cr(VI) and Cr(V) intermediates.

The pro-aging effect of glucose signaling on life span correlated with an increase in reactive oxygen species and a decrease in oxidative stress resistance and respiration rate. Chromium(III) protects organism from oxidative stress associated with reactive oxygen species. The results demonstrate that chromium in a utilizable form, like dietary restriction, prevents hyperglycemia, hyperinsulinemia, protein glycation and extends life span. Chromium, like dietary restriction, increases longevity by preventing development of symptoms associated with insulin resistance.

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