Journal of Elementology ISSN 1644-2296

Żarczyńska K., Krzebietke S. 2020.
The effect of chromium on ruminant health.
J. Elem., 25(3): 893-903. DOI: 10.5601/jelem.2020.25.1.1963

RECEIVED: 3 February 2020
ACCEPTED: 5 April 2020

REVIEW PAPER

THE EFFECT OF CHROMIUM ON RUMINANT HEALTH*

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Abstract

Chromium (Cr) is a micronutrient that occurs in the natural environment in different oxidation states. Natural compounds contain chromium in the +3 oxidation state, whereas chromic(VI) acid derivatives are industrial products with strong toxicity. Hexavalent chromium compounds can adversely affect the respiratory system and the gastrointestinal tract, cause skin changes, and exert carcinogenic, mutagenic, embryotoxic as well as teratogenic effects. Research indicates that both organic and inorganic trivalent chromium compounds improve carbohydrate, lipid, and protein metabolism. These compounds are found in many enzymes, and they influence antioxidant processes, regulation of immune responses, and the secretion of hormones and selected vitamins in the body. In animals, Cr has been found to increase fat-free body mass, improve reproductive parameters, enhance growth, increase feed conversion efficiency, boost immunity, and decrease mortality. It has been suggested that Cr supplements can intensify the effects of insulin, decrease the plasma levels of non-esterified fatty acids (NEFAs), decrease triglyceride concentrations in the liver, and improve glucose tolerance, thus improving the performance and productivity of cattle in the perinatal period. Symptoms of chromium deficiency, including decreased feed intake, lower weight gains, reproductive disorders, and higher lipid levels, are observed in cattle fed diets that are low in this nutrient, and in animals that are exposed to considerable and prolonged stress. In ruminants, chromium supplementation is recommended during thermal stress, in the perinatal period, and during infections.

Keywords: chromium, ruminants, essential nutrient, toxicity.

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* This work was funded by the Department and Clinic of Internal Diseases, Faculty of Veterinary Medicine, University of Warmia and Mazury in Olsztyn, Poland.

INTRODUCTION

Chromium (Cr) is a micronutrient and a transition metal, which continues to attract the interest of scientists and consumers, mainly as a dietary supplement. The name of the element is derived from the Greek word *chroma* meaning color because chromium salts and minerals are intensely colored. The Earth's crust contains around 102 ppm of Cr, mainly in the form of mineral chromite and crocoite, in different oxidation states (-2 to +6). In living organisms, Cr occurs in different concentrations, mostly in two valence states: trivalent chromium (Cr^{3+}) and hexavalent chromium (Cr^{6+}) (Soltan 2010). Cr(III) is one of the most stable ions in biological systems. It does not cross cell membranes, and it is a thousand times less toxic to living cells than Cr(VI). In turn, Cr(VI) is a strong oxidant, and it is toxic to both humans and animals. However, Cr(VI) is easily reduced to a trivalent state in living organisms (Kośla et al. 2018). Chromic(VI) acid and its derivatives have numerous industrial applications, and they pose a significant environmental threat due to their toxicity and undesirable side-effects. Trivalent chromium (Cr^{3+}) has a different toxicological profile in animals. The first report on the biochemical role of Cr(III) in glucose metabolism in mammals was published in 1959 (Schwarz, Mertz 1959). Since then, Cr has been regarded as an essential nutrient for living organisms. Chromium(III) is present in enzymes and ribonucleic acids, and its compounds accelerate blood coagulation and increase the activity of β-glucuronidase. Trivalent Cr participates in antioxidant processes, nucleic acid synthesis, immune responses, hormonal metabolism, and the metabolism of selected vitamins (Anderson 1995). Research conducted in the 1990s has demonstrated that Cr is an essential nutrient for many animal species, including ruminants. These studies revealed that organic and inorganic chromium compounds improve carbohydrate and lipid metabolism, regulate serum insulin levels, increase fat-free body mass, and decrease mortality in mammals (Pechova, Pavlata 2007).

CHROMIUM METABOLISM

Similarly to most nutrients, Cr(III) is absorbed by passive diffusion in the intestines, but its bioavailability is relatively low (Dowling et al. 1989). Absorbed Cr enters the bloodstream and is transported to tissues. In the body, Cr is bound by two protein complexes: transferrin and chromodulin. The mechanism by which Cr(III) is transported to cells has not yet been fully elucidated. According to Clodfelder et al. (2004), Cr can cross cell membranes by binding to the transferrin receptor. Inside cells, Cr forms an endosome, and the transferrin-chromium complex is decomposed due to changes in pH. Chromium then binds to apochromodulin (apo-oligopeptide of LMWCr) in the cytoplasm, to form an active LMWCr compound which activates tyrosine kinase that phosphorylates the insulin receptor.

The availability of Cr in the gastrointestinal tract is determined by dietary Cr intake, its chemical form, and the presence of other nutrients in the diet. Like other micronutrients, Cr is more effectively absorbed in organic (chromium picolinate, chromium citrate, chromium polynicotinate, chromium gluconate, chromium propionate) than in inorganic form (Pechova, Pavlata 2007). The intestinal availability of chromium chloride is very low (0.5-2%), whereas chromium picolinate is absorbed in 10-20%. Vitamins C and niacin, oxalic acid and selected amino acids (glycine) enhance Cr absorption, mainly through their chelating effects. High concentrations of magnesium, zinc, phosphates, calcium, iron, titanium, and vanadium decrease Cr availability. Surgent et al. (1979) hypothesized that excess iron levels in hereditary hemochromatosis may interfere with Cr transport by competing for transferrin binding. However, excess dietary Cr can decrease transferrin saturation with iron ions, and it can lead to anemia in extreme cases (Lukaski 1999). Dietary Cr is rapidly absorbed by ruminants. In a study by Anke et al. (2005), Cr(III) was detected in goat milk already 30 minutes after consumption, and its concentration remained high for 3 to 6 hours. Chromium is present in all animal tissues at a concentration of several to several dozen μg kg^{-1}, but rarely exceeds 100 μg kg^{-1} (NRC 2005). Chromium levels are highest in the spleen, liver and kidneys, but they are lower in the pancreas, heart, muscles, lungs, brain and bones. In living organisms, Cr is excreted primarily with urine and, in very small amounts, with feces and sweat (Kośla et al. 2018).

THE ROLE OF CHROMIUM IN CARBOHYDRATE AND LIPID METABOLISM

In the late 1950s, Schwarz and Mertz (1959) demonstrated that healthy responses to elevated glucose levels in the bloodstream were disrupted in rats fed Cr-deficient diets. Rats began to effectively metabolize glucose when products rich in Cr (porcine kidney) were incorporated in their diets. A compound that was probably responsible for restoring normal glucose tolerance was isolated from porcine kidney homogenates, and it became known as the glucose tolerance factor (GTF). The GTF is composed of Cr(III), nicotinic acid, and amino acids glycine, cysteine and glutamic acid. Other theories implicating Cr in the glucose tolerance mechanism were proposed over the years. Sun et al. (2000) found that Cr modifies glucose metabolism via the oligopeptide chromodulin. As a result, Cr is involved in the autoamplification system for insulin signaling to maintain the insulin receptor in active conformation, which reinforces the effects of insulin and increases glucose tolerance (Khan et al. 2014). It is also believed that Cr increases the number of insulin receptors and activates the insulin receptor through its phosphorylation (Vincent 2004). Wu et al. (2005) demonstrated that Cr(III) influences the expression of the glucose transporter (GLU4) in skeletal muscles and adipocytes. The above mechanism could explain the role

of Cr in improving carbohydrate and lipid metabolism in rats. This discovery paved the way for research into the effects of Cr on the regulation of glucose metabolism and its applicability in the treatment of type 1 diabetes (Lewicki et al. 2014), type 2 diabetes (Vincent 2004, Lewicki et al. 2014), insulin resistance and glucose intolerance (Vincent 2014), gestational diabetes (Jovanovic et al. 1999) and steroid-induced diabetes (Moukarzel 2009). Tolerance tests were carried out to evaluate the effects of Cr on glucose and insulin metabolism in cattle. Glucose solution was administered intravenously, and serum glucose and insulin levels were measured several times until they were restored to baseline values. Calf diets supplemented with chromium picolinate (CrPic) (Bunting et al. 1994) or chromium propionate (CrPro) (Sumner et al. 2007) increased glucose clearance after intravenous infusion without affecting serum insulin levels. In turn, the supplementation of milk replacers with chromium chloride or chromium-nicotinic acid complex at 0.4 mg kg^{-1} DM did not affect glucose clearance after intravenous infusion in calves with underdeveloped rumen (Kegley et al. 1997). However, insulin levels after glucose administration were lower in calves receiving chromium chloride, which points to higher glucose sensitivity in this group of animals. Subiyatno et al. (1996) found that dietary supplementation with Cr and amino acid complexes at 0.5 mg Cr kg^{-1} increased insulin sensitivity in primiparous, but not in multiparous dairy cows. Hayirli et al. (2001) administered different concentrations of chromium-L-methionine to multiparous cows from three weeks prepartum to four weeks postpartum and conducted glucose tolerance tests 10 days prepartum and 28 days postpartum. Chromium supplements did not affect glucose clearance or serum insulin levels prepartum, whereas postpartum glucose and insulin concentrations in the blood serum decreased in cows receiving Cr infusions relative to control animals.

Sano et al. (1991) demonstrated that insulin resistance in cattle begins before parturition and persists until early lactation. These findings suggest that perinatal insulin resistance could initiate metabolic disorders, and that Cr supplementation can minimize the risk of ketosis (Debras et al. 1989). However, Cr supplements did not influence the clinical symptoms of ketosis caused by health problems during lactation (Smith et al. 2005).

Research into the effects of Cr on lipid metabolism has clearly demonstrated that this micronutrient has a beneficial influence on the lipid profile in animals (Vincent 2010). Chromium supplements containing organic yeast improve livestock performance characteristics such as meatiness, fat scores, weight gains, feed conversion, and the content of polyunsaturated fatty acids in meat (Pollard et al. 2002). According to McNamara and Valdez (2005), chromium propionate enhanced lipid synthesis in adipose tissue and inhibited lipolysis. The above authors speculated that Cr from chromodulin binds to the insulin receptor, which improves glucose transport. In the work of Besong et al. (2001), the supplementation of cattle diets with chromium amino acid chelate in the form of chromium picolinate decreased triglyceride

concentrations in the blood serum and the liver and serum β-hydroxybutyrate levels. Chromium propionate supplements administered to transition cows decreased the serum levels of NEFAs (Soltan 2010). Other studies demonstrated that Cr supplementation before parturition and in early lactation improved feed intake and increased milk production (Hayirli et al. 2001, McNamara, Valdez 2005, Smith et al. 2005).

CHROMIUM AND THE IMMUNE SYSTEM

Chromium also exerts beneficial effects on the immune system of ruminants (Spears, Weiss 2008). The production of cytokines (interferon, interleukin-2, tumor necrosis factor α) by peripheral blood mononuclear cells (PBMC) decreased and lymphocyte blastogenesis was enhanced in cows supplemented with Cr at 0.5 mg kg^{-1} feed after stimulation with concanavalin A (Burton et al. 1993). In a study by Faldyna et al. (2003), Cr supplementation had no effect on neutrophil activity. There is evidence to indicate that Cr modulates both humoral and cell-mediated immune responses, but the underlying mechanisms have not been elucidated to date. The immunomodulatory properties of Cr could be attributed to its influence on insulin activity or synthesis of selected cytokines (Borgs, Mallard 1998). The role of Cr in immune system function may also be associated with its indirect antagonistic effects on cortisol (Soltan 2010, Kafilzadeh et al. 2012). Under stress conditions, cortisol is released to meet the body's increased demand for energy and to distribute glucose to tissues with a higher demand for glucose, primarily organs such as the liver and the brain (Kegley, Spears 1995). Supplemental Cr can potentially inhibit cortisol release from the adrenal glands. Elevated cortisol levels exert immunosuppressive effects by inhibiting the production and activity of antibodies, decreasing the counts and activity of lymphocytes, and contributing to the atrophy of lymphoid tissue. Chromium can improve the immune function by reinforcing immune responses to vaccination or suppressing indirect antigen recognition (Lien et al. 2015). Antibody production by the immune system of animals receiving supplemental Cr varied depending on the type of antigen. A daily dose of 5 mg Cr increased the production of antibodies in dairy cows vaccinated against tetanus (Faldyna et al. 2003). Dairy cows supplemented with Cr exhibited stronger anti-OVA (ovalbumin) antibody responses, but supplemental Cr had no effect on their antibody responses to human erythrocytes (Burton et al. 1993). In a study by Burton et al. (1993), supplemental Cr did not increase the production of antibodies in cows immunized with commercial vaccines against bovine respiratory syncytial virus type 1 (BHV1), parainfluenza virus type 3 (PI-3) and infections caused by *Mannheimia haemolytica*. However, the production of antibodies against the bovine viral diarrhea virus (BVDV) increased in supplemented cows. Kegley and Spears (1995) reported that supplemental Cr had no effect on the total concentrations of immunoglobulins M (IgM) and G (IgG) in beef cattle. Haldar et al. (2009) observed an increase in total leukocyte and lymphocyte counts and a higher neutrophil-to-lymphocyte ratio in goats supple-

mented with Cr. Arthington et al. (1997) also found that lymphocyte and neutrophil counts increased in calves receiving supplemental dietary Cr. Chromium probably also influences protein (Vajpayee et al. 2000) and RNA synthesis (Okada et al. 1983) in the nucleus, and participates in maintaining DNA integrity (Bray, West 2005), which could influence the molecular mechanisms by which Cr affects the immune status of living organisms. Both *in vivo* and *in vitro* studies have demonstrated that oxidative stress during the transition period could lead to immune dysfunctions in dairy cattle (Riekerink et al. 2007). Therefore, the immune function of ruminants receiving Cr supplements could also be enhanced through an improvement in the antioxidant system.

CHROMIUM TOXICITY

The toxic effects of hexavalent chromium in humans and animals have been widely described. Hexavalent chromium compounds can adversely affect the respiratory system and the gastrointestinal tract, they can cause skin changes, exert carcinogenic, mutagenic, embryotoxic and teratogenic effects, and compromise the development of infants (Elbetieha, Al-Hamood 1997). Three possible mechanisms have been proposed to explain the toxic effects of Cr(VI) on DNA: direct toxic effects of reactive oxygen species which are formed during the reduction of Cr(VI) to Cr(III); Cr binding to DNA at intermediate oxidation states (V and IV); and the formation of Cr-DNA adducts which leads to the formation of cross-links that disrupt DNA function (Hepburn, Vincent 2003). The first extensive review article describing the mutagenic and genotoxic effects of Cr was published by De Flora et al. (1990). According to the authors, Cr(III) more readily reacts with DNA in cell-free systems, and it does not induce destructive changes in cell cultures. They also noted that Cr(III) was as genotoxic as Cr(VI) in *in vitro* tests when its concentration was a thousand times higher than the concentration of Cr(VI). A review of nearly 60 experiments performed on laboratory animals conducted by the International Agency for Research on Cancer (IARC) revealed that Cr metal and trivalent chromium exerted no carcinogenic effects regardless of the route of administration (IARC 1990). However, according to some authors, trivalent chromium is toxic to living organisms because it compromises the immune system by decreasing white blood cell counts, and it contributes to necrosis (Suwalsky et al. 2008). Subramanian et al. (2006) reported that Cr supplementation can stimulate the production of hydrogen peroxide (H_2O_2) and contribute to increasing lipid peroxidation in intestinal epithelial cells, liver, brain, kidneys, and sperm membranes. A study evaluating the effects of chromium niacinate and chromium picolinate demonstrated that CrPic contributes to greater oxidative stress and DNA damage. The toxicity of CrPic was implicated in renal function impairment, skin blisters and pustules, anemia, hemolysis, tissue edema, liver dysfunction, neuronal cell damage, impaired cognitive, perceptual and motor

activity, chromosomal aberration, enhanced production of hydroxyl radicals, and depletion of antioxidant enzymes (Bagchi et al. 2002, Kośla et al. 2018). These toxic effects are probably caused by CrPic residues. In turn, Stout et al. (2009) demonstrated that CrPic supplements were not toxic or carcinogenic for rodents. However, Cr can compromise fertility by disrupting testicular and epididymal function, decreasing sperm quality, and inducing atrophic changes in the testes and ovaries (Elbetieha, Al-Hamood 1997). The direct toxic effects of Cr on cattle have never been documented in the literature. Dallago et al. (2011) demonstrated that dietary supplementation with chromium picolinate exerted a negative effect on ruminal protozoa in lambs. In another study (Dallago et al. 2015), the authors found that CrPic administered at a daily dose of 0.250, 0.375 and 0.500 mg per animal for 84 days had no adverse influence on hematological or biochemical parameters and did not induce histopathological changes in the liver, kidneys, heart, lungs or testes. According to Lindemann (1996), Cr(III) is less toxic than other essential nutrients such as copper, iodine, zinc, manganese and, in particular, selenium.

CHROMIUM DEFICIENCY AND SUPPLEMENTATION

Chromium deficiencies are rarely noted in ruminants, and they are caused mostly by nutrient-poor diets composed of plants grown on Cr-deficient soils as well as by stress. Chronic stress can alter the demand for micronutrients in animals. Animals experience stress during transport, in response to high temperature, rapid growth, and diets that require full insulin mobilization. Stress responses also differ between animal species and breeds. Stress can induce Cr deficiency in animals whose diets are low in this element. Important stress factors that influence Cr metabolism in cattle include pregnancy and lactation (particularly in high-yielding cows) as well as infections and metabolic diseases in the transition period. Chromium excretion with urine is intensified in response to the above factors. Stress factors compromise renal reabsorption of Cr and increase Cr excretion via urine, and when combined with insufficient dietary Cr intake, they can lead Cr whose symptoms include decreased appetite, lower weight gains, reproductive disorders and elevated blood lipid concentrations (Kośla et al. 2018, Lashkari et al. 2018). The first symptoms of Cr deficiency are insulin resistance and impaired glucose metabolism. Subsequent symptoms include protein metabolism disorders, apathy, and impaired cardiovascular function (Lashkari et al. 2018).

Chromium supplementation poses a considerable challenge in ruminants. In the past, this element had not been included in the nutrient requirements of dairy cattle. Little is known about Cr concentrations in diets for dairy cattle, and there is no information on the bioavailability of Cr contained in the ration. In a study analyzing the composition of cattle diets, Cr was not detected in many samples (Spears 2010). Chromium levels are

difficult to determine in cattle diets due to the low Cr content of feeds, complex analytical methods (graphite furnace atomic absorption spectroscopy), and contamination of feed samples during collection and preparation for analysis (Bunting 1999). Research has demonstrated that the most Cr-rich feed components contain less than 1 mg Cr kg^{-1} DM. In dairy cattle, the adequate daily dietary intake of Cr (chromium propionate) has been set at 0.5 mg kg^{-1} DM (FDA 2009). According to Amata (2013), Cr supplements should be administered during heat stress, pregnancy, early lactation, and infection at 4-5 mg/animal/day in the last three weeks prepartum and at 5-6 mg/animal/day in the first weeks postpartum. The responses to Cr supplementation are also difficult to determine due to the lack of routine methods for diagnosing Cr deficiency in ruminants (Lashkari et al. 2018).

CONCLUSIONS

Despite numerous experiments and clinical trials conducted on humans and animals, the mechanisms underlying the activity and toxicity of Cr and the factors which influence the efficacy of Cr supplements have not been fully elucidated. In recent years, Cr has emerged as one of the most controversial transition metals that are essential for ruminant health. However, due to the inconclusive results of studies investigating the toxicity of trivalent chromium and its interactions with other elements, supplemental Cr could pose health risks and should be administered with utmost caution.

REFERENCES

Amata I.A. 2013. *Chromium in Livestock Nutrition: A Review*. Glo. Adv. Res. J. Agric. Sci., 2(12): 289-306.

Anderson R. A. 1995. *Chromium and parenteral nutrition*. Nutrition, 11: 83-86.

Anke M., Schäfer U., Jaritz M., Seifert M., Müller R. 2005. *Chromium in the food chain – essentiality, metalopharmaceutical effects and toxicity*. Proc. 5th Internat. Symp. on Trace Elements in Human: New Perspectives, Athens/ Greece, 554-581.

Arthington J.D., Corah L.R., Minton J.E., Elsasser T.H., Blecha F. 1997. *Supplemental dietary chromium does not influence ACTH, cortisol, or immune responses in young calves inoculated with bovine herpesvirus-1*. J. Anim. Sci., 75: 217-223. https: //doi. org/10.2527/1997.751217x

Bagchi D., Stohs S.J., Downs B.W., Bagchi M., Preuss H.G. 2002. *Cytotoxicity and oxidative mechanisms of different forms of chromium*. Toxicology, 180: 5-22.

Besong S., Jackson J.A., Trammell D.S., Akay V. 2001. *Influence of supplemental chromium on concentrations of liver triglyceride, blood metabolites and rumen VFA profile in steers fed a moderately high fat diet*. J. Dairy Sci., 84: 1679-85. DOI: 10.3168/jds.S0022--0302(01)74603-6

Borgs P., Mallard B.A. 1998. *Immune-endocrine interactions in agricultural species: Chromium and its effect on health and performance*. Domest. Anim. Endocrinol., 15: 431-438. DOI: 10.1016/s0739-7240(98)00018-6

Bray C.M., West C.E. 2005. *DNA repair mechanisms in plants: crucial sensors and effectors*

for the maintenance of genome integrity. New Phytol., 168: 511-528. DOI: 10.1111/j.1469-8137.2005.01548.x.

Bunting L. 1999. *Chromium and dairy nutrition: what do we know?* In: Proceedings of the Mid--South ruminant nutrition conference, Dallas, Texas., 13-18 pp.

Bunting L.D., Fernandez J.M., Thompson D.L., Southern L.L. 1994. *Influence of chromium picolinate on glucose usage and metabolic criteria in growing Holstein calves*. J. Anim. Sci., 72: 1591-1599.

Burton J.L., Mallard B.A., Mowat D.N. 1993. *Effects of supplemental chromium on immune responses of periparturient and early lactation dairy cows*. J. Anim. Sci., 71: 1532-1539.

Clodfelder B.J., Upchurch R.G., Vincent J.B. 2004. *A comparison of the insulin-sensitive transport of chromium in healthy and model diabetic rats*. J. Inorg. Biochem., 98: 522-533. DOI: 10.1016/j.jinorgbio.2004.01.003

Dallago B.S., Braz S., Marçola T.G., McManus C., Caldeira D.F., Campeche A., Gomes E.F., Paim T.P., Borges B.O, Louvandini H. 2015. *Blood parameters and toxicity of chromium picolinate oral supplementation in lambs*. Biol. Trace Elem. Res., 168(1): 91-102. DOI: 10.1007/s12011-015-0347-y

Dallago B.S., McManus C.M., Caldeira D.F., Lopes A.C., Paim T.P., Franco E., Borges B.O., Teles P.H., Correa P.S., Louvandini H. 2011. *Performance and ruminal protozoa in lambs with chromium supplementation*. Res. Vet. Sci., 90(2): 253-256. DOI: 10.1016/j.rvsc.2010.06.015

De Flora S., Bagnasco M., Serra D., Zanacchi P. 1990. *Genotoxicity of chromium compounds. A review*. Mutat. Res., 238: 99-172. https: //doi.org/10.1016/0165-1110(90) 90007-X

Debras E., Grizard J., Aina E., Tesseraud S., Champredon C., Arnal M. (1989) *Insulin sensitivity and responsiveness during lactation and dry period in goats*. Am. J. Physiol. Endocrinol. Metab., 56: 295-302. https: //doi.org/10.1152/ajpendo.1989.256.2.E295

Dowling H.J., Offenbacher E.G., Pi-Sunyer F.X. 1989. *Absorption of inorganic trivalent chromium from the vascular perfused rat small intestine*. J. Nutr., 119: 1138-1145. DOI: 10.1093/jn/119.8.1138.

Elbetieha A., Al.-Hamood M.H. 1997. *Long-term exposure of male and female mice to trivalent and hexavalent chromium compounds: effect on fertility*. Toxicology, 116: 39-47. DOI: 10.1016/s0300-483x(96)03516-0

Faldyna M., Pechova A., Krejci J. 2003. *Chromium supplementation enhances antibody response to vaccination with tetanus toxoid in cattle*. J. Vet. Med. B Infect. Dis. Vet. Public Health, 50: 326-331. DOI: 10.1046/j.1439-0450.2003.00680.x

Federal Drug Administration (FDA). 2009. Regulatory Discretion Letter from U.S. Food & Drug Administration Center for Veterinary Medicine to Kemin.

Haldar S., Mondal S., Samanta S., Ghosh T.K. 2009. *Effects of dietary chromium supplementation on glucose tolerance and primary antibody response against peste des petits ruminants in dwarf Bengal goats (Capra hircus)*. Animal., 3: 209-217. https: // doi.org/10.1017/ /S1751731108003418

Hayirli A., Bremmer D.R., Bertics S.J., Socha M.T., Grummer R.R. 2001. *Effect of chromium supplementation on production and metabolic parameters in periparturient dairy cows*. J Dairy Sci., 84(5): 1218-1230. DOI: 10.3168/jds.S0022-0302(01)74583-3

Hepburn D., Vincent J. 2003. *Tissue and subcellular distribution of chromium picolinate with time after entering the bloodstream*. J. Inorg. Biochem., 94: 86-93. doi.org/10.1016/S0162--0134(02)00623-2

International Agency for Research on Cancer (IARC). 1990. *Chromium, nickel and welding*. IARC Monogr. Eval. Carcinog. Risks Hum. WHO IARC, Lyon, France, 49: 49-25.

Jovanovic L., Gutierrez M., Peterson C. 1999. *Chromium supplementation for women with gestational diabetes mellitus*. J. Trace Elem. Exp. Med., 12: 91-98. https: //doi. org/10.1002/ /(SICI)1520-670X(1999)12: 2<91: : AID-JTRA6 >3.0.CO;2-X

Kafilzadeh F., Shabankareh H.K., Targhibi M.R. 2012. *Effect of chromium supplementation on productive and reproductive performances and some metabolic parameters in late gestation and early lactation of dairy cows*. Biol. Trace Elem. Res., 149: 42-49. DOI: 10.1007/s12011--012-9390-0

Kegley E.B., Spears J.W. 1995. *Immune response, glucose metabolism and performance of stressed feeder calves fed inorganic or organic chromium*. J. Anim. Sci., 73: 2721-2726. https: //doi.org/10. 2527/1995.7392721x

Kegley E.B., Spears J.W., Eisemann J.H. 1997. *Performance and glucose metabolism in calves fed a chromium nicotinic acid complex or chromium chloride*. J. Dairy Sci., 80: 1744-1750. DOI: https: //doi.org/10.3168/jds.S0022-0302(97)76107-1

Khan N., Choi J.Y., Nho E.Y., Jamila N., Habte G., Hong J.H., Hwang I.M., Kim K.S. 2014. *Determination of minor and trace elements in aromatic spices by microwave assisted digestion and inductively coupled plasma-mass spectrometry*. Food Chem., 158: 200-206. https: //doi.org/10.1016/j.foodchem.2014.02.103

Kośla T., Lasocka I., Skibniewska E.M., Kołnierzak M., Skibniewski M. 2018. *Trivalent chromium (Cr III) as a trace element essential for animals and humans*. Med. Wet., 74: 560-567. DOI: dx.doi.org/10.21521/mw.6035

Lashkari S., Habibian M., Jensen SK. 2018. *A review on the role of chromium supplementation in ruminant nutrition-effects on productive performance, blood metabolites, antioxidant status, and immunocompetence*. Biol. Trace Elem. Res.,186(2): 305-321. DOI: 10.1007/s12011-018-1310-5

Lewicki S., Zdanowski R., Krzyżowska M., Lewicka A., Dębski B., Niemcewicz M. Goniewicz M. 2014. *The role of chromium III in the organism and its possible use in diabetes and obesity treatment*. Ann. Agric. Environ. Med., 21: 331-335. https: //doi.org/10.5604/1232--1966.1108599

Lien T.F., Yang K.H., Lin K.J. 2015. *Effects of chromium propionate supplementation on growth performance, serum traits and immune response in weaned pigs*. Asian-Aust. J. Anim. Sci., 18(3): 403-408.

Lindemann M.D. 1996. *Organic chromium – the missing link in farm animal nutrition?* Feeding Times, 1: 8-16.

Lukaski H. 1999. *Chromium as a supplement*. Annu. Rev. Nutr., 19: 279-302. https: //doi.org/ /10.1146/annurev.nutr.19.1.279.

McNamara J.P., Valdez F. 2005. *Adipose tissue metabolism and production responses to calcium propionate and chromium propionate*. J. Dairy Sci., 88: 2498-2507. DOI: 10.3168/jds.S0022--0302(05)72927-1

Moukarzel A. 2009. *Chromium in parenteral nutrition: Too little or too much?* Gastroenterology, 137: 18-28. https: //doi.org/10.1053/j.gastro.2009.08.048 25

National Research Council (NRC). 2005. *Mineral tolerance of animals, second revised edition*. National Academies Press, Washington, 115-125.

Okada S., Suzuki M., Ohba H. 1983. *Enhancement of ribonucleic acid synthesis by chromium (III) in mouse liver*. J. Inorg. Biochem., 19: 95-103.

Pechova A., Pavlata L. 2007. *Chromium as an essential nutrient: A review*. Vet. Med. Czech., 52: 1-18.

Pollard G.V., Richardson C.R., Karnezos T.P. 2002. *Effects of supplemental organic chromium on growth, feed efficiency and carcass characteristics of feedlot steers*. Anim. Feed Sci. Tech., 98: 121-128. https: //doi.org/10.1016/S0377-8401(02)00010-X

Riekerink R.O., Barkema H.W., Stryhn H. 2007. *The effect of season on somatic cell count and the incidence of clinical mastitis*. J. Dairy Sci., 90: 1704-1715. https: //doi.org/10.3168/ /jds.2006-567

Sano H., Nakai M., Kondo T., Terashima Y. 1991. *Insulin responsiveness to glucose and tissue*

responsiveness to insulin in lactating, pregnant, and nonpregnant, nonlactating beef cows. J. Anim. Sci., 69: 1122-1127. https: //doi.org/10.2527/1991.6931122x

Schwarz K., Mertz W. 1959. *Chromium(III) and the glucose tolerance factor.* Arch. Biochem. Biophys., 85: 292-295. https: //doi.org/10.1016/0003-9861(59)90479-5

Smith K.L., Waldron M.R., Drackley J.K., Socha M.T., Overton T.R. 2005. *Performance of dairy cows as affected by prepartum dietary carbohydrate source and supplementation with chromium throughout the transition period.* J. Dairy Sci., 88: 255-263. DOI: 10.3168/ /jds.S0022-0302(05)72683-7

Soltan M.A. 2010. *Effect of dietary chromium supplementation on productive and reproductive performance of early lactating dairy cows under heat stress.* J. Anim. Physiol. Anim. Nutr., 94: 264-272. DOI: 10.1111/j.1439-0396.2008.00913.x

Spears J.W. 2010. *Chromium supplementation in cattle diets.* 21st Annual Florida Ruminant Nutrition Symp. University of Florida, 143-155.

Spears J.W., Weiss W.P. 2008. *Role of antioxidants and trace elements in health and immunity of transition dairy cows.* Vet. J., 176: 70-76. DOI: 10.1016/j.tvjl.2007.12.015

Stout M.D., Nyska A., Collins B.J., Witt K.L., Kissling G.E., Malarkey D.E., Hooth M.J. 2009. *Chronic toxicity and carcinogenicity studies of chromium picolinate monohydrate administered in feed to F344/N rats and B6C3F1 mice for 2 years.* Food Chem. Toxicol., 47: 729-733. DOI: 10.1016/j.fct.2009.01.006

Subiyatno A., Mowat D.N., Yang W.Z. 1996. *Metabolite and hormonal responses to glucose or propionate infusions in periparturient dairy cows supplemented with chromium.* J. Dairy Sci., 79: 1436-1445. DOI: 10.3168/jds.S0022-0302(96)76502-5.

Subramanian S., Rajendiran G., Sekhar P., Gowri C., Govindarajulu P., Aruldhas M.M. 2006. *Reproductive toxicity of chromium in adult bonnet monkeys (Macaca radiata Geoffrey). Reversible oxidative stress in the semen.* Toxicol. Appl. Pharm., 215: 237-249. DOI: 10.1016/ /j.taap.2006.03.004

Sumner J.M., Valdez F., McNamara J.P. 2007. *Effects of chromium propionate on response to an intravenous glucose tolerance test in growing Holstein heifers.* J. Dairy Sci., 90: 3467-3474. DOI: 10.3168/jds.2006-623

Sun Y., Ramirez J., Woski S.A., Vincent J.B. 2000. *The binding of chromium to low-molecular -weight chromium-binding substance (LMWCr) and the transfer of chromium from transfer and chromium picolinate to LMWCr.* J. Biol. Inorg. Chem., 5: 129-136. https: //doi.org/ /10.1007/s007750050016

Surgent T., Lim T.H., Jenson R.L. 1979. *Reduced chromium retention in patients with hemochromatosis, a possible basis of hemochromatotic diabetes.* Metabolism, 28: 70-79.

Suwalsky M., Castro R., Villena F., Sotomayor C.P. 2008. *Cr (III) exerts stronger structural effects than Cr (VI) on the human erythrocyte membrane and molecular models.* J. Inorg. Biochem., 102: 842-849. DOI: 10.1016/j.jinorgbio.2007.11.020

Vajpayee P., Tripathi R.D., Rai U.N., Ali M.B., Singh S.N. 2000. *Chromium (VI) accumulation reduces chlorophyll biosynthesis, nitrate reductase activity and protein content in Nymphaea alba* L. Chemosphere, 41: 1075-1082. DOI: 10.1016/s0045-6535(99)00426-9

Vincent J. 2004. *Recent developments in the biochemistry of chromium(III).* Biol. Trace Elem. Res., 99: 1-16. https: //doi.org/10.1385/BTER: 99: 1-3: 001

Vincent J. 2010. *Chromium: Celebrating 50 years as an essential element?* Dalton Trans., 39(16): 3787-3794. DOI: 10.1039/b920480f

Vincent J. 2014. *Is chromium pharmacologically relevant?* J. Trace Elem. Med. Biol., 28(4): 397-405. https: //doi. org/10.1016/j.jtemb.2014.06.020 20

Wu Y.T., Sun Z., Che S.P., Wang X, Wang Y, Guo G. 2005. *Regulation of chromium on gene expression of skeletal muscles in diabetic rats.* Wei. Sheng. Yan. Jiu., 34: 184-187.