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Review Article

A comprehensive review on chromium: toxicities and detoxification

Shagufta Andleeb*

Department of Zoology, Division of Science and Technology, University of Education, Lahore, Pakistan

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Abstract
Despite adverse toxicities, chromium is a widely used heavy metal for industrial and health purposes. Regarding its toxicity, the metal has been declared as carcinogen, mutagen, thyroid disruptor and teratogen. On the other hand various biological systems have been bestowed with its detoxification under natural conditions. In this regard, a systematic review of literature of 15 years (2000-2014) was made through PubMed central NCBI and 268 references were found most relevant. These articles were about uses, exposure risks, various kinds and levels of toxicities in living organisms (human, animals and plants), reduction, detoxification, and amelioration. The presently reviewed findings strongly recommend maximally minimizing the use of heavy metal and avoiding the possible exposure risks.
Key words: Chromium, Cr(III), Cr(VI),Chromium picolinate,Cr-CNP,$K_2Cr_2O_7$, Cr Met, carcinogen, mutagen, teratogen

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INTRODUCTION

In this review it is endeavored to grasp and comprehend the literature signifying the dreadful picture of Chromium. Such effort is meant to create awareness among public health departments as well as alarm industrial sector involved in its formulation for multiple purposes to minimize the possible exposure and health risks. This review concentrates on these health risks and unveils the hidden toxicities of the heavy metal allied to its general uses.

Exposure risks of Chromium

Coal and oil combustion, metal fabrication industry, steel dust, leather tanning, playground equipments, dental stainless-steel crowns, surface and ground waters are the major sources of chromium risks (Chillrud *et al.*, 2004;Chillrud *et al.*, 2005;Hamula *et al.*, 2006;Oze *et al.*, 2007; Keinan *et al.*, 2010; Cheng *et al.*, 2014; Sazakli *et al*.,2014).

In addition to above highlighted routes of chromium pollution, some other applications are worth mentioning. Chromium supplements are used in therapy for diabetes (Yong*et al*., 2006;Hynes and Rouvinen-Watt, 2007;Kandadi *et al.*, 2011;Sahin *et al*., 2102; Sundaram *et al.*, 2012) as well as it benefits in hypercholesterolemia-associated disorders (Pattar *et al.,* 2006) improves feed intake and reproductive performance in cows (Sadri *et al.*, 2009;Soltan, 2010) whereas, it has only moderate effects on metabolic and endocrine parameters(Sadri *et al.*, 2012). Diets containing chromium at elevated dose significantly affect the mineral balance and influence positively growth and development of fetus (Aupperle *et al.*, 2001; Iskra and Ianovych, 2011;Prescha *et al.*, 2014). It is used in stents (Tuzcu, 2011; Abhyankar and Thakkar, 2012;Kesavan *et al.*, 2013; Valgimigli*et al.*, 2014).

Chromium picolinate [Cr (pic) 3] is a nutritional supplement, which causes enhancement of endothelium-dependent vasorelaxation (Abebe *et al.*, 2010). It is reported as ameliorative in hyperglycemia (Sundaram*et al*., 2012), however it does not improve glycemic control significantly, but increases the risk for oxidative DNA damage, oxidative stress, inflammation and reduces albuminuria (Mozaffari *et al.*, 2009; Yeghiazaryan *et al.,* 2011; Mozaffari *et al.*, 2012; Landman *et al.*, 2014) with no mortality or abnormal clinical signs (Deshmukh *et al.*, 2009a). Proper use of dose can recover the function of Î'-cells, but it is not effective in improving metabolic syndrome (Iqbal *et al.*, 2009;Huang *et al.*, 2014).Trivalent chromium[Cr(III)] is widely employed as supplement and is used in glucose/insulin homeostasis, maintains metabolism,regulates

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*Corresponding author: s_andleeb@yahoo.com

body composition, andacts as antidepressant in diabetes. Cr (III) complexes have remarkable antibacterial activities (Paez *et al.*, 2013). Chromium (III) decreases glucose concentration in the blood (Lewicki *et al.*, 2014). A new trinuclearCr (III) glycinate complex $[Cr_3O(NH_2CH_2CO_2)6(H_2O)_3]+NO_3$ (CrGly), an analogue of Cr_3 (trinuclear Cr(III) propionate complex) is a potential source of supplementary Cr which does not cause any damage (Staniek *et al.*, 2011). Oligomannuonate and its Cr(III) complexes lower the risk of vascular inflammation, improve insulin sensitivity and stimulate glucose uptake in diabetes (Jain *et al.*, 2007;Hao *et al.*, 2011). CrMet might be of potential value in the therapy and protection of diabetes (Golubnitschaja and Yeghiazaryan, 2012; Herring *et al.*, 2013). Moreover acysteinate complex of chromium CDNC has been declared as potent hypoglycemic compound with anti-inflammatory activity and adjunct (Jain *et al.*, 2010; Jain *et al.*, 2012) for individuals with type 2 diabetes. It is also used as metal-on-metal (MoM) implants in hip arthroplasties(Jantzen *et al.*, 2013). It was found that CrProp (a supplement) has significant insulin-sensitizing and moderate blood-lipid-lowering properties (Krol *et al.*, 2012) and does not prevent the development of insulin resistance in rats fed a high-fat diet(Masharani *et al.*, 2012;Krol *et al.*, 2014). $CrCl_3$ in the diet of pigs has been used to enhance antioxidant defense during their intensive growth(Iskra and Vlizlo, 2013). Various pediatric syrups in Nigeria have been reported to be composed of higher concentrations of different heavy metals including chromium (Nduka and Orisakwe, 2009).

Besides few controlled medical uses, mentioned above, industrial applications of chromium have contaminated our environment, and the heavy metal has a long list of toxic effects: Some categories of the metal toxicities which are of immediate concerns to the scientists and public health officials are narrated in this review.

Dietary supplementation of Cr as Cr-CNP affects milk yield, serum glucose, and influences immunity too(Rhee *et al.*, 2002; Kafilzadeh *et al.*, 2012; Sharma *et al.*, 2012;Wang *et al.*, 2012;Wang *et al*., 2013b). Cr(VI) causes iron deficiency and disruption of homeostasis(Suh *et al.*, 2014), lipid peroxidation (Rembacz *et al.*, 2012), changes in ATPase activity (Atli and Canli, 2013). A mixture of chromated copper arsenate (CCA), used to preserve wood is known to induceantioxidant response (Matos *et al.*, 2013). Chromium along with cobalt toxicity results in inner retinal dysfunction(Chan *et al.*, 2012; Apel *et al.*, 2013a,b),cell dedifferentiation and apoptosis (Nigam *et al.*, 2014).

Dermatological disorders

Hypersensitivity induced by chromium results into allergic inflamed skin, or allergic contact dermatitis (Lim *et al.*, 2010; Lee *et al.*, 2014; Shigematsu *et al.*, 2014).

Growth, metabolism andreproduction

Cr(VI) affects adversely the survival, growth, reproduction, fecundity and fertility and causes ovarian inflammation, disrupted ovarian histoarchitecture and fibrosis (Pereira *et al.*, 2005; Banu *et al.*, 2011; Akbar *et al.*, 2012; Arzate-Cardenas and Martinez-Jeronimo, 2012; Bano *et al.*, 2012; Freitas and Rocha, 2014; Samuel*et al*.,2014). Hexavalent chromium induces intracellular spaces, tissue loosening, loss of gametes, decreased sperm count and motility in rats (Marouani*et al.,* 2012; Wang *et al.,* 2013b,d). The Cr(VI) causes various health problems including menstrual disorders, endocrine disruption, mutation and infertility (Hepburn *et al*., 2003; Stanley *et al.*, 2011; Stanley *et al.*, 2013).

Hormones

$K_2Cr_2O_7$ affects the thyroid gland by inducing a marked oxidative damage and release of reactive oxygen species, which decrease free T3 and T4 and GSH (Hassanin *et al.*, 2013). Serum levels of testosterone, insulin and zinc were significantly increased in male adult rats exposed to chromium(Yousofvand*et al.*, 2013).

Cytotoxic and genotoxic:

Cr(VI) is announced both as cytotoxic and genotoxic to hawksbill sea turtles, sea turtles and sea lion(Wise et al., 2010a; Wise *et al.*, 2014).Chromium induced oxidative stress leads to cytotoxicity(Kuo *et al.*, 2003; Pagano *et al.*, 2003;Borthiry *et al.*, 2007; Sinha*et al.,*2009; Myers *et al.*, 2010; Vasylkiv *et al.*, 2010; Myers, 2012;Soudani *et al.*, 2012; Hu *et al.*, 2013; Cerveira *et al.*, 2014). Cr(VI) may exert its cytotoxic effect through increase of cholesterol level in cells(Guo *et al.*, 2013). Cr(VI) has been found to induce oxidative stress, and various levels of genotoxicity, cytotoxicity and clastogenicity(Chourey *et al.*, 2006;Myers *et al.*,

2008;Chen *et al.*, 2009a;Chen *et al.*, 2009b; Li *et al.*, 2012; Kumar *et al.*, 2013; Pabuwal *et al.*, 2013;Minigalieva *et al.*, 2014).Cr(VI) causes transcription inhibition (Nemec *et al.*, 2010;Nickens *et al.*, 2010), and also cause cancer in humans, in experimental animals and exert genetic toxicity by damaging DNA in bacteria and in mammalian cells both in vitro and *in vivo*(Pritchard *et al.*, 2005; Russo *et al.*, 2005; Scharf *et al.*, 2014; Wong*et al*., 2012). Cr-induced DNA-double strand breaksmay result intelomeric abnormalities (Qi *et al.*, 2000; Zhitkovich*et al*., 2002 ; Peterson-Roth *et al.*, 2005; Xie *et al*., 2008; Bae *et al.*, 2009; Dai *et al.*, 2009; Patlolla *et al.*, 2009b ; Patlolla *et al.*, 2009a; Sun*et al*., 2009 ; Zecevic*et al*., 2009; Hedberg *et al.*, 2010; Liu *et al.*, 2010; Macfie *et al.*, 2010; Myers *et al.*, 2011; Zhang*et al*., 2011; Zhitkovich, 2011; Chervona *et al.*, 2012; Clancy *et al.*, 2012; Zhang*et al*., 2012b ; Chen and Lien, 2013; Mulware, 2013;Fang *et al.*, 2014; Ovesen *et al.*, 2014).DNA and chromosomal damage, reduction in lymphocyte levels and hypersensitivity reactions are major systemic targets of Cr toxicity(Afolaranmi *et al.*, 2008a). Chromium-induced mutation, DNA damage, and ROS generation leads to cancer(Sugden and Martin, 2002; Arakawa *et al.*, 2012; Wang*et al*., 2011; Sughis*et al*., 2012, Morse *et al*., 2013).

Carcinogenicity

Owing to its capability to inhibit the expression of tumor suppressor genes and being an allergen, hexavalent chromium(Cr(IV)) is a known carcinogen (Caglieri*et al*., 2006; Schnekenburger *et al.*, 2007; Salnikow and Zhitkovich, 2008; Arita and Costa, 2009; O'Brien *et al.*, 2009; Smith and Steinmaus, 2009;Stout*et al*., 2009a,b ; Linos *et al.*, 2011; Fan *et al*., 2012; Wise and Wise, 2012; Ding*et al*., 2013; Hu*et al*., 2013; Lamb *et al.*, 2013). Zinc chromate has been found as moreclastogenic than all other chromium (Wise*et al*., 2010b).

Lung Cancer

Being contaminant of water and soil, corrosive and cytotoxic, it can induce inflammatory response, acute and chronic lung tissue toxicity resulting in cancer (Peterson-Roth *et al.*, 2005; Caglieri *et al.*, 2006;Oharra*et al.,* 2006; Borthiry *et al.*, 2008; Beaver *et al.*, 2009a; Beaver *et al.*, 2009b; Myers and Myers, 2009; Nemec and Barchowsky, 2009; Smith and Steinmaus, 2009; Das and Singh, 2011; Hu *et al.*, 2011; Johnson *et al.*, 2011; De *et al.*, 2012; Sughis*et al*., 2012 ; Urbano *et al.*, 2012; Ding *et al.*, 2013; Pesch *et al*., 2013; Seidler *et al.*, 2013a,b; Witt *et al.*, 2013; Zeidler-Erdely, 2013; Abreu *et al.*, 2014). Welders have an increased lung occupational cancer risk(Alexopoulos *et al.*, 2008; Zeidler-Erdely *et al.*, 2013). It occurs at exposures that cause tissue damage. Once inside the cell, reduction of Cr(VI) results in oxidative stress and damages DNA (Proctor *et al.*, 2014). Cr(VI) exposure decreases glutathione, nonproteinthiol,vitamins C and E levels, enzyme activities, histone acetylation level and increases the level of histone biotinylation, malondialdehyde and protein carbonyl in lungs(Soudani *et al.*, 2013b; Xia *et al.*, 2014). Chromium also causes asthma by damaging inner lining of lungs (Schneider *et al.*, 2012; Sughis*et al*., 2012).

Liver

Hexavalent chromium disturbs metabolism and arrest p53-dependent cell cycle in hepatocytes which inhibit mitochondrial respiratory chain complex activity leading to apoptosis(Pan *et al.*, 2012; Xiao *et al.*, 2012;Yang*et al*., 2012; Soudani *et al*.,2013a; Xie *et al.*, 2013). Biomarkers of liver injury such as aspartate and alanine transaminases, lactate dehydrogenase activities, bilirubin, albumin and glucose levels increased, whereas triglyceride and cholesterol levels decreased following the metal induced disturbances (Hamida *et al.*, 2013). Cr(VI) is a carcinogen of liver in human(Pellerin and Booker, 2000;Permenter *et al*., 2011; Kirman *et al.*, 2012; Balakrishnan *et al.*, 2013; Castro *et al.*, 2014). It is known to cause inflammatory responses as well as oxidative stress resulting in hepatic injury (Zhang *et al.*, 2012a; Ahmed *et al.*, 2013b; Fang *et al.*, 2013; Khan *et al.*, 2013; Pacheco *et al.*, 2013, Yang *et al*., 2014).Moreover, it increases malondialdehyde and decreases Glutathione (Kumar and Gangwar, 2012) and induces changes in antioxidant enzymes as well as gene expression in liver (Li *et al.*, 2013).

Kidney

Cr(VI) is also a human carcinogen of kidney(Pellerin and Booker, 2000; Kirman *et al.*, 2012). It reduces total protein, hemoglobin, packed cell volume, total erythrocyte count, mean corpuscular volume, mean corpuscular hemoglobin, total leukocyte count, whereas alanine transaminase, blood urea nitrogen and creatinine increase in response to the toxic effects the metal leading to renal failure(Balakrishnan *et al.*, 2013;Barrera-Oviedo

et al., 2013). Hexavalent chromium causes reversible and irreversible lesions in kidney and even mortality (Castro *et al.*, 2014). It causes increase in malondialdehyde MDA and decrease in Glutathione in kidney(Zhang*et al*., 2008; Zhou*et al.*, 2008; Soudani *et al.*, 2011b; Kumar and Gangwar, 2012; Pablack*et al.,*2014). Functional and structural renal damage has been reported also to be induced by $K_2Cr_2O_7$(Pedraza-Chaverri *et al.*, 2005). The accumulation of chromium in liver and kidneys, demonstrates a dependency on age and an impaired kidney function (Khan *et al.*, 2013; Pablack*et al.*, 2014 ;Sunilkumar, 2014).

Gut

Chromium chloride induces hepatocyte vacuolization and changes in gut endothelium morphology (Ahmed *et al.*, 2013a). While Cr(VI) causes tumor in small intestine(Kirman *et al.*, 2012; Kirman *et al.*, 2013). Hexavalent chromium [Cr(VI)] administered in drinking water to male and female rats and mice causes epithelial neoplasms in small intestine (Collins *et al.*, 2010). Cr(VI) induces intestinal tumors(Stout*et al.*, 2009b; Johnson *et al.*, 2011;Thompson*et al.*, 2011a,b; Thompson *et al.,*2012). Moreover it also induces intestinal adenomas and carcinomas in mice (Thompson*et al.*, 2013),villous cytotoxicity and compensatory crypt hyperplasia in the small intestines of mice (Thompson*et al.*, 2014) and digestive and disorders (Sharma *et al.*, 2012).Changes induced by chromium antioxidant enzymes and gene expression have been observed in intestine, liver and gill of pengzecrucian carp (Li *et al.*, 2013).

Teratogenicity

Gestational exposure to Cr(VI) resulted in increased Cr concentration in the placenta, increased germ cell apoptosis, accelerated germ cell cyst (GCC) breakdown; advanced primordial follicle assembly and primary follicle transition(Ahmad,2013; Sivakumar *et al.*, 2014).Cr(VI) damages the pubertal development, and ovarian histoarchitecture in developing Wistar rats(Samuel *et al.*, 2014). Cr(VI) is an endocrine disruptor mutagen and teratogen (Stanley *et al.*, 2013). Cr can pass through placenta of a healthy male infant which consequently may be characterized with elevated Cr and Co cord blood levels (Fritzsche *et al.*, 2012). Adverse effects on the parameters evaluated for the gravid uteri, external abnormalities in the fetuses, soft tissue abnormalities in the fetuses, or skeletal abnormalities in the fetuses have also been documented(Deshmukh *et al.*, 2009b; Abbas, 2013; Ahmmad, 2013). An increase in mass gain and live-born piglets in sows supplemented with chromium picolinate (CrPic) throughout gestation has recently been reported(Wang *et al.*, 2013b). At 38 weeks of gestation, a healthy male infant was delivered with elevated Cr and Co cord blood levels. At the age of 8 weeks, the infant's Cr was comparable to the cord blood level. At the age of 14 weeks, the infant's development was seemingly uneventful and no signs of toxicity were obvious(Fritzsche *et al.*, 2012). Higher dose of chromium results in severe histological changes in vital organs of fetus as well as decidua (Marouani *et al.*, 2011). However paternal exposure to chromium(III) picolinate has little potential for adverse reproductive effects(McAdory *et al.*, 2011). Gonadosomatic index (GSI), ovarian histopathology, immunocytochemistry of the pituitary gonadotrophs (LHbeta-immunoreactive cells), and serum 17beta-estradiol level revealed distinct dose and duration-dependent effects in a teleost Channapunctatus. Gonadosomatic index was declined with arrest of follicular development(Mishra and Mohanty, 2012; Mishra and Mohanty, 2014). Exposures to chromium is associated with increased oxidative DNA damage in neonates(Ni *et al.*, 2014).Maternal Cr restriction significantly increased body weight and fat percentage, especially the central adiposity in both male and female offsprings(Padmavathi *et al.*, 2010). $K_2Cr_2O_7$ causes disorders in the bone of progeny of Wister rats with increased level of malondialdehyde, but decreased level of glutathione, a non-protein thiol and vitamin C (Soudani *et al.*, 2011a).

Hepatotoxicity has been defined as in liver malondialdehyde content and accumulation of chromium, decrease of glutathione, nonproteinthiols, and vitamin C in the liver of mothers and their suckling pups (Wister rats). Decline of antioxidant enzyme activities such as catalase, glutathione peroxidase, and elevation in liver superoxide dismutase activity in mothers and decrease in their offspring were also noticed. Hemorrhage, leukocytes infiltration cells, and necrosis were more pronounced in the hepatocytes of mothers than in those of their suckling pups(Soudani *et al.*, 2013a). No abnormalities in gross organ morphology of fetuses were detected when given supplemental CrProp(Staniek and Krejpcio, 2009).

Toxicity in plants

Cr(VI) induces oxidative stress in radish and retards growth of radish seedlings, inhibits photosynthesis in algae, decreases growth performance of *Catharanthusroseus* and other various plants by affecting enzymesChoudhary *et al.*, 2012; Didur *et al.*, 2013; Wang*et al.*, 2013c; Rai *et al.*, 2014; Sangwan *et al.*, 2014). Cr(III) induces chromosomal aberration in root tip cells of*Viciafaba*(Qian *et al.*, 2006), whereas Cr(VI) is toxic to barley and rice roots (Song *et al.*, 2014; Trinh *et al.*, 2014). The soil enrichment with Cr raises the content of nitrogen compounds in oats grain and straw, but decreases it in roots(Wyszkowski and Radziemska, 2013).

Toxicity in aquatic life

Industrial wastes have been contaminating the aquatic ecosystem (Flohr *et al.*, 2012). Severe chromium induced muscle, gills, liver and kidney alteration, lifting up of the epithelium, swelling, hyperplasia, hypertrophy, proliferation of chloride cells, lamellar fusions, fused secondary lamella and necrosis was observed in fish (Ciacci *et al.*, 2012; Dwivedi *et al.*, 2012; Svecevicius *et al.*, 2014). It causes oxidative stress in the liver of goldfish *Carassiusauratus*(Velma and Tchounwou, 2013), Cyprinid fish(Wang et al., 2013 a), and in *Labeorohita*(Vutukuru*et al*., 2007 ;Kumari *et al.*, 2014). In addition to other toxicities, it is also genotoxic for fish (Velma *et al*., 2009; Velma and Tchounwou, 2010; Velma and Tchounwou, 2011;Li *et al.*, 2012).

Biological defense mechanism against chromium-induced toxicities:

N-acetylcysteine may prevent chromium hypersensitivity by inhibiting of reactive oxygen species, ROS-induced cell death and cytokine expression(Lee *et al.*, 2014). Peroxisomalpalmitoyl CoA, malondialdehyde, glutathione, catalase, and superoxide dismutase play a major role in chromium detoxification(Gaggelli *et al.*, 2002; Guttmann *et al.*, 2008; Refaie *et al.*, 2009; Iskra and Ianovich, 2012; Volland *et al.*, 2012; Dogan *et al.*, 2014; Kumari *et al.*, 2014). Cytochromes MtrC and OmcA are the terminal reductases for reduction of extracellular Cr(VI) (Belchik *et al.*, 2011).

Amelioration

Various agents have been appreciated for ameliorating and thus protecting from toxic effects of chromium like vitamin C, selenium nanoparticles, phosphorus, propolis(Kaczmarek *et al.*, 2007; Samuel *et al.*, 2012; Hassanin *et al.*, 2013; Sayantan and Shardendu, 2013; Yonar *et al.*, 2014). Some plants extracts like *Lawsoniainermis* Linn, green tea, and rhubarb (*Rheum palmatum*) protect from Cr (VI) induced damages(Guha *et al.*, 2011;Garcia-Rodriguez *et al.*, 2013;Zeng*et al.*, 2013). Surprisingly garlic (*Allium sativum*) has some beneficial effect in preventing Cr(VI)-induced alteration of lipid profile(Gupta *et al*., 2008).

Bioremediation

Bacterial strains*Pseudomonas putida* (Priester*et al*., 2006);*Bacillus* cereus (Tripathi*et al*., 2011);*Bacillus* REP02 (Venil*et al.,* 2011); *Pseudomonasaeruginosa* Rb-1 and *Ochrobactrumintermedium* Rb-2 (Batool *et al.*, 2014); *Brevebacteriumcasei*(Das and Mishra, 2010); *Arthrobacter spp*. and *Pseudomonas sp.*(Dey and Paul, 2013); Acinetobacter AB1 (Essahale *et al.*, 2012; Sheik *et al.*, 2012); *Staphylococcus aureus* and *Pediococcuspentosaceus*(Ilias *et al.*, 2011); *Ochrobactrumintermedium* BCR400 (Kavita and Keharia, 2012); *Geobacteraceae*(Kourtev *et al.*, 2006); *Bacillus cereus*(Kourtev *et al.*, 2009);*Lactobacillus*(Mishra *et al.*, 2012); a novel bacterial strain OS4 of *Stenotrophomonasmaltophilia*(Oves *et al.*, 2013); *Leucobacterchromiiresistens*(Sturm*et al*., 2012);and Yeast (Holland *et al.*, 2007;Holland and Avery, 2009) have potential to reduce and eliminate hexavalent chromium. Regarding phytoremediation, some plants like cotton cultivars by secluding Cr taken up by roots(Daud *et al.*, 2014) and biosorption by Opuntia biomass serves not only a low-cost but also an ecofriendly system(Fernandez-Lopez *et al.*, 2014)**.**

Conclusion

Besides its important role with its very minute quantities in biological systems, industrial use of Cr has contaminated our environment and has created diverse health issues. Thisinformationdictates for strict environmental legislation especially in developing countries.

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