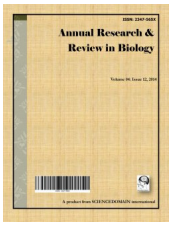

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Effects of Chromium on Human Body

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Authors' contributions

This work was carried out in collaboration between all authors. Author RTA designed the review and produced the initial draft. Author Budiawan managed the literature searches and interpretation of the analyses together with author EIA. Author EIA wrote the revised draft and all authors read and approved the final manuscript.

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ABSTRACT

Chromium is widely used in medical and dental implants, appliances and tools, where sufficient content s of this chemical element can provide a protective corrosion-resistant oxide on the alloy surface. At low concentrations chromium is used for medical purposes, and it is also involved in natural human lipid and protein metabolism. However, at sufficiently high concentrations particularly hexavalent chromium is toxic and carcinogenic. The healthy risks can be expected regardless whether the chromium originates from external sources such as polluted drinking water or internally from corroding dental appliances. As the latter source is likely to provide chromium exposure only at low to modest concentrations, no acute effects are generally expected. The current paper aimed to briefly review the toxicology aspects of chromium in general and in oral exposure from applications, used in dentistry. It was concluded that most likely oral effects are chronic, including carcinogenic impact, but more studies are directed to investigation on the chronic effects of chromium release from dental appliances.

Keywords: Chromium; human; health; toxicology.

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1. INTRODUCTION

Chromium (Cr) is a silvery white transition metal with atomic number of 24, relative atomic mass of 52.996 g/mol, and price between iron and nickel [1]. Inherent brittleness sets the upper limit for its content in commercial alloys mostly to below 30-40% by weight. In medical and dental applications as tools, implants, bridges and other metallic appliances, chromium is a common alloying component. The main benefit of this chemical element in these alloys is the inert protective oxide that forms on the surfaces in suitably oxidizing environments. For full surface coverage by chromium oxide (Cr_2O_3), more than 10% of Cr is required, and typically the range of Cr content is 15 - 28%, for example in stainless steels.

At low concentrations, Cr is involved in natural human lipid and protein metabolism, so that very small amounts are needed for normal human life functions [2]. Much of the daily intake of chromium, typically about 100 µg, is from foods such as grains, fruits and vegetables, potatoes, seafood, mushrooms and egg yolk [2,3]. In addition, low to modest amounts of chromium can appear in other potential sources such as type II anti-diabetic and dietary drugs [2,3]. Chromium also occurs at much higher concentrations in industrial processes that can release potential pollutants to air and drinking water [2].

In dentistry, a variety of chromium-containing alloys can be found in most prosthodontic devices, orthodontic appliances, restorative devices, and in alloys and coatings of standard tools used by dentists [1]. Many of these devices are directly exposed to the oral cavity environment for a prolonged time, maybe years to decades. The natural host-alloy surface interaction will release metal ions to contact oral cells, and become ingested [4]. Metallic ions have been shown to occur at elevated concentrations in saliva of dental patients using prosthodontic devices [4,5,6].

The main attention of the present paper is in chromium ions that can leach out from gradually corroding dental alloys under the influence of human body liquids such as saliva, resulting in potentially significant human exposure. The oral environment can promote metal corrosion due to its temporally variable pH conditions, and other factors such as bacterial activity, various foods, drugs or supplements can also change the balance of oral condition to affect ion release. [5,6].

Chromium ions in solution occur in two common forms, relatively safer Cr (III) and more toxic Cr (VI), and particularly the latter is not similarly biocompatible as solid chromium oxide in human contact [1-6]. In principle chromium therefore represents a potential health risk also when used in dentistry. Some chromium containing alloys for dental applications are shown in Table 1.

Table 1. Alloys with chromium in dental applications

Alloy type	Dental use	Metal elements
Co-Cr alloys	Restorations	Co, **Cr**, Mo, Fe, Mn
Ni alloys, Ni-Ti	Restorations, orthodontic appliances	Ni, Mo, Fe, Be, Mn, **Cr**
Stainless steels	Implants, orthodontic appliances, tools	**Cr**, Fe, Ni, Mn, Mo

Every metal has a characteristic reduction potential to describe its galvanic reactivity. Towards the left end of this galvanic series (shown below) the metal becomes more easily oxidized, and is more easily releasing metal ions particularly in an acidic environment [6,7].

Be, Ti, Mn, Zn, Cr, Ga, Fe, In, Co, Ni, Mo, Sn, H_2, Cu, Hg, Ag, Pd, Pt, Au

← Oxidation Reduction →

In this series chromium is a relatively reactive metal, i.e. easily available for chemical reactions if the metal surface is not fully protected by the oxide. At least partial loss of protection can be expected for example from the influence of heat, low pH, tooth brushing, mastication (repeated mechanical loading) and aging of dental appliances, to result in release of chromium to the oral environment [8,9].

Some release of chromium ions is known to be related by the interaction of chromium in dental devices with saliva, acids, and bacteria [8]. In stainless steel dental implants, ion release may cause high microscopic dental porosity in artificial saliva, with increased pore density in saliva containing fluoride [9,10].

In general, the release of metal ions to the saliva may be slight, but it is accelerated in acidic pH, and release of chromium has been reported from dental devices made by casting, milling, and sintering, on average 0.8-0.9 mg/L in saliva per month [8]. The released amount can increase by exposure to strong oxidizing agents such as fluoride application and acidic products from oral bacteria [8,9,10].

Chromium ions in saliva will be ingested and reach the gastrointestinal tract that can reduce most Cr (VI) to Cr (III), especially post meal [11,12,13]. At the gastrointestinal tract, the Cr (III) ions will be slightly absorbed depending on the form of its chemistry and transit time [14]. When the rest of Cr (VI) ions have been absorbed into the vascular tract, they will be easily infiltrated to red blood cells and become reduced to Cr (III) ions [14]. Some Cr (III) ions will bind to transferrin in blood plasma and circulate throughout the body [14]. Furthermore, about of 60% Cr (VI) ions and 10% of Cr (III) ions will be excreted through the kidneys, and small amonts through hair, nails, milk, and sweat [14].

In the body metabolism pathway, chromium ions can bind to proteins to form complex proteins [14]. Chromium ions can also be detected in bone marrow, lungs, lymph nodes, spleen, kidneys, and liver, with the highest observed concentration in the lung cells [14]. Cr (III) ions have been shown to bind to nucleic acids very strongly, and may keep RNA from heat-induced denaturation [15].

2. HEALTH HAZARDS OF CHROMIUM, RELATED MECHANISMS AND PATHWAYS

Human exposure to sufficiently high chromium concentrations would result in potential harm through its toxic, genotoxic and carcinogenic effects [1,12,16-19]. Chromium is one of eight metals in the top 50 toxic substances in the world in the data issued by the Agency for Toxic Substances and Disease Registry (ATSDR), and WHO has classified chromium as carcinogenic to human beings [8,11,20,21].

Under normal circumstances (Table 2), the majority of chromium ions appear as trivalent Cr (III) or hexavalent Cr (VI) [1-19,22-24]. An important distinction is that most of Cr (III) will be excreted in urine, while most of Cr (VI) will remain in the body [20].

Cr (VI) ions are strongly oxidizing, and of all Cr ions most toxic and with highest risk to trigger carcinogenesis [1,15,18,19]. Under suitable conditions Cr (III) can be oxidized to Cr (VI) by the reaction $2Cr_2O_3 + 3O_2 \rightarrow 4CrO_3$, to increase the toxic impact of chromium exposure [15,18,19].

Cr (VI) is more easily absorbed into the human body than Cr (III) because the active form of Cr (VI) as chromate resembles structurally sulphate and therefore easily penetrates cell membranes, including those of red blood cells, by sulphate transporters [17,20,25]. Many quantitative studies have shown that ion forms of chromium have higher absorption than its less soluble forms, such as chromium in the form of diabetic dietary supplements [14]. The lower is the oral daily intake, the higher will be the gastrointestinal chromium absorption rate [14].

After absorption, Cr (VI) can be reduced back to Cr (III) but this reduction takes place at the cost of inflicted cellular damage. In the metabolic processes of chromium it can induce oxidative stress with glutathione (GS*) radical to oxidize the surrounding environment, with the potential to attack adenine and guanine in DNA and to produce DNA adducts [15,26]. With DNA damage and/or incomplete DNA repair, this can lead to carcinogenesis [26]. The oxidation and reduction processes of chromium are outlined in Fig. 1.

Chromium ions can react with reducing agents such as H_2O, Mn(II), NO_2, Fe(II), S^{2-}, and CH_4 and oxidizing agents such as O_2 (aq), O_3 (aq), Mn(IV), NO_3, Fe(III), SO^{2-}, and CO_2 to produce free radicals.[15] Cr (III) can also be oxidized by materials such as mouthwash, toothpaste and prophylactic gels containing fluorides, povidone iodine and endodontic chemicals [1]. Cr (III) can therefore become more toxic Cr (VI) when subjected to such oxidizing agents in the oral environment.

Table 2. Occurrence and characteristics of Cr(III) and Cr(VI) [18]

Cr(III), trivalent chromium	Cr(VI), hexavalent chromium
$[Cr(H_2O)_6]^{3+}$ $[(H_2O)_5Cr(OH)]^{2+}$, $Cr(OH)_3$	CrO_4^{2-}, $Cr_2O_7^{2-}$ H_2CrO_4, $HCrO_4^-$
More stable in alkaline conditions	More stable in acidic conditions
Less toxic, used as a supplement	Genotoxic and carcinogenic, strong oxidant

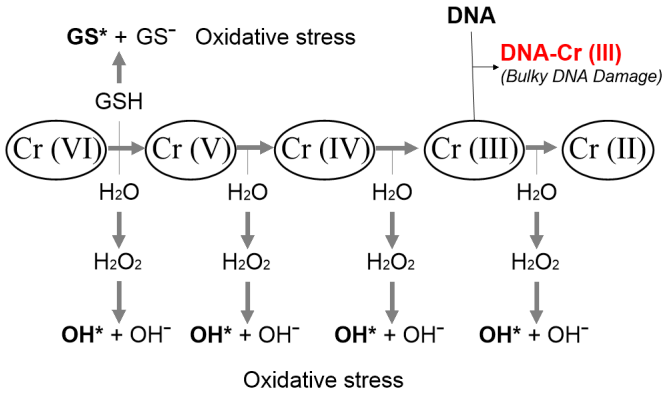

Fig. 1. Reduction and oxidation reactions of chromium ions [26]

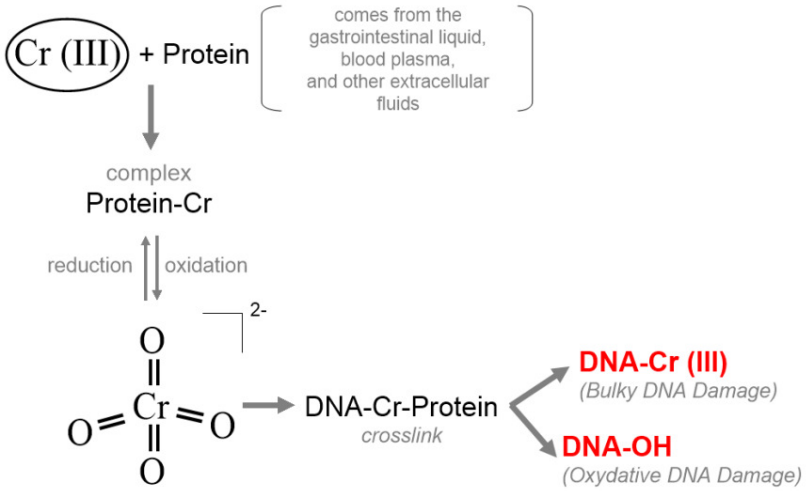

Fig. 2. Reduction and oxidation reactions of chromium ions from anti-diabetic drugs to trigger genotoxicity [27]

Chromium ions originating from antidiabetic drugs can be reduced and oxidized with certain metabolic pathways shown in Fig. 2 above.

In particular, Cr (III) from these drugs can be oxidized in the gastrointestinal medium, blood plasma, and other extracellular fluids into protein complexes and then ionized with DNA resulting in DNA adducts [27]. Therefore chromium-containing anti-diabetic drugs can potentially have genotoxic and carcinogenic effects.

In general human exposure to chromium is mainly through inhalation, ingestion or skin contact [20].

Chromium absorption through inhalation has been demonstrated by subsequent increase in the Cr levels in urine [27-29].

In case of oral exposure and ingestion, Cr (VI) is in most cases absorbed by gastrointestinal mucosa better than Cr (III) [30]. Stainless steel brackets and nitinol wires in orthodontic appliances are known to release chromium ions, with 33.5 ppb Cr reported from saliva initially and 17.9 ppb after 10-12 months of use; three times more chromium ions than nickel ions were released [31].

Occupational studies have indicated that Cr (VI) can be absorbed through the skin [29]. In contrast, Cr (III) shows poor skin absorption in experimental animals [32].

3. EFFECTS AND SAFETY LIMITS OF CHROMIUM EXPOSURE

The effects of chromium exposure on health would depend on dose and organ at risk, and the

exposure is generally by a mixture of Cr (III) and Cr (VI) ions [20]. High concentrations that cause acute effects are often related to pollution of the environment. Acute reaction will only occur at above the chromium LD 50 level (20–250 mg Cr (VI) and 185–615 mg Cr (III) per kg body weight) [11]. The Pacific Gas and Electric Company (PG&E) case in California is an example of many chromium pollution cases that caused both acute and chronic effects to the population.

Existing and suggested limits to chromium exposure are listed in Table 3. The following health effects can be expected:

- **Respiratory challenges**

  Depending on the dose, acute effects include irritation and obstruction of airways, and chronic effects of pulmonary irritation due to exposure through inhalation may occur as asthma, chronic bronchitis, chronic irritation, chronic pharyngitis, chronic rhinitis, congestion and hyperemia, polyps in the upper respiratory tract, tracheobronchitis, and ulceration of the mucous nasal membranes with the perforation possibility of the septum. [17,20,33]

- **Skin**

  Chromium effects often occur in the form of irritation or dermatitis due to allergies. The dermatitis symptoms include dryness, erythema, fissured skin, papules, small vesicles, and swelling [17,20].

- **Cancer**

  Chromium-related cancer often occurs in the respiratory system, mainly as lung, nasal and sinus cancers [20]. Reaction of Cr (VI) with ascorbate (reductant) and hydrogen peroxide (oxidizer) will result in the accumulation of hydroxyl radicals that cause DNA damage, mutations, and increasing cancer potential [17,19]. Alterations in DNA can be found as DNA strand breaks, Cr-DNA adducts, DNA-DNA and DNA-protein crosslinks, and oxidative DNA damage [16,21]. In addition, Cr (VI) has been reported to inhibit epigenetically (by methylation) the tumor suppressor gene $p16^{Ink4A}$ that is frequently altered in cancer. [34].

- **Other health effects**

  Other symptoms may be more severe if the dose exceeds a threshold [20]:

  - Mild symptoms: dizziness, general weakness, eye irritation
  - Severe symptoms: kidney, liver, gastrointestinal, cardiac, hematologic or reproduction disorders, growth problems, nasal perforation, corneal injury
  - Abnormalities of teeth as discoloration and erosion, accompanied by high Cr concentration in tongue papillae.

Table 3. Limits for Cr(III) and Cr(VI) [19-21,24,34]

Defined limit	Cr(III), trivalent	Cr(VI), hexavalent	Sources
LD_{50}*	185-615 mg/kg bw	20-250 mg/kg	WHO [8]
Safe daily dose**	0.03-0.13 µg/kg bw/d**	-	WHO [8]
Normal level	20-30 µg/l (blood),	<10 µg/l (urine, 24 h)	ATSDR [14]
Limit, water***	50 µg/l (total Cr)	0.02 µg/l	WHO, OEHHA [34]
Limit, air****	0.5 mg Cr/m^3	0.05 mg Cr/m^3	ACGIH [24]
Limit, toys*****	-	0.0002 µg/kg bw/d	SCHER [34]

** oral exposure, per kg body weight, estimated acute effect from in vitro tests*
*** per kg body weight per day, corresponding to 2-8 µg per day for a 60 kg person*
**** for drinking water, public health goal (PHG) for Cr(VI)*
***** for atmospheric exposure in 8 h-day or 40 h-week; for insoluble Cr(VI) 0.01 mg Cr/m^3*
****** per kg body weight per day, corresponds to e.g. 0.0002 mg/kg liquid toy material released*
Abbreviations: WHO: World Health Organization; ATSDR: Agency for Toxic Substances and Disease Registry (US); OEHHA: Office of Environmental Health Hazard Assessment (California); ACGIH: American Conference of Governmental Industrial Hygienists (US); SCHER: Scientific Committee on Health and Environmental Risks (EU)

4. DISCUSSION

As can be expected, recently suggested limits for chromium exposure tend to be stricter than in the past. This is partly due to accumulating information from research on the health risks of chromium, and partly because of the adopted principle to limit risks to lowest levels reasonably achievable, particularly for Cr (VI) exposure. The resulting suggested limits for example in case of drinking water are showing this development: while the recommended WHO (2003) limit for total chromium is 50 µg/l, the recent recommended OEHHA (2011) public health goal for Cr (VI) is 0.02 µg/l. The difference is quite large considering typical chromium levels in drinking water, and that common treatment of drinking water by ozone, chlorine and/or chlorine dioxide will oxidise any Cr(III) almost completely to Cr(VI) [35].

The stated limits may reflect some thresholds for example between the naturally required intake of chromium and harmful levels indicated by toxicology studies. However, for Cr (VI) it is debatable whether real thresholds exist in case of carcinogenic impact. In such a case the adopted or recommended limit, or virtual safe dose, may be based on a level of additional risk, for example in terms of level of exposure for one additional cancer case per million comparable subjects at risk for life (70 years). The resulting recommended limit (in Table 3) for Cr (VI) in toys is more than an order of magnitude lower than the current legal (directive) limit in EU [35].

For safe daily dose, WHO was set 2–8 µg Cr (III) per day, which is equivalent to 0.03 to 0.13 µg Cr (III) per kg of body weight per day for 60kg human adult [21]. These results are calculated using an estimate of 0.5-2 µg Cr (III) will be absorbed and deposited in the body, while the other 75% excreted out [21].

The level in red blood cells (RBC) in particular can indicate the exposure to Cr (VI) because of the selective properties of the RBC membrane [24].

In dental applications, exposure of mucosal cells to chromium ions can correspond to about 0.9 mg/L per month, or 30 µg/L per day [8]. With the assumption that the daily saliva secretion is about 1L per day, there will be only about 30 µg of chromium ions in the saliva to interact with the oral environment. This amount will be increased in acidic oral conditions due to poor oral hygiene, fluoride application, acidic food consumption, etc. If only 30 µg of chromium is released in good oral pH condition without any added acidic intervention, the amount will be between the safe limits according to ATSDR (20-45 µg chromium as supplement) [8,11]. Worse outcome is possible under conditions that trigger metal oxidation such as hot condition, low pH, mastication, or some dental treatment such as fluoridation and bleaching.

Apart from the concentration of chromium ions, the time of interaction itself is a risk factor, as we know that prolonged exposure to dental devices and their aging will worsen corrosion. The combination of specific conditions may lead to the increase of chromium ions concentration in oral environment.

After ingestion, the concentration of chromium ions will bedecreased by---- body metabolism. Chromium ions, especially Cr (VI), will be reduced in ingestion tract and blood, and some of it will get excreted via kidneys pathway that lead to concentration decrease in the body.

At low chromium concentrations that do not cause acute effects, significant chronic effects can still occur and should be properly considered. This is likely to apply to chromium released from dental alloys, as it is expected to be initially mostly Cr (III) and even if partially converted to Cr (VI) in the oral environment, only occurring at low to modest concentrations. However, there is very little information on the chronic effects of this type of human exposure to chromium [36].

Levels of human exposure to chromium can be reduced by provision of active absorbants, such as chitosan, activated carbon, a surfactant, or zeolite that can absorb Cr (VI) to mitigate the risk [19,23]. Dentists may need to consider their decisions to install chromium based dental applications depending on simultaneous use of fluorides, poor level of oral hygiene of the patient, and other factors which could induce greater chromium release.

5. CONCLUSION

In summary, human exposure to chromium above safe concentration limits is a recognized risk for the health. Of its two common stable forms, trivalent Cr (III) is a required nutrient and carries low risk, while a significant health risk is associated with hexavalent Cr (VI) that is more easily transported through the cellular

membranes, which could lead to damage in lipids, proteins and DNA. Chromium, released from dental appliances, is likely to be initially mostly Cr (III), but if a part of it is converted to Cr (VI) in oral environment, the potential health risk from chromium exposure is of interest also in dentistry. As the concentration levels are likely to be generally below those causing acute effects, further studies on the possible chronic effects of chromium, released from dental alloys, are necessary.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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