



Review

Hexavalent chromium: Regulation and health effects

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ABSTRACT

Despite the knowledge about heavy metals toxicity on humans, its use is widely spread mainly for industrial processes. Chromium is an element that belongs to this group and although it is present in our daily diet, it can also be harmful for humans, causing skin allergies and increasing the risk of lung cancer, among other health effects reported. In this review, we highlight its nutritional role, its toxicokinetic and toxicodynamic in humans, its regulation in the industry and the biomonitoring proposal of this element in blood and urine samples with the aim to control the level of exposure of the workers in military industry and also of the general population.

1. Introduction

Chromium (Cr) is an element that belongs to the heavy metals group. Its oxidation state ranges from -2 to +6, however, it is found in nature at its more stable forms: trivalent chromium (CrIII) and hexavalent chromium (CrVI) [1]. CrIII plays an important nutritional role, although its mechanisms are not fully understood. On the other hand, due to its capacity to confer hardness and corrosion resistance, and a bright and lustrous appearance to other metals, CrVI and its compounds are widely used for industrial purposes. These compounds are frequently found in the electroplating, leather, metallurgic, chromates, pigments, cement, weapons, ammunition, welding and agricultural fertilizers industries, to mention some of them [1,2].

Despite its wide spread, CrVI is 100 times more toxic than CrIII and it is considered by the International Agency for Research on Cancer (IARC) as a group I human carcinogen agent (International Agency for Research on Cancer, 2016), and several health detriments have been linked to it, such as dermatitis, nasosinusitis, kidney and liver problems, as well as hematological and chromosomal aberrations [4–7].

Inhalation and dermic contact represent the main routes of occupational exposition. The frequency of the effects on workers' health will depend upon the initial route of absorption. In the non-occupational exposition, the most common exposition site is the gastrointestinal tract by means of contaminated food and water.

Knowledge of these effects have led to the regulation of permissible limits of CrVI in air, to which workers industry can be occupationally

exposed [8].

2. Nutritional role of chromium

CrIII is a trace element; salmon, eggs, broccoli, whole grains and some crustaceans are good sources of this metal. According to the Food and Drug Administration (FDA), a daily intake of 120 mcg of Cr is recommended, nevertheless, the National Academy of Sciences' committee states the Cr adequate intake is 25 mcg for women and 35 mcg for men at the ages of 19 and 50, and 20 mcg for women and 30 mcg for men older than 50 years [9,10].

In 1959, Cr was considered an essential element in our diet because it has a role in metabolic pathways of glucose, proteins and lipids; it also forms complexes with nucleic acids and proteins, and it's involved in oxidation-reduction reactions. It has been proposed that the deficiency of CrIII in diets leads to a state similar to diabetes [11–13].

Regarding its role in glucose metabolism, some authors propose that Cr interacts with tyrosine kinase insulin receptors, affecting their activity [14]. It has been proposed the participation of an oligopeptide called chromodulin, which has the property of binding four chromium atoms; the linkage leads to translocation of Glucose transporter GLUT4 to the cell membrane resulting in biological activity. Some other studies show the increase of AMP-activated protein kinase (AMPK) as the mechanism involved [15–17]. Nutritional supplements with Cr, especially chromium picolinate (CrPic), have become popular to lose weight. According to preliminary studies, its use can have beneficial effects in

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certain diseases such as diabetes, metabolic syndrome, polycystic ovary syndrome and atypical depression, however few studies state a clear mechanistic basis for this assertion, so the research on the pharmacological effects of Cr supplementation must continue [18,19]. However, the role of Cr as an essential element is questioned in contrasting studies. DiBona K. et al. conducted a study on Zucker rats; four groups were fed chromium-free diets and then different amounts of Cr for 6 months. The results showed no significant differences between the effects of low-Cr and supplemented Cr diets effects on body composition, glucose metabolism or insulin sensitivity, so they discarded that Cr is an essential nutritional element [20].

3. Cr toxicokinetic

3.1. Absorption

Absorption of chromic compounds can be carried out by different routes, such as inhalation, oral and dermal. Orally, CrIII has a near zero (<1%) absorption, whereas CrVI is absorbed mainly in the duodenum, with the help of intestinal bacteria. Ingested CrVI is efficiently reduced to the CrIII by the gastric juices. When the absorption of not reduced Cr takes place, only 2–10 % of ingested chromium will be incorporated into the bloodstream through the portal vein system to reach the liver, which is able to reduce it [21].

Dermally, chromium at any oxidation state is quickly absorbed if there is damage to the skin or loss of continuity.

By the inhalation route, the uptake rate of CrVI is unknown, although this depends on the solubility of the chromium compound [22]. Also, absorption is dependent upon its oxidation state and particle size [23].

Particles smaller than 5 µm are absorbed by the blood or mucociliary clearance in the pharynx; the rest remain in the lung. The maximum absorption peak of hexavalent chromium is observed at 6 h, with a decrease at 72 h.

3.2. Distribution

CrVI is distributed practically in all tissues; it has been found in lymph nodes, spleen, heart, brain, aorta, pharynx, etc., however, greater distribution sites at 24 h after inhalational exposure are lung, erythrocytes, liver, kidney, spleen and plasma. Some studies show that 140 days after exposure, Chromium was removed completely from these organs except lung and spleen [8]. CrVI reach the fetus by fetal maternal route, crossing the placental barrier; it is also found in breast milk [24].

3.3. Metabolism

When CrVI is ingested, reduction of CrVI to CrIII by the gastrointestinal fluids [23], occurs as a physiological attempt to reduce cell mutagenicity, and this effect is accentuated when there is an increase in the gastric pH [25]. Intracellular reduction occurs both by enzymatic systems and non-enzymatic mechanisms.

- Enzymatic reduction includes microsomes, mitochondrial and cytosolic systems.
- Non-enzymatic reduction is carried out by electron donating mechanisms, such as "thiol" groups (E.g. glutathione) and ascorbate.

When it is inhaled, CrVI is reduced to CrIII in the lung mainly by ascorbate and when this compound is exhausted, reduction is achieved by glutathione. When there is little ascorbate, most of the CrVI is reduced to CrV; however, when adequate amounts are available, it is reduced mostly to CrIII. Another line of reduction is carried out by alveolar macrophages [21]. Once reduced to CrIII, it is eliminated as a Cr-glutathione in bile. The concentration of chromium that is transferred from lung to blood, is three times higher for CrVI than CrIII. [26], however, chromium can remain decades after ceased exposure

depending on concentration and this frequency [27].

3.4. Excretion

Excretion of absorbed chromium occurs primarily via urine. In humans, the kidney excretes about 60 % of an absorbed CrVI dose in the form of CrIII within 8 h of ingestion. Approximately 10 % of an absorbed dose is eliminated by biliary excretion, with smaller amounts excreted in hair, nails, milk, saliva and sweat. After inhalation of hexavalent chromium, certain amounts will be found in urine (up to 80 % is eliminated this way), and it will remain present for at least 3–4 days. In erythrocytes it is released slowly, and it can also be eliminated via the bile [28]. When exposure is oral, elimination will be mostly via bile and feces.

A study in rats found a 3.5–5% biliary elimination 24 h after an intravenous dose of different chromic compounds [29].

A. Aitio, J. Jarvisalo, M. Kiilune et al. [22], suggest a model where chromium half-life in humans is based on distribution and elimination rates within three separate compartments: the fast elimination compartment has a $t^{1/2} = 7$ h, the moderate elimination compartments has a $t^{1/2} = 15$ –30 days, and the slow elimination compartment shows a $t^{1/2} = 3$ –5 years, which is consistent with the previous report from S. Yamaguchi, N. Sano, K. Shimojo, in which they identified inside the liver an elimination kinetics of Cr with three components 2.4 h, 52.8 h y 15.7 days, respectively, which suggest an intra-hepatic tri-compartment distribution [30].

The same team of researchers reports a blood half-life of about 14 days after administration of CrVI [30]. Also Bragt and Vandura report different half-lives for pulmonary chromium clearance, these data suggest that chromium in the lungs is distributed in different compartments or in different valence or chemical states, which explains their different clearance rates [31].

4. Toxicity of Cr: its mechanisms

Chromium is capable of cell impairment, mostly in its hexavalent state. The mechanisms for cytotoxicity and carcinogenicity induced by CrVI is not yet fully understood, however, evidence suggests that transition metals act as catalysts in oxidative deterioration of biological molecules for which it is inferred that the damage is due to oxidative stress.

As previously mentioned, the tetrahedral structure of CrVI is similar to that of sulfates; this facilitates its passage through ion channels as well as sulfate and phosphate transport systems [32,33]. Once chromium enters the blood cells, is reduced into less stable or short-lived intermediates, which bind to intracellular proteins such as hemoglobin; the chromium-hemoglobin complex is very stable and remains within the cell throughout the life of the erythrocyte [34,35]. CrVI get reduced to CrIII, the most stable form among the possible oxidation states of Chromium, through formation of CrV and CrIV. Pentavalent chromium (CrV) is very unstable and highly reactive towards other molecules producing hydroxyl radicals and other ROS [36].

CrVI causes an increase in superoxide dismutase (SOD) enzyme activity, an enzyme involved in dismutation of oxygen radical, and a decrease in catalase (CAT) activity within the erythrocytes, raising the hydrogen peroxide (H_2O_2) production as consequence, which can react with CrVI and CrV to form a hydroxyl radical [37]. Some studies indicate that chromic compounds cause a decrease of reduced glutathione concentrations due to an increase of glutathione disulfide (GSSG), this latter species is a classic marker of oxidative stress in cells [38].

Likewise, it has been observed that Cr can alter antioxidant defenses, decreasing Thioredoxin reductase, an enzyme responsible for reducing thioredoxin, necessary for glutathione metabolism [39].

This ROS production, which predominantly generates hydroxyl ($\cdot OH$) and hydrogen peroxide (H_2O_2) [40], results in damage to cellular proteins, lipids and DNA, through molecular mechanisms such as base modification, single-strand breaks, double-strand breaks, Cr-DNA

adducts, DNA-Cr-DNA adducts, protein-Cr-DNA adducts, chromosomal aberrations, interference with DNA and RNA polymerase activity, mutagenesis, and gene expression alteration. [41–43]

Furthermore, $\cdot\text{OH}$ can react with guanine of the DNA, producing a guanine radical called C-8-hydroxy-adduct. The interaction of $\cdot\text{OH}$ with DNA bases results in double-stranded DNA damage [44]. This clearly leads to a state of oxidative stress; however, the reduction of CrVI will have fewer toxic effects if it is completed extracellularly in body fluids, such as gastric secretions [45]. A study by Donaldson, reports that after an infusion of CrVI in the duodenum or jejunum showed a greater excretion of Cr in urine, compared to oral administration [23,46]

5. Studies in exposed workers

To date, an association between exposure to chromic compounds and severe damage to health has been demonstrated; studies have shown that in workers exposed to Cr, their health was threatened, even with minimal exposure to environmental chromium (CrA) [47,48]. Occupational exposure involves various clinical problems, depending upon the contact route. The two main pathways in occupational exposure are dermal and inhalation.

6. Dermal route

Skin is the largest organ of the body and is considered to have some biotransformation capabilities, so dermal exposure to the Cr may lead to allergic skin reactions, ulcers, dermatitis, eczema, skin corrosion, etc. These problems are observed in industrial workers, mainly in metallurgical, fur and cement production [49]. While CrIII causes skin problems, it has been shown that CrVI is a greater skin sensitizer, even in small quantities than CrIII [50].

Acidity and ion oxidizing power, are considered the main epithelium irritants, responsible for different skin lesions observed [41]. Cr III, used in the production of cement and leather tanning, is chemically converted to CrVI, causing the aforementioned skin lesions. In the case of the wet concrete, since it has a high pH of 12.5–12.9, it may alter the *stratum corneum*, facilitating the penetration of water-soluble compounds, causing irritation and therefore allergic reactions [51].

Contact dermatitis with Cr is a delayed hypersensitivity cell mediated reaction (hypersensitivity type IV). The development of this dermatitis, has been reported to occur in four phases: [52]

- Phase I (refractory phase): No skin inflammation occurs, but the Cr hapten penetrates the skin and is conjugated to epidermal specific proteins.
- Phase II, (induction phase): the conjugate of the hapten interacts with T lymphocytes.
- Phase III, (induction phase): a secondary Cr exposure activates effector cells, releasing the cascade of mediators leading to skin inflammation.
- Phase IV (persistence phase): effector lymphocytes continue to recognize the Cr-hapten conjugate and cutaneous inflammatory reaction persists.

Skin allergies from exposure to chromic compounds in the industry inspired several studies worldwide, and since cement was detected as a major source of exposure dermatitis, these studies gave support to the issuance of a law in Denmark, Finland, Sweden and Germany promulgated in order to add ferrous sulfate (FeSO_4) to the cement. The FeSO_4 reduces the chromate completely and CrIII precipitates, thereby reducing the soluble chromate content in water to less than 2 ppm. After that legislation (1983) skin allergies related to cement decreased significantly according to studies from 1989 to 2007; however severe cases of allergic contact dermatitis due to chromates in cement are still observed relatively often [53–56].

Afterwards, through a cohort study in Denmark, it was found that the

main source of the chromate skin sensitization in workers exposed to CrVI, came from the fur industry. [57] Coincidentally, skin allergies related to the fur industry increased (1985–2007). Denmark's records show a Cr allergy total prevalence of 2.5 % being slightly higher in women than in men, and it was observed that chromic compounds cause more severe and chronic contact dermatitis than other major allergens in the contact dermatitis [58,59]. Finally, in May 2015, a law was implemented in the European Union (EU), in which the content of Cr VI above 3 ppm is prohibited in fur products. This shows the importance of studies to know the impact of regulations upon occupationally exposed population [60].

7. Inhalation

Inhalation of CrVI compounds causes the nasal septum perforation, bronchitis, asthma, pneumonitis, pharyngitis, liver problems and has been associated with bronchial cancer, unlike what occurs when exposure is dermally or even oral. The concentration of CrVI in air and exposure time have also been associated with the incidence and risk of cancer mortality [41,61,62]. The first reported case of cancer in a worker of the pigment industry was over 100 years ago, since then, numerous studies on the electroplating industry and pigments among others, have shown that activities in these industries carry an increase in the occurrence of cases of lung cancer, including those workers who are non-smokers [63,61,64]. Contrastingly, some studies support the exclusion of nasal and paranasal cancer caused by CrVI because there is insufficient evidence to support the development of these cancers by exposure to chromic compounds [65].

In Mexico studies on health effects in occupationally exposed workers have also been conducted. In one of these studies it was reported that of 140 workers and 19 employees in administrative areas, 46.4 % had incomplete perforation of the nasal septum. This percentage included 3 employees who had no direct contact with CrVI. Cases of nasal carcinomas were ruled out [66]. However, some argue that because of the low incidence of sinonasal carcinoma, and occupational exposure to Cr is rare, there could be an underestimation of the relationship existing between these factors. Therefore, any information regarding sinonasal cancer in workers of the chrome plating industry could help add evidence to a possible causal relationship between Cr and sinonasal malignancies [67].

Although is infrequent, occupational asthma is a reported ailment in subjects exposed to the smoke released in stainless steel smelters [68], even when inhaled Cr level is at the minimum level of risk it is $0.02\mu\text{g}/\text{m}^3$. There have been several reported cases of occupational asthma, as a first affliction during exposure to a recognized etiologic agent in the workplace, among other criteria. This condition has been observed in staff working in the leather industry, electroplating, chroming, cements, and welding among others [69] [70].

Some cases report a latency of 12–36 months after initial exposure to the development of asthma and point out that in certain cases, specific IgE antibodies against metal salts conjugates of Cr and cobalt can be the underlying cause of the reaction. However, the presence of these antibodies does not indicate itself a symptomatic response to said allergen [71,72]. There are reports on induced occupational asthma by Cr and platinum (Pt) where the amount of IgE antibodies is related inversely with the number of exposures to chromic salts (potassium dichromate) unlike that reported for platinum salts, (hexachloroplatinate sodium) having a direct relationship in murine models and the authors note that a different immune response for each salt may rely on the IL-4 intracellular and its receptor as the key for discriminating the immune response induced Pt of that induced by the Cr salt. [73]. Other studies suggest that inhalation of particles of CrVI induces an innate neutrophilic inflammatory response in murine models (BALB/c mice), and wherein said inhalation may increase the severity of the course of allergic asthma, as well as altering their phenotype [74].

In the United States, medical follow-ups of the military personnel

exposed to CrVI after being deployed into an industrial water treatment facility in Iraq. Those follow-ups are part of a Post-Deployment Health Assessment (PDHA) and include medical evaluation and biological monitoring. Although the researchers performed those tests, the main objective of the study was to assess risk communication after a known exposure to a toxic industrial chemical. They found that there were significant limitations in the ability of the PDHA to capture occupational and environmental exposures. This indirectly highlights the essential need of relying on the results of the biological monitoring, as an objective measure of occupational exposure. In this particular case, an association between the variables examined (age, cumulative time at the exposure site, smoking, sick call visits in theater, symptoms of dyspnea in theater, abnormal pulmonary function test results, and serum chromium level) with reporting of chromium exposure on the PDHA showed a lack of statistical significance. The researchers conclude that continuous examination and evaluation of the pre-deployment health assessment and PDHA should also be done, in order to capture relevant data to protect soldiers' health and to perform meaningful surveillance [75].

8. Regulations on occupational environmental exposure to CrVI

Given the evidence of the damage caused by the metal and its compounds, various agencies globally have stipulated limit values to regulate occupational environmental exposure to CrVI. The American Conference of Governmental Industrial Hygienists (ACGIH), stipulates the "Threshold Limit Value-Time Weighted Average" (TLV-TWA), the TLV refers to the concentrations in air of various chemical substances, and represents the conditions under which it is estimated that most workers can be repeatedly exposed to these substances, day after day, during a working life, without showing any adverse effect due to exposure. On the other hand, the TWA refers to an average of a worker's daily exposure to a hazardous substance or agent, calculated to an 8-h workday or 40 h a week. The TWA is expressed in units of parts per million (ppm) or mg/m³ [76].

For Cr, the TLV-TWA for Cr used to be 0.05 mg/m³ and 0.01 mg/m³ for soluble and insoluble compounds of CrVI, respectively (ACGIH, 2013), but recently this Agency adopted the proposed changes to the TLVs, and a new TLV of 0.0002 mg/m³ for inhalable hexavalent chromium compounds [Cr(VI)], as well as a Short-Term Exposure Limit (STEL) of 0.0005 mg/m³, inhalable hexavalent chromium compounds, has been established [77].

Similar to the TLV that has been adopted by the ACGIH, other organisms use occupational exposure limits whose names have some variations. The Occupational Safety and Health Administration (OSHA) established a Permissible Exposure Limit (PEL) of 0.005 mg / m³, while the National Institute for Occupational Safety and Health (NIOSH) sets a Recommended Exposure Limit (REL) of 0.0002 mg/m³, although that proposed by NIOSH is suggested but not binding. (Table 1)

In China, the Occupational Exposure Limits (OELs) for hazardous chemicals in the workplace, are stipulated by the Guobiao standards, the China National Standards (GBZ), 2.1–2007, and implemented from Nov 2007. The OEL stipulated for chromium in air (CrA) is 50 µg / m³. In the UK, the Health and Safety Executive (HSE), uses the term "exposure limit in the workplace" (WEL), which, for compounds of CrVI, is worth Cr 0.05 mg/m³ (HSE, 2018). In Europe, the Scientific Committee on Occupational Exposure Limits (SCOEL) created in 1995, as well as the German Research Council (DFG), Foundation have classified the compounds of CrVI as carcinogens category 1 (whose carcinogenicity cannot be excluded), so no recommended limit value is given for specific occupational exposure. However, some countries within and outside the European Union have set these limits [78–80] (Table 1).

9. Identification and quantification of chromium in biological samples

Since CrVI is a cytotoxic and carcinogenic agent, it is necessary to

Table 1

Occupational Exposure Limits (Air concentration of a hazardous substance) [78].

Country	Occupational Exposure Limit	CrVI mg/m ³ 8-h Time Weighted Average (TWA)
Germany	Tolerance Value	0.001
Australia	–	0.05
Austria	Tagesmittelwert/Kurzzeitwert (TMW/KZW)	0.1 (soluble) 0.05 (others)
Canada	Time Weighted Average Exposure Value. (TWAEV)	0.05 0.01
China (GBZ) [95]	Occupational Exposure Limitation (OEL)	0.05
South Korea	–	0.05 (soluble) 0.01 (insoluble)
Denmark	–	0.005
Spain	Environmental Limit Values (VLA)	0.05 (soluble) 0.01 (insoluble)
U.S. (ACGIH)	Threshold Limit Value (TLV)	0.0002
U.S. (OSHA)	Permissible Exposure Limit (PEL)	0.005
U.S. (NIOSH)	Recommended Exposure Limit (REL)	0.0002
Finland	–	0.005
France	Valeur Moyenne d'Exposition (VME, VLE)	0.001
Netherlands	–	0.05 (others) 0.01 (soluble)
Ireland	–	0.05 (soluble) 0.01 (insoluble)
Japan	–	0.05
New Zealand	–	0.05
Sweden	Level limit value/ Short term exposure (LLV, STV)	0.005
Singapur	–	0.05 (soluble) 0.01 (insoluble)
Switzerland	MAK (Maximale Arbeitsplatz Konzentration)	0.05
UK (HSE) [97]	Workplace Exposure Limit (WEL)	0.05

find out the level of exposure that workers of different industries have to this metal. The identification and quantification of Cr VI in biological samples has been proposed as option to monitor levels of exposure.

Several authors propose the use of biological samples such as hair, blood, serum, urine and saliva, some studies have also been conducted in joint fluid and tissues [81,82].

Each of these samples provides different but equally valuable information. For example, in hair samples, the metallic cations form disulfide bonds with the keratin of the hair matrix [83,84] and since hair grows about 10 mm per month, it may reflect past and recent exposure. However, this sample has the disadvantage of being easily contaminated if it's not handled with proper care [85]. Biomonitoring in urine samples is widely used worldwide since the sampling method is noninvasive and relatively easy to obtain. However, the disadvantage of this sample is that it will mainly indicate the value of CrIII but CrVI will not be measurable.

There are different techniques for quantifying Cr, and depending on the purpose of the study, it may be useful to implement speciation techniques. Speciation in biological samples can be divided into three categories: speciation of solid, Off-Line determination (pre-treated samples), and on-line determination (combination of different analytical techniques using an interface) [86]. Some of the techniques used are atomic absorption spectrometry (AAS) with variable flame (FAAS), electrothermal atomic absorption spectrometry (ET-AAS) and inductively coupled plasma mass spectrometry (ICP-MS). AAS technique is not able to reveal the speciation of the chromium present in the sample, the analysis of Cr concentration by AAS results in a total Cr value; in contrast, ICP-MS can be used to determine the oxidation state of an element. The importance of the speciation of the CrIII and CrVI in biological samples is that it helps explain differences in the kinetics, and stability interconversions [87].

Biological samples are considered complex matrices, consequently in order to analyze Cr speciation the urine or saliva are the preferred samples. However, results of saliva analysis could be affected by variables such as the use of dentures, diet or smoking habit. [87,86]

For several decades there has been interest in measuring CrVI in biological samples. This interest stems from the knowledge of its cytotoxicity and genotoxicity, attributed to the oxidizing power of the CrVI. Researchers found that reactivity of CrVI increased inside the cell, which is a highly reducing environment. [88]

9.1. Regulations in biological samples (biomonitoring)

In order to establish reference levels for environmental contaminants, samples are taken in places that are considered to have good control of exposure to the substances of interest. The values found for each searched substance on that environment in 9/10 samples will be taken as the reference value [89]. However, this value only indicates how well exposure is being controlled, but it is not an indicator of personal exposure for workers. Moreover, sometimes it could not be appropriate to specify a reference value, for example in the carcinogenic compounds because these are considered to have no threshold dose.

As said, the reference values for CrA do not provide a complete picture of workers' exposure. To carry out monitoring of exposure for them, biological samples such as urine or blood, among others must be evaluated. Different from the permitted levels of CrA which are well stipulated, data related to the determination of Cr in biological samples is not yet fully clarified. Nevertheless this analysis reflects the actual occupational exposure and can be useful to perform biomonitoring for both exposure and the reduction in levels after possible treatments [90]. The following table presents the values set by some countries regarding urine samples. (Table 2)

Since 1977, several studies have attempted to obtain accurate biomonitoring of Cr. In that year, Gylseth evaluated the Cr exposure by determining urinary Cr (CrU). This study was conducted on a sample of welding workers and found a very strong correlation ($r = 0.95$) between CrA and subsequent CrU after the workday, so they suggested measuring CrU as an indicator of exposure to evaluate it in detail. In 1984, Aitio and Cols, reported that in the leather industry, two workers highly exposed to CrIII sulfate presented high levels of CrU at the end of the workday and even after a holiday period. Similarly, levels were elevated in plasma, attributing this to the inability of CrIII to cross cell membranes. Nevertheless, some studies showed that some chemical products containing CrIII for leather tanning, also had CrVI [91–93].

In 2017, Beattie et al. proposed the use of serial measurements of Cr in biological samples in order to have better control of occupational exposure in workers in the electroplating industry. The measurements

were carried out for 3 years and during this time they gave feedback to workers with their tests results and were encouraged to take actions to decrease exposure. They found satisfactory results regarding levels of CrU. This study also emphasizes the importance of ongoing biomonitoring [2,94]. The following table presents the values set by some countries regarding urine samples. (Table 2)

F. Gil, A.F. Hernández et al., conducted a study on occupationally exposed population to quantify levels of heavy metals in biological samples and correlating the results. The metals tested were cadmium, chromium, manganese, nickel and lead. The samples were whole blood, urine, axillary hair and saliva. They found a lack of correlation between the levels obtained in hair and saliva and those found in blood and urine, probably due to differences in toxicokinetic of these metals. For the amount of Cr, a correlation between urine and the blood levels was observed, intending the latter as a test of the usefulness of blood in biomonitoring exposure [2].

CrVI has a relatively small size, so it might get through erythrocyte membranes by means of voltage-dependent ion channels (sulfate anion channels) [33,87], whereas CrIII is larger, and therefore cannot. Considering this premise, J. Devoy and his group in 2016 developed a study to see if Cr found in the erythrocytes of blood samples was exclusively CrVI. In this study blood samples were spiked with CrIII and CrVI, the results showed that CrIII was undetectable, unlike those containing CrVI, which showed dependent concentration levels of Cr added. Also, they report that the speciation of the CrVI seems not to influence accumulation in erythrocytes. From these results they suggest to extend the study to determine the feasibility of proposing erythrocyte fraction as an indicator of exposure to CrVI [90].

Although the importance of biomonitoring has been demonstrated, and the values of Cr in blood have been confirmed as a biomarker of occupational exposure, there is no specific regulating levels of CrVI in blood (CrB) to date. However, in a study conducted in China in 2015, Ping Li and Cols. analyzed the relationship between the concentration of CrA and the concentration of CrB. As previously mentioned, the occupational exposure limit (OEL) of CrA in China it is $50\mu\text{g} / \text{m}^3$, so measurements of Cr in a factory environment were made and when this was at the OEL, they took blood samples and found that the value of CrB was approximately $20\mu\text{g}/\text{L}$. Both values showed a positive correlation between them, unlike the CrB levels found in general population. This value of CrB ($20\mu\text{g}/\text{L}$) was proposed as a reference value in population occupationally exposed. Germany recently adopted a biological index value for alkali chromates (CrVI) in total blood, emphasizing there is nonspecific limit value for a carcinogenic substance; this value is called "Exposure equivalents for carcinogenic substances" (EKA) and it is consider to be $9\text{--}35\mu\text{g}/\text{l}$ whole blood when CrO_3 in air is $0.03\text{--}0.10\text{mg}/\text{m}^3$, respectively [95,96] (Table 3).

10. Conclusions

Although chromium has a nutritional role whose importance even is being discussed, it is well known that CrVI has harmful effects on health, associated with the exhibition, by different routes of exposure such as oral, dermal, inhalation or ingestion of compounds containing this metal.

Although the open population may be exposed to various sources of chromium contamination, the personnel working in industries such as electroplating, fur, metallurgy, chromate pigments, cement, weapons

Table 2
Limit values for Chromium in urine (UCr).

Organism	Value Type	Chromium (VI)
Great Britain (GB) [98]	Biological Monitoring Guidance Value (BMGV)	$10\mu\text{mol} / \text{mol creat}$
European Commission Scientific Committee on Occupational Exposure Limits (SCOEL) [78]	Guidance Biological Value (BGV)	None
ACGIH [77]	Biological Exposure Index (BEI)	$40\mu\text{mol} / \text{mol creat.}$ ($25\mu\text{g} / \text{g}$)
Germany (DFG) [96]	Exposure equivalents for carcinogenic substances (EKA)	$40\mu\text{g} / \text{L}$
Spain [99]	Biological limit values (VLB)	$25\mu\text{g} / \text{L}$ at the end of the working week.
Mexico [100]	Biological Exposure Index (EWI)	$25\mu\text{g} / \text{L}$ (approx. $40\mu\text{mol} / \text{mol}$)

(Beattie, 2017).

Table 3
Value for biological monitoring in blood.

Country	Value Type	CrB recommended level
China and India [95]	Occupational Exposure Limits (OEL)	$20\mu\text{g} / \text{l}$ with CrA $50\mu\text{g} / \text{m}^3$
Germany [96]	Exposure equivalents for carcinogenic substances (EKA)	$9\text{--}35\mu\text{g} / \text{l}$ with $0.03\text{--}0.10\text{mg}/\text{m}^3\text{CrO}_3$

and ammunition, etc., has a higher risk due to increased exposure to the metal. These facts emphasize the importance of knowing the amount of chromium present not only in the environment, but in every individual. To date, monitoring is performed primarily in urine samples, with the disadvantage that the result obtained will reflect mainly that CrVI has been reduced to CrIII, so that there may be a discrepancy in relation to levels serum. Also, there is no international consensus concerning limit values of CrVI in the environment, neither for values in urine, which all show significant variation according to sources consulted.

As for the blood samples, there is only one suggested value, but more studies are required to officially establish it.

Pawning efforts will continue to obtain values of CrVI in biological samples that indicate the actual exposure, with the aim of control the level of exposure and guarantee the occupational health of the workers in military industry and also of the general population. In addition to providing and strengthening informative conferences for workers about safety measures they should take into account when carrying out their tasks.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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