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REFLECTION

Approach to the problem of heavy metal poisoning: effects and analysis methods

Abordaje de la problemática de intoxicación por metales pesados: efectos y métodos de análisis

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Abstract

Toxic metals, also known as heavy metals, are environmental pollutants and a risk factor for human health worldwide. Therefore, it is necessary to look into the effects of the exposure to these metals, as well as into the proper analytical chemistry methods for their detection in different biological samples.

Based on the above, the objective of this reflection paper is to describe some of the possible health harms related to the presence of some toxic metals such as lead, mercury, and cadmium in humans following their exposure to contaminated environments, and to raise awareness on the importance of using appropriate analytical chemistry methods for their detection and adequately choosing the analysis sample.

Bearing this in mind, a systematic search of information was conducted in Pubmed, Scopus, ScienceDirect and Scielo by means of the following search equations: "poisoning" AND "metals AND analytical chemistry methods", "Body fluids" AND "Toxic metals", "Toxicology" AND "Heavy metals" e "inequality" AND "toxic metals". It was found that there are several analysis methods for detecting toxic metals in humans, mainly atomic absorption spectroscopy, and that their results depend on the appropriate selection of the sample according to the type of exposure. In addition, emphasis was placed on the relationship between the presence of metals in biological fluids and different social factors such as poverty and labor informality, among others, since they can increase exposure to heavy metals and the resulting deterioration of health.

Resumen

Los metales tóxicos, también llamados metales pesados, son sustancias contaminantes del medio ambiente y representan un factor de riesgo para la salud humana a nivel mundial, por lo que es necesario indagar sobre los efectos de la exposición a estos, así como sobre las técnicas de química analítica para su detección en diversas muestras biológicas.

Teniendo en cuenta lo anterior, los objetivos de esta reflexión fueron describir algunas de las afectaciones en la salud relacionadas con la presencia de metales tóxicos como plomo, mercurio y cadmio en el ser humano tras la exposición a ambientes contaminados, y dar a conocer la importancia de usar técnicas de química analítica apropiadas para su detección y de seleccionar adecuadamente la muestra de análisis.

Con este propósito en mente, se realizó una búsqueda sistemática de información en Pubmed, Scopus, ScienceDirect y Scielo utilizando las siguientes ecuaciones de búsqueda: "poisoning" AND "metals", "Body fluids" AND "Toxic metals", "Toxicology" AND "Heavy metals" e "inequality" AND "toxic metals". Se encontró que existen varios métodos de análisis para la detección de metales tóxicos en humanos, principalmente la espectroscopía de absorción atómica, y que sus resultados dependen de la adecuada selección de la muestra de acuerdo con el tipo de exposición. Además, enfatizamos la relación entre la presencia de metales en fluidos biológicos y distintos factores sociales como la pobreza, la informalidad laboral, entre otros, ya que estos pueden aumentar la exposición a metales pesados y el consecuente deterioro de la salud.

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Introduction

Toxic metals, also known as heavy metals, are naturally occurring compounds that are persistent in the environment, non-degradable, and hazardous to human health due to exposure at high concentrations and accumulation over short or long periods of time.[1] In general, unregulated human activities, such as mining and industrial production, among others, have increased the release of toxic metals into the environment, resulting in environmental and public health problems.[2,3]

In fact, the process of industrialization, urbanization and economic growth in recent decades has resulted in the regular release of different compounds, chemical elements and metals, including chromium (Cr), lead (Pb), arsenic (As), copper (Cu), cadmium(Cd), nickel (Ni), among others.[4] These metals are extensively used in various industrial sectors such as electroplating for corrosion resistance, tanning and finishing of leather, in pigments and wood preservatives, battery manufacturing, production of devices for protection against X-rays, among others.[5,6] The widespread use of these elements generates large quantities of waste that are deposited in ecosystems and, since they are not biodegradable, they bioaccumulate in various natural resources over a period of time.[5]

For example, water sources are contaminated by the discharge of wastewater, increasing the concentration of metals in the water and increasing the risks of exposure for various living organisms.[6] When metals enter the aquatic ecosystem, through biogeochemical processes, they are transformed and absorbed by plants, thus entering the food chain and converting the intake of contaminated food and water into one of the main causes of metal poisoning.[7]

It should be noted that multiple metals are considered toxic, the most well-known being mercury (Hg), Pb, Cd, iron (Fe), cobalt (Co), and manganese (Mn).[2] Despite the availability of analytical techniques for the identification and quantification of most toxic metals, the detection and determination of trace concentrations remains a major problem in some parts of the world due to the complexity of their presence in biological samples or matrices.[8,9]

Based on the foregoing, the objectives of this reflection paper are to describe some of the possible health harms related to the presence of heavy metals such as Pb, Hg, and Cd in humans following their exposure to contaminated environments, and to raise awareness on the importance of using appropriate analytical chemistry methods for their detection and adequately choosing the analysis sample (e.g., hair and body fluids).

What are heavy metals?

Industrial and anthropogenic activities have increased human exposure to heavy metals, also known as "toxic metals" in accordance with International Union of Pure and Applied Chemistry (IUPAC),[10] such as Hg, Pb, Cd, As, Cr, among others, primarily due to waste discharged into water sources and ecosystems.[11] Toxic metals frequently react with biological systems when they lose one or more electrons, leading them to form metal cations with affinity to nucleophilic sites of vital macromolecules.[12]

Impact of toxic metals on health

As a result of bioaccumulation in tissues and organs, toxic metals can cause harmful effects.[12] Thus, dysfunctions of the gastrointestinal, renal, or immune systems, as well as nervous system disorders, vascular damage, birth defects, and even cancer may occur. Also, due to the disruption of cellular events such as growth, proliferation, differentiation, damage repair processes, apoptosis, and the production of genomic instability and defects in DNA repair, toxic metal exposure has been thought to be a cause of carcinogenicity. It is worth noting that multiple exposures can have an accumulative effect.[12]

According to Mendiola *et al.*,[13] when heavy metals accumulate in the human body, they can affect male reproductive health, even at relatively low levels of exposure (whether in human, animal, or even in vitro tests). Possible effects may include the disruption of the hypothalamic-pituitary axis or spermatogenesis impairment, resulting in low sperm counts.[13]

Likewise, regarding metals like Hg, Pb and Cd, it is possible that being exposed to such elements may lead to fetal death, birth defects, small-for-gestational-age and premature births, neurological and cognitive impairment, cancer in infants, asthma, and other respiratory diseases.[2,14] On this point, it is important to note that, while placenta serves as a protective barrier for the fetus, it does not provide complete protection against toxic metals such as Pb, Cd, and Hg.[2,14] Remarkably, deficiencies in essential minerals can lead to increased absorption of toxic metals. For example, children with low calcium (Ca), Fe, and zinc (Zn) levels have higher levels of lead in blood, while children with low Fe levels and Fe deficiency anemia have elevated Cu levels in blood.[15]

While heavy metal blood levels are mostly associated with exposure to contaminated environments, the consumption of contaminated food also contributes to this issue. In general, according to the World Health Organization (WHO), the acceptable weekly intake of heavy metals such as Hg, Pb, and Cd in food is 0.0016, 0.025, and 0.015mg/kg body weight, respectively.[16]

How does metal poisoning occur?

Exposure to heavy metals is a common occurrence throughout a person's lifetime due to various human activities, the consumption of contaminated foods, and environmental pollution. No metal is found in isolation; for example, if there is Cd contamination, it is likely to encounter Zn and Pb contamination as well.

Cd and Pb bioaccumulate in human tissues. Cd has a half-life of approximately 17 to 30 years,[17] while Pb has a half-life of 20-30 years.[18] Both of them are rapidly absorbed in the intestine, the lungs and, to a lesser extent, the skin. They bind to albumin by 90%, are distributed to the liver and kidney, and are eliminated through urine, which is the best biomarker for environmental exposure.[17,19]

Regarding Hg, like most metals, it is found in the Earth's crust and is available in three forms: elemental mercury; organic mercury like methylmercury (the most toxic) and ethylmercury; and inorganic mercury, i.e. mercuric mercury. Human beings can be exposed to Hg in many ways, namely, mining, contaminated food, dental amalgams, and when handling products that contain Hg such as lamps or batteries.[19]

In turn, Cd binds to low molecular weight proteins, generating complexes called metallothioneins (Cd-MT) by inducing the synthesis of metallothionein mRNA. These Cd-MT complexes produce reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2), superoxide (O_2^-), hydroxyl radicals (OH^-) and nitric oxide (NO^-), which reduce the levels of the main antioxidant compounds in cells, resulting in cell death and disease.[17]

Each metal and its toxicological characteristics are described below:

Mercury (Hg)

Hg is a dense metal found in water sources, soil, and air in three forms: metallic Hg (Hg^0), inorganic Hg (Hg^{1+}, Hg^{2+}), or organic Hg (methyl or ethyl mercury; MeHg or EtHg), the latter being the most toxic group.[20]

About 80% of metallic Hg vapor is rapidly absorbed by the lungs and distributed throughout the body.[20] It can also cross the blood-brain barrier and the placenta, so its neurotoxicity is greater than that of inorganic Hg, which crosses membranes at a slower rate. Metallic Hg is oxidized in the body to generate the ion (Hg^{+2}).[20] Furthermore, metallic Hg in its liquid form (such as that found in some thermometers)[21] does not appear to be toxic even though it is absorbed by the gastrointestinal tract.[12]

On the other hand, inorganic Hg concentrates in the kidneys and is reabsorbed in the proximal tubules as Cys-S-Hg-S-Cys, or in the basolateral membrane by organic anion transporters. This form of Hg cannot cross the placenta or the blood-brain barrier.[12]

With respect to organic Hg, 95% of it is readily absorbed by the gastrointestinal tract and dispersed throughout the body. In this case, MeHg binds to thiol-containing molecules, such as cysteine. It can cross the blood-brain barrier by forming structures like MeHg-cysteine (methyl-mercury-cysteine).[12,20]

Concerning toxicokinetics, inorganic Hg behaves differently from other Hg forms, since it is estimated that 7 to 15% is absorbed by the gastrointestinal tract after an oral dose. Ingested ionic Hg is rapidly distributed to the blood and organs, while most of it is eliminated through urine and smaller amounts through saliva, bile, sweat, and breast milk.

The elimination half-life of metallic and mercuric Hg may range from a few days to several months, and this can be attributed to the organ of deposition and the redox state. In general, the best test sample to measure chronic exposure to methylmercury is hair.[22]

As for exposure, the WHO has established 5µg/kg total Hg and 3.3µg/kg in the form of MeHg as the limits allowed for weekly consumption through contaminated sources.[6]

Lead (Pb)

Pb is a highly toxic environmental pollutant that affects several human organs.[12] Pb poisoning occurs mainly through the ingestion of contaminated water or food, or by consuming paint pieces that have detached from walls and surfaces.[3] It rapidly enters the bloodstream and seems to impact multiple systems and organs, such as the neurological, cardiovascular, immunological, and kidney systems.[23]

Consequently, it may cause, for example, anemia by inhibiting ferrochelatase and δ-aminolevulinic acid dehydratase (ALAD), enzymes involved in heme synthesis.[12] Similarly, since Pb has a high affinity for the -SH group of glutathione, it degrades it, lowering its levels.[12] Moreover, it is considered a reproductive toxin and an endocrine disruptor.[13]

Regarding exposure, OSHA has established a regulation of 0.5mg/m³ of organic, inorganic and elemental Pb, and 0.075mg/m³ of tetraethyl Pb and tetramethyl Pb in an 8-hour workday for the general industry. In shipyards and construction sites with a usual working day, levels of exposure cannot exceed 0.1mg/m³ of tetraethyl Pb, 0.15mg/m³ of tetramethyl Pb, and 50µg/m³ of Pb in its elemental, organic, and inorganic forms.

Finally, in the industrial and construction sector, the maximum limit is 30µg/m³, and medical removal protection is necessary at levels above 60µg/m³ (temporary elimination of the level of Pb in the blood). Additionally, the National Institute for Occupational

Safety and Health (NIOSH) recommends an exposure limit for Pb and its compounds of 0.05mg/m³ and tetraethyl Pb of 0.075mg/cm³. It also states that 100mg/m³ of Pb and 40mg/m³ of tetraethyl Pb are dangerous for life and health.[6]

Cadmium (Cd)

Once in the body, this metal binds to albumin and erythrocytes in the blood and is subsequently transferred to tissues and organs where it binds to cysteine-rich low molecular weight proteins, also known as metallothioneins (MT), which produce Cd-MT complexes that contain a metal-sulfide coordination cluster site formed by metal ions with a (d^{10}) configuration.[12] The high cysteine content of metallothioneins explains the ability of metal ions to form metal-thiolate complexes through their sulfhydryl groups.[12]

It is worth noting that Cd-MT complexes produce reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2), superoxide (O_2^-), hydroxyl radical, nitroxide anion (NO^-), and also reduce the level of the main antioxidant compounds in the cells by inactivating enzymes and other molecules. As a result, lipid peroxidation (LPO) is generated, and cell death occurs.[17]

Similarly, the Cd-MT complex can be absorbed by the renal tubules, causing damage to the kidneys and appearing in biological fluids such as urine. Thus, the concentration of metallothionein in urine can serve as an indicator of the concentration of Cd in urine, allowing the determination of body burden.[24]

Regarding environmental exposure to Cd, the WHO has established a limit of 5ng/m³ of Cd to guarantee air quality, and the Occupational Safety and Health Administration (OSHA) established 5ug/m³ as the safety limit in the workplace. Concerning water intake, the WHO and some drinking water quality guidelines have determined that the maximum concentration of Cd should be 0.003mg/L, while the Food and Drug Administration (FDA) states that it should be 0.005mg/L in bottled water.[6]

How can toxic metals be measured in biological samples such as hair and body fluids?

There are several methods available for detecting and quantifying toxic metals in biological samples such as hair and body fluids, including atomic absorption spectrophotometry (AAS), inductively coupled plasma (ICP), amalgamation (DMA-1 o DMA-80), and neutron activation analysis (NAA).[25] One of the most common techniques for quantifying Pb is based on the measurement of total Pb in blood samples using atomic absorption spectrophotometry, which, despite exposing the amount of Pb circulating in the blood, does not provide information about the accumulation of this metal in the body.[25]

To determine Pb, Cd, and Hg levels, Mendiola *et al.,*[13] analyzed 181 biological samples, including seminal plasma, blood plasma, and whole blood. Anodic stripping voltammetry (ASV) was used to measure Pb and Cd, while thermal decomposition, amalgamation, and atomic absorption spectrophotometry were employed to analyze Hg levels in the samples.[13]

Some authors have also studied non-conventional matrices, such as meconium from newborns, for the identification and quantification of Pb and Cd.[2] Other researchers, such as Silver *et al.,*[26] have used umbilical cord blood for these analyses.

On the other hand, the presence of Cd in urine shows body burden, particularly the concentration in the organ where it accumulates, the kidney, and can thus be used as an indicator of accumulation following long-term exposure to this metal.[27] Since renal function remains normal, Cd concentration in urine is well correlated with Cd body burden. When Cd-induced irreversible renal tubular dysfunction with microproteinuria occurs, Cd excretion in urine increases due to its release from renal depots.[27]

Which are the most common analytical chemistry methods used to detect and quantify toxic metals in biologic samples?

Different analytical methods are used to detect and quantify toxic metals in biologic samples such as body fluids and hair. Table 1 lists some of the most common analytical chemistry methods. It should be noted that the metal detected is not the only metal that each technique can identify. Although there are multiple techniques available for analyzing toxic metals concentrations in biological samples, due to the cost-benefit ratio, the most widely technique used in Colombia for Pb and Cd analysis in whole blood is graphite furnace atomic absorption spectroscopy; as for Hg, the most frequently methods used in the country are graphite furnace atomic absorption spectroscopy and direct measurement by amalgamation.

Table 1. Analytical chemistry techniques used for heavy metals determination.

Analytical technique	Metal detected	Matrix/ Biological sample analyzed
Anodic stripping voltammetry (ASV)[28]	Lead	Seminal plasma, blood plasma, and whole blood
	Cadmium	
Differential pulse anodic stripping voltammetry (DPASV)[27]	Cadmium	Human urine and hair
Potentiometric stripping analysis (PSA)[27]	Cadmium	Whole blood and urine
Thermal decomposition[29, 30]	Mercury	Seminal plasma, blood plasma, and whole blood
Amalgamation[31]		
Graphite furnace atomic absorption spectrometry (GF-AAS)[32]	Mercury	Seminal plasma, blood plasma, and whole blood
	Lead (flame atomic absorption)[33] Lead in blood[33]	Whole blood, umbilical cord blood, and meconium from newborns
	Cadmium (flame atomic absorption)[33]	Human blood, urine, hair, saliva, and breast milk
Inductively coupled plasma mass spectrometry (ICP-MS)[27,32]	Lead, cadmium, and mercury[34]	Blood and urine
Neutron activation analysis (NAA)[27]	Cadmium	Human kidneys (*in vivo* or *in vitro*)
X-ray fluorescence (XRF)[27]	Cadmium	Human kidneys (*in vivo*)

It could be said that the increased use of toxic metals in industrial processes has resulted in a surge in waste production, which, if improperly disposed of, causes environmental contamination, particularly of soil, air, and water.[8] In light of the foregoing, it should be noted that socioeconomic disparities in certain populations make some of them less protected against toxic metal exposure and have greater contact with contaminated areas and even consume water from contaminated sources.[35]

For instance, Zeng *et al.*[33] reported the presence of cough, phlegm, dyspnea, and wheezing in children in the Guiyu region of China, which were associated with exposure to e-waste containing Pb and Cd in their residential areas. This has resulted in deficiencies of essential elements that have been associated with higher concentrations of toxic metals in the human body after being exposed to them. For example, children with low blood levels of Ca, Fe, and Zn are at greater risk of having high levels of Pb in the blood matrix. Similarly, low levels of Fe not only cause anemia, but are also related to high levels of Cu, Cd, and Pb levels in blood.[26]

It should also be noted that exposure to these toxic elements has adverse effects not only on the renal, cardiovascular, and gastrointestinal health of adults, but also on the development of infants and even embryos, as certain metals, such as Hg, have the capacity of crossing the placental barrier, as mentioned above.[12]

What does the national scenario look like and what are the factors influencing toxic metal poisoning in Colombia?

In Colombia, there are numerous determinants of inequality, particularly those associated with socioeconomic status, which influence the quality of life of individuals.[36] Each of these determinants, among others, poverty, access to public services, education, economic factors, food consumption, and diet quality, is conducive to the development of diseases associated with exposure to toxic metals.[36] There are also social determinants in our country such as lack of health care, rising food prices, armed conflict and forced displacement, poor environmental sanitation, and others that end up impacting nutritional disorders,[36] thus making individuals more exposed to toxic metals and, consequently, to a greater likelihood of their accumulation in their bodies.

It has been reported that people living in poverty are more susceptible to heavy metal poisoning and in Colombia, vulnerable individuals are more prone to suffer from it. For example, poor women of reproductive age have an increased risk of exposure to environments contaminated with these metals, which in turns exposes their children to those metals at prenatal stages and during breastfeeding; children in those families are at higher risk of being exposed to toxic metal agents present in soil, air, water, and food.[37] Furthermore, a correlation has been established between high levels of Pb in the blood of Afro-Colombian children and their socio-economic level, which is usually low, so it is clear that the poorest families are susceptible to experiencing adverse situations related to food security.[38]

It is also known that inequality exposes —directly and indirectly— vulnerable individuals to toxic metals, seriously affecting their health in the short or long term.[39] Activities such as illegal mining, living in areas where hazardous waste is dumped, state neglect, and other activities are evident on a daily basis throughout the Colombian territory, negatively impacting especially areas far from large cities and receiving little attention.

Regarding the detection and quantification of the main toxic metals, the *Instituto Nacional de Salud* (Colombian National Health Institute) developed a protocol included in the *Manual de Referencia para la Vigilancia de las Intoxicaciones por Sustancias Químicas* (Reference Manual for the Surveillance of Poisoning by Chemical Substances), which identifies Hg, Pb, Cd, and Cr as the metals most associated with poisoning.[40] The manual describes the use of body fluids, like blood, to assess recent exposure to toxic metals, and urine, hair, and nails to evaluate chronic exposure.[40] Similarly, although conditions for collection, preservation, and storage of each biological sample for the analysis of heavy metals differ, techniques such as atomic absorption spectrophotometry, graphite furnace, and amalgamation are the most frequently used.[40]

Overall, the detection and quantification of toxic metals in the human body is important to treat metal poisoning, avoid misdiagnosis when symptoms of metal poisoning could be attributed to other conditions, identify areas with higher exposure to metals, and devise government strategies to reduce or eliminate the sources of contaminant diffusion, among others. It is also essential to maintain the wide diversity of biological samples in which this type of analysis can be carried out since, as previously stated, exposure to these metals occurs more frequently in population groups with lower incomes who live or work in areas close to waste areas and/or do not have access to drinking water and food.

Accordingly, it follows that in the absence of basic services, it would not be easy to perform a detection test that requires, for example, renal tissue (*in vivo* by XRF[27]) or even blood, since aseptic space and qualified personnel are necessary for sample collection. These procedures would require moving these individuals to a suitable location (which is not always possible) or carrying the supplies to the site where the population lives (which is costly due to preservation conditions).

Based on the above, it is vital to develop new care strategies aimed at mitigating the impact of metal poisoning in the country, particularly among vulnerable population groups. Therefore, in addition to ensuring regulated and safe work environments, building housing projects with suitable living conditions, and implementing educational interventions about the routes of exposure to heavy metals, it is crucial to conduct periodic evaluations of toxic metal exposure by documenting possible sources of exposure; the frequency, duration, and type of exposure; and the age of the individuals exposed, among other aspects. This approach would allow the identification of individuals at a higher risk of heavy metal poisoning.[38]

Finally, the development of techniques that could use biological samples with less challenging collection conditions such as hair, nails, or other types of tissue, as a sample, would be a significant advance in the detection and quantification of toxic metals, especially in vulnerable populations.

Conclusions

Although there is a wide range of analytical chemistry methods available worldwide for the identification and quantification of toxic metals in humans, accessing them in Colombia is difficult due to the lack of laboratories with adequate equipment and trained personnel to perform such analytical methods. Another issue is the fact that the access to laboratories where biological samples can be collected for analysis by individuals living in rural and remote areas of the country, where exposure to these metals is usually higher, is extremely difficult and sometimes impossible.

Furthermore, exposure to toxic metals is not the only factor involved in metal poisoning processes and their subsequent health effects, as there are other socioeconomic determinants in the country that aggravate this situation and, therefore, result in a greater deterioration of the health condition of individuals chronically exposed to these toxic elements given their social and economic vulnerability. Consequently, we suggest addressing and further investigating this issue by integrating economic, cultural, and social perspectives that allow the formulation of public health policies aimed at reducing the exposure to these contaminants in Colombia.

Conflicts of interest

None stated by the authors.

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