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Potential Exposure and Risk Associated with Metal Contamination in Foods

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Abstract

Humans require several trace elements as components of the diet. Some of these elements are required in extremely small quantities (only micrograms per day). On the other hand, in higher concentrations, some elements may also have deleterious, even lethal, effects. Metals such as arsenic, chromium (Cr), lead (Pb), and mercury (Hg) are naturally occurring chemical compounds. The contamination of food with these metals occurs mainly through human activities, such as farming and industry, or from contamination during food processing and storage. People can be exposed to these metals by ingesting contaminated food or water, and their accumulation in the body can lead to harmful effects over time. The main objective of this chapter is to provide a literature review on the various types of foodborne poisoning caused by the contamination of food with arsenic, Cr, Pb, and Hg and on food safety issues associated with the presence of these metals in food. Research findings from various studies carried out to examine the relationship between metal exposure and the adverse health effects of metals are addressed.

Keywords: Diseases, chemical contamination, metals, food

1. Introduction

Foods can be contaminated with harmful chemicals and microorganisms, which can cause illness in humans. Chemical contaminants can be classified according to the source of contamination and the mechanism by which they enter the food product. In the case of metal residues in food, contamination mostly occurs during food processing and storage [1].

In human nutrition, metals are well recognized by public health agencies, nutritionists, and researchers from various areas of knowledge. Humans require several metals as components

of their diet. Some of the metals are required in extremely small quantities, while some, such as arsenic, chromium (Cr), lead (Pb), and mercury (Hg), in certain amounts can adversely affect the nervous system, kidneys, and other vital organs of the body, which can be life threatening in extreme cases.

In general, sources of contamination are contaminated food and beverages and packaging [1, 2].

Metals can often be inadvertently and unintentionally introduced into food products. If these contaminants are not detected, they can become a major safety hazard for consumers. Metals such as arsenic, Cr, Pb, and Hg exist as naturally occurring chemical compounds. These metals are of particular concern in food because of their toxicity, especially in the case of long-term (chronic) intake, because they can accumulate in the body and cause organ damage particularly in susceptible groups, such as children [2].

Arsenic may be present as a contaminant in many foods, such as grains, fruits, and vegetables, where the metal is present because it is absorbed in the plant through the soil and water, and also trace amounts of arsenic can enter the food chain through the application of agricultural chemicals like fertilizers, which may contain arsenic. While most crops do not readily take up much arsenic from the ground, rice is different because it takes up arsenic from soil and water more readily than other grains. Also, arsenic exposure occurs through the consumption of aquatic food, especially shellfish and animals that feed from the bottom of the sea [3].

Cr exposure occurs mainly through the diet. Food crops that are polluted through contaminated soil or water may contain high concentrations of this metal.

Pb is a toxic substance present in the environment in small amounts, and everyone is exposed to some Pb from daily actions such as inhaling dust, eating food, or drinking water. Tobacco smoking and the use of leaded petrol in vehicles are reported to be major sources of Pb exposure, although the Pb content in petrol has dramatically declined over recent decades, thereby reducing environmental exposure [3].

Hg exposure can occur through dental fillings that contain Hg compounds, occupational exposure, and herbal medicines. However, to date no studies have been able to show an association between amalgam fillings and ill health. Most dietary exposure is in the form of inorganic Hg. However, some fish may bioaccumulate the more toxic organic form, methylmercury, in significant quantities. Thus, diets rich in fish can be a cause of organic Hg exposure [3].

Thus, these metallic contaminants have been evaluated by international authorities, and safe reference values have been established. The maximum concentrations of these contaminants allowed by legislation are often well below toxicological tolerance levels, because such levels can often be reasonably achieved by using good food manufacturing practices. Even so, food contaminant testing is needed to assure the safety and quality of food products. Chemical analysis can be very useful in the food industry, with the development of new techniques to accurately and precisely quantify metals present in low concentrations in foods. These data can be applied in the area of toxicology to prevent diseases through prior diagnosis.

2. Arsenic

2.1. Chemistry of arsenic

Arsenic is a chemical element found in several oxidation states (+III, +V, 0, and -III) and various inorganic and organic forms. Arsenic rarely occurs as a pure element. The most common ores of arsenic are arsenopyrite (FeAsS) and arsenic sulfur compounds [orpiment (As_2S_3) and realgar (As_4S_4)]. The inorganic forms are considered to be of greater toxicity, and the ascending order of toxicity is elemental arsenic < arsenobetaine < methylated forms < arsenate < arsenite < arsine [4]. As(III) and As(V) are apparently of comparable bioavailability but differ in terms of their biochemistry. Preferentially, As(III) binds thiol groups, whereas As(V) does not. So, the oxidation state of arsenic can affect its toxicity [5, 6].

2.2. Occurrence in the environment

Arsenic compounds are used in glass and semiconductor production, as a preservative for wood, and as a feed additive to increase weight gain for poultry and swine [7]. Historically, arsenic compounds were used in agriculture as insecticides or herbicides. Due to its widespread use, it can contaminate the environment. Environmental pollution by arsenic occurs as a result of anthropogenic activities and natural phenomena such as volcanic eruptions and soil erosion [8].

Arsenic can be present as a contaminant in environmental compartments, such as water, soil, and plants, and ultimately can seriously affect the human health through exposures to these contaminated compartments. Inorganic arsenic species are the most important chemical forms of arsenic in natural waters [9].

2.3. Dietary sources of arsenic

Arsenic can be found in fish, shellfish, meat, poultry, dairy products, and cereals. However, in fish and shellfish, organic chemical species are found, and thus the arsenic is less toxic. Marine organisms tend to accumulate more arsenic than those living in freshwater or terrestrial environments, which typically have lower arsenic concentrations of around 0.25 mg kg^{-1} [10–12].

China has established the acceptable level of arsenic in rice as 200 ng g^{-1} , while the Codex Alimentarius Committee on Contaminants in Food considers levels of 200 and 300 ng g^{-1} in polished and raw rice, respectively, to be safe [13]. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) reports that the provisional tolerable daily intake (PTDI) of inorganic arsenic is 0.002 mg kg^{-1} body weight, equivalent to 0.12 mg day^{-1} for an adult of 60 kg [14]. However, if contamination with arsenic trioxide occurs, it should be noted that the minimum lethal dose of this compound is 70–180 mg in humans [15]. In general, high levels of arsenic are found in rice and the concentration can vary from 10 to $510 \text{ } \mu\text{g kg}^{-1}$, when rice is irrigated with contaminated water, contributing to the daily intake of arsenic [16].

Due to the toxicity and the many diseases resulting from the ingestion of arsenic, the concentrations of this metalloid and its species in different types of food need to be investigated. Numerous studies on arsenic levels in food have been conducted, and the results have been published in journals, newspapers, and other media. Figure 1 shows the number of publications per year in the Web of Science on the contamination of food with arsenic, demonstrating the interest of the scientific community.

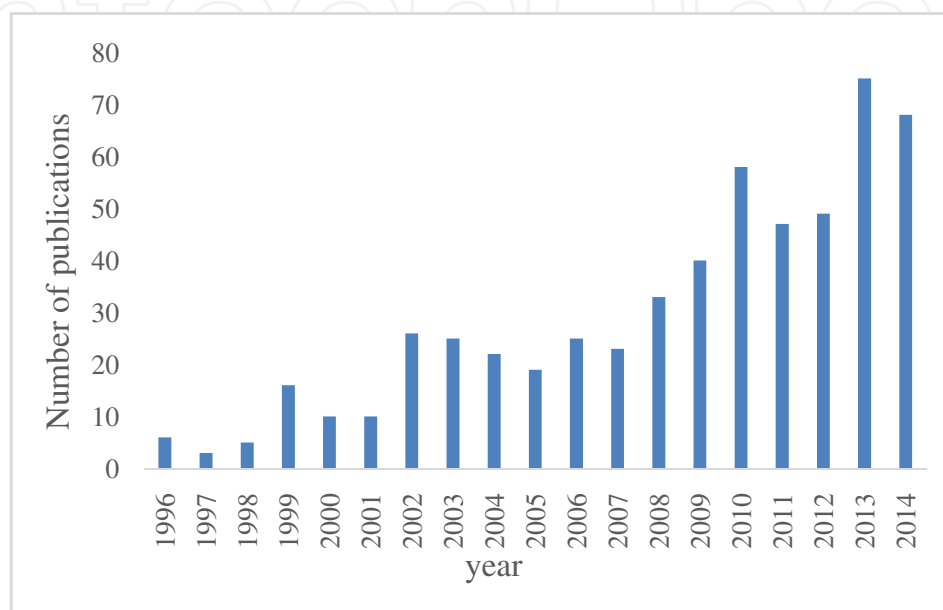


Figure 1. Publications on food contamination with arsenic.

The concentration of arsenic that is safe to human health is under discussion by organizations such as the World Health Organization (WHO), the Food and Agriculture Organization (FAO), the US Food and Drug Administration (FDA), the Food Standards Agency (FSA), and the European Food Safety Authority (EFSA) [17].

The Codex has adopted 0.2 mg kg^{-1} as the maximum level of arsenic in rice. This committee has the task of establishing international food safety and quality standards for consumers worldwide, which are widely used as a basis for national legislation.

To date, the European Union (EU) has not set maximum levels for arsenic in food. However, for water intended for human consumption, the value is 10 mg L^{-1} for total arsenic, with no distinction between the various chemical species of arsenic [18, 19]. Thus, extensive research should be conducted, aimed at more in-depth studies and attaining greater consistency in the data for the creation of relevant legislation regarding arsenic in foods [20–23].

2.4. Routes of entry into plants, animals, and humans

The most important route of exposure to arsenic is the ingestion of foods and beverages, which in most cases are contaminated from the use of irrigation water with a high concentration of the element. In general, the water is contaminated by dissolved minerals and contains different

forms of arsenic [24]. Exposure to arsenic occurs via the oral route (ingestion), inhalation, dermal contact, and the parenteral route [25–27].

Arsenic occurs in both inorganic and organic forms, which exhibit large differences in their metabolism and toxicity. The high toxicity of arsenic is well known because arsenic compounds are readily absorbed by either inhalation or ingestion, the extent of absorption being dependent upon the solubility of the compound.

2.5. Metabolism or transformation in the living system

There is evidence that arsenic has a physiological role related to methionine metabolism [28]. However, the site of action of arsenic remains unknown. Studies with rats fed adequate amino acid-based diets have shown that arsenic deprivation had little effect on growth in rats. However, in rats fed suboptimal methionine, arsenic deprivation resulted in a significant reduction in body weight. It was shown that arsenic deprivation reduces the hepatic concentration of *S*-adenosylmethionine, indicating that arsenic maintains the metabolic pool of *S*-adenosylmethionine [28].

In addition, arsenic status affects DNA methylation in animal and cell culture models, resulting in an apparent hypomethylation of DNA [29]. This process is associated with an increased incidence of cancer. So, there is an amount of dietary arsenic that is harmful or beneficial to humans [30, 31].

2.6. Biological functions

In body, arsenic is present as arsenite and arsenate. Arsenic species interact strongly with sulfhydryl groups of organic molecules. It affects several enzymes, causing damage in several cell systems. Because of their similar properties, arsenate can substitute for phosphate and other phosphate intermediates in several biochemical reactions. At the cellular level, arsenate depletes adenosine triphosphate (ATP) in human erythrocytes, interrupting the production of energy [31, 32].

Although some research has indicated that arsenic is an essential nutrient for rats, chickens, and pigs, however, no studies have been published in the literature to determine the nutritional importance of arsenic in humans [32].

2.7. Mechanisms of toxicity of arsenic

The toxicity of arsenic is highly influenced by its oxidation state and solubility, as well as many other factors [33]. As(III) binds to thiol or sulfhydryl groups on proteins and can inactivate over 200 enzymes. As(V) can replace phosphate, which is involved in many biochemical pathways [34].

Mechanism by which arsenic exerts its toxic effect is due its ability to interact with sulfhydryl groups of proteins and enzymes and to substitute phosphorous in various biochemical reactions [34].

In humans, As(III) is methylated to two major metabolites via a non-enzymatic process to monomethylarsonic acid (MMA), which is further methylated enzymatically to dimethyl arsenic acid (DMA) before excretion in the urine [34].

Various hypotheses have been proposed to explain the carcinogenicity of inorganic arsenic. Nevertheless, the molecular mechanisms by which this arsenic induces cancer are still poorly understood [35, 36].

2.8. Incidence of (acute and chronic) toxicity

Arsenic can cause numerous human health effects. Several epidemiological studies have reported a strong association between arsenic exposure and increased risks of both carcinogenic and systemic health effects [25]. The severity of adverse health effects is related to the chemical form of arsenic and is also time and dose dependent [26, 37, 38]. Among the notable effects and diseases are skin lesions, neurotoxicity, cardiovascular diseases, abnormal glucose metabolism, diabetes, peripheral vascular diseases, coronary heart diseases, myocardial infarction, stroke, gangrene, kidney failure and liver failure, cancer of the internal organs, particularly the bladder and lung, skin pigmentation, keratoses, and skin cancer [24, 26, 34–37].

2.9. Comparative analysis of analytical techniques

Several techniques have been used for the detection of arsenic in foods. Among the combined techniques are the use of chromatography or inductively coupled plasma coupled with mass spectrometry (MS) [39], mass spectrometry–desorption electrospray ionization (MS-DESI) spectrometry, inductively coupled plasma–optical emission spectrometry (ICP-OES), and hydride generation–atomic absorption spectrometry (HG-AAS) [39, 40], which generally allow the chemical speciation of arsenic and other techniques such as capillary electrophoresis coupled to inductively coupled plasma and mass spectrometry (CE-ICP-MS) [41]. However, these techniques are expensive. In this regard, an interesting approach to determining arsenic species with detection by electrothermal atomic absorption spectrometry after cloud point extraction (ETAAS/CPE) was developed by Baig *et al.* [42] and Costa *et al.* [43].

3. Chromium

3.1. Chemistry of chromium

Cr is a naturally occurring element present in the earth's crust and is found in two oxidation states, namely hexavalent chromium (Cr(VI)) and trivalent chromium (Cr(III)). Hexavalent chromium (Cr(VI)) compounds are, in general, more toxic than Cr(III) compounds. Cr rarely occurs as a pure element. The most common ore of Cr is ferrochromite [44, 45].

3.2. Occurrence in the environment

Cr is an element available in the environment, found mostly in minerals, rocks, plants, soil, water, dust, and volcanic gases. Cr can be present as a contaminant in the environment from

various natural and anthropogenic sources [46]. Cr released into the environment as anthropogenic activity occurs mainly from metallurgical and chemical industries such as tannery facilities, chromate production, stainless steel welding, and ferrochrome and chrome pigment production.

The health hazard associated with exposure to Cr depends on its oxidation state, ranging from the low toxicity of the Cr(III) form to the high toxicity of the Cr(VI) form [47]. Cr(III) is an essential trace mineral present in trace amounts in some foods, such as meat, whole grains, oleaginous plants, and legumes.

3.3. Dietary sources of chromium

Cr(III) is considered to be essential to mammals for the maintenance of glucose, protein, and lipid metabolism, whereas Cr(VI) is detrimental to human health even at relatively low concentration levels, because it can be involved in the pathogenesis of some diseases such as liver, kidney, lung, and gastrointestinal cancers [48–50]. Cr(III) is a stable and biologically active state of Cr, and it is found in many types of foods, including egg yolk, whole grains, cereals, coffee, nuts, green beans, broccoli, meat, beer yeast, and drinks produced from grapes. Cr is also available in many dietary supplements and is responsible for the proper functioning of the metabolism of carbohydrates and lipids. Table 1 shows the amounts of Cr that can be found in some foods.

Food	Amounts of chromium ($\mu\text{g } 100 \text{ g}^{-1}$)
Broccoli	11–22 ^b
Dry garlic	60 ^a
Mashed potato	1.5 ^a
Whole wheat bread	4.4 ^a
Champagne	1.1–3.6 ^c
Red wine	0.7–9.0 ^c
White wine	0.7–4.4 ^c
Green grapes	0.3–2.1 ^c
Red grapes	0.2–6.5 ^c
Apple	0.8 ^a
Grape juice	4.0 ^b
Orange juice	1.0 ^a

^aAdapted source by NHI [51].

^bAdapted source by Oliveira and Machine [52].

^cAdapted source by Cabrera-Vique *et al.* [53].

Table 1. Quantity of chromium in some foods.

3.4. Routes of entry into plants, animals, and humans

Cr-containing compounds have been a major concern because of Cr release into the environment and the high risk of Cr-induced diseases in industrial workers occupationally exposed to Cr(VI) [54]. The route of human exposure to Cr is through skin and mainly through inhalation, and the lung is the target organ [55–57]. Non-occupational exposure occurs through ingestion of Cr-containing food and water. Cr content in foods varies greatly and depends on the processing and preparation of foods.

3.5. Metabolism or transformation in the living system

The main path for Cr(III) to get into the organism is through the digestive system. The mechanism of Cr intestinal absorption is not yet fully known, but it is known that Cr(VI) compounds are absorbed better than Cr(III) compounds. Absorbed Cr circulates in blood bound to the β -globulin plasma fraction and is transported to tissues bound to transferrin or other complexes at the physiological concentration [58]. Cr from blood is relatively quickly absorbed by bones, accumulating also in the spleen, liver, and kidneys. Cr is excreted especially by the urinary system.

3.6. Biological functions

Cr plays an important role in carbohydrate, lipid, and glucose metabolism [58–60]. Studies show evidence that Cr acts as a cofactor for insulin, and therefore, Cr activity in the organism is parallel to insulin functions. It is assumed that the activity of Cr is mediated by the anabolic action of insulin. Cr supplementation intensifies amino acid uptake by tissues such as these the binding of Cr to nucleic acids is stronger than in other metal ions [60]. Cr(III) seems to be involved in the structure and expression of genetic information in animals. Also, Cr protects RNA from heat denaturation and, among other functions, promotes the growth of the animals.

3.7. Mechanisms of toxicity of chromium

The toxicity of Cr compounds depends on its oxidation state and solubility [61–63]. Cr(VI) compounds are more toxic than Cr(III) compounds most likely due to the ease with which Cr(VI) can pass through cell membranes and its subsequent intracellular reduction to reactive intermediates [64–66]. As Cr(III) is poorly absorbed by any route, the reduction of Cr(VI) is considered as being a detoxification process. If Cr(VI) is reduced to Cr(III) extracellularly, then Cr(III) is not readily transported into cells, and so toxicity is not observed. Under physiological conditions, Cr(VI) can be reduced Cr(III) by hydrogen peroxide (H_2O_2), glutathione (GSH) reductase, ascorbic acid, and GSH [66, 67].

3.8. Incidence of (acute and chronic) toxicity

Cr is of particular interest because its toxicity is highly dependent upon its chemical forms and concentration. Cr(VI) shows high toxicity and is related to clinical cases such as nasal irritation

and ulceration, hypersensitivity reactions, and dermatitis through contact. The lethal dose is between 50 and 100 mg kg⁻¹, which is much lower than that of Cr(III), with a lethal dose between 1900 and 3300 mg kg⁻¹ (both cases tested by oral ingestion in rats). Furthermore, Cr(VI) is classified as carcinogenic because it penetrates the cell membranes of living organisms [59]. Exposure to Cr(VI) can occur mostly through inhalation, skin contact, and ingestion. Cr(VI) inhalation, for example, besides causing severe irritation of the respiration system, is also carcinogenic. Although the WHO has established a limit for human consumption of 0.005 mg kg⁻¹ body weight per day, no scientific studies have proved that Cr ingestion can cause disease. The potential effects of Cr(VI) vary mainly with the species, the amount absorbed into the bloodstream, and the route and duration of exposure [68–70]. Thus, Cr(VI) is found in most lists of high-toxicity elements for which strict control procedures apply. The difficulty in establishing a recommended dietary allowance (RDA) for Cr is mainly due to the limitations related to estimating the ingestion levels of this mineral, which range from the absence of data on the amount of Cr present in foods, due to analytical difficulties given the trace concentrations, to environmental contamination problems [70].

The ingestion of Cr(VI) is detrimental to human health even at relatively low concentration levels because it may be involved in the pathogenesis of some diseases, such as liver, kidney, lung, and gastrointestinal cancers. Following studies, many authors have suggested that chromium picolinate can cause DNA damage [60, 61], but there is no confirmation of carcinogenesis in animals [62]. There are reports of toxicity after supplementation, but the results of other investigations did not indicate hepatic alterations [64–70]. Based on this impasse, the US Agency of Toxic Substance and Disease Registration concluded that there is no conclusive evidence that supplementation causes liver damage, although it does have proven deleterious effects on the kidneys [67].

3.9. Comparative analysis of analytical techniques

The determination of Cr can be carried out through sensitive techniques that are able to quantify a few micrograms of this element. One of these techniques is graphite furnace–atomic absorption (GF-AAS), consolidated after 1981, and is able to detect Cr concentrations of around 0.2 µg kg⁻¹ in food. More sensitive techniques developed later, such as ICP-MS and ICP-OES [71], are used for the determination of Cr. These techniques quantify only total Cr without promoting speciation, and separation techniques, such as chromatography, are required.

The official method for the analysis of Cr in food samples is ICP-OES using nitric acid and hydrogen peroxide to oxidize organic materials in food samples [71]. This technique has high sensitivity (of the order of 1 ng L⁻¹). However, this equipment is sophisticated and expensive with high operational costs. An option that combines higher sensitivity and lower cost is GF-AAS technique. This technique has important advantages such as a reduced amount of sample and high sensitivity, and the analysis can be carried out with minimal or no sample preparation [71].

4. Lead

4.1. Chemistry of lead

Pb is a heavy metal that has malleability, low melting point, low electrical conductivity, and high corrosion resistance. These properties allow its widespread use in the manufacture of blades and pipes of high flexibility and resistance in welds and coatings in the automotive industry; protective plates against ionizing radiation (e.g. X-rays); alloys; coating cables; and paints, dyes, and plastic additives [72]. Usually, inorganic Pb compounds are found as Pb(II) and rarely found as a pure element. Its most common mineral is galena or lead sulfide (PbS). The solubility of Pb compounds is enhanced at lower pH, suggesting that the increased mobility of the Pb is found in ecosystems under stress acidification [73].

4.2. Occurrence in the environment

Pb is a metal that occurs naturally, making up only about 0.0013% of the earth's crust. However, most Pb concentrations that are found in the environment are the result of human activities such as burning of fossil fuels and mining [74]. Pb can be found in the atmosphere in particulate form, being deposited in water systems, interfering with the characteristics of the water. In other cases, this metal may be found complexed with natural organic compounds [75]. In contact with the ground, Pb can remain for a long time and in various forms (such as insoluble and soluble complexes and colloids) and absorbed by plants, accumulating in the edible parts, causing contamination in humans and animals [74–78].

4.3. Dietary sources of lead

The WHO and the Expert Committee on Food Additives—“JECFA” initially established a provisional tolerable weekly intake (PTWI) for lead of $50 \mu\text{g kg}^{-1}$ body weight for adults. However, after assessing the risk to health, the JECFA later reduced this value to $25 \mu\text{g kg}^{-1}$ body weight, equivalent to $3.5 \mu\text{g kg}^{-1}$ body weight per day (equal to 1.75mg week^{-1} or $1750 \mu\text{g week}^{-1}$ for a person weighing 70 kg) [20, 21].

The Expert Committee noted, however, that some foods with high levels of Pb remain commercially available [22]. A reference value for Pb of 0.01mg L^{-1} in drinking water was established by the WHO. The concentrations in drinking water are typically below $5 \mu\text{g L}^{-1}$, although higher concentrations (above 100mg L^{-1}) have been reported. The EPA regulations establish limits in the form of maximum contaminant levels (MCLs), and the value for Pb in drinking water is 0.015mg L^{-1} , even though the EPA has also established a goal for zero Pb in this regard [23].

4.4. Routes of entry into plants, animals, and humans

The main routes of human exposure to Pb are by ingestion (food, water, and soil), inhalation, and skin [79]. The compounds of tetra-alkyl Pb (Pb tetra acetate, etc.), for example, are rapidly absorbed through the lungs, gastrointestinal tract, and also the skin. Usually, a high level of

metal enters the body through the ingestion of contaminated cereals and vegetables [80]. Once absorbed, inside the body Pb is distributed by the blood reaching the soft tissue and then is deposited in the bones and other hard body parts. It is slowly excreted in urine and feces [79].

4.5. Metabolism or transformation in the living system

In the human body, Pb is not metabolized, but it forms complexes with macromolecules. Pb forms complexes (sulfur groups, $-SH$) through covalent bonds, causing the intoxication of humans [81]. Pb can disturb the metabolic functions in two ways: (1) it accumulates, thereby disrupting the function of vital organs and glands such as the heart, brain, kidney, bone, liver, so on and (2) it moves the vital nutritional minerals from their original location, hindering their biological function [82].

4.6. Biological functions

Pb is a toxic metal that would not have known beneficial effects to the body, and its accumulation over time in the bodies of animals and humans can cause severe illness [83].

4.7. Mechanisms of toxicity of lead

One of the main reasons by which Pb exerts toxic effect is its ability to substitute diverse cations (calcium, zinc, and magnesium) in their binding sites. Pb has a greater affinity than calcium and zinc ions to protein-binding site because of its larger ionic radius and greater electronegativity. For example, Pb interacts with oxygen and sulfur binds to sulfhydryl and amide groups of enzymes, altering their configuration and diminishing their activities, and competes with calcium in skeletal tissue and to interact with proteins [84].

In the blood, Pb is distributed to the remaining tissues, where it accumulates; the amount of metal accumulated depends mainly on the vasculature and metabolic characteristics of each tissue [85]. The half-life of Pb is 35 days in the blood and is about 2 years in the brain, and it can last for decades in bone.

Many investigators have demonstrated that Pb affects biomolecules and hence physiological systems. For example, calmodulin is a protein found primarily in the brain and heart. The binding of calcium ions of this protein allows the binding of this protein to cyclic nucleotide phosphodiesterase and adenylate cyclase with subsequent activation. Thus, this protein modulates the levels of AMP and cyclic GMP [86]. Pb is a more potent activator than calcium for calmodulin. According Kern, Pb modifies several signaling cascades and proteins that participate in the vesicular cycle [87]. The alterations caused by the abnormal protein operation in second messenger systems and exocytic processes greatly contribute to Pb neurotoxicity [87].

Pb affects various cellular organelles, for example, mitochondria and endoplasmic reticulum, in different ways. In the mitochondria Pb affects energy metabolism, while in the endoplasmic reticulum Pb increases the cytoplasmic concentration of calcium with a consequent reduction in ion concentration inside this organelle. Many signaling pathways that are within the endoplasmic reticulum are calcium dependent; because the amount is not appropriate, various processes are impaired. Besides, Pb binds to Ape1 nuclease, whose function is to detect and

repair DNA damage, inhibiting its operation and allowing the accumulation of mutagenic damages [85–88].

4.8. Incidence of (acute and chronic) toxicity

Pb is one of the most common environmental contaminants. This element has no known physiological function in the organism, and its damaging effects can affect almost every organ and system in the body [89]. The main way in which Pb enters the body is through the respiratory route (occupational exposure), followed by the digestive route. Organic Pb compounds can penetrate in the body through skin contact and are rapidly absorbed [90, 91].

Exposure to Pb can result in a wide variety of biological effects, depending on the exposure level and duration. The major diseases related to Pb contamination are shown in Table 2. Pb is toxic to various organs and systems, and its effects may vary from enzyme inhibition and anemia to diseases of the nervous, immune, reproductive, and cardiovascular systems, impaired kidney function, and even death.

Studies have suggested an association between Pb exposure and lung cancer and, to a lesser extent, stomach cancer [90]. Pb is hypothesized to be a carcinogen and to enhance the genotoxic effects of other agents. Renal tumors developed in mice that had received high doses of certain Pb compounds and various other animal studies have shown increases in the yield or genotoxicity of known carcinogens. The US Environmental Protection Agency has determined that Pb is a probable human carcinogen [89–91].

Effects on health	Site of the body affected	Adverse effects
Neurological	Central nervous system, peripheral, and autonomic	Acute and chronic encephalopathy; peripheral neuropathy
Hematological	Blood	Anemia
Endocrine	Bone tissue and serum	Damage to the kidneys and development of cells, teeth, and bones. Possible damage to the thyroid.
Growth	Bone	Reduced growth
Reproductive	Male and female reproductive systems	Reduced fertility, high probability of miscarriages
Carcinogenic	Kidneys and cells—genomic DNA	Carcinogenic to animals and epigenetic involvement in the expression of the modified gene
Cardiovascular	Cardiovascular system	Likely increase in blood pressure, cardiac lesions, and abnormal electrocardiograms
Gastrointestinal	Gastrointestinal tract	Colic
Hepatic	Liver	Reduced functional capacity of the cytochrome P-450 to metabolize drugs

Table 2. Main health effects related to lead contamination [89–91].

4.9. Comparative analysis of analytical techniques

The determination of traces of Pb in various food samples is of great importance because Pb is recognized as a cumulative poison in humans and other animals [92]. The determination of Pb requires procedures that are sufficiently sensitive for detection at the pg L^{-1} level. Traditionally, GF-AAS has been applied in such cases, but the direct determination of Pb in complex matrices is usually difficult owing to matrix interference and separation procedures often being required before the sample analysis [93]. The ICP-MS technique is favored because of its low detection limits [93], although many researchers prefer AAS owing to its simpler and less expensive instrumentation. Lead hydride generation and its application to spectrometry analysis have been reviewed by Madrid and Cámara [94]. HG-AAS is a well-developed technique that can be used for the determination of volatile hydride-forming elements such as arsenic, selenium, antimony, and others at trace levels [95]. The advantages of HG-AAS over other atomic absorption spectrometric techniques such as the flame and graphite furnace methods are increase in atomization efficiency and higher selectivity because the analyte is removed from the matrix as a volatile compound and detection limits at the pg L^{-1} level or lower for the elements cited above. Considering these advantages, this technique could be applied for the determination of Pb, and it is possible to include this element in multi-element analysis schemes involving hydride generation.

The generation of Pb hydride was described by Carrijo et al. [96]. In this study, a flow injection–hydride generation–atomic absorption spectrometry (FI-HG-AAS) system was used for Pb determination. The main characteristics of the flow injection system, that is, high sampling rate and good accuracy, precision, and sensitivity, are maintained.

5. Mercury

5.1. Chemistry of mercury

Hg is a metal found in various chemical forms, which can be divided into the following categories: elemental or metallic Hg, inorganic Hg, mainly in the form of mercuric salts (HgCl_2 and HgS), and mercuric (Hg_2Cl_2) and organic Hg, for example, methylmercury and ethylmercury [68, 72].

Metallic mercury (Hg) is in the liquid state at room temperature and easily volatilizes into the atmosphere forming Hg vapors. Hg is a metal with widespread use, especially the production of scientific precision instruments, electrical industry, dentistry (production amalgams), the production of certain types of toys, mining, metal smelting, among others [97].

5.2. Occurrence in the environment

Hg is a metal found naturally in the earth's crust, occurring in air, soil, and water [98]. It rarely occurs free in nature and is found mainly in cinnabar ore (HgS). It can be found in metal form, as salts of Hg or organic Hg compounds. Once released, Hg remains in the environment among the circulating air, water, sediment, soil, and biota, which assumes various chemical forms.

Most emission to air occurs in the form of elemental Hg, which is very stable and can remain in the atmosphere for months or even years, enabling transport over long distances around the globe [98]. Most of the Hg released by human activities in air is by combustion of fossil fuels, mining, smelting, and combustion waste [99].

The Hg vapor in the atmosphere can be deposited or is converted into the soluble form, returning to the earth's surface in rainwater. From there, two important chemical changes may occur. The metal can be cast again and return the Hg vapor in the atmosphere or may be "methylated" by the microorganisms present in the water sediments, turning into methylmercury [98]. Furthermore, the Hg can also be released directly in the soil or in water by the application of agricultural fertilizer and disposal of industrial waste water [100].

Atmospheric emissions are the major source of environmental contamination, followed by water pollution and soil contamination, when there is improper disposal of effluents and waste [98].

5.3. Dietary sources of mercury

Usually, Hg contamination occurs by the presence of this metal in water, soil, air, or food, mostly in the form of methylmercury [100, 101]. The most important source of exposure through diet for the general population is the consumption of fish and other marine organisms. Hg is concentrated in the tissue of fish, becoming increasingly potent in predatory fish and mammals that feed on small fish. The larger carnivorous fish have higher concentrations than smaller ones [99]. The average daily intake of methylmercury (mainly from fish) that can cause demonstrable effects on the health of sensitive individuals is 300 mg day^{-1} or $4.3 \text{ } \mu\text{g Hg day}^{-1} \text{ kg body weight}^{-1}$ [102].

Industrial products can also be contaminated by Hg during the processing steps. Studies have shown the contamination of Hg in breast milk ($4\text{--}15 \text{ } \mu\text{g kg}^{-1}$) [103], in tea (6 ng g^{-1}) [104], and in products for infant feeding ($0.50 \text{ } \mu\text{g kg}^{-1}$) [105].

5.4. Routes of entry into plants, animals, and humans

The absorption of Hg by humans and animals can be by pulmonary route (inhalation), as well as by gastrointestinal or cutaneous route. In the case of pulmonary route, Hg after inhalation and the presence in the lung is distributed throughout the body, accumulating in various parts of body [106–108]. Soluble compounds are absorbed by mucous membranes following vapor inhalation and by the skin and the sebaceous glands. In the body, organic and inorganic Hg binds GSH [108]. It acts as inactivator because it readily binds to thiol groups of cellular enzymes and disrupts its function by inactivating the metabolism. The non-absorbed Hg is excreted in feces, and absorbed Hg forms are excreted via saliva and skin.

5.5. Metabolism or transformation in the living system

Hg and its organic compounds in low concentrations cause damage to human health. Their concentrations in surface and ground waters are below 0.5 mg L^{-1} . However, aquatic micro-

organisms convert the organic Hg into inorganic Hg compounds, which accumulate in the food chain. Methylmercury is the most relevant toxicant [109]. The gastrointestinal tract is the second way (after airway) through which Hg, already now in its organic form, enters the human body through the consumption of fish, shellfish, and other aquatic organisms.

5.6. Biological functions

Hg has no biological role. All Hg compounds are extremely toxic, particularly methylmercury [109].

5.7. Mechanisms of toxicity of mercury

The mechanism of toxicity of Hg is based on its chemical activity and biological features. The main mechanism of toxicity of Hg compounds involves their reactivity with sulfhydryl groups. Once in the cell, both Hg^{2+} and MeHg form covalent bonds with cysteine residues of proteins and deplete cellular antioxidants [110].

5.8. Incidence of (acute and chronic) toxicity

Metallic Hg and its organic compounds in very low concentrations cause damage to human health (such as neurotoxic, immunotoxic, and teratogenic properties) and can have high persistence and a high bioconcentration factor (BCF), accumulating in animals, fish, and the environment. Hg poisoning levels and the main symptoms and diseases related to acute and chronic poisoning by Hg are shown in Tables 3 and 4, respectively [111].

24-hour urine	
0.00–0.01mg	Non-toxic
0.02–0.09 mg	Danger of poisoning
0.10–0.80 mg	Chronic intoxication
Above 1.00 mg	Acute intoxication
Above 2.00 mg	Subacute poisoning

Table 3. Mercury poisoning levels.

Acute intoxication	Chronic intoxication
Dark gray appearance in the mouth and pharynx	Digestive disorders
Severe pain	Nervous disorders
Vomiting (may even be bloody)	Cachexia
Bleeding gums	Stomatitis
Metallic taste in the mouth	Salivation

Acute intoxication	Chronic intoxication
Burning in the digestive tract	Bad breath
Severe or bloody diarrhea	Loss of appetite
Inflammation of the mouth (stomatitis)	Anemia
Tooth decay and/or loose teeth	Hypertension
Glossitis	Loosening of the teeth
Swelling of the gum mucosa	Central nervous system disorders
Kidney nephrosis	Mild kidney disorders
Serious liver problems	Possibility of chromosomal alteration
Can even cause sudden death (1 or 2 days)	-

Table 4. Main symptoms and diseases related to acute and chronic poisoning by mercury.

5.9. Comparative analysis of analytical techniques

The determination of Hg in food samples is critical to assess the degree of human exposure, and thus reliable analytical techniques with high sensitivity are required. However, in most situations, the determination of Hg species is not an easy task due to low concentrations in the samples and the characteristic volatility [112, 113]. The volatility of Hg requires special consideration when treating the sample. Food sample preparation using a microwave oven has been widely employed [114].

In the case of the quantification of methylmercury in fish samples and seafood, depending on the nature of the sample and the technique used, an additional pre-concentration step is required. Hg determination has been performed using cold vapor coupled to atomic absorption spectrometry (CV-AAS), cold vapor coupled to atomic fluorescence spectrometry (CV-AFS), inductively coupled plasma optical emission spectrometry (CV-ICP-OES), and inductively coupled plasma mass spectrometry (CV-ICP-MS). Hyphenated techniques involving gas or liquid chromatography separations with detection by element-specific detectors such as ICP-MS and atomic absorption/emission are the most commonly reported [114].

6. Conclusions

The information gathered herein highlights the risks associated with arsenic, Cr, Pb, and Hg contamination in foods. Therefore, measures should be taken to reduce exposure of the general population to these contaminants to minimize the risk of adverse health effects. The development of simple strategies suitable for obtaining quantitative information regarding some species of great interest should be encouraged.

In the food industry, analytical chemistry plays an important role, contributing new analytical procedures and instrumentation. Methods for the determination and monitoring of metals are

still scarce. However, there are inherent difficulties associated with the types of samples involved. There are various types of food samples and a great variation in their compositions. This hinders the application of analytical techniques for the fast and accurate monitoring of metals in real samples. More sophisticated techniques are of interest in some fields of application, but these techniques have not yet reached the food industry. Thus, chemists need to direct their attention toward these trends with the aim of narrowing the gap between science and the food industry. These studies require an interdisciplinary approach to cover the various aspects involved and could achieve important advances in toxicology, chemistry, and food science.

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