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Review

Heavy Metal and Metalloid Contamination in Food and Emerging Technologies for Its Detection

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Abstract: Heavy metal and metalloid poisoning in the environment and food has piqued the public's interest since it poses significant hazards to the ecological system and human health. In food, several metals, including cadmium (Cd), lead (Pb), mercury (Hg), tin (Sn), manganese (Mn), and aluminium (Al), and metalloids, including arsenic (As), antimony (Sb), and selenium (Se), pose a severe threat to human health. It is of utmost importance to detect even minute quantities of these toxic elements and this must be efficiently determined to understand their risk. Several traditional and advanced technologies, including atomic absorption spectrometry (AAS), spectrofluorimetry, inductively coupled plasma spectrometry, e-tongues, electrochemical aptasensors, Raman spectroscopy, and fluorescence sensors, among other techniques, have proven highly beneficial in quantifying even the minute concentrations of heavy metals and metalloids in food and dietary supplements. Hence, this review aims to understand the toxicity of these metals and metalloids in food and to shed light on the emerging technologies for their detection.

Keywords: heavy metal; metalloid; detection; human health; food

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1. Introduction

While our diets and bodies include traces of numerous metals, only a handful are required for health and survival. If we do not get enough vital inorganic nutrients, we may experience biochemical lesions in our cells and recognizable clinical signs. It is typical for the symptoms to improve after a sufficient amount of the missing element has been supplied [1,2]. Manufacturers and processors should care more beyond just satisfying the

many regulatory requirements and standards of practice related to metals in food or even making sure their goods do not include any dangerous metals or essential trace elements in proportions high enough to pose health problems for customers. Foods should also be checked for any metals that could hasten spoilage or lower quality [3]. Foods containing even low levels of metals can undergo several unfavourable transformations throughout the cooking and storing processes. Complexes between metal ions and organic compounds can occur in quantities as low as a few mg/kg. Several liquid foods, including fruit juices, milk, beer, and wine, can have their flavour and aroma diminished by iron pollution, according to the research by Borocz-Szabo. Steel corrosion by-products, particularly iron salts, are responsible for odour loss and the development of astringent, metallic, or bitter flavours [1,4].

Most people are exposed to harmful metals/metalloids through their diets. Due to factors such as the rising use of metal-contaminated fertilizers and irrigation water sources, gastrointestinal exposures to metallics have become increasingly important in both developed and developing countries due to the globalization of food sources. However, restrictions on cadmium (Cd) in fertilizers and reductions of lead (Pb) use in fuel and food can have helped to lessen people's exposure to metals. This review will examine these concerns from multiple angles for key hazardous elements—Cd, Pb, mercury (Hg), and arsenic (As). While focusing on Pb, methylmercury (MeHg), and Cd, the "traditional" hazardous metals such as, As in food and drinking water is also included due to rising health concerns. Risk to the community from exposures at a level below those creating overt or clinical signs of toxicity is the primary worry, even if there are isolated occurrences of significant metal poisoning from tainted food. Individuals at risk are taken into account throughout their lifetimes of exposure. Food contamination from the environment (including soil, air, and water), human activities (including the preparation and storage of food), and industrial processes is described in this review. The traditional method of presenting the presence of metals and metalloids, such as As, in food is to express concentrations in terms of milligrams per kilogram of fresh weight, which is the basis for the regulation of contaminants in food. It is essential to remember that fresh weight might differ significantly between foods and samples of the same item [3,5–12].

People's attention has been drawn to the problem of heavy metal and metalloid toxicity in the environment and food because of the severe threats that it presents to ecosystems and human health. Some metals and metalloids found in food are highly harmful to human health. These include Cd, Pb, Hg, tin (Sn), manganese (Mn), aluminum (Al), and metalloids, including As, antimony (Sb), and selenium (Se). Determining the danger posed by these hazardous elements requires accurately detecting even trace amounts. Electrochemical aptasensors, atomic absorption spectrometry, spectrofluorimetry, inductively coupled plasma spectrometry, e-tongues, electrochemical aptasensors, Raman spectroscopy, and fluorescence sensors, among other techniques, have proven helpful in detecting trace amounts of heavy metals and metalloids in food and nutritional supplements. This article intends to inform readers about the growing technologies for detecting these metals and metalloids in food and their toxicity. The detection of heavy metals is currently a hot topic in science. Electronic tongues and bio/chemical sensors are only a few examples of novel sensor technologies that have arisen to address the demand for legislative acts on environmental pollution management and early warning. Recent advances in nanotechnology and sensor technologies have become critical enablers of heavy metal detection [13].

2. Metals in Food Toxicity

2.1. Cadmium (Cd) Toxicity

Cd is discharged into the environment mainly due to human activities and then moves through the ecosystem and ends up in food. As a result of bio-concentration in soil, food is the principal route of exposure for the public at large to Cd. Kidney disease, osteoporosis, diabetes, cardiovascular disease, and cancer are only some of the chronic illnesses linked to long-term Cd exposure [14]. Foods sourced from highly polluted areas have exceptionally

high concentrations of the heavy metal Cd. A significant threat to public health in an area may come from a single pollution source. Due to its widespread use as a staple food, rice is the single most significant contributor to a person's daily intake of Cd [15]. Several specific foods, such as animal kidneys, blood cockle, and local vegetables, also enhance the likelihood of Cd exposure. It is a lengthy process for Cd to be removed from the food chain. Cd concentrations in polluted rice samples from Mae Sot have decreased over the previous decade, but they are still high enough to cause medical conditions for users. Analyses of biomarkers suggested a connection between dietary Cd exposure and unfavourable clinical consequences. While there was a correlation between lower Cd levels in the environment and food, there was no causal relationship between the development of health impacts and those lower levels. As a result, protecting people from Cd exposure is crucial for health policy [16–19].

Cd's PTWI, or provisional tolerable weekly intake, was set at 7 μg/kg body weight in 1988 by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Urinary Cd elimination below 5.24 μg Cd/g creatinine was not linked with higher excretion of β2-microglobulin (β2MG), according to significant meta-analytical research examining the dose–response association between β2MG and Cd excretion in urine. Increased Cd concentrations in the urine seemed to be linked to a sharp rise in β2MG excretion. The threshold level of dietary Cd exposure was calculated to be 0.8 μg/kg body weight per day or around 25 μg/kg body weight per month. The board agreed that a monthly number was more realistic given the lengthy half-life of Cd in human kidneys. Consequently, the previous PTWI of 7 μg/kg body weight was eliminated, and a new PTMI of 25 μg/kg body weight was set [16,20].

The European Food Safety Authority's (EFSA) panel on contaminants in the food chain recommended in 2009 that the PTWI be lowered to the tolerable weekly intake (TWI) level of 2.5 μg/kg body weight [21]. If we want to keep the health risks associated with Cd contamination to a minimum, we need to keep our Cd intakes under the PTMI or TWI. As a result, several nations' primary dietary sources of Cd exposure have been pinpointed. Over a decade, Cd exposure has been found to be highest in rice and grains, seafood, meat, edible offal, and vegetables across all countries [16]. An animal's kidney is the first organ to reach the point where it can no longer be consumed by humans. It is worth noting that animals' kidneys from inside and outside a local contaminated area show Cd levels far beyond the maximum allowable range. Implementing a frequent monitoring program and removing high-risk goods from the food chain will fix the problem.

Additionally, as there is no viable therapy or method for reducing Cd deposition in the body, caution and awareness of particular food contamination should be mandated. The best defense would be not to ingest any Cd at all. The PTMI was surpassed due to the regular consumption of blood cockle containing Cd at a level near the maximum limit stipulated by the Australian and New Zealand Food Standards. Due to its popularity as a food item, it is essential to assess the Cd concentration of blood cockle sold in all areas of Thailand. The native vegetables in Thailand are revered not only for their nutritional value but also for their curative properties. The possible healthcare hazards to a community that consumes more native veggies should be evaluated. Thus, it is essential to learn more about the Cd concentrations of the varieties of local vegetables in polluted sites and their intake [16,22,23] (represented in Table 1 and Figure 1).

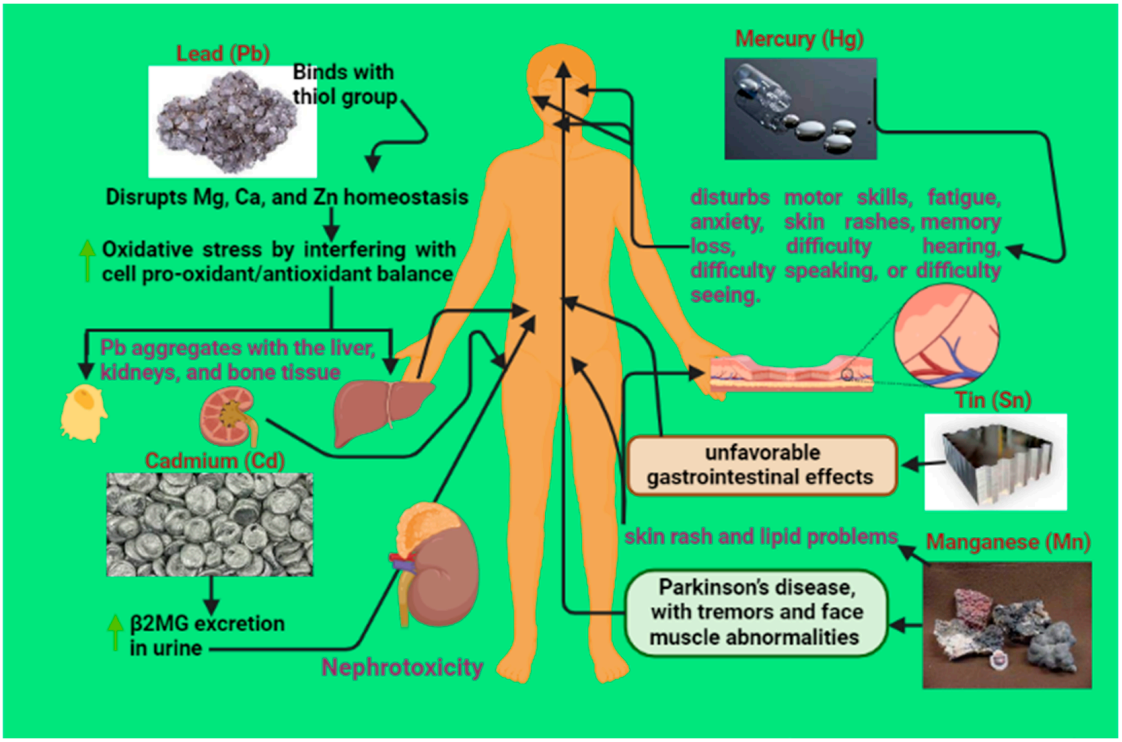

Figure 1. The mechanism of Pb, Cd, Hg, Sn, and Mn and their side effects in different organs.

2.2. Lead (Pb) Toxicity

Most occurrences of Pb poisoning in humans result from ingestion and absorption through the digestive tract [24]. Physical factors and the physicochemical nature of the material consumed influence Pb absorption through the gastrointestinal tract [25]. Soft tissue, such as the liver, the kidneys, and bone tissue, aggregates Pb that is absorbed in the intestines over time [24]. To go from the digestive tract to the rest of the body, Pb binds to haemoglobin in red blood cells (RBCs). The erythrocyte compartment contains over 99% of Pb in blood, with the serum and plasma compartments containing around 1%. Pb content in plasma, as opposed to whole blood, is crucial for Pb distribution throughout different organs. Pb has a half-life of 35 days in the blood and 40 days in soft tissue. Bone can store Pb for up to 30 years, and as people get older, their teeth and bones accumulate more Pb [24]. It is hypothesized that youngsters have a much longer biological half-time for Pb than adults. Toxic Pb levels are thought to block enzymes and disrupt Mg, Ca, and Zn homeostasis because of the interactions between Pb and the thiol groups in proteins. Pb toxicity causes oxidative stress by interfering with cell pro-oxidant/antioxidant balance. Pb-induced oxidative stress is thought to be mitigated by foods rich in antioxidants [26].

According to dose–response analyses, the JECFA estimated a PTWI and found that it was associated with a 3-point drop in intelligence quotient (IQ) in children and an increase of about 3 mmHg (0.4 kPA) in systolic blood pressure in adults [24]. The significance of a change in the IQ or blood pressure distribution among a population increases when seen in these terms. As a result, the JECFA decided that the PTWI was no longer a sufficient health precaution and revoked it. The JECFA concluded that a new PTWI deemed health protective could not be created because the dose–response study did not provide evidence of a critical threshold for the significant impacts of Pb. The JECFA reaffirmed that Pb's neuro-developmental consequences are most concerning for developing fetuses, infants, and children [25,27]. Standards for allowable amounts of Pb in certain foods have been established by the European Commission [28]. The effective diminution of Pb in food is widely credited to interventions such as the abolition of leaded gasoline, the prohibition of Pb in wine bottles, and the end of soldered cans [29]. The damage to the *Homo sapiens* brain is too extensive for treatment to be effective. Hence, the resulting alterations in behaviour

are permanent and uncurable. The WHO and the FAO have approved daily Pb intakes of up to 7 μg/kg body weight or 490 μg of Pb for adults. Although infants and children are especially vulnerable to low Pb levels, no guidelines are provided for them [30,31].

Pb enters the body via various routes, including inhaling Pb-laden dust carried by wind, consumption of Pb-contaminated soils, oral intake of Pb-contaminated water, and consumption of food cultivated in Pb-contaminated areas. There is concern that eating meat from cattle with accumulated Pb in their tissues poses a significant health risk [32,33]. Once into the body, Pb travels through the circulatory system via RBCs. Most of the Pb that enters RBCs is linked to haemoglobin rather than the membrane [31]. As a result of its potential toxicity to the haematological system, Pb exposure has been linked to an increased risk of anaemia [34]. It has been shown by histopathological analysis that Pb ions are taken to the liver, where they might cause long-term harm.

Furthermore, Pb poisoning raises blood enzyme levels and lowers protein synthesis. Pb causes kidney toxicity by altering the kidney's excretory activity and damaging its structure [35–38]. Other organs and tissue systems impacted by Pb exposure include the neurological, cardiovascular, and reproductive systems [34,38,39]. Heavy mineralization of bones and teeth is a substantial strain on the body caused by Pb poisoning [31,40,41] (represented in Table 1 and Figure 1).

2.3. Mercury (Hg) Toxicity

Before widespread poisoning deaths in the 1950s, Hg was not considered a significant contaminant. More lately, health consequences have been identified at relatively lower levels of exposure, and monitoring information must now be evaluated from this perspective. Hg exposure in humans is thought to occur primarily through the ingestion of fish. Most Hg ends up in the ocean due to natural processes and direct commercial releases. MeHg, a by-product of inorganic Hg's methylation, accumulates in aquatic organisms and humans through the food chain. MeHg concentrations in fish have been steadily rising due to human activities, such as the acidity of freshwater streams and lakes and water impoundment for massive hydroelectric plants. As MeHg goes up the aquatic food chain, it becomes increasingly concentrated.

The average MeHg concentration in marine fish is <0.5 ppm, while sharks, sailfish, marlin, and other billfish often have over 1 ppm. A lot more MeHg could be present when there is pollution in the water supply. Dentists are at a higher risk for Hg exposure because they work with Hg amalgams. Researchers have shown that dentists and dental experts have higher levels of Hg in their toenails than the general population or the control group when tested for exposure to the metal through fish consumption [42,43].

Given the unusually high levels of naturally occurring Hg in the Mediterranean basin, it has been intensively researched during the past 20 years. The Hg levels in the bodies of marine animals in this basin are significantly greater than those in the Atlantic for the same (or comparable) species. MeHg is the most common type of Hg in marine life. In coastal fishing villages, pregnant women, in particular, are at risk from the protracted and regular consumption of seafood with high Hg levels. Numerous studies have indicated that fishermen from coastal settlements of the Tyrrhenian Sea have abnormally high levels of Hg in their blood and hair. In certain instances, a rise in blood cell DNA damage has been linked to these quantities. Elevated Hg levels in the hair and blood of people from a fishing community of Madeira have also been detected. There should be a fresh look at these data to determine what preventative measures are required [44]. The incidence of alkyl-Hg poisoning in rural Ghana was studied, totalling 144 cases. The patients had unwittingly consumed maize prepared for planting with ethylmercury chloride. Twenty people were affected and displayed the classic symptoms of alkyl-mercury poisoning. This incident illustrates the grave health risks of using alkyl-Hg compounds as fungicides in agriculture, particularly in a less-educated rural community [45].

A severe infection can develop from Hg exposure. Depending on the kind, dose, manner, and duration of exposure, the most common symptoms of Hg poisoning are im-

paired motor skills, fatigue, anxiety, skin rashes, memory loss, difficulty hearing, difficulty speaking, or difficulty seeing. In extreme cases of MeHg poisoning, Minamata disease can develop [46]. Hg poisoning has been hypothesized to cause pink disease (acrodynia), characterized by a rosy rash and flaking skin. MeHg exposure in youngsters has been linked to various serious health issues later in life, such as renal disease and cognitive impairment. Long-term, low-dose exposure to MeHghas not been fully elucidated. Hg poisoning is one means by which suicide attempts are carried out. Hg levels can be measured in bodily fluids, such as blood, urine, and hair, but the results are not always accurate [43] (represented in Table 1 and Figure 1).

2.4. Tin (Sn) Toxicity

Around 20% of Europe's annual production and around 25,000,000,000 food cans contain plain internally (unlacquered) Sn-coated steel bodies. Roughly 80 billion cans are used as food containers annually around the world. Cans for drinks are also commonly made from tinplate. Over fifteen billion internally lacquered tinplate beverage cans are made and used annually in Europe. Sn can leach into the contents of food and drink through containers made from tinplate, especially if the containers' inside surfaces are left untreated. Maximum allowable levels of Sn in food are usually 250 mg/kg (200 mg/kg in the UK) for solid foods and 150 mg/kg (2.5 mmol/L) for liquids, with a PTWI of 14 mg/kg body weight [47–50]. According to environmental research, Sn species (inorganic and organotin) quickly adsorb onto solid particles [49,51]. As a result, Sn in foodstuffs may adhere to either solid particles (fibers) or pectins. Hydrochloric acid is not a simple solution for releasing Sn that has been fixed in this manner [52]. Similarly, it is challenging to dislodge Sn from solid food using artificial gastric juices, and intestinal enzymes do not play a role in the solubilization of Sn bound to proteins. However, 90% of Sn absorbed into the solid component of meals is released by alkaline digestive secretions [53].

Dietary sources account for most people's exposure to Sn, especially from eating goods stored in unlacquered Sn cans [49,54]. It has been calculated that the average French person consumes 2.7 milligrams of Sn per day, or 0.04 milligrams per kilogram of body weight, from the 5.6% diet of food preserved in Sn cans [54]. As a comparison, the PTWI is 14 mg/kg. Therefore, a daily dose of 2 mg/kg is significantly lower. It has been calculated, however, that a Western adult could consume an additional 109.1 mg of Sn per day, with the vast majority of this amount coming from fruits (fruits contain 500 mg/kg of Sn, while meat contains 2 mg/kg, potatoes contain 22 mg/kg, spinach contains 2 mg/kg, and cereals contain 47 mg/kg) [55].

Some documented data suggest that consuming foods or beverages with Sn concentrations at or below 200 ppm has resulted in negative gastrointestinal symptoms in an undetermined but possibly modest percentage of those exposed. The data backing this claim come from claims of negative impacts with either sparse, imprecise, or dubious reliability. Few informative studies have been conducted, although clinical trials provide more assurance on exposure concentration and dose consequences. At slightly beyond 700 ppm, unfavourable gastrointestinal effects were seen in clinical studies. However, two studies at even larger doses revealed no such effects. Consequently, the available research does not provide a notably thorough profile of the hazardous danger to humans due to acute exposure to divalent inorganic Sn. Over 2.5 million of canned foods are consumed annually in the UK only, and a poll showed that approximately 4% of bare internal tinplate food cans have over 150 mg/kg of Sn. While this is the case, no acute effects due to Sn poisoning in the range of 100–200 ppm have been reported in the last 25 years. These data imply minimal proof that eating foods with Sn contents up to 200 ppm cause immediate gastrointestinal symptoms. However, only more clinical research will produce unambiguous proof that the existing regulatory restrictions offer safety limits for people in the general population [49,56–60] (represented in Table 1 and Figure 1).

2.5. Manganese (Mn) Toxicity

Even though the body needs it, too much of the mineral Mn can be harmful [61–64]. The recommended intake of Mn is 1.8 (women) or 2.3 (men) mg/d, while the upper limit is 11 mg/d, according to the National Academy of Sciences [65]. Most individuals acquire Mn through food, with some vegans consuming >10 mg daily. There is still some doubt as to whether or not ambient Mn might be a source of overexposure, according to the Environmental Protection Agency (EPA)and the Food and Drug Administration [66].

Mn deficiency may result in skeletal abnormalities [67] and poor lipid metabolism [68,69], but it is incredibly uncommon in humans [69–71]. One participant exhibited skin rash after consuming a diet devoid of Mn [68]. Toxicity, on the other hand, is far more prevalent and is present in Parkinson's disease, with tremors and face muscle abnormalities [64]. The evidence linking trace element status, particularly Mn status, to abnormal behaviour is scant, but it exists [72,73]. Increased levels of Mn in hair are associated with aggression in a prison population [74,75]. However, there are limited data to suggest that Mn from high Mn meals may cause concern, and most cases of Mn toxicity have been documented in people exposed to very high levels of Mn dust (such as miners) [73,75,76] (represented in Table 1 and Figure 1).

2.6. Aluminum (Al) Toxicity

Al is present in every kind of food. Corn, yellow cheese, salt, herbs, spices, tea, and tap water can all be good places to start looking for Al [77]. Al can be abundant in natural and processed foods [78–83]. Not all plants have the same Al uptake [84,85]. Plants grown in acidic soil particularly accumulate Al at a higher rate [84,86]. Food contact materials that migrate Al into the food they come into contact with are another possible source of Al in processed foods [87]. Al comes primarily from household wares made of Al. Many metabolic processes, including the recycling of calcium, phosphorus, and iron, can be hampered by Al, which may contribute to human disease. Al salts may impede enzymes, such as hexokinase, acid and alkaline phosphatase, phosphodiesterase, and phosphooxygenase, and bind to DNA and RNA. Nervous and hematopoietic systems and the skeleton are incredibly vulnerable to the ill effects of Al salts. Food, water, and cosmetics stored in Al containers introduce Al to the body. Al neurotoxic action is likely due to Mg ion substitution in ATP, affecting the activity of all ATP-using enzymes. Evidence from experimental models implicates Al salts in the pathogenesis of Alzheimer's disease. Because Al is toxic to the skeletal system, it reduces collagen synthesis and slows down mineralization, weakening resistance and leading to a propensity toward breaking. Anaemia is caused by a lack of erythropoietin, the inhibition of heme-synthesizing enzymes, and the binding of Al to transferrin. Elevated levels of Al have been found in many neoplastic cells, but the carcinogenic effects of Al have neither been confirmed nor refuted. In conclusion, we should implement preventative measures that result in lower Al intake, such as decreasing the consumption of Al-containing foods and beverages and decreasing the use of Al-containing products [77,88–92].

High Al intake has been linked to problems in the nervous system, bones, and blood-forming hematopoiesis. Al intake should be kept below 1 milligram per kilogram of body weight per week, as determined by the European Food Safety Authority. Worldwide, Al consumption varies significantly due to regional differences. An analysis of the findings from different studies demonstrates that people's exposure to Al in their diets varies considerably. In adults, the average weekly exposure was between 0.2 and 1.5 mg/kg of body weight. Maximum exposure of 0.7–2.3 mg/kg body weight was determined for children and adolescents due to their lower body weight. An adult weighing 70 kg would consume 14–105 milligrams of Al per week, while a child weighing 30 kg would consume 21–69 milligrams per week. According to these calculations, some people can obtain their recommended weekly allowance of Al simply by eating the right foods [93]. The FAO/WHO Experts Commission on Food Additives reported in 1989 that the average

daily intake of Al for children is 2–6 mg/kg, and 6–14 mg/kg for adults. Al has a PTWI value of 7 mg/kg [94] (represented in Table 1).

2.7. Chromium (Cr) Toxicity

Except for refined sugar, it appears that canned and other processed foods are higher in Cr than fresh foods. Nonetheless, Cr can be found in abundance in brown sugar and molasses. Sugar cane from the Virgin Islands has been shown to have lower Cr content (0.07 µg/g) than sugar cane from Colombia (0.35µg/g) [95]. Cr can be leached from stainless steel equipment, especially in acidic environments, which is likely to be present during the production of these goods [96]. Some European staples, such as wheat and wheat flour, have a Cr content of 5–10 µg/g dry weight, whereas potatoes and cow's milk have a Cr content of around 5 µg/g dry weight [97]. Weaned toddlers and adults can use these nutritional staples in their diets [98]. Intakes in the general population range from 13 to 49 µg/d, with older adults exhibiting even more significant variation at 27–61 µg/d [99]. Dietary intake above 25 µg (0.5 µmol)/d for adults and between 0.1 and 1.0 µg/kg/d (2 and 19 nmol/k/d) for children and adolescents are considered safe and appropriate. However, any reference nutrient intakes (RNI) for Cr compounds have not yet been established [98,99]. The kidney is the primary organ exposed to some Cr compounds, especially hexavalent Cr compounds, which are carcinogenic and corrosive, and are also delayed contact sensitizers. However, Cr is a vital component of human life. The human body can eliminate the substance from its system by being exposed to hexavalent Cr compounds [100] (represented in Table 1).

2.8. Iron (Fe) Toxicity

More than half of all humans rely on lowland rice as their primary source of nutrition. The productivity of lowland rice is severely hampered by Fe toxicity, a common nutritional condition. Submerged or flooded soils have a deteriorated soil condition, increasing the concentration and uptake of Fe, which contributes to Fe's toxicity [101–103]. Toxic effects from intaking too much Fe exist, and therapeutic dosages can induce stomach upset. As seen in primary and secondary hemochromatosis, hepatic fibrosis, diabetes, and heart failure have all been linked to prolonged Fe overload. Sub-Saharan Africans developed cirrhosis and diabetes after regularly ingesting 50–100 mg Fe/day of highly accessible Fe through their home-brewed beer. To prevent this common Fe toxicity endpoint, a safe upper threshold must be carefully calculated [104] (represented in Table 1).

2.9. Nickel (Ni) Toxicity

Ni is a poisonous metal which primary sources are marine fish and plants watered with untreated sewage. Considering its migration during food processing or packaging, the prospective measurement of Ni levels in food and diet is of utmost importance. Depending on variables such as temperature, pH, contact time, food category, and processing technology, stainless steel appliances and ceramics can be the essential suppliers. Ni intake data are limited and do not reveal significant differences between geographic regions. It is vital to know the bioavailable fraction of Ni and the bioavailable fraction of species that contain it [105]. The adult/lifetime toxicological reference values (TRV) of 20 µg Ni/kg-day are based on post-implantation loss/perinatal death data from a two-generation rat reproductive study [106]. Exposure to Ni carbonyl is the cause of nearly all occurrences of acute Ni poisoning. The earliest consequences include nonspecific symptoms and inflammation of the respiratory tract. Patients who have been severely poisoned may experience significant respiratory and digestive damage. Death typically results from cerebral edema or diffuse interstitial pneumonitis. When Ni carbonyl has been inhaled, sodium diethyldithiocarbamate, an experimental medication, is used to chelate the metal [107]. Consumption of 325 mg causes vomiting, dizziness, and a slowing of heart rate [107–109] (represented in Table 1).

Table 1. The role of heavy metals, the sources of heavy metals, recommended usage of heavy metals, and their side effects.

Metal	Sources	Recommendation of Intake	Side Effects	Reference
Cadmium (Cd)	staple food, rice, and several specific foods, such as animal kidneys, blood cockle, and local vegetables	The European Food Safety Authority's (EFSA) panel on contaminants in the food chain recommended in 2009 that the PTWI be lowered to the tolerable weekly intake (TWI) level of 2.5 µg/kg body weight.	Kidney disease, osteoporosis, diabetes, cardiovascular disease, and cancer	[21]
Lead (Pb)	wind, consumption of Pb-contaminated soils, oral intake of Pb-contaminated water, and consumption of food cultivated in Pb-contaminated areas	The WHO and the FAO have approved daily Pb intakes of up to 7 µg/kg body weight or 490 µg of Pb for adults.	liver, kidneys, and bone tissue	[32,33]
Mercury (Hg)	ingestion of fish, whale sharks, sailfish, marlin, other billfish, and mercury amalgams	-	impaired motor skills, fatigue, anxiety, skin rashes, memory loss, difficulty hearing, difficulty speaking, difficulty seeing, Minamata disease, and acrodynia	[42,43]
Tin (Sn)	Cans for drinks are commonly made from tinplate. Over fifteen billion internally lacquered tinplate beverage cansare made and used annually in Europe	Maximum allowable levels of tin in food are usually 250 mg/kg (200 mg/kg in the UK) for solid foods and 150 mg/kg (2.5 mmol/L) for liquids, with a provisional tolerable weekly tn intake of 14 mg/kg body weight.	unfavourable gastrointestinal effects	[47–50]
Manganese (Mn)	foods, with some vegansconsuming > 10 mg daily	Recommended intake of Mn is 1.8 (women) or 2.3 (men) mg/d, while the upper limit is 11 mg/d, according to the National Academy of Sciences.	Parkinson's disease, with tremors and facial muscle	[64]
Aluminium (Al)	Corn, yellow cheese, salt, herbs, spices, tea, and tap water	Al intake should be kept below 1 milligram per kilogram of body weight per week, as determined by the European Food Safety Authority. Food Additives reported in 1989 that the average daily intake of aluminium for children is 2–6 mg/kg, and for adults, 6–14 mg/kg. Al has a PTWI value of 7 mg/kg.	pathogenesis of Alzheimer's disease, impaired skeletal system, reduced collagen synthesis, slowed down mineralization, weakening resistance, and a propensity toward breaking	[77]
Chromium (Cr)	canned and other processed foods, brown sugar, and molasses	Dietary intake above 25µg (0.5µmol)/d for adults and between 0.1 and 1.0µg/kg/d (2 and 19 nmol/k/d) for children and adolescents are considered safe and appropriate. However, the Panel has not established any reference nutrient intakes (RNI) for Cr compounds.	carcinogenic, corrosive, and delayed contact sensitizers	[98,99]

Table 1. *Cont.*

Metal	Sources	Recommendation of Intake	Side Effects	Reference
Iron (Fe)	lowland rice	To prevent this common iron toxicity endpoint, a safe upper threshold of 25–50 mg Fe/day can be calculated by applying a safety factor of 2.	stomach upset, primary and secondary hemochromatosis, hepatic fibrosis, diabetes, and heart failure	[104]
Nickel (Ni)	marine fish and plants watered with untreated sewage	Consumption of 325 mg causes vomiting, dizziness, and a slowing of heart rate.	respiratory and digestive damage, cerebral edema, or diffuse interstitial pneumonitis	[107–109]

3. Metalloids in Food Toxicity

3.1. Arsenic (As) Toxicity

Millions of people worldwide are at risk from exposure to carcinogenic As. Humans can be exposed to these chemicals through various foods and drinks, including tap water, crops, processed foods, vegetables, mushrooms, animal products, and more. In As pollution hotspots, Bangladesh and West Bengal, India, are at the most significant risk. Researchers have discovered that even rice grown in relatively clean areas, such as Australia, can have dangerous amounts of the toxic element As. Many countries import and export rice, which means this is a worldwide issue [9,110–113].

In rural communities of West Bengal, where clean drinking water was already being delivered, Halder et al. (2013) evaluated the risk of exposure to As [114]. It was discovered that the total daily intake of inorganic arsenic (iAs) was surpassed in 35% of cases, the As concentration in drinking water was <10 µg/Land in 100% of cases, and the As concentration in water was >10 µg/L when the PTDI limit of 2.1 µg/day/kg body weight was taken into account [110,115]. In reality, the WHO suggested a Benchmark Dose Lower Limit (BMDL0.5; suggesting a 0.5% increased incidence of cancer) for As in 2011 after withdrawing the PTDI and PTWI values for As. Lung cancer, bladder cancer, and skin lesion BMDL 0.5 values were established in the study to be 3 µg day/kg/body weight, 5.2 µg/day/kg/body weight, and 5.4 µg day/kg/body weight, respectively [116–118].

In a study, turnip was grown in soilless circumstances to examine its ability to absorb As. Four As species were used in a 4 × 3 factorial experiment examining the effects of As concentrations (1.0, 2.0, and 5.0 mg/L). As speciation was the primary determinant of As's phytoavailability and phytotoxicity, this turnip variety was phytotoxic to organic arsenicals [96]. Higher upward translocation was seen for organic arsenicals compared to inorganic arsenicals, which likely contributed to the greater phytotoxicity and lowered dry matter outputs of these organic treatments. Concentrations in the inner and outer root skin were significantly higher than the regulatory threshold for As in crops used for human consumption (1.0 mg/kg). If turnip plants are grown in polluted nutrient solutions, they will accumulate residues of As at unsafe levels for ingestion by animals or humans [119].

3.2. Antimony (Sb) Toxicity

Sb can leach from food contact polymers into foods or drinks after long storage periods at high temperatures [120]. Sb oxide is in the List of Indirect Additives Used in Food Contact Substances (LIAUFCS) maintained by the U.S. Food and Drug Administration (FDA) [121]. Sb trioxide is not included in the LIAUFCS chemical database. Sb trioxide's Cumulated Estimated Daily Intake (CEDI) from food contact items is predicted by the FDA to be 0.0001 mg/kg body weight daily [120,122,123].

In one study, the researchers used atomic fluorescence spectrometry (AFS) coupled with a hydride generation device (HG-AFS) to examine the levels of Sb leached from polyethylene terephthalate (PET) bottle material in 12 different brands of bottled water sold in Mexican supermarkets. Sb was preconcentrated from the water samples using a Dowex®

1X8-100 ion-exchange resin. Waltham, MA, A The chronic daily intake (CDI) induced by the release of Sb in one brand was 514.3 and 566.2 ng/kg/day, respectively, which is higher than the USEPA-regulated CDI threshold of 400 ng/kg/day. Thus, it appears that the manufacture of PET bottles utilizing an appropriately selected polymer ensures low Sb levels in water samples [124]. The short-term experiments lasted up to 15 days, and the long-term trials lasted up to 220 days, both of which examined the impact of storage time and temperature on Sb migration from PET bottles into mineral water. Measurements of Sb migration were performed using HG-AFS for total determination and using high-performance liquid chromatography (HPLC) in combination with inductively coupled plasma mass spectrometry (ICP-MS) (HPLC-ICP-MS) for speciation analysis. According to this migratory research, there was no Sb movement in waters kept at 4 and 20 °C. After 30 days of storage at 60 °C, substantial Sb migration was seen, but at 40 °C, the maximum limit imposed by the European Union (5.0 µg/L) was not surpassed in any of the samples. In this example, Sb (V) and Sb (III) were found to exceed the EU's maximum limit [125].

3.3. Selenium (Se) Toxicity

Food is the primary source of Se for human beings. Toxic Se levels in the body have been linked to Se-rich food consumed in seleniferous regions [126]. Soil Se levels are a good indicator of the Se levels in food and the population. Geography, weather, the availability of specific proteins, and how meal is prepared all play a role in determining the overall Se content. Se levels in soil and food supply must be tracked regularly. Most Se comes from diet, with absorption rates ranging from 70 to 80%. Generally speaking, organic forms of Se are more bioavailable than inorganic forms of Se. However, this does depend on a person's Se source and nutritional state [127–129]. Symptoms of prolonged Se exposure in humans include hair loss and nail deformities. Human Se status and exposure over the long term can be evaluated by measuring the amount of Se in hair and toenails; this can be contrasted with a short-term evaluation of Se status using blood and urine levels [126,130]. Intriguing research has linked Se consumption to a lower chance of developing prostate and colon cancers. Nevertheless, randomized trials for other forms of cancer have shown mixed results. Males and females are advised to consume 55 µg/day (0.7 µmol/day). The plasma isoform of glutathione peroxidase (GPx) activity plateaus at a particular concentration, and, thus, this suggestion is dependent on that value. Based on selenosis being the adverse consequence, the Tolerable Upper Intake Level (UL) for adults is 400 µg/day (5.1 µmol/day) [131].

4. Detection of Heavy Metal and Metalloid Contaminants in Food Toxicity

4.1. Atomic Absorption Spectrometry (AAS)

Since each element has its own unique set of energy levels, AAS relies heavily on the ability to selectively detect its atoms. To obtain a linear calibration curve (Beers' Law), the monochromator's bandwidth must be larger than the light source's, which is challenging to perform with conventional monochromators. Because of the thousands of lines produced by all of the elements in a sample, the monochromator is a crucial component of an AAS [132].

Experimental findings from 16 different labs have resulted in a technique for detecting Pb, Cd, Zn, Cu, and Fe in meals using AAS following dry ashing at 450 degrees Celsius. Before the actual study began, familiarization samples were used for practice, solutions were passed out, and metal concentrations were evaluated using AAS. Liver paste, apple sauce, minced fish, wheat bran, and milk powder were the five foods tested in this study. Every specimen underwent the same analysis. When calculating the repeatability standard deviation, the researchers employed appropriate sample combinations as split-level combinations. Pb concentrations of 0.040–0.25 mg/kg had a repeatability relative standard deviation of 20–50%, Cd concentrations of 0.001–0.51 mg/kg had a range of 12–352%, Zn concentrations were 0.7–8.0%, Cu concentrations were 0.5–45%, and Fe concentrations were 11–14% [133]. It has been claimed that $Cr^{3+,}$ Fe^{3+}, Cu^{2+}, Ni^{2+}, Co^{2+}, and Zn^{2+} may all be preconcentrated in genuine samples using a straightforward and sensitive technique.

Adsorption of analytes onto activated carbon loaded with bis salicyl aldehyde, 1,3-propane diimine (BSPDI) is the basis of this technique. Nitric acid in acetone is used to elute the metals adsorbed onto the modified activated carbon. Analytical variables, including sample volume and pH, are studied for their effects on the results. Matrix ion effects on analyte retentions are also investigated. Most analyte recoveries are measured in decimal quantities. Some food samples have been tested using this method to effectively determine the amount of these metals present in them [134]. Analytical parameters, such as thulium concentration, pH, reaction time, and others, that affected the quantitative coprecipitation of analytes were studied. This research was also conducted to determine how alkali and certain transition metals impacted the recoveries. For each analyte, the detection limits improved from 0.1 to 1.6 μg/L under the ideal conditions. Certified reference materials were analyzed to verify the validity of the presented coprecipitation process. Cu, Co, Cd, Ni, Mn, Fe, and Pb have all been correctly identified in food and environmental samples using the suggested coprecipitation approach [135]. Altering Fe oxide-silica magnetic particles with a freshly synthesized Schiff base (Fe_3O_4/SiO_2/L) resulted in a flexible and robust solid phase with magnetic properties and a very high adsorption capacity, as reported in another study. X-ray diffraction (XRD) spectrometry, transmission electron microscopy (TEM), and Fourier-transform infrared spectroscopy (FT-IR) spectra all validated the structure of the final product (TEM). The lowest detectable concentrations of Pb(II), Cd(II), and Cu(II), at optimal circumstances, were 0.14, 0.19, and 0.12 μg/L, respectively. Real-world samples have been effectively analyzed using the developed approach, with encouraging outcomes. All of these facts point to the immense potential of this magnetic phase in ecological and biological contexts [136]. Another work displayed that graphite furnace AAS was used to compare the results of dry and wet ashing to calculate the amounts of heavy metals (Pb, Cd, Fe, Cu, Mn, and Zn) in fish samples [137] (represented in Figure 2). Unfortunately, AAS can only be used to analyze solutions, so it has some restrictions. It is also less sensitive than a graphite furnace, calls for a lot of sample material (around 1–3 mL), and has many issues with refractory substances. Its tremendous sample throughput and user-friendliness more than make up for its flaws [138–140]. Many spectrometers were developed over the years with the addition of new technology, but many were eventually abandoned because of issues with sensitivity, background adjustments, and other factors. As a result of prior work, however, high-resolution continuum-source atomic absorption spectrometry (HR-CS AAS) with flame and furnace atomizers is already well established. It paves the way for the development of highly sensitive and effectively background-corrected sequential and simultaneous methods for the determination of a wide range of elements [13,141].

4.2. Spectrofluorimetry

The study of substances that emit light, or fluorescence, is the focus of spectrofluorimetry. It takes advantage of the fact that electrons get even more excited when they collide with other excited electrons or high-energy objects such as photons [142,143].

In one stuy, Al and Zn traces were effectively extracted using cloud point methods before being determined by spectrofluorimetry. Al and Zn in a surfactant solution react with 8-hydroxyquinoline to form a hydrophobic compound, which is subsequently trapped in surfactant micelles. Factors that influenced complexation and phase separation were optimized. Preconcentration of 25 mL of the sample in the presence of 0.12% (v/v) Triton X-114 enabled the detection of 0.79 μg/L of Al and 1.2 μg/L of Zn under the circumstances of the research. Five independent determinations yielded relative standard deviations of 2.72 and 2.1% for Al and Zn, respectively, at concentrations of 40 and 100 μg/L. Recoveries for the spiked samples were very high, between 95% and 104%. This strategy determined Al and Zn concentrations in various samples [144].

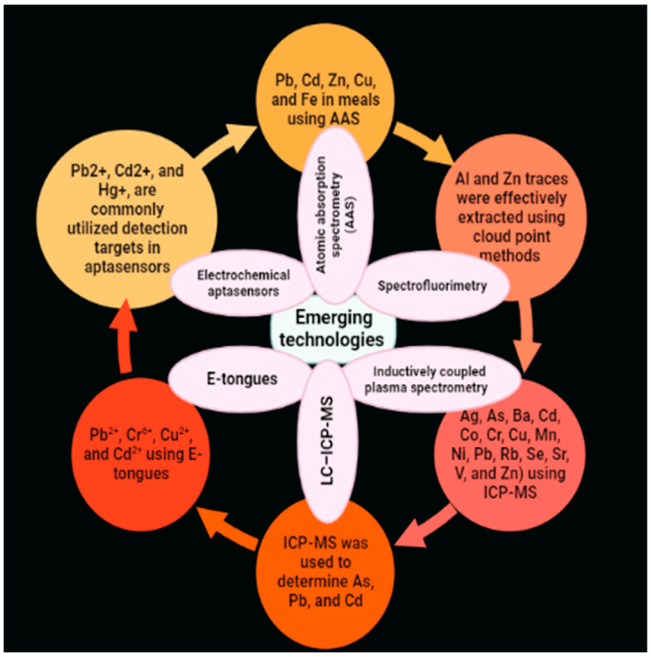

Figure 2. Different emerging techniques, including electrochemical aptasensors, AAS, spectrofluorimetry, inductively coupled plasma spectrometry, LC–ICP-MS, and e-tongues, and their role in the determination of heavy metals in different samples.

A study utilized stopped-flow injection spectrofluorimetry (SFIS) and an effective in situ solvent formation microextraction (ISFME) to measure Cu. The ionic liquid was used as an extractant phase after thiamine was oxidized with Cu(II) to produce hydrophobic and extremely luminous thiochrome (TC). Phase separation followed centrifugation, and SFIS was used to identify the enriched analyte. ISFME is an effective technique for removing metal ions from high-ionic-strength aqueous solutions and concentrating them beforehand. An analysis of performance variables was investigated and optimized. The suggested approach's limit of detection (LOD) was 0.024 µg/L under ideal experimental circumstances, with a relative standard deviation (RSD) of 2.1%. Recovery trials and analysis of standard reference materials were used to gauge the efficacy of the combined process (GBW 07605 Tea). Cu concentrations in water and food samples were satisfactorily determined using the proposed approach [145]. With the help of some cutting-edge reaction strategies, the spectrofluorimetric reagent 2-(-pyridyl)-thioquinaldinamide (PTQA) was recently produced and described. Using PTQA, a new spectrofluorimetric approach for detecting vanadium (V) at Pico-trace levels has been devised. This method is extremely straightforward, ultra-sensitive, and highly selective without extractive chemistry. Direct non-extractive spectrofluorimetric V detection using PTQA has been suggested as a new analytical reagent. In a mildly acidic V solution in 20% ethanol, PTQA is oxidized to form a highly fluorescent oxidized product, making it a novel fluorimetric reagent. V was effectively determined using the proposed model in a wide variety of environmental waters (potable and polluted), biological fluids (human blood, urine, hair, and milk), soil samples, food samples (vegetables, rice, and wheat), and complex synthetic mixtures containing V (IV) and V (V). An analysis of the biological, food, and vegetable samples using the suggested method yielded findings that were similar to those obtained using inductively coupled plasma-optical emission spectroscopy (ICP-OES) and AAS [146]. A bright blue-green colour complex between Al(III) and salicylaldehyde picolinoylhydrazone (SAPH) has been examined as a simple and inexpensive spectrofluorimetric substitute for Al detection in bivalve mollusks. Numerous samples of fresh and canned bivalve mollusks showed that this approach accurately and reliably determined the amount of Al present. The findings revealed that Al concentration was lowest in commercially available fresh wild items

(6–27 mg per 100 g dry weight) and highest in bivalves preserved in cans (75 mg per 100 g dry weight). That is how the study has clarified that there are processing-related variations in Al concentration. Its results demonstrate a straightforward, low-cost, and trustworthy method for routinely determining Al content in seafood for quality control [147]. This method's incredible sensitivity and specificity are some of its main benefits. The speed and accuracy of its diagnosis are another advantages. One major drawback is that not all chemicals exhibit fluorescent properties [148]. Compared to HPLC and similar technologies, which have lengthy run times and complicated operation processes, this one is easier to use and more convenient. In addition, the sensitivity of this approach is significantly better than that of HPLC. Substances can be analyzed to the nanogram scale. As a result, this method's high sensitivity and specificity are undeniable benefits. Quantitative methods can be developed further, allowing for simple measurements of the analyte concentration in the mixture [149] (Figure 2).

4.3. Inductively Coupled Plasma Mass Spectrometry (ICP-MS)

Samples are ionized when using an inductively coupled plasma in ICP-MS. After atomizing the material, atomic and minute polyatomic ions are detected. This method is recognized and exploited for its ability to detect metals and various non-metals in liquid samples at extremely low concentrations. It can detect many isotopes of a single element, making it a versatile tool for isotopic tagging [150,151]. Carrots and other food samples from Latvian farmlands and allotment gardens were analyzed for their levels of 15 heavy metals (Ag, As, Ba, Cd, Co, Cr, Cu, Mn, Ni, Pb, Rb, Se, Sr, V, and Zn) using inductively coupled plasma mass spectrometry (ICP-MS) and AAS. Highly hazardous metals were discovered: Ni at 0.28 mg/kg, Cr at 0.16 mg/kg, Pb at 0.05 mg/kg, and Cd at 0.12 mg/kg (mean values, dry weight). Furthermore, some trace elements (Mn, Rb, and Zn) were found in garden-grown carrot samples that were considerably greater than those found in farmland-grown carrot samples [152,153]. As, Cd, Cr, Cu, Hg, Mo, Ni, Pb, Se, and Zn were among the 19 trace elements examined by ICP-MS and atomic fluorescence in carrots grown on a reclaimed silt from the Illinois River and in reference soil [153,154]. Various sections of plants are harvested for their spices, which are then employed in various dishes. They make for easy samples when gauging daily intakes and examining how components are distributed throughout the plants. Cd is considered hazardous to human health, while As and Se are considerd both necessary and potentially dangerous. Se RDAs are between 50 and 200 μg/day. Adults should consume between 100 and 200 micrograms of As daily. Selenium is harmful at doses higher than 750 μg/day, while the weekly safe intake levels for Cd and As are 7 and 15 μg/day, respectively. With daisies (*Chamomillae Vulgaris*), bay leaves (*Folium Lauri*), mint leaves (*Folium Menthane*), rosehips (*RosaeCaninae*), sages (*Folium Salviae Officinalis*), thyme (*Herba Thymi*), cumin (*Fructus Cummuni*), sumac (*Folium Rhois Coriariae*), linden flowers (*Flos Tilliae*) (ICP-MS) as the samples, Na, K, Mg, Ca, Li, Zn, Fe, Cu, B, Hg, Pb, and Mn were determined using ICP-OES and AAS, and the results were compared to those of earlier investigations. Microwave oven digestion was performed using HNO_3 and H_2O_2 at optimal quantities. The digestion efficiency of the microwave oven was improved by fine tuning the temperature program. The influence of HNO_3 concentration on ICP-MS signals was considered as the samples were examined using the direct calibration method for Cd and the standard addition technique for As and Se. Oyster Tissue 1566b SRM was used to verify the procedures for Cd and As, while BCR Human Hair 397 SRM was used to verify the techniques for Se. While most samples had Cd concentrations between 10 and 100 μg/kg, most samples had As and Se concentrations in the 100–500 μg/kg range. Experiments with HCl, NaCl, $NaNO_3$, CsCl, $CsNO_3$, LiCl, and $LiNO_3$ were conducted to examine the impact of spectral and nonspectral interferences on As signals [155]. ICP-MS has various benefits, including high throughput (approximately 40 specimens per hour), the capacity to measure many elements simultaneously, and low detection limits (0.01 to 0.1 micrograms/L for many elements). The significant initial investment required by the instruments is a crucial draw back. ICP-MS analysis works well with heavier elements,

such as Pb, whereas it has trouble with lighter elements due to interferences. Cr and iron are examples of lighter elements that cannot be assayed using ICP-MS. Mass spectrometry techniques have a distinct benefit in that they can measure isotopes, which could increase their utility for analyzing trace elements [156] (Figure 2).

4.4. Liquid Chromatography–Inductively Coupled Plasma Mass Spectrometry (LC–ICP-MS)

At present, LC–ICP-MS is a crucial method for examining components in biological samples, especially since many modern proteomic methods are inadequate for this purpose. The sensitivity and specificity of ICP-MS for elements can be included in discovery and quantitative proteomic procedures through LC–ICP-MS. About half of all enzymes rely on metals, such as redox-active iron, copper, and manganese, for their biochemical activity [157]. Classical proteomics often misses reduced performance due to the loss of metal-binding ability since strong denaturing reagents remove metals from their parent biomolecules. ICP-MS excels in element-specific identification for many reasons, but its ability to detect endogenous metals is just one of them. After high-resolution chromatographic separation, online atomic spectrometry may detect covalently bound minor and trace elements, such as Se, S, and P. Exogenous metal exposures to biological systems, including those induced by chronic environmental toxicants such as Pb, can be studied in great detail with the help of element-specific detection techniques [158]. It is common knowledge that some elements are crucial to human survival, while others pose serious health risks. A thorough characterization of an element is necessary when considering its advantages and risks. As a result, research into the oxidation states, chemical ligand associations, and complex forms of numerous elements has seen a surge in popularity. The analysis of a sample to determine the presence or absence of a specific chemical species of an element, known as "elemental speciation," often requires the use of a separation technique coupled with an element-specific detector. Numerous techniques have been devised, each employing a unique mechanism for separation and a unique set of detecting tools. However, the combination of liquid chromatography and LC–ICP-MS has quickly become a favourite method for elemental speciation research due to its adaptability, robustness, sensitivity, and multi-elemental capabilities [159,160]. This technique was used to determine the Hg species present in seafood from the Brazilian market [161,162]. Using nontargeted and tailored speciation approaches, such as LC/ICP-MS and complementing techniques, gives a complete picture of metal and metalloid speciation in food [163]. Research has proposed a quick approach for As speciation in food samples using LC–ICP-MS. An anion exchange column was used to distinguish the species by LC. This approach was used to identify As in food samples [164]. ICP-MS was used to determine As, Pb, and Cd; ICP-OES was used to determine Al; DMA was used to determine Hg; and LC–ICP-MS was used to speciate As [165]. This method was also used to measure MeHg and inorganic divalent Hg levels in fish, vegetables, herbs, and cereal goods [166]. Traditional Korean fermented dishes prepared with shrimp and tiny fishes are salted foods. They have a unique taste as well as a long shelf life. However, the complex matrix with high salt concentration makes it challenging to examine their As content. ICP-MS is a practical approach for analyzing these kinds of samples. Interferences must be eliminated before performing As analysis using ICP-MS since the salt (NaCl) has the same mass-to-charge ratio as As [167–169]. One of the hybrid methods must involve the instrumentation required to conduct speciation investigations. It illustrates why ICP-MS has increased the use of standard separation equipment as sample introduction devices during the past decade. Although other hybrid methods have been tried, one of the most effective is HPLC paired with ICP-MS. Because of the many diverse separation processes that may be created with a range of mobile and stationary phases, HPLC is arguably the most widespread and versatile separation technology paired with an ICP-MS. There are a few reasons why this mixture has become so popular. In the conventional mode of operation of an ICP-OES or ICP-MS, sample solutions are pumped into a nebulizer, transformed into fine aerosols, and then transferred to a spray chamber, where the larger aerosol particles are removed, and finally introduced to the plasma, where

they are ionized. The plasma spectrochemical community has optimized the spray chamber and nebulizer to be reliable, versatile, and user-friendly [160]. The many methods of separation and the numerous devices for detecting individual elements have been the subject of several scholarly works. Yet, the combination of liquid chromatography and LC–ICP-MS has become the most preferred approach for elemental speciation research due to its versatility, robustness, sensitivity, and multi-elemental capabilities. Some common LC–ICP-MS applications include the speciation of environmental, biological, and clinical samples [160] (Figure 2).

4.5. E-Tongues

The need for affordable, rapid-response monitoring systems to detect heavy metals and toxins in water supplies has developed alongside rising public awareness of the importance of these issues. E-tongues are multi-sensory displays that use electroanalytical procedures and multivariate statistical approaches to help people see data in new ways, qualitatively and quantitatively [170]. E-tongues are sensor arrays that use the notion of global selectivity, in which the variation in electrical response between materials acts as a fingerprint for the analyzed sample to tell apart chemically identical liquids. They have found widespread application in analyzing a variety of beverages, including wine, fruit juice, coffee, milk, and other beverages, and in detecting minute quantities of contaminants or pollutants in water. Electrochemical measurements and impedance spectroscopy are two of the most used detection principles. For the most part, ultrathin films fabricated in a layer-by-layer method are used as the materials for the sensing units because they provide increased sensitivity and allow for greater control over the molecular architecture of the film. Biosensing utilizes sensing units susceptible to molecular recognition, such as films containing immobilized antigens or enzymes with special recognition for clinical diagnosis, expanding the idea of e-tongues. Since sample recognition is fundamentally a classification task, there has been a recent push to improve e-tongues by applying artificial intelligence (AI) and data visualization techniques [171]. E-tongues are an attractive possibility to confront several current environmental monitoring obstacles, especially those about major contaminants such as heavy metals, due to their simple working, fast reaction, low cost, and effortless integration with other systems (microfluidic, optical, etc.) [170]. The development of e-tongues in the sensor age has sparked a new golden age for tasting and rating food [172]. Potential techniques for quick food assessment include gas chromatography-olfactory (GC-O), chemical sensor technology (electronic nose and tongue), and multivariate data processing techniques [173].

To perform complex liquid analysis, it has been found that a sensor array consisting of several electrodes with no selectivity or poor selectivity is superior to a sensor array consisting of highly selective electrodes [174]. For this reason, an electronic tongue system to detect heavy metal ions in complex liquid media has emerged as a promising option. Sensitive and chemically stable ion-selective chalcogenide glass sensors were created by Vlasov and Legin [175–179]. Furthermore, their study showed how flow injection analysis (FIA) might be combined with a potentiometric e-tongue later. Seven chalcogenide glass sensors were used to take real-time readings of Pb^{2+}, Cr^{6+}, Cu^{2+}, and Cd^{2+} ions at a waste incineration pilot facility [170,180]. In addition to being an enticing alternative to conventional methods, it has other advantages, including low cost, portability, and rapid answers, among others. One of e-tongues' primary advantages is their capacity to determine the total phenolic content and the individual speciation of specified groups or individual compounds. Consequently, this is advantageous since the same device may perform both functions without the need for cumbersome laboratory equipment, whereas with conventional approaches, each task must be performed individually [181] (represented in Figure 2).

4.6. Electrochemical Aptasensors

While conventional heavy metal detecting technologies, such as AAS, have a low detection limit, they also have several drawbacks. Consequently, creating a quick method for online and real-time detection of heavy metals is crucial. As a result of its high sensitivity, specificity, and reliability, the electrochemical aptasensor-based technique holds great promise in detecting heavy metals. Though progress is being made quickly, additional study is needed before this technology can be used for on-site detection. Electrochemical aptasensors for heavy metal detection are a growing area of study and industrial use [182–186].

Aptamers are single-stranded deoxyribonucleic acid (ssDNA) or ribonucleic acid (RNA) generated using the SELEX (Systematic Evolution of Ligands by Exponential Enrichment) technique [187,188]. Fixed sequences at both ends and random sequences in between characterize the oligonucleotide library in the basic process of SELEX [189]. In polymerase chain reaction amplification, primers can bind to a specific place in the fixed sequence. The heterogeneity of the library is ensured by the fact that each nucleic acid molecule has a unique spatial configuration, which is defined by a random sequence of 30-60 nucleotides [190]. SELEX's four most common processes are binding, separation, amplification, and purification [191]. The SELEX procedure [192] improves the purity of oligonucleotides by isolating them from a vast, randomly assembled library by selecting those with a high affinity for the target. The number of SELEX cycles necessary to terminate the process is determined by measuring the enrichment of the DNA library after each cycle [193]. The researchers obtain a targeted aptamer by cloning and sequencing the SELEX fragment, analyzing its secondary structure to establish its affinity, and eventually purifying it [194]. Aptamers are superior to conventional antibodies because of their high specificity and affinity to the targets and their ease of production, stability, and labelling [195]. Aptamers have been utilized extensively for detecting cells, viruses, proteins, carbohydrates, antibodies, and insecticides since their discovery in the 1990s [196–198]. Due to their low molecular weight and unique binding location, metal ions significantly complicate aptamer selection and aptamer-based sensor (aptasensor) development [199–204]. Due to the mass shift and steric hindrance effect, heavy metal ions and aptamers cannot combine [205]. This mixture reduces the versatility and sensitivity of many aptasensors [206]. Heavy metal ions, particularly Pb^{2+}, Cd^{2+}, and Hg+, are commonly utilized detection targets in aptasensors [183,207–209]. Aptamers are of particular interest to scientists because they are versatile binding molecules that are simple to create and alter. Aptamer biosensor research is seeing a rise in the use of electrochemical technologies. The advancement of electrochemical aptasensors has entered a new phase with new materials. Not only do they supply numerous novel approaches to sensor design, but they also give superb nano-sensitive materials. The usage of nanoparticles in electrochemical aptamer sensors is expected to grow as their significance in electroanalysis grows. Given its exceptional properties in electron transmission, graphene is poised to become a crucial material for modifying electrodes. Although most aptamers have been described for a single analyte, future research should concentrate on aptamers that can be employed for the simultaneous, efficient, quick, and precise detection of numerous analytes. Although these sensors operate admirably in a lab, aptamers are easily damaged or deteriorated when subjected to real-world circumstances. Thus, subsequent work must be done to improve the sensors' reliability. It is time-consuming to pretreat food samples, an ongoing challenge for scientists. Presently, testing is expensive when conducted in a lab. It is envisaged that electrochemical aptamer sensors based on nanotechnology will play an increasingly important role in detecting and finding applications in many other areas as research progresses [182,210–213]. As biorecognition elements in sensor creation, aptamers provide numerous advantages over affinity-based (antibody) sensors. Aptasensors are tiny, chemically stable, and affordable. In addition, they offer exceptional elasticity and efficiency in constructing their assemblies, which has resulted in the creation of new sensors with exceptional sensitivity and selectivity [214]. Microenvironment will influence the structure of an aptamer and

its interactions with the ligand target, which is a restriction. In addition, salts' content substantially impacts the configuration of aptamers [215] (represented in Figure 2).

4.7. Raman Spectroscopy

To identify an analyte through molecular bond vibrations, Raman spectroscopy uses the inelastic scattering of light phenomena. Exposure of a sample to laser light results in the scattering of a tiny number of photons. Elastic scattering (i.e., Rayleigh scattering) accounts for the vast majority of the scattering, and its light has the same frequency as the incident light. In elastic scattering (i.e., Raman scattering), about 1 in 106–108 photons are scattered, causing frequency variations (i.e., Raman shifts) between the incident and scattered photons. In this case, either energy is obtained by the photons in the incident light (anti-Stokes Raman scattering) or energy is lost (Stokes Raman scattering) [216–218]. Based on the observed Raman shifts, Raman spectra can be derived. Because each Raman peak in the spectrum indicates a distinct molecular bond, a unique vibrational fingerprint can be generated and used to identify an analyte [219]. Micro-Raman spectroscopy, Raman imaging, and surface-enhanced Raman spectroscopy (SERS) are all examples of Raman spectroscopic techniques often employed to detect food safety issues [220].

Raman spectroscopy is based on the interaction of matter and light and, hence, is non-elastic [221]. The molecules of interest interact with rough metals, such as copper, gold, or silver, resulting in a 4–7-fold boost in Raman spectral strength and SERS [222], and the prospect of detecting it with SERS. The magnitude of the surface-enhanced Raman spectral signal is, as a system, initially determined by the size of the nanostructure. The enhancement effect is maximized when the metal size is less than the wavelength of the incident light and more than the typical electron-free path [223]. The substrates need ultrahigh sensitivity, excellent stability, convenient sampling, and rapid response time, making it challenging to apply SERS for heavy metals detection in food [224,225]. With the help of tip-enhanced Raman spectroscopy (TERS), a nanometric substrate can be precisely manipulated for an ultra-sensitive surface-enhanced Raman scattering (SERS) examination [226,227].

As a non-invasive, user-friendly, sensitive, and quick technique, Raman spectroscopy has the potential to revolutionize the way food safety is evaluated worldwide. Its uses in food safety have been significantly bolstered by the recent development of Raman spectroscopy technologies, which dramatically improve their detection capacities of food pollutants. When it comes to detecting pollutants, Raman spectroscopy is one of the few methods to do so quickly, sensitively, non-destructively, and cheaply across all three categories [216,219,220,228].

The use of SERS techniques to detect Hg ions has been the subject of several published reports. It was shown that using a wide range of SERS substrates was the most effective way to detect low levels of As. To further modify the SERS signal of Raman reporters, As ions can coordinate with certain atoms or aptamers to affect nanoparticle aggregation [229–234]. The coordination of Cu ions with other atoms, such as nitrogen and oxygen, allows for the modification of Raman characteristic peaks or the induction of metal nanoparticle aggregation, both of which are necessary for accurately quantifying copper ions [229,235–239]. Zinc ions may form bonds with nitrogen and oxygen atoms, while Cd ions predominantly form complexes with oxygen atoms; these properties are used to distinguish between the two metals. Zn and Cd, having similar electrical structures, will interfere with one another in the actual detecting application. Therefore, an ultrasensitive and selective SERS sensor must be used to assess trace Zn and Cd ions [240–243]. To detect Pb ions, researchers can either utilize a cofactor, Pb^{2+}-dependent DNAzyme, which has solid catalytic activity for Pb ions, or they can employ a Raman reporter, which can either approach or avoid the noble metal substrate by cleaving the DNA. Another strategy is to indicate the self-aggregation of nanoparticles and produce a higher SERS signal via the coordination of lead ions with certain groups or atoms [229,244–247]. Quantitative detection of Cr ions is based on the fact that Cr ions undergo a shift in the Raman signal when they are complexed with functional

groups or reduced to trivalent Cr [248,249]. Combining SERS with other technologies, such as colorimetry, fluorescence, and microextraction, has been described in recent years for the detection of heavy metal ions to produce more consistent and accurate results. The detection results may be more reliable if these methods are used together [229,250]. Heavy metal ions come in various forms, and it is common for there to be more than one in complex environmental systems. With proper setup, simultaneous detection of numerous heavy metal ions can reduce the workload and open new avenues for innovation in various fields. For this reason, it is crucial to create reliable SERS sensors that can detect numerous heavy metal ions at once in real-world samples [229,251].

Detecting heavy metal ions using SERS in conjunction with other technologies, such as fluorescence, colorimetry, microfluidics, microextraction, immunoassay, and density functional theory (DFT), is becoming increasingly popular as science and technology advance. The limitations of SERS can, on the one hand, be compensated for by other technologies. However, the results are more persuasive when two or three technologies work together. Since several heavy metal ions commonly coexist in real-world samples, interference-free detection of numerous heavy metal ions simultaneously is an essential direction for future progress. Field testing is the most crucial part of heavy metal ion detection. Thus, the size and price of Raman equipment will be the focus of future research. In conclusion, SERS technology shows promising results in detecting heavy metal ions, and it is believed that it will mature into one of the standard detection methods shortly [224,229,252]. Raman spectroscopy has attracted increasing research and clinical facilities' interest over the past decade. As a technique for vibrational spectroscopy, it complements well-established infrared spectroscopy. Substances can be recognized, and chemical changes can be monitored with high specificity using spectral patterns. Raman spectroscopy paired with microscopy is highly practical for imaging biological samples due to the excellent spatial resolution afforded by excitation wavelengths in the visible and near-infrared spectrum [253]. Poor repeatability is a problem of Raman spectroscopy, making it exceedingly difficult to acquire reliable quantitative observations [254].

4.8. Fluorescence Sensors

Recently, much work has been done on creating rapid, sensitive, and selective sensors for detecting heavy metal ions. Because of their unique properties, such as high specificity, sensitivity, and reversibility, fluorescence sensors have recently attracted much attention. Optical sensors, in particular, have many advantages; for example, they can be easily integrated into microfluidic platforms [255] and used to monitor dangerous conditions [256]. Recently, fluorescent optical sensors have become increasingly popular due to their excellent specificity, low detection limits, fast response time, and technological simplicity [257,258]. Their underlying premise is based on the fact that a substance (fluorophore) emits light when activated at shorter wavelengths [259]. This emission fluctuates in strength (or lifespan) according to the concentration of the analyte of interest [260]. Several different materials have been created for the detection of heavy metal ions in water, including porphyrins [261], metal-organic frameworks [262], DNAzymes [263], fluorescent aptamers [264], quantum dots [265], and organic dyes [266].

Since the shift in fluorescence due to coordination occurs quickly and is non-destructive, selective, sensitive, and amenable to screening, methods based on fluorescence detection using small molecules are ideal. These techniques are centred on synthesizing and designing fluorophores that contain coordination ligands and the binding mechanism necessary to detect metal ions in solution. The core fluorophores, including rhodamine, pyrene, anthracene, naphthalimide, aminoquioline, bithiophene, and coumarin, are used with appropriate probes to create fluorescence sensors for Hg^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Fe^{3+}, Ni^{2+}, and Cr^{2+} [267–270]. This approach's excellent sensitivity and specificity are its most outstanding features. Another feature is its speedy diagnostic capability. Not all chemicals fluoresce, which is the biggest disadvantage [148].

5. Conclusions

Pb, Cd, and Hg are the primary metals and As is the primary metalloid of potential health concerns found in foods and dietary supplements. Toxic metal contaminants in pharmaceuticals and nutritional supplements are infrequently detected by routine screening [271]. Setting heavy metal limits is appropriate when heavy metals are likely or certain to contaminate a given product. As a result of their widespread presence in the environment, the constraints of existing analytical techniques, and other factors, setting reasonable health-based limits for some of these metals is difficult. There are several ways to detect heavy metal ions, from time-tested techniques to advanced biosensors [182]. Conventional techniques for detection include, but are not limited to, atomic absorption/emission spectrometry, atomic fluorescence spectroscopy, inductively coupled plasma mass spectrometry, high-performance liquid chromatography, and so on [272–276]. Although these techniques have a high sensitivity for quantifying heavy metal ions, their widespread use is hindered because they necessitate the expertise of trained personnel, are time-consuming and costly to implement, and require specialized laboratory equipment. Several advanced techniques, such as aptasensors and many others, have come to the rescue. Compendial tests for metals in food provide several problems for compendial scientists. Current instrumental techniques detect metals at concentrations well below the indicated permissible daily exposures (PDEs). Therefore, to prevent superfluous testing, it is essential that the evolving criteria for metal levels in compendial therapeutic products be clear about the choice of metals and stated PDE.

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