Review

Genetic Susceptibility as Potential Modifier of Health Risks from Exposure to Toxic Elements

Mariangela Palazzo [†] , Andrea Borghini [*,†] , Elisa Bustaffa , Silvia Baldacci , Francesca Gorini , Fabrizio Minichilli [*]

Posted Date: 23 March 2026

doi: 10.20944/preprints202603.1693.v1

Keywords: toxic elements; heavy metals; gene-environment interaction; single-nucleotide polymorphisms; cardiovascular disease; neurological disorders; cancer risk

 doi:10.20944/preprints202603.1693.v1

Review

Genetic Susceptibility as Potential Modifier of Health Risks from Exposure to Toxic Elements

Mariangela Palazzo †, Andrea Borghini *,†, Elisa Bustaffa, Silvia Baldacci, Francesca Gorini and Fabrizio Minichilli *

Institute of Clinical Physiology, National Research Council, 56124, Pisa, Italy

* Correspondence: andrea.borghini@cnr.it (A.B.); fabrizio.minichilli@cnr.it (F.M.)

† These authors contributed equally to this work.

Abstract

Genetic variability is increasingly recognized as a key determinant of individual susceptibility to heavy metal-induced toxicity. Beyond exposure intensity and duration, inherited differences in genes regulating metal transport, detoxification, and DNA repair can substantially influence internal dose and biological response. To date, research has primarily focused on variants within these pathways, particularly single-nucleotide polymorphisms (SNPs), some of which have been proposed as potential susceptibility markers for toxic element (TE) toxicity. Despite these advances, current findings remain inconsistent. Many studies are limited by small sample sizes, heterogeneous exposure assessment, and insufficient consideration of ethnic-specific allelic diversity and gene-environment interactions. Future research should prioritize large, well-characterized, and ethnically diverse populations, integrating detailed exposure profiling, lifestyle factors, and co-exposures to more accurately define the genetic architecture underlying susceptibility. Therefore, in this review, we summarize the principal toxic metals, synthesize epidemiological evidence linking exposure to adverse health outcomes, and explore the contribution of genetic variability in modulating individual risk of metal-induced disease.

Keywords: toxic elements; heavy metals; gene-environment interaction; single-nucleotide polymorphisms; cardiovascular disease; neurological disorders; cancer risk

1. Introduction

Potentially toxic elements (PTEs) or simply toxic elements (TEs) are a group of substances which are attracting increasing interest in the scientific community for their spread as environmental pollutants and their impact on human health.

In several fields of literature, and especially in environmental sciences, they are commonly referred to as heavy metals or toxic heavy metals, but these terms are recommended to be avoided for the imprecision of their definition. In fact, TEs are a subgroup that may also have lower molecular density and mass and not necessarily be metals in the strict chemical sense (e.g. arsenic is a metalloid). Moreover, heavy metals can include elements that are essential for human physiology at trace levels [1]. Among TEs, arsenic (As), cadmium (Cd), chromium (especially hexavalent chromium, Cr(VI)), lead (Pb), and mercury (Hg) are the most consistently recognized as target toxic elements. Compared to other metals, these elements are particularly significant because they are highly toxic even at low concentrations, persist and bioaccumulate in the environment and living organisms, are widespread due to both natural and human activities, and are prioritized by international health and environmental agencies for monitoring and risk assessment. Generated by both natural and anthropogenic processes, these elements are widespread contaminants [2]. Their persistent nature promotes accumulation in environmental matrices and biomagnification along the food chain, leading to human dietary intake. In addition, inhalation of contaminated air represents a separate way of exposure, particularly in industrial areas and occupational settings [3].

 doi:10.20944/preprints202603.1693.v1

Due to their widespread presence in air, water, soil, and food, toxic metals pose a significant public health concern. Unlike organic pollutants, toxic metals are non-biodegradable and cannot be broken down into less harmful substances. As a result, they accumulate overtime, creating long-term risks to human health. In this context, a growing body of epidemiological and toxicological evidence indicates that exposure to As, Cd, hexavalent chromium Cr(VI), Pb, and Hg is associated with a wide range of adverse health outcomes. These effects involve multiple organs and systems, including the nervous, renal, cardiovascular, immune, endocrine, and reproductive systems [4].

Given their pervasive nature and serious health risks, it is crucial to understand the factors that contribute to differences in susceptibility among individuals [5]. In fact, not all individuals exposed to similar levels of TEs develop the same health effects, reflecting substantial inter-individual variability.

A central mechanism underlying this phenomenon is gene-environment (G×E) interaction, whereby the effects of environmental exposures on disease risk are influenced by an individual's genetic profile [6]. Among genetic determinants, single-nucleotide polymorphisms (SNPs) are the most common type of variation, present in a population with a frequency ≥1% [7]. They can be considered as internal contributing factors in susceptibility of individuals to TEs effects. In this regard, SNPs are considered relevant as they belong to essential pathways, such as TEs transport and detoxification, oxidative stress and DNA repair [8–10].

However, deeper investigations about mechanisms underlying genetic influence on response to toxic elements are needed and robust evidence about their potential role as disease predictors are required. Understanding the interplay between genetic factors and environmental exposures can be crucial for identifying individuals at higher risk of adverse health outcomes, improving risk assessment, and informing preventive or therapeutic strategies. Therefore, this review aims to describe the main toxic elements, examine epidemiological data of related health risks, and highlight the role of genetic variability in modulating susceptibility or providing partial protection against TE-related toxicity, based on the evidence available to date.

2. Sources of Toxic Elements and Routes of Exposure

Toxic elements are dispersed across ecosystems through a combination of natural and human-driven processes, contributing to their widespread presence in the atmosphere, hydrosphere, and lithosphere. They are constituents of Earth's crust, and they are gradually released into air, water, and soils following some natural events, such as rock weathering, volcanic activity, and geochemical cycling. These pathways establish background concentrations that vary with local geology and environmental conditions. However, over the last century, a broad spectrum of human activities, ranging from waste management to agricultural and industrial practices, have been substantially intensifying TEs fluxes and expanding their distribution across environmental compartments [11,12].

In detail, As is naturally released into soils and waters through the oxidation and weathering of As-bearing minerals; moreover, As-rich fluids and gases, produced from geothermal systems and volcanic activity, mobilize the element into surrounding surface waters and groundwater. Additionally, As can be found as persistent contaminant in soils, sediments, and former industrial or agricultural sites, because of its past and extensive use in pesticides, animal feed additives, medicinal products, and wood preservatives. Currently, major anthropogenic sources include mining and smelting of metal ores (especially gold and sulfide deposits), coal combustion, and various industrial processes (e.g., glass, alloys, electronics), which release As into air, water, and waste streams [13].

Cd is naturally present as a trace component of zinc, lead, and copper ores and is released through the weathering of cadmium sulfide and volcanic emissions, contributing to its dispersion into soil, sedimentary deposits, and air. Anthropogenic Cd mainly comes from industrial processes (e.g., mining, smelting, and battery production, wastewater discharge). Additional inputs stem from agricultural use of fertilizers and some pesticides containing Cd impurities and from disposal or incineration of Cd-containing consumer products such as batteries, plastics, pigments, and paints [14].

 doi:10.20944/preprints202603.1693.v1

Cr(VI) naturally origins from geochemical and microbially mediated oxidation of Cr(III)-containing minerals, especially in manganese oxide-rich or ultramafic soils [15]. Anthropogenic sources mainly include industrial operations such as mining, electroplating, leather tanning, and the production of pigments and dyes, along with inadequate management of industrial waste. These activities release Cr(VI) into the environment via effluents, solid residues, and air emissions, leading to contamination of soils, water bodies, and the atmosphere [16].

Natural Pb sources originate from mineral weathering, forest fires, and vegetation particles, with trace amounts naturally occurring in various igneous and sedimentary rocks. Human activities are responsible for an increase in Pb levels of more than 1000-fold over the last three centuries. This enrichment is primarily driven by industrial processes, such as mining, smelting, battery production, and the manufacturing of Pb-based paints, as well as combustion of fossil fuels, like coal and leaded gasoline, along with the use of lead-arsenate pesticides [17].

Natural Hg is released through geological and biological processes, including volcanic eruptions, the weathering of minerals, and emissions from oceans, soils, and burning biomass. Anthropogenic sources contribute about two-thirds of atmospheric mercury, substantially altering its natural cycle through industrial processes such as mining, cement production, and metal manufacturing, with coal and fossil fuel combustion as leading contributors [18].

In consequence to TEs sources and contaminated compartments, environmental and occupational exposures occur predominantly through ingestion and inhalation, with dermal contact and absorption generally representing a minor route.

Dietary intake though ingestion of contaminated food or drinking water accounts for a major way of exposure to: As, notably with rice and other crops grown in As-rich soils [19]; Cd, especially in vegetables, cereals and potato, but also some fishes [20]; Cr(VI), mainly through drinking water especially in areas impacted by industrial or geogenic contamination [21]; Pb, mostly contained in potatoes, carrots and vegetables [22] and drinking water from lead service lines or living in areas with environmental Pb contamination [23]; Hg, predominantly from consumption of fish and sea mammals [24].

Inhalation exposure represents the other major route of TEs intake, especially, but not exclusively, in occupational settings: high levels of As, Cd, and Pb were detected in foundry workers in correlation with their specific tasks [25]; mercury vapor exposure can occur during dental practices, as well as industrial processes [24]; whereas Cr(VI) inhalation mainly concerns occupational environments, such as chrome plating, welding, and surface treatment industries [26]. However, inhalation of TEs can worryingly occur in common social environments. Recent evidence indicates that airborne metals in households, educational settings, offices, commercial spaces, and public transport systems can lead to both non-carcinogenic risks and elevated lifetime carcinogenic risks for elements such as As, Cd, Cr, and Pb, with indoor exposure generally posing a greater threat than outdoor air, with a frequence exceeding international thresholds [27].

Moreover, another relevant contributor to TEs intake is represented by smoking: the combination of tobacco and rolling paper can substantially increase the exposure burden to several TEs, including As, Cd, Cr, Hg, and Pb [28]. Particularly, tobacco plant was discovered to be an efficient accumulator of Cr, As, and Pb in root tissues, while Cd is revealed in all parts of the plant, especially in the leaves for its more volatile nature [29]. The leaves were also identified as the part of *Nicotiana tabacum* where Hg accumulates the most [30]. Importantly, exposure to TEs, in particular Pb Cd, and As, via tobacco smoke does not affect only active smokers, but also poses significant risks to passive smokers, including household members exposed to secondhand and thirdhand smoke. This is particularly concerning for children, who are more susceptible to TEs accumulation in household dust and its subsequent ingestion or inhalation [31].

Dermal exposure to TEs is possible, but absorption is less frequent and significant than ingestion and inhalation routes. As, especially in its most toxic form, arsenite [32], can penetrate the skin [33]. Cd showed measurable skin bioaccessibility and cytotoxicity, especially in contaminated soils [34]. Polluted soils, along with leather products, represent sources of dermal exposure also to Cr(VI) [35].

 doi:10.20944/preprints202603.1693.v1

Pb can also be absorbed through the skin, particularly in occupational settings, contributing to overall body burden despite its relatively lower dermal uptake [36]. Hg, especially inorganic forms, is absorbed through the skin, based on concentration, skin integrity, and vehicle, and can cause systemic toxicity, as seen in cases of mercury poisoning from skin-lightening cosmetics [37].

Environmental studies about sources and levels of TEs will keep growing, as a comprehensive evaluation is essential in predicting their potential health impacts.

3. Biomonitoring and Health Effects of Toxic Elements

Given their widespread distribution and persistence in the environment, human exposure to TEs is frequent, making the evaluation of their health effects increasingly relevant. In recognition of their potential impact on public health, several TEs - particularly As, Cd, Pb, and Hg- were included by the World Health Organization (WHO) among the top ten chemicals of major public health concern [38]. To assess human exposure to these elements, biomonitoring approaches are widely used, measuring TE concentrations in accessible biological matrices through spectrometric techniques and subsequently evaluating exposure-disease relationships through epidemiological studies. Blood and urine represent the most used matrices for TE biomonitoring, although other matrices, including saliva, hair, nails, teeth, and breast mill, may also provide useful information, each presenting specific advantages and limitations [39]. The choice of matrix often depends on the specific element and the timing or form of exposure. For instance, As exposure is commonly assessed through urinary measurements [40], while Pb levels are typically determined in whole blood [41]. Cr (VI) is preferentially measured in the erythrocytic fraction [42], while Cd can be detected in blood as an indicator of recent exposure or in urine to reflect chronic exposure [43]. Similarly, Hg can be measured in both blood and urine depending on the chemical species involved: urine is more suitable for inorganic Hg forms (including elemental mercury and mercury vapor), whereas blood is the preferred matrix for methylmercury, the organic form mainly derived from fish consumption [44].

A growing body of epidemiological evidence has correlated TE concentrations in the human body with adverse health outcomes affecting multiple physiological systems, particularly cardiovascular, neurological, and oncological diseases, which significantly impact global morbidity, mortality, and quality of life [4]. Chronic exposure to toxic TEs, including As, Cd, Pb, Hg, and Cr(VI), is increasingly recognized as an environmental contributor to major non-communicable diseases. In the cardiovascular system, exposure to several TEs has been associated with increased risk of cardiovascular diseases, particularly ischemic heart disease, the leading cause of mortality worldwide [45]. Meta-analyses indicate elevated risks associated with Pb, Cd, and As exposure, with more recent pooled analyses confirming increased cardiovascular disease risk also for Hg [46], while evidence for Cr(VI) remains limited and inconsistent [47]. Neurological disorders represent another major health concern linked to TE exposure. Alzheimer's disease (AD), the most common cause of dementia accounting for approximately 60–70% of cases, has been associated with chronic exposure to several TEs [48]. Epidemiological studies have reported higher Cd levels in AD patients and evidence linking Cd exposure to cognitive decline [49], while Hg and Pb have also been associated with cognitive impairment and increased dementia risk [50]. In addition, cumulative Pb exposure has been linked to significantly higher incidence of AD [51], while altered As metabolism patterns, elevated blood Cr levels, and Cr(VI)-induced neurotoxicity have also been implicated in neurodegenerative processes [52–54]. Importantly, TE exposure is not limited to adult health effects: prenatal or early-life exposure to Pb, Hg, and As has been associated with impaired neurodevelopment, including deficits in cognitive and motor functions as well as behavioral disorders [55].

Beyond cardiovascular and neurological outcomes, several TEs exhibit well-established carcinogenic potential. According to the International Agency for Research on Cancer (IARC), As, Cd, and Cr(VI) are classified as Group 1 human carcinogens, inorganic Pb compounds as Group 2A, and methylmercury as Group 2B. Epidemiological studies consistently associate As exposure with increased risk of multiple malignancies, including lung, breast, liver, stomach, and hematological

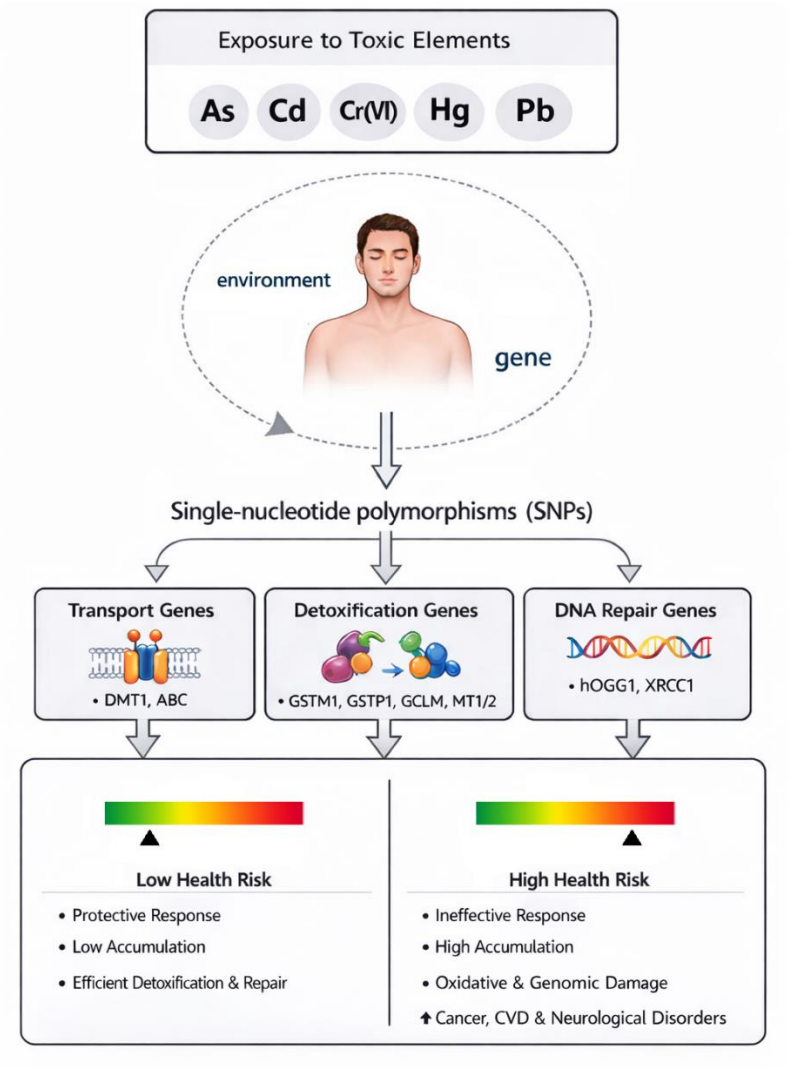
 doi:10.20944/preprints202603.1693.v1

cancers [56]. Cd exposure has been linked to pancreatic [57], prostate [58], liver [59], renal [60], breast [47], and thyroid [61] cancers, while Pb exposure is associated with increased incidence and mortality of several cancers, particularly those of the gastrointestinal and urinary tracts [62]. Hg has also been implicated in thyroid cancer risk [63], and Cr(VI) exposure has been associated with modest but significant increases in overall cancer incidence and mortality, particularly for respiratory and gastrointestinal cancers [64]. Overall, these findings highlight TEs as significant environmental risk factors contributing to the onset and progression of several chronic diseases.

4. Gene-Environment Interaction: The Role of Single-Nucleotide Polymorphisms in Susceptibility to Toxic Element-Induced Effects

Multifactorial diseases, specifically cancer, CVD, and neurological disorders, are conditions resulting from the interaction of multiple factors. Among the primary determinants, genetic background and environmental exposures play a central role. In addition to acting independently, these factors interact to modulating phenotypic outcomes within the framework of G×E interaction, a dynamic relationship where the environment can modify the expression of genes, and genetic makeup determines sensitivity to environmental factors.

In this regard, variability within the genome, particularly in the form of SNPs, contributes to differences in individual responses to environmental exposures [65]. SNPs, by modulating susceptibility to TEs, can be functionally classified into key biological pathways, reflecting the multifaceted nature of their metabolism and toxicity: metal transport, detoxification, and DNA repair [8] (Figure 1). Best characterized SNPs are summarized in Table 1.



 doi:10.20944/preprints202603.1693.v1

Figure 1. Gene-environment interaction in exposure to toxic elements: single-nucleotide polymorphisms can affect susceptibility to disease risk. Image partially generated with AI Microsoft Copilot 365. Abbreviations: As: arsenic; Cd: cadmium; Cr(VI): hexavalent chromium; Hg: mercury; Pb: lead; SNPs: single-nucleotide polymorphisms; DNA: deoxyribonucleic acid; CVD: cardiovascular disease.

4.1. Transport

SNPs in genes encoding metal transporter proteins play an important role by directly influencing the uptake, distribution, and elimination of TEs.

Divalent Metal Transporter 1 (DMT1), encoded by *SLC11A2* located on chromosome 12q13 in humans, is a transmembrane protein that allows the cellular entry of some divalent cations, including Cd, Pb, cobalt, manganese, nickel, zinc, and copper into the cells. DMT1 is also referred to as DCT1 (Divalent Cation Transporter 1), NRAMP2 (Natural Resistance Associated Macrophage Protein 2), and SLC11A2 (Solute Carrier Family 11, member 2). In a study conducted by Kim et al., the relationship between the *DMT1* IVS4+44 C/A polymorphism and clinical parameters was investigated in 662 male Korean workers occupationally exposed to Pb. The findings suggested that this variant in the *DMT1* gene may increase the risk of lead-associated hypertension in exposed individuals [66]. Moreover, from another study investigating the role of *SLC11A2* (*DMT1*) polymorphism rs224589 and enrolling 113 workers occupationally exposed to Pb, it emerged that individuals carrying the heterozygous CA genotype (54%) for *SLC11A2* showed higher blood Pb concentrations compared with both homozygous CC (wild-type) and AA (mutant) individuals. Furthermore, a significant inverse correlation was observed between blood Pb levels and hemoglobin exclusively in the CA subgroup, indicating a greater vulnerability to lead-related hematological alterations in correlation with this polymorphism [67].

Similarly, genetic variants of ATP-binding cassette transporters critically regulate the intracellular accumulation of TEs by mediating their transport outside from the cells. Polymorphisms in genes encoding for ABC transporter can influence Hg accumulation and perinatal outcomes. Offspring carrying the *ABCC1* rs11075290 C-allele have significantly higher cord blood Hg levels and present increased odds of small-for-gestational-age. Similarly, carriers of *ABCB1* rs2032582 GG genotype accumulate more mercury in cord blood and show a greater reduction in mental development index [68].

4.2. Detoxification

Substantial evidence is reported about the contribution in TEs toxicity exerted by SNPs of genes involved in detoxification processes, such as glutathione-related genes and metallothioneins, for their role in binding and metabolism of TEs.

4.2.1. Glutathione-Related Genes

Genes involved in the glutathione pathway are key mediators of detoxification processes, contributing to the conjugation and clearance of toxic compounds, while also counteracting oxidative stress. Genetic variants in these genes, including those encoding glutathione S-transferases (*GSTM1, GSTT1, GSTP1*) and the modifier (*GCLM*) and catalytic (*GCLC*) subunits of glutamate-cysteine ligase, can affect enzymatic function and glutathione biosynthesis, ultimately shaping interindividual susceptibility to TEs-induced toxicity. A study including a Chinese population of 850 subjects exposed to high levels of As in drinking water identified polymorphisms in glutathione-related genes *GSTO1* (rs11191979, rs2164624, rs4925), *GSTO2* (rs156697, rs2297235), and *PNP* (rs3790064) as associated with increased risk of As-induced skin lesions in individuals exposed to high-dose inorganic arsenic, for the impairment in body's ability to methylate and detoxify arsenic efficiently consequently to the presence of these variants [69].

GSTP1 rs1695 polymorphism (AG + GG genotypes) is associated with increased urinary percentage of inorganic arsenic (%InAs) and decreased primary methylation index, indicating

 doi:10.20944/preprints202603.1693.v1

reduced efficiency of these individuals in methylating inorganic As to its less toxic metabolites and increased susceptibility to its toxicity [70]. Altered methylation and reduction steps in As metabolism was confirmed by a recent genome-wide association analysis that reported how genetic variation in the flavin-containing monooxygenase and *GSTO* gene clusters significantly impacts on blood and urinary levels of As metabolites [71].

Moreover, glutathione-related genes can play an important role in individual risk for arsenic-induced carotid atherosclerosis. *GSTT1* polymorphism was correlated with high urinary As levels and higher carotid intima-media thickness (IMT), evaluated as marker of subclinical vascular damage in a cohort of Italian young adults exposed to environmental As [72].

Interestingly, polymorphisms can be also associated with protective effects. A meta-analysis including 9 articles and 3324 subjects found that *GSTM1* null genotype (rs4025935) was significantly associated with a lower susceptibility to As poisoning [73].

The presence of SNPs of this pathway also contributes to the toxic effects observed in populations occupationally exposed to Cd. *CAT* rs7943316, *GSTP1* rs1695, *GSTM1* null genotype, and *GSTT1* null genotype in workers were linked to differences in the phenotypic expression of antioxidant enzymes, suggesting that individuals carrying these genotypes may be more susceptible to oxidative damage from Cd exposure [74].

Genetic polymorphisms in glutathione (GSH)-related genes influence Hg levels. Notably, carriers of the *GCLM* rs41303970 TT genotype exhibited lower Hg concentrations in both blood and hair compared with C-allele carriers, suggesting more efficient mercury elimination or reduced retention. Conversely, individuals with the *GSTM1* null genotype showed higher Hg, indicating greater accumulation of this TE [75].

GSTP1 rs1695 and *CAT* rs1001179 substantially increase the risk of lung cancer in the context of elevated Cr exposure [76]. Toxic effects due to Hg exposure could be revealed in the presence of *GCLC* rs1555903-C allele, as it correlates with lower estimated glomerular filtration rate in non-exposed individuals and lower beta-2-microglobulin in exposed individuals, both markers of impaired renal function. Similarly, the combined effect of *GSTA1* rs3957356-C and *GSS* rs3761144-G alleles is associated with higher urinary Hg levels in exposed individuals, suggesting these variants may also contribute to increased metal retention and potentially greater toxicity. Conversely, *GCLM* rs41303970-T allele is associated with protection against toxicity, as this SNP is linked to higher urinary Hg clearance, indicating enhanced elimination of this TE [77].

A cross-sectional study with 236 adults reported that *GCLC* rs17883901 is linked to enhanced antioxidant response, with higher concentrations of GSH as a function of Pb levels and *GCLM* rs41303970 exerts a protective effect against Pb accumulation, as carriers of at least one polymorphic allele for this gene have significantly lower blood and plasma Pb levels compared to those with the non-polymorphic genotype [78].

Genotyping of the *GSTM1, GSTT1, and GSTP1* genes was performed to investigate their potential association with heavy metal concentrations in 140 children exposed to Pb and Cd near an abandoned mining area in Kabwe, Zambia. The study found that the *GSTT1* null genotype was positively correlated with both blood Pb and Cd levels, while the *GSTP1* Ile/Val genotype (rs1695) was associated with a higher risk of Pb toxicity. This risk was even greater when these genetic variants co-occurred [79].

Furthermore, maternal polymorphisms in GSH-related genes can influence TEs levels, with consequences on perinatal and birth outcomes. Pregnant women with *GSTM1-null* and *GSTT1-null, GCLM* rs41303970 variants exhibit increased Hg accumulation and heightened oxidative stress, which were linked to an increased risk of preterm birth and reduced weight in offspring. Additionally, more frequence of children with lower mental development index occurs when mothers carry the rare G allele of *GSTP1* rs1695. Moreover, increasing Hg exposure is associated with lower psychomotor development index among *GCLC* rs761142 TT carriers [68].

 doi:10.20944/preprints202603.1693.v1

4.2.2. Metallothioneins

Metallothioneins (MTs) are cysteine-rich proteins that bind and sequester toxic elements, thereby reducing their bioavailability and protecting cells from metal-induced toxicity and oxidative stress [80]. Due to their abundant thiol groups, MTs bind biologically essential metals to help maintain metal homeostasis, as well as bind heavy metals to facilitate their transport and detoxification. Among all MT isoforms – including MT1, MT2, MT3, and MT4 – MT1A and the MT2A subtypes are the predominantly expressed isoforms in humans.

A study enrolling 321 women revealed that SNPs of metallothionein 1A and 1B, *MT1A* rs8044719 and *MT1B* rs1599823, and *2A*, *MT2A* rs28366003 and *MT2A* rs10636, are associated with lower urinary Cd, indicating increased tissue retention and susceptibility to this TE [81]. In an analysis of 616 individuals, the *MT2A* gene polymorphism rs28366003 GG genotype was associated with significantly higher blood Cd and Pb levels compared to other genotypic subgroups [82], suggesting that individuals carrying the GG genotype may be more susceptible to metal toxicity and should take extra precautions to protect their health from the harmful effects of TEs.

MT1A gene polymorphisms rs11640851 and rs8052394 are associated with negative correlation between creatinine-adjusted urine uric acid concentrations and cumulative blood Pb exposure, indicating that these genotypes may increase susceptibility to Pb-induced renal tubular dysfunction as reflected by uric acid excretion [83].

Regarding susceptibility to Hg exposure, *MT1M* rs2270837 AA genotype and *MT2A* rs10636 CC genotype are associated with lower urinary Hg levels, while *MT1A* rs8052394 GA and GG genotypes and *MT1M* rs9936741 TT genotype are associated with lower hair Hg levels [84]. Influence on Hg levels by SNPs of metallothioneins was subsequently demonstrated by another study with 165 women, in which *MT1M* rs9936741 was confirmed to be associated with significantly lower hair total Hg levels, suggesting a protective effect against accumulation, while *MT1M* rs2270836 was linked with higher hair Hg levels, indicating increased susceptibility to retention of this TE [85].

Overall, further investigations are needed on these genetic polymorphisms to better understand their impact on TEs and TE-induced adverse effects.

4.3. DNA Repair: Focus on the Base Excision Repair Pathway

Polymorphisms in DNA repair genes, including hOGG1 and XRCC1, contribute to interindividual differences in disease susceptibility and cellular responses to DNA damage by altering the efficiency of the base excision repair pathway, which is involved in removing oxidative lesions and maintaining genomic stability.

The *hOGG1* Ser326Cys variant is associated with reduced enzymatic activity and impaired removal of oxidative DNA lesions, particularly 8-oxoguanine, leading to increased DNA damage accumulation and genomic instability. This polymorphism is linked to elevated risk of cancer and other oxidative stress–related disorders, as well as altered sensitivity to chemotherapy and radiotherapy. Similarly, *XRCC1* variants such as Arg399Gln and Arg194Trp influence BER efficiency by modifying protein interactions within the repair complex. The Arg399Gln polymorphism is associated with decreased repair capacity and greater cancer risk, particularly under exposure to genotoxic agents, whereas the role of Arg194Trp appears less defined, with some evidence suggesting a potential protective effect. Overall, these variants may modulate individual susceptibility to environmental toxins and ionizing radiation [86].

hOGG1 Ser326Cys (rs1052133) and *XRCC1* Arg399Gln (rs25487) polymorphisms can influence susceptibility to TEs. Borghini et al. reported that these polymorphisms in DNA repair genes are associated with increased susceptibility to As exposure in a cohort of 241 Italian young adults. Carriers of the *hOGG1* Cys allele and the *XRCC1* Gln allele exhibited significantly shorter leukocyte telomere length in the context of higher urinary As levels, indicating enhanced genomic instability. These findings suggest that the combination of elevated As exposure and these DNA repair gene variants exacerbate telomeric DNA damage and may contribute to the development of arsenic-related health effects, highlighting a gene-environment interaction that increases individual

 doi:10.20944/preprints202603.1693.v1

vulnerability [87]. Moreover, *hOGG1* rs1052133 and rs159153 polymorphisms interact with As exposure and methylation capacity to increase the risk of urothelial carcinoma [88].

hOGG1 rs1052133 and *XRCC1* rs25487 are frequently associated with increased DNA damage in workers exposed to Cd, indicating reduced DNA repair capacity and greater susceptibility to genotoxic effects [9]. *hOGG1* rs1052133, along with other polymorphisms in DNA repair genes, *XPA* rs1800975, and *XPC* rs2228000 are also associated with modulation of DNA instability biomarkers in workers occupationally exposed to Pb [89]. Moreover, individuals carrying *XRCC1* Arg399Gln (rs25487) and *hOGG1* Ser326Cys (rs1052133) polymorphisms exhibited increased DNA damage and oxidative stress when exposed to Hg [90].

Interestingly, the impact of *XRCC1* polymorphism on the genotoxicity exerted by exposure to hexavalent chromium appears controversial. *XRCC1* Arg399Gln (rs25487) homozygous variant genotype (Gln/Gln) is associated with increased chromosomal aberrations and greater susceptibility to chromosomal damage in workers exposed to this TE [91]. This result is in contrast with another study reporting that *XRCC1* Arg399Gln (rs25487) variant is associated with reduced DNA damage in individuals occupationally exposed to Cr(VI), indicating a protective effect of this polymorphism against Cr(VI) toxicity [92]. This discrepancy likely reflects differences in the endpoints measured, population characteristics, or exposure levels. Other DNA repair polymorphisms, correlated with Cr effects, are *XPD* Lys751Gln (rs13181) and *XPC* Lys939Gln (rs2228000), that are associated with increased susceptibility to lung cancer in individuals exposed to this element [93]. Moreover, the interaction between chromate exposure and the *XRCC3* rs2295152 T allele has a significant effect on micronuclei frequency, indicating a gene-environment interaction that increases susceptibility to chromate-induced genetic damage [94].

Table 1. Best characterized single-nucleotide polymorphisms as promising markers of genetic susceptibility to TEs exposure. Circles in Effect column are green when SNPs are correlated with a protective action, red with increased toxic effects.

Toxic element	Pathway	Reference	Gene	SNP	Effect	
As	Detoxification	[69]	GSTO1	rs11191979	impairment in body's ability to methylate and detoxify arsenic efficiently, ↑ risk of skin lesions	🔴
				rs2164624		
				rs4925		
			GSTO2	rs156697		
				rs2297235		
			PNP	rs3790064		
		[70]	GSTP1	rs1695 AG + GG genotypes	↓ efficiency in methylating inorganic As, ↑ urinary percentage of inorganic arsenic, ↑ toxicity	🔴
		[72]	GSTT1	+ genotype	↑ urinary As levels and ↑ carotid intima-media thickness	🔴
		[73]	GSTM1	rs4025935 null genotype	↓ As poisoning	🟢
	DNA repair	[87]	hOGG1	rs1052133 Ser326Cys	↑ urinary As levels, ↓ leukocyte telomere length, ↑ genomic instability	🔴
			XRCC1	rs25487 Arg399Gln		
		[88]	hOGG1	rs1052133	↑ risk of urothelial carcinoma	🔴
				rs159153		
Cd	Detoxification	[74]	CAT	rs7943316	altered expression of antioxidant enzymes, ↑ oxidative damage	🔴
			GSTP1	rs1695		
			GSTM1	null genotype		

 doi:10.20944/preprints202603.1693.v1

			GSTT1	null genotype		
		[79]	GSTT1	null genotype	↑ blood Cd levels	
		[81]	MT1A	rs8044719	↑ tissue Cd retention, ↓ urinary Cd	
			MT1B	rs1599823		
			MT2A	rs28366003		
				rs10636		
		[82]	MT2A	rs28366003 GG genotype	↑ blood Cd levels	
	DNA repair	[9]	hOGG1	rs1052133	↓ DNA repair capacity, ↑ genotoxic effects	
			XRCC1	rs25487		
Cr(VI)	Detoxification	[76]	GSTP1	rs1695	↑ risk of lung cancer	
			CAT	rs1001179		
	DNA repair	[91]	XRCC1	rs25487 Arg399Gln	↑ chromosomal aberrations and susceptibility to chromosomal damage	
		[92]	XRCC1	rs25487 Arg399Gln	↓ DNA damage	
		[93]	XPD	rs13181 Lys751Gln	↑ susceptibility to lung cancer	
			XPC	rs2228000 Lys939Gln		
		[94]	XRCC3	rs2295152 T allele	↑ micronuclei frequency and genetic damage	
Hg	Transport	[68]	ABCC1	rs11075290 C-allele	↑ cord blood Hg levels and ↑ odds of small-for-gestational-age	
			ABCB1	rs2032582 GG genotype	↑ cord blood Hg levels and ↓ mental development index	
	Detoxification	[75]	GCLM	rs41303970 TT genotype	↓ Hg concentrations in blood and hair, ↑ efficient mercury elimination	
			GSTM1	null genotype	↑ Hg accumulation	
		[77]	GCLC	rs1555903 C allele	↓ estimated glomerular filtration rate (eGFR) in non-exposed individuals and ↓ beta-2-microglobulin in exposed individuals, impairment of renal function	
			GSTA1 + GSS	rs3957356 C allele + rs3761144 G allele	↑ Hg retention	
			GCLM	rs41303970 T allele	↑ urinary Hg clearance, ↑ elimination	
		[68]	GSTM1	null genotype	↑ Hg accumulation, ↑ oxidative stress, ↑ risk of preterm birth and ↓ weight in offspring	
			GSTT1	null genotype		
			GCLM	rs41303970		
			GSTP1	rs1695 G allele	↓ mental development index in offspring	
			GCLC	rs761142	↓ psychomotor development index	

 doi:10.20944/preprints202603.1693.v1

				TT genotype		
		[84]	MT1M	rs2270837 AA genotype	↓ urinary Hg levels, ↑ Hg retention	
			MT2A	rs10636 CC genotype		
			MT1A	rs8052394 GA and GG genotypes	↓ hair Hg levels	
			MT1M	rs9936741 TT genotype		
		[85]	MT1M	rs2270836	↑ hair Hg levels	
				rs9936741	↓ hair Hg levels	
	DNA repair	[90]	XRCC1	rs25487 Arg399Gln	↑ DNA damage and oxidative stress	
			hOGG1	rs1052133 Ser326Cys		
Pb	Transport	[66]	SLC11A2	IVS4+44 C/A	↑ risk of hypertension	
		[67]	SLC11A2	rs224589 CA genotype	↑ blood Pb concentration and ↑ hematological alterations	
	Detoxification	[78]	GCLC	rs17883901	↑ antioxidant response	
			GCLM	rs41303970	↓ blood and plasma Pb levels	
		[79]	GSTT1	null genotype	↑ blood Pb levels	
			GSTP1	rs1695 Ile/Val genotype	↑ risk of Pb toxicity	
		[82]	MT2A	rs28366003 GG genotype	↑ blood Pb levels	
		[83]	MT1A	rs11640851	↓ uric acid elimination, ↑ renal dysfunction	
				rs8052394		
	DNA repair	[89]	hOGG1	rs1052133	↑ DNA instability and genotoxicity biomarkers	
			XPA	rs1800975		
			XPC	rs2228000		

Abbreviations: ↓: decrease of; ↑: increase of; As: arsenic; Cd: cadmium; Cr(VI): hexavalent chromium; Hg: mercury; Pb: lead; SNPs: single-nucleotide polymorphisms; DNA: deoxyribonucleic acid;.

5. Conclusions and Future Perspectives

TEs are bioaccumulative and exert a wide range of adverse effects in the human body, including cancer, neurological, and cardiovascular disorders. Their accumulation is influenced not only by the level of environmental exposure but also by biological processes governing absorption, distribution, metabolism, and elimination, which vary between individuals and strongly affect internal metal burden and toxicity outcomes. Investigating genetic variants and their interactions with environmental factors provides crucial insight into individual susceptibility to toxic element-induced health risks. It is now well established that genetic background represents a central component of the complex network of determinants defining sensitivity to metals, while additional internal and external factors – such as lifestyle, nutritional status, and co-exposures – also modulate responses. The interplay between interindividual genetic differences and environmental influences contributes to unique phenotypes and distinct responses to toxic exposures.

 doi:10.20944/preprints202603.1693.v1

Identifying variations in genes involved in toxic element metabolism is therefore essential, as such knowledge enhances understanding of individual susceptibility, identifies high-risk populations, and supports the development of targeted preventive and therapeutic strategies. Among the candidate genes extensively studied are those involved in transport, detoxification, and DNA repair, including *DMT1, GSTP1, MT2A, hOGG1,* and *XRCC1*. Various studies have explored the impact of SNPs within these genes, and some variants have been proposed as potential susceptibility markers for toxic element toxicity. However, findings remain inconsistent due to limitations such as small sample sizes, insufficient allelic diversity among populations, and differences in exposure assessment.

To overcome these gaps, future research should adopt multicentric study designs encompassing larger and more diverse populations with varying exposure levels (high, moderate, and low). Harmonization of measurement techniques, integration of epidemiological data with computational exposure models, and the use of artificial intelligence for data analysis can enhance reliability and predictive power. Additionally, combining multi-omics approaches – such as genomics, epigenomics, and exposomics –allows for a comprehensive characterization of the exposome, capturing both internal biological responses and external environmental exposures that collectively shape individual risk profiles.

Recent advances in induced pluripotent stem cell (iPSC) technology offer a complementary strategy for investigating the health effects of toxic metals. By reprogramming accessible cells (e.g., blood cells) into iPSCs and differentiating them into tissue-specific cell types, researchers can model human biology with high precision. These human-derived systems enable direct investigation of gene-environment interactions, identification of genetic variants influencing susceptibility, and detection of early cellular and molecular changes prior to clinical disease onset. This approach supports earlier prevention strategies, facilitates the discovery of novel biomarkers and therapeutic targets, and advances predictive, and precision medicine tailored to individual risk profiles [95,96].

Incorporating these integrative strategies, such as multicentric studies, advanced cellular models, AI-driven data integration, and multi-omics analyses, can significantly reduce existing gaps in our understanding of toxic element exposure and toxicity, ultimately improving risk assessment, prevention, and intervention strategies at both the individual and population levels.

Author Contributions: Conceptualization, A.B., and F.M.; writing—original draft preparation, M.P. and A.B.; writing—review and editing E.B., S.B., F.G., and F.M.. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Ministry of Health as part of the National Plan for Complementary Investments - "Health, Environments, Biodiversity, and Climate", project name PNC INSINERGIA, project code (National Research Council) PRR.AP015.165.

Acknowledgments: We acknowledge the use of AI assistance, specifically ChatGPT (version 5.0), in the revision of certain parts of this paper to enhance language quality, clarity, and conciseness.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AD	Alzheimer's disease
As	Arsenic
Cd	Cadmium
Cr	Chromium
Hg	Mercury
IARC	International Agency for Research and Cancer
MTs	Metallothioneins
Pb	Lead

 doi:10.20944/preprints202603.1693.v1

PTEs	Potentially toxic elements
PVC	Polyvinyl Chloride
SNPs	Single-nucleotide polymorphisms
TEs	Toxic elements
WHO	World Health Organization

References

1. Pourret, O.; Hursthouse, A. It's Time to Replace the Term "Heavy Metals" with "Potentially Toxic Elements" When Reporting Environmental Research. *Int. J. Environ. Res. Public Health* 2019, *16*, 4446. https://doi.org/10.3390/ijerph16224446
2. Angon, P.B.; Islam, M.S.; Kc, S.; Das, A.; Anjum, N.; Poudel, A.; Suchi, S.A. Sources, Effects and Present Perspectives of Heavy Metals Contamination: Soil, Plants and Human Food Chain. *Heliyon* **2024**, *10*, e28357. https://doi.org/10.1016/j.heliyon.2024.e28357
3. Järup, L. Hazards of Heavy Metal Contamination. *Br. Med. Bull.* **2003**, *68*, 167–182. https://doi.org/10.1093/bmb/ldg032
4. Cheng, Y.F.; Zhao, Y.J.; Chen, C.; Zhang, F. Heavy Metals Toxicity: Mechanism, Health Effects, and Therapeutic Interventions. *MedComm* **2025**, *6*, e70241. https://doi.org/10.1002/mco2.70241
5. Zeise, L.; Bois, F.Y.; Chiu, W.A.; Hattis, D.; Rusyn, I.; Guyton, K.Z. Addressing Human Variability in Next-Generation Human Health Risk Assessments of Environmental Chemicals. *Environ. Health Perspect.* **2013**, *121*, 23–31. https://doi.org/10.1289/ehp.1205687
6. Ottman, R. Gene-Environment Interaction: Definitions and Study Designs. Prev. Med. 1996, 25, 764–770. https://doi.org/10.1006/pmed.1996.0117
7. Azizzadeh-Roodpish, S.; Garzon, M.H.; Mainali, S. Classifying Single Nucleotide Polymorphisms in Humans. *Mol. Genet. Genomics* **2021**, *296*, 1161–1173. https://doi.org/10.1007/s00438-021-01805-x
8. Joneidi, Z.; Mortazavi, Y.; Memari, F.; Roointan, A.; Chahardouli, B.; Rostami, S. The Impact of Genetic Variation on Metabolism of Heavy Metals: Genetic Predisposition? *Biomed. Pharmacother.* **2019**, *113*, 108642. https://doi.org/10.1016/j.biopha.2019.108642
9. Pinto, T.G.; Dias, T.A.; Renno, A.C.M.; Dos Santos, J.N.; Cury, P.R.; Ribeiro, D.A. The Impact of Genetic Polymorphisms for Detecting Genotoxicity in Workers Occupationally Exposed to Metals: A Systematic Review. *J. Appl. Toxicol.* **2025**, *45*, 1070–1079. https://doi.org/10.1002/jat.4711
10. Kumar, P. Genetic susceptibility to heavy metal toxicity. In *Heavy Metal Toxicity and Neurodegeneration*; Kumar, P.; Gogia, N., Eds.; Elsevier: Amsterdam, The Netherlands, 2025; pp. 179–201.
11. He, Z.L.; Yang, X.E.; Stoffella, P.J. Trace Elements in Agroecosystems and Impacts on the Environment. *J. Trace Elem. Med. Biol.* **2005**, *19*, 125–140. https://doi.org/10.1016/j.jtemb.2005.02.010
12. Briffa, J.; Sinagra, E.; Blundell, R. Heavy Metal Pollution in the Environment and Their Toxicological Effects on Humans. *Heliyon* **2020**, *6*, e04691. https://doi.org/10.1016/j.heliyon.2020.e04691
13. Garelick, H.; Jones, H.; Dybowska, A.; Valsami-Jones, E. Arsenic Pollution Sources. *Rev. Environ. Contam. Toxicol.* **2008**, *197*, 17–60. https://doi.org/10.1007/978-0-387-79284-2_2
14. Sattar, S.; Yahya, M.; Aslam, S.; Hussain, R.; Mukkarram Shah, S.M.; Rauf, Z.; Zamir, A.; Ullah, R.; Shahzad A. Environmental Occurrence, Hazards, and Remediation Strategies for the Removal of Cadmium from the Polluted Environment. *Results Eng.* **2025**, *25*, 104322. https://doi.org/10.1016/j.rineng.2025.104322
15. Ao, M.; Sun, S.; Deng, T.; Zhang, F.; Liu, T.; Tang, Y.; Li, J.; Wang, S.; Qiu, R. Natural Source of Cr(VI) in Soil: The Anoxic Oxidation of Cr(III) by Mn Oxides. *J. Hazard. Mater.* **2022**, *433*, 128805. https://doi.org/10.1016/j.jhazmat.2022.128805
16. Ukhurebor, K.E.; Aigbe, U.O.; Onyancha, R.B.; Nwankwo, W.; Osibote, O.A.; Paumo, H.K.; Ama, O.M.; Adetunji, C.O.; Siloko, I.U. Effect of Hexavalent Chromium on the Environment and Removal Techniques: A Review. *J. Environ. Manag.* **2021**, *280*, 111809. https://doi.org/10.1016/j.jenvman.2020.111809
17. Cheema, A.I.; Liu, G.; Yousaf, B.; Abbas, Q.; Zhou, H. A Comprehensive Review of Biogeochemical Distribution and Fractionation of Lead Isotopes for Source Tracing in Distinct Interactive Environmental Compartments. *Sci. Total Environ.* **2020**, *719*, 135658. https://doi.org/10.1016/j.scitotenv.2019.135658
18. Kim, M.K.; Zoh, K.D. Fate and Transport of Mercury in Environmental Media and Human Exposure. *J. Prev. Med. Public Health* **2012**, *45*, 335–343. https://doi.org/10.3961/jpmph.2012.45.6.335

 doi:10.20944/preprints202603.1693.v1

19. Baker, B.A.; Cassano, V.A.; Murray, C.; ACOEM Task Force on Arsenic Exposure. Arsenic Exposure, Assessment, Toxicity, Diagnosis, and Management: Guidance for Occupational and Environmental Physicians. *J. Occup. Environ. Med.* **2018**, *60*, e634–e639. https://doi.org/10.1097/JOM.0000000000001485
20. Zhang, H.; Reynolds, M. Cadmium Exposure in Living Organisms: A Short Review. *Sci. Total Environ.* **2019**, *678*, 761–767. https://doi.org/10.1016/j.scitotenv.2019.04.395
21. Tumolo, M.; Ancona, V.; De Paola, D.; Losacco, D.; Campanale, C.; Massarelli, C.; Uricchio, V.F. Chromium Pollution in European Water, Sources, Health Risk, and Remediation Strategies: An Overview. *Int. J. Environ. Res. Public Health* **2020**, *17*, 5438. https://doi.org/10.3390/ijerph17155438
22. Nag, R.; Cummins, E. Human Health Risk Assessment of Lead (Pb) through the Environmental-Food Pathway. *Sci. Total Environ.* **2022**, *810*, 151168. https://doi.org/10.1016/j.scitotenv.2021.151168
23. Lanphear, B.; Navas-Acien, A.; Bellinger, D.C. Lead Poisoning. *N. Engl. J. Med.* **2024**, *391*, 1621–1631. https://doi.org/10.1056/NEJMra2402527
24. Clarkson, T.W.; Magos, L.; Myers, G.J. The Toxicology of Mercury—Current Exposures and Clinical Manifestations. *N. Engl. J. Med.* **2003**, *349*, 1731–1737. https://doi.org/10.1056/NEJMra022471
25. Freire, B.M.; Gonzaga, R.G.; Pedron, T.; Monteiro, L.R.; Lange, C.N.; Pedreira Filho, W.D.R.; Batista, B.L. Occupational Exposure to Potentially Toxic Elements in the Foundry Industry: An Integrated Environmental and Biological Monitoring. *Environ. Sci. Pollut. Res. Int.* **2021**, *28*, 34630–34641. https://doi.org/10.1007/s11356-021-13099-y
26. Viegas, S.; Martins, C.; Bocca, B.; Bousoumah, R.; Duca, R.C.; Galea, K.S.; Godderis, L.; Iavicoli, I.; Janasik, B.; Jones, K.; Leese, E.; Leso, V.; Ndaw, S.; van Nieuwenhuyse, A.; Poels, K.; Porras, S.P.; Ruggieri, F.; Silva, M.J.; Verdonck, J.; Wasowicz, W.; HBM4EU Chromates Study Team. HBM4EU Chromates Study: Determinants of Exposure to Hexavalent Chromium in Plating, Welding and Other Occupational Settings. *Int. J. Environ. Res. Public Health* **2022**, *19*, 3683. https://doi.org/10.3390/ijerph19063683
27. Khoshakhlagh, A.H.; Ghobakhloo, S.; Peijnenburg, W.J.G.M.; Gruszecka-Kosowska, A.; Cicchella, D. To Breathe or Not to Breathe: Inhalational Exposure to Heavy Metals and Related Health Risk. *Sci. Total Environ.* **2024**, *932*, 172556. https://doi.org/10.1016/j.scitotenv.2024.172556
28. Zumbado, M.; Luzardo, O.P.; Rodríguez-Hernández, Á.; Boada, L.D.; Henríquez-Hernández, L.A. Differential Exposure to 33 Toxic Elements through Cigarette Smoking, Based on the Type of Tobacco and Rolling Paper Used. *Environ. Res.* **2019**, *169*, 368–376. https://doi.org/10.1016/j.envres.2018.11.021
29. da Silva, C.P.; de Almeida, T.E.; Zittel, R.; de Oliveira Stremel, T.R.; Domingues, C.E.; Kordiak, J.; de Campos, S.X. Translocation of Metal Ions from Soil to Tobacco Roots and Their Concentration in the Plant Parts. *Environ. Monit. Assess.* **2016**, *188*, 663. https://doi.org/10.1007/s10661-016-5679-3
30. Uwiringiyimana, E.; Gao, J.; Zhang, D.; Biswash, M.R.; Shi, Y.X. Bioaccumulation and Translocation of Hg and Cr by Tobacco in Sichuan Province, China: Understanding the Influence of Soil pH. *Environ. Monit. Assess.* **2023**, *195*, 1193. https://doi.org/10.1007/s10661-023-11806-5
31. Lopez-Galvez, N.; Mahabee-Gittens, E.M.; Quintana, P.J.E.; Merianos, A.L.; Dodder, N.G.; Hoh, E.; Stone, L.; Watanabe, K.; Matt, G.E. Environmental Tobacco Smoke Is a Major Contributor to Lead, Cadmium, and Arsenic in Settled House Dust. *Chemosphere* **2026**, *394*, 144820. https://doi.org/10.1016/j.chemosphere.2025.144820
32. Patel, K.S.; Pandey, P.K.; Martín-Ramos, P.; Corns, W.T.; Varol, S.; Bhattacharya, P.; Zhu, Y. A Review on Arsenic in the Environment: Contamination, Mobility, Sources, and Exposure. *RSC Adv.* **2023**, *13*, 8803–8821. https://doi.org/10.1039/d3ra00789h
33. Ouypornkochagorn, S.; Feldmann, J. Dermal Uptake of Arsenic through Human Skin Depends Strongly on Its Speciation. *Environ. Sci. Technol.* 2010, *44*, 3972–3978. https://doi.org/10.1021/es903667y
34. Wang, J.; Gao, P.; Li, M.Y.; Ma, J.Y.; Li, J.Y.; Yang, D.L.; Cui, D.L.; Xiang, P. Dermal Bioaccessibility and Cytotoxicity of Heavy Metals in Urban Soils from a Typical Plateau City: Implication for Human Health. *Sci. Total Environ.* **2022**, *835*, 155544. https://doi.org/10.1016/j.scitotenv.2022.155544
35. Liu, C.; Liu, C.; Juhasz, A.L.; Dong, W.J.; Ma, L.Q. Human Health Risks of Chromium in Bright-Colored Leather Products: Speciation-Based Insights into Dermal Permeation. *Environ. Int.* **2025**, *200*, 109538. https://doi.org/10.1016/j.envint.2025.109538

 doi:10.20944/preprints202603.1693.v1

36. Niemeier, R.T.; Maier, A.; Reichard, J.F. Rapid Review of Dermal Penetration and Absorption of Inorganic Lead Compounds for Occupational Risk Assessment. *Ann. Work Expo. Health* **2022**, *66*, 291–311. https://doi.org/10.1093/annweh/wxab097
37. Chan, T.Y. Inorganic Mercury Poisoning Associated with Skin-Lightening Cosmetic Products. *Clin. Toxicol.* **2011**, *49*, 886–891. https://doi.org/10.3109/15563650.2011.626425
38. World Health Organization (WHO). 10 Chemicals of Public Health Concern. Available online: https://www.who.int/news-room/photo-story/detail/10-chemicals-of-public-health-concern (accessed on 19 February 2026).
39. Gil, F.; Hernández, A.F. Toxicological Importance of Human Biomonitoring of Metallic and Metalloid Elements in Different Biological Samples. *Food Chem. Toxicol.* **2015**, *80*, 287–297. https://doi.org/10.1016/j.fct.2015.03.025
40. Buekers, J.; Baken, K.; Govarts, E.; Martin, L.R.; Vogel, N.; Kolossa-Gehring, M.; Šlejkovec, Z.; Falnoga, I.; Horvat, M.; Lignell, S.; Lindroos, A.K.; Rambaud, L.; Riou, M.; Pedraza-Diaz, S.; Esteban-Lopez, M.; Castaño, A.; Den Hond, E.; Baeyens, W.; Santonen, T.; Schoeters, G. Human Urinary Arsenic Species, Associated Exposure Determinants and Potential Health Risks Assessed in the HBM4EU Aligned Studies. *Int. J. Hyg. Environ. Health* 2023, *248*, 114115. https://doi.org/10.1016/j.ijheh.2023.114115
41. Barbosa, F., Jr.; Tanus-Santos, J.E.; Gerlach, R.F.; Parsons, P.J. A Critical Review of Biomarkers Used for Monitoring Human Exposure to Lead: Advantages, Limitations, and Future Needs. *Environ. Health Perspect.* **2005**, *113*, 1669–1674. https://doi.org/10.1289/ehp.7917
42. Ndaw, S.; Leso, V.; Bousoumah, R.; Rémy, A.; Bocca, B.; Duca, R.C.; Godderis, L.; Hardy, E.; Janasik, B.; van Nieuwenhuyse, A.; Pinhal, H.; Poels, K.; Porras, S.P.; Ruggieri, F.; Santonen, T.; Santos, S.R.; Scheepers, P.T.J.; Silva, M.J.; Verdonck, J.; Viegas, S.; HBM4EU Chromates Study Team. HBM4EU Chromates Study—Usefulness of Measurement of Blood Chromium Levels in the Assessment of Occupational Cr(VI) Exposure. *Environ. Res.* **2022**, *214*, 113758. https://doi.org/10.1016/j.envres.2022.113758
43. Adams, S.V.; Newcomb, P.A. Cadmium Blood and Urine Concentrations as Measures of Exposure: NHANES 1999–2010. *J. Expo. Sci. Environ. Epidemiol.* 2014, *24*, 163–170. https://doi.org/10.1038/jes.2013.55
44. So, S.C.A.; Tsoi, M.F.; Cheung, A.J.; Cheung, T.T.; Cheung, B.M.Y. Blood and Urine Inorganic and Organic Mercury Levels in the United States from 1999 to 2016. *Am. J. Med.* **2021**, *134*, e20–e30. https://doi.org/10.1016/j.amjmed.2020.06.023
45. Lamas, G.A.; Bhatnagar, A.; Jones, M.R.; Mann, K.K.; Nasir, K.; Tellez-Plaza, M.; Ujueta, F.; Navas-Acien, A.; American Heart Association Council on Epidemiology and Prevention; Council on Cardiovascular and Stroke Nursing; Council on Lifestyle and Cardiometabolic Health; Council on Peripheral Vascular Disease; Council on the Kidney in Cardiovascular Disease. Contaminant Metals as Cardiovascular Risk Factors: A Scientific Statement from the American Heart Association. *J. Am. Heart Assoc.* **2023**, *12*, e029852. https://doi.org/10.1161/JAHA.123.029852
46. Cheema, S.; Hussain, S.I.; Faheem, M.S.B.; Jalal, A.A.; Rifai, M.; Dar, A.; Burhan, M.; Shahid, A.; Ali, M.S.; Anwar, A.; Khalid, M.; Samadi, S. Toxic Heavy Metal Exposure and Heart Health: A Systematic Review and Meta-Analysis of 324,331 Patients. *BMC Cardiovasc. Disord.* **2025**, *25*, 792. https://doi.org/10.1186/s12872-025-05248-9
47. Liu, X.; Zhang, D.; Wu, X.; Tu, J.; Gong, C.; Li, Y.; Cui, W.; Chen, J.; Lu, S. Urinary metals as influencing factors of coronary heart disease among a population in Guangzhou, China. *Ecotoxicol. Environ. Saf.* **2022**, *241*, 113746. https://doi.org/10.1016/j.ecoenv.2022.113746
48. Bashir, B.; Jarial, S.; Sood, S.; Vishwas, S. Heavy Metals and Alzheimer's Disease: A Review. In *Heavy Metal Toxicity and Neurodegeneration*; Kumar, P., Gogia, N., Eds.; Academic Press: 2025; pp. 225–230. https://doi.org/10.1016/B978-0-443-36575-1.00020-0
49. Kooshki, A.; Farmani, R.; Mehrpour, O.; Naghizadeh, A.; Amirabadizadeh, A.; Kavoosi, S.; Vohra, V.; Nakhaee, S. Alzheimer's Disease and Circulatory Imbalance of Toxic Heavy Metals: A Systematic Review and Meta-Analysis of Clinical Studies. *Biol. Trace Elem. Res.* **2025**, *203*, 1871–1885. https://doi.org/10.1007/s12011-024-04326-x

 doi:10.20944/preprints202603.1693.v1

50. Song, Y.; Chen, Y.; Fu, Z.; Wen, Y.; Zhao, W.; Li, J.; Wang, H.; Du, Y.; Deng, Y. Heavy Metal Exposure and Cognitive Impairment: An Umbrella Review of Meta-Analyses. *J. Hazard. Mater.* **2025**, *498*, 139881. https://doi.org/10.1016/j.jhazmat.2025.139881
51. Wang, X.; Bakulski, K.M.; Walker, E.; Mukherjee, B.; Dodge, H.; Albin, R.L.; Paulson, H.L.; Park, S.K. Exposure to Lead and Incidence of Alzheimer's Disease and All-Cause Dementia in the United States. *Alzheimers Dement.* **2026**, *22*, e71075. https://doi.org/10.1002/alz.71075
52. Yang, Y.W.; Liou, S.H.; Hsueh, Y.M.; Lyu, W.S.; Liu, C.S.; Liu, H.J.; Chung, M.C.; Hung, P.H.; Chung, C.J. Risk of Alzheimer's Disease with Metal Concentrations in Whole Blood and Urine: A Case-Control Study Using Propensity Score Matching. *Toxicol. Appl. Pharmacol.* **2018**, *356*, 8–14. https://doi.org/10.1016/j.taap.2018.07.015
53. Strumylaite, L.; Kregzdyte, R.; Kucikiene, O.; Baranauskiene, D.; Simakauskiene, V.; Naginiene, R.; Damuleviciene, G.; Lesauskaite, V.; Zemaitiene, R. Alzheimer's Disease Association with Metals and Metalloids Concentration in Blood and Urine. *Int. J. Environ. Res. Public Health* **2022**, *19*, 7309. https://doi.org/10.3390/ijerph19127309
54. Wise, J.P., Jr.; Young, J.L.; Cai, J.; Cai, L. Current Understanding of Hexavalent Chromium [Cr(VI)] Neurotoxicity and New Perspectives. *Environ. Int.* **2022**, *158*, 106877. https://doi.org/10.1016/j.envint.2021.106877
55. da Silva, A.S.; Santos, R.M.S.; De Marco, P.G.; Rezende, V.H.M.; Martins, T.C.; Silva, J.R.; Romano-Silva, M.A.; Miranda, D.M. Neurodevelopmental Outcomes Associated with Early-Life Exposure to Heavy Metals: A Systematic Review. *Int. J. Environ. Res. Public Health* **2025**, *22*, 1308. https://doi.org/10.3390/ijerph22081308
56. Rahmani, A.; Khamutian, S.; Doosti-Irani, A.; Shokoohizadeh, M.J.; Shirmohammadi-Khorram, N.; Sahraeei, F.; Khodabakhshi, M.; Ahangaran, N. The Association of Arsenic Exposure with Mortality Due to Cancer, Diabetes, Alzheimer's and Congenital Anomalies Using Poisson Regression. *Sci. Rep.* **2023**, *13*, 15456. https://doi.org/10.1038/s41598-023-42744-4
57. Lee, F.J.; Inchai, H.; Lin, J.T.; Koh, D.; Lin, R.T. Dose-Response Relationship of Cadmium and Pancreatic Cancer Risk: A Meta-Analysis. *Occup. Environ. Med.* 2025, *82*, 407–414. https://doi.org/10.1136/oemed-2025-110163
58. Firmani, G.; Chiavarini, M.; Dolcini, J.; Quarta, S.; D'Errico, M.M.; Barbadoro, P. The Association Between Cadmium Exposure and Prostate Cancer: An Updated Systematic Review and Meta-Analysis. *Int. J. Environ. Res. Public Health* **2024**, *21*, 1532. https://doi.org/10.3390/ijerph21111532
59. Zhang, L.; Wang, Y.; Li, T.; Zhuo, W.; Zhu, Y. Elevated Serum and Hair Levels of Cadmium as a Risk Factor for Liver Carcinoma: A Meta-Analysis. *Nutr. Cancer* 2023, *75*, 1438–1447. https://doi.org/10.1080/01635581.2023.2192887
60. Lee, H.; Jo, Y.; Jung, M.; Lee, J.H.; Kim, T.H.; Lee, J.; Kim, D.J.; Rahmati, M.; Smith, L.; Pizzol, D.; Son, Y.; Park, J.; Ahn, S.H.; Yon, D.K.; Choi, D.W.; Kang, J. Heavy Metal Exposure and All Health Outcomes: An Umbrella Review of Meta-Analyses. *J. Hazard. Mater.* **2026**, *503*, 141141. https://doi.org/10.1016/j.jhazmat.2026.141141
61. Abdelgawwad El-Sehrawy, A.A.M.; Hsu, C.Y.; Saleh, E.A.M.; Moharam, M.M.; Rekha, M.M.; Kundlas, M.; Premkumar, J.; Ray, S.; Hussein, A.R.; Kadhim, M.A. Associations between Cadmium and Lead Exposure and Thyroid Disorders: A Systematic Review and Meta-Analysis. *J. Trace Elem. Med. Biol.* **2025**, *92*, 127781. https://doi.org/10.1016/j.jtemb.2025.127781
62. Vagnoni, G.; Bortolotti, E.; Checchi, S.; Saieva, C.; Berti, G.; Doccioli, C.; Caini, S. Lead (Pb) in Biological Samples in Association with Cancer Risk and Mortality: A Systematic Literature Review. *Cancer Epidemiol.* **2024**, *92*, 102630. https://doi.org/10.1016/j.canep.2024.102630
63. Webster, A.M.; Pinion, D.; Pineda, E.; Aboueisha, H.; Hussein, M.H.; Fawzy, M.S.; Toraih, E.A.; Kandil, E. Elucidating the Link between Thyroid Cancer and Mercury Exposure: A Review and Meta-Analysis. *Environ. Sci. Pollut. Res.* **2024**, *31*, 12841–12855. https://doi.org/10.1007/s11356-024-32031-8
64. Deng, Y.; Wang, M.; Tian, T.; Lin, S.; Xu, P.; Zhou, L.; Dai, C.; Hao, Q.; Wu, Y.; Zhai, Z.; Zhu, Y.; Zhuang, G.; Dai, Z. The Effect of Hexavalent Chromium on the Incidence and Mortality of Human Cancers: A Meta-

 doi:10.20944/preprints202603.1693.v1

Analysis Based on Published Epidemiological Cohort Studies. *Front. Oncol.* **2019**, *9*, 24. https://doi.org/10.3389/fonc.2019.00024

65. Virolainen, S.J.; VonHandorf, A.; Viel, K.C.M.F.; Weirauch, M.T.; Kottyan, L.C. Gene-Environment Interactions and Their Impact on Human Health. *Genes Immun.* **2023**, *24*, 1–11. https://doi.org/10.1038/s41435-022-00192-6
66. Kim, H.K.; Lee, H.; Kim, H.J. A Polymorphism in DMT1 Is Associated with Lead-Related Hypertensive Status. *Mol. Cell. Toxicol.* **2013**, *9*, 415–420. https://doi.org/10.1007/s13273-013-0051-y
67. Mani, M.S.; Dsouza, V.L.; Dsouza, H.S. Evaluation of Divalent Metal Transporter 1 (DMT1) (rs224589) Polymorphism on Blood Lead Levels of Occupationally Exposed Individuals. *Toxicol. Lett.* **2021**, *353*, 13–19. https://doi.org/10.1016/j.toxlet.2021.10.002
68. Sadana, A.A.S.; Bakri, S.; Tokonami, S.; Nugraha, E.D.; Amqam, H.; Muniroh, M. Genetic Modulation of Mercury Exposure on Perinatal and Birth Outcomes: A Systematic Review and Meta-Analysis of Gene-Environment Interactions. *J. Xenobiot.* **2026**, *16*, 28. https://doi.org/10.3390/jox16010028
69. Luo, L.; Li, Y.; Gao, Y.; Zhao, L.; Feng, H.; Wei, W.; Qiu, C.; He, Q.; Zhang, Y.; Fu, S.; Sun, D. Association between Arsenic Metabolism Gene Polymorphisms and Arsenic-Induced Skin Lesions in Individuals Exposed to High-Dose Inorganic Arsenic in Northwest China. *Sci. Rep.* **2018**, *8*, 413. https://doi.org/10.1038/s41598-017-18925-3
70. González-Martínez, F.; Sánchez-Rodas, D.; Cáceres, D.D.; Martínez, M.F.; Quiñones, L.A.; Johnson-Restrepo, B. Arsenic Exposure, Profiles of Urinary Arsenic Species, and Polymorphism Effects of Glutathione-S-Transferase and Metallothioneins. *Chemosphere* **2018**, *212*, 927–936. https://doi.org/10.1016/j.chemosphere.2018.08.139
71. Tamayo, L.I.; Tong, L.; Davydiuk, T.; Vander Griend, D.; Haque, S.E.; Islam, T.; Jasmine, F.; Kibriya, M.G.; Graziano, J.; Chen, L.; Le, X.C.; Ahsan, H.; Gamble, M.V.; Pierce, B.L. Genetic Variation in the FMO and GSTO Gene Clusters Impacts Arsenic Metabolism in Humans. *PLoS Genet.* **2025**, *21*, e1011826. https://doi.org/10.1371/journal.pgen.1011826
72. Stea, F.; Faita, F.; Borghini, A.; Faita, F.; Bianchi, F.; Bustaffa, E.; Minichilli, F.; Andreassi, M. G.; Sicari, R. Arsenic and Subclinical Vascular Damage in a Sample of Italian Young Adults: A Cross-Sectional Analysis. *Environ. Sci. Pollut. Res. Int.* **2016**, *23*, 20307–20314. https://doi.org/10.1007/s11356-016-7260-6
73. Jin, B.; Wan, S.; Boah, M.; Yang, J.; Ma, W.; Lv, M.; Li, H.; Wang, K. GSTM1 and GSTT1 Null Genotype Polymorphisms and Susceptibility to Arsenic Poisoning: A Meta-Analysis. *Biol. Trace Elem. Res.* **2021**, *199*, 2085–2095. https://doi.org/10.1007/s12011-020-02325-2
74. Khan, S.A.; Nurulain, S.M.; Qureshi, R.N.; Zafar, A.; Riaz, Z.; Shoukat, A.; Muneer, Z.; Bibi, N.; Raza, S.; Hussain, S.; Shah, S.T.A. Exposure to Heavy Metals, Antioxidant Status, and the Interaction of Single Nucleotide Polymorphisms in the Genes CAT rs7943316, GSTP1 rs1695, as well as GSTM1 and GSTT1 Genes, among Workers in Occupational Settings. *Environ. Toxicol. Pharmacol.* **2024**, *108*, 104452. https://doi.org/10.1016/j.etap.2024.104452
75. Barcelos, G.R.; Grotto, D.; de Marco, K.C.; Valentini, J.; Lengert, A.V.; de Oliveira, A.Á.; Garcia, S.C.; Braga, G.Ú.; Schläwicke Engström, K.; Cólus, I.M.; Broberg, K.; Barbosa, F. Jr. Polymorphisms in Glutathione-Related Genes Modify Mercury Concentrations and Antioxidant Status in Subjects Environmentally Exposed to Methylmercury. *Sci. Total Environ.* 2013, *463–464*, 319–325. https://doi.org/10.1016/j.scitotenv.2013.06.029
76. Baszuk, P.; Janasik, B.; Pietrzak, S.; Marciniak, W.; Reszka, E.; Białkowska, K.; Jabłońska, E.; Muszyńska, M.; Lesicka, M.; Derkacz, R.; Grodzki, T.; Wójcik, J.; Wojtyś, M.; Dębniak, T.; Cybulski, C.; Gronwald, J.; Kubisa, B.; Wójcik, N.; Pieróg, J.; Gajić, D.; Lener, M.R. Lung Cancer Occurrence—Correlation with Serum Chromium Levels and Genotypes. *Biol. Trace Elem. Res.* **2021**, *199*, 1228–1236. https://doi.org/10.1007/s12011-020-02240-6
77. Medina Pérez, O.M.; Flórez-Vargas, O.; Rincón Cruz, G.; Rondón González, F.; Rocha Muñoz, L.; Sánchez Rodríguez, L.H. Glutathione-Related Genetic Polymorphisms Are Associated with Mercury Retention and Nephrotoxicity in Gold-Mining Settings of a Colombian Population. *Sci. Rep.* **2021**, *11*, 8716. https://doi.org/10.1038/s41598-021-88137-3

 doi:10.20944/preprints202603.1693.v1

78. Gomes, W.R.; Devóz, P.P.; Luiz, B.L.C.; Grotto, D.; Batista, B.L.; Barbosa, F., Jr.; Barcelos, G.R.M. Polymorphisms of Genes Related to Metabolism of Lead (Pb) Are Associated with the Metal Body Burden and with Biomarkers of Oxidative Stress. *Mutat. Res. Genet. Toxicol. Environ. Mutagen.* 2018, *836 Pt B*, 42–46. https://doi.org/10.1016/j.mrgentox.2018.05.016
79. Yohannes, Y.B.; Nakayama, S.M.M.; Yabe, J.; Toyomaki, H.; Kataba, A.; Nakata, H.; Muzandu, K.; Ikenaka, Y.; Choongo, K.; Ishizuka, M. Glutathione S-Transferase Gene Polymorphisms in Association with Susceptibility to Lead Toxicity in Lead- and Cadmium-Exposed Children near an Abandoned Lead-Zinc Mining Area in Kabwe, Zambia. *Environ. Sci. Pollut. Res. Int.* **2022**, *29*, 6622–6632. https://doi.org/10.1007/s11356-021-16098-1
80. Yang, R.; Roshani, D.; Gao, B.; Li, P.; Shang, N. Metallothionein: A Comprehensive Review of Its Classification, Structure, Biological Functions, and Applications. *Antioxidants* **2024**, *13*, 825. https://doi.org/10.3390/antiox13070825
81. Adams, S.V.; Barrick, B.; Christopher, E.P.; Shafer, M.M.; Makar, K.W.; Song, X.; Lampe, J.W.; Vilchis, H.; Ulery, A.; Newcomb, P.A. Genetic Variation in Metallothionein and Metal-Regulatory Transcription Factor 1 in Relation to Urinary Cadmium, Copper, and Zinc. *Toxicol. Appl. Pharmacol.* **2015**, *289*, 381–388. https://doi.org/10.1016/j.taap.2015.10.024
82. Kayaaltı, Z.; Aliyev, V.; Söylemezoğlu, T. The Potential Effect of Metallothionein 2A -5A/G Single Nucleotide Polymorphism on Blood Cadmium, Lead, Zinc and Copper Levels. *Toxicol. Appl. Pharmacol.* **2011**, *256*, 1–7. https://doi.org/10.1016/j.taap.2011.06.023
83. Yang, C.C.; Chen, H.I.; Chiu, Y.W.; Tsai, C.H.; Chuang, H.Y. Metallothionein 1A Polymorphisms May Influence Urine Uric Acid and N-Acetyl-Beta-D-Glucosaminidase (NAG) Excretion in Chronic Lead-Exposed Workers. *Toxicology* **2013**, *306*, 68–73. https://doi.org/10.1016/j.tox.2013.02.007
84. Wang, Y.; Goodrich, J.M.; Gillespie, B.; Werner, R.; Basu, N.; Franzblau, A. An Investigation of Modifying Effects of Metallothionein Single-Nucleotide Polymorphisms on the Association between Mercury Exposure and Biomarker Levels. *Environ. Health Perspect.* **2012**, *120*, 530–534. https://doi.org/10.1289/ehp.1104079
85. Chan, P.H.Y.; Chan, K.Y.Y.; Schooling, C.M.; Hui, L.L.; Chan, M.H.M.; Li, A.M.; Cheung, R.C.K.; Lam, H.S. Association between Genetic Variations in GSH-Related and MT Genes and Low-Dose Methylmercury Exposure in Children and Women of Childbearing Age: A Pilot Study. *Environ. Res.* **2020**, *187*, 109703. https://doi.org/10.1016/j.envres.2020.109703
86. Vodicka, P.; Stetina, R.; Polakova, V.; Tulupova, E.; Naccarati, A.; Vodickova, L.; Kumar, R.; Hanova, M.; Pardini, B.; Slyskova, J.; Musak, L.; De Palma, G.; Soucek, P.; Hemminki, K. Association of DNA Repair Polymorphisms with DNA Repair Functional Outcomes in Healthy Human Subjects. *Carcinogenesis* **2007**, *28*, 657–664. https://doi.org/10.1093/carcin/bgl187
87. Borghini, A.; Faita, F.; Mercuri, A.; Minichilli, F.; Bustaffa, E.; Bianchi, F.; Andreassi, M. G. Arsenic Exposure, Genetic Susceptibility and Leukocyte Telomere Length in an Italian Young Adult Population. *Mutagenesis* **2016**, *31*, 539–546. https://doi.org/10.1093/mutage/gew017
88. Huang, C. Y.; Pu, Y. S.; Shiue, H. S.; Chen, W. J.; Lin, Y. C.; Hsueh, Y. M. Polymorphisms of Human 8-Oxoguanine DNA Glycosylase 1 and 8-Hydroxydeoxyguanosine Increase Susceptibility to Arsenic Methylation Capacity-Related Urothelial Carcinoma. *Arch. Toxicol.* **2016**, *90*, 1917–1927. https://doi.org/10.1007/s00204-015-1590-x
89. Nunes, E.A.; Silva, H.C.D.; Duarte, N.A.A.; de Lima, L.E.; Maraslis, F.T.; Araújo, M.L.; Pedron, T.; Neves Lange, C.; Freire, B.M.; Matias, A.C.; Batista, B.L.; Barcelos, G.R.M. Impact of DNA Repair Polymorphisms on DNA Instability Biomarkers Induced by Lead (Pb) in Workers Exposed to the Metal. *Chemosphere* **2023**, *334*, 138897. https://doi.org/10.1016/j.chemosphere.2023.138897
90. Andreoli, V.; Sprovieri, F. Genetic Aspects of Susceptibility to Mercury Toxicity: An Overview. *Int. J. Environ. Res. Public Health* **2017**, *14*, 93. https://doi.org/10.3390/ijerph14010093
91. Halasova, E.; Matakova, T.; Musak, L.; Polakova, V.; Letkova, L.; Dobrota, D.; Vodicka, P. Evaluating Chromosomal Damage in Workers Exposed to Hexavalent Chromium and the Modulating Role of Polymorphisms of DNA Repair Genes. *Int. Arch. Occup. Environ. Health* **2012**, *85*, 473–481. https://doi.org/10.1007/s00420-011-0684-x

 doi:10.20944/preprints202603.1693.v1

92. Zhang, X.; Zhang, X.; Zhang, L.; Chen, Q.; Yang, Z.; Yu, J.; Fu, H.; Zhu, Y. XRCC1 Arg399Gln Was Associated with Repair Capacity for DNA Damage Induced by Occupational Chromium Exposure. *BMC Res. Notes* **2012**, *5*, 263. https://doi.org/10.1186/1756-0500-5-263
93. Sarlinova, M.; Majerova, L.; Matakova, T.; Musak, L.; Slovakova, P.; Skereňová, M.; Kavcová, E.; Halašová, E. Polymorphisms of DNA Repair Genes and Lung Cancer in Chromium Exposure. *Adv. Exp. Med. Biol.* **2015**, *833*, 1–8. https://doi.org/10.1007/5584_2014_82
94. Long, C.; Liu, J.; Hu, G.; Feng, H.; Zhou, D.; Wang, J.; Zhai, X.; Zhao, Z.; Yu, S.; Wang, T.; Jia, G. Modulation of Homologous Recombination Repair Gene Polymorphisms on Genetic Damage in Chromate Exposed Workers. *Environ. Toxicol. Pharmacol.* **2019**, *66*, 126–132. https://doi.org/10.1016/j.etap.2019.01.004
95. Fontanelli, L.; Castronovo, A.; Ferri, C.; Vozzi, F.; Recchia, F.A.; Borghini, A. iPSC-Derived Endothelial Cells as Experimental Models for Predictive and Personalized Strategies in Cardiovascular and Cerebrovascular Disease. *Int. J. Mol. Sci.* **2026**, *27*, 780. https://doi.org/10.3390/ijms270207
96. Chandy, M.; Obal, D.; Wu, J.C. Elucidating Effects of Environmental Exposure Using Human-Induced Pluripotent Stem Cell Disease Modeling. *EMBO Mol. Med.* **2022**, *14*, e13260. https://doi.org/10.15252/emmm.202013260