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Metabolic and genetic derangement: a review of mechanisms involved in arsenic and lead toxicity and genotoxicity

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Urbanisation and industrialisation are on the rise all over the world. Environmental contaminants such as potentially toxic elements (PTEs) are directly linked with both phenomena. Two PTEs that raise greatest concern are arsenic (As) and lead (Pb) as soil and drinking water contaminants, whether they are naturally occurring or the consequence of human activities. Both elements are potential carcinogens. This paper reviews the mechanisms by which As and Pb impair metabolic processes and cause genetic damage in humans. Despite efforts to ban or limit their use, due to high persistence both continue to pose a risk to human health, which justifies the need for further toxicological research.

KEY WORDS: arsenic trioxide; DNA damage; human health; metal availability; oxidative stress; reactive oxygen species

Potentially toxic elements (PTE), such as lead (Pb), cadmium (Cd), arsenic (As), zinc (Zn), silver (Ag), chromium (Cr), and copper (Cu), occur naturally in metal-rich areas such as ultramafic or karst (1, 2). However, the major sources of exposure are anthropogenic as consequence of industrial and urban development, such as metal processing in mining, petroleum refining and combustion, smelting, other metal-based industrial operations (3, 4), production of chemical-based fertilisers (5), transportation (road and maritime traffic) (6), and even personal care products such as face cosmetics, skin lightening products, and herbal cosmetics (7). Rural areas are not spared, as long-range transboundary emissions can affect even the most remote regions (8, 9).

Humans are mainly exposed through inhalation, ingestion, and/or skin, and reports associate exposure with varying metabolic changes affecting the heart, kidney, liver, brain, developing foetus, and even the DNA (10–14). PTEs have also been associated with cancer, Parkinson's disease, and rare autoimmune disorder and/or degenerative diseases (15–17). They can also elicit genotoxic, cytotoxic, and carcinogenic effects (15, 16).

The aim of this paper is to review current knowledge about the sources of emission, human exposure, and mechanisms of toxicity and genotoxicity, as well as the carcinogenic potential of As and Pb, two elements that rank the highest on the Substance Priority List (SPL) issued by the Agency for Toxic Substances and Disease Registry (ATSDR) (18). Despite the efforts to ban or limit their use, both are highly persistent in the environment and continue to pose a risk to human health, which justifies the need for further toxicological research.

ARSENIC

Arsenic is a metalloid that occurs naturally in soil and many kinds of rocks (19). It occurs in three major chemical forms. The most common organic As compounds are arsanilic acid ($C_6H_8AsNO_3$), methylarsonic acid (MMA) ($CH_3AsO_3H_2$), and dimethylarsinic acid (DMA) ($C_2H_7AsO_2$) (20–23). In addition to them, there are arsenolipids, predominantly present in fish and seafood. They appear in nine main structural groups, of which arseno-fatty acids (AsFAs) and arseno-hydrocarbons (AsHCs) are of particular interest due to their cytotoxicity, comparable to that of inorganic As (23). Inorganic compounds include arsenic trioxide (As_2O_3), sodium arsenate ($NaAsO_2$), lead arsenate ($PbHAsO_4$), arsenic trichloride ($AsCl_3$), calcium arsenate ($Ca_3(AsO_4)_2$), and arsine gas (AsH_3).

Arsenic has three ionised states: pentavalent arsenate (As^{V+}), trivalent arsenite (As^{III+}), and arsines (As^{III-}), and either of these states can be found in inorganic and organic forms. However, the trivalent or pentavalent states are the most common and mobile (24). The inorganic forms are generally considered more toxic, with trivalent arsenite being most toxic (22).

Humans are exposed to As through contaminated drinking water, medicines, cosmetics, or diet, as shown in Table 1. Upon

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Table 1 Main sources and routes of exposure of As

Main sources	Sources	Route of exposure
Earth crust	Rocks (e.g., volcanic eruptions), naturally enriched areas (e.g., serpentine areas)	Ingestion/ Inhalation
Dietary sources	Seafood, contaminated water, accumulation in food crops, fruits and grains	Ingestion
Medicinal sources	Arsenic trioxide treatment for acute promyelocytic leukemia Arsenic-based drugs in veterinary medicine	Ingestion
Cosmetics	Skin lightening products and fairness creams	Intradermal
Industrial sources	Pesticide production, wood preservatives, microelectronics production, microwave devices, and lasers	Ingestion/inhalation
Air	Use of pesticides and agrochemicals, industrial sources	Inhalation

ingestion or inhalation, inorganic and organic As is readily absorbed in the gastrointestinal tract ($\geq$75 % for As^{III+}, As^{V+}, MMA, and DMA) or lungs, respectively (14). Arsine gas (AsH_3) is the most toxic form of As, and inhalation of over 32 mg/m^3 is lethal after exposure of more than one hour. With inhalation of 80–160 mg/m^3, death occurs in less than an hour, and with inhalation of >800 mg/m^3 it is instantaneous (22, 25).

However, dermal absorption is less likely (26, 27). Whichever the route, absorbed As is mainly transported by the blood and deposited in the liver, kidney, lungs, skin, and, to a lesser extent, bones and muscles (28, 29). In the body, pentavalent arsenate is reduced to arsenite, which is further methylated in the liver into MMA^V and DMA^V, which are eliminated in urine and faeces (30, 31). Methylation was previously considered as a detoxification process, as both products are readily excreted by the kidneys. In contrast, recent studies have shown that methylated trivalent arsenite is as toxic, if not even more toxic, than their parent compound or inorganic forms (32–34).

The symptoms of As toxicity depend on the chemical form, exposure route and duration, and individual health. Acute As poisoning can result in nausea, vomiting, erythropenia, leukopenia, and a pricking sensation in the hands and legs. Skin lesions, systemic damage, nasal perforations, and vascular diseases are associated with long-term exposure (13). Chronic toxicity is known as arsenicosis. Chronic arsenicosis can facilitate the development of skin, lung, liver, and bladder cancer (35–37).

Mechanisms of toxicity

The mechanisms of As toxicity and genotoxicity in humans are not yet fully understood. Most toxicologically relevant data originate from *in vitro* studies. Important to note, As toxicity depends on its chemical form.

Arsenate and phosphate group

Arsenate (pentavalent) is a phosphate analogue with similar chemical structure and properties, which is why it replaces phosphate in several biological reactions. One reaction that has been studied *in vitro* (22) is glycolysis. In normal glycolysis, glucose is catabolised by phosphates to generate adenosine triphosphate (ATP) (38).

Arsenate, however, interrupts ATP generation through a mechanism called arsenolysis (22). During normal glycolysis, phosphate is linked enzymatically to D-glyceraldehyde-3-phosphate to form 1,3-bisphospho-D-glycerate. Arsenate may replace phosphate to form an unstable product 1-arsenato-3-phospho-D-glycerate, which is further hydrolysed into arsenate and 3-phosphoglycerate, bypassing the generation of ATP from 1,3-biphospho-D-glycerate (22, 39). Arsenolysis may also occur during oxidative phosphorylation. In the mitochondria, ATP is synthesised from phosphate and adenosine diphosphate (ADP), but in the presence of arsenate, ADP-arsenate is formed instead (39, 40). The resulting decline in ATP generation can affect the normal functioning of cellular systems.

Arsenite and thiol groups

Arsenite (trivalent) can also diminish ATP generation via its reaction with thiol, that is, sulphydryl, groups (-SH), which have a major role in the activity of certain enzymes, coenzymes, and receptors. Arsenite binding to critical thiol groups in such molecules can interfere with some biochemical reactions and result in cellular toxicity (29, 41). An example that has been studied *in vitro* is that of pyruvate dehydrogenase, an enzyme in the citric acid cycle. Arsenite's affinity for thiols, especially dithiols, alters the lipoic acid moiety and consequently inhibits pyruvate dehydrogenase activity (39, 40), which, in turn, can impair cellular respiration and reduce ATP generation (29, 42). Methylated trivalent arsenicals such as MMA^{3+} have been shown to be even more potent inhibitors of pyruvate dehydrogenase, GSH reductase, and thioredoxin reductase, all of which contain thiol groups (43). Inhibition of these enzymes can alter key redox reactions and may eventually lead to cytotoxicity or even cell death (41, 44).

Arsenic and oxidative stress

Another mechanism of As toxicity is the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that leads to oxidative stress in cells and can result in cellular damage and death (15, 45). Detectable levels of superoxide anion ($O_2 \cdot^-$), hydrogen peroxide(H_2O_2), hydroxyl radical (OH), and nitric oxide (NO) have been found in human vascular smooth muscle cells (VSMC (46,

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47), human-hamster hybrid cells (48, 49) and vascular endothelial cells (28) exposed to As. Even at environmentally relevant concentrations or at non-lethal concentrations (below 5 μmol/L), As can still stimulate $O_2^{\cdot-}$ and H_2O_2 generation (50). In addition, it can also affect antioxidant enzymes (such as with GSH, see above) (51, 52).

Arsenolipids

Currently, only a few studies have assessed the potential risk of arsenolipids for human health. Arseno-hydrocarbons (AsHCs) are more toxic than arseno-fatty acids (AsFAs). Arsenolipids also lower the levels of cellular ATP (53–56). The mechanism is unclear but may be related to mitochondrial membrane damage and disrupted mitochondrial function. Studies with *Drosophila melanogaster* have shown that AsHCs can pass the blood-brain barrier (BBB) and affect development (54, 55). AsHCs can also enter the milk of lactating mothers after ingestion of fish. Exposure via breastmilk has been shown to affect neurodevelopment in infants and can be linked to the attention deficit hyperactivity disorder (ADHD) (53, 56).

Mechanism of genotoxicity

Various forms of As are genotoxic. Even methylated arsenicals, formerly thought to be harmless, can induce chromosome aberrations and are potent DNA-damaging agents (57). Arsenic and arsenic-containing compounds can activate or indirectly cause genetic changes or damage (58–60).

Potential mechanisms of As genotoxicity include ROS generation, chromosome aberrations (chromatid breaks and gaps), sister chromatid exchange, and the induction of micronucleated cells (61, 62). In recent studies, As has been linked to epigenetic modifications through key mechanisms of gene regulation and DNA methylation (63). ROS can react chemically with DNA resulting in the structural damage of chromosomes, which can further lead to cellular transformation and possibly to tumour proliferation (23, 64). Arsenic-induced chromosome aberrations originate from ROS-mediated single- or double-strand DNA breaks. The latter usually arise at sites where there are single-strand breaks nearby, on the opposite DNA strands, or due to endonuclease action (2, 33, 2, 65). If this happens at the late G1 phase or S phase (DNA synthesis) due to insufficient time for repair, chromatid-type or chromosome-type aberrations may occur in the subsequent metaphase (33). In a study by Kligerman et al. (66), MMA^{III} and DMA^{III} induced chromosome mutation in mouse lymphoma cells. Structural aberrations can also affect important regions on chromosomes, leading to various detrimental effects. Although the mechanism of alterations is not fully understood, aberrations in the expression of growth control genes are a key step toward carcinogenesis.

Inorganic As has been shown to modulate the expression of transcription factors – proteins controlling the transcription of genetic information from DNA to mRNA – by causing oxidative stress through intracellular redox reactions (17, 67). In response to oxidative stress, certain early response genes are activated to protect against and prevent further damage. The major pathways involved in arsenic-induced ROS are nuclear factor kappa B (NF-ϰB), tumour suppressor protein (p53) activating protein-1 (AP-1), Nrf2-antioxidant response element (ARE) signalling pathway, microRNAs (miRNAs), mitophagy pathway, tyrosine phosphorylation system, and mitogen-activated protein kinases (MAPKs) (1, 32, 68). Both NF-ϰB and AP-1 are stress-response transcription factors that regulate the expression of genes involved in cellular antioxidant defence.

At low concentrations and shorter exposure periods, arsenite has been shown to induce both of these transcription factors in normal cells (69, 70).

NF-ϰB dimers are normally present in the cytoplasm of unstimulated cells, but are inactive due to interaction with specific inhibitors (71). Production of ROS at As levels ranging from 1 to 10 μmol/L stimulates NF-ϰB (32). Concentrations above 10 μmol/L induce phosphorylation and degradation of NF-ϰB inhibitors, leading to the release of NF-ϰB dimers, which then move to the nucleus and induce transcription of target genes (31, 72, 73). Some reports (72, 74) suggest that arsenite can interfere with the DNA binding of NF-ϰB, although this was observed at physiologically non-relevant concentrations. AP-1, on the other hand, is maintained within the nucleus and is composed of homodimers or heterodimers of Jun and Fos proteins (32). Trivalent methylated arsenicals are potent inducers of AP-1-dependent gene transcription and its regulator proteins (75). Transactivation of AP-1 is achieved through phosphorylation of its activation domain by c-Jun N-terminal kinase (JNK) (75).

The ARE pathway protects cells from oxidative damage thanks to the Nrf2 -induced expression of cytoprotective genes. Nrf2 is regulated by its repressor, kelch-like epichlorohydrin-associated protein 1 (Keap1) (76, 77). In the presence of excess reactive species, cysteine residues in Keap1 are s-alkylated and Nrf2 accumulates and translocates to the nucleus, where it binds to the ARE motif in the promoter region of target genes and antioxidant enzymes (32). Arsenite can impair Nrf2 ubiquitination and activate the Nrf2-induced antioxidant signalling pathway (77). The Nrf2 pathway may play a dual role in As toxicity, depending on the dose, exposure time, and cell types. Exposure of human skin fibroblasts to As_2O_3 at concentrations ranging from 0 to 10 μmol/L for 24 h upregulated the expression of Nrf2 and its downstream target gene HO-1, which resulted with reduced levels of ROS (78). In human choriocarcinoma JAr cells, As increased oxidative stress with the production of H_2O_2, leading to an increase in Nrf2/small Maf DNA binding activity and HO-1 expression (79). Similar results have been observed in mouse lymphatic endothelial cells (80).

In addition, As may induce epigenetic modifications by altering DNA methylation. The cell uses DNA methylation as an epigenetic mechanism to control gene expression. Thus, genes can either be expressed or repressed depending on the type of regulatory element

in which methylation occurs. Arsenic can either induce hypomethylation or hypermethylation, with the former being more common (81).

Methylation of arsenite is necessary for its excretion. However, methyl groups are also required for normal function of DNA methyltransferases (81, 82). Demanelis et al. (63) described two mechanisms of how As impairs DNA methylation: by lowering the expression of DNA methyltransferases 3 and DNA methyltransferases 1 (83–85) and by depleting methyl groups as it is being metabolised and making them unavailable for DNA methyltransferases and DNA methylation.

Genotoxicity of As is a useful property in some cases, for example in antitumor therapy. Arsenic trioxide (As_2O_3) has shown some potential in the treatment of hypertrophic scars (78). Li et al. (86) reported that varying concentrations of As_2O_3 significantly inhibited cell proliferation, activation of caspase-3 (mediator of cell death), and JNk activation (86) in hepatocellular carcinoma (HepG2) cells. Antiproliferative effects of As on hepatocellular carcinoma have been studied extensively over the years and reported in several papers (87–89). However, recent findings by Chen et al. (90) suggest that hypoxic hepatocellular carcinoma cells develop resistance against As_2O_3 due to upregulation of the transcription factor HIF-1α. Similar antitumor effects of As_2O_3 have been observed in glioma cells, in which As exerts anti-tumour effects via apoptosis and autophagy (91–93). While this is promising, the use of As for treatment calls for great caution, because normal cells respond differently to As exposure, and further studies are needed to ensure high target specificity and eliminate adverse effects.

Mechanism of carcinogenicity

The International Agency for Research on Cancer (IARC) classifies inorganic As as a group I carcinogen (63). Potential mechanisms of As carcinogenicity include genotoxicity, tumour production, co-carcinogenesis, cell proliferation, altered DNA methylation, ROS production and oxidative stress (94), and production of dimethyl arsenate (DMAv), which at extremely high concentrations is carcinogenic in rat bladder (95, 96).

LEAD

Lead (Pb) is a widely used element due to its softness, malleability, ductility, poor conductibility, and resistance to corrosion. Its extensive use has brought about human exposure in various ways, mainly through environmental pollution. For many years now, it has been banned in petrol, paint, and several other applications, but being a non-biodegradable element, it persists in the environment, and is easily accumulated in all ecosystems. Pb is highly toxic (4, 97, 98), especially for the nervous system development in children. In 2017, the Institute for Health Metrics and Evaluation (IHME) estimated that Pb exposure accounted for 1.06 million deaths and 24.4 million disability-adjusted life years (DALYs) worldwide due to long-term effects on health (99). Table 2 shows the main sources and routes of human exposure.

Ingestion and inhalation dominate, while absorption through the skin is minimal and mostly concerns organic tetraethylated and tetramethylated Pb. When Pb-contaminated food, water, or soil is ingested, it is easily absorbed by the digestive system (100). When inhaled from polluted air, it is directly absorbed through the lungs (smaller particles) or cleared by the mucociliary transport (larger particles) only to be swallowed and absorbed in the gastrointestinal tract (28).

Absorbed Pb is transported by the blood to soft (e.g., liver, kidney, brain, spleen, ovary, and prostate) and mineralising (bone, teeth) tissues. Its elimination takes about 30–40 days from the first and about 10–20 years from the second (99, 100).

Lead has no physiological function in the human body but impairs multiple biochemical processes, and affects the renal, reproductive, and nervous (especially in children) systems (101, 102).

Table 2 Main sources and route of exposure of Pb

Main sources	Sources	Route of exposure
Earth crust	Naturally enriched areas (e.g., black shale areas)	Ingestion and dermal contact
Dietary sources	Contaminated food, lead accumulated in plants (e.g., urban agriculture), game hunting meat	Ingestion
Medicinal sources	Some traditional medicines	Ingestion
Cosmetics	Lipstick, Nail polish	Intradermal (organic forms only)
Industrial sources	Lead-based paints, mining and smelting, lead acid battery production, solder and glassware production, recycling activities	Ingestion/Inhalation
Recreational activities	Use of indoor firearms, recreational shooting activities and/or fishing activities	Inhalation, dermal contact, ingestion
Air	Combustion of lead-based gasoline, tobacco smoke, leaded aviation fuel	Inhalation
Drinking water	Lead pipes	Ingestion
Soil	Contaminated soil	Ingestion (mainly in children)

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Until 2012, having a blood Pb level of 10 μg/dL or above was considered "level of concern" in children. Since 2012, the US Centers for Disease Control has lowered this threshold to 5 μg/dL (103–105). This reference value was then also adopted for adults by the National Institute for Occupational Safety and Health (NIOSH) in 2015 (106). According to the World Health Organization (WHO), there is no safe blood Pb concentration. Flannery and Middleton (107) have recently published an extensive report regarding blood Pb levels in children and adverse effects associated with reference values. Table 3 summarises symptoms of Pb toxicity, depending on its concentration in blood.

Mechanisms of toxicity

The mechanisms of Pb toxicity include oxidative imbalance (that could lead to oxidative stress), interference with enzymes, and various phenomena at the molecular level, including single nucleotide polymorphisms and epigenetic modifications, while recent studies also report changes in regulatory RNA or microRNA (miRNA) molecules (108, 109). Oxidative stress, however, is considered the major mechanism of Pb-induced toxicity.

Lead and oxidative stress

Lead induces oxidative stress via the generation of ROS [such as hyperoxides ($HO_2 \cdot$), singlet oxygen, and hydrogen peroxide (H_2O_2)] and depletion of intrinsic antioxidants that counter ROS (110–112).

Pb leads to the generation of ROS mostly by inhibiting δ-aminolevulinic acid dehydratase, which catalyses porphobilinogen (PBG) formation (113, 114). This, in turn, results in the accumulation of of δ-aminolevulinic acid (ALA) through the negative feedback loop. ALA is a potent neurotoxin associated with neurological damage and the inhibition of Na^+, K^+-ATPase, and adenylate cyclase activities (115, 116). Increased ALA levels generate free ROS, especially H_2O_2 and superoxide radicals. These radicals cause lipid peroxidation and, by interaction with oxyhaemoglobin, they contribute to further generation of hydroxyl radicals (117). These, in turn, oxidise haemoglobin and impair oxygen transport to tissues. Hydroxyl radicals can also trigger red blood cell lysis (117).

Lead and thiol groups

Under normal circumstances, intrinsic antioxidants rise to mitigate ROS effects (118, 119). However, Pb can impair glutathione, one of the body's main antioxidants, as it binds covalently with the thiol group in glutathione, glutathione reductase (GR), glutathione peroxidase (GPX), and glutathione-S-transferase (110, 119). A similar mechanism has been reported for other antioxidant enzymes such as catalase (CAT) and superoxide dismutase (SOD) (120). Along with inactivating these enzymes through covalent binding, Pb replaces zinc ions, which are important cofactors for their activity (110, 121).

In this sense, SOD, GPX, and CAT levels inversely correlate with increased blood Pb levels (122). For example, Kshirsagar et al. (123) reported that a 458 % increase in blood Pb (p<0.001) in occupationally exposed individuals was accompanied by a 50.4 % decrease in SOD (p<0.001) and a 34.33 % decrease in CAT (p<0.001) levels compared to non-exposed individuals.

Another enzyme whose activity is impaired by Pb is glucose-6-phosphate dehydrogenase (G6PD), which also contains numerous thiol groups. It supplies cells with nicotinamide adenine dinucleotide phosphate (NADP). Its reduced form, NADPH, serves as a donor of reducing equivalents in the antioxidant system. Since red blood cells lack other NADPH-producing enzymes, their survival depends on NADPH supplied by G6PD. Animal studies report varying effects of Pb on G6PD but all point to three possible and concurrent mechanisms of action. The first involves higher demand for NADPH and, ultimately, higher G6PD activity in red blood cells in response to increased ROS (124, 125). The second involves G6PD inhibition due to a formation of a Pb and thiol group complexes in the enzyme (126, 127). This, however, is more likely to occur *in*

Table 3 Symptoms of Pb toxicity at different blood lead concentrations [adapted from Rehman et al. (103)]

Acute Toxicity	Mild toxicity (40–60 μg/dL)	Moderate toxicity (60–100 μg/dL)	Severe toxicity (>100 μg/dL)
Metallic taste	Myalgia	Arthralgia (especially nocturnal)	Lead palsy (wrist or foot drop)
Abdominal pain	Paraesthesia	Muscular exhaustibility	A bluish black lead line on gums (Barton's line)
Constipation or diarrhoea	Fatigue	Tremor	Lead colic (intermittent severe abdominal cramps)
Vomiting	Irritability	Headache	Lead encephalopathy
Hyperactivity or lethargy	Abdominal discomfort	Diffuse abdominal pain	
Ataxia		Anorexia, metallic taste, vomiting	
Behavioural changes		Constipation	
Convulsions and coma		Weight loss	
		Hypertension	

vitro than *in vivo*. The third involves glutathione depletion, which in turn increases the demand for NADPH (121, 128).

Altogether, Pb exposure may both increase or decrease G6PD activity, depending on concentration, duration of exposure, and the integrity of the cellular antioxidant system (118, 129).

Lead and ions

Another significant mechanism of Pb toxicity is substitution of divalent cations vital for biological processes like Ca^{2+}, Mg^{2+}, Fe^{2+}, Zn^{2+} and monovalent cations like Na^+ (110, 121). Pb^{2+}, for example, can replace Ca^{2+} at binding sites and activate or inhibit them, depending on its level (121, 130). This effect is the most prominent in the nervous system. After replacing Ca^{2+}, Pb can cross the BBB and accumulate in astroglial cells (110, 121). The neurotoxic effect on immature astroglial cells is particularly pronounced, as they play an important role in the development of BBB (131).

Mechanism of genotoxicity

Several studies using different Pb-containing compounds in various biological systems have provided evidence of direct or indirect interaction between Pb and genetic material. Genotoxic effects observed *in vitro* and in animal and human studies range from the production of free radicals, inhibition of DNA repair to DNA double-strand breaks, chromosome aberrations, sister chromatid exchange (SCE), and increased micronucleus (MN) frequency (132, 133).

Recent studies have linked increased Pb levels to chromosome aberrations and sister chromatid exchange (SCE). Das and De (134) reported chromatid breaks as the main aberration in 100 patients with high blood Pb levels. Other chromosome abnormalities observed include chromosome breaks and dicentrics (109, 134). Older studies have reported no Pb-related increase in SCE frequency or have attributed an increase in that parameter to tobacco use in research subjects (135, 136). However, there are several recent studies (137–139) that associate Pb-exposure with an increase in SCE frequency.

Another marker of genotoxicity is micronucleation. Micronuclei are formed as a result of chromosome breaks (originated from unrepaired or incorrectly repaired DNA lesions) or mitotic spindle dysfunction. Their formation may be induced by oxidative stress or exposure to clastogens, including Pb (140–142). Balasubramanian et al. (143) reported an increase in MN frequency and DNA damage in workers exposed to Pb compared to the control group, which was related to years of exposure and accumulated genome damage.

Oxidative stress triggered by Pb can induce the formation of 8-hydroxy-2-deoxyguanosine (8-OHdG), which is a molecular marker for DNA oxidative damage. Its concentration in urine was reported to be significantly higher in workers exposed to Pb (144). Higher 8-OHdG levels were also reported in human lymphoblastoid TK6 cells exposed to Pb (145).

Another potential mechanism of Pb genotoxicity is the signalling pathway of the nuclear factor erythroid 2-related factor 2 (Nrf2). Nrf2 and NF-*κ*B are the two key transcriptional factors that interact to regulate cellular redox status in response to oxidative stress and inflammation, respectively. Pb-induced oxidative stress can disrupt this interaction impairs cell proliferation, cell cycle progression and, eventually, leads to cell death (146). Oxidative stress induced in bovine granulosa cells by Pb concentrations ranging from 1 to 10 µg/mL downregulates both Nrf2 and NF-*κ*B and their downstream genes (147). Similar observations of oxidative stress, including downregulation of Nrf2, inflammation, and apoptosis were made in rat testis (148).

Mechanism of carcinogenicity

The IARC classifies Pb as a group 2A carcinogen (149). Pb-induced carcinogenicity is owed to increased oxidative stress, membrane alterations, impaired cell signalling, and impaired neurotransmission (150). It likely starts with ROS damaging the DNA, disrupting DNA repair and affecting genes that regulate the growth of tumour cells (151).

By inhibiting δ-aminolevulinic acid dehydratase, Pb favours the accumulation of ALA, which triggers ROS production, but also acts as a carcinogen (116). ALA-mediated oxidative DNA damage occurs through the production of 8-OHdG, 8-hydroxyguanine (8-oxo-7,8-dihydroguanine), and 8-oxo-7,8-dihydro-2-deoxyguanosine (8-oxodG) (116, 152). A number of studies has reported positive correlation between ALA levels and markers of oxidative stress and carcinogenesis (116, 137, 141, 153). Furthermore, hydroxyl radicals (HO•) generated by ALA attack DNA strands and interact with its nucleobases to produce various oxidation products. All DNA nucleobases are susceptible to HO•. The 8-oxodG lesion (HO• interaction with guanine) is the most abundant and is promutagenic (141). Unrepaired 8-oxodG can lead to genomic instability through transversions and the formation of double-strand breaks (116, 154). Furthermore, several studies (155–157) have revealed the epigenetic function of 8-oxodG, and its role in carcinogenesis through gene regulation.

CONCLUSION

This review sheds new light on the mechanisms of toxicity and genotoxicity of As and Pb. Both PTEs have been proven to affect various metabolic processes and impair the function of some organ systems, cause genetic damage, prevent DNA repair, and consequently promote carcinogenesis and tumour growth.

Both elements are still persistent in the environment, with millions of people at risk of exposure. In this sense, previously implemented strategies for preventing, monitoring, limiting and managing exposures to As, Pb, and other PTEs, heavy metals in particular, should be strictly followed. Engineering solutions can limit most occupational exposures, and it is essential to monitor

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levels of heavy metals so that such solutions can be implemented. Good occupational hygiene is another effective method of limiting exposure.

Since both As and Pb are highly persistent in the environment, regardless of the fact that their primary sources have been removed, they still may contaminate water, soil, and food crops. To prevent and minimise secondary exposure, effective soil remediation and food monitoring are needed.

This review shows that the knowledge about both PTEs is still insufficient, and that it is necessary to regularly revise the existing concepts and accumulate data relevant for risk assessment. In this regard, it is recommended to focus on findings obtained using various sensitive genotoxicity tests and novel *omics* approaches, which could help to better understand the process of carcinogenesis triggered by high levels of exposure to As and Pb.

Conflict of interests

None to declare.

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Metabolički i genski poremećaji – pregled mehanizama toksičnosti i genotoksičnosti arsena i olova

Urbanizacija i industrijalizacija su u porastu u cijelome svijetu. S obama ovim fenomenima izravno su povezana zagađivala iz okoliša, poput potencijalno toksičnih elemenata (PTE). Dva elementa koja izazivaju najveću zabrinutost su arsen (As) i olovo (Pb) u tlu i vodi, bilo da su tamo došli prirodnim putem ili zbog ljudske djelatnosti. Oba su i potencijalno kancerogena. U ovom preglednom radu razmatraju se mehanizmi kojima As i Pb ugrožavaju metaboličke procese i izazivaju oštećenja genoma. Unatoč zabranama i naporima da se ograniči njihovo korištenje, oba su elementa perzistentna u okolišu i predstavljaju rizik za ljudsko zdravlje, zbog čega je potrebno nastaviti s njihovim toksikološkim istraživanjima.

KLJUČNE RIJEČI: arsen trioksid; ljudsko zdravlje; metali; oksidacijski stres; oštećenje DNA; reaktivne kisikove vrste; toksikologija; zakonska regulativa