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Environmental Toxins and Their Organ-Specific Effects: A Comprehensive Review of Human Exposure and Accumulation

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Abstract: Environmental pollutants lead to problems in ecosystems differently depending on the extent of their toxicity, and thus their arrival to humans leads to health problems at different levels. The danger of any substance introduced into the environment can be determined depending on its quantity (dose). In addition, based on the overdose, it can be considered (whether it is alien or original) is toxic. Poisoning is the harmful effect that occurs as a result of ingestion, inhalation, or contact with a toxic substance. Potential toxic substances include chemical, biological, and physical toxins, fungi, plants, and animal toxins. Environmental pollutants are heavy metals (lead, cadmium, mercury, etc.), pesticides, organic materials, food additives, etc. The severity of the toxic effect depends primarily on the concentration and persistence of the final toxic substance. The final toxic substance is often the original chemical to which the organism is exposed. In other cases, the final toxic substance is a metabolite of the original compound, reactive oxygen species, or nitrogen (ROS, RNS) generated during Transformation into a toxic substance. Exposure to lead can affect proteins that interfere with their enzymatic functions or ability to bind other cellular components, leading to DNA damage and induction of oxidative stress. Asbestos can also damage DNA and affect gene expression. Exposure to acrolein irritates the bronchi, while mercury causes neurological symptoms.

This review deals with understanding toxic environmental pollutants that affect humans, the extent of accumulation of toxic substances in organs, and methods of exposure to them.

Keywords: Environmental, pollutants, toxicity, effects, organs.

السموم البيئية وتأثيراتها على الأعضاء: مراجعة شاملة لتعرض الإنسان وتراكمها

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المستخلص: تؤدي الملوثات البيئية إلى مشاكل في النظم البيئية بشكل مختلف حسب مدى سميتها، وبالتالي فإن وصولها إلى الإنسان يؤدي إلى مشاكل صحية على مستويات مختلفة. يمكن تحديد خطورة أي مادة تدخل إلى البيئة حسب كميتها (جرعتها). بالإضافة إلى ذلك، بناءً على الجرعة الزائدة، يمكن اعتبارها (سواء كانت غريبة أو أصلية) سامة. التسمم هو التأثير الضار الذي يحدث نتيجة تناول مادة سامة أو استنشاقها أو ملامستها. تشمل المواد السامة المحتملة السموم الكيميائية والبيولوجية والفيزيائية والفطريات والنباتات والسموم الحيوانية. الملوثات البيئية هي معادن ثقيلة (الرصاص والكادميوم والزئبق وغيرها)، والمبيدات الحشرية، والمواد العضوية، والمضافات الغذائية، وما إلى ذلك. وتعتمد شدة التأثير السام في المقام الأول على تركيز المادة السامة النهائية وثباتها. غالبًا ما تكون المادة السامة النهائية هي المادة الكيميائية الأصلية التي يتعرض لها الكائن الحي. وفي حالات أخرى، تكون المادة السامة النهائية عبارة عن مستقلب للمركب الأصلي، أو أنواع الأكسجين التفاعلية، أو النيتروجين (ROS,RNS) المتولد أثناء التحول إلى مادة سامة. يمكن أن يؤثر التعرض للرصاص على البروتينات التي تتداخل مع وظائفها الأنزيمية أو قدرتها على ربط المكونات الخلوية الأخرى، مما يؤدي إلى تلف الحمض النووي وتحفيز الإجهاد التأكسدي. يمكن أن يؤدي الأسبستوس أيضًا إلى إتلاف الحمض النووي والتأثير على التعبير الجيني. التعرض للأكرولين يهيج القصبات الهوائية، بينما يسبب الزئبق أعراضا عصبية. تتناول هذه المراجعة فهم الملوثات البيئية السامة التي تصيب الإنسان، ومدى تراكم المواد السامة في الأعضاء، وطرق التعرض لها.

الكلمات المفتاحية: البيئة، الملوثات، السمية، التأثيرات، الأعضاء.

Introduction (Environmental toxins)

Environmental pollution is related to human life, directly or indirectly, which raises enormous controversy, for example, water pollution is increasing rapidly due to wastewater discharges from industries where heavy metals such as lead, cadmium, and others cause problems in the ecosystem depending on their toxicity and thus their arrival to humans leads to health problems because The accumulation of ions causes a major health risk. Therefore, such environmental toxins cause great concern for the environment and thus for human health (Carolin et al., 2017).

The term "xenobiotic" or "pollutant" refers to any foreign chemical substance that is either present within an organism or unexpectedly found at a concentration higher than the allowable limits in the environment. Examples of such substances include pesticides, hydrocarbons, dioxins, carcinogens, drugs, and food additives. High persistence and ubiquity are characteristics of pollutants, which allow them to coexist and interact with the environment for extended periods along with their converted products (Mathew et al., 2017). The WHO divided pesticides into four classifications according to their toxicity: extremely dangerous, highly dangerous, moderately dangerous, and slightly risky (Yadav and Devi, 2017). A vast number of organic pollutants were to be divided into four classes: particularly acting chemicals (class 4), reactive chemicals (class 3), less inert chemicals (class 2), and inert chemicals (class 1) (Verhaar et al., 1992).

Botanical xenobiotics, such as phytotoxins, zootoxins, and bacteriocins, are substances generated by living things primarily for defensive purposes. Naturally occurring amines like serotonin may also be among them. Artificial compounds known as synthetic xenobiotics are harmful to living things or turn poisonous over time because of their modification or build-up (Gadzała-Kopciuch et al., 2004). One example of a xenobiotic process is bioaccumulation, whereby the molecule begins to accumulate in the organism at higher concentrations because of inadequate metabolism. When a drug is exposed in tiny amounts, this process either accumulates continuously or happens when a material is exposed in large quantities over a shorter period (Satyanarayana et al., 2012).

Heavy metals exert significant toxicological effects across multiple organ systems, including neurotoxicity, nephrotoxicity, carcinogenicity, hepatotoxicity, immunological toxicity, cardiovascular toxicity, skin toxicity, reproductive and developmental toxicity, and genotoxicity. Studies indicate that manganese disrupts mitochondrial function and triggers apoptosis in neural cells, contributing to neurodegenerative diseases like Alzheimer's and Parkinson's.

Arsenic has been extensively studied for its neurotoxic effects, altering synaptic transmission and neurotransmitter balance through MAPK signaling pathways and calcium-mediated mechanisms, which are implicated in neurodevelopmental changes and neurodegenerative disorders. Cadmium's nephrotoxic properties, characterized by oxidative stress and cellular damage in renal tissues, are well-documented, leading to renal failure and an increased susceptibility to cancer.

Research on lead and mercury highlights their cardiovascular toxicity, contributing to hypertension, atherosclerosis, and cardiac dysfunction through oxidative stress pathways and endothelial dysfunction. Chromium's severe dermatological reactions, including contact dermatitis and systemic contact dermatitis, are well-documented in the literature, underscoring its impact on skin health.

Furthermore, reproductive and developmental toxicity studies underscore arsenic's adverse effects on fertility and fetal development, while genotoxic effects of these metals involve DNA damage, chromosomal abnormalities, and disruption of genetic integrity. These findings collectively emphasize the broad-ranging and detrimental impacts of heavy metals on human health, necessitating stringent regulatory measures and ongoing research efforts to mitigate their adverse effects.

Mechanism of toxicity

The damage caused by reactive oxygen species (ROS) is mainly due to multi-generational toxicity, as it also causes damage to genetic mechanisms (Li *et al.*, 2022).

The clinical symptoms of lead poisoning may be partially attributed to various cellular mechanisms that are impacted by lead exposure. Certain cell types and exposure levels may influence each mechanism's contribution differently. Lead can interfere with a protein's capacity to bind other cellular components or to perform its enzymatic functions. Additional pathways entail oxidative stress induction and nucleic acid damage (Szymanski, 2014).

Asbestos can cause DNA damage, alter gene transcription, and change protein expression. These effects are crucial in controlling the growth and division of all the main target cells in the lungs, including mesothelial cells and bronchial and alveolar

epithelial cells. The cumulative dose and duration after the initial asbestos exposure determine the toxic consequences of asbestos, which have revealed some of the pathogenic pathways behind asbestos-related lung illnesses (Kamp, 2009).

Acrolein has tremendous biological activity, although its chemical structure is not complex (Moghe, *et al.*, 2015). Acrolein is extremely cytotoxic to a wide variety of cell types in both human and animal lines of study (Rashad *et al.*, 2022). Local tissues, whose cells are immediately exposed to acrolein, are the target organs of acrolein poisoning. (Abraham *et al.*, 2011). Inhalation of acrolein causes irritation and inflammation of the airways, followed by hyperplasia and metaplasia of the respiratory epithelium (Faroon *et al.*, 2008). The respiratory system's cells, such as human umbilical vein endothelial cells, lung epithelial cells, bronchial epithelial cells, and nasal epithelial cells, are more exposed to the harmful (Liu *et al.*, 2022).

Human exposure to heavy metals has been linked to serious health issues that worsen with time. These issues can impact the liver, heart, brain, and kidneys, among other major organs. They can also increase the production of reactive oxygen species (ROS), cholestasis, excessive liver fat, liver necrosis, and vascular lesions (Hamdy *et al.*, 2018). This is primarily caused by oxidative stress reactions, antioxidant depletion, and nitric oxide synthase enzyme activity, all of which cause hepatocyte destruction. A matter of considerable interest that has been demonstrated to exist is the "shift in diet/lifestyle," which results in diseases that interfere with metabolic processes, such as hepatotoxicity **(Figure 1)** (Harischandra et al., 2019).

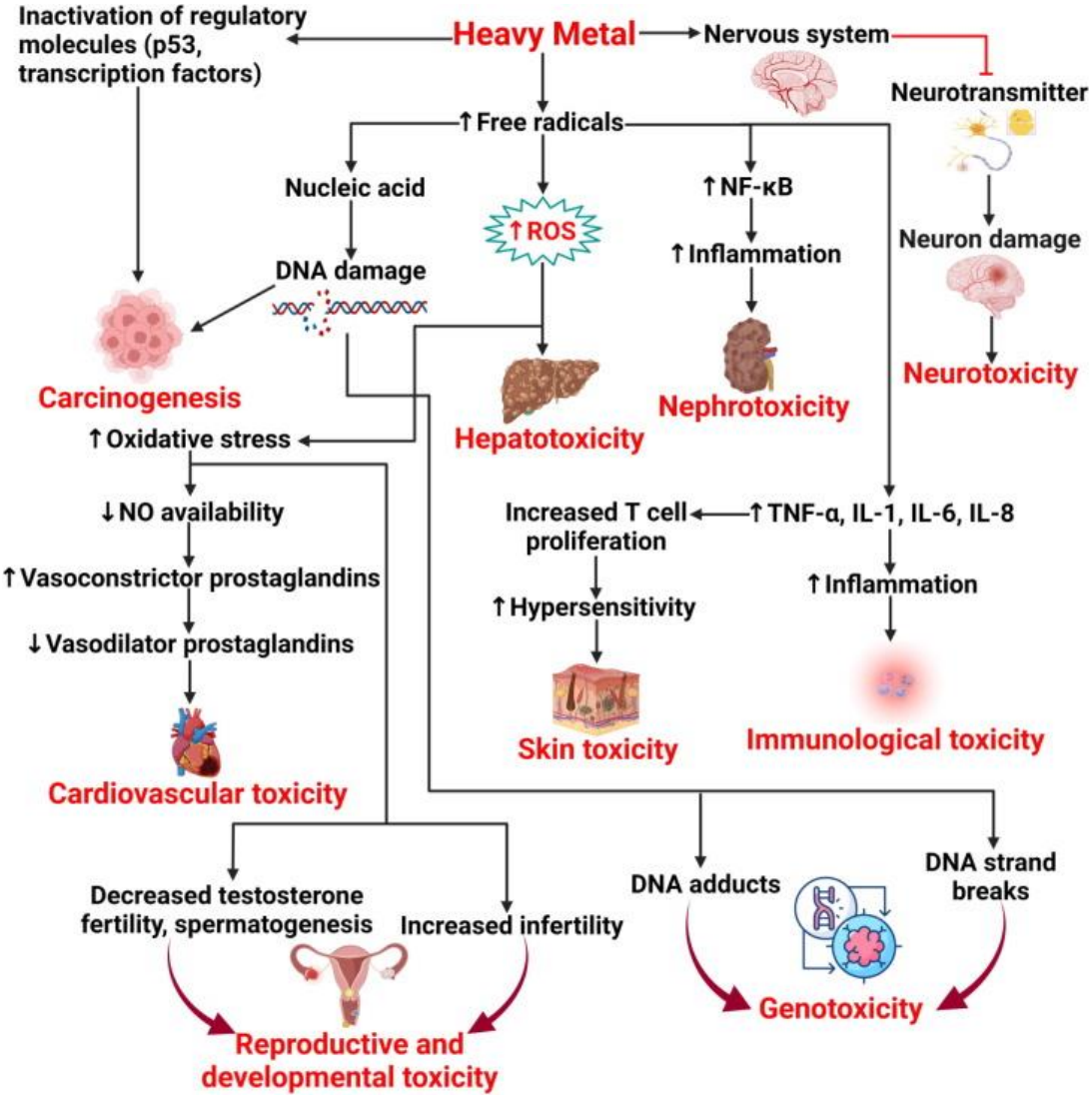

Figure .1. The effect of excessive exposure to heavy metals on the body's organs

Source: Harischandra et al., 2019

Both man-made and natural contaminants contain mercury. Processed mercury can be released into the atmosphere, where it can accumulate over time and find its way into the soil, water, and atmosphere cycles. Toxic levels of mercury result from the hazardous effects of exposure to mercury or its derivatives vary based on the chemical type and mode of exposure. Fish and seafood that have been polluted are the main sources of methylmercury (MeHg) exposure for humans, but wildlife that has been exposed to

mercury by ingestion of contaminated lower organisms was also exposed. MeHg poisoning has been linked to neurological development impairment in newborns and children as well as damage to the nervous system in adults. Mercury enters the food chain by one or more precise mechanisms that are still mostly unknown and likely differ throughout ecosystems (Rice *et al.*, 2014).

High quantities of mercury in human blood, urine, and hair caused by elemental mercury exposure in artisanal gold mining areas cause neurological symptoms (Steckling *et al.*, 2014). Inhaled and absorbed into the bloodstream, the vaporized elemental mercury readily passes through the blood-brain barrier. Over time, intracellular oxidation of gaseous Hg^0 results in the accumulation of ionic Hg^{2+}, which damages the kidneys and remains in the brain (Ha *et al.*, 2017). Interestingly, compared to inorganic mercury, organic mercury is more strongly linked to many of these neurological symptoms linked to Hg0 exposure (Bose-O'Reilly *et al.*, 2017).

Types of toxins **(Biological toxicant, Physical toxic and Food contaminants)**

Because a single virus, bacterial cell, or maybe a parasite or worm, can proliferate to generate an extremely severe illness, measuring biological toxicity can occasionally be challenging. The compromised immune system's strength and capacity to combat the infection determine biological toxicity (Aljamali *et al.*, 2021). Furthermore, bacterial toxins are neurotoxins. Botulinum neurotoxin is produced by *Clostridium botulinum* and is absorbed by the body when contaminated food is consumed. It diffuses through the intestinal mucosa and enters the bloodstream through the intestinal villi. It affects the motor neuron terminals after passing via the blood. The toxin inhibits the release of several neurotransmitters, including aspartate, dopamine, and acetylcholine, etc. The *Clostridium botulinum* bacterium is born in conditions in which oxygen is low, spores that resist heat and then grow and spread widely and then secrete toxins known as (*botulinum toxin*), which are considered a deadly type of poison as it impairs nervous functions and may result in muscular or respiratory paralysis In some cases, it may cause death, but it is considered a relatively rare and non-contagious disease. There are 7 patterns of *botulinum toxin* symbolized by the English letters (A to G), and four of these patterns infect humans and cause human botulism poisoning. They are (A, B, E). In some rare cases, type F). In contrast, the other three types infect birds, mammals, and fish and cause them some diseases (Aljamali, 2015).

The bacterium *Clostridium tetani* produces tetanus toxin, which enters the body through wounds and eventually travels to the adrenergic, sensory, and motor neurons (Popoff and Poulain, 2010). Likewise, *Aspergillus flavus* and *Aspergillus parasiticus* produce aflatoxin, a fungus toxin that can induce DNA mutations by forming DNA adducts. This leads to illnesses such as cancer (Berthiller *et al.*, 2013).

Food poisoning can occur from consuming food infected with bacteria or the toxins these organisms create. It can also happen from consuming food contaminated with many kinds of viruses, bacteria, parasites, and toxic compounds, such as poisoning from eating mushrooms. More than 80% of cases of food poisoning are due to bacterial food poisoning. Either bacteria excreting their toxins or bacteria growing inside the intestine and breaking down the intestinal wall are the usual causes of food poisoning (Rasool *et al.*, 2020; Aljamali, 2015).

Most cases (60-90%) of food poisoning are due to bacteria. Enterotoxins, which can be further classified as endotoxins (which stay inside the cells of microorganisms and are released when cells are destroyed) or exotoxins (toxins secreted from microorganisms into the surrounding environment), are responsible for the harmful activity of these bacteria in the digestive system. When Gram-positive bacteria develop, they mostly release exotoxins (Haverstick *et al.*, 2017).

Furthermore, Foodborne Pollutants when plants and microbes transform inorganic forms of selenium into organic forms, selenium, a food contaminant, and moves up the food chain. Symptoms of selenium poisoning, also known as selenosis, include exhaustion, hair loss, diarrhea, deformities, and more (Dolan *et al.*, 2010).

The emission of pollutants, their dispersion, and the possibility of their deposition or chemical transformation can affect temperature, wind, and humidity, as climate is considered one of the important factors that affect air quality. Thus, a change in climate leads to an increase in air problems in several areas, especially those with a high population density, and this is what affects It directly affects human health after there has been a change in environmental systems in general (Kinney, 2008; Fiore et al., 2015).

The climate is changing directly and indirectly, and this is caused by changes in temperature due to air pollution, which causes a high rate of death and cancer in humans (Lou et al., 2019). In the United States, the health effects caused by PM2.5 are greater than the effects caused by the ozone layer (Tagaris et al., 2009). The climate is also affected when excessive amounts of nitrogen compounds are released into the atmosphere, due to biological emissions from terrestrial ecosystems (Peel et al., 2013).

Materially harmful substances are materials, such as coal dust, asbestos fibers, and silicon dioxide granules that physically interfere with biological processes. If inhaled, these materials can all eventually result in death. Because it damages tissues, it is physically toxic, yet it is not poisonous directly unless it interferes with the organism's biological activities. Because an excess of water in the body causes a sharp drop in the concentration of essential ions, excessive water consumption can be toxic to the body. Not a hazardous chemical gas (Rasool *et al.*, 2020).

Plastics are used particularly extensively in the recent, with some scientists seeing them as key indicators of specific historical epoch (Campanale et al., 2020). Human exposure to microplastics exposes them to many health problems because they are considered environmental pollutants, and this is something that only a few people know. Knowledge about the toxicity of plastic particles is still limited, but when exposed to them, they may cause oxidative stress, chronic inflammation, and increased risk of tumors, as they are exposed to them in various ways, including inhalation, ingestion, and skin contact (Prata et al., 2020).

Microplastics may affect various body systems. When swallowed, the digestive system is affected, leading to infections and gastrointestinal symptoms. They may also cause chemical toxicity, which includes the accumulation of environmental toxins such as aromatic hydrocarbons and heavy metals (Bouwmeester et al., 2015; Abbasi et al., 2021). Microplastics may cause abdominal pain due to an imbalance between harmful and beneficial bacteria (Jin et al., 2019).

The irregular use of nanotechnologys leads to negative effects on human health and the environment in general (Taghavi et al., 2013). Cosmetic products, dyes, coatings, catalytic additives and paints all contain major products for nanoparticles (Hansen et al., 2016)

There are several major mechanisms for cytotoxicity of nanoparticles (NPs) such as physicochemical properties, contamination with toxic element, fibrous structure, high surface charge and radical species generation. The reason behind the toxicity of these substances is the increased surface area to volume ratio and thus their higher chemical reactivity increases reactive oxygen species (ROS) (Fard et al., 2015).

Route of exposure

The four ways that one can be exposed to the environment are by inhalation, oral ingestion due to contamination, hand-to-mouth contact (drinking food, drinkware, and water), and cutaneous touch (Poojari *et al.*, 2019).

All of the chemicals that are exposed to in the environment are combined here. This is because of two things. In the atmosphere, antimony trioxide is thought to be the most common type (and other oxides to a lesser extent) (Sundar and Chakravarty, 2010). On the other hand, antimony is mostly in the +V oxidation state when it dissolves in aqueous solutions (Verdugo *et al.*, 2017).

Second, both in vivo and in the environment are capable of interconversion (Saerens *et al.*, 2019). In addition, exposure to naturally occurring poisonous compounds can happen when food, drink, polychlorinated biphenyls (PCPs), or direct physical contact (dermal or oral) with toxic plants and their active components. Food consumption is a well-known source of natural hazardous chemicals, and while PCP ingestion and sewer emissions may pose an environmental danger in certain situations, they are unlikely to represent the main channel of exposure (Onesios *et al.*, 2009).

Two hazardous metals that are commonly found in the environment are lead (Pb) and cadmium (Cd). Due to their propensity to consume Pb through pica behavior and to absorb comparatively more Pb from inhalation and food than adults, children in contaminated environments are more susceptible to metal exposure (Manton *et al.*, 2000). Nephrotoxicity, osteoporosis, and cardiovascular disease are among the most severe forms of chronic toxicity associated with lead (Cd) (Järup and Åkesson, 2009).

The public may be exposed to pyrethroid insecticides (PYRs) through food and water contamination or by eating traces of PYRs in food (Kiljanek *et al.*, 2013). Their combined dangers should therefore be taken into account (xue *et al.*, 2014). (PYRs) are applied indoors for the goal of controlling pests. This causes them to remain persistent in the air for a long time, and PYR residues have been found in food, textiles, residential houses, and even people (Trunnelle *et al.*, 2014). Globally, PYRs are the most frequent source of environmental pollution (Stehle and Schulz, 2015), and in experimental animal genotoxicity, they have been demonstrated to cause cytotoxicity, carcinogenicity, and oxidative stress (Assayed *et al.*, 2010).

As a contact allergen, benzothiazolinone (BIT) most frequently causes sensitization and irritation as adverse effects. Additionally, mice who inhale BIT stimulate the production of MUC5AC, a protein linked to mucus hypersecretion in airway inflammatory disorders. It is a mild contact sensitizer in guinea pigs and a severe eye irritant in rabbits (Kwak *et al.*, 2019). Although the physical and chemical characteristics of nickel (Ni) play a role in the widespread use of Ni compounds, numerous studies have

demonstrated the primary correlation between nickel and allergic contact dermatitis following skin contact, as well as respiratory effects like toxicity and/or carcinogenicity following inhalation exposure (Genchi *et al.*, 2020).

The target organs (Diseases and symptoms)

Public health is still globally threatened by air pollution (Kelly and Fussell, 2015). Over all other known environmental diseases combined, ambient air pollution is a major cause of death (Manisalidis *et al.*, 2020). Cardiovascular illnesses are responsible for about 3 million of the 7 million premature deaths linked to air pollution (Maji *et al.*, 2018).

Particulate matter (PM) is classified into various size categories that influence how it enters the respiratory and cardiovascular systems and how deeply it penetrates. While larger particles, such PM_{10}, primarily affect the upper respiratory tract, $PM_{2.5}$ can enter the circulatory system and penetrate both the upper and lower respiratory systems, directly affecting health and raising the risk of disease (Xie *et al.*, 2013). $PM_{2.5}$ damages blood vessels and initiates systemic inflammation by stimulating macrophages and epithelial cells to generate pro-inflammatory cytokines inside the respiratory airways and lung alveoli (Thangavel *et al.*, 2022).

One preventable risk factor for human early mortality is smoking (Samet, 2013). Of the average 5,600 constituents in cigarette smoke, 158 exhibit toxicological characteristics. Cigarette smoke is a complex and dynamic aerosol (Thorne and Adamson, 2013). There is a strong correlation between smoking and a number of vascular, pulmonary, and cancer disorders. After the age of 70, it is estimated that 50% of smokers have some kind of chronic obstructive pulmonary disease (COPD). Patients with COPD also often have pulmonary emphysema and chronic bronchitis, which are conditions that induce gradual alveolar structural loss and ongoing airway inflammation (Pope *et al.*, 2011). Reactive oxygen species (ROS) both inside and outside the mitochondrial respiratory chain are produced at higher rates in smokers' smoke (Aravamudan *et al.*, 2014).

CO gas is a colorless, odorless, tasteless and nonirritant (Raaijmakers *et al.*, 2020). CO poisoning causes tissue hypoxia and induces organ damage, such as the heart, lungs, brain, muscles, and kidneys. The reason for organ damage is not only hypoxia but also inflammation, oxidative stress, apoptosis, and neuron necrosis cause organ damages, too (Kim *et al.*, 2019). The symptoms of acute and chronic CO poisoning are a wide variety such as dizziness, vomiting, headache, syncope, myalgia, weakness, confusion, changes in consciousness, and death (Saritas *et al.*, 2016). Long-term and/or recurrent exposure to low-concentration CO gas is defined as chronic CO poisoning (Gunes *et al.*, 2020).

Asbestos fibers are inhaled and subsequently deposit in the lung parenchyma, causing a variety of disorders that are linked to the development of fibrotic and inflammatory processes in the respiratory system (Musk *et al.*, 2020). Chronic pulmonary fibrosis and asbestosis can result from asbestos exposure (Arakawa *et al.*, 2016). According to epidemiological research, asbestos exposure can also result in interstitial pneumonia (Attanoos *et al.*, 2016). Furthermore, research indicates that cumulative asbestos exposure is the primary cause of asbestos-related mortality; even in the event that direct asbestos dust exposure ends, there is still a significant risk of death (Henderson *et al.*, 2004). Several investigations have demonstrated that asbestos inhalation can cause malignant transformation in the gastrointestinal tract, larynx, kidneys, liver, pancreas, ovaries, prostate, and hematological system in addition to the bronchopulmonary system (Ainagulova *et al.*, 2022).

As a byproduct of several industrial operations, including waste incineration, smelting, chlorine bleaching of paper pulp, and the production of some herbicides and pesticides, dioxins (TCDD) are environmental pollutants that fall under the category of persistent organic pollutants (Matés *et al.*, 2010). Dioxins build up in the food chain and can be inhaled by humans through contaminated air or food (Maqbool *et al.*, 2016). The most toxic dioxin is 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD) (Patrizi and Siciliani, 2018). After entering the body, TCDD often accumulates in adipose tissue, where its half-lives range from seven to eleven years (Srogi, 2008). Owing to the increased lipophilicity. Biologically harmful consequences such as cytotoxicity, immunotoxicity, developmental toxicity, reproductive problems, endocrine disruption, fatty liver, cardiovascular illnesses, genotoxicity, teratogenesis, tumor promotion, and cancer have been linked to TCDD (Dömötörová *et al.*, 2012).

Almost all food types are processed and produced using food additives to achieve desired results. To put it simply, it is something that is added to food to improve its flavor, appearance, or other desired qualities. Teratogens are substances that might cause physical or functional abnormalities in a human embryo or fetus when they are exposed to a pregnant mother. Cocaine and alcohol are two of its examples. The quantity of teratogenic material present, the length of the exposure, and the embryo's developmental stage all have an impact on the embryo (Vaclavik *et al.*, 2008). Anencephaly, anophthalmia, aberrant cardiac looping, tail degeneration, node degeneration, and brain flexure (only cephalic flexure and micro phthalmia, no branchial flexure) were all

present in all experimental groups in proportion to the total number of chick embryos. Merely 50% of the body's development is slowed down by mites and limb buds (Weerasooriyagedara, 2018). When rats were fed polyethylene glycol (a dietary ingredient), TNFα and IL-6 rose (Yousef *et al.*, 2022). Because aspartame damages cells during pregnancy, giving it to rats slows down the growth of the fetus (Shalaby *et al.*, 2019).

Lead is a hazardous heavy metal with many affinities that can build up in the environment over time, causing pollution and perhaps contaminating food. Additionally, lead from the environment can enter the body through the skin, mucous membranes, digestive tract, and respiratory system (Teerasarntipan *et al.*, 2020). Adults are allowed a daily lead consumption of 1.3 μg/kg BW and children 0.6 μg/kg BW, respectively, according to the Joint FAO/WHO Expert Committee on Food Additives (JECFA). When lead buildup occurs in the body, it can harm the reproductive, neurological, and circulatory systems as well as the related tissues and organs like the brain, kidney, liver, and cardiovascular organs (Evans *et al.*, 2018). The neurological system is the organ most susceptible to the toxicity of lead, and children are more susceptible than adults are. Lead mostly affects children's central nervous systems and adults' peripheral nervous systems, particularly developing children's central nervous systems (Elrasoul *et al.*, 2020). Lead can directly harm neurons, but it can also cause the body to produce oxygen-free radicals (Jomova and Valko, 2011).

Depending on the chemical type of mercury a person is exposed to, the intoxication symptoms they experience can change. Three types of mercury-related chemical species exist: elemental mercury (Hg^0), organic mercury species like methylmercury (MeHg), and inorganic compounds that contain ionic mercury (Hg^{2+}). The kidneys, lungs, immunological systems, reproductive organs, and central nervous systems can all suffer significant harm and irreversible negative effects from exposure to various chemical forms of mercury (Faial *et al.*, 2015).

Toxic fumes released during the vaporization of mercury or burning of objects containing mercury can easily contaminate the respiratory system. Mercury breathed into the body has an average biological half-life of sixty days (Scott and Sloman, 2004). When mercury vapor is oxidized, it can become lipid soluble, which means that it can potentially accumulate in the liver, brain, and renal cortex. According to estimates, mercury in the brain can have a half-life of up to 20 years (Friberg and Mottet, 1989).

Human exposure to divalent mercury species (Hg^{2+}) is extremely dangerous and is typically found in chemical waste from pharmaceutical, cosmetic, and laboratory products. The neurological, reproductive, and renal systems are all harmed by this species (Zahir *et al.*, 2005). In addition to altering the skin, Hg2+ ions can cause immunological and digestive disorders in cases of acute poisoning (Syversen and Kaur, 2012).

Fat streaks or foamy cells in the artery wall can also result from acute Hg^{2+} poisoning and atherosclerosis (Steinberg, 2009). Along with lip tremors, excessive salivation, tooth loss, anorexia, and weight loss, the most common signs of subacute or chronic Hg^{2+} ion poisoning include gastrointestinal symptoms, neurologic abnormalities, and renal impairment (Rafati-Rahimzadeh *et al.*, 2014). According to reports, rats exposed to low concentrations of Hg^{2+} ions saw a decrease in the number of neurons and astrocytes in the motor cortex as well as cell death through cytotoxicity and apoptosis induction (Teixeira *et al.*, 2018). Apart from the chemical type of mercury and its intoxication, the concentration, quantity, and frequency of exposure are associated factors that determine the accumulation of mercury in the body (WHO, 2010).

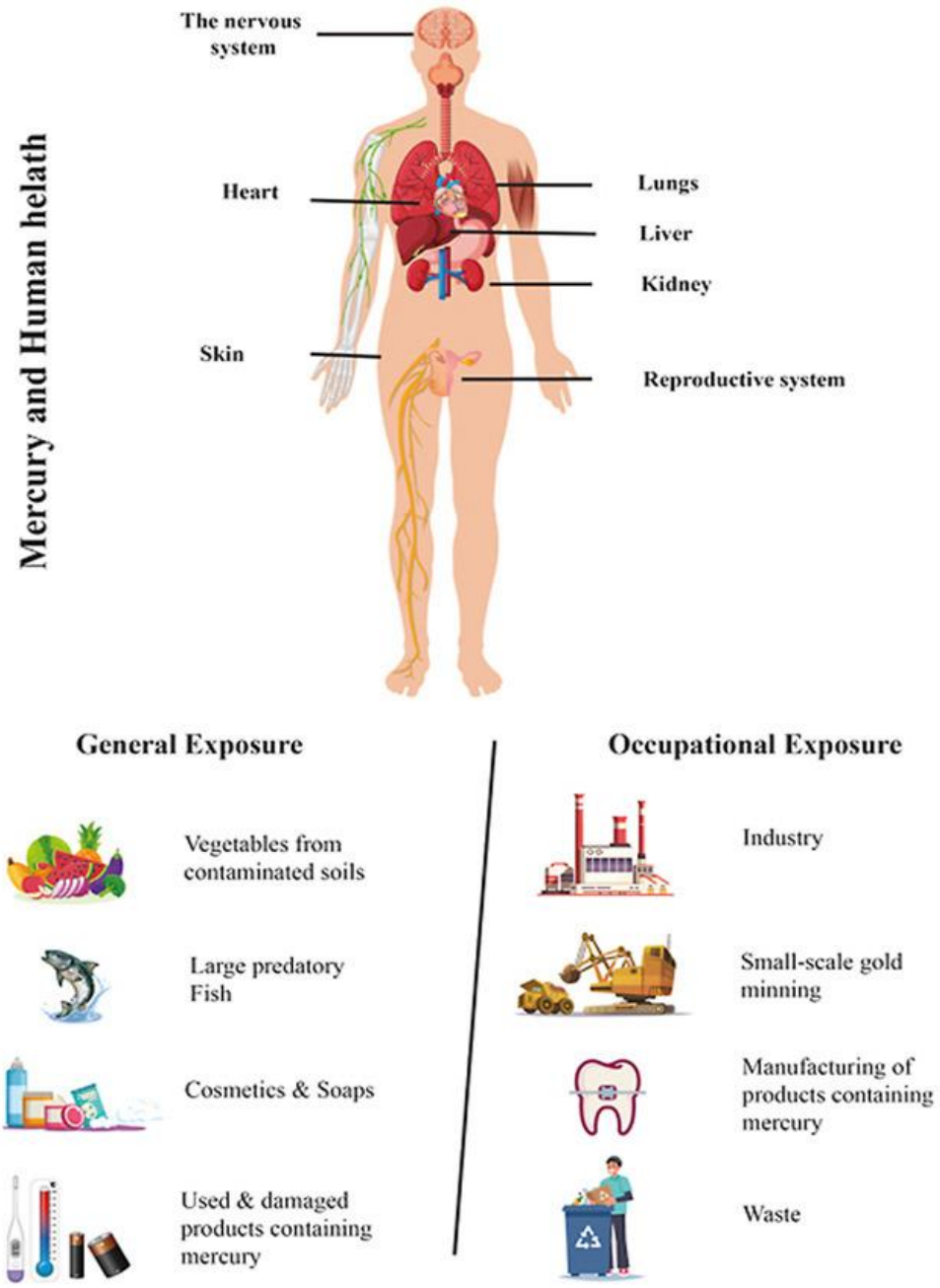

Figure .2. Human exposure to mercury from the environment

Source: Pavithra, et.al. (2023).

Increased mucosal permeability, bacterial translocation, and mucosal inflammation can result from bacterial overgrowth and altered gut microbiota caused by alcohol. Increased exposure of liver tissues to lipopolysaccharides (LPS), also known as endotoxins, results from this disruption of mucosal integrity. LPS subsequently triggers the activation of hepatic stellate cells and Kupffer cells via stimulating innate immune receptors, such as Toll-like receptors (TLRs). Inflammatory cascades that cause liver damage and fibrosis are initiated by this process (Vassallo *et al.*, 2015). Given the significance of gut dysbiosis in alcoholic liver disease (ALD), probiotics seem like appealing choices for the management or avoidance of alcohol-induced liver damage. The pathological spectrum of ALD includes cirrhosis, increasing fibrosis, steatohepatitis, and simple steatosis (Thursz *et al.*, 2018). In people with ALD, acute alcoholic hepatitis can be a chronic or acute disease. Severe cases of this illness may result in high death rates of up to 65% (Drinane and Shah, 2013).

Many human endocrine glands can be affected by environmental pollution, as synthetic chemicals have a negative effect by inhibiting and metabolizing hormones, imitating, preventing and transporting hormones (Di Ciaula and Portincasa, 2021). Chemicals include fungicides, nonylphenols, plant estrogens, and insecticides. These substances can enter the body in several ways, including absorption through the skin, ingestion, or inhalation (Yilmaz et al., 2020).

Exposure to endocrine-disrupting chemicals may cause long-term health effects. Studies in the United States have shown that children may be exposed to these substances through consumer goods, drinking water, food, and personal care products (Braun, 2017).

The danger of these substances lies in their biological accumulation in adipose tissue because they are lipophilic and therefore their half-life will be very long in the body. Because their effect develops in a latent manner, it is difficult to evaluate their effect. They may appear at later ages and sometimes they do not appear in some people (Yilmaz et al., 2020).

Deepening the analysis (Cumulative and synergistic, Genetic and Epigenetic Changes and Vulnerable Populations)

Many studies have shown that there is a relationship between the development of cancer and environmental pollutants. Although there is awareness about environmental pollutants and the major health problems they cause, there is little knowledge about the interaction of mixtures of pollutants. Although the levels of pollutants are low, due to synergistic interactions, it is possible to the effects of these pollutants develop to cause major health problems (Lagunas-Rangel et al., 2022). A toxic reaction is a process (reaction) that occurs after an organism is exposed to more than one chemical substance, and it is possible that the effect of this reaction is greater than the effect of the toxic substances if they were alone, as many studies indicate such a process. (National Research Council and National Research Council, 1980; Krishnan and Brodeur, 1991).

Organic pollutants, which are considered by-products of the pharmaceutical and chemical industries in general, may reach the aquatic environment or soil from several sources and through several means. Since the nature of these pollutants is thermodynamically unstable and under dynamic soil conditions, they are eventually converted into compounds with low toxicity. If these pollutants were in small proportions, but if the quantity of these pollutants increased, the level of toxicity would also rise, in addition to the stability of these compounds in soil and water, they may pose a great danger (Ramakrishnan et al., 2011).

When the level of toxicity in soil and water increases, it will certainly reach living organisms, especially humans, through the food chain. When these pollutants reach humans with their toxicity, they will change and affect gene expression through various genetic mechanisms, such as histone modifcations, deoxyribonucleic acid (DNA) methylation and microRNA (miRNA) expression (Sharavanan et al., 2020).

Consequently, Polluting chemicals have been divided according to their ability to change the DNA sequence, as this classification and information is important for determining environmental risks to reduce exposure, and some studies indicate that the effect of these materials may extend beyond DNA (Jirtle and Skinner, 2007). These toxic pollutants may reach stem cells and may be transmitted to other lineages, and their harm continues for long periods and accumulates. It is proven that the accumulation of these substances leads to many human diseases, including cancer (Humphrey et al., 2019).

Environmental factors can affect the growth processes of the fetus and infant, as exposure to environmental pollutants can permanently change the structure of the body, giving an opportunity for the development of serious chronic diseases in the future, including respiratory diseases, heart diseases, neurological diseases, and others (Heindel et al., 2015). Some evidence has clarified between the environmental cause and the resulting disease (or resulting effect). For example, some studies have shown the relationship between exposure to organophosphate pesticides and neurological development, air pollution, and respiratory health, mercury and mental retardation (Wigle et al., 2008; Stillerman et al., 2008).

The environment of the infant may be an environment that encourages the reception of pollutants. For example, when radon is present in a certain room, it will not be distributed evenly, as the air near the ground contains a higher concentration than the air above. This makes the environment of the infant near the ground (microenvironments) different from the environment of the adult person. The entry of the polluted substance into the child's body can be summarized in the following steps: (1) Absorption (2) Distribution (3) Metabolism (4) Toxic effect. Since the biological environment is constantly changing over time, each of these steps depends on the child's stage of development (Bearer, 1995).

There may be some factors that prompt us to focus on the child's condition in relation to air pollution, including: the lungs are underdeveloped and less able to repair themselves, nasal breathing in adults reduces some concentrations of pollution, while in children they breathe through the mouth, and children spend most of their time outdoors. Outside, the concentration of air pollution is higher, and children have immature immune systems, which plays an important role in developing asthma (Bateson and Schwartz, 2007).

When talking about life before birth, exposure to pollutants certainly reaches the fetus. Pollution of ecosystems, plants treated with chemicals, polluted water and poor air quality, all of these reasons allow pollutants to reach pregnant women, as it has been proven that poor fertility resulting from environmental pollution includes all types of mammals, and not only that, the biggest problem is that the number of cells The germs present in the ovaries are constant during fetal life and these cells are not renewable, which means that all these pollutants that affect females affect the hormonal balance and thus will inevitably affect reproductive performance (Canipari et al., 2020). Males can also have their reproductive ability affected by environmental pollutants (Skakkebaek, 2003).

In fact, previous research on the relationship of environmental pollutants and their effect on fetuses has shown that the duration and concentration of exposure is sufficient to cause weakness in the fetus's neuroendocrine system, so it is recommended to reduce exposure to pollutants, whether by dose or by period (Bellingham et al., 2016).

Treatment of pollutants

When diseases and negative effects resulting from environmental pollutants increased, the world paid increased attention to environmental problems and developed, at the very least, solutions to them. In the year 1970, the Clean Air Act was approved, which is summed up in two goals: One of them is that the Environmental Protection Agency must determine the maximum permissible concentrations in the air, the second thing is to set specific standards for exhaust emissions for new cars (Freeman, 2002).

After pollutants whether organic or inorganic, caused many toxic effects on cells, these pollutants were treated in many ways including chemical and physical ones to reduce the organic load and then biological treatment, but at the same time these methods take a long time (Chowdhary et al., 2018).

Among the reasons that have helped to exacerbate global warming and disrupt the food chain are liquid waste and sewage. To treat these environmental problems and their effects, biological, chemical methods (which may be coagulation, neutralization or disinfection), or physical methods (aeration or filtration), mechanical (flotation or screening), as it has been proven that following these methods is effective in treating these environmental problems (Afolalu et al., 2022).

Some of the modern technologies that can provide a solution to environmental problems and pollution are nanotechnology, as its role lies in: preventing or reducing pollution, sensing pollutants and treating them. Mehndiratta et al explained the mechanism by which nanotechnology works to solve environmental problems is that nanoparticles have a high surface energy that enables them to catalyze reactions at a much faster rate, and they also have a large surface area that enables them to absorb an amount of pollutants, and therefore these two features can reduce energy consumption during Transform or help prevent the release of pollutants. In its role in treatment, due to the nano-size of the particles, it enables them to reach areas that are difficult to reach, and thus they can sense pollutants and treat them (Mehndiratta et al., 2013).

Some studies have also shown that recycling and purifying wastewater, following a greening policy and using environmentally friendly chemicals according to the strategies set by the European Union will be a fruitful solution to solve environmental problems (Saxena et al., 2017).

Conclusion:

It has been proven that toxic environmental pollutants pose a danger to humans, which leads to health problems in various organs. The severity of the effect of the contaminated substance depends on several factors, including concentration, frequency, method of exposure, and the extent of the body's ability (or organ in particular) to eliminate (process) the contaminated substance. As for the side effects caused by toxic pollutants, many of them include DNA damage, affecting gene expression, stimulating oxidative stress, and may cause irritation of the bronchi.

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