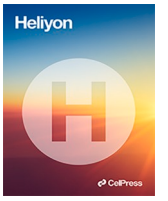
Heliyon 9 (2023) e19496

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Environmental pollutants and their effects on human health

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ARTICLE INFO

Keywords:
Particulate matter(PM)
Pollution
Health
Disease
Mortality
Morbidity

ABSTRACT

Numerous environmental contaminants significantly contribute to human disease, affecting climate change and public and individual health, resulting in increased mortality and morbidity. Because of the scarcity of information regarding pollution exposure from less developed nations with inadequate waste management, higher levels of poverty, and limited adoption of new technology, the relationship between pollutants and health effects needs to be investigated more. A similar situation is present in many developed countries, where solutions are only discovered after the harm has already been done and the necessity for safeguards has subsided. The connection between environmental toxins and health needs to be better understood due to difficulties in quantifying exposure levels and a lack of systematic monitoring. Different pollutants are to blame for both chronic and acute disorders.

Additionally, research becomes challenging when disease problems are seen after prolonged exposure. This review aims to discuss the present understanding of the association between environmental toxins and human health in bridging this knowledge gap. The genesis of cancer and the impact of various environmental pollutants on the human body's cardiovascular, respiratory, reproductive, prenatal, and neural health are discussed in this overview.

1. Introduction

Chemicals that are harmful to human health and have gotten into the environment due to human activity are called environmental pollutants. Additionally, environmental pollution is caused by natural events like volcanic eruptions. Human activities introduce pollutants by polluting the water, air, and soil. Inhalation, oral absorption, and ingestion are the three main ways that contaminants reach the human body. To indicate the amount of a specific pollutant that is consumed, the word "dose" is frequently employed. The dose is dependent on exposure duration and intensity. Depending on the exposure level, different health effects may result. Although Industrialization develops a country, it introduces a large number of pollutants into the environment, which harms the health of those exposed [1]. Exposure to environmental pollution is a significant source of health risks all over the world.

In general, hazardous substances from both natural and man-made sources pollute the air. The main sources of contaminants

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https://doi.org/10.1016/j.heliyon.2023.e19496
Received 29 March 2023; Received in revised form 23 August 2023; Accepted 24 August 2023
Available online 25 August 2023

include automobile emissions, power plants, burning garbage, chemical companies, and volcanic eruptions contaminants like sulfur dioxide (SO2), carbon monoxide (CO), nitrogen oxides (NOx), heavy metals, biological contaminants, ozone, tobacco smoke, etc. are all released into the air that is inhaled When these pollutants are ingested, they interfere with the body's internal functioning, causing diseases like cancer, cardiovascular, reproductive, prenatal central nervous system, and respiratory health issue. Tobacco smoke, which consists of harmful chemicals like benzene, cadmium, arsenic, formaldehyde, and nicotine is responsible for health illnesses. It will cause cancer, not only to the smoker but also affect passive smoker (who is exposed to tobacco smoke and is not a smoker). A person may develop asthma, bronchitis, throat infection, and a burning sensation in the eyes. Exposure to biological pollutants like bacteria, viruses, house dust, mites, cockroaches, and pollen can cause asthma, hay fever, and other allergic diseases, and volatile organic compounds cause eye, nose, and throat irritation, headaches, nausea, and loss of coordination. Prolonged exposure may cause damage to the parts of the body, mainly the liver. Lead exposure can harm the brain and digestive systems, and in certain circumstances, it can result in cancer. Exposure to ozone causes itching in the eyes, burns, may develop respiratory disorders like asthma, and our resistance to colds and pneumonia will be lowered. In winter, children may suffer from respiratory problems from exposure to oxides of nitrogen. Depending on the exposure's type and intensity, the effect may be either short- or long-term. Short-term effects range from irritation of the eye, skin, nose, and throat, coughing, headaches, nausea, and dizziness to severe conditions like asthma, bronchitis, and lung and heart problems. Long-term effects will be neurological, reproductive, respiratory, and cancer [1,2].

Table 1
Major environmental pollutants, their sources, and impact on human health.

POLLUTANTS		SOURCE	IMPACTS ON HUMAN HEALTH	REF
Heavy metals	**Lead**	Paints, Lead-acid batteries	Encephalopathy, Peripheral Neuropathy, Anemia. Damage to the Liver, kidney, and brain, neurobehavioral changes, and abnormalities in fertility and pregnancy	[15] [16]
	Mercury	Thermal power plants, hospital waste	Hypertension, Myocardial infarction, Proteinuria, cardiovascular diseases.	[15]
	Arsenic	Wood preservatives, pesticide	Respiratory Cancer, Dermatomes, Genetic toxicity	[14, 17]
	Nickel	Smelting operations, battery industries	Cancer, Dramatis	[15]
	Cadmium	Tobacco smoke, batteries	Proteinuria, Glucosuria, Osteomalacia, Aminoaciduria, Emphysemia	[15]
	Sulfur dioxide (SO_2)	Fossil fuels combustion	Irritated airways and lungs. Prolonged exposure may lead to chronic bronchitis	[16] [18]
	Carbon monoxide (CO)	Vehicular emission, Open fire	Cardiovascular and pulmonary diseases, asphyxiation.	[19]
	Nitrogen oxides (NO_x)	Fuel combustion	NO_x gases can exacerbate respiratory illnesses and cardiovascular disease	[20]
Particulate matters	**$PM_{2.5}$, PM_{10}**	Vehicular emission, Agricultural waste, Fuel, and wood burning	Chronic Pulmonary disease, bronchitis, asthma, respiratory and cardiovascular illness and mortality stroke, change in blood pressure.	[16] [20] [21]
Pesticides	**Organochlorine compound**	Dichloro-diphenyl-trichloroethane, DT, Dichlorodiphenyldichloroethane, Dicofol, Eldrin, Dieldrin	Damage human liver, kidney, neural and immune systems, and induces birth defects cancer, causes neurotoxicity, reproductive toxicity Inflammation of the upper respiratory tract and bronchitis, blood effects such as aplastic anemia	[22]
	Organophosphorus Compound	Malathion, parathion, diazinon, fenthion, dichlorvos, chlorpyrifos, ethion.	Reproductive Effects Immunotoxicity Cancer and Immunosuppression Hypertension tachycardia, and paralysis	[23] [24]
	Carbamates	Sprays	Impair child development and IQ Decrease lung function Central nervous system tumor	[24]
	Pyrethrin &Pyrethroids	Sprays, dust, and pet shampoos	Paranesthesia, respiratory tract, eyes, and skin irritations cardiovascular disease	[24]
Plastics	**High-density polyethylene**	Plastic containers, pipes	Mild dermatitis, Respiratory damage, Hormone disruption	[25]
	Low-density polyethylene	Shrink wraps, squeeze bottles	Mild dermatitis, Burning sensation in eyes, Asthma	[25]
	Polyvinyl chloride	Cosmetic containers wrap	Respiratory damage, immune system damage	[25]
Plastic-Additives	**Bisphenol A**	Food storage containers,	Ovarian disorder	[25]
	Phthalates	Personal care products, Vinyl flooring, Polyvinyl chloride plastics	Endocrine disruptor Interference with testosterone, sperm motility, testicular cancer	[8, 25]
	Dioxins	Tobacco smoke, Combustion of wood, coal, oil, Pesticides	Carcinogen interferes with testosterone	[25]
	Polycyclic aromatic hydrocarbons (PAHs)	Tobacco smoke, burning coal, oil, gas, wood, garbage	Developmental and reproductive toxicity	[25]
	Polychlorinated biphenyls (PCBs)	Contaminated fish, meat, and dairy products	Interferes with thyroid hormone	[25]

Exposure to soil in which the presence of unwanted chemicals/substances higher than the normal concentration disturbs the health of living organisms. Anthropogenic sources of soil contamination are chemicals used in or produced as a byproduct of industrial processes, wastewater, domestic, livestock, pesticide, and petroleum-derived products. These chemicals are introduced intensively into the soil by using fertilizers and pesticides, accidently by discharging untreated sewage water and sewage sludge from oil spills, or by leaching from landfills and organic pollutants Atmospheric deposition results from smelting, incomplete combustion of many substances, radionuclide deposition from weapon testing, and nuclear accidents. Production and consumption of plastic are also rising nowadays. It is usually discharged into the soil, which degrades into its additive like bisphenol A, phthalates, dioxins, polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), and heavy metals, which are carcinogenic and toxic. Exposure to soil that is contaminated with plastic additives increases the risk of cardiovascular diseases. Pharmaceuticals, hormones, and biological pollutants like bacteria, viruses, and endocrine disruptors are emerging pollutants, that have recently appeared in the atmosphere and are usually not monitored. These contaminants can enter the human body through the nose, mouth, and skin. Exposure to such soil can cause different acute and chronic health problems. Short-term health problems like headaches, coughing, chest pain, nausea, and skin or irritation. People who continuously work with soil or reside nearby such areas are affected by inhalation because dust particles in the air are inhaled easily, causing different health issues. In some countries, people consume soil in the name of culture, which results in direct exposure to soil. Children under three are always at high risk because they are easily exposed to soil. Exposure to heavy metals causes skin contact problems. Prolonged exposure may disturb the functioning of the central nervous system and damage organs. Long-term exposure may increase cancer risk [3].Crops produced from soil with high levels of contaminants are highly toxic. Consumption of these causes major health risks. Many soil contaminants are recognized as neurotoxic. Lead, polychlorinated biphenyls (PCB), As (arsenic), and Hg(mercury) are used in industries referred to as contaminants with neurotoxic potential [4].

A natural resources like water is required for human usage and development [5].One of the largest issues the world is presently dealing with water pollution, which is harmful to both the environment and human health. It is the output of both organic and artificial human activities [6]. Agricultural, domestic, industrial, and radioactive waste are the most relevant pollutant sources [7]. The most commonly discharged component is a carbonic compound, which includes detergents, other cleaning materials, and organic industrial wastes [8]. Toxins in industrial waste are the major cause of immunosuppression, reproductive failure, and severe poisoning [6]. Rivers of the US have been found to have groundwater that has been impacted by high amounts of pesticides and their intermediate products including triazines and chloroacetanilides [9–11]. Water pollution may also develop from naturally occurring contaminants such as arsenic or fluoride [8]. Fertilizers used in agricultural activities are considered chief contributors to heavy metal contamination in water [12]. There is a connection between water pollution and acute waterborne diseases, which include hepatitis, cholera, diarrhea, typhoid vomiting, skin problems and kidney problems spreading through polluted water [13,14]. Diarrhoeal disease represents a significant health problem in developing countries and affects travelers who visit these countries [11].

Table 1: Major environmental pollutants, their sources, and impact on human health Pollutants and health effects are less studied because of the need for more information on exposure to pollutants in less developed countries, where waste management could be better, there is higher poverty, and the application of new technologies is limited The same situation is observed in many developed countries, as they find solution methods after the damage happens, and precautionary conditions are also lower. The association between environmental pollutants and health could be better characterized because of the difficulty in measuring the level of exposure, and the lack of detailed monitoring [26]. Different pollutants are responsible for chronic and acute diseases (Table 1). Also, the study becomes difficult when disease conditions are observed after long-term exposure. To fill this gap, this review studies the current state of knowledge about the link between environmental pollutants and human health. This review includes different environmental pollutant exposures and their effects on respiratory, reproductive, neural, and cardiovascular systems, as well as the development of cancer in the human body.

2. Methodology

This review summarises and analyses primary information created and provided by other academic and professional researchers who studied pollutants and their effects on health. Using the search terms particulate matter, disease, pollution, health, mortality, and morbidity, we looked up relevant studies on Google Scholar, PubMed, and Sci-Hub. The search was conducted without regard to a specific date. The extensive search that survived title and abstract screening produced a collection of over 350 studies, including journal articles, conference papers, master's theses, and doctorate dissertations. Searches were restricted to document titles and keywords, which typically contain the research topics. The inclusion criteria for articles were: 1. publication in a peer-reviewed journal; 2. inclusion of pollutants as an exposure; 3. inclusion of respiratory, reproductive, prenatal, cancer, and cardiovascular health effects as an outcome; and 4. investigation of associations between pollutants and respiratory, reproductive, prenatal, cancer, and cardiovascular health effects. The exclusion criteria for articles were: 1. articles other than in the English language; 2. articles that did not involve the health effects of pollutants; and 3. articles that did not include humans. After the filtration based on the inclusion and exclusion criteria, a total of 139 works of literature were used in the review [27,28].

1.1Respiratoryhealth Exposure to pollutants and respiratory illnesses are strongly associated. Industry and vehicle emissions contain chemicals like carbon monoxide, ozone (O_3), nitrogen dioxide (NO_2), sulfur dioxide(SO_2), heavy metals, and particulate matter. Soil and water contaminated with pesticides, heavy metals, and plastic additives also disturb respiratory health. Humans who are exposed to these pollutants have been seen to develop upper and lower respiratory tract illnesses, including bronchitis, pneumonia, chronic obstructive pulmonary disease, and coughing up phlegm. Inhaling harmful particles and gases from the environment weakens the lung's natural defenses by increasing epithelial permeability, reducing mucociliary clearance, and limiting macrophage function. Studies on humans, animals, and in vitro organisms have shown that inflammatory cells like neutrophils, T lymphocytes, macrophages,

and mast cells are recruited and activated more frequently. Intracellular oxidative stress is brought on by the production of inflammatory mediators like cytokines and chemokines, free radicals including superoxide, hydrogen peroxide, and hydroxyl radicals, as well as the depletion of antioxidant and enzyme defenses. This causes inflammation by regulating the redox-sensitive transcription factors nuclear kB and activator protein-1 and signaling through the mitogen-activated protein kinase pathway [29](Fig. 1).Pollutants are more likely to affect some demographic groups than others. These demonstrate an increase in mortality linked to exposure, primarily to sulfates and particulates. These groups are vulnerable because their biological defense mechanisms are less effective than those of the general population. Smoking behavior is also linked to exposure to air pollutants Comparing people of the same age who smoke to those who don't, smokers have a 30% lower lung capacity Some diseases like asbestosis and mesothelioma are specific to particular pollutants, i.e, asbestos, and bagassosis caused by exposure to organic dust [26](Pesticide exposure has been associated with wheezing, coughing, tightness in the chest, dry or sore throat, inflammation of the airways, and shortness of breath. According to a study of employees at bottling plants, people who process pesticides run a significant risk of developing respiratory issues, including persistent cough in women. Additionally, throughout the work shift, pesticide workers experienced an increase in symptoms like coughing, wheezing, tightness in the chest, irritation of the throat, and dryness [30] Some research has established the impact of environmental pesticides on childhood asthma, despite the lack of information on adult populations [31,32].A study in Tanzania found that people who were exposed to lambda-cyhalothrin(a pyrethroid Insecticide) had symptoms including runny nose, coughing, or throat irritation [33] A study in Spain showed an association between exposure to organochlorine pesticides and recurring lower respiratory tract infections in infants [34] A study demonstrates that exposure to insecticides like aerosols activates symptoms, falls in lung function, and may promote hyper airway responses in persons with asthma, although the mechanism underlying this effect has not been identified [35].Burning plastic bags causes long-term health issues, severe lung damage, and respiratory conditions like asthma and emphysema by emitting toxins into the atmosphere [36]. Chlorine is contained in polyvinyl chloride and is emitted as it burns, having an impact on the human respiratory system [37]. A prospective birth cohort study found a link between a child's urine bisphenol A (BPA) content and asthma in children [38,39]) Heavy metals like lead (Pb) and cadmium (Cd)are found in cigarette smoke causing emphysema and chronic obstructive pulmonary disease in generations that are exposed to it. Chemical pneumonitis is brought on by Cd fume exposure. Compared to the digestive system, the lungs absorb Cd at a significantly higher rate [40,41]Because smoking during pregnancy is a source of Cd, maternal cigarette smoking also had an impact on the relationship between manganese(Mn) and child blood pressure [42]. Some research has also shown that maternal smoking during pregnancy can promote Cd [43]accumulation in the placenta. In a study, an association between Mn levels in urine samples of young adults with pulmonary functions is found [44].

2.1. Reproductive and prenatal health

2.1.1. Reproductive health

Reproduction is adversely affected by environmental contamination. Exposure to small amounts of contaminants also significantly impacts male and female reproductive function [45].Exposure to environmental toxicants down-regulates the production of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase and increases oxidative stress. In response, ROS are generated, harming the lipids, proteins, carbohydrates, and DNA in cells [46].Oxidative stress plays a role in causing abnormalities in germ cells and apoptosis, which is responsible for infertility in males [46] [–] [48]. The sperm affected may transmit genetic harm to the developing embryo, causing early pregnancy loss or other developmental problems [49] Maternal exposure to $PM_{2.5}$ during pregnancy or before pregnancy decreases the antioxidant ability of reproductive organs. It causes the oxidative stress response and reproductive function to decline by producing reactive oxygen species(ROS) [50–52].Granulocytes and oocytes exposed to $PM_{2.5}$ may experience mitochondrial malfunction, activation of the apoptotic pathway, and induction of apoptosis [53].Testicular cells undergo apoptosis and necrosis as a result of acute toxicant exposure. Public exposure is typically chronic and sublethal [46,54].Chemokines and pro-inflammatory factors are produced when $PM_{2.5}$ enters the blood [55]It leads to the generation of more free radicals, while inflammatory cells induce more adhesion factors and cytokines, which intensify damage and make a cascade of developing reactions, eventually resulting in systematic inflammatory and immune responses. The level of DNA methylation in the genome's non-coding repeating elements changes as a result of exposure to $PM_{2.5}$. This alteration impacts genomic instability or gene expression and contributes to oxidative stress, inflammation, and health problems [53]). (Fig. 2).

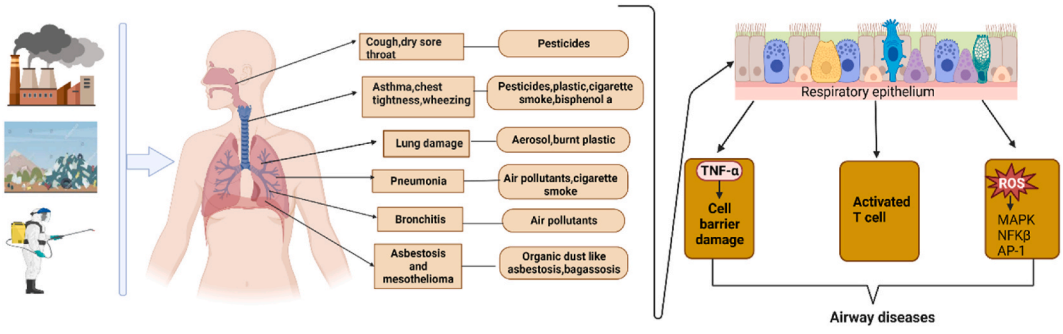

Fig. 1. Impact of environmental pollutants on the respiratory system.

According to epidemiological research, exposure to particulate matter causes problems in gametogenesis and lowers a person's ability to reproduce. These also have an impact on the quantity and quality of gamete [56]).A cross-sectional study utilizing data from a census in Barcelona discovered a statistically significant correlation between a rise in air pollution from traffic and a statistically significant decline in conception rates [57]The investigation of the semen from a group of toll collectors who work on highways showed oligospermia and impaired sperm motility [58]Specific levels of pesticide exposure raise he risk of sperm abnormalities, infertility, spontaneous abortion, birth malformations, and child development retardation [59].Cotton field workers exposed to pesticides showed adverse reproductive problems such as stillbirths, abortions, neonatal deaths, and congenital defects, which are indicative of chromosomal abnormality in germ cells [60].Numerous studies have found a positive interrelation between occupational pesticide exposure and fetal death [61,62]). A study showed that exposure to phenoxy herbicides causes spontaneous abortion in farm families [63]). Phthalate exposure can harm the male reproductive system. Mono-ester metabolites, which are created in the liver, are responsible for the majority of reproductive issues [64,65].Phthalate exposure results in the human condition known as testosterone deficiency syndrome (TDS), which is characterized by lowerm counts, cryptorchidism, hypospadias, and testicular cancer [66]Workers in the plastic industry are exposed to intricate chemical combinations that are used and created during the production process [64]. Miscarriages, infertility, and poor reproductive outcomes were discovered in a study of women who work in the plastics industry [67]. Exposure to the inorganic form of As shows acute, subchronic, genetic, developmental, and reproductive toxicity [17].

2.1.2. Prenatal health

Prenatal health is significantly affected by environmental pollutants. Studies have demonstrated that the fetus is negatively impacted by prenatal exposure to environmental contaminants such as nitrogen dioxide, tobacco smoke, and particle matter [68]. Glutathione depletion, redox activity, and heme oxygenase-1 activation are all increased by man-made pollution, which may increase the risk of mitochondrial dysfunction and genetic epigenetic consequences [69,70]. During pregnancy, these mechanisms may disturb placental hemodynamics with subsequent reduction of oxygen supply nutrients [70,71]When pollutants are exposed to the human body, relative oxygen species are produced, which then causes oxidant injury and pro-inflammatory effects. Damage to the mitochondria also occurs, which impairs ATP synthesis [69]. The chemical component increases subcellular damage and organic pollutants cause oxidative reactions when they are carried through the lung epithelium. Other cytotonic mechanisms include lysosomal damage, protein unfolding, conformational disruption, aggregation, and fibrillation, as well as DNA damage, histone modification-dependent chromatin remodeling complexes, DNA methylation, and noncoding RNA, all of which impair protein transcription. **(Fig. 2).** Similar to genetic mutations, prenatal protein expression changes or reductions may have long-lasting effects on how organs, immature cells, and systems grow. Reduced activation of placental growth factor receptors may result from interactions between ultrafine particles and membrane proteins. Chronic exposure to particulate matter results in oxidative damage that causes subclinical pulmonary and systemic inflammation. Possible mechanisms of the harmful effects of ultrafine particles include increased blood viscosity and coagulation, which affect endothelial and vascular function and result in placental perfusion [70].

In the third trimester of pregnancy, a smaller head circumference of the fetus is seen, when exposure levels to pollutants are higher

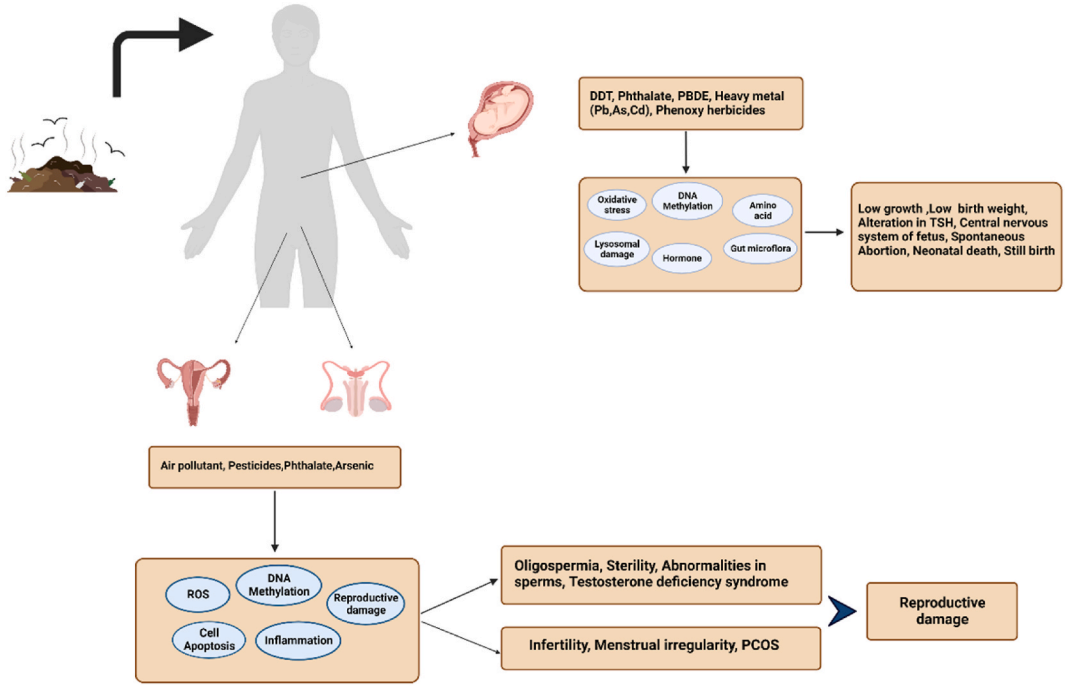

Fig. 2. Effect of environmental pollutants on reproductivity and prenatal health.

[68]. According to a Chinese study, prenatal DDT exposure decreased infant weight [72]According to a study, DDT, beta HCH, and HCH residues in the cord and maternal serum are passed on to unborn children through the placenta and have an impact on their thyroid hormone levels [73] In, exposure to prenatal pesticides resulted in perinatal death [74].The presence of PBDEs in breast milk, adipose tissue, or serum was confirmed by some of the studies examined [75,76]. Human fetuses' liver tissue and cord blood were found to have PBDE that had been exposed to them in utero [77]. In-utero exposure to PBDE was detected in the liver tissue of human fetuses [78] and cord blood [79].PBDE starts accumulating in the second trimester, inducing carcinogenesis, and endocrine dysfunction, causing reproductive and developmental pathology or damage to the central nervous system. Subjects residing adjacent to an electronic waste dump had significantly higher testosterone hormone (TSH) and serum concentrations [80,81] Some pregnancies result in abortions, stillbirths, and fetal abnormalities when couples try to get pregnant. Environmental pollutants like heavy metals may contribute to this. Paternal or maternal exposure may result in this. Most of these situations are found in developing nations. Heavy metals like As, Cd, and Pb are transported to the fetus through the placenta [82]The level of heavy metals in the blood is elevated, which causes problems in pregnancy. The placenta allows the transportation of thalidomide or mercury to the fetus and accumulation in the fetal tissues [83,84]. Pb is stored in humans for a longer period. During pregnancy, Pb is released from the skeleton due to the decrease in calcium(Ca) concentration, as Pb concentration increases because of the Ca in the mother's bone to fulfill the requirements of the fetus [85,86].According to a study by Aylward and associates, people of Bangladesh had greater levels of As in their urine [79]. Milton and coworkers studied the association between stillbirth, spontaneous abortion, and neonatal death with As exposure [87]. According to data, those exposed to As at levels greater than 50 micro g/L had a higher chance of stillbirth, spontaneous abortion, and infant death, whereas those at levels lower than 50 micro g/L had a lower risk [88].A correlation between As exposure and obstetric difficulties, gestational diabetes, gestational hypertension, spontaneous abortion, neonatal death, and stillbirth has been demonstrated in some research [83].

2.2. Cancer

Numerous environmental contaminants have mutagenic and carcinogenic properties. Environmental contaminants have been linked to between 70 and 80% of all cancer forms. Less research has been done on the biological mechanisms of pollution-related carcinogenesis. However, several inverse models demonstrate, how pollution affects cancer and cell growth. The nonlinear dose-response relationship between air pollution and DNA adducts has been validated by a metanalysis. Numerous genes and micro-RNAs can be hypomethylated and activated during transcription in human epithelial cells exposed to $PM_{2.5}$, altering signaling pathways that are associated with cancer. Gene silencing and gene mutation are particularly important during the carcinogenic process when they can influence tumor suppressor genes. Carcinogenesis involves several stages, including start, promotion, and progression. Pollutant effects on cancer cell transformation are impacted by both individual and time-dependent dosages, despite being thoroughly studied and understood. Certain carcinogens and their combinations disrupt various molecular processes by inducing tumor suppressor gene (TSG) inactivation and the activation of oncogenes, cell proliferation in somatic cells, inhibition of apoptosis, chromosome instability, a change in a cell cycle dependent on TP53 activation, and the activation of energetic dysregulation [89].(Fig. 3).

A study found that lung cancer has increased among occupational groups exposed to combustion products of fossil fuels [90].PAH present in coal is a major source of organic pollution, which is released during combustion, coking, pyrolysis, and other coal

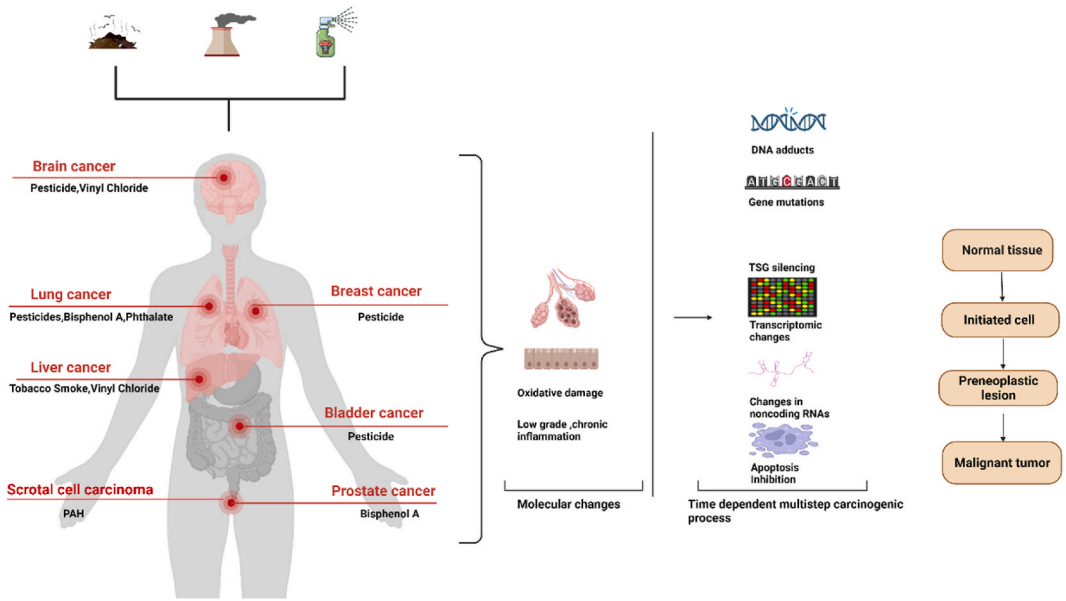

Fig. 3. Environmental pollutants causing cancer in humans.

preparation processes [91]and is absorbed on the surface of particulate matter in the air in urban places [57].Lloyd and colleagues' study with coke oven workers observed that lung cancer is associated with workers exposed to low, medium, and high exposures to coal combustion [92,93] Scrotal cell carcinoma was reported in 1775 due to coal soot in British sweeps, and PAHs were the carcinogen responsible for it [94]A study in the USA with pesticide applicators using herbicides like imazethapyr and imazaquin found an association with bladder cancer [95].Occupational and environmental exposure to farming increases the risk of getting either squamous cell carcinoma or urothelial cell carcinoma of the urinary bladder, according to a study done in Egypt [96]. [96] The risk of breast cancer was greater in an Australian study of women who said they had "ever noticed" pesticide spray drifting from agricultural areas [97]. Users of herbicides like acetochlor had a higher chance of developing lung cancer than nonusers, according to a US study including pesticide applicators from Lowa and North Carolina as participants [98]. Some studies show that bisphenol A, a plastic additive, increases the risk of breast cancer, prostate cancer, metabolic disorder, endometrial hyperplasia, recurrent miscarriages, sterility, and polycystic ovarian syndrome. Both phthalates and BPA can enter the newborn's body through pregnancy, fetus, and breastfeeding [99]A systematic review and analysis showed that the phthalate metabolites MBzP and MiBP were negatively associated with breast cancer among females [80]Di (2-Ethylhexyl) phthalate (DEHP) is a carcinogen. Its inhalation from the environment increases cancer risk [100] There is an association between breast cancer and women who work in the plastic industry [67]. Direct or indirect exposure to heavy metals induces the disruption of intracellular processes via a complex pathway. In the analysis of the pathway, we found some genes and processes common to the toxic effects of As, Cd, Cr, and Ni. These processes might be candidates as markers of heavy metal-induced carcinogenesis [101].

2.3. Neural health

Environmental pollutants are responsible for different types of neurological disorders. Exposure to environmental pollutants like industrial waste, pesticides, automobile exhaust, laboratory waste, and the burning of terrestrial waste are the primary sources of neurotoxicity [102](Exposed PM2.5 can enter the alveolar region, where it reaches the brain and the bloodstream [102,103](103). Ultrafine particulate matter (UFPM) enters the brain through the olfactory nerves through the blood-brain barrier to other regions such as the central cortex and the cerebellum [103]. These particles quickly reach the central nervous system, where they can trigger the body's immunological response in astrocytes, microglia, and neurons to produce ROS which increases lipid peroxidation and neuroinflammation in different parts of the brain [102]. Blood-brain barrier disruption, protein aggregation, oxidative stress, mitochondrial dysfunction, and DNA damage are some of the pathogenic mechanisms that occur simultaneously in nearly all neurological disorders. [11,104]**.(Fig. 4).**

According to epidemiological studies, being exposed to particulate matter increases the possibility of acquiring neurological conditions like Alzheimer's [105]. An in vitro study showed that burning cow dung produces biomass smoke. Exposure to this increases the chance of strong cell inflammation [106]The majority of pesticides used in agriculture are created to impact the nervous

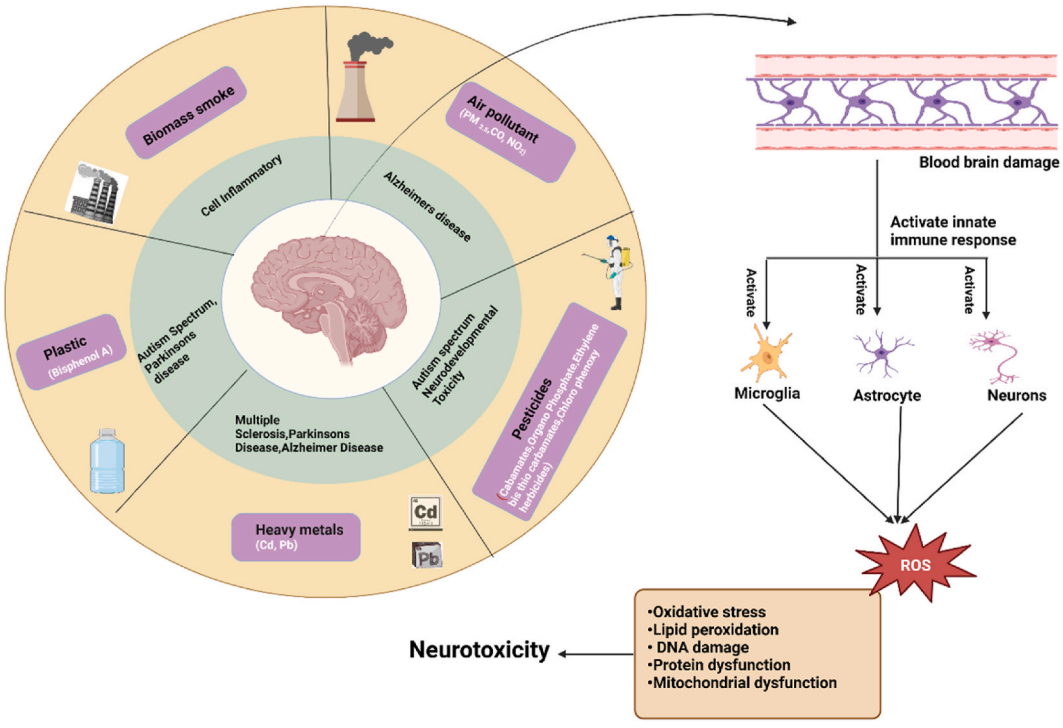

Fig. 4. Environmental pollutants and neural health.

system of pests. As a result pesticide exposure induces neurotoxicity in humans due to the similarity in neurochemical reactions. Neurodevelopmental abnormalities like disability in learning, attention deficit hyperactivity disorder, autism spectrum disorders, developmental delays, and problems in behavior are normally observed. Pesticides like carbamates, organophosphates, ethylene bis thiocarbamates, and chlorophenoxy herbicides may develop neurodevelopmental toxicity [107]According to a survey, 17% of youngsters under the age of 18 are suffering from developing disabilities [108]. In a review, 201 pesticides are mentioned as neurotoxic, but 5 are firmly documented as neurotoxic [4](Studies on animals show that most industrial chemicals cause developing neurotoxicity, even if the exposure is in trace amounts, which are harmless to adult animals. The higher levels of organophosphate metabolites in the mother's urine during pregnancy have been linked to reflex defects in newborns in California, USA(81). There was no association found between neurodevelopment and metabolites specific to chlorpyrifos and malathion. Organochlorine compounds are used as pesticides that stimulate the central nervous system negatively. By inhibiting calcium ion influx and Ca–Mg ATPase, cyclodines like GABA antagonists endosulfan and lindane release neurotransmitters [109]The majority of studies demonstrate that developmental neurotoxicity is more common, even when exposure occurs in tiny amounts and has serious, long-lasting effects. The fetus's neurodevelopment is impacted by prenatal PBDE exposure [110].BPA alters brain activity and behavior, and it causes neurodegenerative illnesses like Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis as well as neuro-developmental disorders like attention deficit and hyperactivity disorder and autism spectrum disorder. Murine BPA exposure affects the brain's capacity for memory and learning [111,112].Children aged 0–12 years who have higher urine concentrations of phthalate metabolites had worse behavior and cognitive outcomes [113] like multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's' disease, Wilson disease, and Alzheimer's disease [114,115].Accumulating inorganic and methylated forms of As near different parts of the brain disturbs the normal functioning of the brain. Lead accumulates in other parts of the brain, mainly in the hippocampus [116], and its exposure disturbs memory, language, executing the task, command following, and reasoning negatively [117]. Exposure to thallium (Ta) develops fatigue, hallucination, lack of sensation, delirium, emotional changes, crania; nerve deficit [118].Experimental research revealed that Pb, As, and MeHg heavy metal combinations adversely damage the central nervous system [119] Heavy metal like Hg and Pb in the hair has been linked to cognitive impairment and memory problems, according to epidemiological studies [120]. Inpregnancy, skeletal Pb is present in the bone, mobilized, and passed to the fetus through the placenta. During nursing, breast milk transfers lead from the mother's skeleton to the fetus. The accumulated Pb will inhibit the development of the fetus's central nervous system.

2.4. Cardiovascular health

Various diseases and fatalities are brought on by exposure to pollutants. Within this group, cardiovascular illness accounts for more than 60% of cases [121]. These are the leading cause of death and disabilities [122,123]The deaths due to cardiovascular disease attributable to environmental causes are larger than those attributable to metabolic, tobacco use, and behavioral risk factors ([122–124]Airborne particulate matter suspended in the air increases cardiovascular disease risk based on its [20]size [21,125,126] J. Nitrogen oxide (NO_2), elemental carbon, and $PM_{2.5}$ and PM_{10} were linked to cardiovascular disease, stroke, and alterations in blood pressure [127].(Target tissues such as the heart and blood vessels are negatively impacted, when fine and ultrafine particles enter the systemic circulation through the alveolar epithelium. Inhaled particulate particle deposits in alveoli in the circulatory system. ROS production contributes to oxidative stress. Production of ROS and alteration of Ca+2 levels are the primary two pathways for particle-induced cardiovascular effects. ROS affects morbidity and mitochondrial function [128].Oxidative stress triggers the

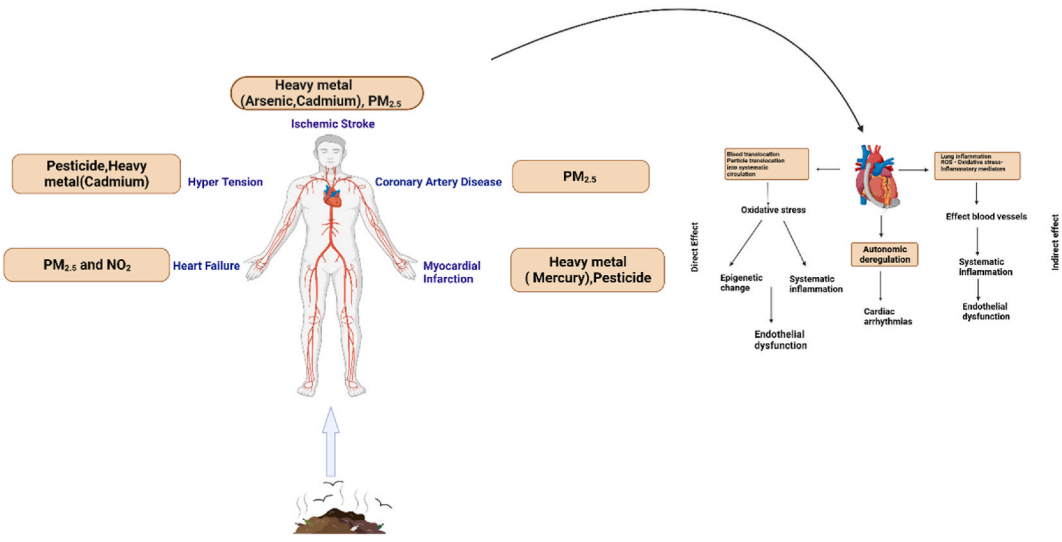

Fig. 5. Effects of environmental pollutants on the cardiovascular system.

activation of the transcription factors AP-1 and NF-k, which increases the gene expression of inflammatory mediators and results in systemic inflammation [129].Therefore, particulate matter-induced oxidative stress, inflammation, and cardiac arrhythmias are the two main pathways for developing cardiovascular illnesses such as myocardial infarction and atherosclerosis [130].(Fig. 5). According to research by the American Heart Association, the inflammatory response to particulate matter increases acute phase reactants (such as C-reactive protein, fibrinogen, and D-dimer), endothelial dysfunction, and blood coagulability in healthy individuals [131].Through the production of inflammatory mediators, fine and ultra-fine particles enter the blood circulation or indirectly affect pulmonary inflammation and initiate venous thromboembolism, thrombosis, and plaque formation [132].The reduction of activated partial thromboplastin time (aPTT) and the prothrombin time by particulate matter, increases coagulation [131,133].The immediate result of the metals bound to the particulate matter is what causes it to be hypercoagulable. Regardless of changes in the DNA sequence, epigenetic alterations alters the expression of genes. One of the causes of cardiovascular illness brought on by particulate matter is epigenetic change. Particulate particles make the blood vessels fibrillate more. Heart arrhythmias, which are symptoms of heart disorders, are brought on by disruption in the regular cardiac cycle [134]. However, mounting evidence suggests that soil and water pollutants may harm cardiovascular health through a variety of mechanisms, including inflammation and disruption of the body's natural cycle. But soil and contaminants are a less visible danger to human health than dirty air particulates.

According to cohort research from the UK, long-term exposure to NO_2 and particulate matter is associated with an increased risk of heart failure [121]. According to a meta-analysis of 35 studies, higher greater levels of pollution on the day of exposure ($PM_{2.5}$ level of 10 microg/cm3) were linked to a 2.12% increase in hospitalization or heart attack fatalities ([123,124] Exposure to heavy metals may develop cardiovascular diseases. Exposure to Pb shows a high risk of hypertension and increased blood pressure in animal models, which is reversible with chelation [123].According to a recent cross-sectional study from China, higher Pb level in the blood was associated with carotid artery plaques and cardiovascular disease, including coronary diseases, myocardial infarction, or stroke [135] Data from the national health and nutrition examination survey (NHANES) revealed that the interaction of chronic physiological stress and Pb level in the blood significantly increased the risk of cardiovascular mortality. In low and middle-class countries, soil pollution with heavy metals is associated with cardiovascular disease because their populations are too exposed to these environmental pollutants (Burroughs Peña & Rollins, 2017).Methyl mercury is known to be a neurotoxicant. Recent data shows that it is associated with a dose-dependent increase in death from cardiovascular disease and non-fatal myocardial infarction [123,136].The association is documented between peripheral arterial disease, coronary heart disease, and type 2 diabetes. A weaker association between exposure to As and stroke is reported [123,137]A decrease in exposure to As reduced death due to cardiovascular disease [123,138]. According to NHANES higher Cd levels in Korea were associated with a higher risk of stroke and hypertension [139]The risk of fatal or nonfatal coronary artery disease is increased by long-term exposure to air pollution [140].It is believed that long-term exposure to $PM_{2.5}$ increases cardiovascular risk through continuous plaque progression, whereas short-term exposure stimulates plaque rupture in concert, increasing the risk of cardiovascular problems [121](Chronic ischemic heart disease, acute ischemia events, and heart failure are all associated with both short- and long-term exposure to air pollution [125,141,142])According to a Korean study, prolonged exposure to air pollution increases the risk of mortality from a stroke [104,121]. In a women's health initiative study, a risk of 35% was observed for stroke and death from cerebrovascular disease and an 86% higher risk is observed with an increment of 10 mg/m cube in l chronic(long time) exposure of $PM_{2.5}$ [140,143],. Pesticide exposure is strongly associated with acute myocardial infarction, heart failure, and arterial hypertension during pregnancy, but heterogeneity is also observed among the included studies [140,141].

2.5. Future challenges and measures and implications

The problem of pollutants might be greatly reduced with the employment of strong governmental measures, modern infrastructure, and technology. Unscrupulous human behavior is a serious problem that makes overcoming the current obstacles challenging. There are a number of challenges to achieving the aim of a clean environment, including the public's disinterest in pollution control measures and an inadequate ecological management system. A major loss of investments in infrastructure facilities could occur from the public's disinterest in some government actions [119]. It will take decades to reform everything, which is a huge undertaking. But to determine the course of future actions, the definition of this change's objectives and a consensus over its spirit are required.

The latest technology must be used to manage pollution. Research on specific contaminants is required to assess the accumulation mechanism. Public awareness of pollution is important. The government should provide research data on health trends related to pollution to raise public understanding of pollution generation and management.

3. Conclusion

Although pollutants are not new to the environment, their exposure still poses the greatest threat to humanity and is a significant cause of environmental illness and mortality. Urbanization, industrialization, mining, and exploration are some of the human activities that have had the most impacts on worldwide environmental pollution. While knowledge and tighter legislation in developed countries have helped to a greater extent in conserving their environment, both developed and developing countries share this responsibility. Despite its increased attention due to its severe long-term effects, pollutants still has an influence.

Ethical clearance

The study is a part of a Indo-Japan MEXT Project with the ethical clearance (NU/CEC/2021/109 dated 14/06/21)

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This work is supported byJapan Society for Promotion the of Science (MEXT- Government of Japan (Sanction No: 20KK0222))

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