Journal of Toxicological Studies 2024, 2(1), 1135.
https://doi.org/10.59400/jts.v2i1.1135

Review

Chemical health hazards and toxicity of environmental pollutants on humans, animals and others: An overview

Suresh R. Naik[1,*], Dipesh Gamare[2], Amisha Bhopatrao[3]

[1] D. Y Patil Institute of Pharmaceutical Sciences & Research, Pune 411018, India
[2] Department of Pharmaceutics, Yashwantrao Bhonsale College of Pharmacy, Sawantwadi 416510, India
[3] Department of Pharmaceutical, Sciences and Biotechnology, Technological University of the Shannon, N37 HD68 Dublin, Ireland
*** Corresponding author:** Suresh R. Naik, srnaik5@rediffmail.com

CITATION

Naik SR, Gamare D, Bhopatrao A. Chemical health hazards and toxicity of environmental pollutants on humans, animals and others: An overview. Journal of Toxicological Studies. 2024; 2(1): 1135. https://doi.org/10.59400/jts.v2i1.1135

ARTICLE INFO

Received: 29 February 2024
Accepted: 2 April 2024
Available online: 23 April 2024

Abstract: Toxicology, rooted in ancient civilizations and evolving through pivotal historical figures like Paracelsus and Alice Hamilton, has become a multidisciplinary field encompassing various branches such as pharmacology, medical, forensic, and environmental toxicology. This exploration embarks on a journey through time and science, unravelling the intricate interplay between chemicals and pollutants and their profound impacts on human, animal, and environmental well-being. Spanning from ancient practices like the use of hemlock in Greek capital punishment to modern-day concerns surrounding industrial chemicals and pesticides, the review delves into the mechanisms by which toxins disrupt biochemical pathways and induce organ dysfunctions. From heavy metals and pesticides persistent effects on the nervous and reproductive systems to the carcinogenic properties of polychlorinated biphenyls (PCBs), hydrocarbons, polycyclic aromatic hydrocarbons (PAHs), and volatile organic compounds (VOCs). The review highlights the diverse range of toxicants and their widespread impact on human health. Additionally, the review underscores the importance of proactive measures to mitigate exposure to harmful substances, advocating for the development of antidotes, bioremediation techniques, and stricter environmental regulations. By addressing the urgent need for comprehensive strategies to combat toxicological hazards, this review aims to contribute to ongoing efforts to safeguard public health and environmental sustainability in the face of evolving chemical threats.

Keywords: hydrocarbons; pesticides; heavy metals; volatile organic solvents; endocrine disrupting chemicals; environmental pollutants; toxicity

1. Introduction

Ancient toxicology provides a fascinating perspective covered by Elsevier in ancient Egypt: the death of Cleopatra, hemlock (Greek capital punishment), the case against Socrates, poisoning in ancient Rome, the snake as a biological symbol, poisonous medicine in ancient China—aconite (Chinese poison arrow) [1]. The uses of poison vary widely, such as the use of arsenic to achieve the “milk and roses” complexion many women envied and the treatment of syphilis with mercury [2]. Toxicology, or Agada Tantra, is one of the eight clinical specialties of Ayurveda and has been exclusively associated with healing cases of envenomation [3]. In the medieval and Renaissance periods, medicine and toxicology were mostly filled with beliefs in folklore, superstitions, and religion. Subsequently, a new era started with Paracelsus, a Swiss physician alchemist (1493–1541), who is considered the father of toxicology. Paracelsus demonstrated the specific toxicity of chemicals in plants and animals. He also stated that there is nothing that is not poison. The judicious use

of the right dose differentiates poison from remedy and also moots the concept of a dose-response relationship [4]. Georgius Agricola published the book "De Re Metallica" on mining and metallurgy in 1556 [5]. Thereafter, during the mid-19th century, Alice Hamilton carried out pioneering work in the field of industrial toxicology, particularly dealing with industrial chemicals and metals in the USA. Her work largely helped in understanding the occupational diseases associated with mining operations [6]. Henri Becquerel, a French physicist and Nobel laureate, while studying phosphorescence in uranium salt, discovered radioactivity in 1896 [7]. From 1900 to 1930, there was an emergence of chemical elixirs, many chemicals of therapeutic importance, warfare chemicals, and insecticides. During this time, the U.S. Food and Drug Administration and the Drug and Cosmetics Act were developed. Thereafter, many toxicological regulatory bodies were established, including the International Union of Toxicology, the International Society for the Study of Xenobiotics, the Academy of Toxicological Sciences, and the American Board of Toxicology, and many important toxicological books were published [8]. Also, many accidents and disasters of toxicological significance occurred, such as the Bhopal disaster (the release of methyl isocyanate from a Union Carbide production plant), the eruption of a carbon dioxide bubble in Lake Nyos, chemical spillage and fire at the Sandoz Laboratory, which led to tons of chemical spillage into the Rhine river in Basel, and the Chornobyl accident (nuclear power plant meltdown and harmful radioactive waste release), which resulted in atmospheric poisoning to millions of people, and many more events have occurred, causing numerous toxicological and harmful effects on humans and the environment at large [9].

Furthermore, our modern scientific knowledge, advanced analytical methods, and technology helped us to understand how poisons/toxins/toxicants and therapeutic agents act differently on the human body and organ functions and their underlying mechanism(s) of action [10]. Some of the observations on toxicology research helped us to use toxic compounds as a tool for the development of animal models for pharmacological screening (e.g., MPTP, toxins of plant and microbial origin). Modern toxicology helped us in developing research methodologies, including in *vitro* techniques, and move away from the traditional approaches of animal testing to harm-free roots of experimentation [11].

The word toxicology is derived from the Greek word "toxion", and the scientific study "logos" was coined in the 17th century [2]. Today, toxicology encompasses diverse scientific disciplines such as biology, chemistry, pharmacology, medicine, etc., and deals with the study of adverse effects on humans, animals, and other living organisms [12]. Furthermore, it even includes the practice of diagnosis and remedial measures for the treatment of toxin/toxicant effects (in short, management of toxicity). Alternatively, some scientists have defined broadly toxicology as a science of study to characterize the effects of chemicals, gases, pollutants, biologicals, xenobiotics, drugs, and toxins on humans and other living organisms. Thus, definitions of toxicology have undergone many transformations over the years. The term toxicity is the inherent capacity of chemicals or foreign substances to cause injury, harmful effects, and health hazards [13].

The multidisciplinary toxicology has been classified into different branches, all with some similarities but many differences. They are medical toxicology, analytical toxicology, applied toxicology, foreign toxicology, industrial toxicology, immune toxicology, genetic toxicology, environmental toxicology, reproductive toxicology, and investigative and regulatory toxicology (refer **Figure 1**). Each branch of toxicology has been briefly defined and explained in the figure itself. Hence, they will not be discussed or elaborated.

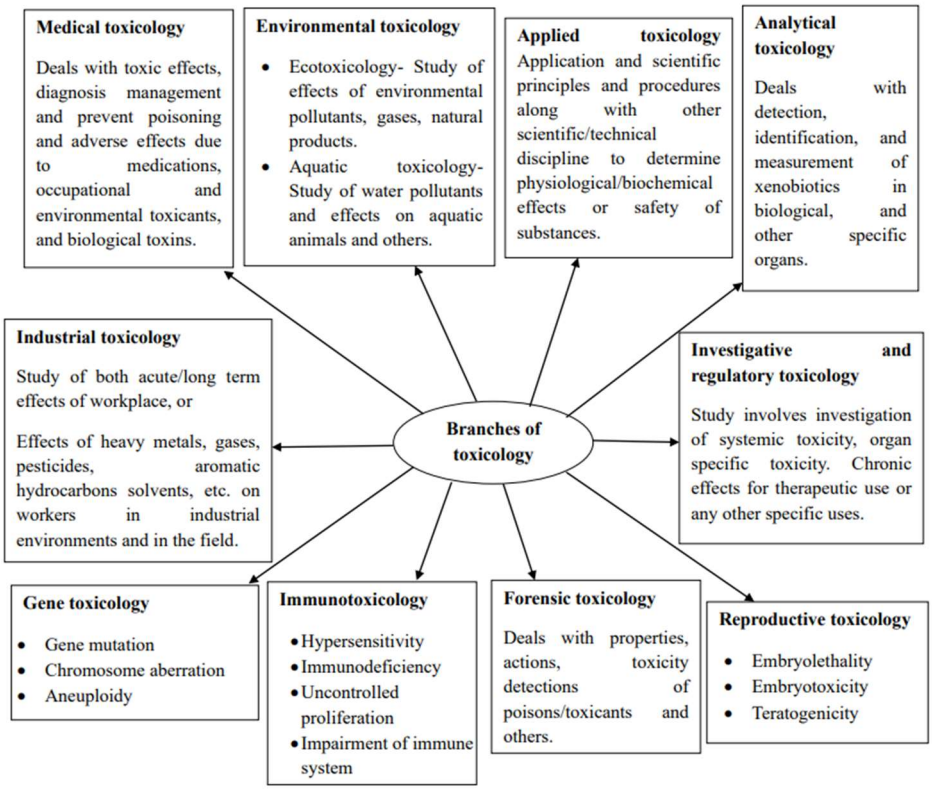

Figure 1. Enumerates various branches of toxicology.

The aim of this review is to elucidate the toxic and adverse effects of various chemicals on the human body and organ functions. Additionally, it seeks to present the state-of-the-art knowledge in the field of toxicology, with special emphasis on toxic manifestations, associated mechanisms, and their outcomes on human health. Furthermore, this review aims to provide an overarching environmental perspective within which humans, animals, and other organisms coexist.

2. Environmental pollutants and their effect on human health, animals, and others

Many chemicals exposure/ingestion leads to biological effects by interfering with functions associated with specific biochemicals or metabolic pathways and/or macromolecules within the tissue (e.g., warfarin inhibits vitamin K-dependent post-translational modifications of clotting factors in hepatic tissue) [14]. In addition, vapor, chemicals, solvents, pure hydrocarbons, containing hydrogen and carbon (chief components of different types of fuels, also exist in the form of gas, liquid, solid, or polymers) to partially oxidized hydrocarbons to organic compounds

containing chlorine, sulphur and nitrogen, polyunsaturated biphenyls (mainly polychlorinated biphenyls and its congeners) used in plastics, fluorescent lighting ballast, transformers, capacitors, organochlorine pesticides, other new generation pesticides, herbicides; asbestos, silica, cigarette smoke all these substances known to induce ill effects/toxic adverse effects on the human body as well as various organ functions and ultimately manifest various disorders or diseases [15] (**Figure 2**).

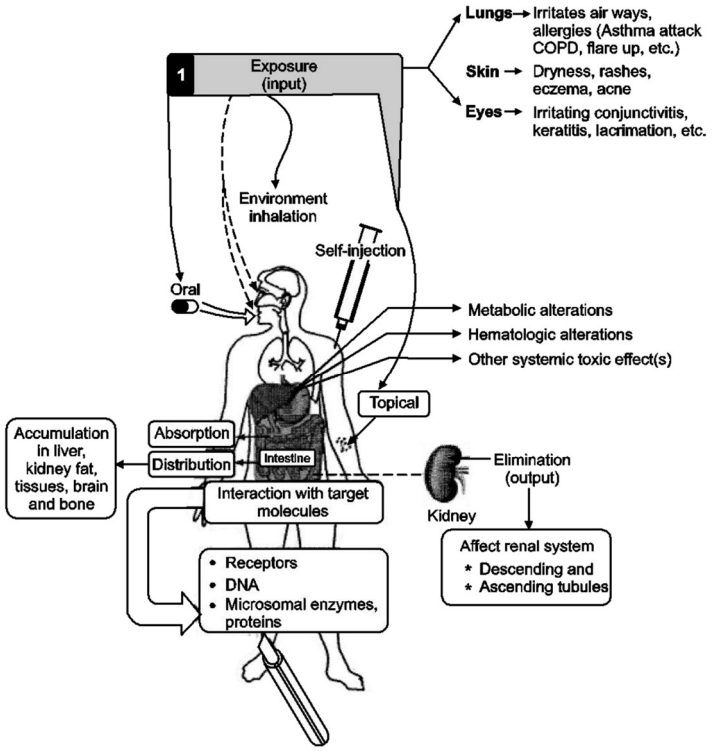

Figure 2. The exposure of environmental chemicals, gases, particles, ingestion including drug treatment, and various aspects on physiological events and general effects on the human body.

2.1. Effects of gases, aerosol, solvents, and chemicals

Environmental pollutants such as gases, dust, aerosols, and volatile organic compounds in the presence of sunlight react with nitrogen oxide emitted from industrial facilities, electric utilities, and motor vehicle exhaust to form ozone, which in turn helps the formation of fine particles. Furthermore, chemicals from the environment include inorganic metals (mercury, arsenic, antimony, lead, cadmium, silicon, zinc, chromium, manganese, etc.), salts of metals (oxide, sulphates of metals, and others), ammonia, nitrates, etc. Organic chemicals like pesticides, herbicides, preservatives, antibiotics, biotoxins, artificial colours, hydrocarbons, organic heavy metals, and carcinogenic compounds also persist in the atmosphere, water, and foods [16,17].

When such pollutants enter the human body via inhalation or skin contact (at the workplace) and reach alveoli, they are absorbed rapidly and then distributed to various organs via the blood stream. The particles retained in the alveoli exert toxic effects locally (refer to **Figure 2**). Furthermore, chemicals or toxins from exogenous sources, when ingested, inhaled, or absorbed in the body either from water, air,

foods, drugs, etc., also produce toxicity either by the parent molecules present or its metabolic products formed by its metabolism in different organs. High blood flow organs (brain, kidney) are also vulnerable to toxic effects of chemicals. Cardiac tissue is more sensitive to toxin-induced alterations of ionic gradients.

Effects of air pollutants such as metal particles (originated from industries, fertilizer usage, burning of fossil fuels, etc.) and water pollutants largely dissolved chemicals, metal salts, and persistence in water and food, when entering the body, cause cellular damages in vital organs (viz., liver, lungs, kidneys) (**Figures 2–5**).

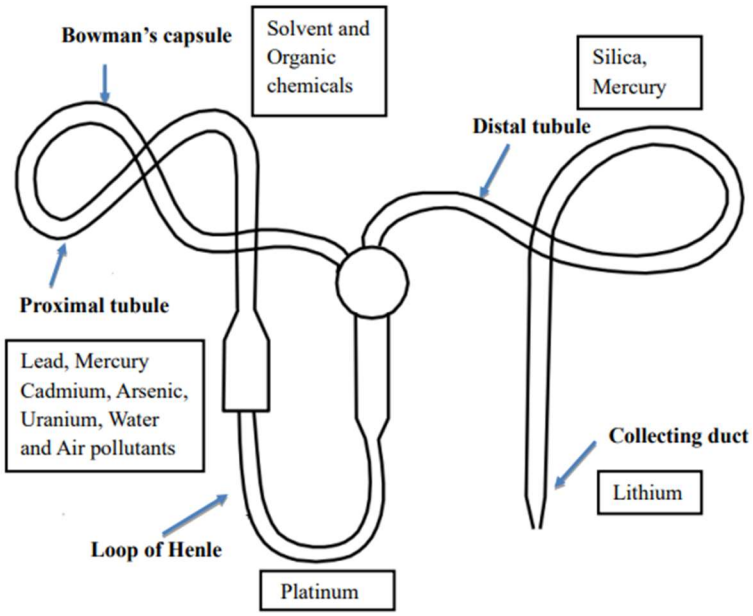

Figure 3. Metals affecting different intricate structural part of kidney.

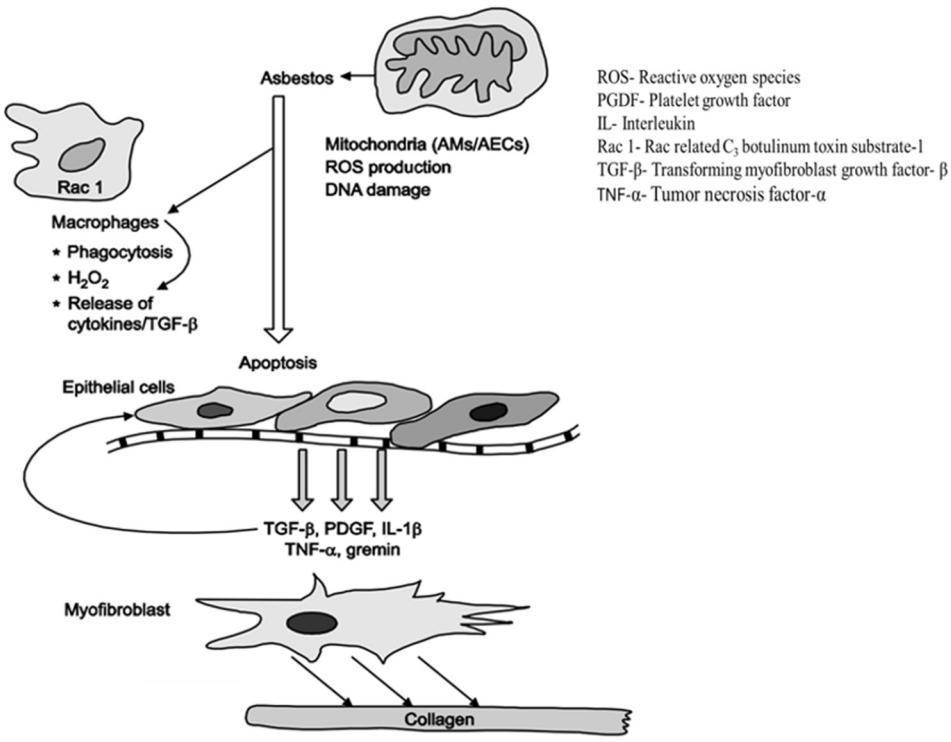

Figure 4. Underlying molecular mechanisms of asbestos induced lung disease.

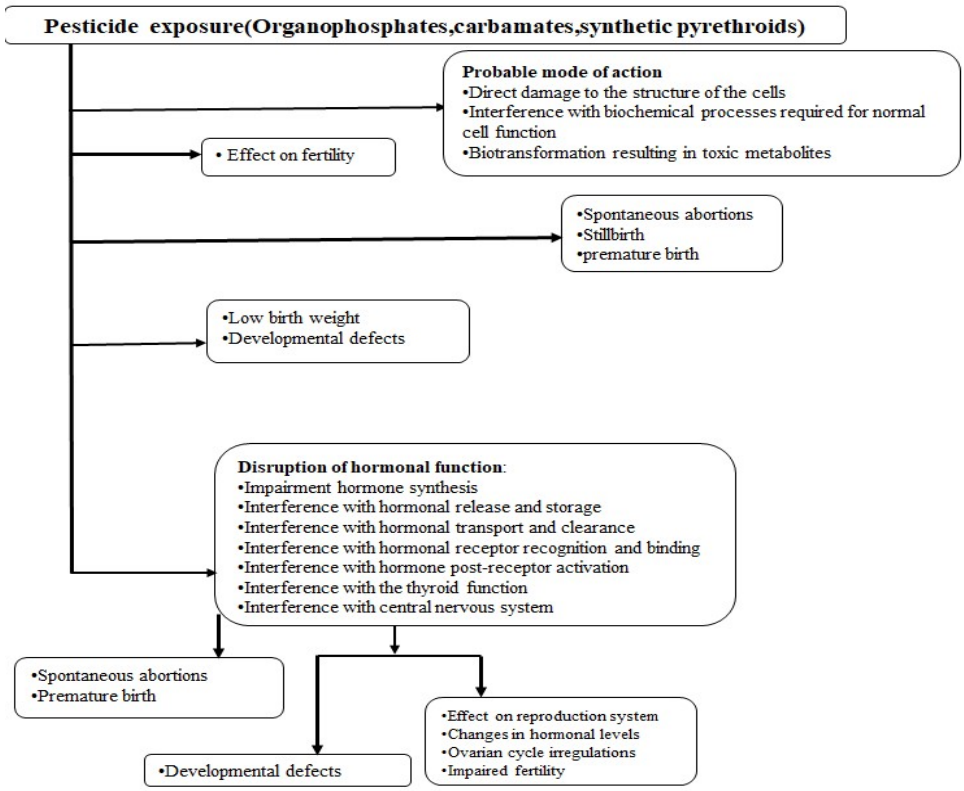

Figure 5. Potential effects of pesticides on developmental and reproduction processes in humans.

Similarly, exposure to corrosive chemicals leads to local irritations/caustic effects at the site of location due to the denaturation of macromolecules (proteins) and cleavage of chemical bonds required for the function of biomolecules, which are often termed non-selective. Heavy metals, which cannot be metabolized, persist in the body and induce toxic effects by combining with one or more reactive groups (ligands) that are essential for physiological functions (particularly –O, S– and N–containing ligands, which are known to form –OH, –COO–, $–OPO_3H$, C=O, –SH, –S–S, $–NH_2$ and –NH) leading to oxidative stress and culminating in impairment of the endogenous antioxidant enzyme defensive system, viz., superoxide dismutase (SOD), glutathione (GSH), glutathione S-transferase (GST), and catalase [18].

2.2. Asbestos

A fibrous silicate mineral used widely in building materials, a range of manufactured goods (automobile clutch, brake, and transmission parts), heat-resistant fabrics, packaging materials, gaskets, and coatings. The chronic exposure of asbestos, especially at the workplace, or inhalation of asbestos fibres can lead to serious lung disorders. Many of them are described below.

Asbestosis is a chronic interstitial lung disease largely caused by the inhalation of asbestos fibers (composed of mineral silicates formed due to damaged and degraded asbestos material in the environment) affecting people working in the shipyard, mining, painting, aerospace, building construction, installation of the asbestos board, sprayer, and asbestos stripping, insulation workers. In addition,

general community exposure to road surfaces, playground material, and chemical paints.

The three diseases that are most commonly associated with asbestos exposure are asbestosis, mesothelioma (a rare type of cancer that occurs in the region of the chest wall), and lung cancer. Asbestosis is caused by the inhalation of asbestos fibres over an extended period. Once these fibres enter the lungs, they can cause inflammation and scarring of the lung tissue. Over time, this scarring is known as fibrosis. Further, the fibre in the lungs leads to the accumulation of macrophages turned into fibroblasts; the other participating biological events are: 1) Reactive oxygen species originating from immune cells and phagocytes in response to asbestos fibres cause oxidative injury (type 1 alveolar cells, development of fibroblast growth factor beta) that results in fibrosis. 2) Macrophages produce tissue necrosis factor, interleukins, and stimulation of the phospholipase C pathway. Such mediators are generated due to the above-mentioned pharmacological events, which play a key role in stimulating lymphocytes and myofibroblasts, leading to the proliferation of fibroblasts and an increase (2-fold) in the number of cells in the matrix. Macrophages-derived fibroblast growth factor, platelet, and insulin-like growth factor also participate in the development of fibrosis, such as biological alterations in the lungs, which leads to a significant combination of fibrosis, pleural thickening, and inflammation, resulting in progressive impairment of lung function [19,20]. The reported major clinical symptoms are shortness of breath, persistent cough with mucus, clubbing of fingers, and inability to perform day-to-day physical activities. It is estimated that there are more than 55,000 deaths per year in the world due to asbestosis [21,22] (**Figure 4**).

Increased levels of ROS, cytokines, and growth factors due to chronic exposure to asbestos may produce harmful effects on the lungs. The pathogenesis of asbestos-induced pulmonary diseases derived from a long-term interplay between constant or persistent free radical production and expression of cytokines, growth factors, and other inflammatory cell products.

2.3. Pesticides and herbicides

Pesticides are synthetic chemical compounds used for plant protection and to kill pests/insects. Pesticides are used to eliminate or control a large spectrum of agricultural pests, including vectors of human and animal disease. Herbicides are chemicals used in agriculture and known as weed killers.

2.3.1. Organophosphates

Organophosphates are comprised of diverse groups of chemical compounds (diazinon, phosmet, malathion, parathion, chlorpyrifos, and many more) and are largely used as pesticides and herbicides, as well as nerve agents in chemical warfare. Organophosphate exerts toxicity in mammals through the inhibition of acetylcholinesterase, which results in the accumulation of excess acetylcholine. The accumulated acetylcholine manifests with cholinergic toxidrome, which includes effects on both nicotinic and muscarinic receptors and CNS. The mortality rates caused by organophosphate insecticides range globally from 2% to 25%. The serious effect is respiratory collapse (bronchospasms), which may be the major cause of

death. Respiratory distress is also accompanied by bradycardia. The onset of clinical symptoms varies based on the type of compound and manifests immediately, and reversal can take many weeks. Most organophosphate compounds are readily absorbed in the body after inhalation or ingestion. However, systemic absorption via dermal exposure is comparatively slow. Overstimulation of nicotinic receptors causes myoclonic jerking, which finally results in flaccid paralysis due to depolarization blockade. The clinical symptoms are hypertension, sweating, tachycardia, miosis-induced blurred vision, diaphoresis, and leucocytosis with the left shift [23–25].

OPs exposure to humans (males) induces adverse effects on semen normal quality and morphology. This effect is mainly due to DNA of spermatozoa and alterations in testicular somatic cell functions [26] (refer **Figures 4** and **6**). Most of the pesticides, including OPs and their metabolites, affect any of the reproductive or developmental end points in multiple mammalian species, including humans (**Table 1**). Chronic sub-lethal doses to birds reduced fertility, suppression of egg formation, and chick rearing behaviour [27]. OPs on chronic exposure are also reported to induce lung, kidney, liver, and breast cancer (**Table 1**).

Table 1. Biochemical and cellular effects of pollutants (of environmental origin) that lead to carcinogenesis*.

Source	Type and nature of carcinogen involved/present	Name of the chemical	The nature of damage at molecular/cellular level	likely occurrence of cancer
Food and dietary constituents	Aflatoxin (food and dietary) Food additives and preservatives	Aspartame (artificial sweetener) Butylated hydroxy-anisole Titanium dioxide Sodium nitrate Sodium nitrite	Formation of DNA adducts Formation of DNA replication Epigenetic modification DNA damage Tumour angiogenesis by up-regulating VEGF	Hepatic cancer Variety of cancer Lung cancer Esophageal cancer
	Chloropropanols		-	-
	Ethylene oxide used for ripening fruits		Disruption of cellular proteins controlling the life cycle of the cells that causes DNA adducts.	Breast cancer
	Potassium bromates (used for baking)		Oxidative DNA damage	Hematopoietic cancer
	Benzene		Deletion of chromosome	Renal tumour
	Bisphenol A (used in coating food containers)		Evasion of apoptosis	Breast cancer
	Heterocyclic amines		DNA damage	Colorectal, breast and lung cancer
	Pesticides (phosphates TBT, DDT, DENP, PCBs, TCDD)		Endocrine disrupting chemicals phosphates causes epigenetic modification	Lung kidney liver and breast cancer
	Plastic materials contain polycyclic aromatic hydrocarbons (PAHs), vinyl chloride		DNA damage ^{53}P mutation and amplification MDM2 gene	Lung-cancer, angiosarcomas, blood vessel tumor, liver, brain, renal and breast cancer
	Cigarette smoke contains (PAHs), N-nitrosamines, volatile organic hydrocarbons, heavy metals		DNA adducts formation, permanent somatic mutations in critical genes, somatic mutations cause clonal growth	Variety of cancers including lung cancer

*Adopted from [17].

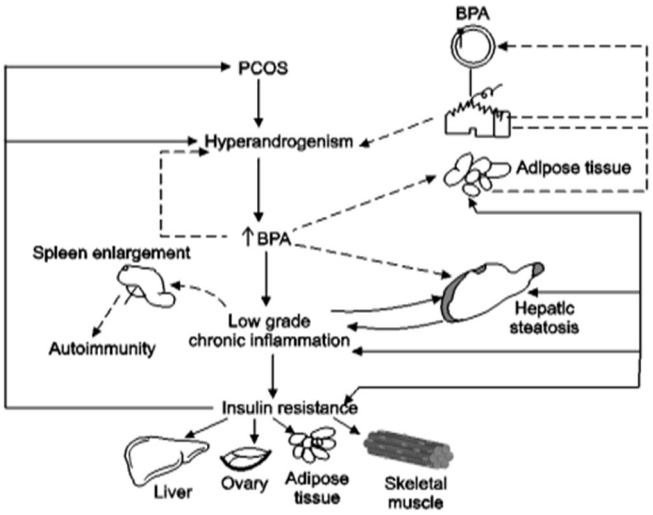

Figure 6. The Pathway Associated Toxicity with BPA and Other EDC (endocrine-disrupting chemicals).

2.3.2. Carbamates

Exposure to carbamates and its derivatives causes inhibition of kisspeptin neurons, which lead to low levels of gonadotropin-releasing hormone (GnRH) in the hypothalamus, which consequently inhibit the synthesis of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in the anterior pituitary. Such hormonal changes ultimately compromise steroid synthesis in the testis. This effect causes a reduction of epididymal and testicular sperm counts as well as testosterone concentration. Thus, chronic carbamate exposure led to male fertility problems (**Figure 5**).

Carbamates are derived from N-methyl carbamic acid and have been classified as Class II by the Environmental Protection Agency and World Health Organization, indicating they are moderately toxic. Some carbamate derivatives are considered endocrine-disrupting chemicals (EDC) based on their specific adverse effects. (Refer to **Figures 6** and **7),** which depict the profile of action of EDS (endocrine disrupting substances).

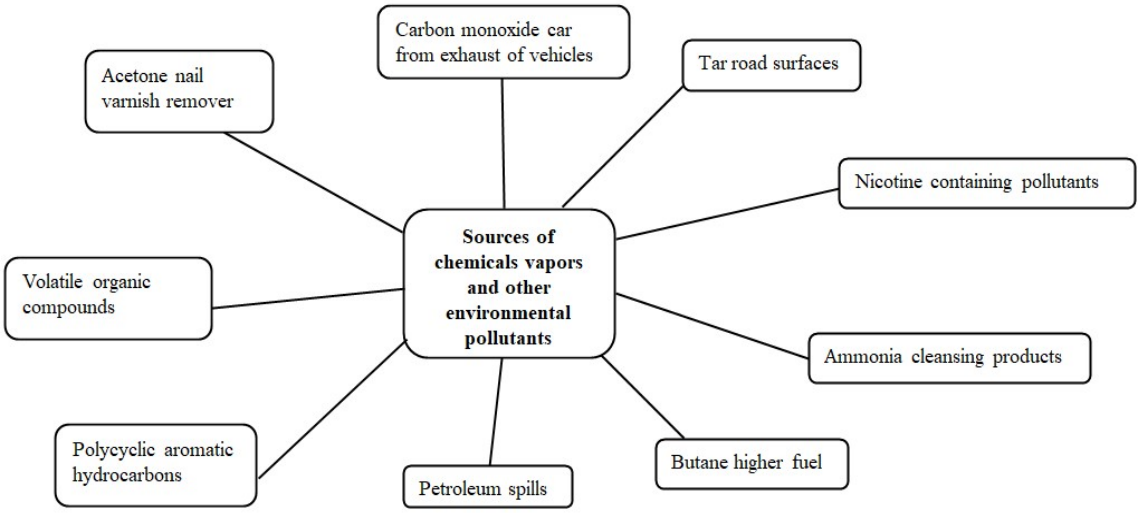

Figure 7. Exposure of chemicals, vapours, and other environment pollutants at workplace.

Carbamates inhibit acetylcholinesterase and melatonin receptors. The clinical symptoms following ingestion inhalation or exposure are tachycardia, hypertension and mydriasis, and flaccid paralysis at a toxic level. Both organophosphates and carbamates induce similar types of toxicity (derived from muscarinic and nicotinic receptors). However, the toxicity symptoms subsided after 24 to 48 h in carbamate-induced intoxication as compared to organophosphates. This is because during the phosphorylation of organophosphates to acetylcholinesterase, carbamate-cholinesterase bonds hydrolyse rapidly within hours [28–30].

Extensive usage of carbamates for increased food production and other purposes; their residual contents are alarmingly high in soil, wastewater effluents, and many food products all over the world [28].

2.3.3. Pyrethroids

Pyrethroids are synthetic insecticides composed of an acid and alcohol derived from pyrethrins and used in controlling insect pests in agricultural production and public and animal health. Pyrethroids exert both mammalian and insect toxicity by modifying voltage-gated sodium channels in neuronal membranes and thereby disrupting the electrical signalling throughout the central and peripheral nervous systems. The major toxicity symptoms include impaired motor coordination, tremors, convulsions, burning, and itching sensations. Pyrethroids act as potential dermal and respiratory allergens, and chronic exposure can result in contact dermatitis or asthma-like clinical conditions. Death occurs in humans largely due to respiratory failure. Pyrethroids are more toxic to insects due to their limited ability to eliminate these compounds. At high concentrations, pyrethroids act on GABA-gated chloride channels, nicotinic Ach receptors, and intracellular gap junctions and induce seizures. They are also reported to be toxic to aquatic organisms, including fish, at an extremely low level (4 parts per million). Beneficial insects such as bees, dragonflies, mayflies, and bottleflies are extremely sensitive and can be eradicated [31].

The recent research reports demonstrated the influence of oxidative stress generated by pyrethroids on the modification of DNA, RNA, proteins, and lipids both in cells and extracellularly [32]. The molecular basis of patho-mechanisms of the pyrethroid effects is detrimental in nature.

2.3.4. Rotenone, a phytoinsecticide

Rotenone, a plant product (isoflavone), is used as a broad-spectrum insecticide in a large number of crops. It mainly acts by inhibiting the oxidation of the reduced form of nicotinamide adenine dinucleotide (interfering with the electron transport chain within the complex system in mitochondria). Thus, creating reactive oxygen species (ROS), which can damage DNA and other components of mitochondria. Rotenone is toxic not only to insects and fish but also to humans and animals.

The rotenone study in animals demonstrated that low doses induce oxidative damage and death of dopaminergic neurons and exhibit symptoms of Parkinson's disease. The dust preparation is highly irritating to the eyes (causing conjunctivitis), skin (causing contact dermatitis), rhinitis, and pharyngitis [33].

Acute poisoning is characterized by respiratory stimulation followed by respiratory depression, ataxia, convulsions, and death due to respiratory arrest. And it is not a human carcinogen.

2.3.5. Herbicides

Herbicides are routinely used to control noxious plants or for falling or inhibiting growth of unwanted plants such as agricultural weed. Bioherbicides are phytotoxins, pathogens, and other microbes used as biologic weed control. Chemical herbicides, mainly chlorophenoxy, glyphosate, and bipyridyl herbicides, are the most widely used for the destruction of weeds or undesirable vegetation. Biosynthetic pathways of amino acids are the major site of action of herbicides. Bipyridyliums and heteropentalenes induce generations of superoxide radicals by energy divergence from photosystem I of photosynthesis [34]. It is also reported that lipid synthesis is the site of action of a broad array of herbicides that are used for controlling monocot weeds. The chemical grouping of dioxins is highly toxic and can cause problems with reproduction development and the immune system. They are also known for disrupting endocrine hormones and leading to cancer. In humans, 2,4-dioxane in large doses can cause coma and muscle hypotonia. In animal experiments, herbicides have demonstrated a fair degree of nephrotoxicity and hepatotoxicity. Occupational hazards, particularly with the chlorophenoxy herbicides, have been implicated in cancer risk. A greater degree of exposure to chlorophenoxy herbicides has been associated with soft tissue sarcoma and non-Hodgkin lymphoma. Glyphosate is reported to be an irritant to the eyes and skin. Female mice treated with tridiphane, a dinitroaniline herbicide, exerted embryotoxicity during early pregnancy [35].

Paraquat and diquat belong to the bipyridyl group and are the most important herbicides reported to cause liver damage in animals and humans. The cytotoxicity of paraquat established by an increase in lipid peroxidation and complete oxidation of both NADPH and NADH occurs at a lower concentration than LC50 level. Furthermore, it also stimulates glucose oxidation at subtoxic doses [36]. The study of paraquat and diquat demonstrated inhibition of microsomal mixed function oxidase (MFO) and NADPH oxidation in lung and kidney microsomal preparations in a concentration- and concentration-dependent manner. It is documented that the degree of NADPH oxidation is an important biological event and is considered to be an important index in the inhibition of xenobiotic metabolism [37]. Its toxicity rating is 4, which places the probable human lethal dosage at 50–500 mg/kg. Paraquat accumulates slowly in the lungs by a special active process, which leads to inflammation, edema, and alveolitis and then develops progressive fibrosis. Paraquat may induce the pathogenesis of dopaminergic neurons via oxidative stress [38]. Symptoms observed after the oral injections are mainly hematemesis and bloody stools. A few days later, delayed toxicity manifests such as respiratory distress and progressive development of congestive haemorrhagic pulmonary edema associated with the widespread cellular proliferation. Death may occur after several weeks of ingestion. No successful method of treatment is available for such toxicity manifestations till today. Organic herbicides (amide compounds) are more toxic to animals. Haemolysis, methemoglobinemia, and immunotoxicity have occurred on experimental exposure [39].

3. Environmental and occupational-specific organic chemicals

3.1. Volatile organic compounds (VOCs)

All halogenated hydrocarbons and aromatic hydrocarbons are volatile solids and liquids and are also known to emit gases. The concentration of many VOCs is consistently higher indoors (ten times) than outdoors. Household products such as paints, varnishes, wax, disinfectants, air fresheners, cosmetics, degreasing and hobby products, pesticides, preservatives, fuels, aerosol sprays, cleansers, and dry clean clothing all have ingredients of organic chemicals and release organic compounds while using them. They can expose themselves, and even stored materials also release very high organic compounds. The elevated concentration can persist in the air for a longer time. Similarly, office equipment (copiers, printers, correction fluids, photographic solutions, graphics) also contains organic compounds. The most common toxic symptoms reported on short/long exposure to these diverse volatile organic chemicals are eye, skin, and throat irritation, headache, allergic skin reactions, emesis, nausea, etc. Excessive exposure may cause liver, kidney, CNS, and visual disorders [40].

Exposure to solvents and organic chemicals of a liquid nature is a major health risk in the workplace. Vapours of solvents accumulate in confined places and persist for a long time. Solvents enter the body by inhalation, swallowing, and skin contact. Solvents and their vapours and mist induce a variety of effects on human health, such as narcotic effects, fatigue, dizziness, and toxic manifestations. Higher levels of these solvents may cause unconsciousness. In addition, they are known to induce skin disorders and dermatitis. Some solvents even enter the blood circulation via the skin [41]. Furthermore, solvents also induce liver, kidney, heart, and blood vessels, bone marrow, and CNS and manifest toxic effects. Benzene, carbon disulfide (CS2), carbon tetrachloride (CCl4), and toluene solvents are excreted mainly via the kidney (urine), skin (sweat), and lungs by exhalation. Ventilation is the most important while handling and using solvents. Personal protective equipment (aprons, gloves, masks, and filters) should be considered and available [42–44].

Major national exposures to benzene occur through tobacco smoking. Low levels of exposure to benzene cause headaches, loss of appetite, gastrointestinal disturbances, and irritation of the nose and throat. Long-term benzene exposure in humans induces hematopoietic toxicities, of which the most alarming effects are agranulocytosis and leukemia (acute myelogenous leukemia). The other path of exposure is non-occupational type to benzene, which occurs due to combustion of fossil fuels, automobile gasoline (petrol pump workers and other oil refinery unit operations, regular vehicular traffic, and consumption of contaminated water) [45].

Other effects of long-term exposure to organic solvents associated with aromatic organic chemicals cause aplastic anaemia which results in erythropoiesis. Also causes respiratory effects (pulmonary inflammation, forced vital capacity, and forced expiratory volume) and thyroid functions (changes in TSH levels, T3, T4) by the toxic substances present solvents and air pollutants via influencing hormones of the hypothalamic-hypophyseal-axis [46–49]. Shoe factory workers who are exposed to organic solvents suffer from chronic airway impairment and non-bronchial hyper-

responsiveness [50]. The carbon monoxide emitted by internal combustion of engines from motor vehicles readily enters the blood through the respiratory system and binds over 200 times more firmly to Hb than oxygen to form carboxy haemoglobin which interferes with blood oxygen transport capability and finally results in hypoxia, consequently stimulating erythropoiesis. Such biochemical events induce the production of a greater number of RBCs and haemoglobin in circulating blood [51] (**Figure 5** and **Table 2**).

Table 2. Gaseous and Solvent based pollutants, their toxicity, and clinical symptoms.

Environmental gaseous pollutants	Nature of toxicity and clinical symptoms
Carbon monoxide	Restrict oxygen supply to tissue/organs via binding to haemoglobin, headache, vomiting, dizziness, seizures, and coma.
Chlorine, ammonia, sulphur dioxide, nitrogen oxide	Local irritant gas-corrosive action leading to cough, wheezing, pneumonia
Cyanide	Restricting cellular oxygen used via binding to cytochrome a3, producing headache, nausea, vomiting, convulsions, and coma
Hydrogen sulphide, ozone	Same as above. Formation of highly reactive free radicals, intermediate produces bronchitis, emphysema and pulmonary fibrosis.
Benzene	Targeting pluripotential bone marrow, stem cells as well as other stem cells, excessive bleeding. Produce bone marrow injury, aplastic anaemia, leucopenia, thrombocytopenia, leukemia, changes in blood vessels of antibodies, myeloma, lymphoma.
Toluene	CNS depression skin and eye irritation. It is fetotoxic.
carbon tetrachloride	Cytochrome P_{450} mediated activation of free radicals (oxidant), produces nausea, vomiting, stupor, convulsions, coma and death. Potent hepatotoxic.

Adopted from [17].

3.2. Polycyclic aromatic hydrocarbons (PAH)

Ubiquitous environmental pollutants are generated during incomplete combustion of organic materials, e.g., coal, oil, petrol, and wood. Some of them originate from open burning, petroleum spillage or coal deposits, and volcanic activities. Other sources of PAHs are the surface of lakes, streams, and oceans, coal gasification and liquefying plants, carbon black, coal tar pitch, coke, and aluminium production petroleum refineries, as well as motor vehicle exhaust. They are used as intermediates in pharmaceuticals, agricultural products, thermosetting plastics, lubricating materials, and other chemical industries [52]. They are lipophilic and hence readily absorbed from the GI tract of mammals and distributed to various tissues, but largely localized in body fat [52,53]. Workplace exposure to high levels of pollutants and mixtures containing PAHs causes irritation, inflammation, nausea, vomiting, and diarrhoea. Anthracene and benzopyrene elicit allergic reactions both in animals and humans. Chronic exposure to PAHs may cause decreased immunity, cataracts, nephrotic and hepatic damage, asthma-like symptoms, and pulmonary function abnormalities [54]. The basic biochemical underlying mechanisms involved the binding of reactive epoxides and dihydrodiols of PAH metabolites to cellular proteins and DNA. Such molecular events result in disruptions and cell damage, which lead to mutations, developmental malformations, tumors, and cancer. PAHs induce moderate to high acute toxicity in fish and birds [52].

Carbon tetrachloride is an important chemical used for multiple purposes. Generally, people are exposed to carbon tetrachloride (CCl4) through consumption of contaminated drinking water. Low-level inhalation produces irritation of the eyes; at higher levels, it produces nausea, vomiting, depression, incoordination, paresthesia, seizures, coma, and death [55].

Non-lethal acute exposure can occur in 7 hours to several days and induce liver and kidney damage. The liver damage is from enhanced lipid peroxidation, largely due to free radical intermediates, which cause intracellular and intramembranous lipid destruction. Also due to the formation of metabolite phosgene, which is also responsible for hepatotoxicity [56,57] (refer to **Table 1** and **Figure 5**).

3.3. Polychlorinated biphenyls (PCBs)

Polychlorinated biphenyls, polychlorinated dibenzo-p-dioxin (PCDDs), or die oxides, of which the most important is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). In addition, there is a larger group of dioxin-like compounds, including certain polychlorinated dibenzofurans (PCDFs) and co-planer biphenyls [58]. PCBs are oily liquids and solids and stable mixtures that are persistent to extreme temperatures and pressure. Industrial production of PCBs began in 1929; it is estimated that 1.2 to 1.5 million metric tons have been produced. They are used in many products, from lubricants to pesticides, paper adhesives, plastic paint, and flame retardants. Animal studies demonstrated that PCBs could affect the immune, endocrine, and reproductive systems, but such effects are not established in humans [59]. When PCBs are fed to animals in large doses over a shorter period (4 to 6 weeks), they can induce cancer. However, humans exposed to high levels for prolonged periods did not cause cancer. Therefore, they are classified as cancer-causing chemicals [60]. Numerous documented studies indicated environmental and occupational exposure to such chemicals, especially from building construction (refer to an earlier statement on chemicals and pollutants) and waste cycling sites (highest PCB contamination). PCB-contaminated working place, workers often suffer from different health problems such as psychological and neurobehavioral deficits, dementia, impaired immune systems, cardiovascular disorders, and cancer. Furthermore, accumulation can induce adverse effects on the reproductive system, which are manifested in offspring. Despite a ban on their use in the 1970s, their resistance to chemical and thermal degradation results in bioaccumulation in marine animals/organisms and humans. Hence PCBs continue to be a serious problem to the environment and humans at large, and the same has been included in EDS. They have been reported to induce in humans predominantly developmental toxicity, immunotoxicity, metabolic diseases such as type-2 diabetes, thyroid disorders, and impairment of female and male reproductive health [61].

BPA affects the liver-spleen axis, increases androgen activity, and causes low-grade inflammation in the development of polycystic ovarian syndrome (PCOS) (refer to **Figure 8**).

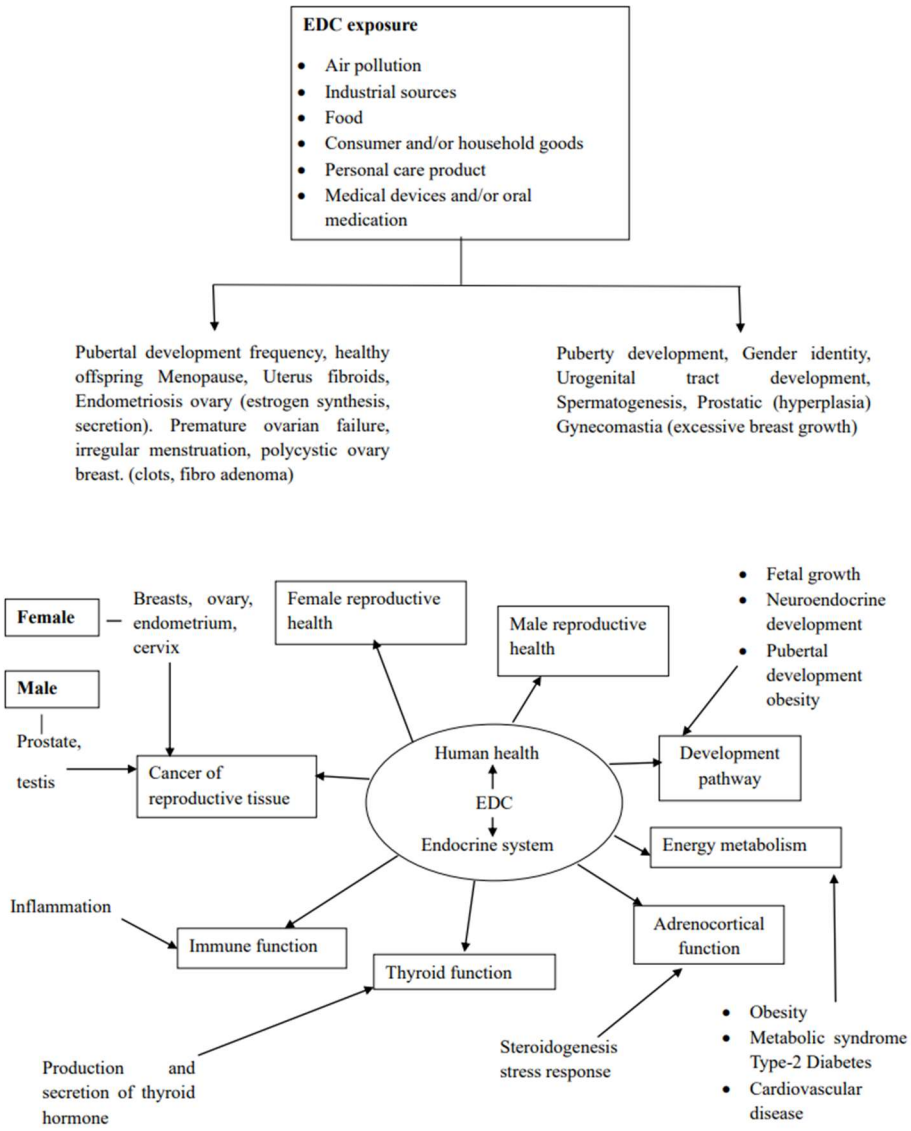

Figure 8. The schematic representation of effects of EDCs (endocrine-disrupting chemicals) on Human Health.

4. Antidotes for chemical and metal poisoning

Some selective chemicals for insecticide acute intoxications are available only in a small number. Some of the chemical antidotes are outlined below:

Atropine is a muscarinic receptor antagonist; hence, it has been used to block the access of increased acetylcholine to muscarinic receptors. It is an important antidote for insecticide intoxication in organophosphates and carbamates. However, the dose of atropine used depends upon the state of intoxication. The second dote is pralidoxime, which is less effective, and its doses used vary very much [62,63].

Penicillamine (D-b, b-dimethyl cysteine)

Penicillamine is an effective chelator of copper, mercury, zinc, and lead and thereby accelerates the excretion of these metals in urine. N-acetylpenicillamine is more effective than penicillamine in protecting, especially from the toxic effects of mercury. Animal studies have demonstrated polycarboxylic acid chelators ($CaNa_2$

EDTA) and calcium trisodium diethylenetriaminepentaacetate EDTA. (Pentate calcium trisodium; Ca-DTPA) can be effective when administered immediately after exposure to cadmium. Dimercaprol and penicillamine are used to treat chronic exposure to arsenic. In methyl mercury poisoning, L-cysteine can be infused into the arterial blood, entering the dialyser to convert methylmercury into diffusible form. This method has been found to be effective in humans [64]. In acute cyanide poisoning, antidotes such as sodium nitrate and sodium thiosulphate are reported to be very effective by intramuscular route in various clinically relevant animal models [65].

Enhancement of detoxification of toxic agents: Some toxic substances are hepatotoxic and metabolised by the liver via cytochrome P450. In such cases, treatment with N-acetylcysteine shall serve as a substitute for glutathione. This will bind and inactivate the reactive metabolite and minimize the hepatic toxicity of the toxicant [66]. Chelators are known to form covalent bonds specifically with cationic metals. The chelators form a metal complex and are then excreted in urine, which may enhance excretion of the heavy metals. However, chelators are not specific to heavy and essential metals, and some of the chelators induce serious adverse effects. Hence, physicians need to outweigh the risks associated with chelation therapy. Dimercaprol is used to chelate mercury and arsenic along with calcium disodium edetate to treat lead intoxication. It is to be administered intramuscularly, as it is not effective by oral route. Since dimercaprol is known to elevate blood pressure and heart rate, physicians should be careful when it is used, especially in hypertensive people [67].

Succimer, a derivative of dimercaprol, is effective by oral route and its lack of effects on blood pressure and heart rate. Today, succimer is approved for the treatment of lead toxicity. Further, it is also found effective in the chelation of other heavy metals. Calcium disodium edetate is used for lead and other heavy metals intoxication intravenous or intramuscularly only. However, it is known to cause kidney damage, but the damage is reversible after the stoppage of treatment [22,68].

5. Summary and conclusion

In the present review, we try to present the impact of chemicals and pollutants on humans, animals, and environmental health. We explained and discussed various pollutants, such as industrial chemicals, pesticides, heavy metals, and air pollutants. Also referred to are the sources, pathways of exposure, and toxic events on physiological and organ functions of the body. These pollutants elicit a large spectrum of toxic effects on CNS, CVS, respiratory system, liver, kidney, etc. by interfering with or impairing biochemical and metabolic pathways, viz., oxidative, mitochondrial electron transfer system, enzyme inhibition, voltage-gated channel(s). Local skin, eye, and mucus membrane irritation are produced by denaturation of macromolecules and/or cleavage of chemical bonds. Clinical symptoms are diverse and related to the specific organ system and the type and nature of chemicals or toxicants. The genetic effects via mutational or larger damage of genetic apparatus led to different types of cancer and also reproduction and developmental-related effects on offspring.

Overall, our review underscores the urgent need for proactive approaches to address the impact of chemicals and pollutants on human, animal, and environmental health. A concerted research work needs to be pursued to develop new generations of antidots and antagonists and bio-remedial measures for minimizing air and water pollution. Exploring isolation of new microbes whose metabolites and enzymes may be helpful in removing chemicals and other harmful pollutants from the environment in eco-friendly ways.

Furthermore, a better understanding of the cellular and molecular mechanism(s) responsible for the developmental effects of air pollution on human body and organ systems is also essential because it may lead to the development of specific therapeutic interventions. It is needless to say that any efforts/approaches towards diminishing emissions and thereby improving air quality would be warranted.

Conflict of interest: The authors declare no conflict of interest.

References

1. Arihan O, Arihan SK, Touwaide A. The Case Against Socrates and His Execution. In: Wexler P (editor). Toxicology in Antiquity. Academic Press; 2019. pp. 117-129. doi: 10.1016/b978-0-12-815339-0.00007-x
2. Luch A. Molecular, Clinical and Environmental Toxicology. Birkhäuser Basel; 2009. doi: 10.1007/978-3-7643-8336-7
3. Manohar Pr. Toxicity of Ayurveda medicines and safety concerns: The need to revive the branch of toxicology in Ayurveda. Ancient Science of Life. 2014; 34(1): 1. doi: 10.4103/0257-7941.150761
4. Guggenheim KY. Paracelsus and the Science of Nutrition in the Renaissance. The Journal of Nutrition. 1993; 123(7): 1189-1194. doi: 10.1093/jn/123.7.1189
5. Franklin M. De Re Metallica: The treatise of Georgious Agricola revisited. Annals RCPSC. 1994; 27(3): 163-166.
6. Kowalska M, Steplewski Z. Alice Hamilton (1869-1970): a pioneer of occupational medicine and public health. Med Pr. 1999; 50(1): 67-73.
7. Rootwelt K. Henri Beckquerel's discovery of radioactivity, and history of nuclear medicine—100 years in the shadow or on the shoulder of Röntgen. Tidsskr Nor Laegeforen. 1996;116(30): 3625-3629.
8. Hulla JE, Kinter LB, Kelman B. A Standard of Knowledge for the Professional Practice of Toxicology. Environmental Health Perspectives. 2015; 123(8): 743-748. doi: 10.1289/ehp.1408643
9. Hayes AN, Touwaide A. Toxicology, The History of. In: Wexler P (editor). Encyclopedia of Toxicology. Academic Press; 2014. pp. 731-745. doi: 10.1016/b978-0-12-386454-3.00673-4
10. Gundert-Remy U, Barth H, Bürkle A, et al. Toxicology: a discipline in need of academic anchoring—the point of view of the German Society of Toxicology. Archives of Toxicology. 2015; 89(10): 1881-1893. doi: 10.1007/s00204-015-1577-7
11. Blesa J, Phani S, Jackson-Lewis V, et al. Classic and New Animal Models of Parkinson's Disease. Journal of Biomedicine and Biotechnology. 2012; 2012: 1-10. doi: 10.1155/2012/845618
12. Anadón A. Perspectives in Veterinary Pharmacology and Toxicology. Frontiers in Veterinary Science. 2016; 3. doi: 10.3389/fvets.2016.00082
13. Krewski D, Acosta D, Andersen M, et al. Toxicity Testing in the 21st Century: A Vision and a Strategy. Journal of Toxicology and Environmental Health, Part B. 2010; 13(2-4): 51-138. doi: 10.1080/10937404.2010.483176
14. Danziger J. Vitamin K-dependent Proteins, Warfarin, and Vascular Calcification. Clinical Journal of the American Society of Nephrology. 2008; 3(5): 1504-1510. doi: 10.2215/cjn.00770208
15. Ware GW. Reviews of Environmental Contamination and Toxicology. Springer New York; 1991. doi: 10.1007/978-1-4612-3080-9
16. Shetty SS, Deepthi D, Harshitha S, et al. Environmental pollutants and their effects on human health. Heliyon. 2023; 9(9): e19496. doi: 10.1016/j.heliyon.2023.e19496
17. Naik SR. Nirali Prakashan Topics in Toxicology. 2022; 127-168.

18. Litwack G, Ketterer B, Arias IM. Ligandin: a Hepatic Protein which Binds Steroids, Bilirubin, Carcinogens and a Number of Exogenous Organic Anions. Nature. 1971; 234(5330): 466-467. doi: 10.1038/234466a0
19. Kamp DW, Graceffa P, Pryor WA, et al. The role of free radicals in asbestos-induced diseases. Free Radical Biology and Medicine. 1992; 12(4): 293-315.
20. Fujimura N. Pathology and pathophysiology of pneumoconiosis. Current Opinion in Pulmonary Medicine. 2000; 6(2): 140-144. doi: 10.1097/00063198-200003000-00010
21. Thada PK, Ata F, Ali M, et al. Clinical characteristics and outcomes of patients with Herpes Zoster Infection in the context of SARS-CoV-2 infection. A case report and a systematic review. Qatar Medical Journal. 2022; 3. doi: 10.5339/qmj.2022.41
22. Whalen K. Lippincott's Illustrated Reviews: Pharmacoloy, 4th ed. Lippincott Wiliams and Wilkins; 2009.
23. Robb EL, Regina AC, Baker MB. Organophosphate Toxicity. StatPearls Publishing; 2023.
24. Jokanović M. Neurotoxic effects of organophosphorus pesticides and possible association with neurodegenerative diseases in man: A review. Toxicology. 2018; 410: 125-131. doi: 10.1016/j.tox.2018.09.009
25. Naughton SX, Terry AV. Neurotoxicity in acute and repeated organophosphate exposure. Toxicology. 2018; 408: 101-112. doi: 10.1016/j.tox.2018.08.011
26. Sultatos LG. Mammalian toxicology of organophosphorus pesticides. Journal of Toxicology and Environmental Health. 1994; 43(3): 271-289. doi: 10.1080/15287399409531921
27. Mitra A, Maitra SK. Reproductive Toxicity of Organophosphate Pesticides. Available online: https://www.remedypublications.com/open-access/reproductive-toxicity-of-organophosphate-pesticides-1072.pdf (accessed on 12 January 2023).
28. Silberman J, Taylo A. Carbamate toxicity. StatPearls Publishing; 2024.
29. Dias E, Garcia e Costa F, Morais S, et al. A Review on the Assessment of the Potential Adverse Health Impacts of Carbamate Pesticides. In: Claborn D (editor). Topics in Public Health. IntechOpen; 2015. pp. 197-214. doi: 10.5772/59613
30. Morais S, Dias E, Pereira ML. Carbamates: Human Exposure and Health Effects. Available online: http://www.alanwood.net/pesticides (accessed on 12 February 2024).
31. Ramchandra AM, Victor PJ. Pyrethroid Poisoning. Indian Journal of Critical Care Medicine. 2019; 23(S4). doi: 10.5005/jp-journals-10071-23304
32. Hołyńska-Iwan I, Szewczyk-Golec K. Pyrethroids: How They Affect Human and Animal Health? Medicina. 2020; 56(11): 582. doi: 10.3390/medicina56110582
33. Lupescu A, Jilani K, Zbidah M, et al. Induction of apoptotic erythrocyte death by rotenone. Toxicology. 2012; 300(3): 132-137. doi: 10.1016/j.tox.2012.06.007
34. Duke SO. Overview of herbicide mechanisms of action. Environmental Health Perspectives. 1990; 87: 263-271. doi: 10.1289/ehp.9087263
35. De Coster S, van Larebeke N. Endocrine-Disrupting Chemicals: Associated Disorders and Mechanisms of Action. Journal of Environmental and Public Health. 2012; 2012: 1-52. doi: 10.1155/2012/713696
36. Magalhães N, Carvalho F, Dinis-Oliveira R. Human and experimental toxicology of diquat poisoning: Toxicokinetics, mechanisms of toxicity, clinical features, and treatment. Human & Experimental Toxicology. 2018; 37(11): 1131-1160. doi: 10.1177/0960327118765330
37. Aldrich TK, Fisher AB, Forman HJ. Paraquat inhibits mixed-function oxidation by rat lung. Journal of Applied Physiology. 1983; 54(4): 1089-1093. doi: 10.1152/jappl.1983.54.4.1089
38. McCormack AL, Atienza JG, Johnston LC, et al. Role of oxidative stress in paraquat-induced dopaminergic cell degeneration. Journal of Neurochemistry. 2005; 93(4): 1030-1037. doi: 10.1111/j.1471-4159.2005.03088.x
39. Venkatesh HN, Jeru Manoj M, Ghosh D, et al. Environmental pollutants leading to carcinogenesis: process of natural selection of human cells due to chronic inflammation and sustained stress environment. International Journal of Environmental Science and Technology. 2015; 12(7): 2415-2426. doi: 10.1007/s13762-015-0790-5
40. US EPA. Technical overview of volatile organic compounds. Available online: https://www.epa.gov/indoor-air-quality-iaq/technical-overview-volatile-organic-compounds (accessed on 23 January 2023).
41. Verma N, Pandit S, Gupta PK, et al. Occupational health hazards and wide spectrum of genetic damage by the organic solvent fumes at the workplace: A critical appraisal. Environmental Science and Pollution Research. 2022; 29(21): 30954-30966. doi: 10.1007/s11356-022-18889-6

42. Dalvi RR. Mechanism of the neurotoxic and hepatotoxic effects of carbon disulfide. Drug Metabolism and Drug Interactions. 1988; 6(3-4): 275-284. doi: 10.1515/dmdi.1988.6.3-4.275
43. Cruz SL, Rivera-García MT, Woodward JJ. Review of Toluene Actions: Clinical Evidence, Animal Studies, and Molecular Targets. Journal of Drug and Alcohol Research. 2014; 3: 1-8. doi: 10.4303/jdar/235840
44. Weber LWD, Boll M, Stampfl A. Hepatotoxicity and Mechanism of Action of Haloalkanes: Carbon Tetrachloride as a Toxicological Model. Critical Reviews in Toxicology. 2003; 33(2): 105-136. doi: 10.1080/713611034
45. Yardley-Jones A, Anderson D, Parke DV. The toxicity of benzene and its metabolism and molecular pathology in human risk assessment. Occupational and Environmental Medicine. 1991; 48(7): 437-444. doi: 10.1136/oem.48.7.437
46. Uzma N, Khaja Mohinuddin Salar B, Kumar B, et al. Impact of Organic Solvents and Environmental Pollutants on the Physiological Function in Petrol Filling Workers. International Journal of Environmental Research and Public Health. 2008; 5(3): 139-146. doi: 10.3390/ijerph5030139
47. Cabello-López A, Chávez-Gómez NL, Torres-Valenzuela A, et al. Audiometric findings of printing press workers exposed to noise and organic solvents. International Journal of Audiology. 2020; 60(1): 8-15. doi: 10.1080/14992027.2020.1795735
48. Lan Q, Zhang L, Li G, et al. Hematotoxicity in Workers Exposed to Low Levels of Benzene. Science. 2004; 306(5702): 1774-1776. doi: 10.1126/science.1102443
49. Lees-Haley P. The implications of limitations in hydrocarbon research for neuropsychological assessment. Archives of Clinical Neuropsychology. 1997; 12(3): 207-222. doi: 10.1016/S0887-6177(96)00035-2.
50. Paggiaro P, Lastrucci L, Pede CD, et al. Respiratory pathology caused by exposure to solvents in the shoe industry: description of 3 clinical cases. Giornale Italiano di Medicina del Lavoro. 1985; 7(4): 149-152.
51. Blumenthal I. Carbon Monoxide Poisoning. Journal of the Royal Society of Medicine. 2001; 94(6): 270-272. doi: 10.1177/014107680109400604
52. Abdel-Shafy HI, Mansour MSM. A review on polycyclic aromatic hydrocarbons: Source, environmental impact, effect on human health and remediation. Egyptian Journal of Petroleum. 2016; 25(1): 107-123. doi: 10.1016/j.ejpe.2015.03.011
53. Pathiratne KAS, De Silva OCP, Hehemann D, et al. Occurrence and Distribution of Polycyclic Aromatic Hydrocarbons (PAHs) in Bolgoda and Beira Lakes, Sri Lanka. Bulletin of Environmental Contamination and Toxicology. 2007; 79(2): 135-140. doi: 10.1007/s00128-007-9092-z
54. Yu Y, Jin H, Lu Q. Effect of polycyclic aromatic hydrocarbons on immunity. Journal of Translational Autoimmunity. 2022; 5: 100177. doi: 10.1016/j.jtauto.2022.100177
55. Case study in environmental Medicine: Carbon tetrachloride toxicity. Available online: https://www.atsdr.cdc.gov/emes/health_professionals/csemcarbon.html (accessed on 23 February 2024).
56. Boll M, Weber LWD, Becker E, et al. Pathogenesis of Carbon Tetrachloride-Induced Hepatocyte Injury Bioactivation of CCl4 by Cytochrome P450 and Effects on Lipid Homeostasis. Zeitschrift für Naturforschung C. 2001; 56(1-2): 111-121. doi: 10.1515/znc-2001-1-218
57. Stoyanovsky DA, Cederbaum AI. Metabolism of Carbon Tetrachloride to Trichloromethyl Radical: An ESR and HPLC-EC Study. Chemical Research in Toxicology. 1999; 12(8): 730-736. doi: 10.1021/tx9900371
58. Safe S. Polychlorinated Biphenyls (PCBs), Dibenzo-p-Dioxins (PCDDs), Dibenzofurans (PCDFs), and Related Compounds: Environmental and Mechanistic Considerations Which Support the Development of Toxic Equivalency Factors (TEFs). Critical Reviews in Toxicology. 1990; 21(1): 51-88. doi: 10.3109/10408449009089873
59. Johnson GW, Quensen, III JF, et al. Polychlorinated Biphenyls. Environmental Forensics. 1964: 187-225. doi: 10.1016/b978-012507751-4/50032-x
60. Khidkhan K, Mizukawa H, Ikenaka Y, et al. Biological effects related to exposure to polychlorinated biphenyl (PCB) and decabromodiphenyl ether (BDE-209) on cats. PLOS ONE. 2023; 18(1): e0277689. doi: 10.1371/journal.pone.0277689
61. Montano L, Pironti C, Pinto G, et al. Polychlorinated Biphenyls (PCBs) in the Environment: Occupational and Exposure Events, Effects on Human Health and Fertility. Toxics. 2022; 10(7): 365. doi: 10.3390/toxics10070365
62. Eddleston M, Buckley NA, Eyer P, et al. Management of acute organophosphorus pesticide poisoning. Lancet. 2008; 371(9612): 597-607. doi:10.1016/S0140-6736(07)61202-1
63. Freeman G, Epstein MA. Therapeutic Factors in Survival after Lethal Cholinesterase Inhibition by Phosphorus Insecticides. New England Journal of Medicine. 1955; 253(7): 266-271. doi: 10.1056/nejm195508182530702
64. Randa D, Bjorn K. The Pharmacological Basis of Therapeutics, 13th ed. McGraw Hill; 2018.

65. Bebarta VS, Brittain M, Chan A, et al. Sodium Nitrite and Sodium Thiosulfate Are Effective Against Acute Cyanide Poisoning When Administered by Intramuscular Injection. Annals of Emergency Medicine. 2017; 69(6): 718-725. doi: 10.1016/j.annemergmed.2016.09.034
66. Vairetti M, Di Pasqua LG, Cagna M, et al. Changes in Glutathione Content in Liver Diseases: An Update. Antioxidants. 2021; 10(3): 364. doi: 10.3390/antiox10030364
67. Flora SJS, Pachauri V. Chelation in Metal Intoxication. International Journal of Environmental Research and Public Health. 2010; 7(7): 2745-2788. doi: 10.3390/ijerph7072745
68. Mann KV, Travers JD. Succimer, an oral lead chelator. Clinical Pharmacist. 1991; 10(12): 914-922.