Chapter

Health Impacts of Air Pollution

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Abstract

Urban air pollution has become a salient environmental issue in many Asian countries due to their rapid industrial development, urbanization, and motorization. Human-induced air pollution has been and continues to be considered a major environmental and public health issue. Its severity lies in the fact that high levels of pollutants are produced in environments where damage to human to concentration, duration of exposure health and welfare is more likely. This potential is what makes anthropogenic air pollution an important concern. Extreme air pollution episodes were reported for the Meuse Valley, Belgium, in 1930; Donora, PA, and the Monongehela River Valley in 1948; and London in 1952. These episodes are significant in that they provided solid scientific documentation that exposure to elevated ambient pollutant levels can cause acute illness and even death. The most devastating events contributed to important efforts to control ambient air pollution. The International Agency for Research on Cancer (IARC) assessment concluded that outdoor air pollution is carcinogenic to humans, with the particulate matter component of air pollution mostly associated with increasing cancer incidence especially lung cancer. Pollutant effects typically occur in some target organs. These can be straightforward; i.e. pollutants come into close contact with the affected organ.. Such is the case for eye and respiratory irritation. Effects may be indirect. For example, Pollutants can enter the bloodstream from the lungs or gastrointestinal system through the respiratory route. Effects may then be distant from the immediate organ of contact. A target organ can have no immediate and intimate contact with atmospheric contaminants.. The primary organs or target organs are the eyes and the respiratory and cardiovascular systems.

Keywords: Urban Air Pollution, Human Health Effects, Respiratory and Cardiovascular Disease

1. Introduction

Air pollution is the presence of unwanted substances in the air in sufficient quantities to produce adverse effects. Undesirable substances can affect human health, vegetation, human property or the global environment including creating esthetic slurs in the form of brown or foggy air or offensive odors. Outdoor or ambient air pollution has been recognized as one of the major concerns that have high potential for its deleterious effects on health. Increased urbanization, human activities and changing urban setting in the country have resulted in elevated air pollution and the occurrence of urban heat islands.

The classification of air pollutants is based mainly on the sources producing pollution. There are four main air pollution sources namely major, area, mobile and natural sources. Major sources include the emissions from power stations,

refineries, petrochemicals, manure industries, metalworking and other industrial facilities, and municipal incineration. Indoor sources include household cleaning operations, printing facilities and gas stations. Mobile sources include motor vehicles, cars, rail lines, airways and others. Last but not least, natural sources include physical disasters such as forest fires, volcanic eruptions, dust storms, and agricultural burning [1].

Particulate matter air pollution less than 2.5 μm has received great international attention due to its diverse contribution to the global burden of disease. Study done by Brauer et al [2] mentioned that majority of the planet still resides in areas where the World Health Organization Air Quality Guidelines of 10 $\mu g/m^3$ (annual) and 25 $\mu g/m^3$ (24hrs) is exceeded. Ground level measurement of $PM_{2.5}$ or lower are still limited in most of the places in the world. Therefore, studies are required to evaluate and provide insight in high risk as to the exposure and risk as many of the form of air pollution are beyond the control of individual and require policy at national and international levels.

Studies over the past two decades have assessed the relationship between size distribution of particulate matter and trace metal concentrations in urban areas. In the past, numerous researchers in Europe have carried out experiments to investigate particle-based metal particle size distribution [3–5].

The inorganic components constitute a small portion by mass of the particulates; however, it contains some trace elements such as As, Cd, Co, Cr, Ni, Pb and Se which are human or animal carcinogens even in trace amounts [6, 7]. The high level of Pb can induce severe neurological and hematologic effects on the unprotected population particularly in children, whereas both Cd and Ni are known to cause cancer-causing effects on humans by inhalation. Workplace exposure to Cd is an important risk factor for chronic pulmonary diseases [8]. Cr (VI) have been recognized to cause toxicity and carcinogenicity in the bronchial tree [9, 10]. Exposure to Mn is associated with an increase in neurotoxic deficiencies [11]. Elevated levels of Cu may cause respiratory irritation [10, 12].

PAHs have attracted a substantial amount of attention due to their persistent, bio-accumulative, carcinogenic and mutagenic properties related to health problem such as cataracts, kidney and liver damage, and jaundice [13]. The maximum concentrations of airborne PAHs are typically occur in the urban environment due to increased vehicle traffic and the spread of air pollutants. Given the high urban population density, the risk from human exposure to airborne PAHs in highest [14].

Global Burden of Disease Study (GBD) 2015 indicated that ambient particulate matter pollution accounted for 4.2 million deaths and 103 million healthy life-years lost in 2015, representing 7.6% of total global mortality and making it the fifth-ranked global risk factor.

2. Particulate matter

The term particulate matter (PM) or atmospheric aerosols is a mixture of solid particles and/or liquid droplet that may vary in concentration, composition and also size distribution. Aerosols can be defined as suspensions of solid or liquid in a gas. Therefore, aerosols include both the particle and the gas in which they are suspended. Although aerosol and particle are different, they are often used interchangeably throughout the literature to refer to the particle only.

Aerosol particulates in the atmosphere come from a wide mixture of natural and anthropogenic sources. Primary particulates are released directly as liquids or solids from sources such as biomass combustion, incomplete fossil fuel combustion, volcanic eruptions and suspension of road, ground and mineral dust, sea salt

and biological materials caused by wind or traffic. Secondary particulates, on the other hand, are formed by the conversion of gas into particulates in the atmosphere. Primary gaseous species might undergo chemical reaction to produce low-volatility products. Then, these products partitions to the particulate phase, i.e. new particles are formed by nucleation and condensation of gaseous precursors [15].

Small aerosol particles predominantly contribute to number concentrations; however they only play a smaller role for the volume distribution. On the other hand, larger particles play a role for the volume distribution but do not contribute substantially to the number concentration [16]. Particles are conventionally divided into different size of fractions; based on the physical and chemical processes involved in the particle formation and growth. The different size of fractions is generally called "modes" [17].

The nucleation (or ultrafine) mode resides in the range below 0.02 μm of particle diameter and usually presents its maximum number-density around 5-15 nm of particle diameter. H_2SO_4, NH_3 and H_2O are examples of precursor gases to form new particles by homogenous nucleation in the ambient atmosphere. However, due to the condensation by other condensing gases, organic and inorganic components, the newly formed particles rapidly grow bigger. These particles have hours lifetime in the atmosphere as they rapidly coagulate with larger particles or grow into larger sizes due to condensation. Classical nucleation theory shows that the nucleation highly depends on the concentrations of the gaseous precursors, relative humidity and temperature. In particular, the nucleation is favored by decreases in the temperature and/or increases in the relative humidity [18].

Aitken mode particles range from 0.02 to 0.1 μm and originate either from primary particles, natural and anthropogenic, or by growth of nucleation mode particles. Secondary Aitken mode particles are likely to be formed by coagulation of ultrafine particles, by condensation and by liquid phase reactions. Combustion process is a primary source that has very large emissions of Aitken mode particles. Aitken mode particles are present at relatively stable concentration in the atmosphere; indicating a long residence time of Aitken particles at ambient atmosphere. The accumulation mode covers the range between 0.1 and up to 1 μm. Aitken mode particles have a tendency to grow to accumulation mode particles due to coagulation and liquid phase reactions occurring in cloud droplets. Hoppel et al. [19] stated that the mass transfer by condensation and/or nucleation/coagulation is not enough to cause any significant change in particles size compared with the observed growth.

3. Health effects of particulate matter

Particulate pollution includes particulate matter with a diameter of 10 micrometers (μm) or less, referred to as PM10, and extremely fine particulate matter with a diameter of 2.5 micrometers (μm) or less. Particles contain tiny liquid or solid droplets which may be inhaled and cause adverse health effects. PM10 when inhale can enter the lungs and the bloodstream. Fine particulate matter, PM2.5, represents a greater health risk (**Table 1**) [1].

There is consistent evidence for the relationship between atmospheric particulate matter and public health outcomes for adverse health effects [20]. The range of effects is extensive, including effects on the respiratory and cardiovascular systems that extend to children and adults in the general population [20–22], but also including lung cancer [21, 22].

The risk for various outcomes has been shown to increase with exposure and there is little evidence for a threshold below which no adverse health effects would be anticipated [20]. In one WHO report [23, 24], the importance to public health

Particle size	Penetration degree in human respiratory system
11 μm	Passage into nostrils and upper respiratory tract
7–11 μm	Passage into nasal cavity
4.7–7 μm	Passage into larynx
3.3–4.7 μm	Passage into trachea bronchial area
2.1–3.3 μm	Secondary bronchial area passage
1.1–2.1 μm	Terminal bronchial area passage
0.65–1.1 μm	Bronchioles penetrability
0.43–0.65 μm	Alveolar penetrability

Table 1.
Penetrability according to particle size.

of the long-term effects of particulate matter exposure outweighs the importance of short-term effects. The short-term effects of exposure have been recognized in many time series studies, and short-term (24-hour) and long-term (yearly average) guidelines are suggested [24]. PM2.5 and PM10 are recommended for assessment and control as fine and coarse particles have diverse sources and can have multiple effects. With respect to ultrafine particulate matter, there is insufficient information to support a quantitative assessment of the potential health effects of exposure [25].

Particle size and surface area are important characteristics from a toxicological point of view. Pope & Dockery [21]; Schlesinger et al. [22] recently review the current understanding of particulate matter, its size and its health effects.

Study done by Pope & Dockery [21]; Schlesinger et al. [22] proved that the relationship between fine particulate matter, PM2.5, and most health effects is greater than between PM10 and health effects. Ultrafine particulate matter contributes little to the mass concentration of particulate matter; however, it affects the surface in large numbers and is of interest to toxicological studies [22]. Study done by Nel et al. [26] concluded that as the size of a particle decrease, its surface area increases, thus allowing a greater proportion of its atoms or molecules to be displayed on the surface. Furthermore, particle size is crucial for penetration and deposition efficiency into human lungs, since ultrafine particles ability to penetrate the membranes of the respiratory tract and enter the blood circulation.

Particulate organic matter in ambient air is a complex mixture of chemicals, i.e. polycyclic aromatic hydrocarbons (PAHs). The International Agency for Research on Cancer (IARC) classified some PAHs, i.e. benzo[a]pyrene, as human carcinogens [27]. Another group that has gained interest in recent years is metals. Schlesinger et al. [22] have summarized current knowledge regarding trace metals and their health impact. The assessment of the risk associated with exposure to PAHs is still a challenge. PAHs present in ambient air mainly as a complex mixture and the interactions among components may lead to additively, synergistic or antagonistic effects. In addition, a study conducted by Topinka et al. [28] shows that organic matter extracted from $PM_{2.5}$ are likely to induce DNA adducts and oxidative DNA damage in in-vitro cell-free assay experiments.

The toxicological findings strongly suggest that transition metals such as V, Cr, Mn, Fe, Ni, Cu and Zn are components in PM with toxic capability based on their potential for oxidative activity and the production of reactive oxygen species [22]. Soil dust is composed of crust elements (Si, Ca, Al and Mg) and is existent in ambient PM2.5, but bigger segments are present in coarse mode.

Windblown soils, dust, at least in rural areas, are not considered a significant health risk however natural crusty materials may be contaminated with road dust generated by moving vehicles. Contaminants may contain a range of constituents, including PAHs and various metals that can alter the toxicology of crust particles.

Several studies indicated that particles produced from burning of biomass for domestic heating have increased and become one of the major sources of $PM_{2.5}$ in Europe and other parts of the world [29, 30]. Incomplete combustion of biomass produces a multitude of different organic species as well as trace metals. In a assessment of some epidemiological studies carried out in areas where wood smoke is prevalent. Boman et al. [31] concluded that particulate matter from wood smoke appears to be at least as deleterious as particulate matter from other sources.

In 2016, air pollution was ranked sixth in terms of global burden of disease and that 7.5% of all deaths were attributable to ambient air pollution (4.1 million deaths) [32]. Globally, ambient air pollution is responsible for about 27.5% of all lower respiratory infection deaths and 27% of all deaths due to chronic obstructive pulmonary disease [32]. The World Health Organization (WHO) estimates that about 26% of deaths due to ambient air pollution in 2012 occurred in South East Asia [33].

South East Asia population is not only exposed to local sources of air pollutants (for example, industrial and traffic related air pollutants) but it also exposed to regional smoke from the seasonal forest fires (or 'haze') that occur in Sumatra and Kalimantan. The fine particulate pollution from these forest and peat fires can reach hazardous levels for extended periods of time, posing severe health risks to millions of people across Malaysia. These forest fires are also a major cause of transboundary air pollution throughout South East Asia. The forest fires occur in the dry season, (known as the South-west monsoon season, April to September) and tend to be more severe in the El Nino years. During this monsoon season, the prevailing wind direction is south westerly, and the smoke from forest fires in Sumatra are commonly transported towards Malaysia. The most severe haze episode from these forest fires occurred in 1997. Since then, there have been severe haze episodes from forest fires every two to three years, for example, in 2005, 2006, 2009, 2010, 2011, 2012, 2013, 2014 and 2015 [34]. The last major transboundary haze episode occurring in 2015 has been estimated to have resulted in 91,600 excess deaths in Indonesia, 6,500 deaths in Malaysia and 2,200 deaths in Singapore [35].

During the haze episodes, the main air pollutant of concern is PM2.5. The health impacts of PM2.5 are related to concentration, duration of exposure and individual susceptibility. PM2.5 pollution is causally related to cardiovascular (myocardial infarction, hypertension, heart failure, arrhythmias) and respiratory disease (chronic obstructive pulmonary disease and lung cancer [32]. Long-term exposure to PM2.5 has also been linked to adverse birth outcomes, childhood respiratory disease and possibly neurodevelopment and cognitive function, and diabetes [36, 37]. PM2.5 is also associated with systemic inflammation with associated increases in acute phase proteins such as C-reactive protein and fibrinogen [38]. These biomarkers have been consistently linked to subsequent cardiovascular disease and death [37].

4. Trace metals

Toxic heavy metals are one of the major hazardous that affects us today. Atmospheric deposition of toxic heavy metals has stimulated profound research all over the world due to effects on living organisms. Toxic metals like lead (Pb), cadmium (Cd), arsenic (As) and chromium (Cr) can essentially attack specific areas in the human body upon exposure [39]. Their dispersal and transport through

Natural sources	% released into the atmosphere
Biogenic	• 50% Hg, Mo
	• 30–50% As, Cd, Cu, Mn, Pb and Zn
Volcanic Gas	• 40–50% of Cd and Hg
	• 20–40% of the As, Cr, Cu, Ni, Pb, and Sb
Sea aerosols	• 10% various heavy metals

Table 2.
Share of releases of trace metals from natural sources.

the atmosphere can be worsened by anthropogenic and natural phenomena. High levels of these trace metals in air can cause ecotoxic effects on plants, animal as well as humans.

In the air, trace metals are combined with sediment dust and respirable airborne particulate matter [40]. They can be released from air through precipitation or direct dry deposits in various environmental compartments near or away from their source. An in-depth investigation of the levels of trace metals in the atmosphere is therefore both essential and fundamental to ensure a more secure environment.

Naturally trace metals can be in the form of vapor ions dissolved in water and in the form of minerals or salts in rock, soil and sand. Pacyna [41], stated biogenic sources represent over half of the Hg and Mo emitted to the atmosphere, and approximately 30–50% of the As, Cd, Cu, Mn, Pb and Zn freed (**Table 2**). Soils can be responsible for substantial releases of trace metals to the atmosphere.

Trace metals are not only brought into the environment from natural sources, they are also introduced through human activities [42]. Waste incineration sites, agricultural runoff, vehicle emissions and urban effluents release trace metals to the environment [43]. Industrial sources can pose a significant threat, particularly in densely populated areas. Combustion of fossil fuels from stationary sources can be important in dispersing trace metals into the atmosphere [44].

5. Metal toxicity

A toxic material is a substance that has an adverse effect on health. Many chemicals could be classed as toxic, but some are more toxic than others. When metals bind to the sulfhydryl groups in proteins, they may move essential elements, interrupt function or obstruct the activity of the sulfhydryl group leading to toxicity [45]. Trace metals like mercury, lead, arsenic, zinc, copper, gold, cobalt and cadmium can be highly toxic and easily accessed by living organisms. Plants may exhibit different signs of toxicity according to type of metal and plant. Generally, in humans, heavy metal toxicity may range from reproductive defects to lung damage [46, 47] while in plants, they may cause damage to root systems, disrupt the proper functioning of the stomata and inhibit growth [48, 49],

Over the last 50 years, there has been a rapid rise in the number of significant trace elements associated with water pollution incidents. The release of cadmium into the Jinstu River in Japan resulted in serious bone damage [50].

Even chromium is an essential micronutrient, chromatic salts can have serious effects on the skin, nasal septum and lungs [46]. Homeostatic mechanisms generally work to control gastrointestinal absorption, so entering the body through other routes bypasses this control. Another example is Zn, whereby inhalation of zinc oxide vapors can cause an allergic reaction leading to metal smoke fever [51].

Large number of metals such as Cd, Pb and Hg have no recognized biological significance in human and exposure of small amounts may be toxic [52]. "Trace metals" is a broad collective term that includes any metal that is toxic and has a relatively high specific density as well [52]. Common indications of intoxication (Cd, Pb, As, Hg, Zn, Cu and Al) encompass gastrointestinal disturbances, diarrhea, stomach ulser, hemoglobinuria, ataxia, paralysis, vomiting and seizures, depression and pneumonia [52].

Metals intrude with the biochemistry of the organism during common metabolism processes. In the acidic middle of the stomach, they transform into stable oxidation states and merging with the body's biomolecules like proteins and enzymes to establish solid and stable chemical bonds, replacement of hydrogen or essential metals in an enzyme and, therefore, inhibit its functioning [52].

Metallic ions in the body's metallo-enzymes can be easily substitute by another similar sized metallic ion. Occasionally, the enzymes of a whole sequence coexist in the form of a single multi-enzymatic complex hence replacing an essential metal by an interfering metal blocks the biological reaction of the enzyme function. One example is the substitution of Zn by Cd and caused detrimental effects on body chemistry [53].

Therefore, the metal remains incorporated in the tissue and will effect in a variety of bio-malfunctions, not all evenly severe [52]. The most toxic forms of interference metals are their most stable oxidation states, since these very stable forms of biotoxic compounds are difficult to isolate with detoxification therapies [52].

6. Trace elements in whole blood

Heavy metals and trace elements can be measured in whole, serum, urine and other tissues. In blood, metals are distributed between the non-cellular (plasma/serum) and intra-cellular compartment (predominantly erythrocytes). For examples, lead (Pb) is known to have a strong affinity for erythrocyte [54]. Thus Pb is measured primarily in whole blood. Levels of metals in blood and serum have been extensively studied in different samples to identify the exposure of human population. Pregnant mother and their growing fetuses are especially vulnerable to exposure to pollutants. Air and water pollution, exposure to toxic elements, and exposure to persistent organic compounds have been associated with adverse pregnancy and developmental outcome [55, 56].

In addition to that, trace elements are also required in the body for its normal function. Macrominerals refer to minerals that adults need in quantities greater than 100 mg/day. The principal (macro-nutrients) consist of sodium, potassium, chloride, calcium, magnesium and phosphorus. Trace elements (trace mineral) are commonly stipulated as minerals required by adults between 1 and 100 mg/day. The group of trace minerals is composed of iron, copper and zinc. Ultra-trace minerals are defined as minerals that are needed in quantities under 1 mg/day. These consist of chromium, manganese, fluoride, iodide, cobalt, selenium, silicon, arsenic, boron, vanadium, nickel, cadmium, lithium, lead and molybdenum [57].

7. Polycyclic aromatic hydrocarbon (PAHs)

PAHs comprise diverse groups of compounds whose structure comprises at least two benzene groups and assorted functional groups that may include more than one element. They can be eliminated or converted to even more toxic compounds via chemical reactions such as sulfonation, nitration or photooxidation. For example,

under certain conditions, traces of nitric acid may convert some PAHs into nitro-PAHs [58].

Organic compounds can be released from their sources in gas phase or can be associated with particles by nucleation and condensation, forming particulate matter. PAHs can be found in the particulate and gaseous phases, depending on their volatility. Low molecular weight PAHs (LMW PAHs) with two or three aromatic rings are released in the gas phase. High molecular weight PAHs (HMW PAHs) of five or more rings are generated in the particulate phase.

The particulate form of PAHs is first found in the high-temperature gas phase. Nevertheless, when the temperature drops, the gas-phase PAHs adsorb or settle on the fly ash particles. Smaller particles offer more surface area for PAH adsorption. Environmental temperature is very important for the distribution of PAH gas particles. PAH can be formed in any incomplete combustion or high temperature pyrolytic process involving fossil fuels, or more generally, materials containing C and H [59].

The mechanisms by which PAHs are formed and emitted can be divided into two processes: pyrolysis and pyrosynthesis in any fuel combustion system. Pyrolysis is the development of smaller, unstable fragments from a heated an organic compound. Fragments are extremely reactive free radicals whose average life expectancy is very short. Through recombinant reaction, these free radicals result in more stable PAHs and this process is known as pyrosynthesis. For instance, B (a) P and other PAHs are formed by pyrolysis of methane, acetylene, butadiene and other compounds [60].

The formation of PAHs in pyrolysis oils was attributed by Diels-Alder responses of alkenes to form cyclic alkenes. In cyclic alkene dehydrogenation responses, stable rings of aromatic compounds from which PAH compounds are formed. Nonetheless, complex hydrocarbons need not necessarily decompose into small fragments prior to the recombinant process. Compounds with multiple rings are susceptible to partial cracking. Moreover, phenyl radicals also play a significant role in addition to intermolecular and intramolecular hydrogen transfers at intermediate constituent in high-temperature process which result in PAH formation [60].

8. Toxicity and carcinogenicity of PAHs

Elevated levels of PAHs in air cause numerous adverse effects on different types of organisms, inclusive plants, birds and mammals. A few studies have shown a significant positive association between lung cancer mortality in humans and PAH exposure from coke oven exhaust, cover tar and tobacco smoke. Concurrently, certain PAHs were shown to react with near ambient levels of NO_2 + HNO_3 and with O_3 in synthetic atmospheres, to form directly mutagenic nitro-PAH and oxy-PAH [61].

Some of the PAHs and their metabolites can induce stable genetic alterations that have the potential to irreversibly alter the control of cell division. This may result in tumor growth and cancer in fish and mammals. Due to solubility of PAHs in fatty tissue, they may bioaccumulate and transferred in the food chain. Certain PAHs have been specified as possible or probable cancer causing in humans, notably benzo (a) anthracene, chrysene, benzo (b and k) fluoranthene, benzo (a) pyrene and others [62]. Epidemiological studies have demonstrated that individuals exposed to mixtures containing PAHs have increased lung cancer rates [63].

It is known that the lower molecular weight PAHs is less harmful. They are predominantly discovered in the vapor phase in an urban air where they can react with other pollutants (O_3 and NO_x) to form more toxic derivatives. For example, PAHs react with NO_3 will form carcinogenic nitro-derivatives [64].

Particles smaller than 10 μm are more potent to incorporate larger quantities (unit mass) of PAHs because of their large area-to-volume ratio. That is a major concern because smaller particles are retained by the lung. In the human respiratory system, particles greater than 10 μm in diameter could not reach the thorax. Particles between 2.1 and 10 μm are preferably trapped by the pharynx, trachea and bronchi while particles less than 2.1 μm can reach bronchial and terminal alveoli. Consequently, harmful physical action of inhalable particles (i.e., development of lung emphysema) is ascertained with chemical impact as a result of their toxicity [65].

Humans may be exposed to PAHs by inhaling contaminated air or cigarette smoke, ingesting food with PAHs, and skin absorption of soil or materials that contain PAHs. Ingestion and inhalation are the two principal routes of exposure to the general population [27, 66]. For some professions, such as coal tar roofers and coking plant workers, skin absorption may be the primary route of exposure to PAHs [67].

Once PAHs have penetrated the human body, they undergo a series of biotransformation processes. During Stage I metabolism, PAHs are oxidized by cytochrome P450 enzymes to develop reactive epoxy intermediates, followed by hydrolysis to form hydroxylated derivatives (OH-PAHs). In Phase II metabolism, PAHs-OH are combined with glucuronic acid and/or sulphate to increase metabolite solubility in water and for ease of removal by urine, bile or stool [68]. Urinary OH-PAHs have been used as biomarkers to assess human exposure to PAHs, with 1-hydroxypyrene (1-PYR) as the most commonly used indicator in biomonitoring studies [69].

9. PAHs in whole blood

Blood measurement for DNA adducts of PAHs have been employed as a markers for PAHs exposure in human populations. Environmental monitoring documents the presence of a environmental pollutants, but the biological consequences of exposure to the organism are found only intracellularly [70, 71]. Protein-adduct formation is considered a surrogate of DNA adducts formation, but only the latter results in critical mutagenic changes [72].

Benzo(a)pyrene B(a)P is a potent carcinogen that have been used a proxy marker for PAHs in environmental sample. Individual metabolism transforms B(a)P to benzo epoxide (a) pyrene diol (BPDE), that establish adducts with DNA and proteins and hydrolysed to BPDE tetrols that are eliminating from the individual body [73]. The concentrations of human serum albumin (HSA) is more than a thousand fold greater than that in DNA in human blood and unlike DNA adducts, HSA adducts are not repair. Therefore, BDPE-HSA should be relatively stable biomarker of B(a)P exposure, with human half life of 20 days that ensures integration B(a)P exposure over about a month [74].

Over the years many studies have contributed to validation of PAH-DNA adduct measurements in human DNA using immunoassays, the most-sensitive of which is the chemiluminescence immunoassay (CIA) [75]. A cohort study of US military soldiers displaced from an area with a clean environmental zone to a much more polluted area showed a substantial increment in the levels of HAP-DNA adducts in blood cells for each individual [76, 77]. In addition, a tremendously higher rate of PAH-DNA adducts for blood cells was observed in young adults sampled in Mexico City during the dry season when atmospheric PAH concentrations were higher, in comparison to the rainy season, when PAH levels were decrease [78].

10. Volatile organic compounds

Volatile organic compounds (VOCs) are defined as photochemically reactive organic species with a high vapor pressure in the Earth's atmosphere [79]. VOCs include a wide range of compounds such as carbonyls, organic acids, alcohols, alkanes, alkenes, aldehydes, esters, paraffins, ketones and aromatic hydrocarbons [80]. The physical and chemical properties of VOCs and their residence times in the atmosphere (ranging from a few minutes to several months) often lead to threats towards the environment and human health [81].

VOCs originating from biogenic sources play crucial roles in atmospheric chemistry because they are strong ozone precursors that supply essential OH radicals in ambient air for the formation of tropospheric ozone [82, 83]. VOCs has been identified for formation of photochemical smog, stratospheric ozone depletion and the formation of organic acids which contribute to environmental acidification by lowering the pH of rainwater [84–86]. From a human health perspective, their toxic nature and ability to form fine aerosols pose that contribute to health risks, such as asthma, headaches, dizziness, visual disorders and memory impairment [87–90].

11. Health effects of VOCs

The volatilization characteristics of VOCs allow them to enter living organisms through three main routes; by inhalation, dermally and orally through contaminated water or food in order of importance [81]. Toxicokinetic studies showed distribution to lipid-rich tissues such as the brain, bone marrow and body fat [91]. Children and the elderly are the most vulnerable groups due to their higher metabolic rate and weak immune systems [92]. BTEX and carbonyl compounds are classified as toxic air pollutants able to cause adverse health effects even at low concentrations by affecting different target organs e.g. central nervous system, respiratory system, liver, kidneys and reproductive system [93]. Benzene can be absorbed through various tissues such as tissues in the brain, bone marrow cells and also tissues containing high amounts of lipid, with succeeding genotoxic action. Prolonged exposure to benzene may have effects on neurological, immunological, endocrine and blood disease disorders such as aplastic anemia and myeloid leukemia [94]. As a result benzene is the most regulated substance in the world being classified as 'Group 1, carcinogenic to humans', by the International Agency for Research on Cancer (IARC).

When human exposed to toluene, the vaporized toluene will be absorbed to the respiratory tract. According to Pierrehumbert [95], inhalation is the most important route for toluene exposure. About 80% of toluene vapor will be absorb in the first exposure and the absorption is decreasing afterwards. It is known that pulmonary absorption is faster than oral absorption. Oral absorption takes around 2–3 hour to get contact with blood, compare to inhalation absorption which takes only 20–3-minutes at the concentration of 100 ppm. The half life of toluene in human blood is around 3.4 hour but likely to increase to 0.5–2.7 days with the greater amounts of body fat. Due to its solubility, toluene can passess through the placenta, amniotic fluid, human neonates then end up in edipose tissues. This was proved by a study from Fabietti et al. (2—24) which found 0.76 ug/kg concentration of toluene in human breast milk. Apart from the neurotoxicity of toluene, recent studies found that toluene has been linked with color vision loss [96]. The most evidences are the effect on blue yellow discrimination but in few cases, the red green discrimination might be experiences [97]. On top of that, the prolonged exposure of small dose to toluene may effect the lens eyes and outer retinal layer [98, 99].

IARC [100] assessed ethylbenzene as demonstrating sufficient evidence of carcinogenicity in animals and therefore is classified as a possible human carcinogen. Rodent bioassays by Scott et al. [101], clearly showed enough evidence of carcinogenic activity following inhalation exposure in male rate. The carcinogenicity is depends on the incidences of renal neoplasms after exposure to dose up to a 750 ppm. In human body, ethylbenzene is effectively absorbed through the inhalation and expeditiously circulated. Both in human and rodents, ethylbenzene is metabolized through hydroxylation to produce phenylethanol and will excrete via urination [100]. Urinary excretion is believed to be the main pathway of ethylbenzene elimination both in human and animal studies following inhalation exposure. Human appears to have acute symptom of ethylbenzene on ocular irritation and respiratory tract. Furthermore, affects on hematological changes might be experiences. Acute toxicity studies on animal are almost the same as have been detected in human, however the differentiated between human is that acute toxicity in animal demonstrated by neurobehavioral and neurological effects.

Respiration appears to be the major pathway of exposure to xylene. Approximately 60% of inhaled xylene goes to lungs. As xylene is well metabolized in human bodies; more than 90% is bio transformed to methylhippuric acid, where it is excreted in urine. Vapors xylene in the lung alveoli dispersed into the blood and are distributed across human body by the circulatory system [102]. Nevertheless, xylene do not have tendency to accumulate in human body. Acute exposure of xylene results in irritation of eyes, nose, throat as well as gastrointestinal effects, and neurological effects. Meanwhile, CNS, kidney, cardiovascular and respiratory effects have been discovered due to xylene exposure. In addition, a study conducted by Adams et al. [102] suggest that chronic exposure to xylene as also associated to a variety of disease, leukopenia, electrocardiogram abnormalities, dyspnoea and cyanosis.

Table 3 shows the carcinogenic and non-carcinogenic effects of selected VOC compounds, target organs and their critical health effects.

Compounds	USEPA cancer classification	Target organ	Precursor effect/ tumor type	Critical effects
Benzene	A	Blood	Leukemia	Decreased lymphocyte count
Toluene	D		—	Neurological effects
Ethylbenzene	B2	Kidney	Tumors	Developmental toxicity
Xylene	D		—	Impaired motor coordination
Formaldehyde	B1	Nasal Cavity	Squamous cell carcinoma	
Acetaldehyde	B2	Nasal	Nasal squamous cell carcinoma or adenocarcenoma	Olfactory degeneration

Adapted from Kitwattanavong et al. [103].
Sources: Integrated Risk Information System. The Risk Assessment Information System [104].
USEPA cancer classification: A = human carcinogen; B1 = probable human carcinogen; B2 = probable human carcinogen; C = possible human carcinogen; D = not classifiable as to human carcinogenicity; E = evidence of non-carcinogenicity for humans.

Table 3.
The health effects of the main BTEX and carbonyl compounds.

12. Ozone

Ozone is developed upon the reaction of the dioxygen and a single oxygen in the existence of a molecule of the third body that can absorb the heat of the reaction. The unique highly responsive and short-lived oxygen (O) can be produced by photolysis of nitrogen dioxide (NO2) or by ionization of O2.

The stratosphere and troposphere are composed of background ozone. Stratospheric ozone is confined to the tropopause (between 8 and 15 km high) a region it is known as the ozone layer. Stratospheric ozone is referred to as the "good" ozone, considering the ozone layer is crucial for the absorption of life-threatening ultraviolet (UV-B) rays to human health. Given that immediate contact with ground-level ozone can induce detriment to living cells, organs and species, including individual, animals and plant life, ground-level ozone is considered to be a "bad" ozone.

According to Nuvolene et al. [105] and Koman & Mancuso [106], the documented health effects of ozone are

- Ozone can create undesirable respiratory effects like difficulty breathing and inflammation of the respiratory tract in the general individual (breathlessness and pain during deep breathing). These effects can worsen pulmonary illnesses such as asthma, emphysema and chronic bronchitis.

- Prolonged exposure to ozone is likely one of many contributing factors to the development of asthma.

- Exposure to ozone is likely to result in premature death, and there is stronger evidence for mortality from respiratory diseases.

- Children are at increased risk from ozone exposure, as children have a relatively higher dose per body mass and children's lung is still developing.

Even at really low levels, tropospheric ozone result of a vary of health problem including worsened asthma, decreased pulmonary ability, and increased sensitiveness to respiratory diseases including pneumonia and bronchitis. Persistent exposure to ozone over several months can permanently damage the lungs [107]. Ozone can irritate lung airways and cause inflammation much like a sunburn [108, 109]. Other symptoms include wheezing, coughing, pain when taking a deep breath, and breathing difficulties during exercise or outdoor activities [109].

13. Carbon monoxide

Carbon monoxide is produced from the incomplete combustion of fossil fuel such as petrol, coal, wood, and natural gases. The health effects of CO breathing include headache, vertigo, nausea, vomiting and eventually loss of consciousness.

The affinity of carbon monoxide to hemoglobin is far superior to that of oxygen. Along this vein, severe intoxication may occur in individuals susceptible to elevated levels of carbon monoxide for an extended period of time. As a result of oxygen loss due to competitive binding of carbon monoxide, hypoxia, ischemia and cardiovascular diseases are discovered [1].

14. Environmental burden of disease of air pollution and tempereture

Air pollution is currently considered as the most significant environmental cause of disease, whereby kills about 3 million people annually and majorly affected the Western Pacific and South East Asia regions [33]. Short-term exposure to air pollutants are associated with Chronic Obstructive Pulmonary Disease (COPD), cough, shortness of breath, wheezing, asthma, respiratory disease, and high morbidity (hospitalization). Meanwhile, the long-term effects associated with air pollution are chronic asthma, pulmonary insufficiency, cardiovascular diseases, and cardiovascular mortality [1].

The differential effect of air pollution on health, which is particularly deleterious for older people, children and people with limited resources, is of major concern to global health populations. It is estimated that airborne fine particulate pollution is responsible for approximately 3% of adult cardiopulmonary mortality worldwide [110]. Air pollution is expected to have similar negative impacts in developing countries, with Asian countries accounting for about two-thirds of the world's burden [110]. Beelen et al. [111] had found a relationship between mortality and long-term exposure to particulate matter, fine particles, and nitrogen compounds.

Elevated air pollution is usually related with extreme events such as increasing in ambient temperature. Engardt et al. [112] indicated that ozone levels are directly driven by weather since ozone-generating photochemical reactions of air pollutants (nitrogen oxides; methane; volatile organic compounds, VOCs) need high temperatures and bright sunshine.

The associations between ambient temperatures and human health have been widely studied, and growing evidences have revealed that exposure to ambient temperatures may increase the risks of a range of respiratory diseases, cardiovascular diseases, and other disease [113–115]. Although most previous studies found significant relationships between ambient temperature and morbidity or mortality [116, 117], only few had assessed the disease burden attributable to ambient temperatures. It was demonstrated that heat-related mortality and morbidity rapidly increase when temperatures were above optimal. Recently study done by Yiju Zhao et al. [118] highlighted high and low temperature increase the morbidity risk of respiratory disease. Meanwhile, study done by Chung et al. [119] discovered excess mortality due to high ambient temperature was expected to be profound in Korea.

The disease burden of a population and how the burden is distributed across different subpopulations (e.g infants, women) are important pieces of information for defining strategies to improve population health. Burden of disease (BOD) is a comprehensive measurement of mortality and morbidity in a single index, which is manifested as disability-adjusted life years (DALY). DALY is estimated by summing the years of life lost (YLL) and years lost due to disability (YLD). Estimation of burden of disease had advantaged over other epidemiological indexes because of its simplicity, comprehensiveness, and applicability for policy-making process.

The Environmental burden of Disease (EBD) series continues the effort of BOD to generate reliable information, by presenting methods for assessing the environmental burden of outdoor air pollution at national and local levels, as what had been described in World Health Report [120]. Worldwide global burden of disease between 1990 and 2015 shows COPD mortality rates and DALYs were observed in South-East Asia region with 39 deaths per 100,000 people and 791 DALYs per 100,000 people in 2015, followed by Western Pacific region with 25 deaths per 100,000 people and 421 DALYs per 100,000. Ischemic stroke, Trachea, Bronchus and Lung cancer, Ischemic heart disease's DALYs and death rate were generally

higher in all the regions with South-East Asia having 943 DALYs per 100,000 people and 38 deaths per 100, 000. Exposure to air pollution caused over 7.0 million deaths and 103.1 million lost years of healthy life in 2015, caused an estimated 7.6% of total global mortality in 2015 [121]. The WHO estimation report for Malaysia's Environmental burden of disease was published in 2009 [24]. Estimates were based on Comparative Risk Assessment, evidence synthesis and expert evaluation for regional exposure and WHO country health statistics 2004. Cardiovascular disease, respiratory infections, COPD, asthma and lung cancers were among the disease listed. The preliminary estimations for the diseases were 2.5, 1.6, 1.4, 1.2 and 0.5 DALYs/1000 capita, per year, respectively [120].

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