Human health effects of air pollution

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The effect of air pollutants on human health and underlying mechanisms of cellular action are discussed.

Abstract

Hazardous chemicals escape to the environment by a number of natural and/or anthropogenic activities and may cause adverse effects on human health and the environment. Increased combustion of fossil fuels in the last century is responsible for the progressive change in the atmospheric composition. Air pollutants, such as carbon monoxide (CO), sulfur dioxide (SO2), nitrogen oxides (NOx), volatile organic compounds (VOCs), ozone (O3), heavy metals, and respirable particulate matter (PM2.5 and PM10), differ in their chemical composition, reaction properties, emission, time of disintegration and ability to diffuse in long or short distances. Air pollution has both acute and chronic effects on human health, affecting a number of different systems and organs. It ranges from minor upper respiratory irritation to chronic respiratory and heart disease, lung cancer, acute respiratory infections in children and chronic bronchitis in adults, aggravating pre-existing heart and lung disease, or asthmatic attacks. In addition, short- and long-term exposures have also been linked with premature mortality and reduced life expectancy. These effects of air pollutants on human health and their mechanism of action are briefly discussed.

Keywords: Air pollutant; Human health; Cellular actions; Detoxification

1. Introduction

Although a number of physical activities (volcanoes, fire, etc.) may release different pollutants in the environment, anthropogenic activities are the major cause of environmental air pollution. Hazardous chemicals can escape to the environment by accident, but a number of air pollutants are released from industrial facilities and other activities and may cause adverse effects on human health and the environment. By definition, an air pollutant is any substance which may harm humans, animals, vegetation or material. As far as humans are concerned an air pollutant may cause or contribute to an increase in mortality or serious illness or may pose a present or potential hazard to human health. The determination of whether or not a substance poses a health risk to humans is based on clinical, epidemiological, and/or animal studies which demonstrate that exposure to a substance is associated with health effects. In the context of human health, “risk” is the probability that a noxious health effects may occur.

2. Pollutant categories

The main change in the atmospheric composition is primarily due to the combustion of fossil fuels, used for the generation of energy and transportation. Variant air pollutants have been reported, differing in their chemical composition, reaction properties, emission, persistence in the environment, ability to be transported in long or short distances and their eventual impacts on human and/or animal health. However, they share some similarities and they can be grouped to four categories:

1. Gaseous pollutants (e.g. SO2, NOx, CO, ozone, Volatile Organic Compounds).
2. Persistent organic pollutants (e.g. dioxins).
3. Heavy metals (e.g. lead, mercury).
4. Particulate Matter.

**Gaseous pollutants** contribute to a great extent in composition variations of the atmosphere and are mainly due to combustion of fossil fuels (Katsouyanni, 2003). Nitrogen oxides are emitted as NO which rapidly reacts with ozone or radicals in the atmosphere forming NO2. The main anthropogenic sources are mobile and stationary combustion sources. Moreover, ozone in the lower atmospheric layers is formed by a series of reactions involving NO2 and volatile organic compounds, a process initiated by sun light. CO, on the other hand, is a product of incomplete combustion. Its major source is road transport too. While the anthropogenic SO2 results from the combustion of sulphur-containing fossil fuels (principally coal and heavy oils) and the smelting of sulphur containing ores, volcanoes and oceans are its major natural sources. The latter contribute only \(~2\%\) of the total emissions. Finally a major class of compounds that fuel combustion and especially combustion processes for energy production and road transport are the major source of emission are the so called volatile organic compounds (VOCs). This is a class of compounds, which includes chemical species of organic nature such as benzene. Even though the majority of gaseous pollutants are inhaled and mainly affect the respiratory system they can also induce haematological problems (CO, benzene) and cancer.

**Persistent organic pollutants** form a toxic group of chemicals. They persist in the environment for long periods of time, and their effects are magnified as they move up through the food chain (bio-magnification). They include pesticides, as well as dioxins, furans and PCBs. Generally, the generic term “dioxins” is used to cover polychlorinated dibenzo-dioxins (PCDDs) and polychlorinated dibenzo-furans (PCDFs) while polychlorinated biphenyls (PCB) are called “dioxin like compounds” and can act similarly in terms of dioxin-type toxicity (Schechter et al., 2006). Dioxins are formed during incomplete combustion and whenever materials containing chlorine (e.g. plastics) are burned. Emitted in the atmosphere, dioxins tend to deposit on soil and water but, being water-insoluble, they do not contaminate ground water sources. Most dioxins in plants come from air and dust or pesticides and enter the food chain where they bio-accumulate due to their ability to be stably bound to lipids.

**Heavy metals** include basic metal elements such as lead, mercury, cadmium silver nickel, vanadium, chromium and manganese. They are natural components of the earth’s crust; they cannot be degraded or destroyed, and can be transported by air, and enter water and human food supply. In addition, they enter the environment through a wide variety of sources, including combustion, waste water discharges and manufacturing facilities. To a small extent they enter human bodies where, as trace elements, they are essential to maintain the normal metabolic reactions. However, at higher (although relatively low) concentrations they can become toxic (Jarup, 2003). Most heavy metals are dangerous because they tend to bio-accumulate in the human body. **Bioaccumulation** means an increase in the concentration of a chemical in a biological organism over time, compared to the chemical’s concentration in the environment. Compounds accumulate in organisms any time they are taken in and stored faster than they are broken down (metabolized) or excreted.

**Particulate matter** (PM) is the generic term used for a type of air pollutants, consisting of complex and varying mixtures of particles suspended in the breathing air, which vary in size and composition, and are produced by a wide variety of natural and anthropogenic activities (Poschl, 2005). Major sources of particulate pollution are factories, power plants, refuse incinerators, motor vehicles, construction activity, fires, and natural windblown dust. The size of the particles varies (PM2.5 and PM10 for aerodynamic diameter smaller than 2.5 \(\mu\)m and 10 \(\mu\)m respectively) and different categories have been defined: **Ultrafine** particles, smaller than 0.1 \(\mu\)m in aerodynamic diameter, **Fine** particles, smaller than 1 \(\mu\)m, and **Coarse** particles, larger than 1 \(\mu\)m. The size of the particles determines the site in the respiratory tract that they will deposit: PM10 particles deposit mainly in the upper respiratory tract while fine and ultra fine particles are able to reach lung alveoli. So far, no single component has been identified that could explain most of the PM effects. Among the parameters that play an important role for eliciting health effects are the size and surface of particles, their number and their composition. The composition of PM varies, as they can absorb and transfer a multitude of pollutants. However, their major components are metals, organic compounds, material of biologic origin, ions, reactive gases, and the particle carbon core. There is strong evidence to support that ultra fine and fine particles are more hazardous than larger ones (coarse particles), in terms of mortality and cardiovascular and respiratory effects. In addition, the metal content, the presence of PAHs and other organic components such as endotoxins, mainly contribute to PM toxicity.

### 3. Routes of exposure

Humans enter in contact with different air pollutants primarily via inhalation and ingestion, while dermal contact represents a minor route of exposure. Air pollution contributes, to a great extent, to the contamination of food and water, which makes ingestion in several cases the major route of pollutant intake (Thron, 1996). Via the gastrointestinal and respiratory tract, absorption of pollutants may occur, while a number of toxic substances can be found in the general circulation and deposit to different tissues. Elimination occurs to a certain degree by excretion (Madden and Fowler, 2000).

### 4. Health effects

Sporadic air pollution events, like the historic London fog in 1952 and a number of short and long term epidemiological studies investigated the effects of air quality changes on human health. A constant finding is that air pollutants contribute to increased mortality and hospital admissions (Brunekreef
and Holgate, 2002). The different composition of air pollutants, the dose and time of exposure and the fact that humans are usually exposed to pollutant mixtures than to single substances, can lead to diverse impacts on human health. Human health effects can range from nausea and difficulty in breathing or skin irritation, to cancer. They also include birth defects, serious developmental delays in children, and reduced activity of the immune system, leading to a number of diseases. Moreover, there exist several susceptibility factors such as age, nutritional status and predisposing conditions. Health effects can be distinguished to acute, chronic not including cancer and cancerous. Epidemiological and animal model data indicate that primarily affected systems are the cardiovascular and the respiratory system. However, the function of several other organs can be also influenced (Cohen et al., 2005; Huang and Ghio, 2006; Kunzli and Tager, 2005; Sharma and Agrawal, 2005).

4.1. Effects of air pollutants on different organs and systems

4.1.1. Respiratory system

Numerous studies describe that all types of air pollution, at high concentration, can affect the airways. Nevertheless, similar effects are also observed with long-term exposure to lower pollutant concentrations. Symptoms such as nose and throat irritation, followed by bronchoconstriction and dyspnoea, especially in asthmatic individuals, are usually experienced after exposure to increased levels of sulphur dioxide (Balmaes et al., 1987), nitrogen oxides (Kagawa, 1985), and certain heavy metals such as arsenic, nickel or vanadium. In addition particulate matter that penetrates the alveolar epithelium (Ghio et al., 1987), nitrogen oxides (Kagawa, 1985), and certain heavy metals reduces lung function (Rastogi et al., 1991; Tager et al., 2005), while the latter are also responsible for asthma, emphysema, and even lung cancer (Kuo et al., 2006; Nawrot et al., 2006). Emphysema-like lesions have also been observed in mice exposed to nitrogen dioxide (Wegmann et al., 2003).

4.1.2. Cardiovascular system

Carbon monoxide binds to haemoglobin modifying its configuration and reduces its capacity to transfer oxygen (Badman and Jaffé, 1996). This reduced oxygen availability can affect the function of different organs (and especially high oxygen-consuming organs such as the brain and the heart), resulting in impaired concentration, slow reflexes, and confusion. Apart from lung inflammation, systemic inflammatory changes are induced by particulate matter, affecting equally blood coagulation (Riediker et al., 2004). Air pollution that induces lung irritation and changes in blood clotting can obstruct (cardiac) blood vessels, leading to angina or even to myocardial infarction (Vermyle et al., 2005). Symptoms such as tachycardia, increased blood pressure and anaemia due to an inhibitory effect on haematopoiesis have been observed as a consequence of heavy metal pollution (specifically mercury, nickel and arsenic) (Huang and Ghio, 2006). Finally, epidemiologic studies have linked dioxin exposure to increased mortality caused by ischemic heart disease, while in mice, it was shown that heavy metals can also increase triglyceride levels (Dalton et al., 2001).

4.1.3. Nervous system

The nervous system is mainly affected by heavy metals (lead, mercury and arsenic) and dioxins. Neurotoxicity leading to neuropathies, with symptoms such as memory disturbances, sleep disorders, anger, fatigue, hand tremors, blurred vision, and slurred speech, have been observed after arsenic, lead and mercury exposure (Ewan and Pamphlett, 1996; Ratnake, 2003). Especially, lead exposure causes injury to the dopamine system, glutamate system, and N-methyl-D-Aspartate (NMDA) receptor complex, which play an important role in memory functions (Lasley and Gilbert, 2000; Lasley et al., 2001). Mercury is also responsible for certain cases of neurological cancer. Dioxins decrease nerve conduction velocity and impaired mental development of children (Thomke et al., 1999; Walkowiak et al., 2001).

4.1.4. Urinary system

Heavy metals can induce kidney damage such as an initial tubular dysfunction evidenced by an increased excretion of low molecular weight proteins, which progresses to decreased glomerular filtration rate (GFR). In addition they increase the risk of stone formation or nephrocalcinosis (Damek-Poprawa and Sawicka-Kapusta, 2003; Jarup, 2003; Loghman-Adham, 1997) and renal cancer (Bofietta et al., 1993; Vamvakas et al., 1993).

4.1.5. Digestive system

Dioxins induce liver cell damage (Kimbrough et al., 1977), as indicated by an increase in levels of certain enzymes in the blood (see following discussion on the underlying cellular mechanisms of action), as well as gastrointestinal and liver cancer (Mandal, 2005).

4.2. Exposure during pregnancy

It is rather important to mention that air pollutants can also affect the developing foetus (Schell et al., 2006). Maternal exposure to heavy metals and especially to lead, increases the risks of spontaneous abortion and reduced fetal growth (pre-term delivery, low birth weight). There are also evidences suggesting that parental lead exposure is also responsible for congenital malformations (Bellinger, 2005), and lesions of the developing nervous system, causing important impairment in newborn’s motor and cognitive abilities (Garza et al., 2006). Similarly, dioxins were found to be transferred from the mother to the fetus via the placenta. They act as endocrine disruptors and affect growth and development of the central nervous system.
5. Cellular mechanisms involved in air pollutants actions

Common cellular mechanism by which most air pollutants exert their adverse effects is their ability to act directly as oxidants of lipids and proteins or as free radicals generators, promoting oxidative stress and the induction of inflammatory responses (Menzel, 1994; Rahman and MacNee, 2000). Free radicals (reactive oxygen and nitrogen species) are harmful to cellular lipids, proteins, and nuclear- or mitochondrial-DNA, inhibiting their normal function (Valko et al., 2006). In addition, they can interfere with signaling pathways within cells (Valko et al., 2006). In eukaryotic aerobic organisms including humans, free radicals are continuously generated during normal metabolism and in response to exogenous environmental exposures (e.g. irradiation, cigarette smoke, metals and ozone). When free radical concentration increases, due to an overwhelming of organism’s defense, a state of oxidative stress occurs. This oxidative state has been implicated in a wide variety of degenerative diseases such as atherosclerosis, heart attacks, stoke, chronic inflammatory diseases (rheumatoid arthritis), cataract, central nervous system disorders (Parkinson’s, and Alzheimer’s disease), age related disorders and finally cancer.

Furthermore, the toxic effects of heavy metals, apart from inducing oxidative stress, can be also attributed to their ability to substitute diverse polyvalent cations (calcium, zinc, and magnesium) that function as charge carriers, intermediaries in catalyzed reactions, or as structural elements in the maintenance of protein conformation. Indeed, metals accumulate in cellular organelles and interfere with their function. For example it has been observed that lead accumulation in mitochondria induces several changes such as inhibition of Ca^{2+} uptake, reduction of the transmembrane potential, oxidation of pyridine nucleotides, and a fast release of accumulated Ca^{2+} (Chavez et al., 1987). Moreover, metals bind to proteins (Goering, 1993) and inhibit a large number of enzymes, including the mitochondrial ones (Rossi et al., 1993). Nucleic acid binding proteins are also involved, while it has been shown that metals can also bind to DNA, affecting the expression of genes. For example nickel enters the nucleus, interacts with chromatin and silences the expression of genes such as tumor suppressor genes, inducing carcinogenesis (Costa et al., 2003). Finally, some metals interfere with various voltage- and ligand-gated ionic channels exerting neurotoxic effects. For instance lead affects the N-methyl-D-aspartic acid (NMDA) receptor, subtypes of voltage- and calcium-gated potassium channels, cholinergic receptors and voltage-gated calcium channels (Garza et al., 2006; Toscano and Guilarte, 2005).

Dioxin causes a broad range of adverse effects (Birnbaum, 1994): they alter metabolism by inducing a number of metabolic enzymes (e.g. CYPs, glutathione-transferase, tyrosine kinase etc.), homeostasis, through hormone modulation (e.g. estrogens, androgens glucocorticoids, insulin, thyroid hormones) and their receptors, and growth and differentiation by interfering with growth factors (e.g. EGF, TGF-β, TNFα) and their receptors. At the cellular level, dioxins interact with the aryl hydrocarbon receptor (AhR) (Schwarz et al., 2000) which has a basic helix-loop-helix domain, acting as a transcription factor after nuclear translocation, allowing interaction of dioxins with DNA. The receptor-ligand complex binds to specific sites on DNA, altering the expression of a number of genes.

As far as cancer is concerned from the data presented above it becomes clear that most pollutants play an important role in the initiation, promotion and progression of cancer cells (Fig. 1).

6. Natural protection

In our day-to-day life we are exposed in different kinds of pollutants. Health impacts, as already described above, depend on the pollutant type, its concentration, length of exposure, other coexisting pollutants and individual susceptibility.
People living in cities are exposed to a greater extent, as a consequence of increased industrialization and demands for energy and motor vehicles. Occupational exposure is also an important factor that should be taken into consideration. During the last decade, health effects of air pollution are studied more in developed countries, while more and better environmental monitoring data are required in order to set up threshold levels. In addition efforts should be intensified by taking the appropriate measures, in order to reduce the possibility of human pollutant exposure.

The human body, in order to protect itself against the potential harmful insults from the environment, is equipped with drug or xenobiotic metabolising enzymes (DMEs or XMEs) that play a central role in the biotransformation, metabolism and/or detoxification of xenobiotics or foreign compounds, including different kinds of pollutants. XMEs include a variety of enzymes such as cytochrome P450 (P450 or CYP), epoxide hydrolase, glutathione transferase, UDP-glucuronosyltransferase, sulfotransferase, NAD(P)H quinone oxidoreductase 1, and aldo-keto reductase. These enzymes mainly participate in the conversion of xenobiotics to more polar and water-soluble metabolites, which are readily excreted from the body. Finally, it should be noted that, in many cases, the chemically reactive metabolites produced during metabolism, are equally harmful and therefore undergo additional metabolism to inactive products. Hence, the final outcome of a compound modulating the detoxification enzyme systems is the result of the effects on the different metabolic pathways.

A number of substances of dietary nature are beneficial, protective, and supportive of good health and the body’s own natural chelation mechanisms. They include nutrients with natural chelating properties, which may help to detoxify the body, such as antioxidants, herbs, minerals, essential amino acids, other detoxifying or protective agents, and fiber (Kelly, 2004). Among them dietary antioxidants contribute to the organism’s antioxidant defense system, that includes a series of antioxidant enzymatic (e.g. peroxidase) and non-enzymatic compounds (such as glutathione, or food-derived like vitamin E, or polyphenols), as well as damage removal/repair enzymes.

Several natural compounds, such as vitamins C, E, and A and polyphenols, found in the majority of plant foods, interfere with or scavenge ROS concentration within cells and subsequently protect the organism from the adverse effects of oxidative stress. Indeed, as it has been shown by our group that the antioxidant activity of plasma in humans following a diet rich in vegetables, fruits and olive oil was increased in that the antioxidant activity of plasma in humans following oxidative stress. Indeed, as it has been shown by our group and polyphenols, found in the majority of plant foods, including different kinds of pollutants. XMEs include a variety of enzymes such as cytochrome P450 (P450 or CYP), epoxide hydrolase, glutathione transferase, UDP-glucuronosyltransferase, sulfotransferase, NAD(P)H quinone oxidoreductase 1, and aldo-keto reductase. These enzymes mainly participate in the conversion of xenobiotics to more polar and water-soluble metabolites, which are readily excreted from the body. Finally, it should be noted that, in many cases, the chemically reactive metabolites produced during metabolism, are equally harmful and therefore undergo additional metabolism to inactive products. Hence, the final outcome of a compound modulating the detoxification enzyme systems is the result of the effects on the different metabolic pathways.

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Several natural compounds, such as vitamins C, E, and A and polyphenols, found in the majority of plant foods, interfere with or scavenge ROS concentration within cells and subsequently protect the organism from the adverse effects of oxidative stress. Indeed, as it has been shown by our group that the antioxidant activity of plasma in humans following a diet rich in vegetables, fruits and olive oil was increased in comparison to a normal diet (Kampa et al., 2002). This increase can be mainly attributed to polyphenols which exhibit a wide range of biological activities, including anti-tumorigenic, anti-mutagenic, anti-inflammatory, and antiviral actions (Bravo, 1998; Hertog and Hollman, 1996) mainly due to their antioxidant properties and their ability to exert inhibitory effects by affecting basic cellular functions. Indeed the beneficial role of polyphenols in preventing cancer can be in part attributed to their ability to modify enzymes that activate or detoxify environmental carcinogens.

7. Conclusion

This brief review presents the adverse effects of a number of (air) pollutants in human health. As shown, major impairments of different organs can be observed. The main conclusion drawn is that, in view of increased exposure of humans in a diversity of pollutants, dietary interventions, rich in plant-derived foods, may protect or decrease their effects on different organs. This conclusion is supported by a number of epidemiological studies on the beneficial effect of a Mediterranean-type diet on human health.

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