

Air Pollutants Causing Diseases, Their Detection and Measurement Using Different Hyphenated Analytical Techniques: A Quick Insight

Deepika Bairagee¹, Neelesh Mahehwari², Praveen K. Soni², Rituraj Singh Chundawat², Supriya Shidhaye², Anju Goyal³

¹Department of Pharmacy, Acropolis Institute of Pharmaceutical Education and Research, Indore, Madhya Pradesh, India, ²Department of Pharmacy, School of Pharmacy, Sangam University, Bhilwara, Rajasthan, India, ³B N Institute of Pharmaceutical Sciences, B N University, Udaipur, Rajasthan, India

Abstract

Air pollution, a significant environmental risk factor, is regarded to be the root cause of certain ailments, including asthma, lung cancer, and ventricular hypertrophy. According to the World Health Organization, some of the major air pollutants include lead, carbon monoxide (CO), sulfur oxides, CO at ground level, and particle pollution. Both short-term and long-term exposure to polluted air can have a number of toxicological consequences on the human body, including respiratory and cardiovascular problems, neuropsychiatric issues, eye irritation, skin conditions, and chronic illnesses like cancer. Different advanced analytical techniques such as gas chromatography-mass spectrometry, infrared radiation absorption, and laser, where laser radiation is sent through a sample of atmosphere to be investigated either as transmission, or the scattering of the light all the way through a different physical process, produce a variety of different techniques for monitoring air quality. This article has detailed the primary air pollutants, their sources of emission, their effects on human health, and the methods used to detect them to discover solutions to minimize them.

Key words: Air pollutant, gas chromatography–mass spectrometry, infrared radiation absorption, laser, respiratory diseases

INTRODUCTION

Due to pollution and/or human activity, excessive pollutants in the form of particles, gases, and biological molecules enter the atmosphere.

Solids, liquids, and gases can all be considered forms of pollution.^[1] With significant effects on both human health and the environment, air pollution may be one of the most detrimental developments of recent decades. Single cigarettes, as well as natural sources such as volcanic eruptions, massive amounts of vehicle emissions, and industrial operations, among others, are all causes of air pollution.^[2,3]

Air pollution contributes to chronic diseases such as cancer, cardiovascular dysfunction, inflammation, and respiratory infections.^[4,5] As a result, millions of people every year pass away as a result of pollution.^[6,7]

One of the most recent studies^[8] discovered a connection between air pollution, a serious health risk, and male infertility.

Finding both qualitative and quantitative reasons for air pollution is essential in the modern world. A plausible mechanism of action by which the pollutant causes toxicity must be identified for proper patient care. These types of data are helpful for environmental and health experts, especially policymakers, clinicians, and others who are directly or indirectly involved in problem regions.^[9-11]

Address for correspondence:

Deepika Bairagee, Department of Pharmacy, Acropolis Institute of Pharmaceutical Education and Research, Indore, Madhya Pradesh, India.
E-mail: bairagee.deepika@gmail.com

Received: 21-04-2022

Revised: 08-03-2023

Accepted: 05-05-2023

A FEW CONTAMINANTS IN THE AIR AND THEIR TOXICITY

Any element in the air that has the potential to endanger human health or have a detrimental impact on the environment is considered air pollution. The six main air pollutants that affect both human health and ecology are lead (Pb), carbon monoxide (CO), sulfur oxides (SOx), nitrogen oxides (NOx), ground-level ozone (O₃), and CO (World Health Organization). The two types of pollutants are primary and secondary.

Secondary pollutants, such as O₃, are common. Dust, fumes, smokes, mists, gaseous pollutants, hydrocarbons, volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs), and halogen derivatives are just a few of the pollutants suspended in the air that, at high concentrations, make people more susceptible to a number of illnesses, including cancer.^[12-15]

DIFFERENT AIR POLLUTANT AND THEIR TOXIC EFFECTS ON HEALTH PARTICLE POLLUTANTS

Particle particles make up a significant portion of air pollutants. To put it another way, they are a collection of particles found in the open air. They range in size from 2.5 to 10 μm (PM 2.5–PM 10).^[16,17] The size of particle pollution is linked to the beginning and progression of lung and cardiovascular illnesses.

Smaller particles can quickly reach the lungs through deep inhaling. They create problems with the heart and blood vessels once they reach the lungs. In addition, a number of scientific studies have demonstrated that fine particle pollution causes early mortality in those who have heart and/or lung disease, including cardiac dysrhythmias, nonfatal heart attacks, aggravated asthma, and reduced lung functions in patients with heart and/or lung disease. Particulate pollution can cause moderate-to-serious diseases depending on the degree of interaction.

The most prevalent clinical signs of respiratory illness, which are caused by air pollution, include wheezing, coughing, dry mouth, and limitations in activities owing to breathing issues.^[18-20] The primary reasons for the decrease in life expectancy are the growth in cardiac and lung cancer. Asthmatic bronchitis and chronic obstructive pulmonary disease (COPD), which are both serious disorders with a detrimental effect on the quality of life, are brought on by reduced lung function in babies and adults.

Strong evidence on the impact of prolonged exposure to particulate matter on cardiovascular and cardiopulmonary mortality is provided by cohort studies.^[21-23]

Ozone at ground level (O₃)

O₃ is a colorless gas that is essential to the atmosphere and is found in the troposphere. NOx and VOCs, which are generated from natural sources and/or human activities, combine chemically to produce ground-level ozone. O₃ is believed to have a possible connection to a higher risk of respiratory conditions, particularly asthma.^[24]

Because O₃ is a strong oxidant, it may take electrons from other molecules. Polyunsaturated fatty acids are abundant in the surface fluid lining of the respiratory tract and the cell membranes that lay underneath it. The accessible double bonds in these fatty acids are unstable. To produce ozonides, O₃ attacks unpaired electrons and progresses through unstable zwitterions or trioxolane (depending on the presence of water).

Lipohydroperoxides, aldehydes, and hydrogen peroxide are formed when they recombine or break down. The proliferation of lipid radicals and auto-oxidation of cell membranes and macromolecules is assumed to begin through these mechanisms. In epidermal keratinocytes, it also raises the chance of DNA damage, which leads to cellular dysfunction.^[25]

At a concentration that has been consistently observed in many metropolitan locations, O₃ causes a range of harmful consequences in people and experimental animals.^[26] Morphologic, functional, immunologic, and metabolic changes are among the side effects. Although a significant part of breathed O₃ penetrates the lungs because of its poor water solubility, its responsiveness is brushed by the nasopharynx of resting rats and humans in roughly 17% and 40%, respectively.^[27] On an ecological level, O₃ can inhibit carbon uptake in trees, resulting in deforestation, which might have long-term implications for the global food supply.^[28,29]

CO

CO is a colorless and odorless gas created by fossil fuels, especially when combustion is inefficient, such as when coal and wood are burned. With a 250-fold greater affinity than oxygen, CO binds to hemoglobin. Depending on the CO content and exposure time, mild-to-severe poisoning may happen.

Headache, dizziness, weakness, nausea, vomiting, and eventually loss of consciousness are all symptoms of CO poisoning. Symptoms are similar to those of other disorders including food poisoning or viral infections. The loss of oxygen caused by the competitive binding of CO to the heme groups of hemoglobin results in the creation of carboxyhemoglobin, which is poisonous (COHb).

COHb levels <2% have no known negative health consequences in humans, however levels greater than 40%

may be lethal. Known mechanisms of underlying CO toxicity include hypoxia, apoptosis, and ischemia.^[30] If an individual's COHb level increases by more than 5% as a result of CO exposure, circulatory changes occur.

In the early 1990s, the Health Effects Institute (HEI) conducted a series of research on cardiovascular illness to see if COHb levels in the range of 2–6% may cause angina pectoris.^[31] The findings revealed that early angina can develop in certain situations, although the risk of ventricular arrhythmias remains unknown. As a result, lowering ambient CO can lower the risk of myocardial infarction in people who are susceptible to it.

Sulphur dioxide (SO₂)

SO₂ is a colorless, highly reactive gas that is regarded as a significant contaminant in the atmosphere. The primary contributors to CO₂ emissions include industrial processes, fuel consumption, and volcanic eruptions. For the health of humans, animals, and plants, SO₂ is extremely harmful. When patients with respiratory organ disease are exposed to SO₂, they are more likely to develop skin and respiratory organ disorders.

Respiratory irritation and malfunction, as well as worsening of underlying cardiovascular disease, are the main health concerns associated with high SO₂ concentrations. The most frequent clinical symptoms linked with SO₂ exposure include bronchospasm, pulmonary edema, pneumonitis, and acute airway blockage. It is absorbed mostly in the upper airways. It can produce bronchospasm and mucus discharge in humans as a sensory irritant.

Residents in industrialized areas who are exposed to SO₂ at low concentrations (<1 parts per million [ppm]) in polluted ambient air may get severe bronchitis. When opposed to nose breathing, mouth breathing allows more SO₂ to penetrate the lungs. Increased airflow during deep, fast breathing improves gas penetration into the lungs' deeper parts.

As a result, persons who exercise in dirty air breathe more SO₂ and are more prone to experience discomfort. When SO₂ accumulates in the airway, it dissolves as sulfite or bisulfite in the surface lining fluid and is easily transported throughout the body. The sulfite appears to interact with sensory receptors in the airways to generate bronchoconstriction that is both locally and centrally mediated.

The eyes (lacrimation and corneal opacity), mucous membrane, and skin can all be damaged by SO₂ (redness, and blisters). The Environmental Protection Agency states that the annual limit for SO₂ in the US is 0.03 ppm (EPA). Due to SO₂'s solubility in water, it causes acid rain and soil acidification. SO₂ decreases the quantity of oxygen in the sea, resulting in the death of marine creatures and plants.^[32]

NOx

NOx are significant ambient air pollutants that have been linked to an increased risk of respiratory illnesses.^[32] They are traffic-related air pollutants since they are mostly generated by vehicle engines.

They are lung irritants that, if breathed at a high enough dose, can cause pulmonary edema. Although NO₂ is generally less hazardous than O₃, it can nonetheless create serious toxicological issues. T-lymphocytes, particularly CD8+ cells and natural killer cells, have been demonstrated to be affected by exposures of 2.0–5.0 ppm, which play a crucial role in the host's defense against viruses. Epidemiological studies have demonstrated that elevated NO₂ levels lower the frequency of respiratory illnesses in children. Coughing and wheezing are the most frequent symptoms of NOx poisoning, although other symptoms include irritation of the eyes, nose, or throat, headache, dyspnea, chest discomfort, diaphoresis, fever, bronchospasm, and pulmonary edema. According to another study, NOx levels between 0.2 and 0.6 ppm are safe for humans.^[33]

Lead

Lead, often known as plumb, is a poisonous heavy metal utilized in a variety of industries.^[34] Both indoor and outdoor sources of Pb pollution are possible. It is released by automobile engines, particularly those powered by fuel containing Pb tetraethyl. Smelters, battery facilities, irrigation water wells, and wastewater treatment plants are additional sources of Pb emissions into the environment.^[34,35]

The purpose of the examination was to determine the blood Pb level in traffic cops. As a result of this study, Pb exposure has been recognized as one of the major contributors to environmental pollution.^[36] Pb is highly hazardous to toddlers and fetuses at even low doses.^[37] The body's soft tissue, bones, and blood all contain Pb.

Pb can harm the kidneys, the neurological system, and other organs since it is not easily eliminated.^[38] The most frequent symptoms of Pb poisoning are abdominal discomfort, anemia, hostility, constipation, headaches, irritability, loss of attention and memory, diminished sensations, and sleep difficulties.

Pb poisoning causes a variety of issues, including high blood pressure, infertility, digestive and renal failure, and muscle and joint discomfort. Pb absorption by the lungs is influenced by particle size and concentration. Approximately 90% of Pb particles ingested from the ambient air are tiny enough to be reserved.

Pb that has been retained in the body is absorbed through the alveoli and causes poisoning. Pb is a potent neurotoxin, and newborns and children are among the most vulnerable

populations. Pb has been connected to childhood hyperactivity, antisocial behavior, learning disabilities, memory impairment, and mental retardation.^[39,40]

As a result, lowering the Pb level in the ambient air is critical.^[41] Pb exposure is common and often goes unnoticed.^[42] Pb poisoning can impact several sections of the body, including the cardiovascular, renal, and reproductive systems, but the neurological system is the main target for Pb toxicity.^[43] The inhibition of N-methyl-D-aspartate receptors by Pb disrupts the normal operation of intracellular second messenger systems. Pb may also serve as a second messenger, causing protein alteration through a variety of physiological mechanisms such as protein kinase activation or deactivation.

Other air pollutants

The majority of other important air contaminants are classed as carcinogenic or mutagenic. VOCs such as benzene, toluene, ethyl benzene, and xylene, PAHs such as acenaphthene, *benzopyrene*, anthracene, and acenaphthylene, and other organic pollutants such as dioxins are some of the pollutants suspected to be responsible for the occurrence and development of cancer in humans. All of these are unwelcome chemical pollutants created almost entirely by industrial processes and human activities.^[44-46]

HEALTH HAZARDS

In terms of health risks, air toxicants are any odd suspended substance in the air that interferes with the normal operation of human organs. The respiratory, cardiovascular, ophthalmologic, dermatologic, neuropsychiatric, hematologic, immunologic, and reproductive systems are the principal harmful consequences of air pollution exposure, according to published evidence. However, long-term molecular and cell damage may result in a variety of malignancies.^[47,48] However, even modest amounts of air toxicants have been found to be harmful to vulnerable groups such as children and the elderly, as well as individuals with respiratory and cardiovascular illnesses.^[49]

Respirator disorders

As most pollutants enter the body through the lungs, the respiratory system may be considered the first line of defense against the onset and progression of disorders brought on by airborne contaminants. Inhaled pollutants produce varied levels of harm in the respiratory system depending on the dosage and deposition in target cells. The initial consequence in the upper respiratory system is inflammation, particularly in the trachea, which causes voice problems. Air pollution is recognized as a significant environmental risk factor for several respiratory diseases, including lung cancer and asthma.^[50,51] Air, pollutants, especially PMs, and other

respirable substances such dust, O₃, and benzene may develop as a result of exposure to air toxicants.^[52-58] Some studies^[59-61] have discovered a connection between air pollution from traffic and/or industry and a higher risk of COPD. The treatment for illnesses brought on by other toxic substances is identical to the therapy for respiratory ailments brought on by air pollution.

Cardiovascular dysfunctions

A connection between air pollution and cardiac-related illnesses has been discovered by several experimental and epidemiologic studies.^[62-66] Air pollution has been related to changes in white blood cell counts, which may have an effect on cardiovascular health. On the other hand, a study utilizing animal models found a connection between air pollution exposure and hypertension.^[67] Both the right and left ventricles can get enlarged as a result of exposure to elevated NO₂ levels in the air caused by traffic.^[68,69] Treatment for cardiovascular illness should be undertaken in addition to antidote therapy, which is only accessible for a few cardiotoxic substances like CO.

Problems related to neuropsychiatry

There has been much discussion on the relationship between the neurological system and exposure to dangerous chemicals that are in the air. However, it is currently believed that these dangerous substances harm the nervous system. Among the detrimental impacts of air pollution on the nervous system are neurological issues and mental illnesses. Particularly in infants, neurological impairment can have catastrophic consequences. On the other side, psychiatric disorders lead to antagonism and antisocial behavior. Recent studies have found links between air pollution and neurobehavioral hyperactivity, criminal conduct, and inappropriate behavior for one's age.^[70,71] Neuroinflammation,^[72] Alzheimer's disease,^[73] and Parkinson's disease^[73] have all been associated with an elevated risk of air pollution.^[74] According to certain studies,^[74-76] there is a correlation between high air pollution levels in megacities and aggressive behavior and anxiety.

Other long-term complications

The skin is both the first organ to be contaminated by a pollutant and the first line of defense against a foreign virus or infectious agent. The first organ to be impacted by pollution is the skin. The first organ to get contaminated is the skin. The absorption of contaminants from the environment by this organ is equal to respiratory uptake.^[77]

It has been demonstrated that air pollutants from traffic, such as PAHs, VOCs, oxides, and PM, have an influence on skin aging and cause pigmented spots on the face.^[78-80] Toxic air pollutants, whether breathed or absorbed via the skin, have

the potential to harm internal organs.^[81] Hepatocarcinogen compounds are present in several of these contaminants.^[82,83] There is some evidence that air pollutants, particularly traffic-associated air pollution, play a role in the occurrence of autism and related diseases in fetuses and children.^[84-87]

One possible cause of autism and other brain disorders has been the disruption of the endocrine system by chemical contaminants.^[88] Several studies have found associations between air pollution exposure and late-pregnancy fetal head size,^[89] fetal growth,^[90] and low birth weight.^[91,92] Several environmental variables, such as poor air quality, can impact several disorders connected to immune system dysfunction.^[93,94] Poor air quality in people can cause serious immune system problems, including abnormally high blood levels of the complement component C3 and the immunoglobulins (Ig) IgA and IgM. It results in chronic inflammatory diseases of the respiratory system.^[95]

Exposure to these immunotoxicants at different periods may result in immunological dysfunction, which can raise the risk of a number of illnesses, including neuroinflammation and a reduced innate immune response in the brain.^[96] On macrophages, air pollutants alter antigen presentation by upregulating stimulatory molecules such as CD80 and CD86.^[97]

The eye is a sensitive organ to the harmful effects of airborne pollutants, including domestic air pollution.^[98] Air pollution's clinical impact on the eyes might range from asymptomatic eye issues to dry eye syndrome. Over time, exposure to air pollution raises the risk of developing retinopathy and other visual disorders.

Furthermore, there is no evidence linking air pollution to eye irritation, dry eye syndrome, and some of the more serious or blinding diseases.^[99,100] Air pollution is connected to short-term increases in the number of patients attending the ophthalmological emergency department, according to studies.^[101,102]

DETECTION TECHNIQUES

Gas chromatography-mass spectrophotometry (GC-MS)

Most greenhouse gases, including CO₂, CH₄, SF₆, and N₂O, as well as CO, are measured using gas chromatography [Figure 1]. One of the inlets of gas chromatography is an inert carrier flow.

The column's walls are covered with the stationary phase, which interacts with the under-investigation gas constituents. Each component enters the detector at a different time due to the interaction between the sample and the stationary phase in the column, allowing for the separation of their

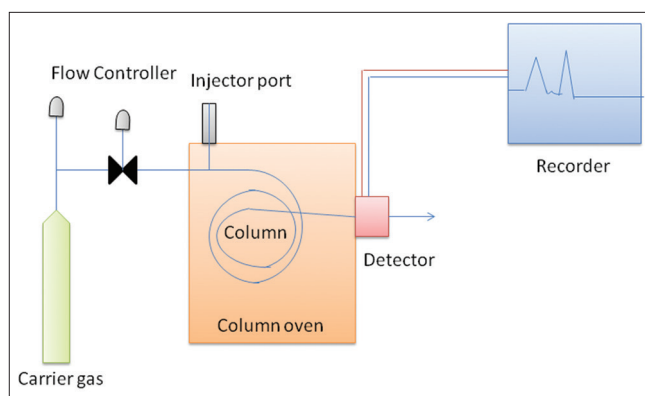


Figure 1: Schematic diagram of a gas chromatograph

measurements. For monitoring organic contaminants in the environment, GC-MS is an excellent instrument. The cost of GC-MS equipment has decreased significantly, while its reliability has grown, contributing to its growing use in environmental investigations. In air, soil, and water, it is commonly used to detect dibenzofurans, dioxins, herbicides, sulfur, pesticides, phenols, and chlorophenols.^[103]

Ultraviolet fluorescence method

The absorption of photons by gases at different wavelengths is the basis for spectrophotometry [Figure 2]. When light with a known intensity spectrum passes through a sample, the intensity spectrum of the departing radiation may be used to estimate the gas's composition. Following the Beer-Bouguer-Lambert-Law, the absorption wavelengths where intensity declines considerably represent a material's footprint, but the exact values of wavelength-dependent extinction offer information on concentration:

$$I = I_0 \exp(-cL\epsilon) \quad (\text{Eq. 1})$$

where I denotes the radiation intensity, c the concentration, the absorptivity coefficient, and L the optical path length.

Spectrophotometry is divided into two components. One is infrared spectrophotometry, which relies on molecule rotation and vibration excitation at wavelengths more than 800 nm, and the other is ultraviolet-visible spectrophotometry, which relies on electron excitation and atomic absorption at wavelengths between 200 and 800 nm.

The SO₂ concentration is determined using the ultraviolet fluorescence technique, which involves exposing the sample to ultraviolet (UV) irradiation with powerful SO₂ molecule excitation. As the atom's higher energy level is moved to its ground state, energy is released as fluorescing radiation. The radiation, which is proportional to the SO₂ level, is detected using a photomultiplier tube.

The measurement of ozone concentration is based on ultraviolet absorption, or photometry, which is dependent on

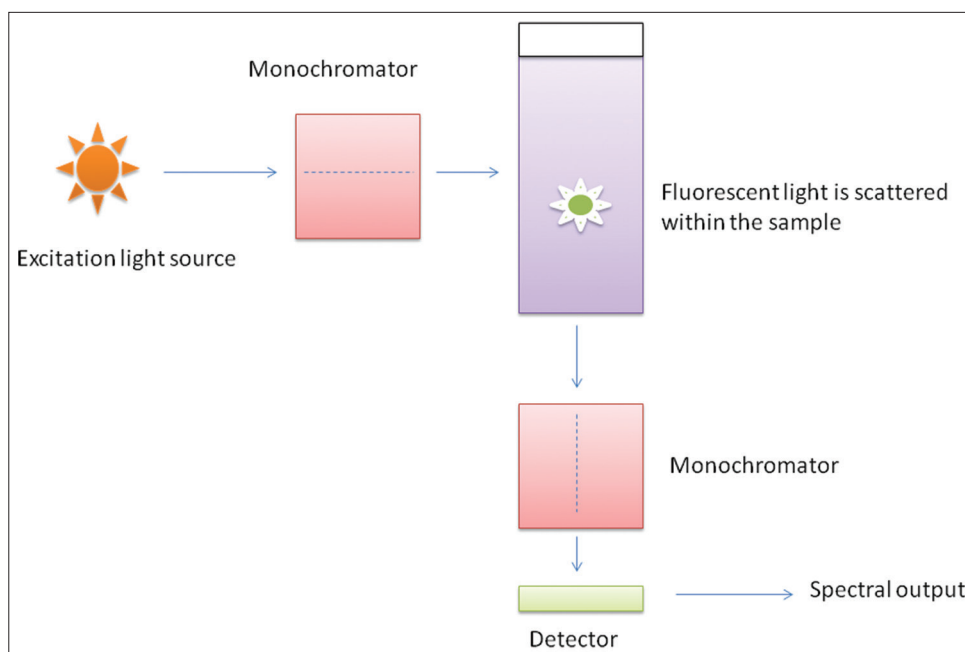


Figure 2: Ultraviolet fluorescence spectrophotometer

ozone's absorption of light with a wavelength of 254 nm. UV light and clean air are used as radiation sources (zero). The described approach satisfies the demanding requirements for O_3 measurement^[104] by automatically compensating for pressure and temperature.

Chemiluminescence analyzer

The most frequent method for measuring NO , NO_2 , and NO_x concentrations is chemiluminescence [Figure 3]. The basis of this approach is based on the ozone-induced excitation of nitrogen molecules. The release of radiation as chemiluminescence occurs when the molecule is translated into the fundamental energy state. A photomultiplier tube detects this radiation.

The architecture of the analyzer allows for the collection of data on nitrogen monoxide (NO), nitrogen dioxide (NO_2), and NO_x concentrations. The approach is based on the fact that NO_2 is produced when NO reacts with ozone. This NO_2 molecule is energized and emits radiation with a wavelength of 1100nm:



Photomultiplier tubes boost the liberated radiation and provide immediate information about the NO content. The measurement is done in two steps: first, the sample is separated and then passed through a converter that converts all NO_2 to NO . Then, a constant volume of ozone is added

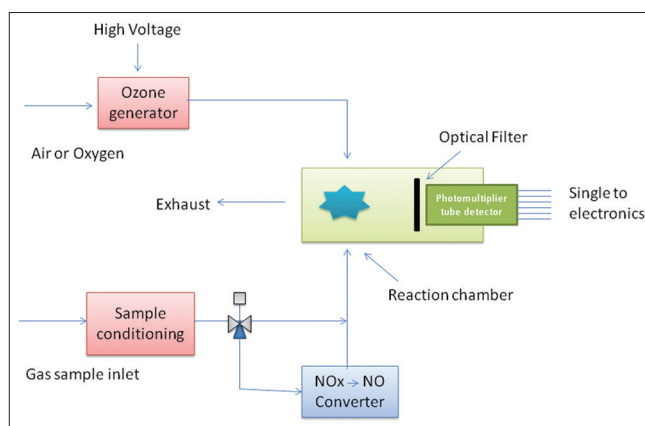


Figure 3: Chemiluminescence analyzer

before it enters the measurement chamber. The concentration of total NO_x components can be determined by evaluating the intensity of emitted radiation. To learn more about each component, the same experiment is run without the converter, which just allows the original NO concentration to be evaluated. Based on the measured amounts of NO_x and NO , the concentration of NO_2 is computed. Although a comparable method for measuring ozone concentrations using either NO or ethane (C_2H_4) is available, chemiluminescence analysis is more generally employed for ozone concentration measurement due to cost and safety concerns.^[105]

Laser spectroscopy

The field of laser spectroscopy [Figure 4] is continuously evolving and expanding. The potential and recognized applications of laser spectroscopy to chemical and biological

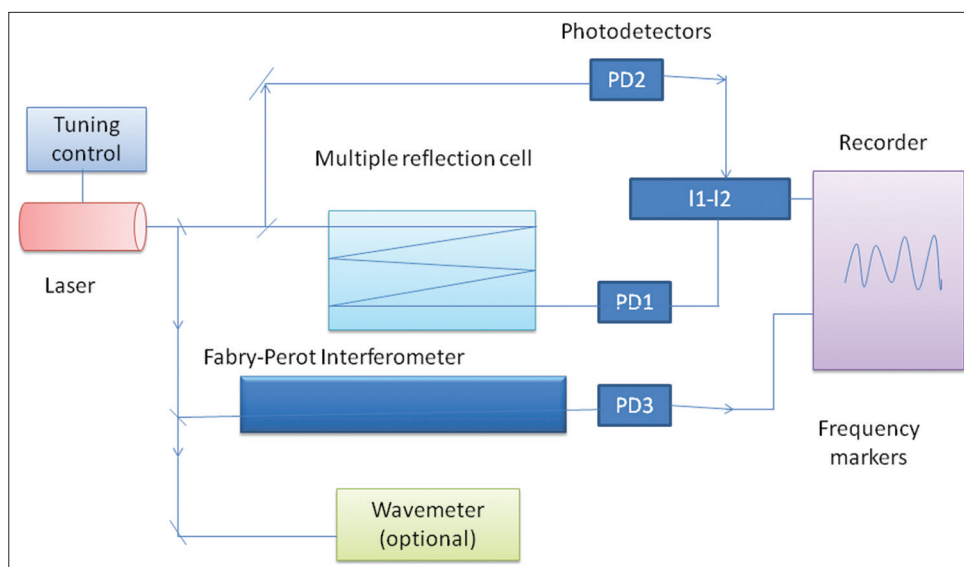


Figure 4: Functioning of laser spectroscopy

issues, as well as its usage in medicine as a diagnostic and therapeutic tool, can be considered the most important developments.^[106] Its contributions to the solution of environmental problems are also noteworthy.

Fourier-transform infrared spectroscopy (FT-IR) spectrophotometry

FT-IR spectrophotometry infrared spectrophotometry [Figure 5] is typically used to quantify pollutant gas emissions such as CO, CO₂, NO, SO₂, and hydrocarbons. It is also commonly used to detect CO₂ and CO in ambient and interior air quality tests. Gases such as NO and O₃ that absorb a lot of light in the UV region are analyzed using ultraviolet spectrophotometry.

The absorption lines usually overlap and cannot be easily differentiated in a complicated system with many components, such as contaminated air. One method to solve this issue is to broaden the wavelength range of the radiation and identify other absorption lines from which the components may be recognized, either by separating the sample and adding a reactant that neutralizes one of the colliding components or by employing a chemical filter.

The method of IR-correlation absorption spectrometry is used to determine CO concentration. An infrared source emits infrared light that passes through two parallel cells, one of which contains a background gas that does not absorb it and the other of which contains the flowing sample of ambient air that is being studied. The ratio of the CO concentration to the energy differential between the reference cell and the sample cell.

Many chemical species with absorbance spectra in the two IR atmospheric window zones are significant to the clean air

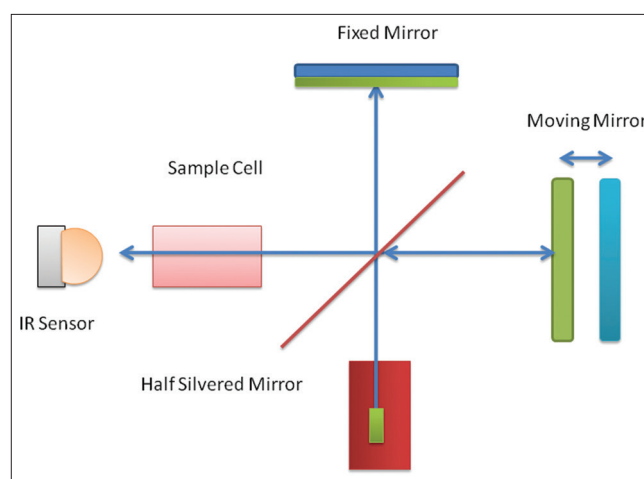


Figure 5: Mechanism of infrared spectrophotometry

act amendment and worldwide monitoring investigations. The first ranges from 750 to 1200 cm⁻¹ (13.3–8.3 mm), while the second ranges from 2100 to 3000 cm⁻¹ (4.2–3.3 mm). CO₂ and H₂O, for example, may be easily identified at 756 and 771 cm⁻¹, O₃ at 1043 and 1064 cm⁻¹, CO at 2100 and 2177 cm⁻¹, N₂O at 2191 and 2223 cm⁻¹, and CH₄ at 2840 and 2930 cm⁻¹. To construct an interferogram, the FT-IR employs a Michelson interferometer with a huge aperture of around 5.0 cm diameter. The interferogram (a modulated beam) is sent by FT-IR systems so that it can be distinguished from unmodulated IR energy generated by the background when it reaches the receiver. The interferogram is transformed into a spectrum using the Fourier transform.

The many benefit of FT-IR is that it can identify several species at the same time since it detects the full spectral band at once. The retromirror is normally 24" in diameter, while the source and receiver telescope lenses are usually 12" to 15" in diameter. The IR energy between 750 and 4000

wavenumbers (cm^{-1}) is converted into an electrical signal using a mercury-cadmium-telluride detector chilled in liquid nitrogen.

The automation of quantitative analysis using multicomponent classical least squares (CLS) was a key development in the application of FT-IR spectrophotometry for gas analysis (CLS). CLS employs Beer's Law, which states that $I(n) = I_0(n) \exp(-A(n))$ with $A(n) = a(n)CL$, where I and I_0 are the measured and transmitted intensities, n is the wavenumber (cm^{-1}), $A(n)$ is the absorbance, $a(n)$ is the absorption coefficient, C is the concentration of the absorption gas, and L is the radiation path length through the gas. The absorption Coefficient incorporates the distinctive "fingerprint" forms of the absorption spectra of the individual species, and the absorbance is related to the concentration-path length product, CL . CLS fits are made between the observed spectrum and a collection of reference spectra while also fitting a linear baseline over the wavenumber area given. Each reference spectrum is created using a dry air combination at one-atmosphere total pressure.^[107]

Light detection and ranging (LDAR)

LDAR is a ground-based remote sensing method for obtaining high temporal and spatial resolution concentration fields [Figure 6]. Similar to spectrophotometry, it operates on the premise that when a beam of light is produced, materials absorb it at a particular wavelength and scatter it back as isotropic light. LIDAR uses a monochromatic laser beam at the component's absorption wavelength to detect backscatter from the atmosphere. Its rapid measurement rate allows it to take measurements in a variety of directions in a short amount of time (similar to weather radars), which may be seen as a continuous concentration field.

A distinct absorption LIDAR (DIAL) is frequently used to generate two laser beams, one tuned to the absorption wavelength and the other tuned slightly below or above

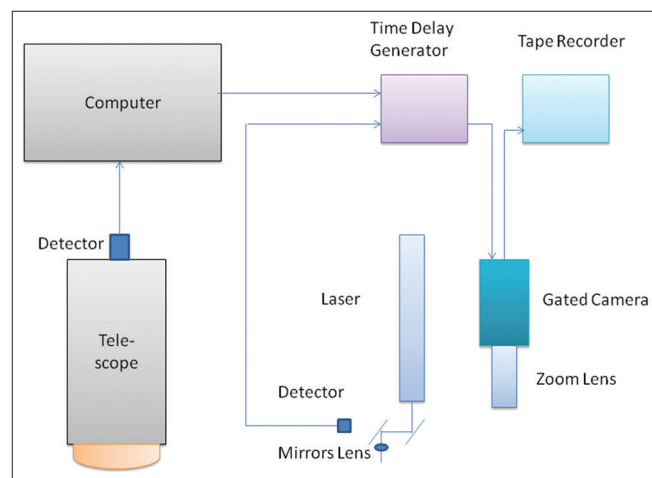


Figure 6: Schematic diagram of light detection and ranging

it, which serves as the reference beam. This technique eliminates measurement errors brought on by global radiation entering the detector. The beams are alternately emitted, and the difference in backscatter values can be considered the backscatter to the studied.^[108]

CONCLUSION

Air pollution has a significant influence on human health, triggering and inducing a variety of illnesses that result in high morbidity and mortality, especially in developing nations like India and Iran. As a result, air pollution control is critical and should be at the top of the government's priority list. In these centuries, regulators and politicians must update all rules and regulations pertaining to air pollution. A robust environmental protection agency must lead the coordination between several agencies involved in air pollution. Budgets for administration, research, development, monitoring, and air pollution protection should all be sufficient for an efficient environmental protection agency.

REFERENCES

1. Vallero D. Fundamentals of Air Pollution. USA: Academic Press; 2014.
2. Robinson DL. Air pollution in Australia: Review of costs, sources and potential solutions. Health Promot J Austr 2005;16:213-20.
3. Habre R, Coull B, Moshier E, Godbold J, Grunin A, Nath A, *et al.* Sources of indoor air pollution in New York city residences of asthmatic children. J Expo Sci Environ Epidemiol 2014;24:269-78.
4. Rumana HS, Sharma RC, Beniwal V, Sharma AK. A retrospective approach to assess human health risks associated with growing air pollution in urbanized area of Thar Desert, Western Rajasthan, India. J Environ Health Sci Eng 2014;12:23.
5. Yamamoto SS, Phalkey R, Malik AA. A systematic review of air pollution as a risk factor for cardiovascular disease in South Asia: Limited evidence from India and Pakistan. Int J Hyg Environ Health 2014;217:133-44.
6. Zhang W, Qian CN, Zeng YX. Air pollution: A smoking gun for cancer. Chin J Cancer 2014;33:173-5.
7. Brucker N, Charão MF, Moro AM, Ferrari P, Bubols G, Sauer E, *et al.* Atherosclerotic process in taxi drivers occupationally exposed to air pollution and co-morbidities. Environ Res 2014;131:31-8.
8. Bellini P, Baccini M, Biggeri A, Terracini B. The meta-analysis of the Italian studies on short-term effects of air pollution (MISA): Old and new issues on the interpretation of the statistical evidences. Environmetrics 2007;18:219-29.
9. Vermaelen K, Brusselle G. Exposing a deadly alliance: Novel insights into the biological links between COPD and lung cancer. Pulm Pharmacol Ther 2013;26:544-54.

10. Kan H, Chen B, Zhao N, London SJ, Song G, Chen G, *et al.* Part 1. A time-series study of ambient air pollution and daily mortality in Shanghai, China. *Res Rep Health Eff Inst* 2010;154:17-78.
11. Zhou N, Cui Z, Yang S, Han X, Chen G, Zhou Z, *et al.* Air pollution and decreased semen quality: A comparative study of Chongqing urban and rural areas. *Environ Pollut* 2014;187:145-52.
12. Loomis D, Huang W, Chen G. The International Agency for Research on Cancer (IARC) evaluation of the carcinogenicity of outdoor air pollution: Focus on China. *Chin J Cancer* 2014;33:189-96.
13. Kjellstrom T, Lodh M, McMichael T, Ranmuthugala G, Shrestha R, Kingsland S. Air and water pollution: Burden and strategies for control. In: *Disease Control Priorities in Developing Countries*. New York: Oxford University Press; 2006.
14. Rodopoulou S, Chalbot MC, Samoli E, Dubois DW, San Filippo BD, Kavouras IG. Air pollution and hospital emergency room and admissions for cardiovascular and respiratory diseases in Doña Ana County, New Mexico. *Environ Res* 2014;129:39-46.
15. Carugno M, Consonni D, Randi G, Catelan D, Grisotto L, Bertazzi PA, *et al.* Air pollution exposure, cause-specific deaths and hospitalizations in a highly polluted Italian region. *Environ Res* 2016;147:415-24.
16. Sadeghi M, Ahmadi A, Baradaran A, Masoudipoor N, Frouzandeh S. Modeling of the relationship between the environmental air pollution, clinical risk factors, and hospital mortality due to myocardial infarction in Isfahan, Iran. *J Res Med Sci* 2015;20:757-62.
17. Sahu D, Kannan GM, Vijayaraghavan R. Carbon black particle exhibits size dependent toxicity in human monocytes. *Int J Inflam* 2014;2014:827019.
18. Bentayeb M, Simoni M, Norback D, Baldacci S, Maio S, Viegi G, *et al.* Indoor air pollution and respiratory health in the elderly. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 2013;48:1783-9.
19. Guillam MT, Pédrone G, Le Bouquin S, Huneau A, Gaudon J, Leborgne R, *et al.* Chronic respiratory symptoms of poultry farmers and model-based estimates of long-term dust exposure. *Ann Agric Environ Med* 2013;20:307-11.
20. Gao Y, Chan EY, Li L, Lau PW, Wong TW. Chronic effects of ambient air pollution on respiratory morbidities among Chinese children: A cross-sectional study in Hong Kong. *BMC Public Health* 2014;14:105.
21. Zhou M, Liu Y, Wang L, Kuang X, Xu X, Kan H. Particulate air pollution and mortality in a cohort of Chinese men. *Environ Pollut* 2014;186:1-6.
22. Pelucchi C, Negri E, Gallus S, Boffetta P, Tramacere I, La Vecchia C. Long-term particulate matter exposure and mortality: A review of European epidemiological studies. *BMC Public Health* 2009;9:453.
23. Jerrett M, Finkelstein MM, Brook JR, Arain MA, Kanaroglou P, Stieb DM, *et al.* A cohort study of traffic-related air pollution and mortality in Toronto, Ontario, Canada. *Environ Health Perspect* 2009;117:772-7.
24. Gorai AK, Tchounwou PB, Tuluri F. Association between ambient air pollution and asthma prevalence in different population groups residing in Eastern Texas, USA. *Int J Environ Res Public Health* 2016;13:378.
25. McCarthy JT, Pelle E, Dong K, Brahmabhatt K, Yarosh D, Pernodet N. Effects of ozone in normal human epidermal keratinocytes. *Exp Dermatol* 2013;22:360-1.
26. Lippmann M. Health effects of ozone. A critical review. *JAPCA* 1989;39:672-95.
27. Hatch GE, Slade R, Harris LP, McDonnell WF, Devlin RB, Koren HS, *et al.* Ozone dose and effect in humans and rats. A comparison using oxygen-18 labeling and bronchoalveolar lavage. *Am J Respir Crit Care Med* 1994;150:676-83.
28. Gerrity TR, Weaver RA, Berntsen J, House DE, O'Neil JJ. Extrathoracic and intrathoracic removal of O₃ in tidal-breathing humans. *J Appl Physiol* (1985) 1988;65:393-400.
29. Fares S, Vargas R, Detto M, Goldstein AH, Karlik J, Paoletti E, *et al.* Tropospheric ozone reduces carbon assimilation in trees: Estimates from analysis of continuous flux measurements. *Glob Chang Biol* 2013;19:2427-43.
30. Wilkinson S, Mills G, Illidge R, Davies WJ. How is ozone pollution reducing our food supply? *J Exp Bot* 2012;63:527-36.
31. Akyol S, Erdogan S, Idiz N, Celik S, Kaya M, Ucar F, *et al.* The role of reactive oxygen species and oxidative stress in carbon monoxide toxicity: An in-depth analysis. *Redox Rep* 2014;19:180-9.
32. Allred EN, Bleecker ER, Chaitman BR, Dahms TE, Gottlieb SO, Hackney JD, *et al.* Short-term effects of carbon monoxide exposure on the exercise performance of subjects with coronary artery disease. *N Engl J Med* 1989;321:1426-32.
33. Chen TM, Gokhale J, Shofer S, Kuschner WG. Outdoor air pollution: Nitrogen dioxide, sulfur dioxide, and carbon monoxide health effects. *Am J Med Sci* 2007;333:249-56.
34. Hesterberg TW, Bunn WB, McClellan RO, Hamade AK, Long CM, Valberg PA. Critical review of the human data on short-term nitrogen dioxide (NO₂) exposures: Evidence for NO₂ no-effect levels. *Crit Rev Toxicol* 2009;39:743-81.
35. Balali-Mood M, Shademanfar S, Rastegar Moghadam J, Afshari R, Namaei Ghassemi M, Allah Nemati H, *et al.* Occupational lead poisoning in workers of traditional tile factories in Mashhad, Northeast of Iran. *Int J Occup Environ Med* 2010;1:29-38.
36. Mousavi SR, Balali-Mood M, Riahi-Zanjani B, Yousefzadeh H, Sadeghi M. Concentrations of mercury, lead, chromium, cadmium, arsenic and aluminum in irrigation water wells and wastewaters used for agriculture in Mashhad, Northeastern Iran. *Int J Occup Environ Med* 2013;4:80-6.
37. Manuela C, Francesco T, Tiziana C, Assunta C,

- Lara S, Nadia N, *et al.* Environmental and biological monitoring of benzene in traffic policemen, police drivers and rural outdoor male workers. *J Environ Monit* 2012;14:1542-50.
38. Farhat A, Mohammadzadeh A, Balali-Mood M, Aghajanpoor-Pasha M, Ravanshad Y. Correlation of blood lead level in mothers and exclusively breastfed infants: A study on infants aged less than six months. *Asia Pac J Med Toxicol* 2013;2:150-2.
 39. Farhat AS, Parizadeh SM, Balali M, Balali M, Khademi GR. Comparison of blood lead levels in 1-7 year old children with and without seizure. *Neurosciences (Riyadh)* 2005;10:210-2.
 40. Lidsky TI, Schneider JS. Adverse effects of childhood lead poisoning: The clinical neuropsychological perspective. *Environ Res* 2006;100:284-93.
 41. Lidsky TI, Schneider JS. Lead neurotoxicity in children: Basic mechanisms and clinical correlates. *Brain* 2003;126 (Pt 1):5-19.
 42. American Academy of Pediatrics Committee on Environmental Health. Lead exposure in children: Prevention, detection, and management. *Pediatrics* 2005;116:1036-46.
 43. Kianoush S, Balali-Mood M, Mousavi SR, Shakeri MT, Dadpour B, Moradi V, *et al.* Clinical, toxicological, biochemical, and hematologic parameters in lead exposed workers of a car battery industry. *Iran J Med Sci* 2013;38:30-7.
 44. Kianoush S, Balali-Mood M, Mousavi SR, Moradi V, Sadeghi M, Dadpour B, *et al.* Comparison of therapeutic effects of garlic and d-penicillamine in patients with chronic occupational lead poisoning. *Basic Clin Pharmacol Toxicol* 2012;110:476-81.
 45. Kansal A. Sources and reactivity of NMHCs and VOCs in the atmosphere: A review. *J Hazard Mater* 2009;166:17-26.
 46. Kameda T, Akiyama A, Toriba A, Tang N, Hayakawa K. Atmospheric formation of hydroxynitropyrenes from a photochemical reaction of particle-associated 1-nitropyrene. *Environ Sci Technol* 2011;45:3325-32.
 47. Schecter A, Birnbaum L, Ryan JJ, Constable JD. Dioxins: An overview. *Environ Res* 2006;101:419-28.
 48. Nakano T, Otsuki T. Environmental air pollutants and the risk of cancer. *Gan To Kagaku Ryoho* 2013;40:1441-5.
 49. Kampa M, Castanas E. Human health effects of air pollution. *Environ Pollut* 2008;151:362-7.
 50. Makri A, Stilianakis NI. Vulnerability to air pollution health effects. *Int J Hyg Environ Health* 2008;211:326-36.
 51. Weisel CP. Assessing exposure to air toxics relative to asthma. *Environ Health Perspect* 2002;110 Suppl 4:527-37.
 52. Brunekreef B, Beelen R, Hoek G, Schouten L, Bausch-Goldbohm S, Fischer P, *et al.* Effects of long-term exposure to traffic-related air pollution on respiratory and cardiovascular mortality in the Netherlands: The NLCS-AIR study. *Res Rep Health Eff Inst* 2009;139:5-71.
 53. Valavanidis A, Vlachogianni T, Fiotakis K, Loidas S. Pulmonary oxidative stress, inflammation and cancer: Respirable particulate matter, fibrous dusts and ozone as major causes of lung carcinogenesis through reactive oxygen species mechanisms. *Int J Environ Res Public Health* 2013;10:3886-907.
 54. Tam WW, Wong TW, Wong AH, Hui DS. Effect of dust storm events on daily emergency admissions for respiratory diseases. *Respirology* 2012;17:143-8.
 55. Beelen R, Hoek G, van den Brandt PA, Goldbohm RA, Fischer P, Schouten LJ, *et al.* Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). *Environ Health Perspect* 2008;116:196-202.
 56. Bahadar H, Mostafalou S, Abdollahi M. Current understandings and perspectives on non-cancer health effects of benzene: A global concern. *Toxicol Appl Pharmacol* 2014;276:83-94.
 57. Johannson KA, Vittinghoff E, Lee K, Balmes JR, Ji W, Kaplan GG, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis associated with air pollution exposure. *Eur Respir J* 2014;43:1124-31.
 58. Kelly FJ. Oxidative stress: Its role in air pollution and adverse health effects. *Occup Environ Med* 2003;60:612-6.
 59. Stoner AM, Anderson SE, Buckley TJ. Ambient air toxics and asthma prevalence among a representative sample of US Kindergarten-age children. *PLoS One* 2013;8:e75176.
 60. Chung KF, Zhang J, Zhong N. Outdoor air pollution and respiratory health in Asia. *Respirology* 2011;16:1023-6.
 61. Zeng G, Sun B, Zhong N. Non-smoking-related chronic obstructive pulmonary disease: A neglected entity? *Respirology* 2012;17:908-12.
 62. Ko FW, Chan KP, Hui DS, Goddard JR, Shaw JG, Reid DW, *et al.* Acute exacerbation of COPD. *Respirology* 2016;21:1152-65.
 63. Nogueira JB. Air pollution and cardiovascular disease. *Rev Port Cardiol* 2009;28:715-33.
 64. Snow SJ, Cheng W, Wolberg AS, Carraway MS. Air pollution upregulates endothelial cell procoagulant activity via ultrafine particle-induced oxidant signaling and tissue factor expression. *Toxicol Sci* 2014;140:83-93.
 65. Brook RD. Cardiovascular effects of air pollution. *Clin Sci (Lond)* 2008;115:175-87.
 66. Andersen ZJ, Kristiansen LC, Andersen KK, Olsen TS, Hvidberg M, Jensen SS, *et al.* Stroke and long-term exposure to outdoor air pollution from nitrogen dioxide: A cohort study. *Stroke* 2012;43:320-5.
 67. Steenhof M, Janssen NA, Strak M, Hoek G, Gosens I, Mudway IS, *et al.* Air pollution exposure affects circulating white blood cell counts in healthy subjects: The role of particle composition, oxidative potential and gaseous pollutants – The RAPTES project. *Inhal Toxicol* 2014;26:141-65.
 68. Sun Q, Yue P, Ying Z, Cardounel AJ, Brook RD, Devlin R, *et al.* Air pollution exposure potentiates hypertension through reactive oxygen species-mediated

- activation of Rho/ROCK. *Arterioscler Thromb Vasc Biol* 2008;28:1760-6.
69. Leary PJ, Kaufman JD, Barr RG, Bluemke DA, Curl CL, Hough CL, *et al.* Traffic-related air pollution and the right ventricle. The multi-ethnic study of atherosclerosis. *Am J Respir Crit Care Med* 2014;189:1093-100.
 70. Van Hee VC, Adar SD, Szpiro AA, Barr RG, Bluemke DA, Diez Roux AV, *et al.* Exposure to traffic and left ventricular mass and function: The multi-ethnic study of atherosclerosis. *Am J Respir Crit Care Med* 2009;179:827-34.
 71. Newman NC, Ryan P, Lemasters G, Levin L, Bernstein D, Hershey GK, *et al.* Traffic-related air pollution exposure in the first year of life and behavioral scores at 7 years of age. *Environ Health Perspect* 2013;121:731-6.
 72. Haynes EN, Chen A, Ryan P, Succop P, Wright J, Dietrich KN. Exposure to airborne metals and particulate matter and risk for youth adjudicated for criminal activity. *Environ Res* 2011;111:1243-8.
 73. Calderón-Garcidueñas L, Mora-Tiscareño A, Ontiveros E, Gómez-Garza G, Barragán-Mejía G, Broadway J, *et al.* Air pollution, cognitive deficits and brain abnormalities: A pilot study with children and dogs. *Brain Cogn* 2008;68:117-27.
 74. Calderón-Garcidueñas L, Solt AC, Henríquez-Roldán C, Torres-Jardón R, Nuse B, Herritt L, *et al.* Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid beta-42 and alpha-synuclein in children and young adults. *Toxicol Pathol* 2008;36:289-310.
 75. Rotton J, Frey J, Barry T, Milligan M, Fitzpatrick M. The air pollution experience and physical aggression 1. *J Appl Soc Psychol* 1979;9:397-412.
 76. Evans GW. The built environment and mental health. *J Urban Health* 2003;80:536-55.
 77. Jones JW, Bogat GA. Air pollution and human aggression. *Psychol Rep* 1978;43:721-2.
 78. Goldsmith LA. Skin effects of air pollution. *Otolaryngol Head Neck Surg* 1996;114:217-9.
 79. Singh B, Maibach H. Climate and skin function: An overview. *Skin Res Technol* 2013;19:207-12.
 80. Vierkötter A, Schikowski T, Ranft U, Sugiri D, Matsui M, Krämer U, *et al.* Airborne particle exposure and extrinsic skin aging. *J Invest Dermatol* 2010;130:2719-26.
 81. Drakaki E, Dessinoti C, Antoniou CV. Air pollution and the skin. *Front Environ Sci* 2014;2:11.
 82. Potera C. More human, more humane: A new approach for testing airborne pollutants. *Environ Health Perspect* 2007;115:A148-51.
 83. Motta S, Federico C, Saccone S, Librando V, Mosesso P. Cytogenetic evaluation of extractable agents from airborne particulate matter generated in the city of Catania (Italy). *Mutat Res* 2004;561:45-52.
 84. Ito Y, Ramdhan DH, Yanagiba Y, Yamagishi N, Kamijima M, Nakajima T. Exposure to nanoparticle-rich diesel exhaust may cause liver damage. *Nihon Eiseigaku Zasshi* 2011;66:638-42.
 85. Roberts AL, Lyall K, Hart JE, Laden F, Just AC, Bobb JF, *et al.* Perinatal air pollutant exposures and autism spectrum disorder in the children of nurses' health study II participants. *Environ Health Perspect* 2013;121:978-84.
 86. Kalkbrenner AE, Daniels JL, Chen JC, Poole C, Emch M, Morrissey J. Perinatal exposure to hazardous air pollutants and autism spectrum disorders at age 8. *Epidemiology* 2010;21:631-41.
 87. Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. Traffic-related air pollution, particulate matter, and autism. *JAMA Psychiatry* 2013;70:71-7.
 88. Becerra TA, Wilhelm M, Olsen J, Cockburn M, Ritz B. Ambient air pollution and autism in Los Angeles County, California. *Environ Health Perspect* 2013;121:380-6.
 89. de Cock M, Maas YG, van de Bor M. Does perinatal exposure to endocrine disruptors induce autism spectrum and attention deficit hyperactivity disorders? Review. *Acta Paediatr* 2012;101:811-8.
 90. Ritz B, Qiu J, Lee PC, Lurmann F, Penfold B, Erin Weiss R, *et al.* Prenatal air pollution exposure and ultrasound measures of fetal growth in Los Angeles, California. *Environ Res* 2014;130:7-13.
 91. Liu S, Krewski D, Shi Y, Chen Y, Burnett RT. Association between maternal exposure to ambient air pollutants during pregnancy and fetal growth restriction. *J Expo Sci Environ Epidemiol* 2007;17:426-32.
 92. Stieb DM, Chen L, Eshoul M, Judek S. Ambient air pollution, birth weight and preterm birth: A systematic review and meta-analysis. *Environ Res* 2012;117:100-11.
 93. Yucra S, Tapia V, Steenland K, Naeher LP, Gonzales GF. Maternal exposure to biomass smoke and carbon monoxide in relation to adverse pregnancy outcome in two high altitude cities of Peru. *Environ Res* 2014;130:29-33.
 94. Vawda S, Mansour R, Takeda A, Funnell P, Kerry S, Mudway I, *et al.* Associations between inflammatory and immune response genes and adverse respiratory outcomes following exposure to outdoor air pollution: A HuGE systematic review. *Am J Epidemiol* 2014;179:432-42.
 95. Behrendt H, Alessandrini F, Buters J, Krämer U, Koren H, Ring J. Environmental pollution and allergy: Historical aspects. *Chem Immunol Allergy* 2014;100:268-77.
 96. Hadnagy W, Stiller-Winkler R, Idel H. Immunological alterations in sera of persons living in areas with different air pollution. *Toxicol Lett* 1996;88:147-53.
 97. Dietert RR. Distinguishing environmental causes of immune dysfunction from pediatric triggers of disease. *Open Pediatr Med J* 2009;3:38-44.
 98. Saxon A, Diaz-Sanchez D. Air pollution and allergy: You are what you breathe. *Nat Immunol* 2005;6:223-6.
 99. West SK, Bates MN, Lee JS, Schaumberg DA, Lee DJ, Adair-Rohani H, *et al.* Is household air pollution a risk factor for eye disease? *Int J Environ Res Public Health*

- 2013;10:5378-98.
100. Klopfer J. Effects of environmental air pollution on the eye. *J Am Optom Assoc* 1989;60:773-8.
 101. Rozanova E, Heilig P, Godnić-Cvar J. The eye – A neglected organ in environmental and occupational medicine: An overview of known environmental and occupational non-traumatic effects on the eyes. *Arh Hig Rada Toksikol* 2009;60:205-15.
 102. Chang CJ, Yang HH, Chang CA, Tsai HY. Relationship between air pollution and outpatient visits for nonspecific conjunctivitis. *Invest Ophthalmol Vis Sci* 2012;53:429-33.
 103. Amirav A, Gordin A, Poliak M, Fialkov AB. Gas chromatography-mass spectrometry with supersonic molecular beams. *J Mass Spectrom* 2008;43:141-63.
 104. Murphy R, Stedmon CA, Wenig P, Bro R. OpenFluor-an online spectral library of auto-fluorescence by organic compounds in the environment. *Anal Methods* 2014;6:658-61.
 105. Shah SN, Lin JM. Recent advances in chemiluminescence based on carbonaceous dots. *Adv Colloid Interface Sci* 2017;241:24-36.
 106. Wu X, Yamilov A, Liu X, Li S, Dravid VP, Chang RP, Cao H. Ultraviolet photonic crystal laser. *Appl Phys Lett* 2004;85:3657-9.
 107. Riviere C, Myhra S. *Handbook of Surface and Interface Analysis: Methods for Problem-Solving*. USA: CRC Press; 2009.
 108. Jochem A, Höfle B, Rutzinger M. Extraction of vertical walls from mobile laser scanning data for solar potential assessment. *Remote Sens* 2011;3:650-67.

Source of Support: Nil. **Conflicts of Interest:** None declared.