Environmental Health Impacts of Natural and Man-Made Chemicals

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Summary and Keywords

Humans have been exposed to naturally occurring toxic chemicals and materials over the course of their existence as a species. These materials include various metals, the metalloid arsenic, and atmospheric combustion particulates, as well as bacterial, fungal, algal, and plant toxins. They have also consumed plants that contain a host of phytochemicals, many of which are believed to be beneficial, such as plant polyphenols. People are exposed to these various substances from a number of sources. The pathways of exposure include air, water, groundwater, soil (including via plants grown in toxic soils), and various foods, such as vegetables, fruit, fungi, seafood and fish, eggs, wild birds, marine mammals, and farmed animals.

An overview of the various health benefits, hazards and risks relating to the risks reveals the very wide variety of chemicals and materials that are present in the natural environment and can interact with human biology, to both its betterment and detriment.

The major naturally occurring toxic materials that impact human health include metals, metalloids (e.g., arsenic), and airborne particulates. The Industrial Revolution is a major event that increased ecosystem degradation and the various types and duration of exposure to toxic materials. The explosions in new organic and organometallic products that were and still are produced over the past two centuries have introduced new toxicities and associated pathologies. The prevalence in the environment of harmful particulates from motor-vehicle exhaust emissions, road dust and tire dust, and other combustion processes must also be considered in the broader context of air pollution.

Natural products, such as bacterial, fungal, algal, and plant toxins, can also have adverse effects on health. At the same time, plant-derived phytochemicals (i.e., polyphenols, terpenoids, urolithins, and phenolic acids, etc.) also have beneficial and potential beneficial effects, particularly with regard to their anti-inflammatory effects. Because inflammation is associated with most disease processes, phytochemicals that have antioxidant and anti-inflammatory properties are of great interest as potential nutraceuticals. These potentially beneficial compounds may help to combat various cancers; autoimmune conditions; neurodegenerative diseases, including dementias; and psychotic conditions, such as depression, and are also essential micronutrients that promote health and well-being. The

cellular and molecular mechanisms in humans that phytochemicals modulate, or otherwise interact with, to improve human health are now known.

In the early 21st century, some of the current pollution issues are legacy problems from past industrialization, such as mercury and persistent organic pollutants (POPs). These POPs include many organochlorine compounds (e.g., polychlorinated biphenyls, pesticides, polychlorinated and polybrominated dibenzo-dioxans and -furans), as well as polycyclic aromatic hydrocarbons (PAHs), nitro-PAHs, and others. The toxicity of chemical mixtures is still a largely unknown problem, particularly with regard to possible synergies. The continuing development of new organic chemicals and nanomaterials is an important environmental health issue; and the need for vigilance with respect to their possible health hazards is urgent. Nanomaterials, in particular, pose potential novel problems in the context of their chemical properties; humans have not previously been exposed to these types of materials, which may well be able to exploit gaps in our existing cellular protection mechanisms.

Hopefully, future advances in knowledge emerging from combinatorial chemistry, molecular modeling, and predictive quantitative structure-activity relationships (QSARs), will enable improved identification of the potential toxic properties of novel industrial organic chemicals, pharmaceuticals, and nanomaterials before they are released into the natural environment, and thus prevent a repetition of past disastrous events.

Keywords: human health, pollutants, metals, arsenic, polycyclic aromatic hydrocarbons, polyphenols, airborne particles, nanomaterials, ecosystem degradation

Background

Humans have been exposed to bioactive environmental chemicals throughout their evolution. Many beneficial natural products are present in plants and foodstuffs (e.g., vegetables, fruit, fungi, fish, and shellfish); harmful toxic natural products are also present in plants and foodstuffs, such as fungal toxins (e.g., rye ergot, aflatoxins, and ochratoxins) and the algal toxins in fish and shellfish (Abrahams et al., 2004; Bennick, 2002; Christensen, Moran, & Weibe, 1999; Del Rio, Rodriguez-Mateos, Spencer, Tognolini, Borges, & Crozier, 2013; Kennedy & Wightman, 2011; Lippmann, Yeates, & Albert, 1980; Malloy & Marr, 2001; Matricardi et al., 2000; Postolache et al., 2008; Rook, 2013; Skaug, Helland, Solvoll, & Saugstad, 2001). Chemical pollutants have also been present across geological time periods, such as toxic metals and metalloids in soil and water, as have harmful combustion products, such as polycyclic aromatic hydrocarbons (PAHs) and sulphur, oxygen, and nitrogen heterocyclic compounds (Ariza-Ariza, Mestanza-Peralta, & Cardiel, 1998; Ayangbenro & Babalola, 2017; Wilson & Jones, 1993). Combustion products have been produced by wildfires and the cooking of food and, of course, from the clearing of forested land for agriculture and industry (Gavrilescu, Demnerová, Aamand, Agathos, & Fava, 2015). Harmful particulates have been present in the form of volcanic dust, soot particles, and airborne arsenic-contaminated soil particles. Algal and bacterial toxins have

probably also been present in airborne nano-droplets of seawater throughout the course of human evolution (see Moore, 2015). Airborne plant and fungal materials, such as pollen, spores, and plant fragments, containing both beneficial and harmful natural products, have been inhaled and ingested with respiratory mucus as well (Moore, 2015).

Exposure to natural products, both beneficial and toxic, have helped to drive the evolution of the battery of enzymes that are responsible for their metabolism and detoxication. These enzymes are often referred to as the “drug metabolizing enzymes” and primarily constitute the phase I cytochromes P450 (CYPs), the phase II conjugating enzymes, and various esterases (Nebert & Dieter, 2000). These biotransformation enzymes are mainly associated with the intestine and the liver, and they provide humans with a powerful set of tools for removing the harmful products that are naturally present in foodstuffs, though this can be a double-edged sword in that some harmful organic chemicals (xenobiotics) can be activated by biotransformation enzymes to more toxic forms, including carcinogens. In addition, biotransformation enzymes are crucial in the generation of many essential chemicals, such as prostaglandins and steroids, which are necessary for endocrinological signaling and cell signaling. Without this exposure to the various environmental products, both beneficial and harmful, we probably would be less well equipped to deal with the chemical challenges provided by the current environment (Nebert & Dieter, 2000).

Other evolutionary drivers for cellular defense processes have included exposure to toxic metals and metalloids (e.g., arsenic), which are widely present in the environmental geochemistry (Radivojević, Rehren, Kuzmanović-Cvetković, Jovanović, & Northover, 2013). Throughout prehistorical and historical periods, many toxic metals and metalloids have been exploited in the manufacture of tools, plumbing, and weapons (e.g., copper, mercury, lead, arsenical bronze, and bronze) and, in more recent times, in industrial usage (e.g., iron, steel, cadmium, zinc, silver, uranium, thorium polonium, and plutonium). These evolutionary drivers have influenced the detoxication pathways for toxic metals and metalloids and include metal-binding metallothioneins, antioxidant protection, and intra-lysosomal sequestration (Kiselyov et al., 2011; Sternlieb & Goldfischer, 1976).

An overview of the various health benefits, hazards, and risks shows the very wide variety of chemicals and materials that are present in the natural environment and can interact with human biology, both to its betterment and detriment.

Exposure Pathways for Chemical Pollutants and Biogenic Products

Chemical Pollutants

Toxic chemical contaminants (pollutants) are released into the soil, water, or air from accidental or intentional chemical spills, by leaking landfills or dumps, through spraying, or from vehicle- and industrial-combustion processes. Pollutants follow certain pathways

from the time of release to the point of human contact. People become exposed to pollutants by touching, breathing, or ingesting substances that contain the chemical (Figure 1; Agency for Toxic Substances and Disease Registry, 2017; Aylward, Kirman, Schoeny, Portier, & Hays, 2013; Eisenberg & McKone, 1998).

Human health is at risk of disease from contaminants if

1. there is direct exposure to a contaminant; or
2. the contaminant is toxic (i.e., a pollutant).

A complete exposure pathway, with the following components, has to be present for disease to occur:

1. Transport media—how the contaminant is transported through the environment.
2. Exposure point—how people come into contact with the contaminant.
3. Exposure route—how the contaminant enters the body.
4. Receptor population—how susceptible the human population is to the contaminant.

Effective risk assessment can provide a means to reduce risks and also to block or ameliorate relevant pathways and exposure scenarios. Before starting such a risk assessment, an exposure assessment is required. However, assessing how much of a toxic contaminant people have been exposed to can be difficult and frequently has to be partially based on assumptions and previous data (Figure 1; Agency for Toxic Substances and Disease Registry, 2017; Eisenberg & McKone, 1998).

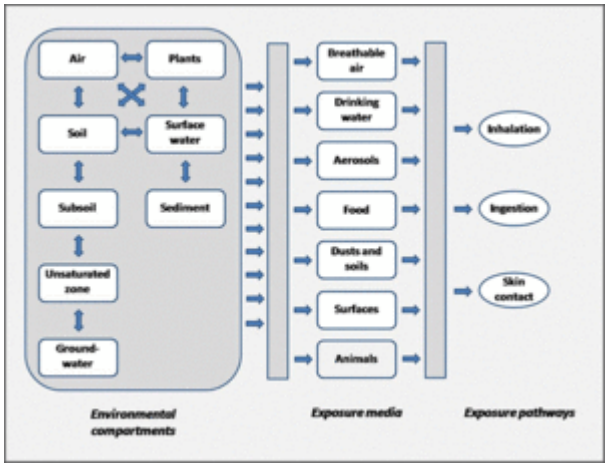

Figure 1. Links among environmental media, exposure media, and exposure routes.

Adapted from Eisenberg and McKone (1998).

Pollutants usually enter the body by three general routes: inhalation, ingestion, or skin absorption (Figure 1). The amount of pollutant (dose) depends on the duration and intensity of the exposure and, crucially, the amount that reaches the human organ in which the relevant effects can occur (e.g., the liver, lung, brain, or immune system).

Exposure to mixtures of pollutants can occur simultaneously from many sources and through multiple routes (Agency for Toxic Substances and Disease Registry, 2017; Eisenberg & McKone, 1998). Pathways of exposures to lead, for example, include air pollution from traffic and industrial emissions, drinking water, food, tobacco smoke, dusts, paints and other industrially produced commodities, and soil. Effective exposure assessment generally requires detailed knowledge about the spatial distribution of the pollutants of concern, the temporal variations in pollution levels, and the various processes of exposure.

The degradation of ecosystems by chemical pollutants and other environmental stressors can, through multiple mechanisms, affect the quality of the water we drink, the food we eat, and the air we breathe and impact our vulnerability and exposure to natural hazards (Myers et al., 2013). There is already strong evidence that the changes are pervasive and affect almost every natural system on Earth, and that the rate of adverse change is accelerating. They impact, both directly and indirectly, most of the diseases that make up the global burden of disease (Myers et al., 2013). It is not yet possible to quantify the burden of disease associated with the disruption of these natural systems to the same degree that has been achieved with other types of environmental health risks (Myers et al., 2013). Nonetheless, it is probable that the health burden associated with ecosystem degradation will be found to be comparable to that of other types of environmental health risk that contribute to the global burden of disease.

Consequently, the range of variables that may need to be examined is often considerable and may need to include many different environmental pollutants (e.g., hazardous chemicals, radioactivity, dusts, and particulates) from many different sources (e.g., energy production, industry, pesticide use), released either continuously or sporadically and either under controlled conditions (i.e., in deliberate permitted discharges) or accidentally (Agency for Toxic Substances and Disease Registry, 2017; Eisenberg & McKone, 1998).

Monitoring enables responsible environmental agencies to confirm previous assumptions and assessments that pollution levels may be unacceptably high. Monitoring also enables them to set priorities for making improvements based on the available resources.

Natural Biogenic Products

Plants, algae, fungi, and bacteria produce a vast and diverse assortment of organic compounds, the great majority of which do not appear to participate directly in growth and development. These biogenic substances are generally referred to as *secondary metabolites*. The function of many of them is unknown, but they are increasingly being identified, often because of their potential use as nutraceuticals (Bennick, 2002; Carluccio et al., 2003; Del Rio et al., 2013; Kennedy & Wightman, 2011). Many of these compounds enter the environment and the human food chain; increasingly, they are being found to be bioactive in mammals, including humans.

Although natural products are noted for the complexity of their chemical structures and biosynthetic pathways, they have been thought to be biologically insignificant and somewhat ignored until fairly recently. However, interest in them was stimulated by their utility as dyes, polymers, fibers, glues, oils, waxes, flavoring agents, perfumes, and drugs (Hussain et al., 2012). Recognition of the biological properties of myriad natural products has fueled the current focus in this field—namely, the search for new drugs, including nutraceuticals, antibiotics, insecticides, and herbicides (Del Rio et al., 2013).

Importantly, the growing appreciation of the highly diverse biological effects produced by natural products has prompted an explosion of interest in them and an intensive re-evaluation of the possible roles natural compounds play in plants, especially in the context of their ecological and human health interactions. Many of these biogenic compounds are present in water and soil and as aerosols, either as volatile compounds or associated with airborne particles. Consequently, the routes of human exposure are similar to those that have previously been presented for chemical pollutants (see Figure 1; Eisenberg & McKone, 1998).

However, it is not just plants that produce bioactive natural products: bacteria, archaea, algae, fungi, and animals (e.g., coelenterates, mollusks, insects, arachnids, fish, amphibians, reptiles, and mammals [monotremes]) can also generate many toxic and some beneficial products (Tringali, 2011). However, the focus here is primarily allocated to bacterial, algal, fungal, and plant products.

Toxic Inorganic Chemical Pollutants

Toxic Metals

Metals such as lead, copper, and tin have been used for thousands of years. Lead was used in plumbing systems by the Phoenicians and the Romans. The Romans also used lead-lined containers for the heat reduction of grape must, which was then added to wine during production as a preservative and a flavor sweetener, giving the wine a lead content (Nriagu, 1983; Patterson, Shirahata, & Ericson, 1987).

With the arrival of the Industrial Revolution, many more metals entered the environment in significant quantities. Some metals are toxic when they form soluble compounds; however, certain metals have no biological role (i.e., are not essential minerals) or are toxic only when in a particular chemical form (Jaishankar, Tseten, Anbalagan, Mathew, & Beeregowda, 2014; Tchounwou, Yedjou, Patlolla, & Sutton, 2012). Not all heavy metals are particularly toxic; some heavy metals are essential at low concentrations (e.g., iron, copper, manganese, cobalt, zinc, selenium, molybdenum, and chromium), and some, such as bismuth, have low toxicity (Tchounwou et al., 2012). However, many metals *are* toxic; even small amounts of lead, for example, may have negative health effects. Toxic heavy metals include cadmium, iron, manganese, mercury, lead, and nickel and the radioactive metals thorium, uranium, and plutonium. Although iron and manganese are considered to

be essential, in higher concentrations they are toxic. Metals with lower atomic weights, such as beryllium and lithium, can be toxic in certain circumstances. The toxicity of some metals can be countered by binding to proteins known as mettallothioneins, which also have a role in alleviating oxidative stress (Ruttkay-Nedecky et al., 2013).

Toxic metals can sometimes mimic the action of an essential element in the body, perturbing normal metabolic processes and leading to various pathologies. Metalloids (e.g., arsenic, polonium) are sometimes included in the definition of heavy metals. Radioactive metals have both radiological toxicity and chemical toxicity (Tchounwou et al., 2012). Metals in a valence state that is abnormal for human metabolism may also become toxic, such as chromium(III), which is an essential trace element, although chromium(VI) is a carcinogen (Tchounwou et al., 2012).

Toxic metals such as copper, cadmium, lead, and mercury can bioaccumulate in the body and in food-chain organisms, often becoming sequestered in lysosomes (Beyersmann & Hartwig, 2008; Carmona-Gutierrez, Hughes, Madeo, & Ruckenstuhl, 2016; Jaishankar et al., 2014; Moore, Depledge, Readman, & Leonard, 2004; Sternlieb & Goldfischer, 1976; Tchounwou et al., 2012). Therefore a common characteristic of toxic metals is the chronic nature of their toxicity and resultant pathology (Jaishankar et al., 2014; Tchounwou et al., 2012).

Toxicity is frequently a function of solubility, whereas the insoluble compounds of metals, as well as the metallic forms, often exhibit negligible toxicity (Jaishankar et al., 2014; Tchounwou et al., 2012). The toxicity of any metal depends on its physical chemical speciation and ligand binding. Some organometallic chemical species, such as methylmercury and tetraethyl lead, can be extremely toxic; in other cases, organometallic derivatives are less toxic, for example, the cobaltocenium cation (Egorochkin, Kuznetsova, Khamaletdinova, & Domratcheva-Lvova, 2013). Lead, in the form of tetraethyl lead, was also used as a petrol additive for much of the 20th century despite the ready availability of alternatives, such as ethanol (Gidlow, 2004).

Toxic Metalloids (Arsenic)

Ingestion and inhalation of toxic metalloids is very widespread globally due to contaminated soils and water (Flanagan, Johnston, & Zheng, 2012; World Health Organization [WHO], 2017). Dietary exposure to arsenic is widespread due to the accumulation of arsenic by some varieties of rice (Meharg, 2004; Food Standards Agency, 2016). The consumption of fish and shellfish can also result in exposure to arsenic in the form of arsenobetaine, although this route is believed to be relatively nontoxic. The inhalation and ingestion of airborne soil dust comprising arsenic-rich particles, as well as of leafy vegetables that are grown in that soil, is a route of chronic exposure to arsenic and is believed to contribute to skin and urinary cancers (Argos et al., 2010; WHO, 2017). The recent health problems from arsenic in the groundwater in Bangladesh and West Bengal are an example of the harm the consumption of environmentally occurring arsenic can cause (Flanagan et al., 2012; Smith, Lingas, & Rahman, 2000; WHO, 2017). Pathologies arising

from long-term chronic exposure to arsenic include thickening of the skin, darkening of the skin, abdominal pain, diarrhea, heart disease, stroke, and numbness, as well as cancers including as lung, bladder, and skin cancers (Smith et al., 2000; Tchounwou et al., 2004).

Arsenic perturbs cell function by inhibiting pyruvate dehydrogenase (PDH) complex, resulting in type I cell death, also known as apoptosis (Tchounwou et al., 2012). Arsenic also prevents the use of thiamine, resulting in symptoms that resemble thiamine deficiency. The presence of arsenic in cells stimulates the production of hydrogen peroxide (H_2O_2), which can contribute to oxidative stress (Balakumar & Kaur, 2009). In addition, inorganic arsenic trioxide found in ground water affects membrane potassium channels resulting in neurological disturbances, cardiovascular problems, neutropenia, high blood pressure, central nervous system dysfunction, anemia, and death (Hughes, 2002; Hughes, Beck, Chen, Lewis, & Thomas, 2011).

Exposure to arsenic plays a key role in the pathogenesis of vascular endothelial dysfunction because it inactivates endothelial nitric oxide synthase: this inhibition can lead to a reduction in the generation and bioavailability of nitric oxide (Hughes et al., 2011). As previously mentioned, chronic arsenic exposure induces oxidative stress, which may affect the structure and function of the cardiovascular system (Balakumar & Kaur, 2009). Furthermore, arsenic exposure has been shown to induce atherosclerosis by increasing blood-platelet aggregation and reducing fibrinolysis. Arsenic exposure may also cause arrhythmia by increasing the QT interval and accelerating cellular calcium overload. Finally, chronic arsenic exposure induces cardiovascular pathogenesis by upregulating the expression of tumor necrosis factor-α, interleukin-1, vascular cell adhesion molecule, and vascular endothelial growth factor (Balakumar & Kaur, 2009).

Toxic Non-Metals

Gaseous nitrogen dioxide (NO_2), sulphur dioxide (SO_2), and carbon monoxide (CO) are significant atmospheric pollutants (Chen, Yan, Chiu, & Cheng, 2007; Harrison & Beddows, 2017). Environmental NO_2 exposure may increase the risk of respiratory-tract infections through the pollutant’s interaction with the immune system (Harrison & Beddows, 2017). Sulphur dioxide (SO_2) can also contribute to respiratory symptoms in healthy individuals, as well as in those with underlying pulmonary disease (Chen et al., 2007). Controlled experimental exposure studies have demonstrated that SO_2 can cause changes in air passage physiology, including increased resistance to air flow. Chronic exposure to carbon monoxide is linked to increased risk for adverse cardiopulmonary events, including death. Tramuto et al. (2011) have found that exposure to ambient levels of air pollution (NO_2, SO_2, and CO) is an important determinant of emergency room (ER) visits for acute respiratory symptoms, particularly during the warm weather. ER admittance can also be used as an indicator to evaluate the adverse effects of air pollution on respiratory health Tramuto et al., 2011).

Particulates and Materials

Air pollution introduces a multiplicity of pollutants into the atmosphere that can cause harm to humans (Brauer et al., 2012; Harrison & Beddows, 2017; Kim et al., 2013; Kinney, 2008; WHO, 2013). The adverse health effects of air pollution, observed from both indoor and outdoor environments, have been of considerable concern because of the significant exposure risk, even at relatively low concentrations of pollutants. It is estimated that more than two million deaths occur globally each year as a direct consequence of air pollution through injury to the lungs and the respiratory system (Shah et al., 2013). Around 2.1 and 0.47 million deaths annually are believed to be caused by fine particulate matter (PM) and ozone, respectively (Chuang, Yan, Chiu, & Chen, 2011; Shah et al., 2013).

Airborne Particulates

Airborne environmental PM poses more danger to human health than that of ground-level ozone and other common air pollutants, such as carbon monoxide (Chuang et al., 2011; Shah et al., 2013; Steiner, Bisig, Petri-Fink, & Rothen-Rutishauser, 2016). PM consists of a heterogeneous mixture of aerosolized solid and liquid particles that varies continuously in size and chemical composition in space and time (WHO, 2013). The chemical constituents of PM are sufficiently diverse to include nitrates, sulphates, elemental and organic carbon, organic compounds (e.g., PAHs and heterocyclic aromatics), biological compounds (e.g., endotoxin, cell fragments), and metals (e.g., iron, copper, nickel, zinc, and vanadium; Atkinson, Fuller, Anderson, Harrison, & Armstrong, 2010; Atkinson, Kang, Anderson, Mills, & Walton, 2014; Atkinson, Mills, Walton, & Anderson, 2014; Atkinson et al., 2016; Harrison Beddows, 2017; Moore, 2015; Steiner et al., 2016; WHO, 2013).

Aerosolized PM is a key indicator of air pollution, and the particles are introduced by a variety of natural and human activities (Harrison & Beddows, 2017; Steiner et al., 2016; WHO, 2013). As PM can remain aerosolized for a considerable period of time and travel over lengthy distances in the atmosphere, it can cause a wide range of diseases that can lead to a significant reduction of human life span. The size of the particles in atmospheric PM has been directly linked to their potential for causing health problems. Specific particles of concern include “inhalable coarse particles,” with a diameter of 2.5 to 10 μm, and “fine particles,” smaller than 2.5 μm in diameter, as well as ultrafine particles that are in the nanoparticle range (≤ 100 nm in at least one dimension). Because the source–effect relationship of PM remains unclear, it is not always easy to define the potential harmful effects from individual sources, such as the long-range transport of pollution (Steiner et al., 2016; WHO, 2013).

However, because of the potent role of PM and its associated pollutants, detailed knowledge of their impacts on human health is of critical importance. Particle exposure is responsible for a variety of health problems, including premature death in people with heart or lung disease; nonfatal heart attacks; irregular heartbeat; aggravated asthma; decreased lung function; and increased respiratory symptoms such as irritation of the airways, coughing, or difficulty in breathing (Atkinson et al., 2010; Atkinson, Kang et al., 2014; Atkinson, Mills et al., 2014; Atkinson et al., 2016; Cadelis, Tourres, & Molinie, 2014;

Correia et al., 2013; Fang, Naik, Horowitz, & Mauzerall, 2013; Kelly & Fussell, 2015; Meister, Johansson, & Forsberg, 2012).

Asbestos

The major diseases linked to chronic exposure to asbestos are asbestosis and mesothelioma (Alleman & Mossman, 1997). Asbestos occurs naturally in the air outdoors and in some drinkable water, including water from natural sources (Culley, Zorland, & Freire, 2010; Pawełczyk & Božek, 2015). Even non-occupationally exposed individuals can have significant amounts of asbestos fiber in their lungs (Feder et al., 2017). Asbestos from natural geologic deposits is known as *naturally occurring asbestos* (NOA). Any risks associated with exposure to NOA are not yet fully understood (Culley et al., 2010). Baumann et al. (2015) have indicated that NOA may pose an increased risk for malignant mesothelioma; however, further geochemical and epidemiological investigation will help to clarify the asbestos types that pose the highest risk.

Toxic Organic Chemical Pollutants

There has always been exposure to organic chemical contaminants over the course of geological time. Contaminants have entered the environment as the products of combustion and the natural seepage of petroleum derivatives (Abdel-Shafy & Mansour, 2016; Dong & Lee, 2009, Manzetti, 2013). However, with the onset of coal burning and, later, the Industrial Revolution, the contamination of the environment, including foodstuffs, by coal tar products, dyestuffs, nitroaromatics (e.g., from explosives, many synthetic chemical processes, and vehicle exhausts), plastics and plasticizers, synthetic rubbers, halogenated organics (e.g., polychlorinated biphenyls [PCBs], dioxins, and furans), pesticides, herbicides, petroleum products, and partial combustion products (i.e., polycyclic aromatics, S-, N-, & O-heterocyclics) increased exponentially, and has started to be effectively controlled only in recent decades (Shifrin, 2014). Many of these compounds have entered the environment via water; others have been present in smoke, often associated with soot particles. Internal-combustion engines have exacerbated the problem by generating carbon-based nano- and micro-particles that bind polycyclic aromatics and heterocyclics (Atkinson et al., 2010; Atkinson, Kang et al., 2014; Atkinson, Mills et al., 2014; Atkinson et al., 2016; Chuang et al., 2011; Harrison & Beddows, 2017; Moore, 2015; Shah et al., 2013; Steiner et al., 2016; WHO, 2013). Vehicle engines also produce nanoparticles of iron (i.e., magnetite) that have been demonstrated to enter the mammalian airways and olfactory nerves (Maher et al., 2016).

Polycyclic Aromatic Hydrocarbons (PAHs)

Combustion products, particularly, the polycyclic aromatic hydrocarbons are probably the single most widespread group of organic xenobiotic contaminants and are considered to be persistent organic pollutants (POPs; Table 1; EUGRIS, 2018; Net et al., 2015; Reid, Jones, & Semple, 2000). PAHs are a group of more than 100 different chemicals that are released from burning coal, petroleum oil, petrol, diesel, domestic- and industrial-waste

materials, tobacco, wood, and other organic substances such as barbequed meat and fish (Abdel-Shafy & Mansour, 2016; Dong & Lee, 2009; Manzetti, 2013). PAHs occur naturally when they are released from forest fires and volcanoes and can also be manufactured for specific uses. Other activities that produce PAHs include driving motorized vehicles, agricultural burning, roofing or working with coal-tar products, soundproofing and waterproofing, coating pipes, steelmaking, and surfacing roads with asphalt (Abdel-Shafy & Mansour, 2016; Dong & Lee, 2009; Manzetti, 2013).

Exposure to PAHs occurs by breathing polluted air, wood smoke, vehicle exhaust, or cigarette smoke or by eating contaminated food or drinking contaminated water. PAHs are often attached to aerosolized particles, such as smoke, cigarette smoke, vehicle exhaust, tire dust and road dust, wildfires, volcanoes, agricultural burning or wood burning, municipal- and industrial-waste incineration, and releases from hazardous waste sites (Atkinson et al., 2010; Atkinson, Kang et al., 2014; Atkinson, Mills et al., 2014; Atkinson et al., 2016; Dong & Lee, 2009; Guo, Wu, Huo, & Xu, 2011; Kelly & Fussell, 2015; Manzetti, 2013; Steiner et al., 2016). Exposure to PAHs and their biotransformed derivatives can result from inhaling soil dust or having skin contact with the soil in areas near where coal, wood, gasoline, or other products have been burned, or from the soil at hazardous waste sites, former manufactured-coal-gas sites, and wood-preserving facilities (Guo et al., 2011; Tian, Vila, Yu, Bodnar, & Aitken, 2018).

Exposure to PAHs has also been linked to cardiovascular disease; PAHs are also among the complex mixture of pollutants in tobacco smoke and particulate air pollution, exposures to which may well contribute to cardiovascular disease (Hecht, 2003; Limon-Pacheco & Gonsebatt, 2009).

PAHs have been causally linked to skin, lung, bladder, liver, and stomach cancers in well-established animal model studies, as well as in epidemiological studies (Guo et al., 2011). The structure of a PAH influences whether and how the individual compound is carcinogenic (Guo et al., 2011; Yu, 2002). Some carcinogenic PAHs are genotoxic and induce mutations that initiate cancer; others are not genotoxic and facilitate the promotion or progression of cancer as co-carcinogens (Guo et al., 2011; Yu, 2002). Genotoxic PAHs, such as benzo[a]pyrene, usually have four or more aromatic rings and a “bay region,” a structural pocket that increases the reactivity of the molecule to the phase I and phase II metabolizing enzymes. Mutagenic biotransformation products of PAHs include diol epoxides, quinones, and radical PAH cations (Yu, 2002). These reactive products can bind to DNA at specific sites, forming bulky complexes called *DNA adducts* that can either be stable or unstable (Yu, 2002). Stable adducts may lead to DNA replication errors; unstable adducts react with the DNA strand, removing a purine base (either adenine or guanine). Such mutations, if they are not repaired, can transform genes that are encoding for normal cell-signaling proteins into cancer-causing oncogenes (Guo et al., 2011; Yu, 2002). Quinones can also repeatedly generate reactive oxygen species that can independently damage DNA by casing oxidative damage to the DNA molecule (Yu, 2002). Furthermore, photochemical reaction, photo-transformation, and the phototoxicity of PAHs and their oxy-

genated, nitrated, halogenated, and amino-substituted derivatives can contribute to the toxicity and carcinogenicity of PAHs (Yu, 2002).

Enzymes in the phase I cytochrome P450 family (e.g., CYP1A1, CYP1A2, CYP1B1) together with phase II enzymes can biotransform PAHs to diol epoxides (Guo et al., 2011; Kim et al., 1998). PAH exposure can increase production of the cytochrome enzymes, a process known as *induction*, allowing the enzymes to convert PAHs into mutagenic diol epoxides at greater rates (Guo et al., 2011). Biotransformed PAH molecules bind to the aryl hydrocarbon receptor (AhR) and activate it as a transcription factor that increases production of the cytochrome P450 enzymes (Nebert & Dieter, 2000). And at times, the biotransformation processes may, conversely, protect against PAH toxicity. Smaller PAHs, with 2 to 4 aromatic hydrocarbon rings, are often more potent as co-carcinogens during the promotional stage of cancer (Guo et al., 2011; Hecht, 2003).

Oxidative stress following exposure to PAHs may also result in cardiovascular disease by causing inflammation, which has been recognized as an important factor in the development of atherosclerosis and cardiovascular disease, depression, cancers, and neurodegenerative diseases (Del Rio et al., 2013; Dillard & German, 2000; Limon-Pacheco & Gonsebatt, 2009; Moore, 2015; Pérez-Hernández, Zaldívar-Machorro, Villanueva-Porras, Vega-Ávila, & Chavarría, 2016; Salminen & Kaarniranta, 2009; Salminen, Kaarniranta, & Kauppinenc, 2013; Seidel, Azcárate-Peril, Chapkin, & Turn, 2017; Sita, Hrelia, Tarozzi, & Morroni, 2016). Relevant biomarkers of exposure to PAHs in humans have been associated with inflammatory biomarkers, which are recognized as important predictors of cardiovascular disease, suggesting that oxidative stress resulting from exposure to PAHs may be an important mechanism of cardiovascular disease in humans (Hecht, 2003; Limon-Pacheco & Gonsebatt, 2009).

Numerous epidemiological studies in Europe, the United States, and China have linked in-utero exposure to PAHs, via parental occupational exposure or air pollution, with poor fetal growth, reduced immune function, and faulty neurological development, including lower IQ (Perera et al., 2012; Peterson et al., 2015; Polanska et al., 2014).

Nitroaromatics

Nitroaromatic compounds are produced as derivatives and intermediates in many industrial chemical processes, as well as from motor-vehicle exhaust emissions (Henderson, Royer, Clark, Harvey, & Hunt, 1982). This class of compounds includes nitro derivatives of benzene, biphenyls, naphthalenes, benzanthrone, and polycyclic aromatic hydrocarbons, plus nitroheteroaromatic compounds (Kovacic & Somanathan, 2014). Many of these compounds are toxic and some may be carcinogenic, and a large number of commonly used drugs incorporate a nitroaromatic component in their structure, some of which may contribute to adverse health effects such as oxidative stress (Kovacic & Somanathan, 2014).

PCBs, Dioxins, and Furans

Persistent organic pollutants (POPs), such as polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzo-furans (PCDFs), commonly termed *dioxins*, and polychlorinated biphenyls (PCBs), are groups of contaminants that are very persistent and widely distributed in the environment (Table 1; EUGRIS, 2018; Kelly, Ikonomou, Blair, Morin, & Gobas, 2007). These types of persistent pollutants are a potential risk to human health: their harmful toxic properties include carcinogenicity, immunotoxicity, and a range of endocrine effects related to reproduction (Nakatani, Yamamoto, & Ogaki, 2011). Compared to other means of exposure, such as inhalation and dermal contact, ingestion via food consumption, including seafood, is the principal route of human exposure to these pollutants, accounting for more than 90% (Bordajandi, Martín, Abad, Rivera, & González, 2006; Pacini et al., 2013). And there is well-established evidence that human consumption of fish products is one of the main contributors to the total dietary intake of these compounds (Bocio, Domingo, Falcó, & Llobet, 2007).

Table 1. EUGRIS: Comparative Table of Persistent Organic Pollutants (POPs) Selected for Environmental and Toxicological Studies

POPs Selected at the Stockholm Convention (2001)	Organic Pollutants (or Proposed POPs) With an Assigned TEF or REP*	Emerging POPs
Aldrin **Chlordane** **DDT** **Dieldrin** **Endrin** **Heptachlor** **Hexachlorobenzene** **Mirex** **Toxaphene** **PCBs** **PCDDs/PCDFs**	**PCBs** **PCDDs/PCDFs** **PCNs** **PBDEs** **PBDDs/PBDFs** **PBBs** **PAHs**	**PBDEs** **PBDDs/PBDFs** **PBBs**

Note. *toxic equivalent factor,

**relative potency; EUGRIS = European groundwater and contaminated land remediation information system.

Adapted from EUGRIS: Portal for Soil and Water Management in Europe, “Further Description.” PBBs – polybrominated biphenyls, PBDEs – polybrominated diphenyl ethers, PBDDs & PBDFs – polybrominated dibenzo-p-dioxans & dibenzo-p-furans, PCNs – polychleorinated naphthalenes.

Organochlorine Pesticides

Some types of organochlorine compounds have significant toxicity to plants or animals, including humans (Jayaraj, Megha, & Sreedev, 2016; Nicolopoulou-Stamati, Maipas, Kotampasi, Stamatis, & Hens, 2016; Sparling, 2016). Dioxins, which are produced when organic matter such as wood is burned in the presence of chlorine, and some insecticides, such as DDT, are POPs that pose dangers when they are released into the environment. DDT, which was widely used to control insects in the mid-20th century, also accumulates in food chains and causes reproductive problems (e.g., eggshell thinning) in certain bird species (Sparling, 2016).

Many countries have now phased out the use of some types of organochlorine compounds including DDT (Jayaraj et al., 2016; Sparling, 2016). However, persistent DDT, PCBs, and other organochlorine pollutants continue to be found in humans and mammals across the

planet, long after their production and use has stopped or been restricted (Table 1; EU-GRIS, 2018; Jayaraj et al., 2016; Kelly et al., 2007; Sparling, 2016). Very high concentrations are frequently are found in marine mammals; they are generally concentrated in mammals, and have been found in human breast milk (Pirsaheb, Limoee, Namdari, & Khamutian, 2015; Tsygankov, Lukyanova, & Boyarova, 2018).

Herbicides

Some herbicides can cause a range of adverse health effects, ranging from skin irritation to death (Nicolopoulou-Stamati et al., 2016). Exposure can arise from improper agricultural application that results in the herbicide coming into direct contact through the inhalation of aerosol sprays or from food consumption as a result of incorrect or illegal usage. Some herbicides can be transported by leaching or surface runoff that can contaminate groundwater or geographically removed surface water sources (Nicolopoulou-Stamati et al., 2016). The conditions that can promote herbicide transport include intense rainstorms and soils that have a limited capacity to adsorb and retain the herbicides. The physical chemical properties that increase the likelihood of herbicide transport include persistence (i.e., resistance to degradation) and high water solubility (Nicolopoulou-Stamati et al., 2016).

Phenoxy herbicides can often be contaminated with dioxins, such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), and studies have suggested that such contamination can result in a small rise in cancer risk after occupational exposure to these herbicides (Nicolopoulou-Stamati et al., 2016). Furthermore, triazine exposure has been implicated in increased risk of breast cancer, although a causal process remains unclear (Nicolopoulou-Stamati et al., 2016).

Glyphosate has generally been considered an environmentally safe herbicide because it is assumed to be inactivated quickly after spraying because of its rapid adsorption onto particles in the soil, and its subsequent degradation by the soil microbiota (Myers et al., 2016). Furthermore, the mechanism by which glyphosate kills plants is thought to be relatively unique to plants and some microorganisms, including bacteria, algae, and fungi, and thus should not represent a threat to mammals, although recent research indicates potential impacts on rat gut microbiota and shortened pregnancies in women who are exposed during pregnancy (Lozano et al., 2017; Parvez et al., 2018). However, evidence from several studies now shows that glyphosate-based herbicides, via various mechanisms, can adversely influence mammalian health (Myers et al., 2016). Additionally, the half-life of glyphosate, which gives an indication of its persistence in the soil and water, may be longer than was previously thought (Bento et al., 2016).

Prevalence of Parkinson’s disease is believed to increase with occupational exposure to pesticides, although there is insufficient evidence for a direct causal link (Brown, Rumsby, Capleton, Rushton, & Levy, 2006; Myers et al., 2016; Nicolopoulou-Stamati et al., 2016). In addition to the health effects caused by individual herbicides, many commercial

herbicide mixtures often contain other chemicals, including inactive ingredients, which may contribute to induction of adverse impacts on human health (Hernández et al., 2013).

Plasticizers

Plasticizers are additives used in the manufacture of plastics; most commonly, the phthalate esters used in polyvinylchloride (PVC) applications (Wei et al., 2015). Numerous concerns have been expressed over the safety of some plasticizers, specifically because some low-molecular-weight ortho-phthalates have been classified as potential endocrine disruptors, and some developmental toxicity has been reported in mammals (Meeker, Sathyanarayana, & Swan, 2009). More human studies of the adverse health effects associated with plastic additives are urgently required; recent advances in measuring the exposure biomarkers and transcriptomics hold out considerable promise in improving the epidemiological evidence (Meeker et al., 2009).

Bisphenol A

Bisphenol A (BPA) is employed to make particular epoxy resins and other plastics (Konieczna, Rutkowska, & Rachoń, 2015; Meeker et al., 2009). Epoxy resins containing BPA are used to line water pipes, and as coatings on the inside of many food and beverage cans (Konieczna et al., 2015; Meeker et al., 2009). An estimated 4 million tonnes of BPA chemical have been produced annually for the manufacture polycarbonate plastic.

BPA is a xenoestrogen, exhibiting estrogen-mimicking hormone-like properties that have raised concern about its suitability in some consumer products and food containers (Konieczna et al., 2015; Meeker et al., 2009; Rochester, 2013; Srivastava, Gupta, Chandolia, & Alam, 2015; Vogel, 2009). Since 2008, a number of governments and the European Union have investigated its safety, which has prompted some withdrawal of polycarbonate products containing BPA (European Food Safety Authority, 2017). Animal studies have demonstrated an association between endocrine-disrupting chemicals (including BPA) and obesity and type-2 diabetes (Provvisiero et al., 2016; Velmurugan, Ramprasath, & Gilles, 2017); and have highlighted the possible role of the gut microbiota in the transformation of some endocrine-disrupting chemicals, which may contribute to type-2 diabetes epidemic.

BPA exposure disrupts pancreatic β-cell function in vivo, which can modify insulin sensitivity and insulin release (Alonso-Magdalena et al., 2006). However, the relationship between bisphenol A exposure and obesity in humans is unclear, though an epidemiological investigation has indicated that BPA may be a factor in the etiology of type-2 diabetes (Provvisiero et al., 2016; Sowlat, Lotfi, Yunesian, Ahmadkhaniha, & Rastkari, 2016).

Pharmaceuticals & Personal Care Products

Adverse effects in humans resulting from exposure to contaminant pharmaceuticals and personal-care products (PPCPs) in the environment are still largely speculative (Boxall et al., 2012; Ebele, Abdallah, & Harrad, 2017). PPCPs have been detected in water bodies

throughout the world; however, the effects of these chemicals on humans are as yet unknown (Boxall et al., 2012; Ebele et al., 2017). The term PPCPs also applies to environmental persistent pharmaceutical pollutants (EPPPs). The European Union has summarized pharmaceutical residues that have the potential to contaminate water and soil, the antibiotic contribution to antimicrobial resistance, and other micropollutants under the heading “priority substances” (European Environment Agency, 2013).

Natural Products

Bacterial Products

Bacterial Toxins

Bacterial endotoxins are ubiquitous in the environment and can often represent important components of bioaerosols (Table 2; Guan & Holley, 2003; Liebers, Raulf-Heimsoth, & Brüning, 2008). High exposure to endotoxins can occur in rural environments and at various workplaces (e.g., sites of industrial composting, waste collecting, the textile industry, etc.). The adverse effects of inhaled environmental endotoxins on human health have been described in several studies, and the presence of endotoxins in the blood is called *endotoxemia*. However, research has indicated that exposure to endotoxins in children can modulate the innate immune system and provide protection against asthma (Stein et al., 2016).

Table 2. Summary of Various Types, Sources, and Targets or Effects of Potential Biogenic Chemicals That Could Influence Human Health if Ingested or Inhaled

Biogenic Product	Origin	Potential Biological Target or Effect
Bacterial toxins	Food, water, soil particles, bioaerosols, seawater aerosols	Inhibition of specific cell-signaling systems (PI3K, mTORC1)
Cyanobacterial and algal toxins	Seafood, freshwater, seawater, seawater aerosols, soil particles	Inhibition of specific cell-signaling systems (PI3K, mTORC1), neurological target, others
Antibiotics	Food (e.g., farmed fish), soil particles	Inhibition of specific cell-signaling systems (PI3K, mTORC1)
Polyphenolics (flavonoids, anthocyanins, procyanidins, proanthocyanidins, catechins, tannins, humics, etc.), isothiocyanates	Fruit, vegetables, soil particles, higher plant abrasion particles, pollen grains, fern spores, fungal spores, macroalgal fragments (brown, green, and red)	Inhibition of specific cell-signaling systems (PI3K, Akt, mTORC1), PTEN, MAPK/ERK (related to cancer), COX-2, AMPK, autophagy, apoptosis, anti-cancer properties, cardiovascular protection, enhanced brain function
Mycotoxins	Fungal spores, soil particles, hay-derived particles, moldy food	Inhibition of specific cell-signaling systems (PI3K, mTORC1), asthma, respiratory effects, carcinogenesis

Pyrrolizidine alkaloids	Food, higher plant abrasion particles, pollen grains	Carcinogenic, tumorigenic and anticancer properties
Terpenoids (monoterpenes, diterpenes, triterpenes)	Fruit, vegetables, volatiles from higher plants (VOC)	PI3K/AKT/mTOR pathway, apoptosis, autophagy, others

Source: Adapted from Moore (2015).

Mechanistic investigations have shown that at the cellular level, Toll-like receptor 4 (TLR4) and IL-1 receptor, as well as surface molecules like CD14 play a pivotal role in the endotoxin activation cascade (Liebers et al., 2008; Rylander, 2002). Damage to the endothelial layer of blood vessels caused by these inflammatory mediators can lead to capillary leak syndrome, blood-vessel dilation, and a decrease in cardiovascular function, perhaps posing a risk for respiratory disease (Liebers et al., 2008; Rylander, 2002).

Beneficial Bacterial Products

Soil- and plant-associated environments often have a rich and complex microbiota, including bacteria that produce antibiotic metabolites with specific or broad-spectrum activities against coexisting microorganisms (Raaijmakers & Mazzola, 2012). The function and ecological importance of antibiotics have been considered to provide a survival advantage to the antibiotic-producing bacteria in the “chemical warfare” that occurs in a highly competitive but resource-limited soil environment, through the direct suppression of competitors (Bengtsson-Palme, Kristiansson, & Larsson, 2018). Although specific antibiotics may enhance producer persistence when challenged by competitors or predators in soil habitats; at subinhibitory concentrations, antibiotics can exhibit a diversity of other roles in the life history of the producing bacteria.

The environmental relevance of bacterial antibiotics to human health is indirect, and relates predominantly to the isolation and identification of novel antibiotics, particularly those produced by actinomycetes with bioactive properties that are relevant to diseases in humans that are increasingly caused by antibiotic-resistant bacteria (Genilloud, 2017; Wellington et al., 2013). Very low concentrations of antibiotics (i.e., subinhibitory) can alter gene expression and microbial physiology in ways that may have as yet unknown consequences for the human microbiota (Bruchmann, Kirchen, & Schwartz, 2013). Antibiotic resistance develops through complex interactions, with antibiotic resistance appearing through de-novo mutation under clinical antibiotic selection or, frequently, by acquiring mobile genes that have evolved in bacteria, which are naturally present in the environment (Bengtsson-Palme et al., 2018; Wellington et al., 2013). The reservoir of antibiotic-resistance genes in the environment is likely the result of a combination of naturally occurring resistance and those that are present in animal and human waste, and the poten-

tial result of the selective evolutionary effects of pollutants, which can co-select for mobile genetic elements carrying multiple resistant genes (Wellington et al., 2013).

Algal Products

Algal Toxins

Many species of algae are known to produce bioactive toxic metabolites (i.e., phycotoxins) that cause various harmful effects, including amnesic shellfish poisoning, diarrhetic shellfish poisoning, and neurological disorders such as neurotoxic shellfish poisoning and paralytic shellfish poisoning (Table 2; Berdalet et al., 2016; Fleming, Backer, & Baden, 2005; Fleming et al., 2007, 2011; Moore et al., 2013). Algal toxins found in aquatic ecosystems (harmful algal blooms—HABs) such as domoic acid, saxitoxin, and brevetoxin, which bioaccumulate or are magnified in the food chain by fish and shellfish, and anatoxins from freshwater cyanobacteria (blue-green algae) affect the nervous system; cyanobacteria that contain microcystins or nodularin can cause liver damage, and possibly cancer (Fleming et al., 2005, 2007).

The potential consequences of global warming on the frequency and type of HABs have received relatively little attention and are not well understood (Hallegraeff, 2010). Given the apparent increase in HABs around the world and the potential for an increase of problems related to climate change and ocean acidification, substantial research is needed to evaluate the direct and indirect associations between HABs, climate change, ocean acidification, and human health (Berdalet et al., 2016; Friedman et al., 2017; Hallegraeff, 2010; Moore et al., 2008; Moore et al., 2013). This research will undoubtedly require an interdisciplinary approach that draws on expertise in climatology, oceanography, biology, toxicology, and epidemiology, as well as other disciplines.

Beneficial Algal Products

In contrast to algal toxins, many algal species produce a variety of products that are beneficial to human health. Brevenal is produced by algae that also produce brevitoxins; it has been shown to be beneficial in countering the effects of cystic fibrosis (Potera, 2007). Various bioactive compounds from aquatic algae have been shown to modulate the effects of oxidative stress (Ibañez, Herrero, Mendiola, & Castro-Puyana, 2012; Lee et al., 2013). Because oxidative stress plays an important role in inflammatory reactions and in carcinogenesis, aquatic algal natural products may have the potential for use in anticancer and anti-inflammatory drugs (see Lee et al., 2013). Furthermore, aquatic algae are often rich in dietary fiber (i.e., from plant cell walls that are metabolized by the gut microbiota, providing short-chain fatty acids and other micronutrients), minerals, lipids, proteins, omega-3 fatty acids, essential amino acids, polysaccharides, and vitamins A, B, C, and E (Hamed, Özogul, Özogul, & Regenstein, 2015). Studies on the bioactive products of aquatic algae have revealed numerous potential health-promoting effects, including antioxidative, anti-inflammatory, antimicrobial, and anticancer effects (Lee et al., 2013; Sarojini, Laksshminarayana, & Rao, 2012).

Fungal Products and Toxins

Dietary, respiratory, dermal, and other exposures to toxic fungal metabolites produce the diseases collectively called *mycotoxicoses* (Table 2; Bennett & Klich, 2003). Harmful fungal mycotoxins that pose a health risk to humans and animals have long been known to be associated with mold-contaminated food and feed (Jarvis & Miller, 2005). In recent times, concerns have also been raised about exposures to mycotoxin-producing fungi in indoor environments (e.g., damp homes and buildings), causing adverse respiratory conditions, including asthma. The principal mycotoxins that contaminate food and feed (e.g., aflatoxins, fumonisins, ochratoxins, deoxynivalenol, and zearalenone) are rarely if ever found in indoor environments, but their toxicological properties may provide an insight into the difficulties of assessing the health effects of related mycotoxins produced by indoor molds (Bennett & Klich, 2003; Skaug et al., 2001). Some aflatoxins and ochratoxins are known carcinogens and may be harmful to humans via consumption of contaminated food products (Ostry, Malir, Toman, & Grosse, 2017). *Penicillium* and *Aspergillus* genera of fungi are the major contaminants of both food and feed products and damp buildings, although the species that are encountered, and hence, the suite of mycotoxins can be quite different in these various environments.

The symptoms of a mycotoxicosis depend on the type of mycotoxin; the amount and duration of the exposure; and many poorly understood synergistic effects involving genetics, dietary status, and interactions with other toxic insults (Bennett & Klich, 2003). Mycotoxicoses can also heighten vulnerability to microbial diseases, worsen the effects of malnutrition, and interact synergistically with other disorders and toxins (Bennett & Klich, 2003). Mycotoxins can inhibit protein synthesis, damage macrophage systems, inhibit particle clearance of the lung, and increase sensitivity to bacterial endotoxin (Godish, 2001, pp. 183–184).

Plant Products: Phytochemicals, Beneficial and Harmful Effects

Many phytochemicals have been the subject of considerable research interest owing to their potential benefits for human health as nutraceuticals (Table 2; Banerjee, Biswas, Madhu, Karmakar, & Biswas, 2014; Del Rio et al., 2013; Dillard & German, 2000; Lila & Raskin, 2005; Menendez et al., 2013; Rojo, Villaguala, Avello, & Pastene, 2016; Ward & Pasinetti, 2016; Yao et al., 2004). Phytochemicals, such as terpenoids, phenolics, alkaloids, and fiber, may have the potential to provide such health benefits as

- substrates for biochemical reactions;
- cofactors of enzymatic reactions;
- inhibitors of enzymatic reactions;
- absorbents and sequestrants that bind to and eliminate undesirable constituents in the intestine; ligands that agonize or antagonize cell-surface or intracellular receptors;
- scavengers of reactive or toxic chemicals;
- compounds that enhance the absorption and or stability of essential nutrients;

- selective growth factors for beneficial gastrointestinal bacteria;
- fermentation substrates for beneficial oral, gastric or intestinal bacteria; and
- selective inhibitors of deleterious intestinal bacteria.

There is increasing evidence that polyphenols and certain other phytochemicals can modulate the cell-signaling pathways responsible for the regulation of inflammatory processes and oxidative stress (Bjørklund & Chirumbolo, 2017; Del Rio et al., 2013; Espin et al., 2007; Moore, Shaw, Ferrer Adams, & Viarengo, 2015; Pandey & Rizvi, 2009; Rojo et al., 2016; Tan, Moad, & Tan, 2014; Ward & Pasinetti, 2016; Yao et al., 2004; Zhang, Chen, Ouyang, Cheng, & Liu, 2012). These putative benefits include anti-inflammatory, anti-cardiovascular-disease, anticancer, anti-aging, antidiabetic, antipsychotic, and antineurodegenerative properties (Del Rio et al., 2013; Dillard & German, 2000; Gupta, Singh, & Sharma, 2017; Latorre et al., 2017; Moore, 2015; Pérez-Hernández et al., 2016; Rojo et al., 2016; Seidel et al., 2017; Sita et al., 2016). Many of these phytochemicals are in fact plant toxins that often have antiviral, antibacterial, and antiparasitic properties, and also discourage herbivores because they can contribute to a bitter taste in the plants containing them (Miresmailli & Isman, 2014; Paré & Tumlinson, 1999; Stegelmeier et al., 1999; Wöll, Kim, Greten, & Efferth, 2013).

Beneficial effects attributed to phytochemicals such as polyphenolics, isothiocyanates, and terpenoids in cultured cells do not necessarily translate into observed benefits in whole animals or effects derived from ingestion of fruit and vegetables (Bjørklund & Chirumbolo, 2017; Del Rio et al., 2013; Dillard & German, 2000; Salminen, Lehtonen, Suuronen, Kaarniranta, & Huuskonen, 2008; Seidel et al., 2017; Waladkhani & Clemens, 1998). Major phytochemicals such as polyphenols have relatively low bioavailability because they are only poorly absorbed in the small intestine, and are thus passed to the colon (Cardona, Andrés-Lacuevac, Tulipania, Tinahonesb, & Queipo-Ortuñoa, 2013; Marín, Miguélez, Villar, & Lombó, 2015, Nasef, Mehtaand, & Ferguson, 2014). Here, the microbiome of the colon is largely responsible for the metabolic biotransformation of polyphenols that are converted into bioactive products, such as hydroxyphenolic acids, dihydroresveratrol (from resveratrol) and urolithins (Cardona et al., 2013; Cuervo et al., 2016; Kawabata et al., 2015; Koppel, Rekdal, & Balskus, 2017; Latorre et al., 2017; Marín et al., 2015; Nasef et al., 2014; Rojo et al., 2016; Saha et al., 2016). Urolithins are further conjugated largely to glucuronides by phase II biotransformation in the liver (Mertens-Talcott, Jilma-Stohlawetz, Rios, Hingorani, & Derendorf, 2006). These bioactive metabolites are more readily absorbed and bioavailable than the parent compounds.

Furthermore, ingested plant polyphenols also appear to profoundly influence the microbial composition and metabolic capability of the gut microbiome, essentially a feed-forward system that functions as an additional systemic organ (Cuervo et al., 2016; Dueñas et al., 2014; Seidel et al., 2017).

Inflammatory reactions underlie many disease conditions, particularly those that are age-related, such as cancers, neurodegeneration, and dementias (Del Rio et al., 2013; Dillard & German, 2000; Moore, 2015; Pérez-Hernández et al., 2016; Salminen & Kaarniranta,

2009; Salminen et al., 2013; Seidel et al., 2017; Sita et al., 2016). Recent research has revealed that some polyphenol metabolites are potent inhibitors of various cell-signaling systems that are involved in pro-inflammatory pathways, such as the mTOR (mechanistic target of rapamycin) complex 1 (mTORC1; see Table 2; Bruning, 2013; Saxton & Sabatini, 2017). mTORC1 is one of the “master regulators” of metabolic function in the body, and it sits in the center of a highly complex network of interconnecting cell-signaling pathways (Figure 2; Corradetti & Guan, 2006; Moore, 2015). A major consequence of mTORC1 inhibition is a cytoprotective reduction of inflammatory processes. Unregulated inflammation is known to be a causal factor in cardiovascular disease, depression, neurodegeneration, and dementias, as well as in many cancers (Pérez-Hernández et al., 2016).

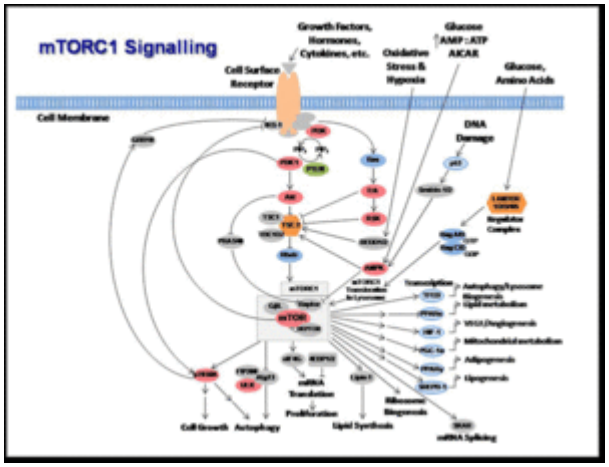

Figure 2. Simplified diagrammatic representation of the PI3K, Akt, mTOR cell-signaling pathway, and associated pathways, as a major regulator of cell function (see Laplante & Sabatini, 2009, 2012, for a more extensive chart of mTOR-related cell signaling). The mechanistic target of rapamycin (mTOR) is an atypical serine/threonine kinase that is present in two distinct complexes. The first, mTOR complex 1 (mTORC1), is composed of mTOR, Raptor, GβL, and DEPTOR and is inhibited by rapamycin. It is a master growth regulator that senses and integrates diverse nutritional and environmental cues, including growth factors, energy levels, cellular stress, and amino acids. It couples these signals to the promotion of cellular growth by phosphorylating substrates that potentiate anabolic processes, such as mRNA translation and lipid synthesis, or that limit catabolic processes, such as autophagy. Overactivity of mTORC1 is believed to trigger inflammatory processes that can result in pathological injury and processes that lead to many cancers and degenerative diseases; and aberrant mTOR signaling is involved in many disease states, including cancer, cardiovascular disease, and diabetes.

Note: PI3K-phosphatidylinositol-3 kinase; PIP_3—phosphatidylinositol 3,4,5 trisphosphate; Akt—serine/threonine kinase Akt or protein kinase B (PKB); mTORC1—mammalian target of rapamycin complex 1; PTEN—phosphatase and tensin homolog; AMPK—5’ adenosine monophosphate-activated protein kinase p27—cyclin-dependent kinase inhibitor; ROS—reactive oxygen species. Activation—↑; inhibition—T. *Source*: Adapted with permission from Cell Signaling Technology (2008, September), mTOR Signaling Interactive Pathway. Danvers, MA.

Polyphenol metabolites appear to modulate specific intracellular signaling pathways (e.g., inhibition of mTORC1 and mTORC2, inhibition of NFκB, activation of AMPK, activation of ACMP and Nrf2-ARE); and there is a substantial body of evidence that phytochemical derivatives can act synergistically on such pathways to promote cytoprotective processes (Figure 2; Beevers, Zhou, & Huang, 2013; Bjørklund & Chirumbolo, 2017; Bode & Dong,

2013; Moore, 2015; Salminen et al., 2008, 2013; Seidel et al., 2017). mTORC1, in particular, is also a nutrient and a stress sensor that regulates cell growth, immunoregulation, translation, lysosomal autophagy, ribosomal biogenesis, apoptosis, and senescence, which, when inhibited, can have beneficial consequences (Table 2; Figure 2; Mizushima, Levine, Cuervo, & Klionsky, 2008; Salminen et al., 2008, 2013; Suter & Lucock, 2017; Suvarna, Murahari, Khan, Chaubey, & Sangave, 2017). It is considered that some of these polyphenol metabolites may act as calorie, or dietary, restriction (CR) mimetics: CR is well known to have beneficial effects in a wide range of organisms by increasing life span and reducing the risk from age-related cancers, cardiovascular disease, and neurodegenerative disease (Moore, 2015; Pérez-Hernández et al., 2016; Salminen & Kaarniranta, 2009; Salminen et al., 2013; Seidel et al., 2017; Sita et al., 2016; Suvarna et al., 2017).

However, a cautionary note needs to be raised because some plant polyphenols may be toxic or even carcinogenic if consumed in excessive quantities (Mennen, Walker, Bennetau-Pelissero, & Scalbert, 2005). The risk of consuming high doses of polyphenols from polyphenol-rich foods is low; nonetheless, the biological interactions of polyphenols can be modified or negated by other ingredients in those foods, such as the cholesterol-increasing lipids in coffee, alcohol in wine, and fat in chocolate (Del Rio et al., 2013; Mennen et al., 2005). Dietary or herbal supplements that contain high (i.e., pharmacologically active) doses of polyphenolics are widely available to the public (Del Rio et al., 2013). Consuming these products can result in polyphenols reaching very high concentrations, and further research is required to ascertain the potential risks. Safety evaluation would be dependent on the nature of the polyphenol-containing product (i.e., a food, food extract, or pure compound); and on whether the proposed use could potentially result in a significant increase in exposure (Schilter et al., 2003).

Overview of Risks and Benefits

The main routes through which harmful pollutants and natural products impact humans are inhalation of atmospheric combustion particulates, eating contaminated food, and drinking polluted water (Kelly & Fussell, 2015). The chemical pollutants of most concern are the ubiquitous PAHs (both naturally occurring and anthropogenic) and other anthropogenic and synthetic POPs (EUGRIS, 2018; Net et al., 2015, Reid et al., 2000), the often naturally occurring metalloid arsenic (WHO, 2017), plasticizers, and fungal mycotoxins in food. Many other chemicals and natural products may be hazardous, but the scale of the problem is much less and often geographically localized, such as the use of mercury in artisanal gold mining, a practice that is rapidly being reduced (U.S. Environmental Protection Agency, 2017).

Many of the environmental toxicity issues considered here have been or are dealt with effectively by the environmental regulation of mercury, lead, cadmium, organochlorines, herbicides, asbestos, and exhaust particulates. However, concerns continue about the pollutants that remain in the environment, particularly persistent organic pollutants (POPs), including PAHs and organochlorines (Table 1; EUGRIS, 2018; Kelly et al., 2007).

Effects of Mixtures

Environmental pollutants and natural products seldom occur in isolation; they are generally present as part of a complex chemical or molecular cocktail. This provides considerable scope for synergistic and antagonistic interactions between bioactive chemicals. Such interactions are poorly understood for many pollutants and natural products; however, it is recognized that lower and higher molecular weight PAHs can interact in the processes of initiation and progression in carcinogenesis and tumorigenesis, as has already been noted (Guo et al., 2011; Yu, 2002). Some phytochemicals, such as polyphenols, are also believed to interact synergistically with cell-signaling processes that are related to inhibiting inflammatory reactions (Del Rio et al., 2013; Dillard & German, 2000; Moore, 2015; Pérez-Hernández et al., 2016; Seidel et al., 2017; Sita et al., 2016).

Assessing the harmful impact of contaminant chemical mixtures in the environment and food is a major concern in environmental health (Cedergreen, 2014; Kienzler, Bopp, van der Linden, Berggren, & Worth, 2016; Kortenkamp, Backhaus, & Faust, 2009; McCarty & Borgert, 2006; Sarigiannis & Hansen, 2012; Tallarida, 2012, 2016; Tang, Busetti, Charrois, & Escher, 2014). Various attempts have been made to relate measured harmful endpoints (e.g., pathology, mortality) to data on the toxicity of individual constituents of the mixture (Doi, 1994). Unfortunately, success has been limited in this respect; and the hypothesis that the “toxicity of a complex mixture is simply the summation of the toxicity of its individual constituents” is now treated with some skepticism, since in this model there is no accounting for emergent interactive antagonistic and synergistic effects (Sahai, 1996). There are numerous instances, even in simple mixtures, of synergistic interactions of drugs used in medical therapeutics (Di Diodato & Sharom, 1997; Kanzawa et al., 1997; Piras, Nakade, Yuasa, & Baba, 1997; Tallarida, 2012; Serrato-Valenti et al., 1997); and there is also evidence for this type of emergent effect in the estrogenic effect of mixed pollutants (Ashby, Lefevre, Odum, Harris, Routledge, & Sumpter, 1997; Kortenkamp & Altenburger, 1998).

Nevertheless, confounding factors include the lack of information about which chemicals are actually present in an environmental mixture, as well as their concentrations and toxicities (Centers for Disease Control and Prevention, 2018; Parvez et al., 2018; Smith et al., 2013; Tyrrell, Melzer, Henley, Galloway, & Osborne, 2013). Furthermore, in a complex-mixture situation, where the chemicals are often associated with particle surfaces or lipid-rich coatings of particles, the probability that catalytic reactions will occur and generate new compounds will be increased, since such reactions as oxidative changes will readily take place in a two-dimensional environment (i.e., surfaces), where the chemicals are highly concentrated (Li, Xiao, Fu, & Bao, 2017).

Essentially, this situation presents a major problem and challenge for both ecotoxicology and environmental toxicology, and one that is also widely recognized in mammalian and human pharmacology and toxicology; and due of the enormous diversity of chemicals, it is very difficult to develop generalized rules that will determine toxicity. Consequently, understanding the toxicity of chemically diverse mixtures is one of the major challenges for

the future in environmental toxicology (Cassee, Groten, van Bladeren, & Feron, 1998; Cedergreen, 2014; European Commission, 2011; Kienzler et al., 2016; Kortenkamp et al., 2009; LeBlanc & Olmstead, 2004; McCarty & Borgert, 2006; Moore et al., 2018; Sarigiannis & Hansen, 2012; Smith et al., 2013; Tallarida, 2012, 2016).

Association of Pollutants with Particulates

The association of pollutants such as PAHs, heterocyclic aromatics, and nitroaromatics with atmospheric particulates also appears to facilitate the toxicity induced by inhalation of combustion particles (Henderson et al., 1982; Kelly & Fussell, 2015; Steiner et al., 2016). In the early 21st century, There is currently considerable research ongoing in this arena, due to the public health concerns about vehicle-exhaust emissions and respiratory and cardiovascular pathologies in the human populations exposed to these materials (Atkinson et al., 2010; Atkinson, Kang et al., 2014; Atkinson, Mills et al., 2014; Atkinson et al., 2016; Kelly & Fussell, 2015; Steiner et al., 2016).

Nutraceuticals

Natural products can have both harmful and beneficial effects. Many of our dietary constituents contain micronutrients, some of which are considered to be nutraceuticals, such as many phenolic and polyphenolic phytochemicals (Banerjee et al., 2014; Del Rio et al., 2013; Dillard & German, 2000; Kawabata et al., 2015; Menendez et al., 2013; Rojo et al., 2016; Suvarna et al., 2017; Ward & Pasinetti, 2016; Yao et al., 2004). Adverse health issues related to the mycotoxin contamination of foodstuffs is still problematic, particularly with the aflatoxins and ochratoxins (Bennett & Klich, 2003).

Another area of current interest is on hormesis and phytohormesis, where exposure to small amounts of toxic pollutants or some phytochemicals is believed to have a stimulatory effect on various cellular or cytoprotective processes (Duke, 2011; Menendez et al., 2013; Moore, 2015; Suter & Lucock, 2017). Again, this is an area of very active investigation, particularly in the context of the potential for phytochemicals to behave as nutraceuticals and have anti-inflammatory, antidementias, anti-aging, and anticancer properties (Del Rio et al., 2013; Dillard & German, 2000; Moore, 2015; Pérez-Hernández et al., 2016; Salminen & Kaarniranta, 2009; Salminen et al., 2013; Seidel et al., 2017; Sita et al., 2016).

Exposure to toxins and natural biogenic products, such as phytochemicals, phycotoxins, mycotoxins, and bacterial toxins has undoubtedly had a beneficial role as an evolutionary driver for cellular cytoprotective systems in humans and many other species (Glenn et al., 2016; Gurley, 2012; Koppel et al., 2017; Lila & Raskin, 2005; Sullivan, Hagen, & Hammerstein, 2008; Suter & Lucock, 2017; Wöll et al., 2013). The phase I and phase II drug metabolizing enzymes that biotransform many of the organic xenobiotics that enter the body, either by ingestion in food or by inhalation, have been selected over the course of hominid evolution (Fiehn, Barupal, & Kind, 2011; Glenn et al., 2016; Gurley, 2012; Sullivan et al., 2008; Wöll et al., 2013). These selective processes have provided the capability for

humans to detoxify many of the organic chemical pollutants (xenobiotics) encountered during their—evolutionary history as a species (approx. 300,000 years)—as well as conferring the ability to activate the vast majority of pharmaceuticals used in current therapeutic applications. Antioxidant protection against reactive derivatives of toxic metal and xenobiotic exposure has also been subject to the same type of evolutionary pressures; and this has endowed humans with the remarkable defensive capacity that is a necessary requirement for surviving in a “sea of poisons” (Bjørklund & Chirumbolo, 2017; Pandey & Rizvi, 2009; Suter & Lucock, 2017).

Emerging Issues

Engineered Nanomaterials

The human health risks from nanomaterials other than combustion particulates are still largely unknown, although considerable concern over their safety has been expressed (Aschberger, Micheletti, Sokull-Klüttgen, & Christensen, 2011; Boxall, Tiede, & Chaudhry, 2007; Maynard et al., 2006; Moore, 2006). Engineered nanoparticles, nanofibers, and nanotubes are increasingly used in industrial products ranging from microelectronics, food, body panels for vehicles and aircraft, and many other uses. Some of this material is finding its way into the environment and may have an impact on the human food chain and possibly human health (Martirosyan & Schneider, 2014; Moore, 2006). New applications for nanomaterials include medical applications for targeted drug delivery. This area of use is likely to grow exponentially.

Plastics, Ecosystem Integrity, and Health

Concerns are growing about the possible risks to ecosystem integrity and human health arising from waste plastic contamination (Galloway, 2015; Revel, Châtel, & Mouneyrac, 2018). Many plastics breakdown in the environment into micro- and nanoparticles; and these particles may then bind conventional chemical pollutants, such as organic xenobiotics (e.g., PAHs). Ingested plastic particles can subsequently be transported to various sites within the cells when they are phagocytosed (microparticles) endocytosed (nanoparticles) into the lymphatic system in the human gut, such as Peyer’s patches in the ileum region of the small intestine (Galloway, 2015; Moore, 2006; Revel et al., 2018). The risks posed by particulate plastics, such as the delivery of adsorbed pollutant chemicals, remain speculative and will only be elucidated by further research (Galloway, 2015).

Only further investigation of possible health risks, coupled with long-term monitoring of the use of nanomaterials in this capacity, is going to demonstrate whether or not there are long-term health risks involved.

Ecosystem Degradation and Use of Sentinel Species

The continued degradation of natural ecosystems by pollution and haphazard development and industrialization continues to pose risks for human health and probably increases the global burden of disease, particularly in countries with developing economies (Myers et al., 2013). Various animal species, including human food animals, have been used to assess the adverse environmental impacts of environmental pollution, within the con-

text of interconnections between ecosystem integrity and human health (Van der Schalie, 1999; Winston et al., 2002). For aquatic and terrestrial environments, these surrogates include mammals, birds, fish, crustaceans, mollusks, and annelid worms. Appropriate environmental deployment of these species as sentinels for adverse health effects can demonstrate that pollutants determined by chemical analysis are biologically available and whether or not they can exert harmful effects (Fossi & Marsili, 1997; Koehler & van Noorden, 2003; Marigómez, Múgica, Izagirre, & Sokolova, 2017; Moore, Allen, & McVeigh, 2006; Moore, Allen, McVeigh, & Shaw, 2006; Sforzini, Moore, Boeri, Bencivenga, & Viarengo, 2015; Sforzini, Moore, Boeri, Benfenati, Colombo, & Viarengo, 2014; Sforzini et al., 2017; Shaw et al., 2011).

Of course, mechanisms of biotransformation and toxicity may well differ in some respects from humans; however, if the animals that are being deployed as environmental sentinels show signs of cell injury and pathology, it is indicative that adverse effects are occurring that can provide an early warning of a potential toxic hazard for human health (Van der Schalie, 1999; Winston et al., 2002).

Novel Chemicals

New industrial chemical products are being produced constantly, and some of these will undoubtedly pose hazards for human health as the drug-metabolizing system is confronted with completely novel molecular structures, not previously encountered during the course of human and earlier evolution (Cronin et al., 2003; Gil, Oberdörster, Elder, Puntes, & Parak, 2014; Keller & Lazareva, 2014; Moore et al., 2004). Current regulatory and environmental health assessments will probably identify which of these novel chemical products pose serious risks as a result of environmental exposure. Such exposure during early life stages (i.e., perinatal exposure) may have effects on the gut microbiome with unforeseen later life consequences (Hu et al., 2016). However, laboratory testing, extrapolation from rodent models, and structure-activity predictions do not necessarily provide the complete hazard picture, and unexpected harmful ecological and human health effects of novel chemicals may well emerge in the future (Cronin et al., 2003; Hu et al., 2016).

Closing Remarks

Toxic materials are a natural component of the environment and have interacted with human biological systems over the time span of human and hominid evolution. Human cytoprotective systems will probably have benefited from evolutionary changes in the longer term from exposure to toxic metals, organic xenobiotics, and toxic biogenic products. Many phytochemicals that are considered to be potentially beneficial at low concentrations are in fact toxic at high concentrations: they are chemical defensive products of the evolution of protective mechanisms in plants to counter pathogens, parasites, and consumption by herbivores (Miresmailli & Isman, 2014; Paré & Tumlinson, 1999; Stegelmeier et al., 1999; Wöll et al., 2013). Exposure to these beneficial products, particularly in food-

stuffs, will also have beneficially influenced the evolution of human cellular processes, particularly anti-inflammatory cell-signaling mechanisms.

Some of the man-made industrial chemicals, such as PCBs and dioxins, accumulate in human tissues because the cellular defensive processes are either blocked or undergo pathological perturbation. Hopefully, future advances in knowledge emerging from combinatorial chemistry, molecular modeling, and predictive quantitative structure-activity relationships (QSARs) will enable improved identification of the potential toxic properties of novel industrial organic chemicals, pharmaceuticals, and nanomaterials prior to their release into the natural environment, and thus prevent a repetition of past disastrous events (Cronin et al., 2003; Gil et al., 2014; Keller & Lazareva, 2014; Moore et al., 2004; Nel et al., 2013).

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