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The toxicology of air pollution predicts its epidemiology

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Abstract

Epidemiologic investigation has successively defined associations of air pollution exposure with non-malignant and malignant lung disease, cardiovascular disease, cerebrovascular disease, pregnancy outcomes, perinatal effects, and other extra-pulmonary disease including diabetes. Defining these relationships between air pollution exposure and human health closely parallels results of earlier epidemiologic investigation into cigarette smoking and environmental tobacco smoke (ETS), two other particle-related exposures. Humic-like substances (HULIS) have been identified as a chemical component common to cigarette smoke and air pollution particles. Toxicology studies provide evidence that a disruption of iron homeostasis with sequestration of host metal by HULIS is a fundamental mechanistic pathway through which biological effects are initiated by cigarette smoke and air pollution particles. As a result of a common chemical component and a shared mechanistic pathway, it should be possible to extrapolate from the epidemiology of cigarette smoking and ETS to predict associations of air pollution exposure with human disease which are currently unrecognized. Accordingly, it is anticipated that forthcoming epidemiologic investigation will demonstrate relationships of air pollution with COPD causation, peripheral vascular disease, hypertension, renal disease, digestive disease, loss of bone mass/risk of fractures, dental disease, eye disease, fertility problems, and extrapulmonary malignancies.

Keywords

Air pollution; particulate matter; ozone; smoking; tobacco smoke pollution

Introduction

The field of epidemiology identified the relationship between human exposure to air pollution and morbidity and mortality [1,2]. Since that exceptional achievement, epidemiologic investigation has successively defined associations of air pollution exposure with non-malignant lung disease, malignant lung disease, cardiovascular disease, cerebrovascular disease, pregnancy outcomes, perinatal effects, and other extra-pulmonary disease including diabetes.

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The development of these breakthroughs into defining the relationships between air pollution exposure and human health closely parallels results of earlier epidemiologic investigation into cigarette smoking and environmental tobacco smoke (ETS), two other particle-related exposures. Humic-like substances (HULIS) have been identified as a chemical component common to cigarette smoke and air pollution particles. Toxicology studies provide evidence that a disruption of iron homeostasis with sequestration of host metal by HULIS is a fundamental mechanistic pathway through which biological effects are initiated by cigarette smoke and air pollution particles. As a result of a common chemical component and a shared mechanistic pathway, it should be possible to extrapolate from the epidemiology of cigarette smoking and ETS to predict associations of air pollution exposure with human disease which are currently unrecognized.

Particle exposures and humic-like substances

Humic substances (HS) are heterogeneous, amorphous organic materials found in all terrestrial and aqueous environments [3]. They include three different fractions: humic acid, fulvic acid, and humin. The humic acid fraction is not soluble in water under acidic conditions (pH<2) but is soluble at higher pH values. Humic acid is the major extractable component of soil HS. Fulvic acid is the fraction of HS which is soluble in water under all pH conditions and remains in solution after removal of humic acid by acidification. Humin is the fraction of HS that is not soluble in water at any pH value.

A substantial mass fraction of tropospheric aerosols (up to 90%) is comprised of natural organic matter which chemically resembles HS with a mixture of aromatic, phenolic, and acidic functional groups [4-6]. This material shares chemical characteristics with HS but differs in having a smaller molecular weight and lower aromaticity; it is designated HULIS [6]. In one study, about 3% of ambient air particulate matter (PM) was estimated to be HULIS [7]. Combustion products such as wood smoke and diesel exhaust particles (i.e. emission air pollution sources) similarly include HULIS at approximately 8% of wood smoke and 5% in diesel exhaust particles [7-9]. HULIS has also been isolated from cigarette smoke particle [8,9]. About 7-10% of tobacco smoke condensate can be characterized as HULIS [8,9].

As a result of having a variety of oxygen-containing functional groups (e.g. carboxylic and phenolic groups), both HS and HULIS complex metal cations [10-13]. The high content of oxygen-containing functional groups in HS and HULIS favors the formation of stable complexes with numerous metals but that with iron is the most favored [14]. The quantity of HULIS isolated from air pollution particles can be correlated with the metal concentration of ambient air PM [10]. Comparable to HS and HULIS, cigarette smoke condensate functions to bind transition metals [15]. The introduction of HULIS, isolated from cigarette smoke condensate, into the lungs of an animal model is followed by its phagocytosis and an intracellular accumulation of iron [9]. Likewise, a material with solubility properties and composition similar to HS can be isolated from smokers' lungs and the retention of this material is associated with iron accumulation [9]. The sequestration of iron and an associated deficiency of cell metal after exposure to HULIS included in air pollution particles and cigarette smoke can initiate pathways leading to biological effect, injury, and

disease [16-23]. The effects of cigarette smoke and air pollution particles on human health can result from an inclusion of HULIS in both.

Interaction of air pollution particles and ozone

Comparable to air pollution particles, exposure to ambient ozone has been associated with increased human mortality (including non-accidental and cardiovascular mortality) [24-27]. This relationship between ozone exposure and human mortality may be non-linear, a threshold is not recognized, and its basis remains unknown.

After reacting with ozone, carbonaceous compounds demonstrate increased surface functionalization (Figure 1A) [28-32]. As indicated by both high-resolution X-ray photoelectron spectroscopy and Fourier transform-infrared spectroscopy, the surface oxygen introduced on these compounds after reaction with ozone is most frequently present in carboxylic acid groups but phenol, lactone, and quinone formation are also observed [33,34]. Soot, a mixture of elemental carbon and organic compounds, is oxidized in the atmosphere leading to the formation of carboxylates [35]. This reaction increases the polarity of soot surfaces and water-solubility of the particles [36-38]. This reaction between ozone and carbon-containing particles appears to generate either HULIS itself or a product which chemically is similar to HULIS; the material includes numerous oxygen-containing functional groups (e.g. carboxylates) and can be water-soluble. Therefore, it can be expected that some portion of the health effects of ozone, including associated mortality, are mediated through its impact on the content of either HULIS itself or a product which chemically is similar to HULIS in air pollution particles. It is possible that other components of air pollution (e.g. nitrogen oxides) also participate in modifying the functional groups at the ambient PM surface and subsequently impact human health through the same pathway [39].

Mechanism of biological effect after particle exposure

In the respiratory tract, PM has consistently demonstrated a capacity to accumulate iron from available cell sources reflecting the particle surface's ability to complex host iron [40,41]. Following exposure to PM containing carbonaceous compounds, this response will also be observed in the lungs [9,42]. Endogenous iron, essential for host function, is complexed by the polyanionic particle surface including both carboxylic and phenolic functional groups [43]. Comparable to other compounds with a capacity to appropriate cell iron, the response to the functional metal deficiency associated with particle exposure will include oxidative stress, activation of cell signaling and transcription factors, and release of pro-inflammatory mediators prior to apoptosis [44-52]. This eventually culminates in the development of tissue inflammation and fibrosis [43,53]. Exposure to other xenobiotic agents with an equivalent capacity to coordinate metal cations impacts comparable inflammatory and fibrotic injuries in humans [54-56].

Interaction between air pollution particles and ozone is suggested to impact human health effects (Figure 1A). Air pollution particles can include a significant concentration of HULIS (i.e. polycarboxylates), and investigation predicts further carboxylation of this PM following ozone exposure. This results in a particle with a greater capacity to impact 1) iron

sequestration resulting in an increased disruption in metal homeostasis and 2) subsequent inflammation and fibrosis. Such interaction between particles and ozone is supported by epidemiological, controlled exposure, animal, and *in vitro* investigation [57-64].

HULIS in the atmosphere has a significant overlap with water-soluble organic compounds (WSOC) [6]. This soluble component of ambient air PM contains compounds more similar to fulvic acid than humic acid and includes many lower molecular weight organic and inorganic species. As a result of their solubility, these compounds can permeate the blood vessels to be distributed systemically (Figure 1B). The capacity to initiate iron sequestration will impact oxidative stress, cell signaling, transcription factor activation, release of pro-inflammatory mediators, apoptosis, inflammation, and fibrosis in exposed cells and tissues predicting a capacity of cigarette smoking, ETS, and air pollution in initiating extra-pulmonary disease.

Predicting the epidemiology of air pollution particles

Particles in cigarette smoke, ETS, and air pollution have a common chemical component (i.e. HULIS) and a shared mechanistic pathway (i.e. disruption of iron homeostasis). The common chemical component and shared mechanistic pathway predict comparable consequences of exposure including biological effects, tissue injuries, and disease. Accordingly, investigation of one of these particles is applicable to the others; morbidity and mortality after cigarette smoking and ETS exposure is expected to be relevant to the impact of air pollution particle exposure on human health.

Epidemiological studies have more thoroughly described the relationships between cigarette smoking and ETS with respiratory morbidity and mortality, relative to air pollution [65-85] (Table 1). Cigarette smoking and ETS are frequently associated with respiratory symptoms (e.g. cough and phlegm) and individuals exposed to ambient air pollution levels can present with these same complaints. Cigarette smoking and exposures to ETS and ambient air pollution particles are all associated with loss of lung function. Cigarette smoking, ETS and air pollution have recurrently been demonstrated to cause asthma and precipitate its exacerbations. While smoking causes chronic obstructive pulmonary disease (COPD) and exacerbates its course, ETS and air pollution can precipitate aggravations; ETS and air pollution have not yet been strongly associated with COPD causation. Smoking, ETS, and air pollution all elevate the risk for both infections and lung cancers.

Systemic distribution of the water-soluble HULIS component in cigarette smoke will disrupt iron homeostasis at extrapulmonary sites and initiate pathways of inflammation and fibrosis. Accordingly, cigarette smoking influences cardiovascular disease (Table 2), non-malignant extrapulmonary disease (Table 3), fertility problems, pregnancy outcomes, effects on the newborn (Table 4), and malignant diseases outside the respiratory tract (Table 5). ETS similarly will impact cardiovascular disease, non-malignant extrapulmonary disease, pregnancy outcomes, and effects on the newborn (e.g. low birth weight). Differences between cigarette smoking and ETS in associations with these diseases likely reflect the lower dose of particle exposure following the latter (15 to 40 mg per cigarette smoked vs. hundreds to approximately 1000 $\mu g/m^3$ respectively).

Comparable to cigarette smoking and ETS, air pollution particles include HULIS, some of which is water-soluble, with a capacity to disrupt metal homeostasis and initiate inflammatory and fibrotic pathways. While the actual mass of particle air pollution a human is exposed to does not approach that of cigarette smoking (~1/100th or less) presumably resulting in less PM dose, the former may demonstrate a greater potential for impacting biological effect following interaction with ozone. Accordingly, investigations with air pollution exposure have demonstrated increases in cardiovascular disease (Table 2), non-malignant extrapulmonary disease (Table 3), pregnancy outcomes, and effects on the newborn (Table 4) comparable to cigarette smoking and ETS exposure. The range of diseases which develops after air pollution closely approximates that observed after ETS exposure. The two cardiovascular diseases which epidemiological investigation has not yet associated with air pollution exposure are peripheral vascular disease and hypertension. The same is true with studies into relationships of air pollution exposure with non-malignant extrapulmonary disease, pregnancy outcomes, and effects on the newborn which parallel results after ETS exposure. Neither ETS nor air pollution exposures have convincingly been demonstrated to increase extrapulmonary malignancies.

As a result of a common chemical component and a shared mechanistic pathway, it should be possible to extrapolate from the epidemiology of cigarette smoking and ETS to predict associations of air pollution particle with human morbidity and mortality. While the total mass of air pollution particle a human will be exposed to will be lower than that of a cigarette smoker, the interactions with other oxidant components (e.g. ozone) will increase the impact. Accordingly, the range of human disease following air pollution potentially is predicted to approach that of a cigarette smoker. It is anticipated that forthcoming epidemiologic investigation will demonstrate a relationship of exposure to air pollution with:

1. COPD causation
2. Peripheral vascular disease
3. Hypertension
4. Renal disease
5. Digestive disease
6. Loss of bone mass/risk of fractures
7. Dental disease
8. Eye disease
9. Fertility problems
10. Extrapulmonary malignancies including breast cancer and leukemias

Epidemiologic research has already suggested associations of air pollution with several of these endpoints including COPD causation, peripheral vascular disease, hypertension, renal disease, digestive diseases, loss of bone, eye disease, breast cancer, and leukemias [86-94].

Conclusions

Cigarette smoke, ETS, and air pollution have a common chemical component and a shared mechanistic pathway. A common chemical component and share mechanistic pathway allow an extrapolation of the results of the epidemiology of cigarette smoking to predict associations of air pollution exposure with human disease.

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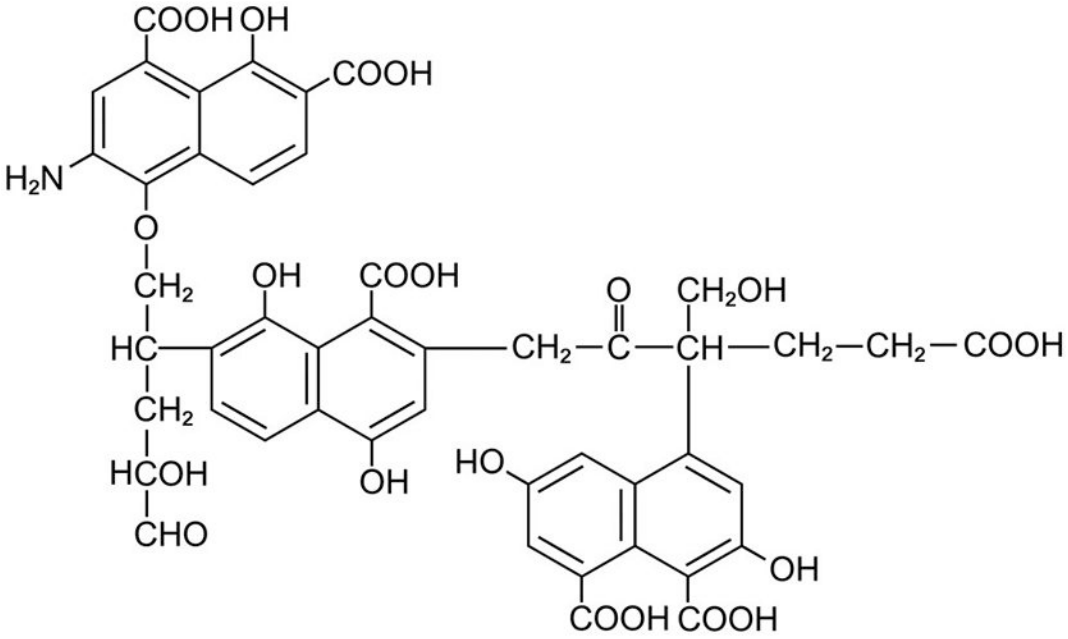

Figures 1A and 1B.

Numerous different sources contribute to the release of carbonaceous particles into the atmosphere (designated by black and brown particles) (Figure 1A). Some of the carbonaceous particles can include HULIS, a polycarboxylic, polyaromatic material (designated by brown particles). Exposure of the ambient air PM to ozone results in additional functionalization of the particle surface with introduction of more phenol, lactone, and quinone groups but especially further carboxylation. The formation of these products increases solubility of components of the PM with systemic distribution following (Figure 1B). Respiratory disease, cardiovascular disease, non-malignant extrapulmonary disease, fertility problems, changes in pregnancy outcomes, effects on the newborn, and extrapulmonary diseases result from the impact of exposure of the tissues to this component of ambient air pollution particle.

Table 1.

Respiratory morbidity and mortality associated with cigarette smoking, ETS, and air pollution particles

	Smoking	ETS	Air pollution
Respiratory symptoms	Yes [77]	Yes [65,77]	Yes [70]
Lung function decline	Yes [77]	Yes [65,77]	Yes [70]
Asthma – causation	Yes [77]	Yes [65,77]	Yes [70]
Asthma - exacerbation	Yes [77]	Yes [65,77]	Yes [70]
COPD – causation	Yes [77]	No	No
COPD - exacerbation	Yes [77]	Yes [65,77]	Yes [70]
Infections	Yes [77]	Yes [65,77]	Yes [70]
Lung cancer	Yes [77]	Yes [65,77]	Yes [70]

Table 2.

Cardiovascular disease associated with cigarette smoking, ETS, and air pollution particles

	Smoking	ETS	Air pollution
Atherosclerosis	Yes [77]	Yes [65,77]	Yes [70,95,96]
Ischemic/coronary heart disease	Yes [77]	Yes [65,77]	Yes [70,97,98]
Cerebrovascular disease	Yes [77]	Yes [99,100]	Yes [101,102]
Peripheral vascular disease	Yes [77]	No	No
Hypertension	Yes [77]	No	No
Other heart disease	Yes [77]	Yes [65,77]	Yes [103,104]

Table 3.

Non-malignant extrapulmonary disease associated with cigarette smoking, ETS, and air pollution particles

	Smoking	ETS	Air pollution
Infections	Yes [77]	Yes [65,77]	Yes [105]
Diabetes	Yes [77]	Yes [65,77]	Yes [106,107]
Renal disease	Yes [77]	No	No
Ischemic diseases of the intestines	Yes [77]	No	No
Liver cirrhosis	Yes [77]	No	No
Other digestive disease	Yes [77]	No	No
Loss of bone mass/risk of fractures	Yes [77]	No	No
Dental disease	Yes [77]	No	No
Eye disease	Yes [77]	No	No
Immunologically mediated disease	Yes [77]	No	No

Table 4.

Fertility problems, changes in pregnancy outcomes, and effects on the newborn associated with cigarette smoking, ETS, and air pollution particles

	Smoking	ETS	Air pollution
Fertility problems	Yes [77]	No	No
Pregnancy outcome	Yes [77]	Yes [108,109]	Yes [110,111]
Effects on the newborn	Yes [77]	Yes [65,77]	Yes [112,113]

Table 5.

Extrapulmonary malignant diseases associated with cigarette smoking, ETS, and air pollution particles

	Smoking	ETS	Air pollution
Laryngeal/lip/pharyngeal cancer	Yes [77]	No	No
Esophageal cancer	Yes [77]	No	No
Stomach cancer	Yes [77]	No	No
Colon cancer	Yes [77]	No	No
Liver cancer	Yes [77]	No	No
Pancreatic cancer	Yes [77]	No	No
Kidney and bladder cancer	Yes [77]	No	No
Leukemia/lymphoma	Yes [77]	No	No
Breast cancer	Yes [77]	No	No
Cervical cancer	Yes [77]	No	No
Endometrial cancer	Yes [77]	No	No
Rare cancers	Yes [77]	No	No
Cancers of unknown site	Yes [77]	No	No