



Review

Air pollution combustion emissions: Characterization of causative agents and mechanisms associated with cancer, reproductive, and cardiovascular effects

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Received 21 December 2006; received in revised form 8 July 2007; accepted 13 August 2007
Available online 17 August 2007

Abstract

Combustion emissions account for over half of the fine particle ($PM_{2.5}$) air pollution and most of the primary particulate organic matter. Human exposure to combustion emissions including the associated airborne fine particles and mutagenic and carcinogenic constituents (e.g., polycyclic aromatic compounds (PAC), nitro-PAC) have been studied in populations in Europe, America, Asia, and increasingly in third-world countries. Bioassay-directed fractionation studies of particulate organic air pollution have identified mutagenic and carcinogenic polycyclic aromatic hydrocarbons (PAH), nitrated PAH, nitro-lactones, and lower molecular weight compounds from cooking. A number of these components are significant sources of human exposure to mutagenic and carcinogenic chemicals that may also cause oxidative and DNA damage that can lead to reproductive and cardiovascular effects. Chemical and physical tracers have been used to apportion outdoor and indoor and personal exposures to airborne particles between various combustion emissions and other sources. These sources include vehicles (e.g., diesel and gasoline vehicles), heating and power sources (e.g., including coal, oil, and biomass), indoor sources (e.g., cooking, heating, and tobacco smoke), as well as secondary organic aerosols and pollutants derived from long-range transport.

Biomarkers of exposure, dose and susceptibility have been measured in populations exposed to air pollution combustion emissions. Biomarkers have included metabolic genotype, DNA adducts, PAH metabolites, and urinary mutagenic activity. A number of studies have shown a significant correlation of exposure to $PM_{2.5}$ with these biomarkers. In addition, stratification by genotype increased this correlation. New multivariate receptor models, recently used to determine the sources of ambient particles, are now being explored in the analysis of human exposure and biomarker data.

Human studies of both short- and long-term exposures to combustion emissions and ambient fine particulate air pollution have been associated with measures of genetic damage. Long-term epidemiologic studies have reported an increased risk of all causes of mortality, cardiopulmonary mortality, and lung cancer mortality associated with increasing exposures to air pollution. Adverse reproductive effects (e.g., risk for low birth weight) have also recently been reported in Eastern Europe and North America. Although there is substantial evidence that PAH or substituted PAH may be causative agents in cancer and reproductive effects, an

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increasing number of studies investigating cardiopulmonary and cardiovascular effects are investigating these and other potential causative agents from air pollution combustion sources.

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Keywords: Combustion emissions; Air pollution; Fine particles (PM_{2.5}); Particulate matter (PM); Exposure; Source apportionment; Coal; Fuel oil; Diesel; Gasoline; Wood burning; Incineration; Cooking; Waste incineration; Tobacco smoke; Mutagenicity; DNA damage; Adducts; Biomarkers; Carcinogenicity; Reproductive effects; Low birth weight; Cardiovascular disease

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1. Introduction

Combustion products of coal (soot and tars) were the first recognized chemical carcinogens. The earliest discovery that coal soot caused cancer in human chimney sweeps was reported Percival Pott in 1775 followed by studies in animals in the 1920s and the discovery of

carcinogenic polycyclic aromatic hydrocarbons (PAH), e.g., benzo[*a*]pyrene (BaP), in the 1930s [1]. In the early 1970s, advances in the identification and evaluation of carcinogens resulted in the initiation of the International Agency for Research on Cancer (IARC) that conducted research and international assessment programs to identify and evaluate the carcinogenic risks to humans

from chemicals and complex human exposure mixtures [2–9]. The development of new methods and approaches to more efficiently identify potential carcinogens [10–12] in complex mixtures through the use of a bacterial mutagenesis bioassay [10] combined with bioassay-directed fractionation and chemical characterization was applied to complex combustion source emissions and air pollution [11,12]. Using this approach, the identification of mutagens in particles from diesel exhaust and urban air, not only confirmed the contribution of PAH to mutagenic activity, but also led to the discovery of highly mutagenic nitroarenes (e.g., nitro-PAH and nitro-lactones) in diesel and urban air particles [11–13]. The IARC Monograph program has evaluated the carcinogenic risk of chemicals to humans, including the carcinogenicity of PAH [2,3,7] and nitro-PAH [6] (<http://monographs.iarc.fr>). The third monograph evaluated the cancer risk of PAH and heterocyclic compounds [2] found in coal-tars and other combustion products. Later, monographs in this series have evaluated air pollution combustion emissions and related complex mixtures of PAH and polycyclic aromatic compounds (PAC) [3–6], aluminum and coke production industries [4], coal-tars and soot [5], diesel and gasoline engine exhausts and nitro-PAH [6]. The two most recent evaluations are summarized in *Lancet Oncology*, included PAH [7] and household solid fuel combustion (coal and biomass) and high-temperature frying [8]. The IARC Monograph program has evaluated a wide range of combustion emissions includes industrial sources [4,5], motor vehicles [6], and residential combustion sources such as cooking emissions and indoor heating sources [8], and tobacco smoke [9].

The role of air pollution in human cancer has been reported in a number of reviews [14–16] and recent studies in the U.S. and Europe [17,18]. This review addresses the chemical, mechanistic, animal, and human evidence for a link between particulate air pollution from combustion sources and a series of adverse health effects that may be linked by common causative agents and mechanisms. These health outcomes include cancer, reproductive effects, cardiovascular disease, and related intermediate effects.

2. Combustion emissions: chemical and bioassay characterization, source apportionment, and human exposure

2.1. Chemical and bioassay-directed characterization of combustion particle emissions

The complex mixtures emitted from combustion and related sources include particles, semi-volatile matter,

and gases. The airborne particles less than 2.5 μm ($\text{PM}_{2.5}$), often called fine or respirable particles, may be referred to in older literature as soot since most fine particles from combustion have a high content of black elemental carbon. The particulate organic matter (POM) or organic extractable matter associated with $\text{PM}_{2.5}$ includes thousands of chemical ranging from alkanes and aromatic compounds to polar substituted aromatics and carboxylic acids. Hundreds of individual organic compounds have been identified in the organic atmospheric aerosol [14,19]; however, together these compounds constitute less than 10% of the organic carbon (OC) of urban and rural aerosol [20,21]. The unresolved organic mass includes polar compounds (e.g., phenols, tetrols, acids, and oxidation products of alkenes such as isoprene) that are difficult to identify by gas chromatography without derivatization [22], large insoluble polymeric molecules possibly of biogenic origin [23–26], and humic acids and other humic like substances (e.g., polycarboxylic acids) [27,28]. A number of substances of natural origin such as wood dust [29] and some naturally occurring plant products and substances [30] produced by molds such as mycotoxins (e.g., aflatoxin) have also been shown to be carcinogenic to humans, however there is little evidence suggesting the biogenic mass in fine particles contains these compounds. More research is needed to chemically and biologically characterize the non-combustion related biologic mass (including proteins, lipids, cellular debris, and other substances) associated with $\text{PM}_{2.5}$.

The mutagenicity and carcinogenicity of airborne combustion particles was initially attributed primarily to PAH [1–4]. More recently, it was discovered that a wider range of polycyclic aromatic compounds found in combustion emissions and air pollution are both mutagenic and carcinogenic. These compounds include substituted aromatic hydrocarbons such as nitroarenes (e.g., nitro-PAH) [6,11,12] and nitro-PAH lactones (e.g., nitropyrene lactones, nitrophenanthrene lactones, and 3-nitrobenzanthrone) found in ambient air and diesel particles [13,31]. One of these compounds, 3-nitrobenzanthrone, an unusually potent mutagen in the Ames bacterial mutagenesis assay, recently has been reported to induce tumors in rodents [32,33]. The primary source of polycyclic aromatic compounds in air pollution is from combustion of fossil fuels (e.g., coal, oil, gasoline and diesel fuel), vegetative matter (e.g., wood, tobacco, paper products, and biomass) and synthetic chemicals (e.g., from plastics and other chemical products in incinerated municipal, hospital and hazardous wastes). The organic extractable mass from carbonaceous soot particles emitted from several

well-studied combustion sources (coal, diesel, and tobacco) induce tumors in animals, mutations in cells, and have been clearly implicated in epidemiologic studies as human carcinogens [3–6]. Incomplete combustion products, however, also contain gaseous chemicals that are carcinogenic, such as benzene, aldehydes, and alkenes (e.g., 1,3-butadiene) and the volatile and semi-volatile PAH (e.g., pyrene) and other smaller aromatic molecules that partition between the gas and particle phase [14,23].

2.2. Coal related emissions

The tars and soot produced from coal through heating, combustion and related processes (e.g., pyrolysis and reductive distillation) contain organic pollutants in both the gaseous phase and in fine particles [1]. Coal has been used for residential and industrial heating, power generation, and in industrial processes (e.g., steel mills, aluminum smelters, coke ovens). Coal-tars and soot from chimneys were first recognized in the 1775 as a cause of scrotal and other skin cancers in chimney sweeps [1,5]. In the 1980s, occupational exposures to emissions from coke production, coal gasification, aluminum production, and iron and steel founding were found to cause respiratory cancer in humans by the International Agency on Research on Cancer (IARC) [4,5].

Historically, coal combustion has been associated with respiratory symptoms and mortality [34] resulting from relatively short-term episodes of high air pollution. The most famous of these episodes occurred in London in 1952 [35], however many other episodes have occurred in areas predominantly impacted by coal combustion such as those in the Meuse Valley, Belgium in 1930 [36,37], and in Donora, Pennsylvania [38]. In the 1990s, extensive studies of the health impact of air pollution from coal combustion including both coal fired power plants and residential coal heating were conducted in Eastern Europe, including Northern Bohemia (Teplice, Czech Republic) and other parts of the Black Triangle (southeastern Germany and Poland) [39]. These studies have documented a wide range of health effects including respiratory effects in children [40], genetic damage [41,42], male and female reproductive effects [43,44], cardiopulmonary and cancer mortality [45]. Lung cancer was also found to be highly elevated in women exposed to indoor air pollution from cooking and heating with coal burned inside small homes without venting to the outdoors in Xuan Wei, China [46] and more recently a comprehensive evaluation of the carcinogenicity of household solid fuel combustion found evidence of carcinogenic risk to humans [8].

Coal combustion emissions including coal-tars and soot have been documented as human carcinogens since the late 1700s [1] and in many more recent evaluations [4,5,8,46]. In the 1930s, coal soot (black particles) and the tars extracted from them were fractionated and applied to animal skin to identify the carcinogenic fractions that were ultimately identified as carcinogenic polycyclic aromatic hydrocarbons (PAH) [1]. Although these mixtures are very complex, PAH are still considered the primary human cancer causative agents present in coal combustion emissions [2–5,7,8]. These early studies have been reviewed extensively by Searle [1], IARC [3–7] and an international panel of experts convened by the European School of Oncology to review air pollution human cancer [14]. Bioassay-directed chemical and bioassay studies have been applied to both fossil fuels (e.g., coal and petroleum combustion products) and vegetative fuels (e.g., wood and other biomass) [11,12,47–49]. These studies demonstrate that the aromatic neutral fractions containing PAH are responsible for a predominant fraction of the mutagenic and tumorigenic activity of coal tar and coal combustion emissions. In some reductive distillations of coal, such as the coking process found in coke ovens, in addition to PAH, aromatic amines and heterocyclic aromatic compounds (e.g., aza-arenes) are also formed [4,5]. Coke oven emissions, in contrast to the oxidative coal combustion processes, contain a significant basic fraction containing these aromatic nitrogen-containing compounds that include mutagenic and carcinogenic aromatic amines and nitrogen heterocyclic organics [4].

Source apportionment studies of ambient fine particles in northeastern US (Vermont) identified coal-fired power plants located in the mid-west as a major source of fine particles for this region [50,51], in contrast to the western US. A comparative source receptor analysis using the chemical composition of fine particles from three northeastern US locations (Washington, DC, Brigantine, NJ, and Underhill, VT) also found coal combustion was a major source of fine particles at all these sites, however there appeared to be two separate coal sources [52]. The largest source contributing to the PM_{2.5} mass was coal combustion with enhanced secondary sulfate. A second coal combustion source dominant in the winter exhibited a receptor modeling profile with significant organic and elemental carbon [52] suggesting that some homes may be burning coal in residential stoves.

Although coal-tars and emissions from residential coal burning and poorly combusted industrial coal emissions are clearly carcinogenic to humans [4], the impact of modern coal fired power plants on the current

cancer risk of ambient fine particles needs more research. Studies in the 1980s of fly ash particles emitted from utility power plants [53,54] reported the mutagenic activity of the extractable organic matter to be comparable in magnitude to other combustion sources [55]. In a comparative assessment of the impact of coal powered utility plants on the potential cancer risk of various energy sources, these large plants had the lowest mass emission rates of particulate organic mass and mutagenicity per joule of energy [56], however coal-fired power plants are the major energy source for many regions, including the north eastern United States. Additional research is needed to investigate the impact of volatile and semi-volatile organic emissions from coal combustion sources and their atmospheric reaction products.

2.3. Petroleum combustion: diesel, fuel oil, gasoline and related sources

Petroleum products include crude oil, residual oil, heating oil, diesel fuel, gasoline, jet fuel, kerosene, propane and liquefied gases. The consumption of petroleum products in the US has increased over 300% since 1950 with the average person consuming over 3 gal per day to meet their energy needs [57] including transportation and heating and other petroleum requiring products (e.g., such as plastics). The US Environmental Protection Agency (EPA) Technology Transfer Network (TTN), Clearinghouse for Inventories & Emissions Factors (CHIEF) provides an internet access via this site: <http://www.epa.gov/ttn/chief/index.html> for emission inventories, emission factors, speciation databases, documentation, and tools (e.g., the Speciate 4.0 program provides total organic compound and particulate matter speciation profiles of air pollution sources as well as access to speciation software programs developed for public use. The US EPA speciation database includes nine different categories of emissions including those discussed in the sections below.

2.3.1. Fuel oil emissions

The heavier petroleum products, such residual fuel oil (No. 4–6 fuel oils) are carcinogenic on mouse skin and mutagenic both in vitro and in vivo [58]. Residual (heavy) fuel oil has been classified by IARC as possibly carcinogenic to humans (Group 2B) [59]. These fuel oils contain carcinogenic PAH, high sulfur content, ash, carbon residue, and asphaltene compounds (aromatic and naphthenic ring compounds containing nitrogen, sulfur and oxygen) [60]. Combustion of residual oil in industrial or commercial boilers results in the emission of residual

oil fly ash (ROFA). ROFA contains a relatively high content of toxic trace metals (e.g., soluble nickel and vanadium sulfate salts) and compared to coal fly ash is highly toxic to pulmonary alveolar macrophages, in part due to the soluble toxic metals [61–64]. Generally, higher particle and carbonaceous emissions are derived from combustion of heavier petroleum products, e.g., fuel oils (No. 2–6) have higher particle and carbon emission rates than lighter fuels such as kerosene or jet fuel (No. 1 fuel oil) [59–61]. Propane and natural gas have the lowest particle emissions; however they do emit gaseous organics and nitrogen oxides.

The toxicity and mutagenicity of combustion particles, including fuel oil emissions, were first reported in the 1980s [62]. This study compared a wide range of combustion particles; including oil fly ash particles that exhibited relatively high cytotoxicity, excess mortality, and mutagenicity. Studies of inflammation and acute lung injury in rats when residual oil fly ash (ROFA) was administered by intratracheal instillation [64] stimulated an interest in ROFA as a model particle. The biologic effects and potential mechanisms of ROFA toxicity associated with transition metals have been reviewed by Ghio et al. [65]. Limited research has been reported on the organic constituents and the mutagenicity or other genetic or potential cancer risk of ROFA. An occupational study of boilermakers exposed to particles of residual oil fly ash (ROFA) and metal fume that contain carcinogenic PAH and metals [66]. Associations were also found between the exposures to PAH and the urinary biomarker 1-OHP (1-hydroxypyrene) and oxidative DNA injury, as measured by 8-hydroxy-2'-deoxyguanosine (8-OHdG) in urine [66]. These findings provide evidence that ROFA may induce both cancer and non-cancer health effects and the causative agents may include both toxic metals and PAH.

2.3.2. Diesel and gasoline emissions

A major source of air pollution in urban areas is the combustion of diesel and gasoline fuels in cars, buses, trucks and other on-road transportation sources, however additional emissions result from numerous off-road sources (such as lawn mowers, tractors, snow mobiles, construction equipment, and marine vessels) [67]. Although emissions have been reduced by improved control technologies, the number of vehicles and other sources utilizing diesel and gasoline fuels has continued to increase as indicated by EPA trends reports of vehicle miles traveled (<http://www.epa.gov/OMS/fetrends.htm>). Diesel vehicles emit as much as 100 times the elemental carbon (EC) and 20 times the organic carbon (OC) per mile as compared with the newer low emitting gasoline

vehicles [68]. Recent source apportionment studies of fine particle mass ($PM_{2.5}$) across the U.S. and in many other urban locations, where motor vehicles are the primary mode of transportation, report diesel and gasoline vehicles are one of the major sources of particulate matter [69–71]. These studies have primarily relied on EC as a source tracer for diesel. Vehicles are also the dominant source of ultrafine particles near streets and roadways [72]. Until recently, it has been difficult to separate the contribution of diesel and gasoline vehicle emissions to ambient air particulate matter and many earlier source apportionment studies combine these into mobile sources in general. Diesel sources, however, emit relatively high concentrations of both OC and EC whereas gasoline sources emit less EC [71–73]. Other differences between diesel and gasoline particle emissions include specific organic molecular tracers [70] and the OC temperature fractions from thermal analysis [69,73]. These have recently been used to estimate the contributions of these two sources separately [69–71].

The US EPA initiated diesel emissions research in 1977 to evaluate the human health impact of an increase in diesel vehicle emissions [74]. The energy crisis in the early 1970s led to fuel economy standards [75] that encouraged dieselization of the light duty car fleet. It was estimated that by 1985 up to 10% of the new US passenger cars would be diesel powered due to their fuel efficiency. The first diesel characterization research led to the discovery that diesel particles contained relatively large quantities of mutagenic organic compounds [76]. Mutagenesis and carcinogenesis studies of a range of diesel particles was published in the early 1980s [77–84] as well as inhalation cancer and toxicology studies [81,85,86]. Comparative cancer potency studies of diesel and gasoline particle extracts were compared to a series of organic extracts from known human carcinogens (coal tar, a coke oven, tobacco smoke) with respect to their chemical composition [48,78], mutagenicity [49,84], and animal tumor potency [82,83]. The tumor initiation potency of the three known human carcinogens compared to the tumor potency of a series of diesel combustion emissions and one gasoline combustion emission sample was used to estimate the range of relative cancer unit risks from diesel emissions [87,88] in the early 1980s. These early risk estimates using the comparative potency method were within the range of current risk estimates from a large series of animal inhalation and human epidemiology studies reported and evaluated in the US EPA Health Assessment Document for Diesel Engine Exhaust published in 2002 [68].

Bioassay-directed fractionation and chemical characterization studies were used to identify mutagenic

polycyclic aromatic hydrocarbons (PAH) and nitro-PAH in the extractable organic matter from diesel particles [11,76,89]. Animal tumor assays [6,90] also have been used to investigate the contribution of PAH and nitro-PAH to the carcinogenicity of diesel exhaust through bioassay-directed fractionation. In 1986, el-Bayoumy and Hecht [13] had reported the mutagenicity of several K-region lactone derivatives of 1-nitropyrene that were highly mutagenic and may be important in its metabolic activation. Over 10 years later, 3-nitrobenzanthrone (3-NBA) was isolated from both diesel and air particles and shown to be a very powerful direct acting mutagen [31] that may also be formed in atmospheric reactions [32].

Animal cancer studies of diluted diesel exhaust, filtered exhaust, particles and particle extracts have been well documented in a large number of studies from multiple countries and reviewed in the latest EPA Health Assessment Document for Diesel Exhaust [68]. Earlier reviews and assessments of the cancer risk of diesel exhaust were conducted by the International Agency for Research on Cancer [6], and the California EPA [91]. The animal cancer studies include inhalation, lung implantation, and skin application studies. In the 1990s a relatively large number of animal inhalation studies were conducted in the US, Japan, and Europe and are well summarized in a series of health assessment documents [6,68,91].

Cancer epidemiology studies of occupational exposures to diesel exhaust provide the largest body of evidence for the carcinogenicity in humans with the most recent assessment evaluating in detail 22 key lung cancer studies [68]. In addition to lung cancer, cancers of the bladder and lymphatic tissue are the other most common cancers associated with exposures to diesel exhaust. Occupational exposures in these studies include diesel exhaust from buses, taxis, trucks, trains, ships, and other diesel engines used for transportation. The EPA assessment [68] found a persistent association of risk for lung cancer and diesel exhaust exposure in over 30 epidemiologic studies. Meta-analyses of studies reporting the relationship between diesel exhaust exposure and lung cancer risk have been conducted by two groups. The first study by Bhatia et al. [92] analyzed 23 studies that met their criteria for inclusion in the analysis and determined the pooled precision-weighted relative risk of 1.33 (95% CI = 1.24, 1.44). Lipsett and Campleman [93] analyzed 30 studies that met their criteria for inclusion and determined the pooled smoking-adjusted relative risk was 1.47 (95% CI = 1.29, 1.67). Both meta-analyses of lung cancer concluded that the data support a causal association between lung cancer and diesel exhaust

exposure. A special report was also published by the Health Effects Institute [94] from their diesel epidemiology expert panel's assessment of the relationship between diesel emissions and lung cancer. This panel reviewed 35 epidemiologic studies, including 19 case-control and 16 cohort studies of occupational exposure to diesel exhaust. This panel concluded that occupational exposure to diesel exhaust from diverse sources increases the rate of lung cancer by 20–40% in exposed workers [94] and the cancer rate was greater with prolonged exposures.

The human carcinogenic potential of diesel exhaust has now been evaluated by six organizations, including two international organizations, IARC [6], affiliated with WHO, and US agencies including NIOSH [95], NTP [96] and EPA [68], as well as a state environmental agency, the California EPA [91]. As more research is reported, the strength and magnitude of evidence suggests that diesel exhaust is a carcinogenic risk to humans. The most recent assessment by US EPA concludes that diesel exhaust is “likely to be carcinogenic to humans by inhalation” and concludes that based on the evidence for a mutagenic mode of action “a cancer hazard is presumed at environmental exposure levels” [68]. The highest range of estimated environmental exposures to diesel particles are close to or overlapping with the lower range of occupational exposure for which lung cancer increases have been reported. The diesel exhaust exposure–response data available to the US EPA in 2002 had uncertainties that prevented the agency from publishing a quantitative cancer unit risk with confidence [68]. In spite of the progress in

understanding the potential hazards of diesel exhaust, fuels, engines, and control devices are continually being re-engineered. These changes require continual re-evaluations and testing of emissions to ensure emission standards are met. Among the most important goals is to understand the relationship between the source characteristics (engines, operating conditions, etc.), chemical characteristics of the toxic components, and mechanisms of toxicity.

Recent publications [97–99] highlight the lack of a systematic approach to understanding the relationship between the source and toxic emission components as well as between cancer and non-cancer health effects. A recent comparison of two diesel particle samples used in many toxicology studies resulted in very different chemical and toxicologic profiles. One of these samples, a diesel forklift sample available as a standard reference material (SRM 2975) [100,101] has been studied with respect to genotoxicity and chemical composition (e.g., PAH, nitro-PAH, and other mutagenic and carcinogenic components). The original purpose of this sample was to provide a large quantity of a single homogeneous sample for a diesel standard reference material (SRM) to advance standardization of the chemical analysis of the organic and inorganic species as well as organic and elemental carbon [100,101]. The other automobile derived diesel exhaust particle (A-DEP) from Japan [102,103] has been examined for effects on pulmonary inflammation and exacerbation of allergic asthma like responses. The studies by DeMarini et al. [98] and Singh et al. [99] compare the genotoxicity and pulmonary toxicity in both samples as shown in Table 1.

Table 1
Comparison of characteristics of two diesel exhaust particle samples

Characteristics	A-DEP ^a	SRM 2975 ^b
Percent extractable organic mass (EOM)	26.3	2.0
Relative PAH-type mutagenic potency of EOM	18	1
Relative PAH-type mutagenicity of particles	227	1
Relative nitroarene mutagenic potency of particles	8–45	1
Relative distribution of PAH-type activity ^c	3	1
Relative direct-acting activity in hexane/DCM	14	1
Relative direct-acting activity in methanol	1	10
Relative amount of elemental carbon (EC)	1	6.7
Relative amount of organic carbon (OC)	10	1
Major mass by organic fraction	55% non-polar	58% polar
Pulmonary cell toxicity: influx/enhanced cell type	Macrophages	PMN ^d
Lung injury: microalbumin vascular leakage	Yes	Yes

^a Automobile diesel exhaust particles (A-DEP) [102].

^b Standard Reference Material 2975 Diesel Forklift [100,101].

^c EOM in hexane/DCM fraction.

^d PMN: polymorphonuclear (cell inflammation).

The advantage of these companion papers is the direct comparison of these two very different samples in both genetic toxicity and pulmonary toxicity. This was possible due to the relatively large quantity of particles available to the investigators. The limitation of these two different diesel particle sources is that the particle collection methods were not optimized to represent diesel particles that human populations are exposed to in the environment. The SRM 2975 was collected in an evaluation of a particle trap applied to a fleet of diesel forklifts. This sample had no standard dilution and cooling before collection as reflected in the very low percent of organic extractable mass and may also account for the high relative mutagenicity in the more polar fractions [98]. The A-DEP samples were collected at a much colder sampling temperatures onto glass-fiber filters after dilution [98], rather than using Teflon coated filters that minimize secondary chemical reactions. Although these two large samples (SRM 2975 and A-DEP) represent very different diesel engines with different sample collection methods, they illustrate the value of comparing different biologic endpoints with the same set of samples. Although these diesel particles may not reflect realistic diesel particle human exposures, they do provide an important toxicologic and chemical comparison between two very different diesel particles.

Gasoline vehicles, due to their relatively low particle emission rates compared to diesel, have not been as well studied in biologic or toxicologic systems. Recent comparative studies by Seagrave et al. [104] highlight the variation in emissions, toxicity, and mutagenicity of high emitting “white smoker” vehicles. Additional research is needed to characterize the toxicity and cancer risk of the gaseous and semi-volatile organic species from gasoline and diesel as well as their atmospheric transformation products as the engines and fuels change over time.

Gasoline and diesel emissions differ in their carcinogenic PAH emissions [105]. Gasoline vehicles without catalytic converters had the highest PAH emission rate for benzo(a)pyrene (BaP) (6.6 $\mu\text{g}/\text{km}$) compared to gasoline vehicles with catalytic converters that emitted lower concentrations of BaP (0.3 $\mu\text{g}/\text{km}$). Diesel vehicles generally have lower PAH emission rates than gasoline vehicles due to the nitration of PAH to nitro-PAH [106]. Many of the nitro-PAH (e.g., nitropyrene) are more carcinogenic [6] than the parent PAH (e.g., pyrene compared to nitro-pyrene).

The US EPA’s inhalation exposure and risk assessment from mobile source air toxics in the future reported the highest cancer risk from benzene, 1,3 butadiene, several aldehydes, naphthalene (a PAH),

polycyclic organic matter (POM) in addition to diesel particulate matter and organic gaseous emissions [107]. These and related studies have led to a final regulatory rule by the US EPA to reduce mobile source air toxics [108] by lowering benzene in gasoline, reducing exhaust emissions from passenger vehicles operated at cold temperatures, and by reducing emissions from portable fuel containers. These new standards are aimed at reducing the non-methane hydrocarbon (NMHC) exhaust emissions from the exhaust as well as reducing the evaporative emissions for new gasoline-fueled vehicles. In spite of these new assessments and regulations, the US EPA reports predict that inhalation of mobile source air toxics will continue to be a public health concern [107].

2.3.3. Traffic and roadway emissions

Traffic density and intensity is a major source emission including gases, semivolatile organics and both fine and ultrafine particles. A recent review of ambient and traffic-related particulate matter (PM) addresses the chemical characteristics and radical generating capacity of PM (e.g., traffic related PM) as well as the chemical composition as a function of particle size from ultrafine particles ($<0.1 \mu\text{m}$) to coarse particles (PM_{10} – $\text{PM}_{2.5}$) [109]. The density of vehicles (e.g., intensity of traffic) influences the concentration of air pollutants and human exposures closer to major roadways have higher exposure to traffic emissions. De Kok et al. [109] also reviewed the impact of traffic intensity on the mutagenicity, cytotoxicity, and DNA-reactivity of traffic-related PM and the impact of particle size. They conclude that although the smaller PM size fractions show the highest levels of radical formation, that the PAH concentrations appear to be a more important determinant of the radical generating capacity than the level of transition metals or other metals [109]. Exposure biomarkers as well as reproductive and cardiovascular outcomes have recently been studied in geographical locations where distance from a roadway and other measures of traffic are used to estimate exposure to traffic emissions as a function of adverse health outcomes. These studies are discussed in more detail in Sections 4 and 5 below.

2.4. Biomass and vegetative combustion: wood smoke, forest fires, agricultural burning, open burning, cooking emissions, and tobacco smoke

The emissions from burning or combustion of biomass, such as wood, paper, trash, forest fires, agricultural waste as well as tobacco and high temperature

cooking are all characterized by higher organic carbon and particle emission rates compared to high efficiency fossil fuel combustion sources [8,9,47]. Vegetative burning sources generally emit proportionally less elemental or black carbon emissions than diesel soot and other fossil fuel emissions. Biomass combustion sources tend to have higher extractable (soluble) organic emissions that contain characteristically high concentrations of organic tracers derived from the combustion of lignin (e.g., methoxyphenols) and cellulose (e.g., levoglucosan) that differ from the organic tracers found in fossil fuel emissions. Polycyclic aromatic hydrocarbons (PAH) are ubiquitous and are emitted from all combustion processes. Organic tracers of smoke from biomass burning have been reviewed in depth by Simoneit [110]. Biomass burning includes wildfires, campfires, controlled and uncontrolled burning of agricultural crops, forests, waste biomass, and peat fuel. Other vegetative combustion sources including cooking, heating (e.g., woodstoves), and tobacco smoking. Simoneit lists over 50 major biomarker tracers in smoke from biomass burning including levoglucosan, retene, cholesterol, and a series of methoxyphenols [110]. Nicotine and nitrosamines are characteristic markers for tobacco smoke [9]. Fatty acid oxidation products are found in cooking oil fumes [8] and cholesterol is a tracer for meat cooking emissions [70].

2.4.1. Wood smoke, forest fires, and agricultural burning

The pyrolysis products of lignin, cellulose, and other polysaccharides are a major component of the emissions from wood burning, forest fires, and other biomass burning [110]. A review of the pyrolysis products and organic tracers for smoke from incomplete combustion of biomass includes levoglucosan from cellulose and methoxyphenols from lignin. The oxygenated organic compounds, such as the semi-volatile and reactive methoxyphenols derived from lignin constitute up to 30% of the carbonaceous particle mass [110] and serve as specific tracers of biomass combustion of specific plant classes [111] and wood smoke pollution [112,113]. Levoglucosan is a stable and unique cellulose combustion product thereby making it a useful and unique tracer for wood and other cellulose combustion in biomass burning and atmospheric particles [114–116]. A micro-analytical method has recently been developed for the measurement of levoglucosan in air pollution and human exposure monitoring and source apportionment studies [115]. Ambient source characterization of fireplace emissions [117] and winter source apportionment studies have

used organic compounds as molecular source markers in chemical mass balance models in a winter air pollution studies across the United States [118,119]. In these studies, all of the levoglucosan and pimaric acid were attributed to wood combustion. The pimaric acid is a naturally occurring diterpenoid carboxylic acid (resin acid). It is found in high concentrations in softwoods and released to the air during burning, rather than forming as a combustion product. For many years, soil corrected potassium was used as a tracer for woodsmoke and has been validated using carbon dating methods [120,121]. In a recent source apportionment study of airborne fine particles (PM_{2.5}) in Seattle, arsenic was highly correlated with the wood smoke component of ambient fine particles [69]. It appears that even occasional use of some chromated copper arsenate [122] treated wood burned in fireplaces, woodstoves, or trash may be sufficient for arsenic to serve as a source tracer for wood smoke.

Vegetative combustion products, including wood, also emit mutagenic and carcinogenic PAH [123,124] as do nearly all sources of incomplete combustion [2,3,7]. Residential combustion of wood has been estimated to be the largest source of PAH in Sweden and the US based on estimated emissions countrywide [105]. In urban areas, however, mobile sources are generally the major source of exposure to PAH [107]. The mutagenic activity of wood stove emissions and the relationship to PAH have been evaluated in emission studies [125] and in wood smoke impacted air [126,127]. Several studies of the influence of atmospheric transformation on the chemistry and mutagenicity of wood smoke provide evidence that mutagenic products are produced and further chemically modified in the air [128,129].

Forest wild fires and prescribed forest burning result in many of the same emissions as residential wood fireplaces and wood stoves with differences dependent on the fuel (type and condition of the biomass) and burning conditions (e.g., oxygen availability to the combustion, dryness of the biomass material, and other atmospheric and environmental conditions). The smoke emissions have been characterized and emission factors reported in a number of studies [130,131]. A recent comprehensive review of the toxic air emissions from biomass open burning from wild fires, prescribed burning of forests, agricultural burning, yard and land clearing waste, campfires, and a wide range of other open burning sources from landfill fires to household wastes, and fires containing solid anthropogenic fuels (e.g., tires, plastics, vehicles, structures, wiring, fireworks) have been reported in a comprehensive review by Lemieux et al. [132].

Agricultural burning is used on grasslands, crop residues (e.g., wheat stubble), and rangelands in certain regions to dispose of crop debris, control weeds, and disease. The emissions from these agricultural burns can result in tons of increased air pollutants that may impact nearby communities. Biomass burning emits significant quantities of carbon monoxide (CO), carbon dioxide (CO₂), fine particulate matter (PM_{2.5}), volatile hydrocarbons, nitrogen and sulfur oxides, as well as potentially toxic and carcinogenic organic emissions [133,134] such as PAH. Emission factors for PAH species have a wide range depending on the burning conditions. Several independent studies [135,136] have reported wide ranges of PAH emissions from biomass (cereal crop residues and wood fuels) burned in a combustion wind tunnel to simulate open burning of biomass. In the first study of four different cereal crop residues and four different wood fuels, the concentrations of 19 PAH ranged from 120 to 4000 mg/kg fuel [135]. Other studies reported emission factors for PAH, methoxyphenols, levoglucosan, EC, and OC for wheat and Kentucky bluegrass stubble burns [136]. In general, total PAH emission rates increased with increasing particulate matter (PM) emission rates and decreasing combustion efficiency. Other air pollutant emissions associated with forest, grassland and agricultural burning in a range of locations from the United States to Africa [137–139].

Wheat stubble and grass burning has been used by farmers in the northwestern US and in other areas as a method of rapidly disposing of crop residues and releasing nutrients for the next growing cycle. A source apportionment study conducted over several years in Spokane, WA was able to identify and apportion the agricultural burning component of air pollution using inorganic source tracers and wind directional analysis [140]. In the recent review of open burning by Lemieux et al. [132], prescribed burning of savanna and forest fires have the highest CO emission factor as compared to the other open burning sources and also have a relatively high PM emission factor. The most extensive source of emission data for organic air toxics (VOCs, SVOCs, and carbonyls) from the open burning of biomass is presented in the form of emission factors with uncertainty estimates by Andreae and Merlet [131] and is summarized with other data by Lemieux et al. [132].

2.4.2. Cooking emissions

Restaurants, kitchens, stoves, grills, and other sources of cooking, charbroiling and high temperature frying (e.g., stir-frying) are sources of fine particles,

organic aerosols, and organic carbon species that make significant contributions to both indoor and outdoor air pollution [70,141–145]. Cooking emissions have relatively high emission rates of organic mass. Saturated and unsaturated fatty acids (alkanoic and alkenoic acids) are among the major organic compounds emitted during cooking. Rogge, Cass, Simoneit, and co-workers [141,143–145] have reported emission rates for about 150 organic compounds emitted during residential cooking including: *n*-alkanes, *n*-alkanoic acids, *n*-alkenoic acids, *n*-alkanols, *n*-alkanals, *n*-alkan-2-ones, dicarboxylic acids, furans, furanones, amides, steroids, polycyclic aromatic hydrocarbons (PAH), and heterocyclic aromatic amines (HAA). Electric and natural gas appliances were compared with most of the different cooking methods (e.g., pan-frying, stir-frying, sautéing, deep-frying, boiling, and oven baking or broiling). Oven broiling with natural gas had emissions 10-fold higher than oven broiling with electricity. In general, pan-frying and oven broiling with natural gas stoves generally gave the highest overall emissions in these studies. Related studies have also examined highly polar compounds in meat smoke [143] and charbroiling [141,144,145].

An international working group was convened by IARC in 2006 to evaluate the carcinogenicity of household high-temperature frying as well as household solid fuel combustion [8]. The high-temperature frying methods included in the evaluation were stir-frying, deep-frying, and pan-frying. When cooking oils, such as rapeseed or canola oil, are heated to high temperatures (e.g., over 240 °C) the emissions were mutagenic in every *in vivo* rodent assay [146]. There is substantial mechanistic data and experimental animal data that peroxidation products of polyunsaturated fatty acids, such as the dialdehyde, trans,trans-2,4-decadienal (tt-DDE or 2,4-De) [147] are carcinogenic in animals and that they are also probably carcinogenic to humans [8]. Polycyclic aromatic hydrocarbons (PAH) in cooking oil emissions [148] may also play a role in the carcinogenicity of cooking emissions. Mechanistic data supports the likelihood of tt-DDE, formed by heating oils during cooking [147], as being responsible for the mutagenicity and animal carcinogenicity of high temperature emissions reported in both mice and rats [8,149,150].

Residential cooking emissions have the largest impact on the quality of indoor air in the home [151,152]. Characterization of the mutagens present in fumes from cooking meats [153] and cooking oils [154] has also been reported. The highest PAH emissions were found during oven broiling of steaks

and the highest heterocyclic amine emissions were found during pan-frying bacon [146]. Mutagenic and carcinogenic PAH and heterocyclic amines (e.g., methyl-IQ, IQ, PhiP) are the most likely cooking emissions to have an impact on cancer risk, although these constituents are also present in the foods. No studies have examined the human cancer risk to the combined exposures by inhalation during cooking and subsequent ingestion of PAH and heterocyclic amines from cooked foods.

Outdoor air pollution source apportionment studies using organic compounds as molecular source tracers have estimated the contribution of cooking (e.g., from restaurants cooking meat) to the PM_{2.5} mass in a series of cities in the southeastern US and California [70,118,119]. Zheng et al. [119] reported that meat cooking contributed from 5 to 12% of the PM_{2.5} mass. In this study the particle-phase nonanal was all attributed to the meat cooking, whereas only 65% of the 9-hexadecanoic acid was from cooking and the remainder was attributed to wood burning and road dust.

A study in a city in southern Taiwan examined the contribution of PAH emissions and their carcinogenic potencies from cooking sources and traffic to the urban atmosphere [155]. Although the cooking sources contributed less total PAH to ambient air than traffic sources, the cooking sources contributed a much higher proportion of the carcinogenic benzo[*a*]pyrene (BaP) compared to the traffic sources.

2.4.3. Tobacco smoke

The role of tobacco smoking and involuntary smoking (passive smoking) in cancer is very well documented in the scientific literature and was recently re-evaluated by the International Agency for Research on Cancer (IARC) [9]. In this latest IARC Monograph 83 on tobacco smoke published in 2004 the chemistry, exposure, toxicology and epidemiology of both active and passive tobacco smoking is reviewed in detail and evaluated by an international panel of experts. This report concludes that tobacco smoking and tobacco smoke are carcinogenic to humans (IARC Group 1 classification) and that involuntary smoking (exposure to secondhand or 'environmental' tobacco smoke) is carcinogenic to humans (Group 1). The health effects of environmental tobacco smoke or passive smoking was first evaluated by the US EPA in 1993 [156] and was then followed by the California EPA's report on the health effects of exposure to environmental tobacco smoke (ETS) [157]. Recently, the California EPA has released a report proposing that ETS be classified as a

toxic air contaminant [158] for regulation under the California environmental regulations. These reports and other reviews of air pollution and cancer [14–17] provide a comprehensive review of the chemistry, exposure, toxicology, and human health effects of tobacco smoking and exposures to environmental tobacco smoke (ETS). Hecht [159] reviews the chemical carcinogens in tobacco smoke and provides a clear mechanistic framework linking nicotine addiction with lung cancer through exposure to specific carcinogens.

Although tobacco smoke is a vegetative burning source, it is much higher in protein and nitrogen compared to wood and dried agricultural debris that is higher in cellulose and lignin content. Burned wood results in smoke that is more acidic while charbroiling meats with more protein, produce nitrogen-containing emissions. Presumably, it is the presence of the proteins or other nitrogen compounds in tobacco that leads to the formation of nitrogen-containing emissions, such as nicotine, nitrosamines [160], and many other basic nitrogen containing organics found in the mutagenic fraction of cigarette smoke condensate [9]. Over 50 carcinogens evaluated by IARC are present in tobacco smoke including PAH and the nitrogen containing azarenes, *N*-nitrosamines, aromatic amines, and heterocyclic aromatic amines [159]. Hecht's [159] review of tobacco smoke carcinogens focuses on the PAH and the tobacco-specific nitrosamine, NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) that are the most likely to play major role in human cancer. Among the many organic nitrogen containing compounds in tobacco smoke, nicotine a sensitive tracer of human exposure to tobacco smoke exposure [161]. Nicotine's metabolite, cotinine, is one of the best validated biomarkers of exposure to a specific combustion product [162]. The wide use of this biomarker of exposure to tobacco in large population based studies [163] has improved the quantification of human exposure to tobacco smoke in a wide range of classical and molecular epidemiology studies.

2.5. Waste burning and incineration

Combustion of plastics, chemicals, and other wastes (e.g., household, industrial, agricultural, and medical) can lead to the formation of mutagenic and potentially hazardous air pollutants [164–172]. Depending on the location and regulation of wastes, the combustion conditions can range from uncontrolled open burning to high temperature incineration in small to large-scale incinerators, industrial furnaces, and boilers.

Hazardous wastes that are regulated for destruction and removal efficiency of the principle organic hazardous constituents are generally not controlled for the formation of new toxic compounds during transient periods of incomplete combustion. Information on US EPA research on waste incineration can be found on these websites for municipal waste incineration (<http://www.epa.gov/appcdwww/aptb/muniwaste.htm>) and hazardous waste (<http://www.epa.gov/appcdwww/aptb/hazwaste.htm>). The EPA waste combustion research program in organics focuses on combustion-derived products of incomplete combustion (PICs) including PAH, halogenated air toxics [such as chlorinated dioxins/furans (PCDD/F), mixed chlorinated/brominated compounds, and polychlorinated biphenyls (PCBs)]. Research on the mechanisms of formation of organic air toxics enables process modifications that will prevent formation of these pollutants (<http://www.epa.gov/appcdwww/aptb/organics.htm>).

Although monitoring for destruction and removal efficiency is a practical means of controlling the emission of the known hazardous chemical(s) that are incinerated, the potential production of more toxic components created in the incineration process requires evaluation of the toxicity and/or chemistry of the emissions. Plastic wastes initially not considered to be hazardous when burned or incinerated, were found to produce complex mixtures of mutagens [164] and carcinogens, such as PAH [172]. A series of studies of chemical wastes [166,167] also found that incineration led to the formation of new hazardous chemicals.

Chemical and bioassay characterization studies of emissions from chemical solvents and plastic wastes incinerated in a rotary kiln were conducted to determine how the chemical nature of the waste and operating conditions impact the emitted mass, chemical composition, and mutagenic activity [168,169]. The chemical composition and mutagenic activity of the emissions (semi-volatile and particle emissions) was evaluated when the rotary kiln was operated under sub-optimal conditions resulting from batch rotary kiln incineration of surrogate wastes including polyethylene, polyvinylchloride (PVC), toluene, and carbon tetrachloride and several combinations of the single chemicals. Polyethylene emission products were the most mutagenic followed by toluene; however PVC and carbon tetrachloride incineration emissions were not mutagenic in these studies. The mutagenic emission factors (revertants/kilogram of fuel or/mega joule of heat) for the polyethylene and toluene were similar to those for municipal waste combustors. The polyethylene incineration emissions were very potent in the mouse skin

tumorigenicity bioassay as shown in Table 2. Bioassay-directed chemical analysis led to the identification of mutagenic PAH emitted from the polyethylene incineration emissions. PAH emissions also resulted from a batch-type controlled air incinerator where the highest PAH emissions were from high-density polyethylene (HDPE) and less from polypropylene and polyvinyl chloride (PVC), and plastic wastes [168].

Open burning of plastics [164], tires [171], and other chemical waste and mixed waste [165–169] has also been evaluated. Emissions were analyzed for combustion gases; volatile, semi-volatile, and particulate organics; and toxic and mutagenic properties. Alkanes, alkenes, aromatic and PAH were identified in the volatile, semi-volatile, and particulate fractions of these emissions. Organic extracts of the particle samples were mutagenic and similar to residential wood heating emissions.

Mixed chemical wastes were combusted in furnaces and boilers to evaluate the use of such combustion systems for the disposal of the nitrogen-containing pesticide, dinoseb (2-*sec*-butyl-4,6 dinitrophenol), in a fuel-oil/xylene solvent [166,167]. Although, these combustion trials were able to achieve destruction efficiency greater than 99.99%, there is always concern that unknown hazardous chemicals may also be created in the process. These studies evaluated different combustion modifications to minimize the potentially toxic chemicals formed in the combustion process.

Medical wastes generally include plastics, chemicals, and biologically active agents (e.g., pathogens and viruses). Studies of biomedical waste incinerators emissions have reported the release mutagenic emissions [165,169]. Therefore, secondary or tertiary treatment of the emissions is needed to ensure the safety of anything released into the air and require continuous monitoring.

2.6. Comparative tumorigenicity and cancer risk of combustion and related emissions

The best documented vegetative combustion source is tobacco smoke as discussed above. Quantitative assessments of the cancer potency (risk per unit of particle or organic carbon exposure) suggest that tobacco and other vegetative combustion emissions are less carcinogenic per unit of exposure in both animal and human studies as compared to fossil fuel emissions (e.g., coal or petroleum combustion emissions) [80–84,87,88,173–175] (Table 2). Lung cancer mortality was significantly greater in women exposed indoors to smoky coal (low sulfur bituminous coal) as compared to smokeless coal (high sulfur coal) or wood combustion in different communes in Xuan Wei, China County [46].

Table 2

Comparative tumor initiation potency of particulate organic matter from combustion emissions and ambient air in the SENCAR mouse skin tumor initiation assay

Combustion emissions and related samples	Tumor potency ^a	Range ^b	Refs.
Benzo[<i>a</i>]pyrene	77	62–96	[83]
Polyethylene incineration #1 ^c	3.6	2.7–4.8	[169]
Polyethylene incineration #2 ^c	2.4	1.8–3.3	[169]
Smoky coal (China)	2.1	1.8–2.5	[174]
Coke oven emissions	2.1	1.8–2.5	[80,83,176]
Aluminum smelter emissions	0.76	0.51–1.1	[80,83,176]
Smokeless coal (China)	0.73	0.57–0.90	[174]
Roofing tar (coal tar) emissions	0.61	0.41–0.88	[80,83,176]
Nissan diesel emissions	0.61	0.52–0.72	[78,80,83,176]
Ambient air (IACP-mobile source)	0.21	0.16–0.28	[177,178]
Ford van leaded gasoline emissions	0.18	0.15–0.22	[78,80,83,176]
Mercedes diesel emissions	0.16	0.065–0.34	[78,80,83,176]
Oldsmobile diesel emissions	0.16	0.10–0.24	[78,80,83,176]
Wood smoke (China)	0.15	0.12–0.17	[174]
Ambient air (IACP-woodsmoke)	0.095	0.065–0.13	[177,178]
Ford mustang unleaded gasoline	0.071	0.023–0.13	[78,80,83,176]
VW rabbit diesel	0.046	0.028–0.068	[78,80,83,87]
Woodsmoke (softwood)	0.046	0.031–0.063	[176]
Woodsmoke (hardwood)	0.0087	0.0018–0.017	[176]
Cigarette smoke condensate	0.0029	0.0020–0.0038	[78,80,83,176]
Caterpillar diesel emissions	0.0013	0.00–0.010	[78,80,83,176]

^a Maximum likelihood estimate of the dose response slope (papillomas/mouse/mg) from the female mice treated with six doses of emission extracts (comparable studies were also conducted in male mice with comparable results).

^b Lower to upper bound.

^c Replicate blind samples tested in the SENCAR tumor initiation assay.

The smoky coal organic emissions were also higher in PAH content, mutagenic activity, mouse skin tumor initiation potency [173,174].

Comparative tumor studies conducted in both the US and Germany of vegetative emissions (e.g., cigarette smoke and wood smoke) found vegetative emissions have both a lower content of PAH and a lower potency in a series of different animal tumor assays when compared to fossil fuel emissions. Studies by Grimmer et al. [175] using two animal tumor assays (rat lung implantation and mouse skin) showed that cigarette smoke condensate had a lower tumor response than fossil fuel combustion emissions (residential coal furnace emissions, diesel, and gasoline exhaust) and the tumor responses were related to the PAH content of the emissions. Studies conducted in the US to compare the tumor initiation potency in the SENCAR mouse skin assay to human lung cancer risk estimates from epidemiologic data also found that fossil fuel emissions were more tumorigenic than cigarette smoke condensate or woodstove emissions [176] Table 2.

Ambient particles (PM_{2.5}) collected in Boise, Idaho during the winter heating season of 1986–1987 (a period of high use of woodstoves) were combined after chemical analysis and source apportionment to form two composite samples. The sample with the highest wood

smoke content (Ambient air IACP-woodsmoke) that contained 78% woodsmoke and 11% vehicle exhaust) was less tumorigenic (~50%) as compared to the composite with increased (~3 fold) mobile contribution (Ambient air IACP-mobile source) sample that contained 51% woodsmoke and 33% vehicle exhaust [177,178].

A series of new studies to compare the toxicology and carcinogenic potential for a series of combustion emissions from vegetative sources (wood smoke, tobacco smoke, cooking fumes), fossil fuel emission sources (diesel, gasoline, and coal), and road dust are being conducted at the National Environmental Respiratory Center [179]. The initial studies of wood combustion report the exposure characterization and subchronic effects of wood smoke in rats [180–182].

3. Atmospheric transformation and source apportionment: estimating the contribution of sources and transformation products to exposure and risk

3.1. Atmospheric transformation products

Atmospheric transformation reactions may result in the formation or destruction of mutagenic chemicals

in the air. Normal atmospheric processes increased the direct-acting mutagenicity wood smoke and automobile emissions in a smog chamber [128,183]. The gas-phase mutagenic transformation products did not require an exogenous activation system suggesting they were either nitrated organic compounds (e.g., peroxyacetyl nitrate) which may be activated by enzymes present in the bacteria or are reactive species which do not require any activation. In winter field studies in Boise, ID, mutagenic nitro-aromatic and hydroxy-nitro-aromatic species, previously shown to occur primarily from atmospheric transformation reactions, were found in ambient air in the [129,184]. The atmospheric conditions were conducive for photochemical reactions with appreciable concentrations (up to 5 mg/m^3) of nitrous acid (HONO) consistently measured during the winter study. HONO is readily photolyzed to produce hydroxyl radicals that initiate the atmospheric transformation processes. Many of the OH reactions are not strongly affected by temperature, so the reactions can occur even at wintertime temperatures.

Nitro-PAH lactones have been found in smog chambers as irradiation products of phenanthrene under conditions similar to those found in ambient air in southern California [185]. These nitro-lactones account for a major fraction of the mutagenic activity of the reaction products that are in the particle phase. Vapor-phase PAH were converted to nitro-PAH, accounting for major fraction of the mutagenic activity of the reaction products that are in the vapor phase [186]. Chemical analyses of the smog chamber products showed that most of the mutagenicity was due to products derived from acenaphthalene, retene, and pyrene; somewhat less important precursors are 2-methylphenanthrene and benz[a]anthracene [187]. The most mutagenic fractions of the irradiation products of the eight remaining PAH were those containing simple nitro-derivatives. By considering both the extent to which particular PAH reacted to yield mutagenic products in the smog chamber, and the ambient concentrations of these PAH, the most important contributors to ambient mutagenicity are naphthalene, 1- and 2-methylnaphthalene, fluorene, dibenzothiophene, phenanthrene, fluoranthene, and pyrene. Approximately half of ambient mutagenicity can be ascribed to atmospheric reaction products of two-to-four-ring PAH. Not all of the mutagenicity can be ascribed to particular compounds, but much of it is due to nitro-PAH lactones and to simpler nitro-PAH [186–189]. Atmospheric reaction products of naphthalene and phenanthrene have recently been shown to be genotoxic in human

lymphoblasts and appear to undergo oxidative metabolism [190–193].

3.2. Source apportionment methods and applications

Source apportionment has been used to estimate the contribution of sources (e.g., diesel, gasoline and wood combustion sources) to the mass of individual pollutants, total fine particle mass (e.g., $\text{PM}_{2.5}$), and to health effects ranging from in vitro toxicologic effects (e.g., mutagenicity) and human health effects (e.g., mortality) as discussed below. Originally these tools focused on the identification and apportionment of pollutants (such as PM and CO) to their sources as a critical step in air quality management and regulation.

The initial tools used to for source apportionment were either dispersion modeling, receptor modeling [194] or a hybrid method [195]. Dispersion modeling relies on emission factors which are used as input data for atmospheric dispersion models using meteorologic and geographical information. Receptor modeling uses ambient measurements of the parameter being apportioned (e.g., particle mass) with simultaneously measured tracer analysis. The tracers used are generally individual chemical species, or other measures of $\text{PM}_{2.5}$ constituents (e.g., inorganic ions, trace metals, organic and elemental carbon) whose presence in the atmosphere is primarily due to its emission from a single source category. The chemical mass balance (CMB) receptor model has been used in conjunction with emissions inventories for making source apportionment estimates [196,197]. Other receptor modeling approaches use a mathematical method (e.g., multiple linear regression analysis) to separate contributions from individual sources or source categories and estimate source emission profiles.

Due to an increased focus on understanding and controlling the sources of fine particle particles ($\text{PM}_{2.5}$), there has been an effort in the 1990s to develop and apply improved receptor models to apportion the sources of $\text{PM}_{2.5}$ [198]. Several alternative multivariate models, positive matrix factorization (PMF) [199,200] and UNMIX [201,202] have been applied to this problem in a number of urban areas [50–52,140,202–204]. A direct comparison the multivariate receptor models PMF and UNMIX to EPA's Chemical Mass Balance model using the traditional chemical species from the visibility (IMPROVE) network at a central urban site in Seattle, Washington [69]. Recently, more sophisticated and powerful

models for source apportionment, such as the multilinear engine (ME) are being evaluated [205–207].

3.3. Contribution of combustion sources to indoor and personal exposure

Indoor exposures to $PM_{2.5}$ and its combustion components are expected to differ from outdoor exposures due to factors including infiltration efficiency, indoor sources and human activities. The sources that contribute to personal $PM_{2.5}$ exposures are also impacted by time spent in different environments and personal activities. Understanding the sources contributing to human exposures is important to interpreting health studies and critical to setting effective control policies. The source apportionment techniques used above have had limited application in the 1990s to indoor, personal, or total human exposure assessment [208–210]. In a recent study of $PM_{2.5}$, PMF was found to be a useful approach apportioning the sources of personal exposure to $PM_{2.5}$ using personal, indoor, and outdoor filter-based particle measurements of both trace elements as well as light absorption coefficient to simultaneously apportion the sources of indoor, outdoor and personal air [211]. Several other recent studies have applied receptor modeling to assessment of personal exposure to $PM_{2.5}$ [212,213].

Elevated morbidity and mortality have been associated with outdoor PM mass concentrations in many epidemiologic studies as reviewed in the recent EPA air quality criteria document for PM [67]. Personal human exposure to PM, however includes both indoor and outdoor source emissions as well as PM generated by personal activities. The identification of sources and the assessment of their relative contribution to total indoor and personal exposures can provide valuable information for epidemiologists and regulatory agencies. Only recently have researchers possessed the tools and technologies to be able to examine the health effects of individual PM components [214–223] and source types [224–229]. These efforts have been based on either traditional factor analysis or a priori source profiles.

Few studies have attempted to apply total human exposure assessment techniques to cancer risk assessment. Human exposure to various PM sources is important to understanding how specific outdoor PM components or sources contribute to cancer risk of PM concentrations as measured at an outdoor monitoring site. An indoor and outdoor source apportionment study of exposures to woodsmoke and mobile sources was conducted in Boise, Idaho during the winter when wood stoves were a common source of heating [178]. The

ambient concentrations of PM extractable organic matter (EOM) averaged $15.3 \mu\text{g EOM}/\text{m}^3$ from wood smoke fine particles and $4.2 \mu\text{g EOM}/\text{m}^3$ from mobile sources. Human exposures for the same period are estimated to average $9.5 \mu\text{g EOM}/\text{m}^3$ from wood smoke and $2.1 \mu\text{g EOM}/\text{m}^3$ from mobile sources. Annual exposure concentrations are expected to be lower due to both atmospheric conditions and seasonal use of wood stoves. The annual estimates were $3.4 \mu\text{g EOM}/\text{m}^3$ for wood stove smoke and $1.2 \mu\text{g EOM}/\text{m}^3$ auto exhaust. Thus, wood smoke accounted for about 73% of the annual exposure to EOM [178].

A wide range of approaches has been used to apportion exposure, from simple physical models to sophisticated statistical approaches. Physical models were used by Koutrakis et al. [230] to estimate the relative contribution of indoor and outdoor aerosol sources to indoor concentrations of particles. The PM characterization data from a large study of total exposure to particles in Riverside, CA [1991 Particle Total Exposure Assessment Methodology Study] was the first analysis to identify and estimate the contribution of major PM sources to personal exposure [210]. This study used positive matrix factorization in the simultaneous analysis of indoor, outdoor and personal data. Later Hopke et al. [212] simultaneously analyzed indoor, outdoor and personal data from the EPA's 1998 Baltimore exposure panel study using the multilinear engine. Recently, Larson et al. [211] used PMF (both PMF2 and PMF3) to apportion $PM_{2.5}$ sources for a central site, outdoor, indoor, and personal PM samples collected from the Seattle exposure and health effects panel study of high-risk subpopulations [213]. In this study, the attenuation of various sources from outdoor to indoor and personal environments are evaluated in the context of total exposure to $PM_{2.5}$. Major sources of $PM_{2.5}$ in Seattle are motor vehicles and wood combustion, with additional contributions from secondary sulfate, sea-salt, oil combustion and resuspended soil, and relatively small contributions from specific industrial sources [69].

Larson et al. [211] examined the attenuation of various sources from outdoor to indoor and personal environments in the context of total exposure to $PM_{2.5}$. This paper and others have recently reported on the effects of personal activities on the personal $PM_{2.5}$ source estimates [213,231,212]. There appear to be robust features in the outdoor particle data that provide information on outdoor source contributions to indoor concentrations and personal exposures [211]. Larson found that both positive matrix factorization methods (PMF2 and PMF3) were able to resolve the indoor and

personal exposures after excluding indoor and personal samples whose mass concentration was > 120% of the corresponding outdoor sample [211]. In this Seattle study, vegetative burning contributed more PM_{2.5} mass on average than any other source in all microenvironments.

3.4. Source apportionment applications to comparative risks

An early source apportionment study combining mutagenicity with air quality monitoring data was conducted by Lewis et al. [120] to determine the potential impact of wood smoke on airborne particulate mutagenicity. This study was conducted in the winter in a relatively simple airshed (Boise, ID) where the only other major combustion sources were automobile and truck traffic. Separate day and night (12 h) samples were analyzed by chemical, physical, and bioassay methods. The fine particles were extracted with an organic solvent and the resulting extracts were assayed in the Ames *Salmonella* mutagenesis bioassay. This approach [120,232] used the availability of source tracers whose ambient concentrations are measured simultaneously with the pollutant of interest (e.g., mass of POM and mutagenicity). The key chemical tracer species used were fine particle lead and potassium, tracers of motor vehicle emissions and wood smoke, respectively. The resulting regression analysis with the two tracers was consistent with emission inventories, showing that, on average, 90% of the measured ambient EOM was contributed by these two sources. The wood smoke contribution dominated during both day and night periods, but made its greatest impact during nighttime periods. The contribution from motor vehicle emissions was greater at the roadway site than at the residential site [120]. This Integrated Air Cancer Project [233] characterized exposure and potential cancer risk of combustion sources. Source apportioned ambient PM_{2.5} samples were also evaluated in comparative mutagenesis bioassays and in the SENCAR mouse skin tumor initiation assay. The mouse skin tumor initiation assay had previously been used to compare the tumor potency of diesel and gasoline emissions to coal derived emissions that were well established as human carcinogens (Table 2). The tumor initiating activity of two ambient PM_{2.5} source apportioned composite samples [177,178] from Boise, Idaho are also shown in Table 2 in comparison to other combustion source samples derived from coal, diesel, wood, and tobacco. The composite ambient PM_{2.5} (labeled Ambient Air (Boise Dominated by Woodsmoke)) was significantly

less potent (0.095 papillomas/mouse/mg) in the skin tumor initiation potency as compared to the sample of ambient PM_{2.5} dominated by vehicle emissions (0.21 papillomas/mouse/mg). Motor vehicle emissions and ambient air dominated by vehicle emissions were more mutagenic and more tumorigenic than wood smoke emissions or ambient PM_{2.5} dominated by wood smoke domination of EOM mass [177,178]. Although these studies found that woodsmoke dominated ambient samples were less mutagenic and less tumorigenic than ambient samples dominated by motor vehicle emissions [120,178], the Boise winter air contained nearly 3-fold higher contribution of wood smoke compared to motor vehicle exhaust particles. Therefore, the net contribution of each source was nearly equivalent.

Epidemiologic studies of health outcomes (e.g., mortality or morbidity) have been combined with ambient outdoor PM characterization data and source apportionment to estimate risks from specific sources. Source apportionment tools have recently been applied in a number of epidemiologic studies to estimate the attribution of health effects either to individual constituents of air pollution or to sources of pollutants, particularly, combustion sources as discussed above [67]. Apportionment of morbidity, mortality, or other adverse health effects from general source categories (e.g., combustion) or specific sources (e.g., traffic or motor vehicle exhaust) associated with outdoor PM mass provides valuable information for both the scientific research community and the regulatory agencies. Assessment of human exposure to various PM sources is an important step in understanding how specific outdoor PM components or sources contribute to the observed associations between PM concentrations as measured at an outdoor monitoring site and adverse health effects. Recent studies relating outdoor air pollutants to indoor air and personal exposure further advance our understanding of the relationship of ambient measurements to human exposure and risk.

4. Biomarkers of combustion exposure, dose, susceptibility, and DNA damage

4.1. Exposure biomarkers

Air pollution exposure biomarkers initially ranged from measurements of air pollutants (e.g., lead) in body fluids (e.g., blood, urine) to measures of exhaled pollutants or their metabolites in breath or body fluids. As this field has advanced, more complex combustion pollutants are now measured in human samples. For example, PAH and nitroaromatic air pollutants are

known to react with protein and DNA to form both macromolecular adducts that can now be measured in blood or tissue samples of human populations. Many organic species, such as PAH, form conjugated products (e.g., glucuronides) that serve as a measure of dose to the target molecules and may have longer half-lives than urinary metabolites (e.g., hydroxylated PAH).

Exposure biomarkers provide a key tool to relate health outcomes to individual personal exposures and to provide measures of confounding exposures. Human exposures to environmental chemicals have been routinely analyzed in blood and urine samples as part of the US National Health and Nutrition Examination Survey (NHANES) [234]. New studies are underway to develop biomonitoring methods and protocols for application to the National Children's Study [235]. This U.S. study of children's health plans to use biomonitoring throughout the life stages. The NHANES ongoing surveys use a stratified, multistage, probability-cluster design to select a representative sample of the population. Recent advances in the analytical measurements of environmental chemicals or their metabolites in whole blood, serum, or urine has increased the reporting of chemical exposures from 27 to 116 chemicals. Requirements and issues considered for application of biomarkers to exposure assessment through the life stages of children as they mature are reviewed by Barr et al. [235] for a large U.S. National Children's Study. This National Children's Study [236] includes several categories of chemicals related to air pollution and combustion source exposures including a series of PAH metabolites of both semi-volatile and particulate associated PAH and serum cotinine, a well established biomarker of smoking and exposure to environmental tobacco smoke in non-smokers. Other chemicals relevant to air pollution exposures are lead and mercury in blood and urine. Previous studies demonstrating the decrease of blood lead levels as lead was removed from gasoline has demonstrated the utility of these exposure biomarkers. In addition to providing a valuable research tool, the current NHANES and future studies (e.g., National Children's Study) will provide physicians and public health workers with reference levels of exposure so that they can recognize unusually high levels of exposure in patients and assess the effectiveness of efforts to reduce chemical exposure.

4.2. Environmental tobacco smoke: cotinine as a model biomarker of exposure

The validation and accepted use of cotinine as a biomarker of exposure to environmental tobacco smoke

(ETS) is a useful example for the development of exposure biomarkers for other air pollution sources [9,237]. Nicotine is a relatively unique source tracer of tobacco smoke and dietary sources of nicotine are very minor since few individuals ingest sufficient nicotine-containing foods and beverages to compromise the validity of cotinine as an estimator of exposure to nicotine from tobacco smoking or exposure to ETS [237,238]. Cotinine measured in blood, saliva, or urine is the most specific and sensitive biomarker of exposure to ETS and meets the criteria for validity used by an NRC panel on ETS exposure and health risks [237–239].

The use of cotinine as a biomarker for tobacco smoke exposure is one of the most successful applications of exposure biomarkers in international and national scale studies. Cotinine analysis of approximately 12,000 blood samples from NHANES III collected from 1988 to 1991 were used to estimate the US population exposures to ETS and to examine the contribution of the home and workplace environment to exposure [240]. This study found measurable levels of cotinine in 88% of the population including a high proportion of non-smokers. They reported ETS exposure (based on cotinine levels) was higher among children, non-Hispanic blacks, and men. Results from NHANES III Phase 2 (1991–1994) show a continuing decline in exposures of the US population to ETS indicating that public health measures taken to reduce ETS exposures have been successful and NHANES IV (1999–2000) will continue to make cotinine and health data available.

In 2006, the U.S. Department of Health and Human Services issued a new Surgeon General's Report on The Health Consequences of Involuntary Exposure to Tobacco Smoke [241]. This report concludes that there is no risk-free level of exposure to secondhand smoke. Non-smokers exposed to secondhand smoke at home or work increase their risk of developing heart disease by 25–30% and lung cancer by 20–30%. Secondhand smoke exposure can cause heart disease and lung cancer in non-smoking adults and is a known cause of sudden infant death syndrome (SIDS), respiratory problems, ear infections, and asthma attacks in infants and children. ETS contains more than 50 cancer-causing chemicals, and is itself a known human carcinogen. Brief exposure to secondhand smoke has immediate adverse effects on the cardiovascular system and increases risk for heart disease and lung cancer. In the U.S. levels of the biomarker for ETS exposure, cotinine, measured in non-smokers have fallen by 70% since the late 1980s, and the proportion of non-smokers with detectable cotinine levels has been halved from 88% in 1988–1991 to 43% in 2001–2002. In spite of this

advance, more than 126 million Americans continue to be regularly exposed to secondhand smoke in the home, at work, and in enclosed public spaces (<http://surgeongeneral.gov/library/secondhandsmoke/>).

More than 50 studies of lung cancer risk in non-smokers exposed to ETS (e.g., spouses of smokers) have been published during the last 25 years and recently reviewed by IARC [9]. The IARC evaluation considered cotinine a highly specific marker of exposure to ETS and the most suitable biomarker for assessing recent exposure to secondhand tobacco smoke uptake and metabolism in adults, children and newborns. Meta-analysis of the cancer epidemiology studies found a statistically significant and consistent association between lung cancer risk in spouses of smokers and exposure to ETS from the smoking spouse and the excess risk increased with increasing exposure [9]. Meta-analyses of lung cancer in never-smokers exposed to secondhand tobacco smoke at the workplace also found a statistically significant increase in risk. The IARC panel's evaluation found sufficient evidence to conclude that involuntary smoking (referred to here as ETS) is a cause of lung cancer in never-smokers.

Recent evaluations of cotinine, and its parent compound nicotine, are highly specific for exposure to secondhand smoke. Because of its favorable biologic half-life and the sensitivity of techniques for quantifying it [162,163], cotinine is currently the most suitable biomarker for assessing recent exposure to secondhand tobacco smoke uptake and metabolism in adults, children and newborns [242–247]. The cancer evaluation of ETS as well as other combustion source mixtures or ambient air particles requires data on human exposure, dose and mechanistic evidence to link exposure to the health outcomes. Hecht, in a series of papers, has presented biochemical data on carcinogen uptake in non-smokers, including children, as well as the mechanisms and steps that link ETS exposure to cancer from tobacco smoke carcinogens [159,242–247]. A limitation in using cotinine is that it does not provide a measure of long-term ETS exposure that would be useful for epidemiologic studies of chronic disease such as cancer and cardiovascular disease. Other biomarkers, such as protein and DNA adducts, that reflect longer term exposure to ETS are discussed later.

4.3. Polycyclic aromatic compounds (PAC)

Polycyclic aromatic compounds (PAC) include the unsubstituted hydrocarbons (PAH) and substituted PAH (e.g., nitro-PAH, oxygenated PAH) that are emitted from a wide range of combustion sources. PAC are

found in urban and rural air, soot particles, and in a wide range of combustion, pyrolysis, and reductive distillation emissions [4,248]. Other sources of PAC exposure in human populations are food, including smoked, charcoal-broiled, and roasted foods that are contaminated by atmospheric deposition or processing (e.g., drying of cereal grains) [105].

Dipple [249] reviewed PAH carcinogens starting with Percival Pott's postulation in 1775 that chimney sweep's scrotal cancer was due to soot exposures [250]. By 1933, Cook et al. [251] had identified the carcinogenic constituent, BaP, in coal soot. Over 500 PAH and PAC have now been detected and many quantified in air and combustion emissions. The carcinogenicity of BaP and its association with soot (or particulate matter) led to routine air monitoring of BaP [2]. Since that period, the range of PAC in measured in both the gas and particle phase of air and emissions has expanded. Research on the atmospheric reactions of PAH has led to the discovery of mutagenic and carcinogenic nitro-PAH [252], nitro-lactones, and other nitroarenes [253]. It has become clear that the gaseous and semi-volatile PAH are present in the atmosphere at higher concentrations than the more carcinogenic 4–5 ring PAH. A large daily air monitoring study of PAH conducted at 35 sites in Canada in the 1990s found that the mean total PAH concentrations varied by almost three orders of magnitude between remote rural sites (with the lowest concentrations) and the higher exposures in source impacted urban locations [254].

Urinary PAH metabolites have been used as biomarkers of PAH exposure in both environmental and occupational studies [255–265]. The hydroxylated metabolite of pyrene, 1-hydroxypyrene (1-OHP) has been the most widely used PAH urinary metabolite as biomarkers of exposure to PAH [255–265]. Pyrene is a semi-volatile non-carcinogenic PAH that is distributed between the gas and particle phase in the ambient air and human exposure samples [266]. There is conflicting evidence on the utility of 1-OHP as a biomarker of exposure to carcinogenic PAH or PAH DNA adducts. A lack of association between DNA adducts and urinary 1-OHP has been reported in garage workers exposed to automobile exhaust [267], but the adduct level correlated with urinary 1-OHP in foundry workers [268]. In a study of human exposure to ambient air pollution, no correlations were observed between 1-OHP and either DNA adducts or PAH–albumin adduct levels [269].

The hydroxylated metabolites of the PAH are excreted in human urine both as free hydroxylated metabolites and as hydroxylated metabolites conjugated to glucuronic acid and sulfate. In many of the studies cited above, the PAH are deconjugated to release

free hydroxylated metabolites for analysis. Methods are also available for quantifying the glucuronides such as 1-hydroxypyrene-glucuronide. Lee et al. [270] compared three analytical methods for 1-hydroxypyrene-glucuronide in urine after non-occupational exposure to PAH. Recently, a series of urinary PAH metabolites were measured in the US National Health and Nutrition Examination Survey (NHANES) conducted by CDC's National Center for Health Statistics [235]. The measurements reported include both free and conjugated forms of the hydroxylated metabolites using an isotope-dilution gas chromatography-high resolution mass spectroscopy method [271].

The CDC Second National Report on Human Exposure to Environmental Chemicals released in 2003 report [235] of a series of 14 urinary PAH metabolites, including metabolites of carcinogenic PAH, were measured in a subset of the US National Health and Nutrition Examination Survey (NHANES). The samples were randomly selected within the specified age range to be a representative sample of the 1999–2000 participants over 6 years of age in the U.S. population. NHANES is a series of surveys designed to collect data on the health and nutritional status of the U.S. population. The purpose of these studies is to establish reference ranges that can be used by physicians and scientists to determine whether a person or group has an unusually high exposure. This survey is also useful in assessing the effectiveness of public health efforts to reduce exposure of the population to specific environmental pollutants. Measurement of these metabolites are thought to reflect exposure to PAH that has occurred within the previous few days, however, more studies of the urinary half-lives of PAH metabolites are needed. This study did not measure personal exposures to PAH and some of the parent PAH can produce more than one urinary metabolite. Geometric mean levels of the demographic groups were compared after adjustment for race/ethnicity, age, gender, urinary creatinine, and log serum cotinine. Children aged 6–11 years had about a two times higher urinary 1-OHP adjusted geometric means than did people in the two other age groups. This age-related difference also has been found by other investigators [264,272]. The urinary 1-OHP levels for children in the CDC Report were similar to levels measured in other studies cited here. No differences were observed for race/ethnicity or gender in the CDC study as has been reported consistent with previous studies [259,263,265]. Since pyrene is present in the environment at much higher concentrations than the 4–5-ring carcinogenic PAH, it is not surprising that it was

detected in 99% of the NHANES 1999–2000 subsample. CDC found the geometric mean level for the overall population to be similar to that of other general populations residing in an urban setting [259–265]. People who work in certain occupations (e.g., carbon electrode production) can have urinary 1-hydroxypyrene levels 100 times higher than the geometric mean level reported for the general US population [256,257]. An additional source of PAH exposure for children is the ingestion of PAH contaminated soil [264].

4.4. Combustion source specific exposure biomarkers

Other organic species emitted from combustion emissions have been investigated as potential exposure biomarkers including aromatic amines from coke ovens, heterocyclic amines from cooking meats [143–146], nitrosamines from tobacco smoke [242–244], and methoxyphenols from wood smoke [112–115]. These are discussed in Section 2 above on each combustion emission source category. It is beyond the scope of this review to discuss all of the possible exposure biomarkers for each of these source specific organic species.

As an example of the recent research to develop a vegetative or wood smoke specific biomarker, the methoxyphenols emitted from lignin pyrolysis are an especially challenging class of chemicals due to their high reactivity and presence in both the gas and particle phase [112–115]. A method has recently been reported for determining methoxyphenols in human urine as a biomarker of exposure to wood smoke [273]. Specific chemicals quantified were guaiacol, 4-methylguaiacol, 4-ethylguaiacol, 4-propylguaiacol, syringol, 4-methylsyringol, 4-ethylsyringol, vanillin, eugenol, and syringaldehyde. Woodsmoke exposures for a relatively short period (2.5 h) resulted in excretion rates of methoxyphenols reflecting the period of wood smoke exposure. The relative increase of guaiacols to syringols found in urine depended on the type of wood burned. Smoked foods and flavorings were reported to be a confounding source of exposure to methoxyphenols that would have to be considered in applying this method to population studies. Although this study did not determine inhalation elimination half-lives for the urinary methoxyphenols, they estimated them to be relatively short (2–3 h) and suggest that short episodic exposures would be detectable for only 1–2 days after an exposure [273]. The development of a method to measure personal exposures to levoglucosan [274] is facilitating the evaluation of urinary methoxyphenols as a biomarker for woodsmoke exposure in a large panel study in Seattle, WA [275]. In

this study, questionnaires were used to account for dietary sources of the methoxyphenols. Methoxyphenols were detected in all urine samples analyzed and a wide dynamic range of metabolite concentrations (1000-fold) was observed.

4.5. Biomarkers of genetic susceptibility, dose, and DNA damage

The role of genetic susceptibility (or genotype) as it may influence the uptake, metabolism, excretion, and binding of metabolites to DNA or protein plays an important role in modern molecular epidemiology studies [276–279]. The interaction of genetic susceptibility and air pollutant exposures in the risk for cancer, adverse reproductive outcomes, and cardiovascular disease has become an important area of biomarker research. Understanding these interactions can help establish the biologic plausibility of an exposure–cancer relationship [280–282].

Genetic differences in metabolism, as measured by genotype, have been shown to influence the exposure–dose relationship for PAH, nitro-PAH, aromatic amines and other combustion organics and risk of a variety of health outcomes from air pollution and combustion emissions. Until recently, most gene–environment studies relied on surrogate exposure measures such as location [283] or job category [284]. This approach led to recognition of the importance of genotype on biomarkers and potential health outcomes [285–287]. These early studies, however, were not able to determine if the genotype was altering the effective exposure, dose, or genetic damage. The use of gene–environment studies became more powerful when exposures are measured at the individual level using personal exposure monitoring [288] and both exposure biomarkers (e.g., urinary metabolites) and biomarkers of dose (e.g., DNA adducts or protein adducts) are deployed together in the same subjects.

Many of the organic components associated with combustion particles or present in the gas phase are metabolized by polymorphic enzymes, that activate and detoxify organic pollutants using certain P450 enzymes such as glutathione *S*-transferase M1 (GSTM1) [289,290] involved in PAH metabolism and *N*-acetyltransferase (NAT2) [291,292] involved in nitro-PAH and aromatic amine metabolism. When biomarkers are used as an exposure measure in a study, knowledge of the impact of genotype on the biomarker is very useful in the final interpretation of the exposure data. Genotype (e.g., GSTM1 and NAT2), as expected, do influence the relationship between personal exposure to PAH and the

formation DNA adducts as well as the excretion of urinary PAH metabolites [288]. Other gene–environment studies in a Czech population used exposure, dose and measures of genetic damage in reproductive outcome studies [41,293–302]. The biomarker measurements were made in urine and blood, and in the reproductive studies were measured in placental tissue [300–302] and sperm [298,299,302]. Reproductive studies in Poland have also measured biomarkers as part of a study of the impact of air pollution on reproductive outcomes [283,302,303].

DNA and protein adducts are also molecular biomarkers of exposure and dose. DNA adduct biomarkers are particularly relevant to cancer risk since they are linked mechanistically to the induction of cancer [304,305] and are viewed as reflecting the dose to DNA. DNA adducts, however, may be repaired and therefore have a shorter half-life than protein adducts that are not repaired and the half-life is related to the turnover of the protein used in the assay (e.g., hemoglobin or albumin). DNA and protein adducts of PAH and related aromatic compounds have been applied to a number of occupational and environmental study populations [306–311].

The ³²P-postlabeling method has been used extensively to detect bulky carcinogen–DNA adducts in both animal and human studies [309–311]. The method is sufficiently sensitive for application to a wide range of tissues and cells (e.g., peripheral lymphocytes) from populations exposed to ambient air pollution to occupationally exposed populations [42,312–318]. A review of research progress in molecular epidemiology studies on occupational and environmental exposures through 1999 concluded that DNA adducts measured by the ³²P-postlabeling method had become the biomarker of choice particularly for PAH and related exposures in both occupational and environmental environments [308,317]. Consensus protocols, standards, and quality assurance methods for ³²P-postlabeling have been developed through a working group and inter-laboratory trial exercise [309,311]. The ³²P-postlabeling method measures many unidentified DNA adducts, however the assay may be used to facilitate the identification of DNA adducts through the use of different diagnostic protocols and fractionation methods prior to characterization of specific adducts. This approach has been used to estimate the contribution of specific categories of DNA adducts, such nitro-PAH DNA [319–322]. Diesel exhaust particulate matter is characteristically higher in nitro-PAH than other combustion emissions. Therefore this approach has become useful in semi-quantitatively characterizing nitro-PAH DNA adducts [320]. These variations on ³²P-postlabeling have been applied to DNA

samples from in vitro and animal exposures as well as from human studies [319].

Protein and DNA adduct methods and their use as biomarkers has been reviewed [323–330]. The techniques available for measurement of protein and DNA adducts include mass spectrometry, immunoassay, high performance liquid chromatography with UV, fluorescence or electrochemical detection, ³²P-postlabeling (for DNA only) and accelerator mass spectrometry. The lowest limits of sensitivity of the protein adduct measurements is less than 1 pmol adduct/g protein, and the procedures for DNA adduct determination have sensitivities ranging from of 1 adduct in 108 to 1 in 1011 nucleotides [324]. Protein adducts, such as 4-aminobiphenyl-hemoglobin adducts (4-ABP), are useful as biomarkers of exposure to tobacco smoke. Protein adducts are especially useful in exposure studies of smaller carcinogenic molecules that are found in air pollution and combustion emissions such as 1,3-butadiene [316].

Biomarkers of oxidative damage have been applied in a number of human studies of air pollution exposures. Oxygen radicals generated by environmental exposures as well as endogenous processes cause damage to DNA, resulting in the formation of 8-hydro-2'-deoxyguanosine (8-OHdG) also known as 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG). These oxidative damage biomarkers can be measured in cells and tissue, such as leukocytes and lung tissue [331] and the repair products can be detected in the urine [332]. Human studies of smokers compared to non-smokers [333] were used to validate the use of urinary excretion of 8-OHdG. Diesel exhaust particles also induce oxidative damage to DNA in experimental animals. [334]. A study of children's nasal respiratory epithelium showed a significant increase of single-strand breaks in DNA as well as 8-OHdG levels in the children exposed to relatively high levels of air pollution compared to controls in Mexico City [335]. Studies of urinary excretion of 8-OHdG in urban bus drivers measured by HPLC using electrochemical detection have also been recently reported [269,336]. These biomarkers of oxidative damage do not always correlate with other markers for damage and binding to DNA, although some of the compounds responsible are expected to produce oxygen radicals during the these processes [269]. The problems associated with the use 8-OHdG as a biomarker of oxidative damage from air pollution and combustion emissions include possible confounding by dietary factors that influence 8-OHdG and analytical problems [337] associated with artifacts introduced during DNA extraction [338,339], however these may be minimized. In addition to the HPLC-

electrochemical detection, immunologic methods [340] have been developed for 8-OHdG. Oxidative damage is an important measure of damage to DNA that can impact multiple health outcomes.

A series of personal PM_{2.5} exposure and biomarker studies reviewed by Sorensen et al. [341,342] included studies of 40–50 subjects. Significant positive associations were observed with biomarkers of oxidative damage (including 8-OHdG in lymphocyte DNA and markers of oxidative damage to lipids and protein in plasma). Several types of DNA damage showed seasonal variation. PAH adduct levels, DNA strand breaks and 8-OHdG in lymphocytes increased significantly in the summer period. These biomarker studies included urinary 1-hydroxypyrene, 8-OHdG and PAH DNA adducts in lymphocytes, markers of oxidative stress in plasma and genotypes of glutathione transferases (GSTs) and NADPH:quinone reductase (NQO1). Urban air pollution contains large amounts of oxidants, including NO_x and compounds that induce the generation of reactive oxygen species.

Unfortunately, many biomarker studies of environmental exposures lack data on personal exposure to particles, PAH or other measurements of the pollutants under investigation. Data on personal exposure were collected in only 9 out of 41 (22%) studies reviewed by Sram and Binkova [295] and ambient air measurements were reported in only 5 or 13% of the studies. It is difficult to relate the observed biomarkers to a specific airborne particle or PAH exposure concentration when no personal external exposures have been monitored. Many studies also fail to adequately account for passive or active smoking, medications, or dietary exposures [318,343,344]. More studies deploying personal air monitoring for PM_{2.5}, PAH, and other direct measures of exposure together with biomarkers of exposure, dose, and cellular damage are needed for biomarker validation. In addition, studies are needed to determine the relationship between ambient pollutant exposure concentrations and biomarker levels. There are examples of studies deploying personal exposure monitoring together with biomarkers [269,288,294,313,345].

5. Cancer, reproductive effects, and cardiovascular disease: common agents and mechanisms

5.1. Mechanistic studies and the search for causative agents

Evidence has been growing since the 1960s to support the theory that chemical carcinogens such as

PAH are metabolized via oxidative pathways to produce electrophilic reactive products (e.g., epoxides) that react covalently with the nucleophilic centers in DNA as well as other nucleophiles in the cell (e.g., proteins). These reactions result in DNA binding and mutations, initiating a multistage process leading to genetic effects, including cancer, cardiovascular damage, and adverse reproductive outcomes. This theory has become the basis for using genetic bioassays to detect mutagenic chemicals as well as biomarkers of oxidative damage and stable carcinogen–DNA adducts and protein adducts in target cells and tissues [276,305,306,346].

An alternative carcinogenesis pathway is the one-electron oxidation pathway that results in the formation of labile (rather than stable) DNA adducts [347–349]. This pathway has been demonstrated for several PAH including the potent carcinogen, dibenzo[*a,l*]pyrene, and benzene. These aromatic compounds are metabolized to phenols, oxidized to catechols and then to quinines. The quinones react with DNA to form depurinating adducts (e.g., N-7 guanine and N-3 of adenine depurinating adducts) resulting in apurinic sites and mutations. It is clear that PAH and related polycyclic aromatic compounds, including aromatic amines, and nitrogen heterocyclic compounds are likely causative agents in the toxicity associated with different combustion source emissions and ultimately in the air pollution. The oxidized and nitrated products also emitted by combustion sources and formed by atmospheric transformation, such as nitro-PAH, PAH lactones, quinines and other aromatic hydrocarbon oxidation products have been shown to form DNA adducts, induce mutations, and tumors.

Airborne particles, diesel and other soot particles as well as tobacco smoke have both been reported to either generate free radicals that lead to the production of biologically damaging hydroxyl radicals [350,351] and or generate reactive oxygen species (ROS) [352–354]. The pathways involved in the generation of ROS may result in the production or release of superoxide, leading to the formation of hydrogen peroxide and the ultimate production of hydroxyl radicals that may damage DNA, lipids, and proteins. A wide range of health effects from cancer to cardiovascular effects have been linked to free radicals and hydroxyl radical generation in animal and human studies through the use of biomarkers of oxidative damage, such as 8-OHdG, discussed in the previous section. A recent study of chemical composition, ROS, and induction of oxidative stress in macrophages and epithelial cells reported that ultrafine particles were more active in generating ROS than coarse or fine particles in Los Angeles [355]. This same

study indicated that cellular heme oxygenase-1 expression (a sensitive marker for oxidative stress) was directly correlated with the high organic carbon and PAH ultrafine particles [355].

5.2. Tumorigenicity, cancer risk and air pollution

Air pollution and cancer was reviewed over the past 10 years [356–360]. The US EPA's Air Quality Criteria Document for Particulate Matter (PM) 2003 [67] also reviews the latest human epidemiologic studies of chronic exposure (PM) and lung cancer. The earlier reviews summarize a substantial number of descriptive ecologic studies (e.g., observations of urban/rural gradients in lung cancer risk, migrant studies) and correlation studies relating lung cancer and air pollution trends. These studies often showed an association between lung cancer and air pollution, however these studies were limited by a lack of human exposure data and control of confounding factors (e.g., tobacco smoke). Case–control studies have also rather consistently shown a higher relative risk of lung cancer associated with living in areas with higher exposures to air pollution that included various measures of air pollution such as total suspended particulate (TSP), high polycyclic aromatic hydrocarbons (e.g., benzo[*a*]pyrene), and areas with high soot concentrations [67]. The quantitative value of case–control studies was limited by the lack of reliable quantitative estimates of the air pollution exposures of the cases and controls.

Epidemiologic prospective cohort studies of chronic exposures to airborne particles provide more power in evaluating the association between long-term exposure to air pollution and the risk of lung cancer. Evaluation of recent long-term exposure studies in the EPA PM Air Quality Criteria Document [67] indicate that a substantial portion of the total mortality reflected cumulative impacts of PM above and beyond those caused by acute exposure. Three large prospective cohort studies were reported in the 1990s using data from the Harvard Six Cities Study [361], American Cancer Society Study [362], and the Adventist Health study [363]. These studies were first extensively evaluated in EPA's 1996 PM AQCD [364].

Two of these large cohort studies, ACS and AHSMOG, have been extended for more years of follow-up and reanalysis [365,366] and the data summarized in Table 3. Both of these US prospective cohort studies examined the relationship between lung cancer mortality and long-term exposure to particulate matter (PM_{2.5} or PM₁₀). The smaller AHSMOG Study [363] followed a cohort of 6338 Seventh Day Adventists

Table 3
Epidemiologic prospective cohort studies of air pollution and lung cancer

Study population	Exposure	Adjusted relative risks RR (95% CI)
AHSMOG (6338 NS/W* 1977–1992) ^a	PM10IQR	5.21 (1.94–13.99) M
AHSMOG (6338 NS/W* 1977–1992) ^b	PM10IQR	2.38 (1.42–3.97) M
ACS~500,000 MF (1979–1983) ^c (1999–2000)	PM _{2.5} Δ 10 μg/m ³	1.08 (1.01–1.16) 1.13 (1.04–1.22)

^a Cancer incidence from Beeson et al. [367].

^b Cancer mortality from Abby et al. [366].

^c Cancer mortality from Pope et al. [365].

with very low smoking prevalence and healthy dietary patterns that reduce the potential for confounding by these factors. Longer-term follow-up studies of this cohort have been conducted for newly diagnosed cancers (cancer incidence) [367] and cancer mortality [366]. Lung cancer for both males and females in the AHSMOG cohort was significantly associated with elevated exposure to PM10. The risk effect estimate was higher in males, who spent more time outdoors increasing their air pollution exposures compared to the females. Ozone showed a stronger association with lung cancer mortality for males and SO₂ was strongly associated with lung cancer mortality for both sexes.

The second, larger ACS-CPS-II study was extended beyond the original report (1979–1983) with additional PM_{2.5} monitoring data for 500,000 participants in 116 metropolitan areas [365]. The extended 16 year follow-up time resulted in a 3-fold increase in deaths and substantially more air pollution exposure data for fine particles and gaseous pollutants. The authors improved the control of other factors such as occupational and dietary exposure variables. The adjusted relative risk (RR) for lung cancer mortality associated with a 10 μg/m³ increase in annual average PM_{2.5} for the 1999–2000 period was a 13% (4–23%, 95% CI) increase in lung cancer mortality. The authors conclude that long-term exposure to combustion-related fine particulate air pollution is an important risk factor for both cardio-pulmonary and lung cancer mortality.

5.3. Cardiovascular effects and mechanistic relationship to cancer

Long-term air pollution exposures to PM_{2.5} were most strongly associated with mortality attributable to ischemic heart disease, dysrhythmias, heart failure, and cardiac arrest in the ACS cohort [368]. For these cardiovascular causes of death, a 10-μg/m³ elevation in PM_{2.5} was associated with 8–18% increases in mortality risk, with comparable or larger risks being observed for

smokers relative to non-smokers. Pope et al. [368] tested three hypothesized pathophysiologic pathways with the ACS cohort data involving: accelerated progression of COPD, inflammation and accelerated atherosclerosis, and altered cardiac autonomic function [368]. The cause of death data did not fit the first hypothesis (accelerated progression of COPD), but did fit inflammation and accelerated atherosclerosis, and altered cardiac autonomic function [368]. Although smoking is a much larger risk factor for cardiovascular disease mortality, exposure to fine particles imposes additional effects that seem to be at least additive to if not synergistic with smoking based on this ACS cohort, the largest prospective cohort study of mortality.

Human, animal and cellular studies are generally consistent with oxidative mechanisms playing a role in the cardiovascular effects of particulate matter. These mechanisms include direct effects of particle components (e.g., free radicals or hydroxyl ions) on the intracellular sources of reactive oxygen species (ROS), indirect effects due to pro-inflammatory mediators released from PM-stimulated macrophages, and neural stimulation after particle deposition in the lungs. Exposure to airborne particles induces a systemic inflammatory response that includes marrow stimulation, and has been proposed to accelerate atherosclerosis. In addition to oxidant mechanisms, exposure to particulate matter also causes an increase in plaque cell turnover and extracellular lipid pools in coronary and aortic lesions [369–371]. Several groups investigating the role of oxidative mechanisms associated with the airborne particle toxicity have proposed and provided evidence for an important mechanistic role of oxidative stress mediated by ROS as a mechanism of PM-induced inflammation and damage [355,369–371]. Exposure to PM air pollution has also been shown to cause a systemic inflammatory response including stimulation of the bone marrow and progression of atherosclerosis. Investigations in animal models have shown that exposure to PM results in the progression of

atherosclerotic lesions toward a more advanced phenotype. Progression of atherosclerosis and increased vulnerability to plaque rupture may underlie the relationship between particulate air pollution and excess cardiovascular death [372,373].

Cardiovascular disease and cancer share risk factors (e.g., smoking), evidence of common mechanisms including oxidative damage, DNA adducts, and the influence of glutathione (GSH) and polymorphisms of glutathione metabolism (e.g., GSTM1 genotype). Early evidence was published in 1973 that human atherosclerotic plaques (or lesions) were monoclonal in origin [374]. This hypothesis was supported by a review of the evidence on the possible involvement of somatic mutations in the development of atherosclerotic plaques [375]. In the mid-1990s, the research tools of genetic toxicology and molecular epidemiology were used in the investigation of heart tissue, cells, and atherosclerotic plaques. The resulting publications from several groups [376–381] provided more evidence for common mechanisms and pathways for cancer and cardiovascular disease. These studies demonstrated by multiple methods that DNA adducts are consistently detectable in different sections of the heart including smooth muscle cells of human abdominal aorta affected by atherosclerotic lesions [376–378], atrial appendages from open heart surgery patients [379], and human thoracic aorta samples from autopsy [380]. Furthermore, DNA alterations increased in atherosclerotic lesions of individuals lacking the GSTM1 genotype (GSTM1 null) [381]. In addition to stable DNA bulky adducts (e.g., possibly related to PAH or other polycyclic organic compounds), very high levels of oxidative DNA damage as measured by 8-OHdG (see discussion of 8-OHdG as an oxidative biomarker in Section 4.5 above) [377–379].

A number of studies now show that glutathione *S*-transferase genotype is a susceptibility factor in smoking-related coronary heart disease [382] and may have the same impact on PM induced atherosclerosis. Reduced glutathione (GSH) plays a critical role as an intracellular defense system providing detoxification of a broad spectrum of reactive species and their excretion as water-soluble conjugates. Conjugation of GSH with electrophiles is catalyzed by GSH *S*-transferases (GST), which constitute a broad family of phase II isoenzymes. Two of the GST encoding genes, GSTM1 (μ) and GSTT1 (θ), have a null genotype due to their homozygous deletion that results in lack of active protein. Polymorphisms within GSTT1 and especially GSTM1 have often been associated with cancer in various organs as well as

with elevated levels of DNA adducts in various cell types. Izzotti et al. [381] demonstrated that levels of DNA adducts in smooth muscle cell DNA from atherosclerotic lesions are consistently increased in individuals having the null GSTM1 genotype, whereas no association was established with the GSTT1 polymorphism. The influence of GSTM1 deletion was better expressed in never-smokers and ex-smokers than in current smokers. These findings are relevant to the epidemiology of atherosclerosis and suggest that metabolic polymorphisms may contribute to the interindividual variability in susceptibility to cardiovascular disease.

5.4. Reproductive effects

Early studies of exposure to environmental tobacco smoke demonstrated transplacental exposures [383]. A small number of studies of the reproductive effects of air pollution were reported prior to the 1990s due to the availability of different national databases containing reproductive outcomes such as infant mortality and congenital abnormalities as well as air pollution levels (e.g., sulfur dioxide and total particulate matter). Studies discussed here on the reproductive effects of air pollution in different geographic regions reflect different sources (e.g., coal and petroleum) and an increasing sophistication in the application of personal exposure monitoring, biomarkers, and more sophisticated exposure modeling. In addition to improved molecular and statistical methods for exposure assessment, genetic susceptibility biomarkers are being applied to understand the impact of different genotypes on the exposure, dose and biologic outcome.

The increasing pollution experienced during an extended period prior to 1990 in regions of Eastern Europe, stimulated scientists in the Czech Republic to examine the relationship between air pollution and congenital anomalies [384], infant mortality [385], and pregnancy outcomes [386] in the population. In the early 1990s the Teplice Program [39] was established to evaluate the impact of air pollution on health in the Teplice District located in Northern Bohemia, Czech Republic. This area is part of the “Black Traingle” including Poland and Eastern Germany. An important aspect of this program was the improvement in air pollution measurements (e.g., PM₁₀, PM_{2.5}, and PAH) and the evaluation of reproductive effects in both females and males. Air pollution levels were quite high when the Teplice Program was initiated and decreased over time as various coal combustion emissions were modified or eliminated. These changes facilitated

studies on the impact of air pollution on reproductive pregnancy outcomes and sperm quality [301]. Exposures to particulate matter early in pregnancy were shown to be associated with intrauterine growth retardation (IUGR) or fetal growth retardation leading to low birth weights based on analysis from the most populated and industrialized district (Teplice) after the first 2 years of this study [43]. A second evaluation of the impact of air pollution on fetal growth retardation in two districts was reported with a much larger sample size to over 4800 pregnancies and additional chemical data including particle mass (PM₁₀ and PM_{2.5}) and carcinogenic PAH (cPAH) that are associated with PM_{2.5} [387]. The extension and analysis of carcinogenic PAH (cPAH) suggest that the cPAH may be responsible for the fetal growth retardation observed in both studies from particulate matter. This second larger population analysis confirmed that the first gestational month was the critical exposure period for fetal growth retardation [387]. These results are consistent with evidence that PAH are a major source of the genotoxic (measured by formation of DNA adducts) and embryo toxic activities of PM_{2.5} organic extracts from air pollution in the Teplice district [388]. Additional studies of the same population found that IUGR was positively related to the level of DNA–PAH adducts in placenta and these DNA adduct levels were dependent on metabolic genotype [389–391]. Reproductive biomarker studies have also been reported by Perera et al. [302,392] on the impact of PAH and air pollution from coal on birth outcomes in a region of Poland.

Epidemiologic case–control studies in Southern California have shown that increased risk of low birth weight and premature birth are associated with increases in ambient air pollution related to traffic and the resulting petroleum combustion products emitted from vehicles. These studies examined and found that residential proximity to heavy-traffic roadways influenced the occurrence of low birth weight and/or preterm birth in infants in Los Angeles County between 1994 and 1996 [393,394]. In earlier work, a simple distance-weighted traffic density measure was used to assess exposure to motor vehicle exhaust [395–397]. Recently, more sophisticated methods for traffic-density determinations are being used in current studies of exposure measures for this birth cohort using methods that take meteorologic and seasonal factors into account.

An epidemiologic case–control study design was used to examine whether residential proximity to heavy-traffic roadways influenced the occurrence of low birth weight and/or preterm birth. Each home location at birth and estimated exposure to traffic-related air pollution

used a distance-weighted traffic density measure that includes residential proximity and traffic levels on roadways surrounding homes. They found an exposure–response relationship for preterm birth with a relative risk (RR) of 1.08 [95% CI = 1.01–1.15] for infants in the highest distance-weighted traffic density quintile. Higher risks were found for low birth weight infants however, exposure–response relations were less consistent. Season had an effect with elevated risks for women whose third trimester fell during fall/winter months and stronger exposure–response relationships were found for all outcomes with elevated pollution in proximity to sources during more stagnant air conditions present in winter months [393].

Reviews of fetal susceptibility factors suggest that higher rates of cell proliferation, greater number of target cells at risk, lower immunologic competence, and decreased capacity to metabolize carcinogens and repair DNA suggest that the fetus may be more susceptible to environmental air pollution exposures [398]. Previous studies in several locations in Poland compared maternal–fetal biomarkers in a cohort of 320 mothers and newborns [302,303]. These studies found that PAH–DNA adducts measured by immunoassay were comparable in mothers and their newborns and that PAH–aromatic adducts measured by ³²P-postlabeling were significantly higher in newborns than in mothers [303]. These differences may be due to the differential specificity of the immunoassay method that is designed to detect only PAH–DNA adducts compared to the postlabeling method that is capable of detecting a wider range of DNA adducts. Recent PAH biomarker studies [398–400] of 530 New York City mothers and newborns (265 pairs) exposed to air pollution and environmental tobacco smoke (ETS) provides a 10–30-fold range of exposure to PAH in these two populations (U.S. and Polish). DNA adducts and cotinine were analyzed in paired blood samples collected from mothers and newborns. Despite the estimated 10-fold lower fetal dose, mean levels of BaP–DNA adducts were comparable, however, the number of newborns with detectable DNA adducts was higher than their mothers. Cotinine levels were also significantly higher in the newborns. These studies show that not only may the fetus be more susceptible, but may receive a higher target dose with the same exposures as the mothers. Studies of the relationship between ambient air pollution and reproductive outcomes are expanding with studies in China [401,402], Korea [403], Brazil [404], and Mexico [405] added to those in the US and Eastern Europe discussed above. These studies have all linked ambient air pollution exposure during pregnancy

with term low birth weight (LBW), intrauterine growth retardation (IUGR), preterm birth, perinatal (including infant) mortality [406] and birth defects [407].

Studies on the impact of exposure to air pollution and tobacco smoke on the genetic integrity of human sperm have also been recently examined in the Czech Republic [39,44]. This study of male reproductive health resulted from community concern about potential adverse effects of air pollution. In addition to routine semen analysis, more sophisticated computer-aided sperm motion analysis, and sperm chromatin structure was assayed. The mean (median) sperm concentration and sperm counts were not associated with district of residence or period of elevated air pollution. Elevated air pollution episodes were significantly associated with decrements in other semen measures [44] including proportionately fewer motile sperm, proportionately fewer sperm with normal morphology or normal head shape, and proportionately more sperm with abnormal chromatin [408]. Aneuploidy in sperm was significantly associated with exposure to air pollutants. FISH was used to detect chromosomes X, Y, and 8 in spermatozoa of non-smoking men 18 years of age. Men exposed to the heaviest air pollution had an elevated level of sperm with an extra Y chromosome (YY8), although other disomies were not increased [297,409,410]. Genetic markers, now used in the evaluation of male reproductive health, highlight subtle but important effects of environmental risk factors. This study also demonstrated that alterations in sperm quality may occur after exposure to periods of elevated air pollution, without changes in sperm numbers [411].

A recent study of semen quality in men employed at motorway tollgates was compared to age-matched men living in the same area [412]. Sperm count, and serum levels of FSH, LH and testosterone were within normal range in both groups. Total motility, forward progression, functional tests and sperm kinetics were significantly lower in tollgate workers versus controls. In a subset of tollgate workers with motility below normal, methemoglobin was inversely correlated with total motility, viability, the hypo-osmotic swelling test, the acridine orange test, the cervical mucus penetration test, linearity, and amplitude of lateral movement of the sperm head, whereas blood levels of lead were inversely correlated with viability and sperm count. Nitrogen oxides and lead adversely affect semen quality as evidenced by the finding that blood methemoglobin and lead were inversely correlated with sperm parameters [412].

Growing concern that occupational [413] and environmental exposures are or may be related to changes in male reproductive health and fertility

resulted in the development of a research framework for studies on the exposure to hazardous substances and male reproductive health [414]. The most serious challenge confronting research in this area is standardizing methods, so that the assessment and comparison of results from existing and future studies is facilitated [415]. Certain occupations – rubber worker, petroleum worker, agricultural chemical worker, painter, welder, and janitor – have been particularly implicated as detrimental to the reproductive health of men [414]. Reports of declining sperm counts over the past 50 years and other trends have led scientists to investigate whether exposure to chemicals in the environment may damage male reproductive health. Biomarkers of chromosomal and genetic damage are increasingly used in the search to understand abnormal reproductive health outcomes, in part because of the possibility that there may be identifiable genetic polymorphisms which make an individual more susceptible to the adverse reproductive effects from exogenous substances. These assays provide promising and sensitive approaches for investigating germinal and potentially heritable effects of exposures to agents and for confirming epidemiologic observations on smaller numbers of individuals. Recently, more efficient technologies for examining chromosomal abnormalities in sperm have been developed.

5.5. *Common agents and mechanisms*

Combustion emissions and their contribution to ambient particulate, semivolatile, and gaseous air pollutants all contain organic compounds that induce toxicity, mutagenicity, genetic damage, oxidative damage, and inflammation. Polycyclic aromatic hydrocarbons and related nitrated and oxygenated aromatic hydrocarbons (e.g., nitro-PAH, quinines and lactones) are either present in all combustion emissions or formed as atmospheric transformation products. It is well established that these electrophilic compounds play a key role in environmental cancer and recent evidence implicates their role in cardiovascular disease and adverse reproductive outcomes.

6. **Note added in proof**

While this paper was in press, a Special Issue of *Mutation Research* edited by Van Schooten et al. [416] was published that reviews the topic of DNA damage, mutagenesis, and cardiovascular disease. The interested reader is encouraged to consult this Special Issue for more details on this important topic.

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