IARC SCIENTIFIC PUBLICATIONS

AIR POLLUTION AND CANCER

EDITED BY KURT STRAIF, AARON COHEN, AND JONATHAN SAMET

IARC SCIENTIFIC
PUBLICATION NO. 161

International Agency for Research on Cancer
World Health Organization

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Preface

Emissions from motor vehicles, industrial processes, power generation, the household combustion of solid fuel, and other sources pollute the ambient air across the globe. The precise chemical and physical features of ambient air pollution, which comprise a myriad of individual chemical constituents, vary around the world due to differences in the sources of pollution, climate, and meteorology, but the mixtures of ambient air pollution invariably contain specific chemicals known to be carcinogenic to humans.

Recent estimates suggest that the disease burden due to air pollution is substantial. Exposure to ambient fine particles ($PM_{2.5}$) was recently estimated to have contributed 3.2 million premature deaths worldwide in 2010, due largely to cardiovascular disease, and 223 000 deaths from lung cancer. More than half of the lung cancer deaths attributable to ambient $PM_{2.5}$ were estimated to have been in China and other East Asian countries (Lim et al., 2012).

In February 2003, the IARC Monographs Advisory Group on Priorities for Future Evaluations recommended that IARC develop a series of Monographs on air pollution. The topic is obviously complex, given the variety of environments where exposures to airborne carcinogens take place, the diversity of the sources, and the numerous components of the air pollution mixture that may contribute to its carcinogenicity. Recognizing this, the 2003 Advisory Group recommended that there be a focused Advisory Group to plan a series of IARC Monographs on air pollution.

In December 2004, this special Advisory Group meeting was convened in Lyon. Participants provided a state-of-the-art overview on topics related to exposure characterization, atmospheric and engineering sciences, epidemiological studies on cancer, results of pertinent cancer bioassays, and data elucidating potential mechanisms of carcinogenicity of compounds related to air pollution. These presentations were followed by discussions in subgroups established according to the structure of the IARC Monographs (exposure, cancer in humans, cancer in experimental animals, and other relevant data) and plenary sessions to identify all major issues that were critical for the development of the series of Monographs. Specifically, the participants were tasked with the following:

- Develop a list of agents and exposures to be evaluated in a series of IARC Monographs on air pollution and cancer.
- Identify the key issues to consider in the evaluations and critical research gaps.

- Make recommendations for bundling related agents into the same meeting.
- Make recommendations on the sequencing and scheduling of the meetings.

According to these recommendations, subsequent Monographs meetings were held over the next few years:

- Volume 92 (October 2005): Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures (IARC, 2010a).
- Volume 93 (February 2006): Carbon black, titanium dioxide, and talc (IARC, 2010b).
- Volume 95 (October 2006): Household use of solid fuels and high-temperature frying (IARC, 2010c).
- Volume 103 (October 2011): Bitumens and bitumen emissions, and some N- and S-heterocyclic polycyclic aromatic hydrocarbons (IARC, 2013).
- Volume 105 (June 2012): Diesel and gasoline engine exhausts and some nitroarenes (IARC, 2013).

As preparation began for the sixth meeting in this series of Monographs on air pollution (Volume 109: Ambient air pollution), the need to provide an overview and detailed background information on different aspects of air pollution and cancer took on renewed importance. To that end, it was decided to update earlier draft manuscripts that had been prepared based on presentations at the initial Advisory Group meeting in 2004. While serving as a Visiting Scientist in the IARC Monographs section, Aaron Cohen worked with Jonathan Samet, chair of the Advisory Group meeting in 2004, and IARC to manage this update and ensure publication before the IARC Monographs meeting on ambient air pollution in October 2013. The book that resulted now includes the following chapters:

- A working group report (written by Jonathan Samet on behalf of the Advisory Group); so as to capture the original recommendations of the Advisory Group, this chapter has not been updated.
- Eleven of the original manuscripts have been completely revised and updated by the original authors or by experts not present at the initial Advisory Group meeting.
- Two of the original manuscripts (by Vineis et al. and Katsouyanni et al.) have been updated with an addendum.

We acknowledge the support and encouragement of all the contributing authors during the development phase of this book. We extend our special thanks to all the authors for their endurance and their updates of the manuscripts. The editors would also like to acknowledge the critical support of Jennifer Brandt, the technical editor of this book, and the excellent support of IARC's publications team: Solène Quennehen, Sylvia Lesage, Karen Müller, and

Nicolas Gaudin. Financial support for the initial Advisory Group meeting was provided by World Health Organization/United States Environmental Protection Agency Cooperative Agreement No. CR 831057. This contribution is gratefully acknowledged.

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Chapter 1. Introduction

Jonathan M. Samet

People take thousands of breaths daily, leading to a total intake of about 10 000 litres of air per day. Consequently, the lung receives significant doses of many air contaminants, even those present at seemingly low and trivial concentrations. Around the world, people spend time in many different kinds of places, often referred to as microenvironments: their homes, workplaces, public places, other indoor environments, transportation, and outdoors. In all of these locations there are sources that emit airborne carcinogens that can be readily detected in indoor and outdoor air. Globally, combustion of fuels for heating, cooking, power generation, and industrial processes is a ubiquitous source. Combustion sources range from the burning of dung in open fires to highly sophisticated, massive combustion sources, such as coal-fired power plants, that may be equipped with control technology for particles and gases. Combustion engines, particularly for motor vehicles, are another worldwide source. Indoors there are carcinogens from tobacco smoking, building materials, and furnishings, as well as the naturally occurring carcinogen radon.

The extent of exposures to indoor and outdoor air pollution is well recognized. There has long been concern that airborne carcinogens contribute to the global burden of cancer, especially of the lung, which receives the most substantial inhaled doses. However, the topic of air pollution and cancer has not been reviewed systematically, particularly in its global dimensions. There is a rationale for undertaking such a comprehensive review: the more than 1.3 million new cases of lung cancer per year worldwide. Even a small contribution from air pollution to this number would strengthen the justification for implementing tighter control measures. In fact, several specific carcinogens or sources of carcinogens in indoor and outdoor air have already been the focus of substantial research and targeted control initiatives (e.g. diesel engines and exhaust, and radon and second-hand smoke indoors). In developing countries, high-level exposures to smoke from biomass fuels occur for billions of children and adults.

Estimates have been made of the burden of cancer attributable to environmental factors and of the contribution of air pollution to lung cancer specifically. Estimates have also been made for specific carcinogens, including radon and lung cancer. These estimates have been in the range of 3–5% for the fraction of lung cancer cases attributable to ambient air pollution. The 2004 estimates of the World Health Organization’s Global Burden of Disease programme covered both outdoor and indoor air pollution. For ambient air pollution, the estimated number of lung cancer deaths worldwide was 62 000

per year (Cohen et al., 2004). Indoor air pollution from solid fuel combustion was estimated to cause 16 000 lung cancer deaths per year, but estimates could not be made for all subregions (Smith et al., 2004).

Workshop summary

To develop an approach for evaluating the carcinogenicity of air pollution, the International Agency for Research on Cancer (IARC) convened a multidisciplinary panel that included epidemiologists, toxicologists, atmospheric scientists, cancer biologists, and regulators. The group was charged with planning a series of Monographs on air pollution and constituents of air pollution, including several agents and mixtures that had been proposed by an ad hoc IARC Monographs Advisory Group on Priorities for Future Evaluations (Table 1.1). Implicit in convening the panel was an assumption that one or more Monographs on air pollution would benefit public health and that sufficient evidence was available to lead to an informative classification. The panel concurred with this general assessment.

Table 1.1. Agents of high priority for evaluation or re-evaluation

Agent (overall evaluation of carcinogenicity to humans)[a]	Priority	Rationale for evaluation or re-evaluation
Carbon black (Group 2B)	High	New epidemiological studies New animal carcinogenicity data Mechanistic discussion (ultrafine particles)
Titanium dioxide (Group 3)	High	New epidemiological studies Mechanistic discussion (ultrafine particles)
Bitumen (USA: asphalt) (Group 2B/3)	High	Several ongoing epidemiological and animal carcinogenicity studies
Diesel engine exhaust		

(Group 2A)	High	New epidemiological studies
Gasoline engine exhaust (Group 2B)	Low	Few epidemiological studies specifically addressing gasoline engine exhaust
		No animal carcinogenicity data
	High	In combination with diesel engine exhaust
Air pollution, outdoor and indoor	High	New epidemiological studies
Sulfur dioxide (Group 3)	Low	New epidemiological studies
High		In combination with air pollution

[a] Group 1, carcinogenic to humans; Group 2A, probably carcinogenic to humans; Group 2B, possibly carcinogenic to humans; Group 3, not classifiable as to its carcinogenicity to humans; Group 4, probably not carcinogenic to humans.

Adapted from IARC (2003).

Planning the approach to developing the Monographs was complicated by the myriad sources of outdoor and indoor air pollution, the highly complex and variable nature of air pollution mixtures in indoor and outdoor places where people spend time, and the need to consider mixtures related to specific sources (e.g. tobacco smoke) along with mixtures of these mixtures (e.g. tobacco smoke and biomass fuel smoke). In addition, the panel was aware that the evidence base has gaps and that research in progress might influence timing of specific Monographs.

In previous Monographs, IARC had reviewed specific air pollutants as well as groups of air pollutants and source-related mixtures (Table 1.2). Dating back to 1983, some of these Monographs warrant updates that have not yet been carried out.

Table 1.2. Some air pollutants, groups of air pollutants, and source-related mixtures previously reviewed by the IARC Monographs Programme

Agent	Overall evaluation of carcinogenicity to humans[a]	Reference
Polycyclic aromatic hydrocarbons	Group 2A/2B/3	IARC (1983)
Nitro-polycyclic aromatic hydrocarbons	Group 3	IARC (1984)
Bitumen (USA: asphalt)	Group 2B/3	IARC (1987)
Benzene	Group 1	IARC (1987)
Asbestos	Group 1	IARC (1987)
Radon	Group 1	IARC (1988)
Diesel engine exhaust	Group 2A	IARC (1989a)
Gasoline engine exhaust	Group 2B	IARC (1989a)
Titanium dioxide	Group 3	IARC (1989b)
Sulfur dioxide	Group 3	IARC (1992)
Trichloroethylene	Group 2A	IARC (1995)
Carbon black	Group 2B	IARC (1996)
1,3-Butadiene	Group 2A	IARC (1999)
Man-made vitreous fibres	Group 2B/3	IARC (2002a)
		IARC

Styrene	Group 2B	(2002b)
Involuntary smoking	Group 1	IARC (2004)
Formaldehyde	Group 1	IARC (2006)

[a] Group 1, carcinogenic to humans; Group 2A, probably carcinogenic to humans; Group 2B, possibly carcinogenic to humans; Group 3, not classifiable as to its carcinogenicity to humans; Group 4, probably not carcinogenic to humans.

In formulating an approach to air pollution and cancer, the panel considered two possible sequences: building from evaluation of specific components to broad air pollution mixtures, and evaluating air pollution more generally first and then moving to identify those components requiring separate evaluation. The panel found reasons to consider both approaches appropriate.

After extensive discussion, the panel proposed a sequence that would begin with a volume on polycyclic aromatic hydrocarbons (PAHs), updating a topic last reviewed in 1983 (IARC, 1983). Because combustion of organic materials, which generates PAHs, figures prominently in producing much indoor and outdoor air pollution, the panel concluded that IARC should begin the sequence of Monographs by updating that volume.

It was decided that a subsequent volume would cover combustion-related contaminants in indoor air, including separate Monographs on biomass fuels, wood smoke, coal combustion, and cooking fuels and fumes. These contaminants represent major exposures for billions of people around the world. Because of the commonalities among these topics, they would best be reviewed by a single panel. The needed expertise would reflect that of the present planning panel but would also need to draw on researchers from developing countries.

Another proposed volume would cover the topic of outdoor air pollution. The panel noted that outdoor air pollution cannot be readily defined; therefore, the Monograph should focus on those pollutants generated by human activities, particularly those entailing combustion and industrial processes. While air pollution is most prominent in urban locations, coverage should extend to rural environments as well.

In addition, there would be a volume directed at engine emissions, including diesel and gasoline engines. Such emissions are, of course, contributors to urban and rural air pollution. They represent a critical source and are subject to control through various technical and regulatory mechanisms. The panel noted

that several new studies would be providing evidence over the next several years.

Many specific components of air pollution might be considered as topics for further Monographs. The panel suggested several such groups (e.g. particulate matter, solvents) but concluded that further decisions would be made as the Monograph series proceeded and new data were evaluated in the context of prior IARC Monographs.

There were other issues noted that merit attention in developing the Monographs. Outdoor and indoor air pollution are mixtures that contain specific carcinogens, some already classified as Group 1 by IARC. The planning panel noted that mixtures containing specific carcinogens should consequently be categorized as carcinogenic as well, unless there are unidentified interactions among the mixture components. There are analogies in prior reviews of mixtures including diesel engine exhaust and second-hand smoke. Within the guidance given by the Preamble to the IARC Monographs, the evaluation of a particular air pollution mixture will hinge on the toxicological and epidemiological evidence on the cancer risk associated with the mixture while also considering the carcinogenic activity of the individual mixture components.

IARC evaluates overall carcinogenicity but does not specifically quantify risk at either the individual or population level. The panel noted that such quantification would be a necessary step in determining the implications of higher-level IARC designations for control strategies.

Going on the assumption that mixtures containing carcinogens are necessarily carcinogenic themselves, the panel noted that a lack of evidence of carcinogenicity from experimental and observational studies could result from inadequacies and difficulties of the research approaches on mixtures. In the chapters in this IARC Scientific Publication, these limitations are discussed in further detail.

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Chapter 2. Geographical distribution of air pollutants

Klea Katsouyanni

In terms of constituents, air pollution has very wide geographical variation and represents many different entities. The proportion of the pollution mix, as well as the levels (concentrations) of the various pollutants, also may vary. However, the information that is available to characterize the air pollution mix is quite limited. Some pollutants or mixtures (e.g. particulate matter [PM]) are measured routinely in many parts of the world, while others are not, although some indication of their levels is available. In addition, air pollution may contain harmful substances of which nothing is known.

Recent scientific evidence, derived mainly from studies in Europe and North America, consistently suggests that urban air pollution causes adverse health effects (WHO, 2003). In the World Health Organization (WHO) Global Burden of Disease project, it has been estimated that urban air pollution worldwide, as measured by concentrations of PM, causes about 5% of all mortality attributable to cancers of the trachea, bronchus, and lung (Cohen et al., 2004). The burden in terms of absolute numbers occurs predominantly in developing countries, but in proportional terms, some of the most affected regions include parts of Europe.

To justify the evaluation of the effects of any environmental exposure within the framework of WHO, it is useful to demonstrate the extent of the exposure and, consequently, of the global public health problem. In addition, a satisfactory characterization of the air pollution mix linked with estimated health effects gives valuable information on the importance of such effects in relation to the various constituents.

Information from different projects that demonstrate the geographical distribution and variability of air pollutants worldwide, in Europe, and in the USA is compiled below.

Which pollutants?

In many parts of the world, monitoring systems for air pollutants have been installed, usually within the framework of governmental regulatory programmes. The older and most extensive of these are in North America and the European Union. The pollutants most frequently monitored are: (i) the

gases: sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone, and carbon monoxide; and (ii) the PM indicators: total suspended particles, black smoke, PM < 10 μm (PM_{10}), and PM < 2.5 μm ($PM_{2.5}$). Data from other parts of the world are available, but access to these and standardization of the monitoring methods are limited (Cohen et al., 2004). Measurements for other pollutants, most frequently constituents of PM, have been undertaken within the framework of specific studies and often provide valuable information on their geographical distribution. However, studies including the investigation of effects of PM constituents tend to be limited in time and seasonal coverage and often concern few areas and few points (often one point) within the areas studied. Generally, they are designed and performed to meet the needs of research projects and not to regularly monitor concentrations of pollutants. Examples of such projects in Europe are the Air Pollution Exposure of Adult Urban Populations in Europe Study (EXPOLIS), the Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air Study (ULTRA), the Relationship between Ultrafine and Fine Particulate Matter in Indoor and Outdoor Air Project (RUPIOH), the Chemical and Biological Characterization of Ambient Air Coarse, Fine and Ultrafine Particles for Human Health Risk Assessment Project (PAMCHAR), and the Air Pollution and Inflammatory Response in Myocardial Infarction Survivors Gene–Environment Interactions in a High-Risk Group Project (AIRGENE).

More information is available on the pollutants that are measured routinely. Since much of the evidence on the harmful health effects of air pollution is focused on the concentrations of PM, attention is being diverted there. Consequently, little information is available on the geographical distribution of specific carcinogens that are more interesting in the present context.

Table 2.1 shows the number of cities for which data on PM (measured as either total suspended particles or PM_{10}) are available, by region of the world. It can be seen that the monitoring systems are much more widespread in North America and Europe.

Table 2.1. Number of cities for which data on particulate matter are available from monitoring sites, by WHO subregion and type of particulate matter

Subregion	Number of cities for which data are available		
	PM_{10} or TSP	PM_{10}	TSP
AFR-D	2	0	2
AFR-E	1	0	1

AMR-A	123	118	25
AMR-B	19	12	12
AMR-D	2	2	2
EMR-B	0	0	0
EMR-D	1	1	0
EUR-A	95	56	43
EUR-B	22	7	17
EUR-C	7	1	7
SEAR-B	2	0	2
SEAR-D	11	11	10
WPR-A	5	5	4
WPR-B	14	3	14
World	304	216	139

PM_{10}, particulate matter < 10 µm; TSP, total suspended particles.

WHO Member States in subregions:

AFR-D: Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Togo;

AFR-E: Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe;

AMR-A: Canada, Cuba, USA;

AMR-B: Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Honduras, Jamaica, Mexico, Panama, Paraguay, Saint Kitts

and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela

AMR-D: Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru;

EMR-B: Bahrain, Cyprus, Islamic Republic of Iran, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates;

EMR-D: Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, Sudan, Yemen;

EUR-A: Andorra, Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom;

EUR-B: Albania, Armenia, Azerbaijan, Bosnia and Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Poland, Romania, Slovakia,

Tajikistan, The former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Uzbekistan, Serbia and Montenegro;

EUR-C: Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine

SEAR-B: Indonesia, Sri Lanka, Thailand;

SEAR-D: Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, Nepal, Timor-Leste;

WPR-A Australia, Brunei Darussalam, Japan, New Zealand, Singapore;

WPR-B: Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Federated States of Micronesia (Federated States of), Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam.

Source: Ezzati et al. (2004); reproduced with permission from the World Health Organization.

Worldwide distribution of air pollutants

Figure 2.1 shows the estimated annual average concentrations of PM_{10} in cities with populations > 100 000 and in national capitals. Table 2.2 gives the numbers represented in Figure 2.1, which were estimated using the Global Model of Ambient Particulates (GMAPS) model developed by the World Bank (Cohen et al., 2004).

Figure 2.1. Estimated annual average concentrations of PM_{10} in cities with populations of > 100 000 and in national capitals. Source: Ezzati et al. (2004); reproduced with permission from the World Health Organization.

Table 2.2. Population-weighted predicted PM_{10} and TSP and percentiles of the distribution of estimated concentrations of PM_{10}

Subregion[a]	Predicted point estimate (µg/m^3)			Percentiles of the distribution of estimated PM_{10} (mg/m^3)				
	PM_{10}	TSP	PM_{10} or TSP	5%	25%	50%	75%	95%
AFR-D	68	195	0.350	32	43	61	72	84
AFR-E	39	104	0.372	30	35	39	44	58
AMR-A	25	39	0.642	24	25	25	25	25
AMR-B	37	79	0.470	35	36	38	39	42
AMR-D	51	146	0.349	37	43	48	53	58

EMR-B	40	118	0.341	23	30	34	39	48
EMR-D	110	276	0.397	62	78	99	110	127
EUR-A	26	49	0.531	25	26	26	27	28
EUR-B	48	118	0.406	41	44	46	48	50
EUR-C	31	90	0.340	21	25	29	33	38
SEAR-B	108	245	0.439	39	86	105	129	151
SEAR-D	84	206	0.409	73	80	84	88	96
WPR-A	32	50	0.646	27	30	32	34	37
WPR-B	89	221	0.403	73	83	89	96	104
World	60	144	0.417	51	56	58	62	65

PM_{10}, particulate matter < 10 μm; TSP, total suspended particles.

[a] For details of WHO subregions, see Table 2.1.

Source: Ezzati et al. (2004); reproduced with permission from the World Health Organization.

High concentrations of PM are observed in many parts of the world, with distinct clusters in South-East Asia, South America, and Africa. There is also wide variability in the estimated PM levels by WHO region. WHO Member States are grouped into six geographical regions: AFRO (Africa), AMRO (Americas), EMRO (Eastern Mediterranean), EURO (Europe), SEARO (South-East Asia), and WPRO (Western Pacific). The highest concentrations of PM (population-weighted) occur in parts of the WHO regions of AFRO (Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Togo), AMRO (Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru), SEARO (Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste), and WPRO (Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Federated States of Micronesia, Mongolia, Nauru, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu,

Viet Nam). The six WHO regions are further divided, based on patterns of child and adult mortality, into subregions ranging from A (lowest) to E (highest).

Distribution of pollutants in Europe

The maps of Europe in Figures 2.2–2.6 represent distributions of NO_2, PM_{10}, black smoke, SO_2, and ozone in several European cities that are part of the Air Pollution and Health: A European Approach (APHEA) project (Katsouyanni et al., 2001); the corresponding numbers (with concentrations typical for the 1990s) are in Table 2.3.

Figure 2.2. Geographical distribution of nitrogen dioxide in Europe. Compiled from Katsouyanni et al. (2001).

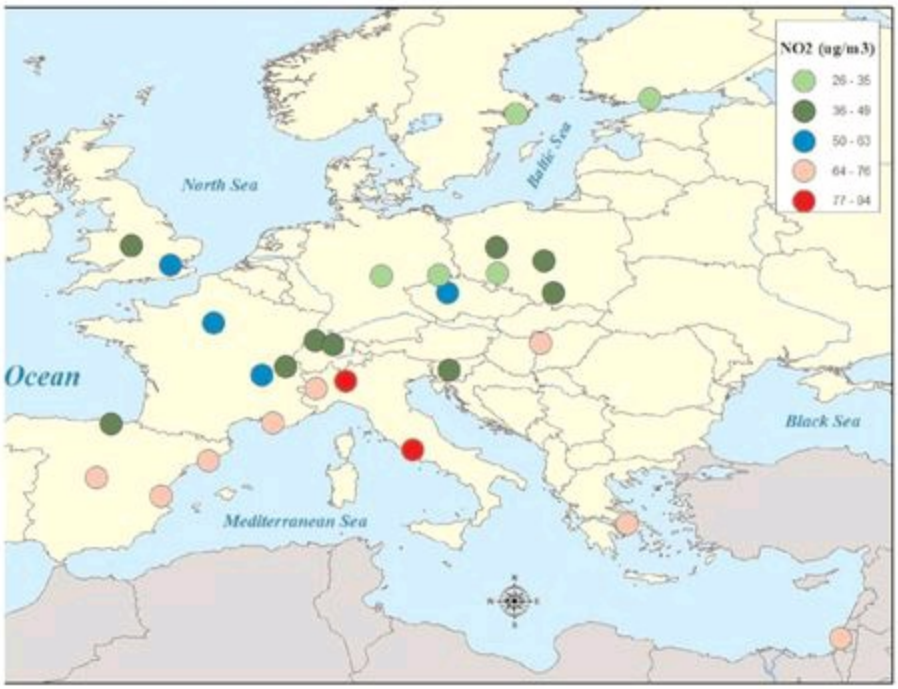


Figure 2.3. Geographical distribution of PM_{10} in Europe. Compiled from Katsouyanni et al. (2001).

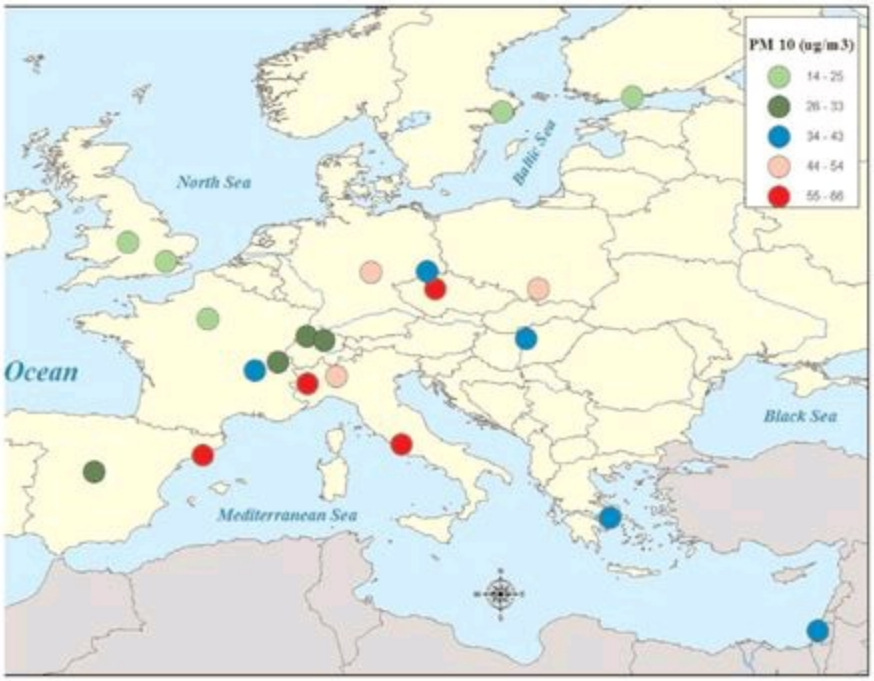


Figure 2.4. Geographical distribution of black smoke in Europe. Compiled from Katsouyanni et al. (2001).

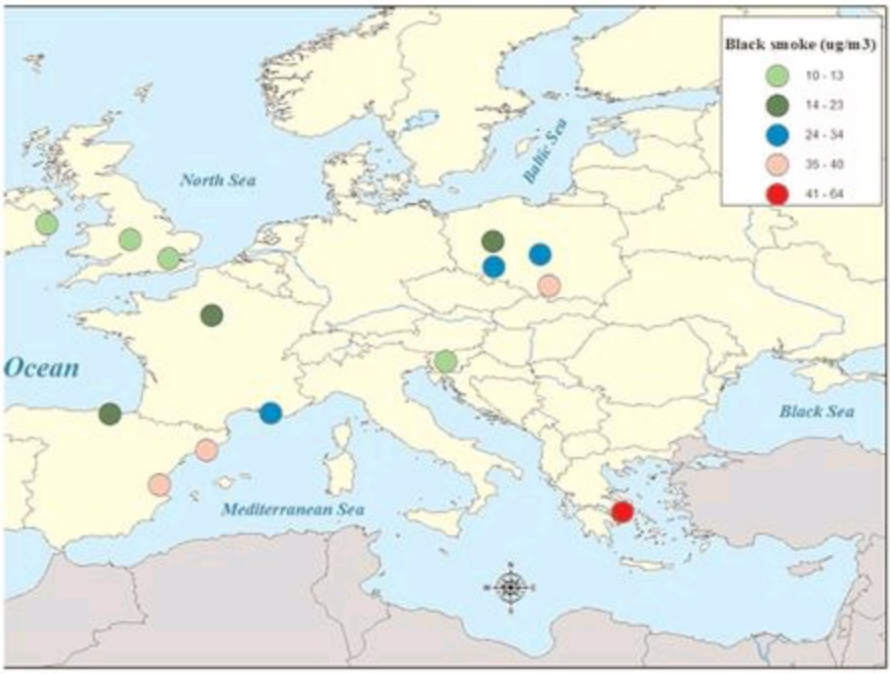


Figure 2.5. Geographical distribution of sulfur dioxide in Europe. Compiled from Katsouyanni et al. (2001).

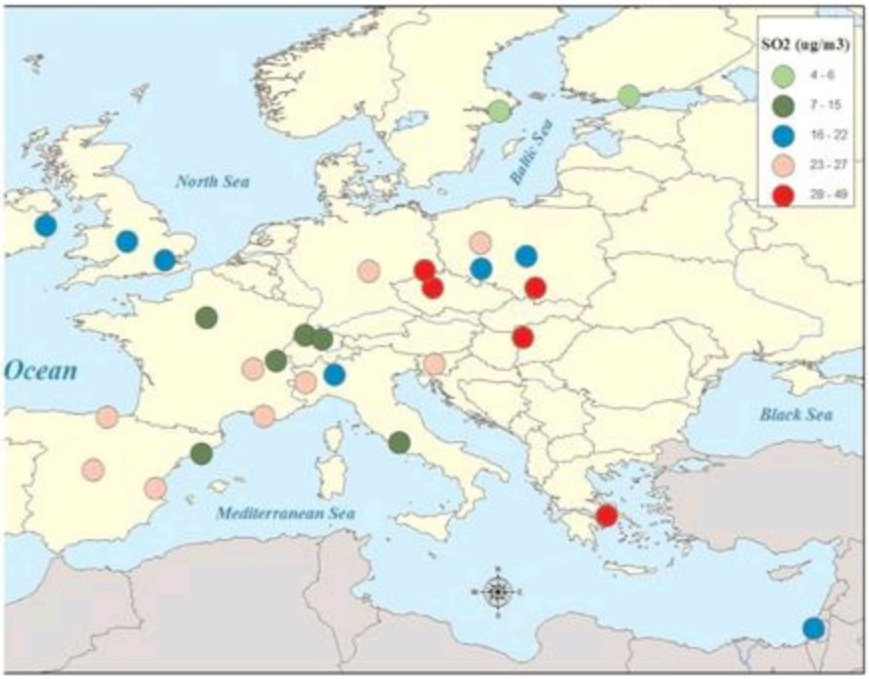


Figure 2.6. Geographical distribution of ozone in Europe. Compiled from Katsouyanni et al. (2001).

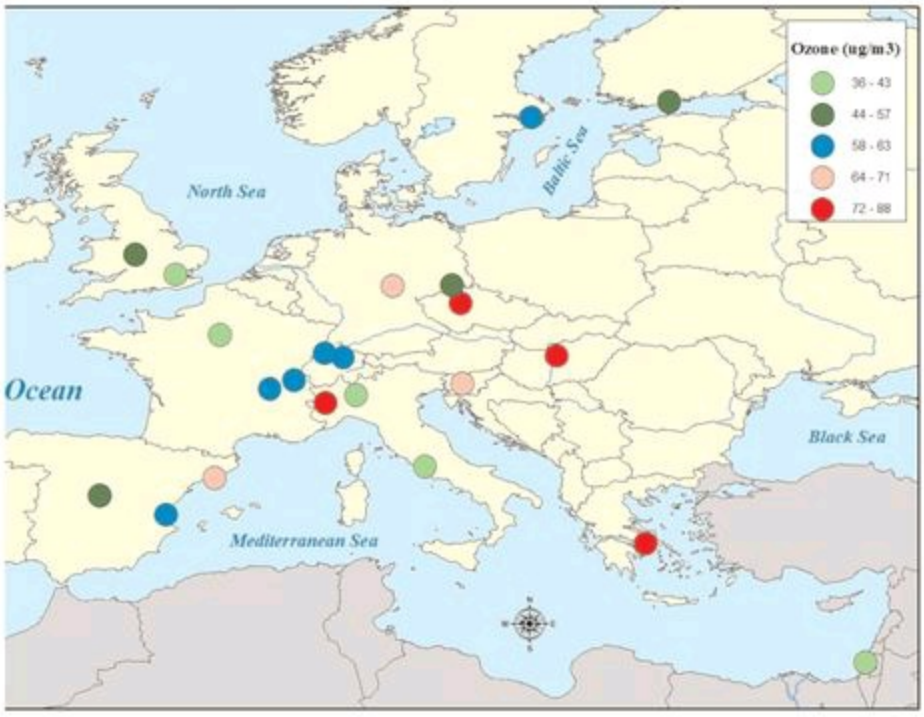


Table 2.3. Air pollutant concentrations in several European cities participating in the APHEA2 Project

City	Study period	Population (× 1000)	Concentration (μg/m^3)				
			PM_{10} (24	Black smoke	Sulfur	Ozone	Nitrog dioxid

			h)	(24 h)	dioxide		(24 h
Athens	1/92–12/96	3073	40	64	46	83	
Barcelona	1/91–12/96	1644	60	39	12	71	
Basel	1/90–12/95	360	28		9	62	
Bilbao	4/92–3/96	667		23	23		
Birmingham	1/92–12/96	2300	21	11	19	56	
Budapest	1/92–12/95	1931	40[a]		39	82	
Cracow	1/90–12/96	746	54[a]	36	49		
Dublin	1/90–12/96	482		10	21		
Erfurt	1/91–12/95	216	48		26	71	
Geneva	1/90–12/95	317	33[a]		9	63	
Helsinki	1/93–12/96	828	23[a]		6	57	
Ljubljana	1/92–12/96	322		13	27	71	
Lodz	1/90–12/96	828		30	19		
London	1/92–12/96	6905	25	11	22	43	
Lyon	1/93–	416	39		23	61	

	12/97					
Madrid	1/92–12/95	3012	33		26	52
Marseille	1/90–12/95	855		34	23	
Milano	1/90–12/96	1343	47[a]		20	38
Paris	1/91–12/96	6700	22	21	15	38
Poznan	1/90–12/96	582		23	23	
Prague	2/92–12/96	1213	66		36	78
Rome	1/92–12/96	2775	57[a]		11	41
Stockholm	1/90–12/96	1126	14		4	63
Tel Aviv	1/91–12/96	1141	43		19	36
Teplice	1/90–12/97	625	42		46	52
Torino	1/90–12/96	926	65[a]		23	88
Valencia	1/94–12/96	753		40	25	59
Wroclaw	1/90–12/96	643		33	21	
Zurich	1/90–12/95	540	28[a]		10	62

PM_{10}, particulate matter < 10 µm.

[a] PM_{10} was estimated using a regression model relating collocated PM_{10} measurements to the black smoke or total suspended particles.

Source: Katsouyanni et al. (2001); adapted with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health.

Substantial variability can be seen in the distribution of the various pollutants. NO_2 has a clear south (high) to north (low) and west (high) to east (low) gradient. The highest concentrations of black smoke and PM_{10} are observed in southern and central eastern Europe. The highest concentrations of SO_2 are in the east, followed by those in the south. The pattern for ozone is not so clear, mostly because of the placement of the monitors in each city. Some high concentrations can be seen in southern Europe, however, due to primary emissions and the climate, and in the north, mainly due to long-range transport. More information on the geographical distribution and composition of PM in Europe is given in Putaud et al. (2004) and Van Dingenen et al. (2004).

Distribution of pollutants in the USA

Figures 2.7–2.9 show the distribution of $PM_{2.5}$ in the USA (Bell et al., 2007). Concentrations of $PM_{2.5}$ are high in the Midwest and eastern USA, as well as in southern California. However, as we can see from Figures 2.8 and 2.9, the geographical distribution varies by season. The highest concentrations are observed in the east and Midwest in the summer, but in the Southwest in the winter.

Figure 2.7. $PM_{2.5}$ averages ($\mu g/m^3$) for 187 counties in the USA, 2000–2005. Source: Bell et al. (2007).

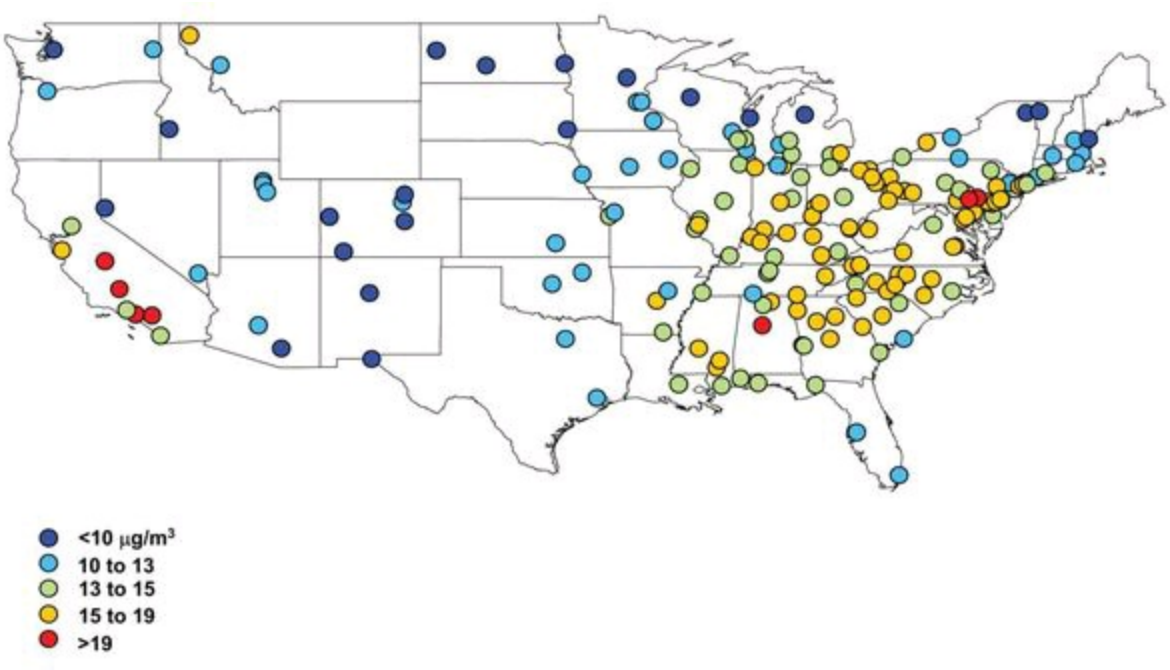


Figure 2.8. Seasonal $PM_{2.5}$ averages ($\mu g/m^3$) for 187 counties in the USA, 2000–2005. Source: Bell et al. (2007).

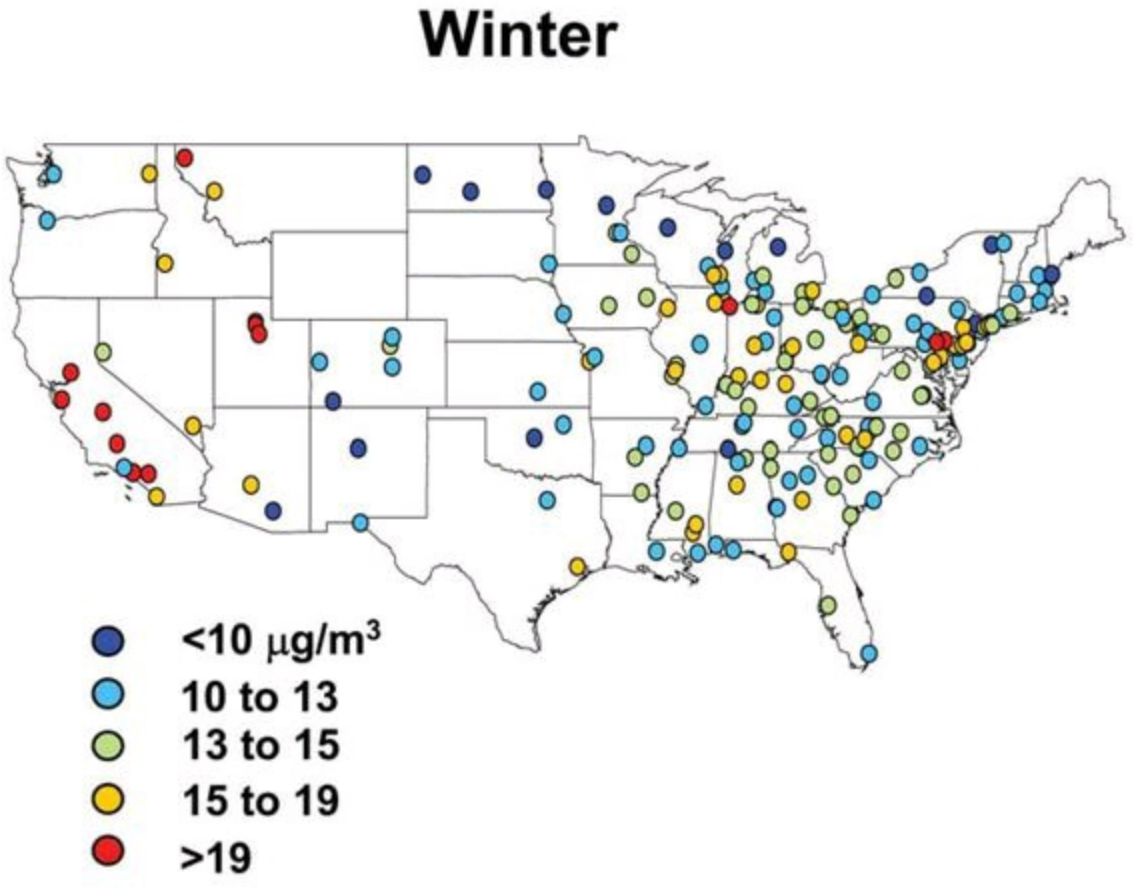
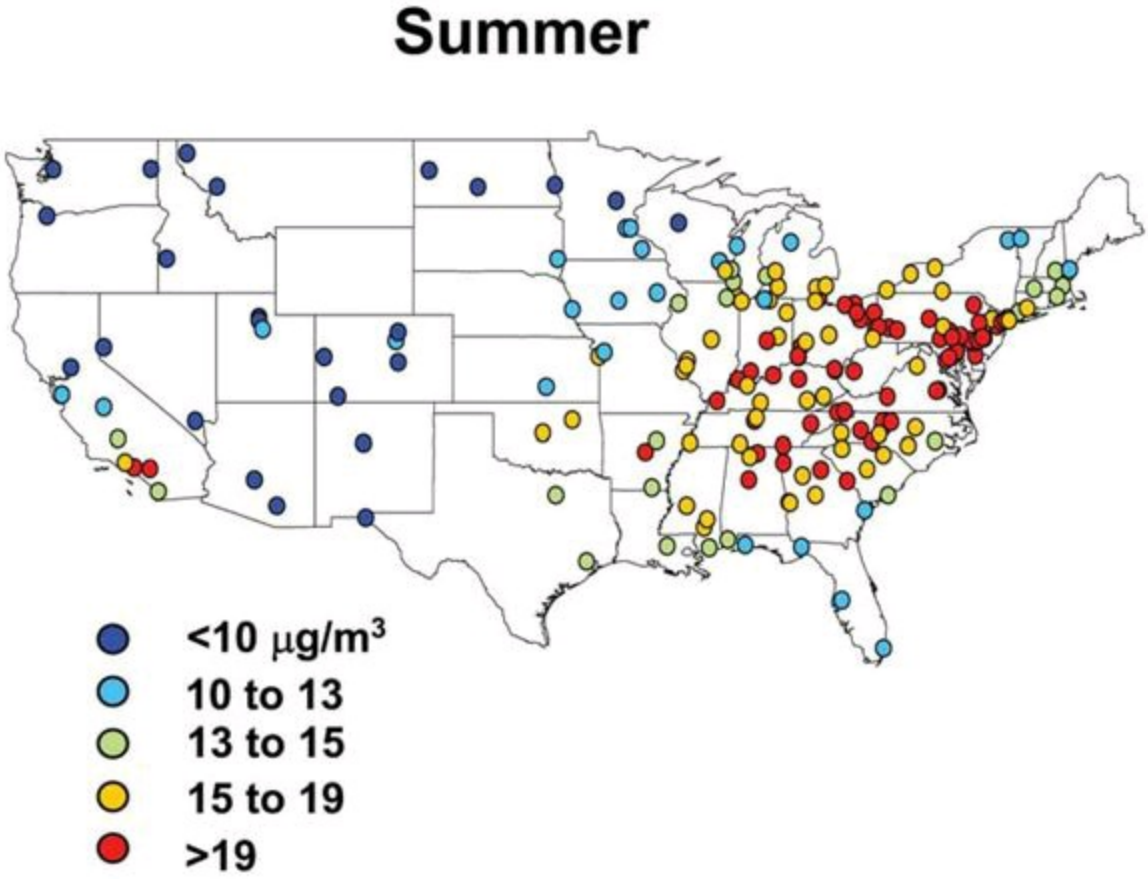


Figure 2.9. Seasonal $PM_{2.5}$ averages ($\mu g/m^3$) for 187 counties in the USA, 2000–2005. Source: Bell et al. (2007).



Is there evidence that the health effects of mixes of pollutants display geographical variation?

In the first phase of the APHEA project, geographical variations in the estimated (short-term) effects of pollutants (PM, SO_2) were observed, with smaller estimates in central eastern European cities and larger estimates in southern and north-western European cities (Katsouyanni et al., 1997). Subsequently, a systematic effort was made within APHEA to identify potential effect modifiers among the variables that characterize the air pollution mix, climate, health status of the population, and geographical areas (Katsouyanni et al., 2001).

Tables 2.4 and 2.5 give the effect modification identified in the APHEA project. In cities with higher long-term NO_2 levels, the estimated effects of PM_{10} were greater; similar effects were seen in cities with higher average temperatures and in those with a larger proportion of elderly persons. The distribution of these effect modifiers explains, to a certain extent, the geographical differences seen in Table 2.5 and is supported by other studies, such as the meta-analysis by Levy et al. (2000).

Table 2.4. Percentage increase in the daily number of deaths associated with an increase of 10 μg/m^3 in PM_{10} concentrations, by levels of important effect modifiers

Effect modifier	Increase in daily number of deaths (%)	
	Low level[a]	High level[a]
Average long-term nitrogen dioxide	0.19	0.80
Average annual temperature	0.28	0.82
Proportion of population aged > 65 years	0.54	0.76

[a] Low level of effect modifier is defined as the 25th percentile and high level as the 75th percentile of the corresponding distribution of effect modifier across cities. The actual levels were 40 mg/m^3 and 70 mg/m^3 for nitrogen dioxide, 9 °C and 14 °C for temperature, and 13% and 16% for the proportion of persons aged > 65 years.

Source: Katsouyanni et al. (2001); adapted with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health.

Table 2.5 Percentage increase in the daily number of deaths associated with an increase of 10 μg/m^3 in PM_{10} concentrations, by geographical area

	Geographical area		
	Southern Europe	North-western Europe	Central eastern Europe
Increase in the daily number of deaths (%)	0.87	0.73	0.22

PM_{10}, particulate matter < 10 μm.

Source: Katsouyanni et al. (2001); adapted with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health.

In the National Mortality, Morbidity and Air Pollution Study (NMMAPS), geographical differences in PM_{10} estimates were also observed, with higher estimates in the north-eastern region of the USA (Samet et al., 1999).

Conclusion and points of discussion

- There is wide geographical variability in concentrations of air pollutants.
- The geographical distribution varies by season.
- Information available today is limited, especially for specific constituents of the air pollution mix that may be of particular interest when the objective of the study is cancer. Those constituents are generally not measured routinely.
- More information is available from parts of the world where the concentrations of pollutants are, in fact, not so high, and less information is available where the exposure is more severe.
- However, in proportional terms, the health effects of exposure to air pollution may be more important in areas of the world where the exposure is not highest, due to interaction with other characteristics of the environment and/or the populations.
- There is evidence from studies of the short-term exposure to air pollution that several variables modify the effects of air pollutants, and some of them are probably related to characteristics of the air pollution mix.

Chapter 2. Geographical distribution of air pollutants

Addendum (2012 update)

Klea Katsouyanni

In general, the conclusions of the 2004 version of this chapter still hold true. However, our understanding of the role of geographical variability of pollutants on human exposure and health effects has advanced. Also, much progress has been made on the methodological study of geographical variation of air pollution, which can be applied to two distinct areas: geographical variation across large areas or continents, and geographical variation within a city or a relatively limited area.

Geographical variation across large areas or continents

In the WHO Air Quality Guidelines: Global update, 2006, a comprehensive chapter covers data from measurements of monitored air pollutant levels worldwide (Sivertsen, 2006). The pollutants covered are mainly PM, NO_2, SO_2, and ozone. The highest concentrations of PM_{10} and SO_2 are in Africa, South-East Asia, and Latin America. However, ozone and NO_2, although highest in Latin America, may be found at very high levels everywhere in the world (including Europe and the USA). Trends show a decline in most areas; however, there is concern that in developing countries and fast-developing cities the situation may deteriorate due to an increase of vehicle traffic, particularly with vehicles that are old and poorly maintained. The data available on $PM_{2.5}$ are still limited, and data on other PM fractions (such as ultrafine particles) and chemical constituents are very sparse. In addition, measurements are not easily comparable due to the techniques used and the varying characteristics of places where monitors are located. All pollutants except ozone have higher concentrations in urban areas (and within urban areas, near heavy traffic roads).

A recent report by the European Environmental Agency (EEA, 2012) indicates

that the most problematic pollutants in Europe are PM and ozone. Levels are determined mostly by emissions within Europe, but also, to a lesser extent, from intercontinental transport. Several pollutants are considered, including benzo[a]pyrene (B[a]P), lead, and benzene (C_6H_6). It is reported that 90–95% of the urban population in Europe is exposed to levels of $PM_{2.5}$ above the WHO air quality guidelines (AQG), 80–81% to corresponding levels of PM_{10}, > 97% to higher levels of ozone, and 93–94% to levels of B[a]P above the WHO guideline. PM exceedances largely occur in central, eastern, and southern Europe, but levels are decreasing. Ozone levels exceed the AQG mainly in southern Europe, and no apparent decreases are observed. There are problems with NO_2 levels everywhere in Europe, especially in urban areas, and an uncertain decreasing trend. SO_2 appears to be problematic in a few countries (the Balkans and Turkey). The EEA report attempted to cover additional pollutants, such as metals and B[a]P, and underlined the lack of monitoring data, with some countries not contributing data at all. From the available data, it appears that the problem with exceedances in heavy metal concentrations is mainly local and associated with industrial sources. B[a]P exposure is mainly problematic in central eastern Europe, but the overall emissions are increasing in the whole continent as well.

It is worth noting that in the WHO Report on Global Health Risks (WHO, 2009), urban outdoor air pollution was included in the 19 leading risk factors for mortality, with greatest effects in middle-income countries.

The lack of adequate monitoring data on the various air pollutants of interest, which is mentioned in all the reports, leads to attempts to develop modelling methods that take advantage of the availability of remote sensing data and the possibility to combine these with chemical-transport models and measurements (where available). Thus, Brauer et al. (2012) generated global estimates for $PM_{2.5}$ and ozone and were able to estimate that a large percentage of the world's population lives in areas with levels of $PM_{2.5}$ exceeding the WHO AQG targets, mainly in South-East Asia, while seasonal ozone levels are exceeded in all continents. They predicted an increasing trend in the global population-weighted exposure to $PM_{2.5}$ and a small decreasing trend for the same exposure to ozone. Evans et al. (2012) estimated the global adult mortality attributable to anthropogenic $PM_{2.5}$ exposure based on remote sensing data. Similar combinations of data and methods can be applied to large analytical epidemiological studies to estimate the retrospective exposure to air pollutants, as has been done, for example, by Hystad et al. (2012) in a case–control study in Canada.

Geographical variation within a city or a relatively

Geographical variation within a city or a relatively limited area

In epidemiological studies where both the within-city and the between-cities spatial contrasts could be taken into account, it has been shown that studying the within-city contrast led to higher relative risk estimates (Miller et al., 2007; Jerrett et al., 2005; Krewski et al., 2009). Thus, efforts to model the geographical variability within cities and then estimate individualized exposure were shown to be very important for the study of air pollution health effects. To achieve this, land-use regression (LUR) models have been developed and applied in the USA and Europe. LUR models are statistical models (in contrast to dispersion models) that link various geographical information system (GIS)-based spatial characteristics (covariates) with fixed site measurements in a relatively homogeneous area. The models can be used either to predict long-term (e.g. annual) averages or to attempt to estimate spatiotemporal variations (e.g. predict daily concentrations). In the former case, the covariates included (in addition to a smooth function of latitude and longitude) may be traffic burden (typically in a buffer around a point in space), the existence of a point source, population density, and green space, for example, whereas in the latter case additional covariates characterizing the weather (e.g. daily temperature) or temporal trends (e.g. day of the week) are included. More details may be found in Jerrett et al. (2005b), Ryan and LeMasters (2007), and Hoek et al. (2008).

In the USA, such models have been applied in the American Cancer Society's Cancer Prevention 2 study (Krewski et al., 2009). The refined spatial estimates resulted in larger estimates of the effects of air pollution. In a study in Boston, Maynard et al. (2007) modelled daily concentrations of black carbon and sulfates and investigated their short-term association with cardiovascular and respiratory mortality. They found very significant associations with black carbon, in spite of the larger errors that are inherent in daily predictions.

Recently in Europe, a large-scale effort has been undertaken within the EC-funded multicity project ESCAPE. LUR models have been built in 20 European areas across the continent for several PM indicators, including PM_{10}, $PM_{2.5}$, coarse PM, and $PM_{2.5}$ absorbance, and in 36 areas for NO_2 and nitrogen oxides (NO_x) (Eeftens et al., 2012; Cyrys et al., 2012). The modelling strategy allowed for local differentiation. With this application it was shown that models with good predictive ability can be developed in many areas and it became possible to compare within-city and between-city geographical contrasts. Better models are built for PM indicators related to the covariates included in the model (i.e. PM absorbance since traffic sources are specifically reflected in the model by traffic load). This effort showed once more that in Europe pollution concentrations display a gradient from north (cleaner) to south (more polluted).

Through the use of LUR models, and possibly other types of validated models,

long-term effects of air pollution can be further studied, taking into account a more personalized exposure estimate for subjects participating in cohort studies. Most studies have taken the residential address as input for this individual estimate. Through the use of technology, additional data may be collected on the average trajectory of an individual (including work address and commuting patterns) (Almanza et al., 2012). In this way, the important within-city contrasts in exposure will be taken into account and yield much better effect estimates. Further improvements can be achieved by bringing in the temporal dimension (Maynard et al., 2007) and estimating short-term effects as well.

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Chapter 3. Characterizing exposures to atmospheric carcinogens

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Organic emissions are predominantly non-polar, lipid-soluble substances with oxygen-to-carbon ratios near zero; atmospheric chemistry transforms these and inorganic emissions into more oxidized, more water-soluble compounds (Chung and Seinfeld, 2002; Liousse et al., 1996). Atmospheric pollutants (particles and gases) are either emitted directly from sources (primary) or formed in the atmosphere (secondary) through chemical reactions involving precursor emissions and often sunlight (Seinfeld and Pandis, 1998). For example, photochemical oxidation forms aldehydes, ketones, acids, organic peroxides, and epoxides from anthropogenic and biogenic aromatics, alkenes, and alkanes (Paulot et al., 2009; Atkinson, 2000; Finlayson-Pitts and Pitts, 2000). In addition, oxygenated and nitro-polycyclic aromatic hydrocarbons (PAHs) are formed from atmospheric processing of combustion-generated PAHs (Fan et al., 1995; Finlayson-Pitts and Pitts, 2000). Similarly, oxides of nitrogen (NO_x; gas-phase species) react to form nitric acid (gas phase) and ammonium nitrate (particle phase); sulfur dioxide is oxidized to acidic or ammonium sulfate (particle phase). Some reactions result in the formation of new particles or add more oxidized material to pre-existing (primary) particles (Ervens et al., 2011; Seinfeld and Pankow, 2003; Weber et al., 1999). For example, freshly emitted combustion particles are dominated by solid materials (black carbon, metals) and viscous organic liquids (e.g. PAHs, alkanes). A substantial portion of this primary particulate organic matter is believed to evaporate as it is diluted with cleaner air (Robinson et al., 2007). Subsequently, sulfates, nitrates, and polar organics formed through gas-phase photochemistry condense onto these primary seed particles (Seinfeld and Pankow, 2003) or form through aqueous chemistry in clouds and wet particles and remain in these particles after water evaporation (Ervens et al., 2011). As a result, atmospheric submicron particles are dominated by secondary oxidized species, except in close proximity to sources (Zhang et al., 2007; EPA, 2009).

The degree of atmospheric ageing (degree of oxidation) of the air pollution mix has a substantial impact on the composition, properties, fate, and effects of the air pollution mixture. Table 3.1 lists organic compounds commonly measured in atmospheric particles. While it is widely known that organic particulate matter (PM) includes alkanes, aromatic hydrocarbons, and dicarboxylic acids, a wide variety of types of organic compounds are present in atmospheric particles, including polyols, sugars, esters, amines, aldehydes, and

even nitrocatechols (Saxena and Hildemann, 1996; Claeys et al., 2012). Typically only about 20% of organic PM is identified at the molecular level (Rogge et al., 1993). Most unidentified organic PM is made up of large, multifunctional compounds, including humic-like materials and oligomers (Lin et al., 2010; Turpin et al., 2000; Rogge et al., 1993). Water solubility affects the fate of some inhaled pollutants. Water-soluble gases (e.g. hydrogen peroxide) diffuse readily to the wetted surfaces in the mouth, nose, and upper airways and are efficiently removed (Wexler and Sarangapani, 1998). In contrast, gas-phase PAHs and ozone are transported into the air-exchange regions of the lung (Hatch et al., 1994).

Table 3.1. Organic compounds commonly measured in atmospheric particles

Compound class
n-Alkanes (C23–C34)
n-Alkanoic acids (C9–C32)
n-Alkenoic acids (C17–C18)
n-Alkanols (C25–C32)
n-Alkanals (C9, C26–C32)
Aliphatic dicarboxylic acids (C2–C9)
Ketocarboxylic acids (C2–C5)
Diterpenoid acids (C20)
Other multifunctional aliphatic acids (C3–C6)
Aromatic polycarboxylic acids (C8–C10)
Polycyclic aromatic hydrocarbons (C16–C24)
Polycyclic aromatic ketones and quinones (C17–C19)
Steroids (Cholesterol, C27)
Nitrogen-containing compounds (C6–C10)

Carbonyls (C2)
Phenol and substituted phenols (C6–C7)
Guaiacol and substituted guaiacols (C7–C11)
Syringol and substituted syringols (C8–C12)
Mono-, sesqui-, and triterpenoids (C10–C12, C30)
Sugars (levoglucosan, C6)

Compiled from Rogge et al. (1993) and Schauer et al. (1996).

Particles also penetrate into the air-exchange regions of the lung, delivering liquid- and solid-phase, water-soluble, and lipid-soluble compounds. Fresh combustion-generated particles comprising solid graphitic carbon, metals, and viscous organic liquids presumably retain their particle form after deposition, although their organics will absorb into lipid-like materials given the opportunity. When secondary particles comprising concentrated aqueous solutions deposit in the lung, they dissolve into the lung surfactant, delivering dissolved chemicals. These (largely) secondary accumulation-mode particles sometimes contain an ultrafine primary core, facilitating the deposition of ultrafine solid particles. Hygroscopic (secondary) particles can also transport water-soluble vapour (e.g. hydrogen peroxide, organic peroxides) into the lower lung (Wexler and Sarangapani, 1998; Morio et al., 2001).

Urban air pollution is a combination of regionally generated pollutants that are substantially transformed through atmospheric processing, predominantly so-called secondary pollutants, and locally generated pollutants that are more likely to be dominated by primary emissions. For example, Lee et al. (2004) reported that fine PM (PM < 2.5 μm in diameter [$PM_{2.5}$]) in urban-industrial New Jersey is dominated by secondary formation and regional transport. They estimated that in the largest cities in New Jersey, no more than 25–30% of $PM_{2.5}$ is emitted or formed locally. In contrast, they reported that about 75% of PAHs in urban-industrial New Jersey are emitted locally. Concentrations of secondary species (e.g. sulfate, ozone, organic acids) are quite homogeneous across cities and large regions (states/nations) in places where regional transport is important (e.g. the eastern USA; Chuersuwan et al., 2000). In contrast, primary pollutants (e.g. carbon monoxide [CO], PAHs, black carbon) are elevated above the regional signal in urban areas, and very close to sources the concentrations of primary pollutants, such as road traffic, can be substantially elevated above the urban mix. Elevated CO concentrations in

street canyons are well documented. Also, several studies have found elevated mass concentrations of black carbon, NO_2, and PAHs and number concentrations of ultrafine particles within 100 or 200 m of major roadways (Roorda-Knape et al., 1998; Zhu et al., 2002; Polidori et al., 2010).

People are exposed to pollutants generated indoors at home or work, outdoors, and in other microenvironments (e.g. in transit). Pollution generated in these diverse environments is produced from a varied mix of sources and therefore will have a different composition and likely different effects (Long et al., 2001). Many pollutants are generated through personal activities. In this case, exposures are generally elevated above ambient (indoor or outdoor) concentrations because the individual is in close proximity to the source, such as when cooking or smoking tobacco products. Globally, the highest exposures to combustion-generated pollutants are found indoors in rural areas of developing countries and are the result of emissions from the combustion of unprocessed solid fuels from cooking (Smith, 2002).

Because people spend a large majority of their time indoors (for residents of the USA, 87% of their time; Klepeis et al., 2001), exposure to outdoor-generated (atmospheric) pollutants (as well as indoor-generated pollutants) predominantly occurs in indoor environments. For some pollutants, indoor sources and personal activities drive exposures, whereas other pollutant exposures are dictated by ambient outdoor sources. In homes without smokers in cities in the USA, particle-phase PAH concentrations found indoors are predominantly from outdoor sources (Naumova et al., 2002), and outdoor-generated $PM_{2.5}$ is the largest contributor to indoor concentrations of $PM_{2.5}$ (Ozkaynak et al., 1996; Meng et al., 2005). Ozone, lead, manganese, cadmium, methyl tertiary butyl ether, carbon tetrachloride, trichloroethylene, and sulfate found indoors have been reported to be dominated by outdoor sources (Weisel et al., 2005; Yocom, 1982). In contrast, indoor sources contribute more than outdoor sources to residential organic PM concentrations (Polidori et al., 2006). Results from the Total Exposure Assessment Methodology (TEAM) study suggest that for most commonly measured volatile organic compounds, exposures are dominated by small sources close to the individual, usually indoors (Wallace, 1986). Formaldehyde, acetaldehyde, asbestos, chloroform, α-pinene, and D-limonene exposures are also dominated by indoor sources (Weisel et al., 2005; Yocom, 1982).

Assuming complete mixing, the concentration of a pollutant found in a home can be described with a single-compartment mass-balance model:

$$V(dC_i/dt) = PVaC_a - VaC_i + Q_i - kC_iV \quad (1)$$

where C_i and C_a are the indoor and outdoor compound concentrations

($\mu g/m^3$), P is the fractional penetration of the compound through the building envelope, a is the air exchange rate (h^{-1}), k is the compound loss coefficient (h^{-1}) describing physical and chemical loss mechanisms indoors, Q_i is the strength of indoor sources ($\mu g/h$), and V is the house volume (m^3). Equation 1 describes the accumulation or depletion of a compound in the home as a function of: (i) the flux (mass/time) of compound into the home from outside due to air exchange, (ii) the flux out of the home with air exchange, (iii) the flux (mass/time) of compound introduced due to formation or emission of the compound indoors, and (iv) the flux (mass/time) lost by deposition or by reaction indoors. At steady state, this equation becomes:

$$C_i = \frac{PaC_a}{a+k} + \frac{Q_i/V}{a+k} = FC_a + C_{pig} = C_{ai} + C_{pig}$$

(2)

This equation describes the indoor compound concentration as the sum of the outdoor contribution (first term, Equation 2; C_{ai}, $\mu g/m^3$) and the indoor contribution (second term, Equation 2; C_{pig}). The quantity Pa/(a + k) or F describes the fraction of C_a that penetrates into and persists in indoor air (EPA, 2009).

Because the penetration through the building envelope (P) and the loss rate indoors (k) vary by pollutant, the composition of ambient air pollution is altered with outdoor-to-indoor transport. Non-polar gases (e.g. benzene, toluene, xylene) have very small loss rates indoors and penetration factors very close to unity, yielding F ≈ 1. In other words, nearly 100% of a non-polar atmospheric gaseous compound is transported indoors and persists. In contrast, polar, water-soluble gases (e.g. formaldehyde, glyoxal, hydrogen peroxide, nitric acid) penetrate the building envelope with lower efficiencies and have larger loss rates indoors (Nazaroff and Cass, 1986; Lunden et al., 2003). For example, the loss rate coefficient (k) for formaldehyde is 0.36 h^{-1} for a typical home (Nazaroff and Cass, 1986). There is some evidence that outdoor-to-indoor transport of some water-soluble vapours (i.e. hydrogen peroxide) is negligible, based on extremely high losses between offices connected by drop ceilings (Li et al., 2002).

The concentration and composition of outdoor-generated $PM_{2.5}$ also changes with outdoor-to-indoor transport (Hodas et al., 2012; Meng et al., 2007). Particle penetration through the building envelope and deposition indoors lead to F values of about 50% for $PM_{2.5}$ (F = 0.3–0.8; Chen and Zhao, 2011). In addition, since penetration and loss rates are different for different PM species and for particles of different sizes, outdoor-to-indoor transport modifies the composition, source contributions, and size distribution of ambient $PM_{2.5}$ (Meng

et al., 2007; Hodas et al., 2012). P and k are a strong function of particle size (Riley et al., 2002; Thatcher and Layton, 1995; Abt et al., 2000). Different particle formation mechanisms (e.g. combustion, abrasion) yield material that differs in composition and size distribution. For example, F for primary fine (< 2.5 μm) soil dust, which is mechanically generated and thus predominantly in supermicron particles, is quite small ($F_{soil} \approx 0.04$; Meng et al., 2007). With the exception of nitrate, the penetration and persistence of secondary aerosol is much larger ($F_{secondary} \approx 0.8$; Meng et al., 2007). There is some evidence that primary combustion-generated particles have somewhat smaller F values ($F_{combustion} \approx 0.5$; Meng et al., 2007; $F_{elemental\ carbon} \approx 0.6$; Lunden et al., 2008), and aerosol physics suggests that infiltration factors for freshly formed ultrafine particles are considerably lower (Riley et al., 2002). Thus, in the indoor environment, PM of outdoor origin has a composition that is enriched in accumulation-mode constituents relative to supermicron and ultrafine particle constituents (Meng et al., 2007).

Aerosol thermodynamics also changes the composition of atmospheric particles found indoors. The most dramatic effect can be seen for nitrate. Particulate ammonium nitrate and gaseous nitric acid are transported indoors, where nitric acid is readily lost by deposition and sorption to indoor surfaces (Lunden et al., 2003; Hering et al., 2007). This loss disturbs the equilibrium between nitrate and nitric acid, resulting in transformation of ammonium nitrate to gaseous nitric acid and ammonia. Thus, only about 12% of ambient outdoor particulate nitrate is found in indoor air ($F_{nitrate} \approx 0.12$ at an air exchange rate of 0.45 h^{-1}; Hodas et al., 2012). In locations where nitrate is a major outdoor particle constituent, this process substantially reduces F for $PM_{2.5}$ as well as substantially altering the particle composition. The implication is that people are exposed to much less ammonium nitrate than found at ambient sampling sites.

Changes in gas–particle partitioning of semivolatile organics (including PAHs, organic acids, and brominated flame retardants) can also occur with outdoor-to-indoor transport. Indoor–outdoor temperature differences can drive this process. Also, indoor concentrations of particulate organic matter are often considerably larger than outdoor concentrations, presumably because of indoor sources of organic PM (Polidori et al., 2006). Since semivolatile organics absorb into organic PM, the presence of additional organic material indoors can drive partitioning of these trace compounds (emitted indoors or outdoors) into the particle phase (Naumova et al., 2003). However, semivolatile organic gases are also lost to indoor surfaces. Changes in gas–particle partitioning of semivolatile species with outdoor-to-indoor transport are unlikely to have a large impact on the bulk composition of PM but could have a noticeable impact on the partitioning and fate of semivolatile organic air toxics.

Outdoor-to-indoor transport of ozone has also been observed to facilitate the oxidation of volatile organic compounds emitted indoors, altering the properties

and fate of these organic emissions. Products of these reactions are more water-soluble than their precursors, and include aldehydes, peroxides, and organic acids (Weschler and Shields, 1999; Li et al., 2002). These reactions can also form secondary organic PM indoors (Weschler and Shields, 1999).

Temporal and geographical variations in F could, under certain circumstances, lead to a downward bias and underestimation of effects derived from epidemiological analyses (Dominici et al., 2000; Zeger et al., 2000; EPA, 2009). Variability in F has been identified as a source of exposure error in epidemiological analyses that use central-site $PM_{2.5}$ as a surrogate for exposure to ambient fine particles (Dominici et al., 2000; Zeger et al., 2000; Hodas et al., 2012) . F varies spatially and temporally because (i) the air exchange rate depends on the housing stock, indoor–outdoor temperature difference, and ventilation practices (e.g. windows); (ii) the atmospheric conditions, season, and source mix affect particle properties (and P, k); and (iii) air conditioning and filtration affect particle losses indoors (Riley et al., 2002; Hodas et al., 2012). In fact, several studies have shown a reduced risk of PM-associated mortality or morbidity with increased prevalence of air conditioning (Janssen et al., 2002; Zeka et al., 2005 ; Franklin et al., 2007; Bell et al, 2009). Air conditioning use increases particle losses indoors, decreases F, and thus decreases exposure to ambient $PM_{2.5}$. Further, homes that use air conditioning are more likely to have their windows closed, reducing air exchange rates (and F) compared with homes with open windows (Breen et al., 2010). Certainly, the use of air conditioning varies seasonally and geographically and is one reason, among others, for heterogeneity in F.

Several studies are currently under way that explore to what degree F modifies associations between air pollutants and health effects in epidemiological studies. One such study found that the variation in ozone mortality coefficients across cities in the USA could be partially explained by variations in air exchange rate and thus variations in the fraction of outdoor ozone found indoors (Chen et al., 2012). Certainly, the epidemiological model matters. For example, in a case–crossover study, factors that differ across subjects but are largely constant within subjects (e.g. differences in air exchange rates or particle losses stemming from differences in housing stock and residential proximity to local sources) would not be expected to contribute to exposure error (or bias) in this type of study design. Similarly, when case–control periods are confined to one calendar month, seasonal variability in F (i.e. due to seasonal differences in the air pollutant mix) would be controlled by design. Matching case and control periods by weekday and hour also addresses, to a degree, within-subject variability in human activity patterns.

In summary, the air pollution mixture is spatially and temporally heterogeneous. Primary pollutants (more lipid-soluble) exhibit steep concentration gradients close to sources, and secondary pollutants (more water-soluble) are often homogeneously distributed on a regional scale. The chemical

and physical properties of the pollutants affect their atmospheric lifetime, penetration and persistence in indoor environments, and lung deposition. Human exposure to the ambient air pollution mixture is affected by: transport of outdoor pollutants into indoor environments; the modifications of the pollutants indoors; and time–activity patterns of people. This is because most exposure to outdoor pollutants comes from exposure to these pollutants indoors. Under some circumstances, variations in the fraction of an ambient pollutant found indoors can affect pollutant–mortality associations that are based on outdoor concentrations.

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Chapter 4. Combustion emissions

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Many of the toxic air pollutants, or air toxics, to which we are exposed are combustion-related (Kinney et al., 2002; Lim et al., 2002; SCAQMD, 2000; Manchester-Neesvig et al., 2003). The International Agency for Research on Cancer (IARC) list of Group 1 carcinogens includes a large number of these agents, including benzene, diesel exhaust, benzo[a]pyrene (B[a]P, a polycyclic aromatic hydrocarbon [PAH]), indoor emissions from coal combustion, and 1,3-butadiene. Gasoline engine exhaust is a Group 2B carcinogen, although it contains benzene, B[a]P, and 1,3-butadiene. (Tobacco smoke is also a combustion product with similarities to other combustion emissions, but is not covered here.) The World Health Organization, in the Global Burden of Disease study, found that emissions from indoor fuel combustion and urban particulate matter (PM) (much of which is combustion-related) are leading causes of premature mortality from environmental exposures (Ezzati et al., 2006). The Multiple Air Toxics Exposure Study II (MATES-II; SCAQMD, 2000) of air toxics in the Los Angeles, California, region found that of the air toxics studied, the four compounds that had the greatest potential risk, combining both the estimated potential exposure and carcinogenicity, were primarily from combustion, including diesel PM, 1,3-butadiene, benzene, and carbonyls (e.g. aldehydes, primarily formaldehyde). Combustion-related sources, including automobiles and indoor heating and cooking, are widespread and tend to be associated with more populated areas, leading to high potential exposures and health risks.

Combustion is the reaction between a fuel and oxidant accompanied by the release of heat:

$$\text{Fuel} + \text{Oxidant} \rightarrow \text{Products} + \text{Heat}$$

Typically, the fuel is carbonaceous, such as gasoline, wood, or coal, and the oxidant is the oxygen in air, although there are non-carbonaceous fuels, notably hydrogen. While such processes are rare, combustion can take place without using air to provide the oxidant. The heat generated by combustion is typically used for cooking, heating, or producing power. The main products of hydrocarbon fuel combustion are carbon dioxide (CO_2) and water. However, combustion can lead to emissions of other compounds due to impurities in the

fuel, the presence of nitrogen in air, or incomplete combustion. Specific sources of potentially carcinogenic air pollutant emissions that involve combustion include internal combustion engines (ICEs) (e.g. diesel, gasoline, turbine), external combustion boilers (as used for electricity generation), cement kilns, biomass burning (for cooking, heating, land management, and unplanned fires), waste combustion, and more (Smith, 2002; Lim, 2004; Zielinska et al., 2004a, 2004b; Lemieux et al., 2004).

Here, we address combustion-related emissions, beginning with a brief discussion of combustion-derived pollutants, the combustion process, and toxic pollutant formation. Combustion sources are identified and the associated types of emissions discussed. Automotive emissions and biomass burning are major contributors to potentially harmful exposures, and are addressed in more detail in other chapters. When source emissions are discussed, potential controls are also identified.

Combustion-derived air toxics

A large fraction, but not all, of the air toxics emitted and/or formed during combustion are organic molecules and carbonaceous structures. Some are relatively simple molecules, such as formaldehyde (HCHO), increasing in complexity to compounds like 1,3-butadiene, aromatics, PAHs, and dioxins. Some sources emit soot, which is condensed organic material, part of which may approach elemental carbon. (Elemental carbon [EC] is currently operationally defined, i.e. it is dependent on the technique used for quantification. Black carbon [BC] is similar, although not identical, to EC, and concentrations of BC and EC tend to be highly correlated.) Soot is not composed of a single type of molecule but is made up of a variety of lower-volatility compounds, including PAHs, possibly on a core of a structure that resembles EC (although it can contain a variety of impurities). Table 4.1 lists several combustion-derived organic air toxics, some of which, such as benzene, 1,3-butadiene, and diesel exhaust, have been classified by IARC as known human carcinogens. A number of these species are semivolatile and may be found either as gases or as part of the PM, including many of the PAHs (Simoneit et al., 2004; Zielinska et al., 2004a, 2004b).

Table 4.1. Examples of combustion-derived air toxics

Gas phase	Particulate matter	Semivolatile[a]

Formaldehyde	Diesel	Polycyclic aromatic hydrocarbons
Acetaldehyde		Polychlorinated biphenyls
Acrolein		Furans
Benzene		
Toluene		
o-, m-, p-Xylenes		
1,3-Butadiene		

[a] May be found in either gas phase or primarily condensed phase as particulate matter.

Inorganic emissions of concern include acids, such as sulfuric and hydrochloric acid, sulfur and nitrogen oxides (NO_x), and minerals. These are usually derived from contaminants in the fuel, although NO_x are formed, in part, from the nitrogen that makes up the bulk of air. Sulfur, which is present in many fossil fuels, is oxidized during combustion to both sulfur dioxide (SO_2) and sulfur trioxide. Sulfur trioxide condenses with water to form sulfuric acid. Chlorine reacts with hydrogen during combustion to form hydrochloric acid. Coal and oil can contain a variety of minerals, including iron and silicon oxides. These minerals typically are emitted as small particles.

Combustion process

Combustion is a complex phenomenon involving chemical reactions and heat and mass transfer occurring on scales from atomic to potentially centimetres (e.g. a car engine), metres (e.g. a coal combustor), or kilometres (forest fires). Unless the fuel and oxidant are both simple molecules (e.g. hydrogen and oxygen, leading to water), the products of combustion can be, and often are, as complex and varied as the combustion processes, forming as many compounds as originally present, if not more. Some of these species, such as 1,3-butadiene and PAHs, are known human carcinogens. Even a molecule as simple as methane burning in air can lead to larger molecules and soot.

The heterogeneity of real-world combustion leads to the complexity of the process and the wide range of compounds that are formed. In and around the combustion zone, the concentrations of species (e.g. the fuel, oxidant, and combustion products) vary by orders of magnitude over molecular scales. Temperature also can change rapidly over a few millimetres (if not less). In addition, flame fronts can move quickly; thus, the fuel can heat rapidly, start to combust, and then cool, quenching further reaction. Similarly, part of the flame can have excess oxygen while another part has excess fuel.

During combustion, the fate of organic fuel molecules is largely determined by the local conditions (e.g. temperature, abundance of oxygen, and time). If ample oxygen is present locally, i.e. directly where the combustion is occurring, the fuel will tend to oxidize and break down to smaller organic molecules until ultimately forming carbon monoxide (CO) and CO_2. For example, consider a mechanism sequence for methane oxidation:

$$CH_4 + OH^\bullet \rightarrow CH_3^\bullet + H_2O$$
$$CH_3^\bullet + O_2 \rightarrow CH_3O_2^\bullet$$
$$CH_3O_2^\bullet \rightarrow HCHO + HO^\bullet$$
$$HCHO + OH^\bullet \rightarrow H_2O + HCO^\bullet$$
$$HCO^\bullet + O_2 \rightarrow CO + HO_2^\bullet$$
$$\bullet\ CO + OH^\bullet \rightarrow CO_2 + H^\bullet$$

where the indicates a very reactive radical intermediate.

A few characteristics of this process are important. First, even for a simple molecule such as methane, the chemistry becomes complicated. This sequence shows only a fraction of the possible reactions; Held and Dryer (1998) show 89 reactions for methanol oxidation, excluding any reactions involving NO_x formation. If one considers combustion in fuel-rich conditions, the combustion mechanism becomes many-fold larger. For a two-carbon molecule, the complexity of the mechanism increases dramatically; more so for more complex molecules. Second, formaldehyde, an air toxic, is produced. It may also be destroyed later, but it is formed and can be emitted if the time for combustion is short (e.g. in an ICE). Larger molecules will lead to the formation of many other, more complex intermediates, including higher aldehydes (e.g. acetaldehyde from ethanol) and other air toxics (e.g. 1,3-butadiene). Third, CO_2 is the final end-product, but only after several intermediate reactions. CO oxidation is relatively slow, so if conditions do not permit more complete combustion (i.e. low temperature, limited availability of oxygen, and short residence times), large quantities of CO can be emitted (e.g. in an automobile engine where residence

time is limited and the car may be forced into an oxygen-limited condition during higher loads). Again, for larger molecules more reactions are required to form those ultimate products.

The above reaction mechanism assumed ample oxygen and sufficient time to react, and did not consider the possibility of organic radical intermediates reacting with each other to form larger organic molecules, which can be important to emissions of toxics. If, instead of reacting with oxygen, the methyl radical ($CH_3^\bullet$) reacts with another methyl radical, ethane can be formed, along with even larger molecules:

$$CH_3^\bullet + CH_3^\bullet \rightarrow C_2H_6 \ldots \rightarrow C_2H_5^\bullet + CH_3^\bullet \rightarrow C_3H_8 \ldots$$

Larger molecules can then continue to react, ultimately forming various air toxics, including PAHs and soot, as discussed below.

In general, the emissions of air toxics from combustion can be reduced by raising the temperature of combustion, increasing oxygen availability, and allowing a longer reaction time. For example, such conditions are in place for coal combustion in power plants, where relatively small (but non-zero) amounts of air toxics are emitted. However, ICEs have a more limited residence time in the combustion region, cooler reaction zones (particularly near the walls), and areas of reduced oxygen. Thus, one finds higher levels of products of incomplete combustion, such as CO, aldehydes, 1,3-butadiene, PAHs, and soot, emitted from such systems.

Polycyclic aromatic hydrocarbon emissions

PAHs can be formed during combustion when carbonaceous (organic) fuels are used. The formation of PAHs is not so surprising when the fuel (or the engine lubricant) already includes aromatics, but even those engines using so-called clean fuels, involving smaller organic molecules, such as methane, can produce PAHs.

Aromatics can grow to PAHs by addition of non-aromatic molecules to an already existing aromatic structure, or by reacting directly with other aromatic radicals. After a two-ring PAH is formed, by further reaction (again either by addition of non-aromatic radical intermediates or by reacting with aromatic radicals), three-ring and higher chains are formed.

Non-aromatic molecules (e.g. alkanes and olefins) also form PAHs, but at

much lower efficiencies. While a variety of mechanisms exist, for example consider the reaction involving acetylene (C_2H_2) and the 1,3-butadienyl radical (C_4H_5):

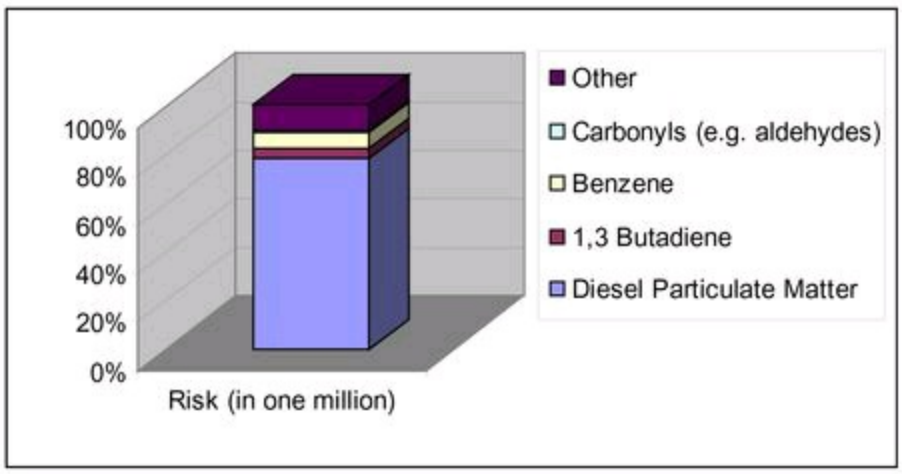
$$C_2H_2 + C_4H_5^{\bullet} \rightarrow C_6H_6 \text{ (benzene)}$$

The benzene can then grow by addition of more organic chain radicals with and without aromatic structures. If significant levels of oxygen are present, the 1,3-butadienyl radical will instead oxidize to aldehydes and other oxygenated organics with fewer carbon atoms.

Soot formation

Current evidence indicates that PM has somewhat greater health impact than other air pollutants. Results from Laden et al. (2000) and others (Metzger et al., 2004) suggest that mobile source-derived and/or carbonaceous PM may have greater impacts than other components. The MATES-II study found that diesel PM is the major air toxic of concern in the Los Angeles, California, region (SCAQMD, 2000) (Figure 4.1). These results raise the question as to the formation of carbonaceous PM emissions, for example soot during combustion.

Figure 4.1. Cancer risks at the MATES-II fixed sites. Risks are shown for all sources, including diesel particulates (top). The "other" portion is primarily non-combustion sources, although it includes PAHs not associated with diesel particulate matter. Compiled from SCAQMD (2000).



Soot formation is related to PAH formation, and aromatic fuels tend to

produce more soot than others (Flagan and Seinfeld, 1988; Haynes, 1991). In one mechanism, PAHs continue to grow as discussed above until they can condense and ultimately form solid particles. Again, even smaller organics can form soot; one mechanism is the formation of PAHs as discussed above, another is via the formation of polyacetylenes and continued reduction of the H:C ratio (soot has a very low H:C ratio, approaching that of EC). For example,

$$C_2H_2 + C_2H^{\bullet} \rightarrow C_4H_2 + H^{\bullet}\ ;\ C_4H_2 + C_2H_2 \rightarrow C_6H_2 + H_2 \ldots\rightarrow C_8H_2$$

This process can continue until much larger, non-volatile structures (i.e. soot) are formed. Soot can also be produced by the removal of hydrogen from liquid carbonaceous fuels.

Critical to soot formation and growth is particle inception, where the first identifiable solid particles are formed. These particles are on the order of a nanometre and are composed of sheets of on the order of 100 carbon atoms. After inception, these particles can grow more rapidly by further reaction with organics on their surfaces and by condensation of non-volatile species as the environment cools. They can also coagulate with other soot particles, leading to long-chain, fractal aggregates composed of hundreds of smaller spheres. The particles can grow by many orders of magnitude, often to diameters of 0.1 µm or more, before being emitted.

Once formed, soot burns out more slowly. These kinetics partially explain why diesel vehicles emit soot even though they are operated fuel-lean (oxygen-rich overall). Near the fuel droplets and on cylinder surfaces, the combustion can be taking place in a fuel-rich environment, leading to formation of PAHs and soot. There is not ample time to oxidize the soot particles when they reach an oxygen-rich zone.

Soot from virtually any source (e.g. diesel engines, biomass burning, cooking of meat) is composed of a large number of different organic molecules, from very large, very low-volatility compounds to semivolatile species that are found simultaneously in appreciable quantities in both the gas and particle phases.

Coke and char formation

Coal and fuel oil combustion can lead to the formation of char and coke. These are the carbonaceous residue particles that remain if the original solid or liquid fuel does not have time to fully combust. Char is formed as the volatile

components in the coal escape due to the high temperatures, leaving the solid, nearly EC structure behind. Coke is formed from the liquid-phase pyrolysis of fuel oil. Ample reaction time can allow oxidation of char and coke.

Ash formation

Coal and, to a lesser extent, heavy fuel oils contain non-combustible materials such as minerals, including silicon, nickel, aluminium, and calcium, and trace quantities of other metals like selenium, cadmium, and so on as inclusions in the fuel. As the fuel burns, these inclusions become molten and agglomerate with each other. A small fraction of the mineral material can also vaporize and then condense as the temperature cools. The particles formed are initially quite small (< 0.01 µm) but grow due to the molten material agglomeration, condensation, and coagulation, leaving a large fraction of the produced particles > 1 µm. Condensing species include vaporized minerals, sulfuric acid, and organics. Chowdhury (2004) reported on the analysis of coal fly ash and found elevated levels of a variety of PAHs, including pycene.

Combustion sources and systems

There are a variety of combustion systems that lead to potentially toxic emissions. In more developed countries, emissions from traditional diesel engines (also referred to as compression ignition [CI] engines) and gasoline-fuelled spark ignition (SI) engines contribute significantly to human exposure. They are discussed briefly below and in more detail in other chapters. Biomass fuel combustion is similarly dominant in rural parts of developing countries and is also discussed in more detail in other chapters. Other major sources of concern are discussed below.

Internal combustion engines

ICEs, primarily diesel (or CI) and gasoline (or SI) engines, are typified by having limited time for combustion in the cylinder. This short time leads to a relative abundance of products of incomplete combustion. When traditional hydrocarbon-based fuels are burned, such products include: CO and NO_x; unburnt organics (e.g. benzene that was present in the fuel); partially oxidized organics, such as aldehydes; products of pyrolysis, such as PAHs; and soot

(Haynes, 1991). Part of the emissions from ICEs are due to incomplete combustion of fuel and lubricating oil (Sheesley et al., 2009; Goldstein, 2012). There is evidence that with time the lubricating oil in the crankcase is enriched in PAHs by leakage from the pistons, further increasing such emissions. ICEs also emit NO_x from fixation of the nitrogen in air. Automotive emissions have evolved over time as various controls, such as catalysts, have been implemented. These controls have dramatically reduced the amounts of emissions (by an order of magnitude for some compounds) but have altered the composition as well, and some pollutants, such as ammonia and hydrogen cyanide, can be formed due to the controls (Baum et al., 2007).

Alternative automotive fuels

ICEs, both CI and SI, can be operated on non-traditional fuels. This is often done to lower emissions, although other reasons exist (e.g. as a renewable energy source). For example, SI engines sometimes operate on alcohols (methanol and ethanol), natural gas (primarily methane), or liquefied petroleum gas (largely propane). Diesel engines can be operated on a range of fuels as well, including natural gas and biodiesel.

SI engines using alcohols and natural gas tend to have simpler, although not necessarily less toxic, emissions compared with those using gasoline. Alcohols used are largely one- and two-carbon molecules and naturally have oxygen present, which can lead to lower CO emissions and much lower emissions of air toxics such as 1,3-butadiene, benzene, and PAHs. While often viewed as a clean-burning fuel, alcohols tend to form greater quantities of aldehydes with the same carbon number as the parent fuel. For example, ethanol use leads to increased emissions of acetaldehyde, and methanol use leads to larger quantities of formaldehyde being produced (NRC, 1996). Like conventionally fuelled vehicles, part of the emissions are due to lubricating oil.

Combustion of municipal or medical solid waste

Combustion is a widely used practice to deal with municipal solid waste (MSW) (trash), competing with landfilling. While it has the advantage of greatly reducing the volume of waste to be disposed of, it can lead to emissions of compounds viewed as potentially toxic. Three classes of compounds stand out: chlorinated organics (e.g. polychlorinated biphenyls [PCBs], dioxins, and furans), PAHs, and mercury.

MSW combustion is typically conducted at relatively lower temperatures and in less than optimal conditions with an inferior, more heterogeneous fuel than in utility boilers and automobiles. Even in controlled combustion with a relatively homogenous fuel, combustion is subject to widely varying conditions, leading to formation of undesirable products. The heterogeneity of MSW exacerbates

problems, including having areas of lower oxygen and temperatures, leading to incomplete combustion. MSW also contains a much wider range of compounds than virtually any other combustion fuel, basically because it comes from whatever may be thrown away. This includes items like batteries, cans, plastics, newsprint, biomass, used oil, paint, and so on. Many of these contain toxic metals such as mercury, lead, and chromium. During the combustion process, these metals can be released, either as a gas or as PM, while a good fraction can be removed as ash. MSW combustion was a dominant source of mercury, although controls are effective at removing this pollutant. A sizable fraction of MSW can contain chlorine and other halogens, which can add to the organic molecules to produce dioxins and dibenzofurans.

MSW combustion emissions can be controlled in a variety of ways. First, the fuel can be prepared to improve the combustion characteristics, for example pelletized. MSW that has potentially harmful compounds can be removed (e.g. waste with harmful metals such as lead and mercury). Combustion can be assisted by burning a higher quality fuel like natural gas to raise the temperature and obtain more complete MSW destruction. Post-combustion controls, such as scrubbers and fabric filters, have substantially lowered emissions.

Electricity generation

Coal is the dominant fossil fuel used for generating electricity and is the closest to being pure carbon. However, it still contains hydrogen and a range of other elements, including sulfur and nitrogen (possibly in relatively large amounts), chlorine, and metals such as iron, selenium, and mercury. The chlorine can react to form hydrochloric acid, the sulfur to form SO_2 and sulfuric acid, and the nitrogen to form NO_x, which is also formed from oxidation of the nitrogen in air. Coal-fired utilities remain one of the largest anthropogenic sources of both SO_2 and NO_x, both of which lead to the formation of acids in the atmosphere. Further, NO_x plays a critical role in driving the photochemical production of ozone and secondary particulates, which include nitrated PAHs and organic and inorganic acids.

Coal combustion is a major anthropogenic source of mercury to the atmosphere, along with MSW combustion (Seigneur et al., 2004). Methylmercury is toxic and bioaccumulates; levels in fish have become dangerously high. Much of the mercury emitted from power plants, however, is in the elemental, gaseous form, which is not assimilated directly by plants and animals. However, elemental mercury does slowly oxidize in the atmosphere and then deposits to the ground and surface waters, where it can enter the food chain. In addition, coal-fired utilities emit fly ash containing a variety of minerals and metals.

Controls on coal-fired utility boilers include filters (baghouses) (for controlling PM), scrubbers (SO_2, PM, mercury), electrostatic precipitators (PM), selective catalytic reduction (NO_x), burner modification (e.g. low NO_x burners), and fuel modification, including the use of cleaner coals, washing, and using alternative fossil fuels such as natural gas. Such controls have effectively reduced emissions by > 80% for NO_x and SO_2 and by > 99% for PM.

Because of environmental and economic concerns, natural gas has become increasingly popular for producing electricity, while the use of fuel oil is declining. Natural gas combustion is typically cleaner than coal combustion for a variety of reasons. The gas phase allows for more homogeneous combustion conditions, and the smaller molecules being burned with ample residence time and excess oxygen lead to almost complete combustion to CO_2 and water. Trace species (e.g. small amounts of sulfur, but virtually no minerals and other contaminants) and thermal fixation of nitrogen do lead to small amounts of air pollutant emissions. When used as the primary fuel, natural gas is usually applied in turbines. Combustion is typically conducted at high temperatures with a reasonably long residence time, leading to more complete combustion and lower air toxics emissions.

Industrial process combustion

Several industries use combustion for purposes such as producing heat and destroying undesirable compounds. An example that may do both is using cement kilns to destroy toxic waste such as PCBs. Cement kilns are used in the process of calcining cement, which requires high temperatures. The residence time during combustion is relatively long, so it was proposed to burn toxic organics, which have a heating value, along with traditional fuels, to destroy the undesirable compounds. While this does destroy almost all of the original organic material, there can be some slippage (typically < 0.01%) in addition to the products of incomplete combustion. Much of the time coal is used, leading to emissions similar to those of coal-fired power plants. Another fuel used by cement kilns is old tyres (or other waste with heating value), which can lead to somewhat higher levels of soot and PAHs, although the long residence time tends to minimize such emissions.

Use of industrial process boilers to provide heat and steam is also widespread. Emissions from such sources are fuel-specific, with coal, natural gas, and oil being the dominant fuels used. Emissions from industrial boilers will be similar to those from utility boilers using the same fuel, recognizing that the controls may not be as extensive since the source is smaller.

While combustion often is cited for increasing emissions, flaring has been used to reduce emissions of volatile organic compounds (VOCs), including toxic compounds such as benzene and 1,3-butadiene. While this approach is effective

at removing the parent VOC, it can lead to the production of lesser amounts of organic toxics, for example PAHs. Catalytic destruction is also used to help remove unwanted VOCs before emission from industrial facilities.

Residential coal combustion

While not widely used in residential applications in developed countries, coal is still used for heating and cooking in developing countries where it is a plentiful resource. In this case, the conditions are not as favourable to complete combustion as in typical industrial or utility facilities, and post-combustion controls will be minimal or non-existent. In such cases, emissions can be quite large and will include soot, char, ash, PAHs, and CO. The enclosed environments further lead to potentially very high exposures (Smith, 2002).

Biomass combustion

Burning modern fuel (usually biomass) occurs both intentionally (e.g. for heating, cooking, or land management) and unintentionally (forest fires). On a worldwide scale this process leads to more PM emissions (and likely more toxics) than does the combustion of fossil fuels, which is typically done under more controlled conditions. In developed countries, however, biomass combustion usually occurs in less densely populated areas and the resulting exposures are not as severe (unless one includes cigarette smoking, the major exposure to air toxics of all sources). However, biomass combustion is still a major contributor to PM in many urban areas (Schauer et al., 1996; Zheng et al., 2000, 2002, 2005) and is discussed in more detail in other chapters.

Anthropogenic fugitive combustion

Building fires can lead to the emissions of PCBs, for example from the formation of PAHs and soot during the low-temperature smouldering and burning of plastics and electrical wiring insulation. This occurred after the attack on the World Trade Center, where the smouldering wreckage led to exposure to air toxics (Pleil et al., 2004). Fires in scrap tyre stockpiles and areas with concentrated refuse catching fire can lead to emissions of toxics (including organic-laden PM) (Christian et al., 2010; Lemieux et al., 2004).

Meat cooking

While meat cooking is not often considered a major source of PM, Cass and co-workers (Kleeman et al., 1999; Zheng et al., 2002) have found surprisingly large quantities of carbonaceous PM in urban areas to be due to meat cooking. In this case, the fat from the cooking process can be volatilized and/or partially

combusted to form less-volatile compounds. The volatilized material then condenses back onto pre-existing particles. Compounds formed from meat cooking include PAHs.

Summary

Combustion is a ubiquitous process leading to environmental air toxics exposures and emissions of a wide range of species. Combustion-generated compounds can be either organic (e.g. aldehydes and PAHs) or inorganic (e.g. acids and metals such as mercury). In more developed countries, motor vehicle emissions (both on- and off-road) play an important role in exposure to air pollution, and key pollutants include PM (diesel and SI), benzene, 1,3-butadiene, aldehydes, and other organics, although levels are decreasing due to enhanced controls. Use of alternative fuels does not eliminate emissions of air toxics, although they will generate mixtures that differ from those of conventional fuels. In developing countries, indoor combustion of biomass or coal is a continuing source of concern, along with increasing exposures to automobile emissions as vehicle fleets grow.

Electricity generation tends to produce lower emissions of organic compounds as combustion is more complete. Power plants do emit PM (the amount largely depending on how well controlled the facility is), sulfur oxides, NO_x, and, of particular concern recently, mercury, although various controls have proven effective at reducing emissions. Historically, MSW combustion has also been one of the major sources of mercury and leads to the formation of halogenated organics such as dioxins and furans.

Control of air toxics emissions from combustion sources generally relies on improving combustion conditions and post-combustion controls, including scrubbers, filters, electrostatic precipitators, flaring (which can form other pollutants), and catalytic destruction.

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Chapter 5. Sources of air pollution: gasoline and diesel engines

Daniel S. Greenbaum

The combustion of gasoline and diesel fuel in vehicle engines produces emissions of several potentially harmful substances. These emissions are not solely the result of the combustion process, nor do they come only from the tailpipe of the vehicle; rather, they result from a combination of the engine design and the fuel characteristics. Also apparent is that evaporative emissions from refuelling, spills onto heated engine parts, and so on can equal emissions from the tailpipe. In addition, analyses have indicated that a significant source of emissions from vehicles is abrasion and wear of tyres and metallic components, resulting in emissions of a variety of metals and carbon compounds.

The primary emissions from motor vehicles come in two predominant forms: major gaseous and particulate air pollutants, which can be found in relatively high amounts in the atmosphere, and so-called air toxics, which usually are found in lower amounts in the atmosphere but can have important health implications. The gaseous and particulate pollutants to which motor vehicles contribute include carbon monoxide (CO), ozone (through its atmospheric precursors volatile organic compounds and nitrogen oxides [NO_x]), fine particulate matter PM_{10} and $PM_{2.5}$ (particles < 10 µm and < 2.5 µm in aerodynamic diameter, respectively), and nitrogen dioxide. The air toxics emitted from motor vehicles include aldehydes (acetaldehyde, formaldehyde, and others), benzene, 1,3-butadiene, a large number of substances identified as polycyclic organic matter (including polycyclic aromatic hydrocarbons [PAHs]), and metals.

The various emissions from motor vehicles are also released by other sources, such as industrial processes, electric power generation, and home heating. As a result, the contributions of motor vehicle emissions to ambient levels of major air pollutants vary among pollutants (Table 5.1). For most pollutants, motor vehicles contribute 25–40% of the ambient levels, although in a few cases (e.g. CO, ultrafine particles [$PM_{0.1}$], 1,3-butadiene) motor vehicle contributions are noticeably higher.

Table 5.1. Estimated average contributions of motor vehicle emissions to ambient levels of major air pollutants in developed countries

Pollutant	Contribution(%)	Reference
Carbon monoxide	~90	EPA (2000)
$PM_{2.5}$	~25–30	DEFRA (2012)
Nitrogen oxides	~40	EPA (2000)
Volatile organic compounds	~35	EPA (2000)
Average air toxics	~21	EPA (1999)
Urban air toxics	~42	EPA (1999)

Location and season play a role in the amount of motor vehicle emissions. For example, in the USA the estimated contribution of vehicles to ambient PM can vary substantially according to region and depends on the relative contributions of other sources such as coal-burning utilities and their contribution of sulfates (Figure 5.1). Contributions also differ between the USA and Europe (e.g. the United Kingdom; Figure 5.2). In developing countries where biomass burning is often a substantial contributor and overall traffic contributes 20–35%, the contribution of vehicle emissions also varies (Figure 5.3). Seasonal variation can affect the contributions, as illustrated in Figure 5.4 in the case of three Indian cities.

Figure 5.1. Sources of $PM_{2.5}$ in typical western and eastern cities in the USA. Reproduced from EPA (2004).

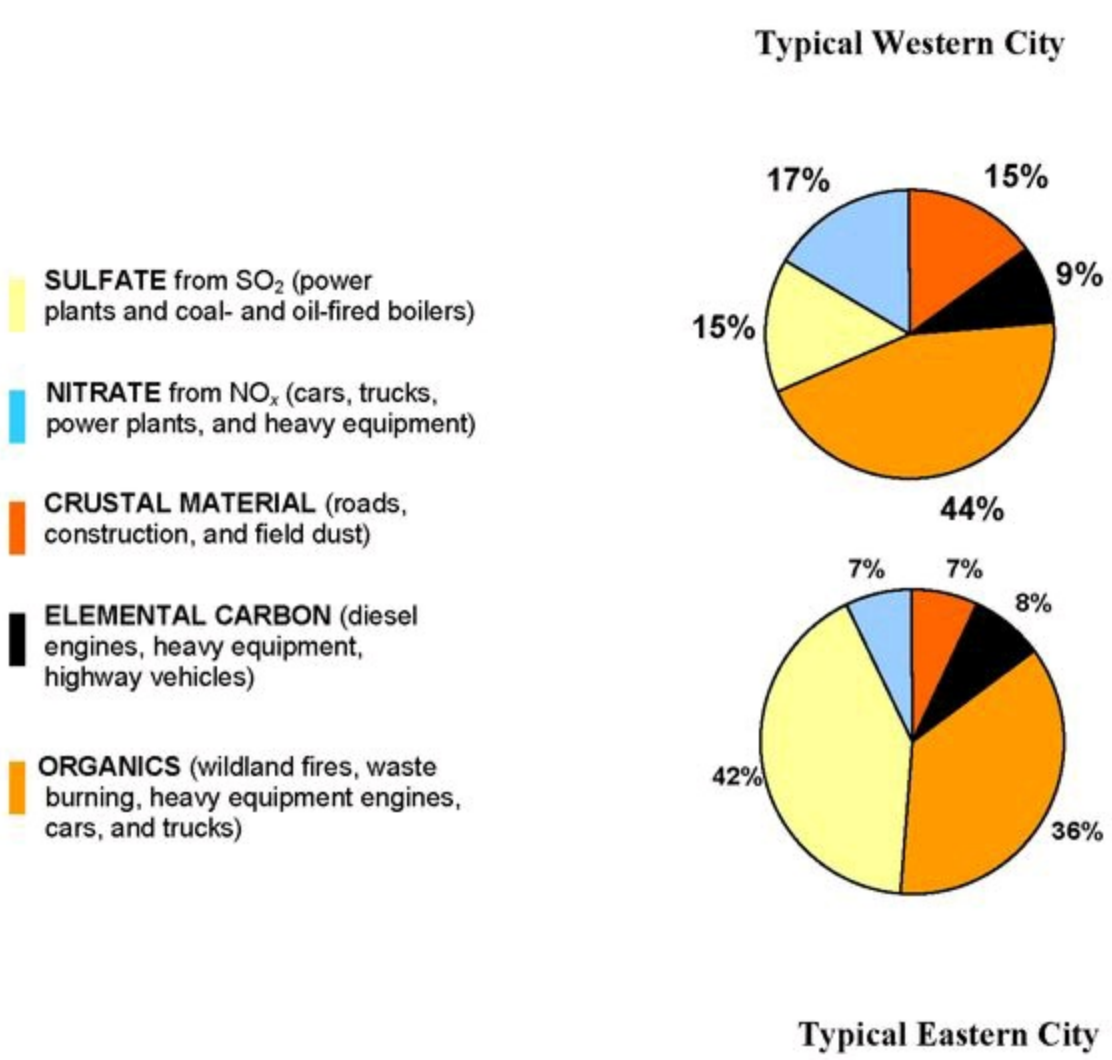


Figure 5.2. The on-road and nonroad contribution to $PM_{2.5}$ in the United Kingdom. Adapted from DEFRA (2012).

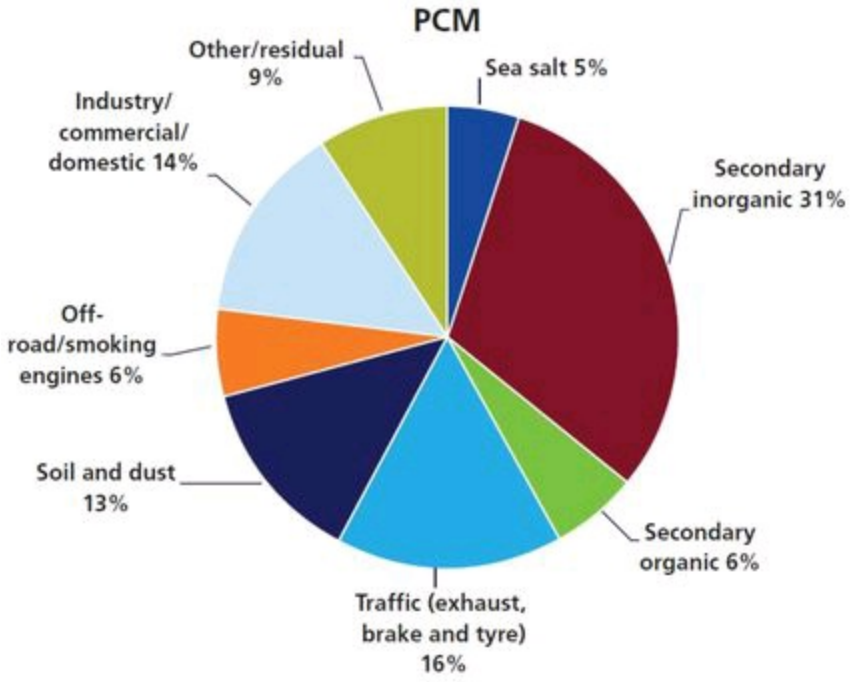


Figure 5.3. Motor vehicles can contribute 25–35% of particulate matter in Asian countries. Source: HEI (2010a); reproduced with permission from the Health Effects Institute.

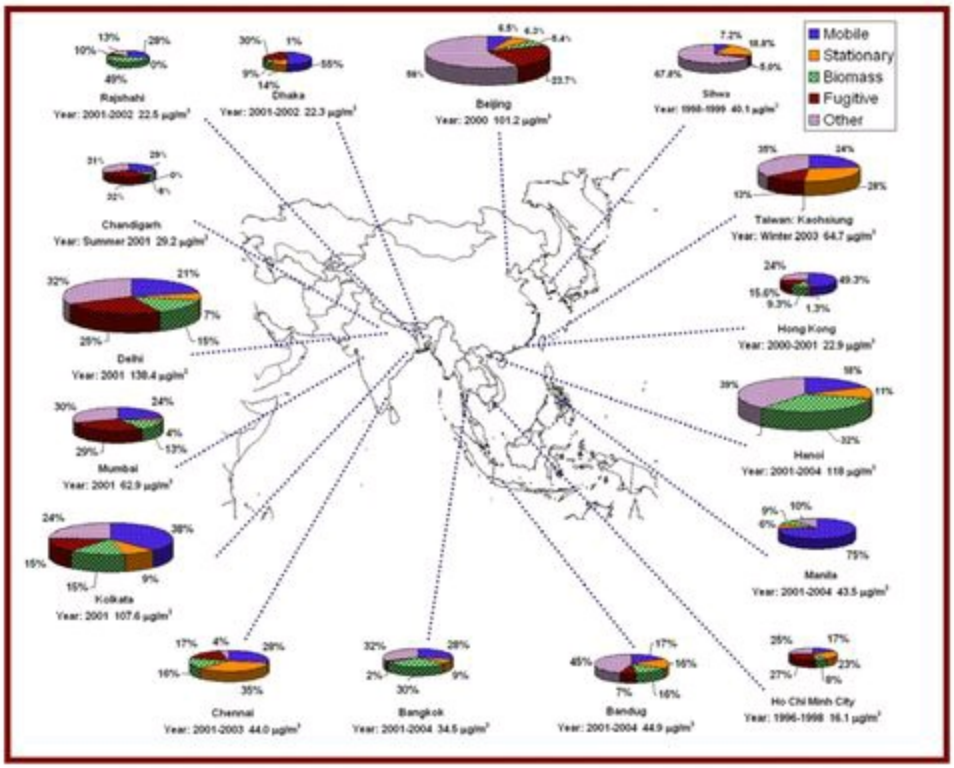
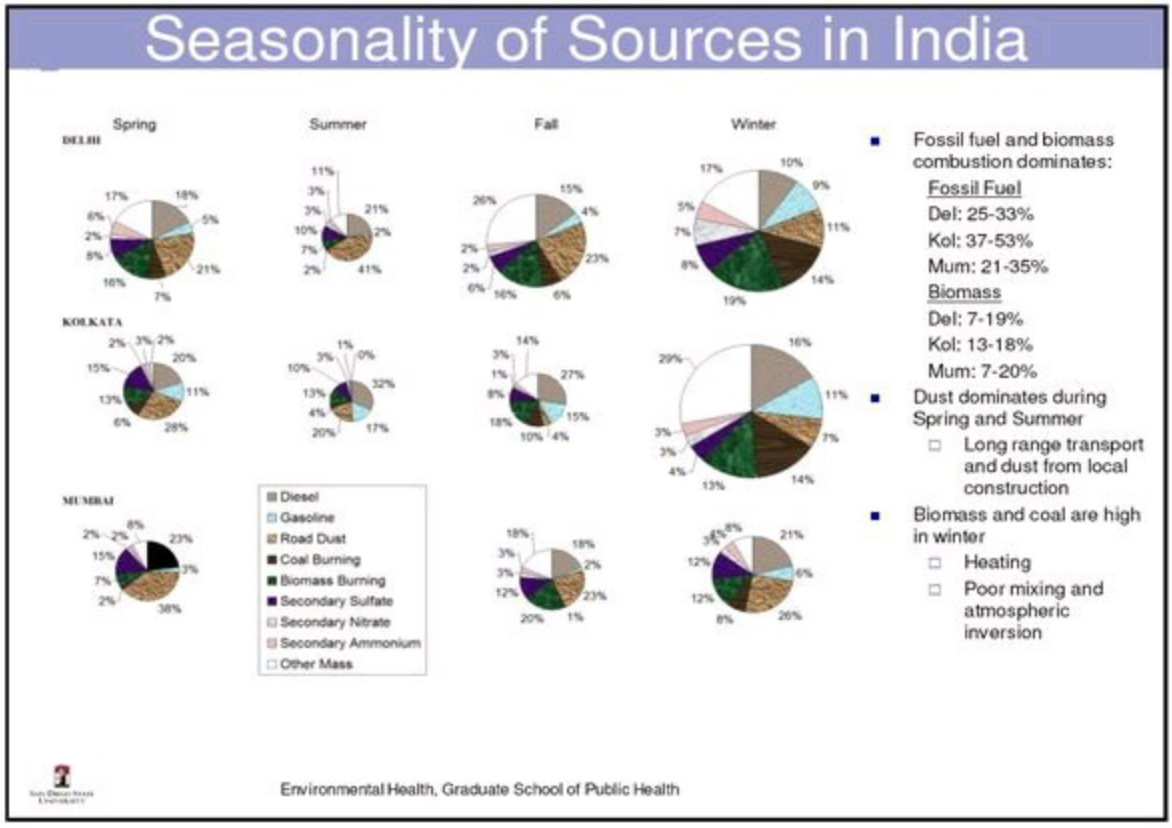


Figure 5.4. Seasonal variation in air pollution sources in India. Adapted from Chowdhury et al. (2007).

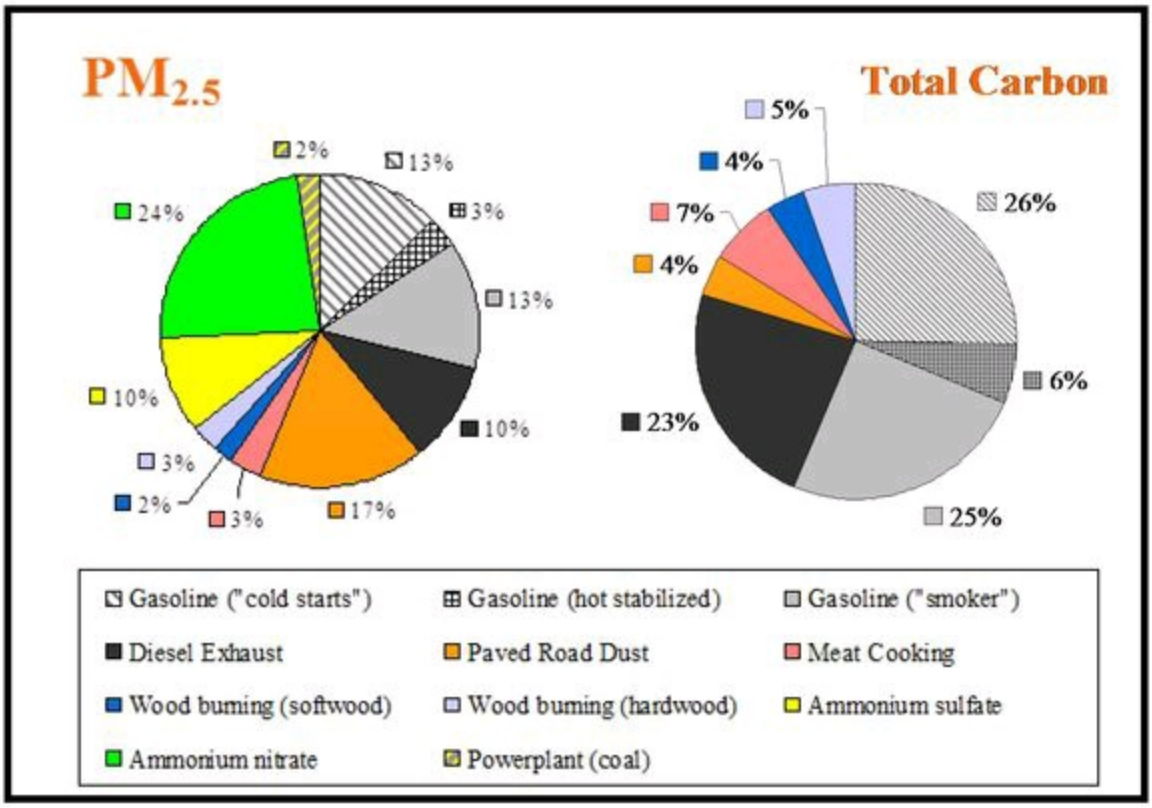


Source: Adapted from Chowdhury et al. (2007).

The relative contributions of diesel and gasoline vehicles can also differ depending on location and the method of source apportionment analysis. Figure 5.5, for example, illustrates a source apportionment for Denver, Colorado, USA, which suggests that gasoline vehicles, especially older, poorly maintained

vehicles, are a larger contributor to levels of ambient particles than are diesel vehicles. Other analyses (Schauer et al., 1996), however, have found that in Los Angeles, California, USA, close to 90% of the vehicle contribution to particles comes from diesel.

Figure 5.5. $PM_{2.5}$ and total carbon source contribution estimates in Denver, Colorado, USA. Source: Northern Front Range Air Quality Study (1998); reproduced with permission from Colorado State University and the Desert Research Institute.



Exposure

While in general motor vehicles contribute a significant portion, although not the majority, of most air pollutants, there are certain circumstances in which motor vehicles can contribute a substantially higher amount to personal exposure. In particular, in urban centres along roadsides and especially in urban street canyons in crowded business districts, mobile source contributions can contribute 2–10 times as much as in general background situations. (While this is true in general, there is one instance–the case of ozone–where urban levels are generally lower than those found outside cities, the result of scavenging of the ambient ozone by high levels of ambient NO_x.) For example, Table 5.2 presents data from the Los Angeles metropolitan area that suggest a 3-fold difference in vehicle contributions to $PM_{2.5}$ levels across the basin. These

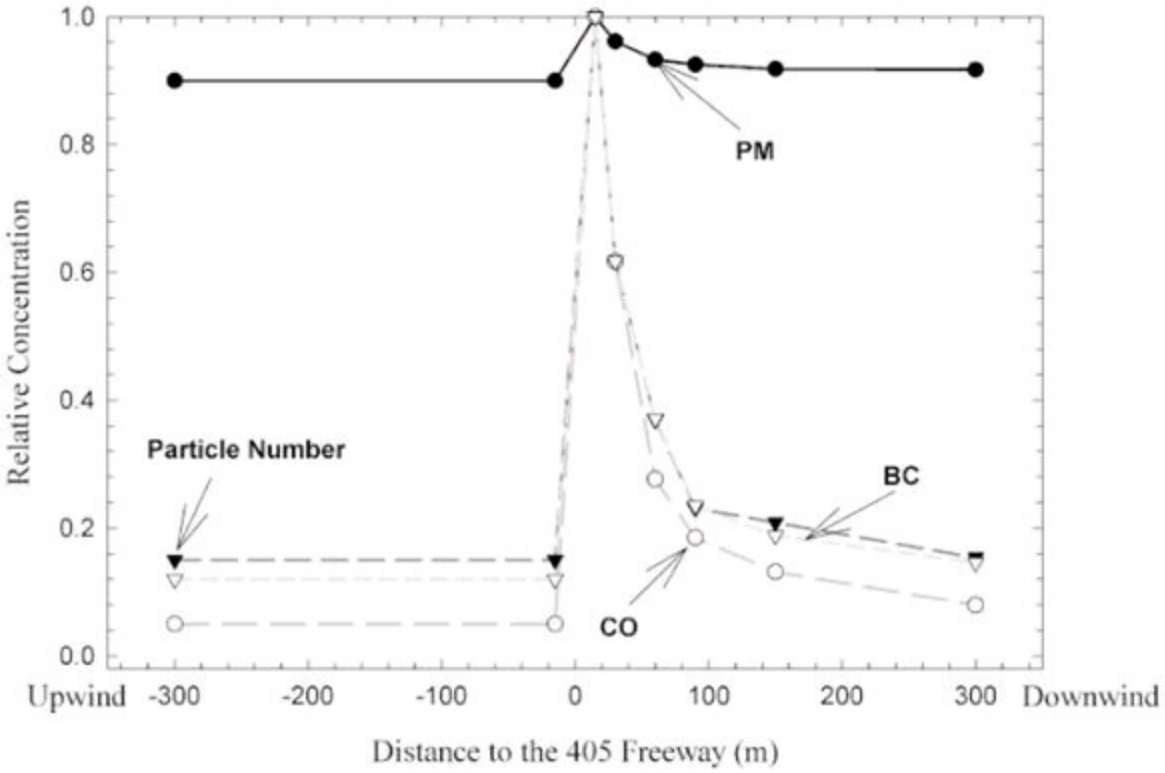
exposures can be especially high in microenvironments, such as roadside locations where concentrations of certain pollutants (e.g. CO and ultrafine particles) can be elevated because of fresh emissions (Figure 5.6). A comprehensive review of the literature on traffic exposure identified the area within 300–500 m of a major road as the most affected by traffic emissions (HEI, 2010b).

Table 5.2. Contribution of motor vehicle primary emissions to ambient $PM_{2.5}$ in the Los Angeles, California, USA, metropolitan area

Location	Diesel contribution (%)	Gasoline contribution (%)	Total vehicle contribution (%)
Pasadena	18.8	5.7	24.5
Downtown Los Angeles	35.7	6.5	42.2
West Los Angeles	18.0	5.7	23.7
Rubidoux	12.8	0.7	13.5

Compiled from Schauer et al. (1996).

Figure 5.6. Proximity to traffic (60, 90, and 300 m). While $PM_{2.5}$ varies very little (5–10%), ultrafine particles, black carbon (BC), and carbon monoxide (CO) decrease within 100 m to < 20%. Source: Zhu et al. (2002); reproduced with permission from Taylor & Francis.



Exposure to high concentrations of these pollutants can have important acute and chronic health implications, particularly for individuals who live long-term in areas with congested traffic. This exposure pattern is of special concern in developing countries where large numbers of people from the lowest socioeconomic strata live on or near roadsides in housing that offers little filtering of outside air.

Trends and the future

A series of measures have been implemented to reduce components of gasoline and diesel fuels that can lead directly or indirectly to harmful health effects caused by vehicle emissions. These actions include the elimination of lead from fuel in much of the world, substantial reductions in benzene content (resulting, for example, in a nearly 50% reduction in ambient levels in the USA; Figure 5.7), and efforts to reduce sulfur in fuel, which can substantially reduce sulfur dioxide (SO_2) ambient levels (e.g. Hong Kong Special Administrative Region; Figure 5.8). In addition to direct reductions of emissions, fuel changes can also facilitate the introduction of advanced emission control technologies (e.g. particle filters).

Figure 5.7. Reductions in ambient benzene levels in the USA. Reproduced from EPA (2002).

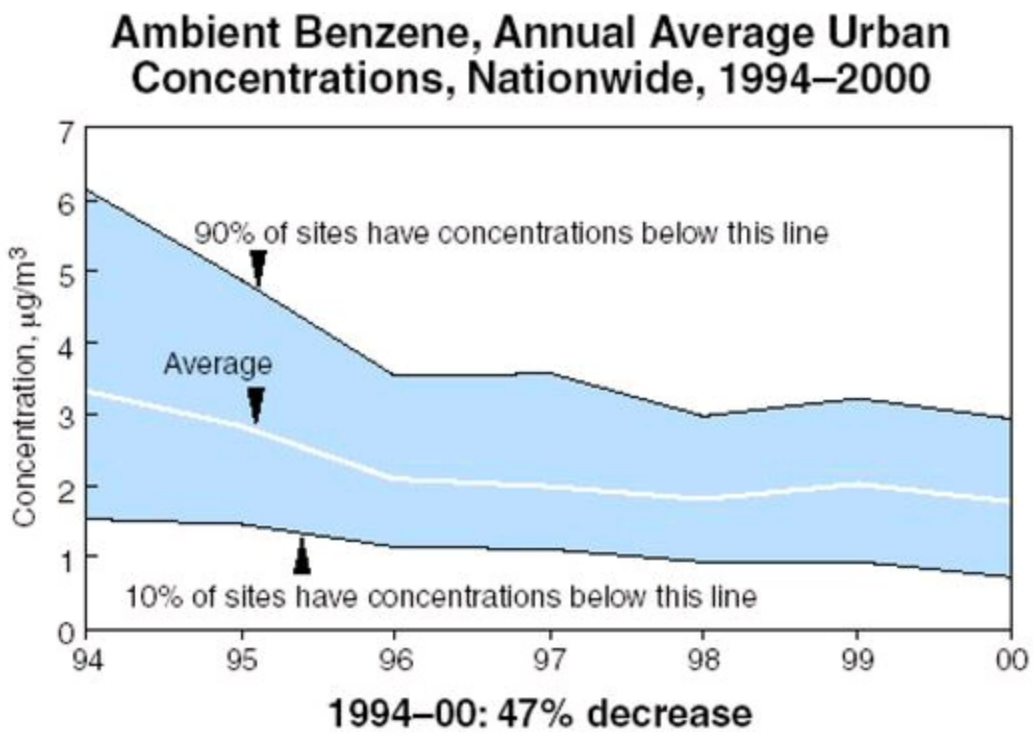
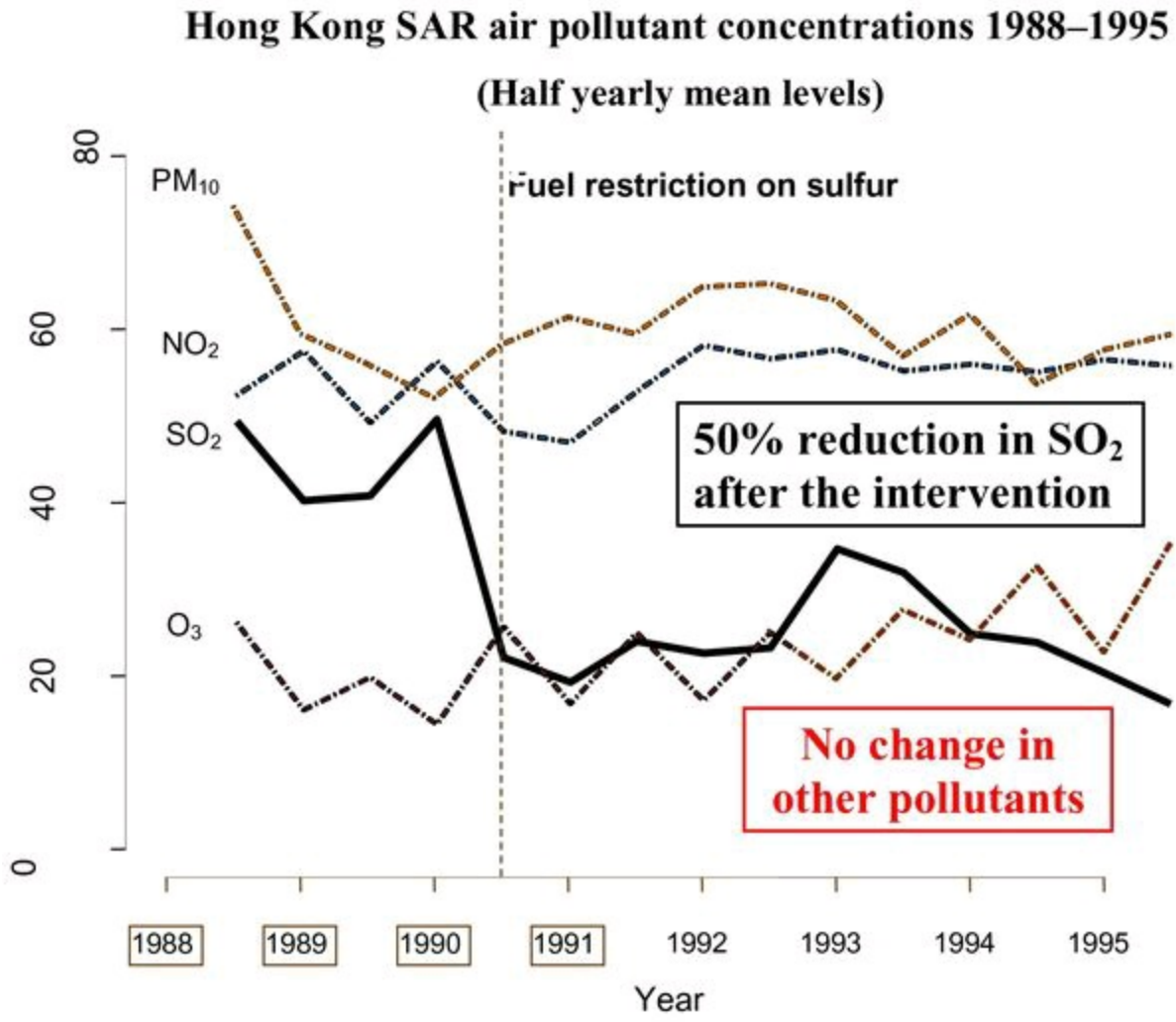


Figure 5.8. Reduction in ambient SO_2 levels in the Hong Kong Special Administrative Region (SAR) after required reduction in fuel sulfur levels. Source: Hedley et al. (2002); adapted with permission from Elsevier.



In 1999, the United States Environmental Protection Agency took steps to

further improve fuel formulation and reduce emissions of light-duty vehicles and, in 2000 and 2004, to impose stringent new fuel and emissions standards for on-road and nonroad heavy-duty vehicles (Figure 5.9). Earlier such actions have resulted in substantial reductions in on-road emissions from diesel vehicles, for instance (Figure 5.10). These new efforts are projected to provide considerable reductions in emissions in coming decades as new model engines are phased into the fleet (Figure 5.11). Comprehensive testing of the newest diesel technology (Figure 5.12) has demonstrated a > 90% reduction in PM emissions (Khalek et al., 2011). However, in the USA, the wide-ranging benefits of the newest standards are not expected to be realized until 2030. Figure 5.9 also illustrates that the European Union and Japan are on a similar path, which is expected to substantially reduce emissions over the 20 years beginning in 2015. Developing countries, especially in Asia and Latin America, have also adopted earlier versions of United States or European vehicle emissions and fuel standards, and, in some cases, are progressively instituting the later, more stringent stages of those rules (Figure 5.13).

Figure 5.9. Transition in USA, European, and Japanese rules for heavy-duty diesel engines, 1975–2010. Source: Johnson (2009); adapted with permission from SAE International.

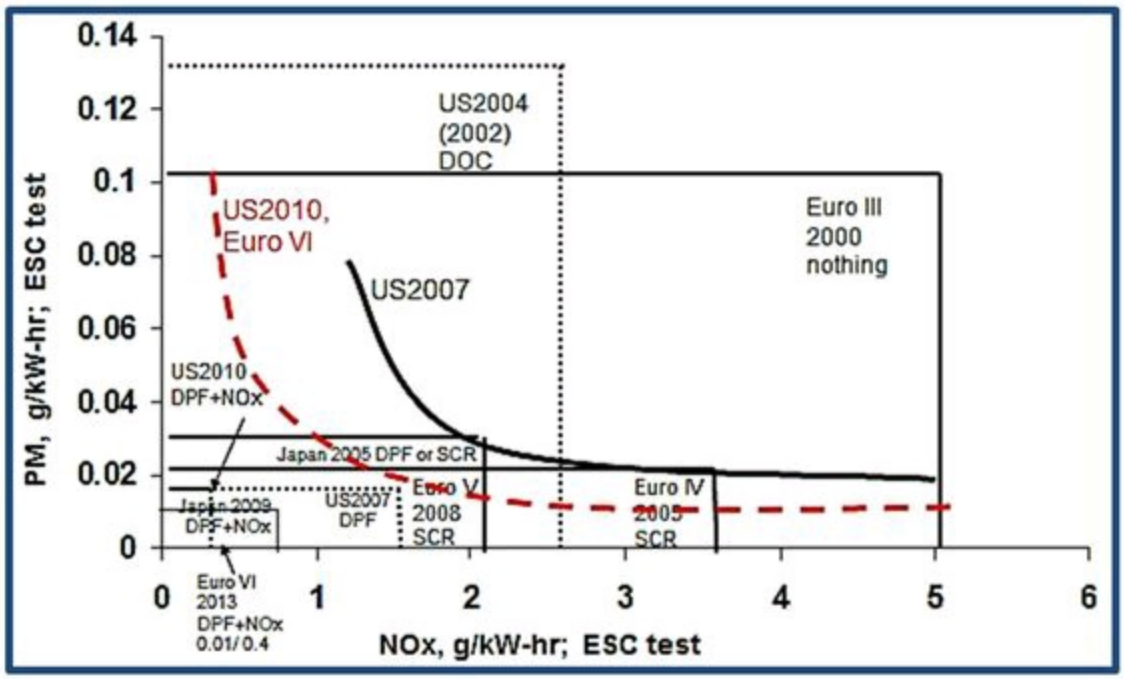


Figure 5.10. On-road diesel reductions in the Tuscarora Tunnel, Pennsylvania, USA, 1975–2000. Source: HEI (2002); reproduced with permission from the Health Effects Institute.

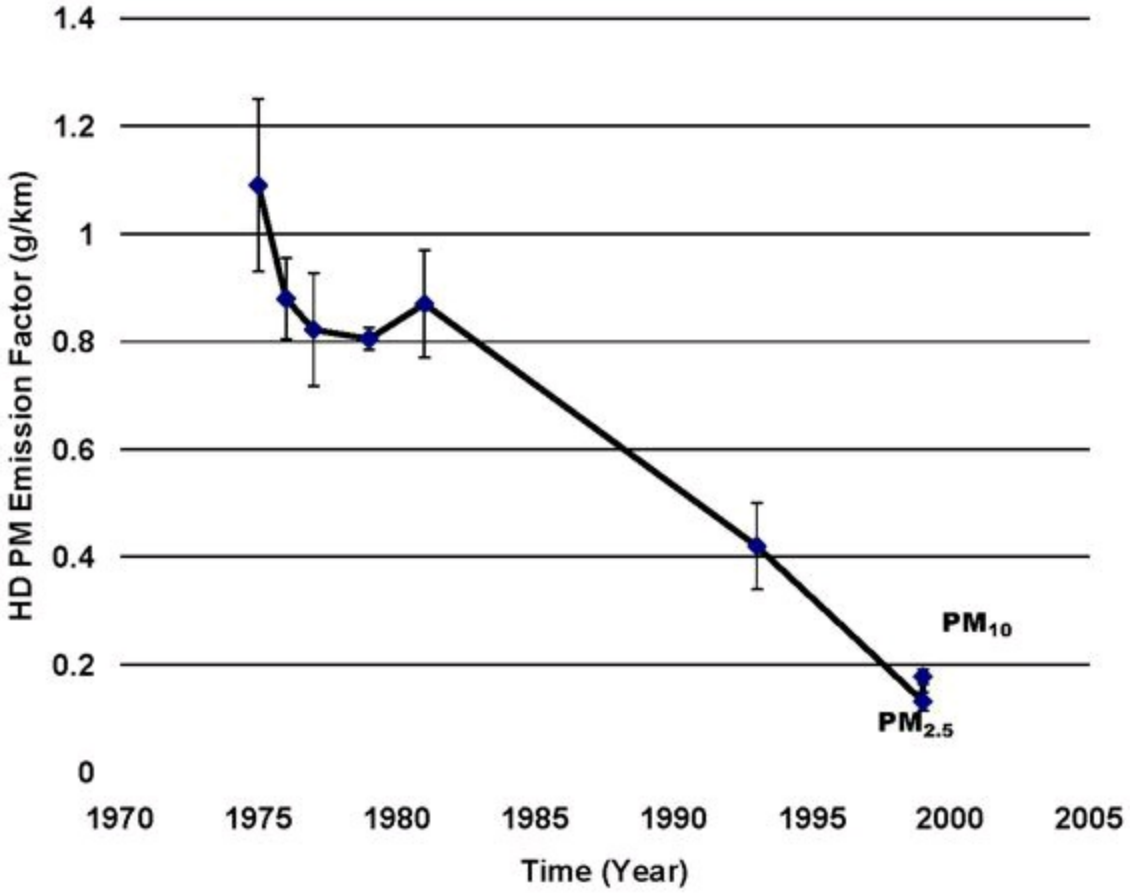


Figure 5.11. Projected reductions in diesel emissions of $PM_{2.5}$ from the United States Environmental Protection Agency's on-road and nonroad diesel rules. C1, commercial marine engines < 5 liters/cylinder; C2, commercial marine engines 5–30 liters/cylinder; C3, commercial marine engines > 30 liters/cylinder. Reproduced from EPA (2012).

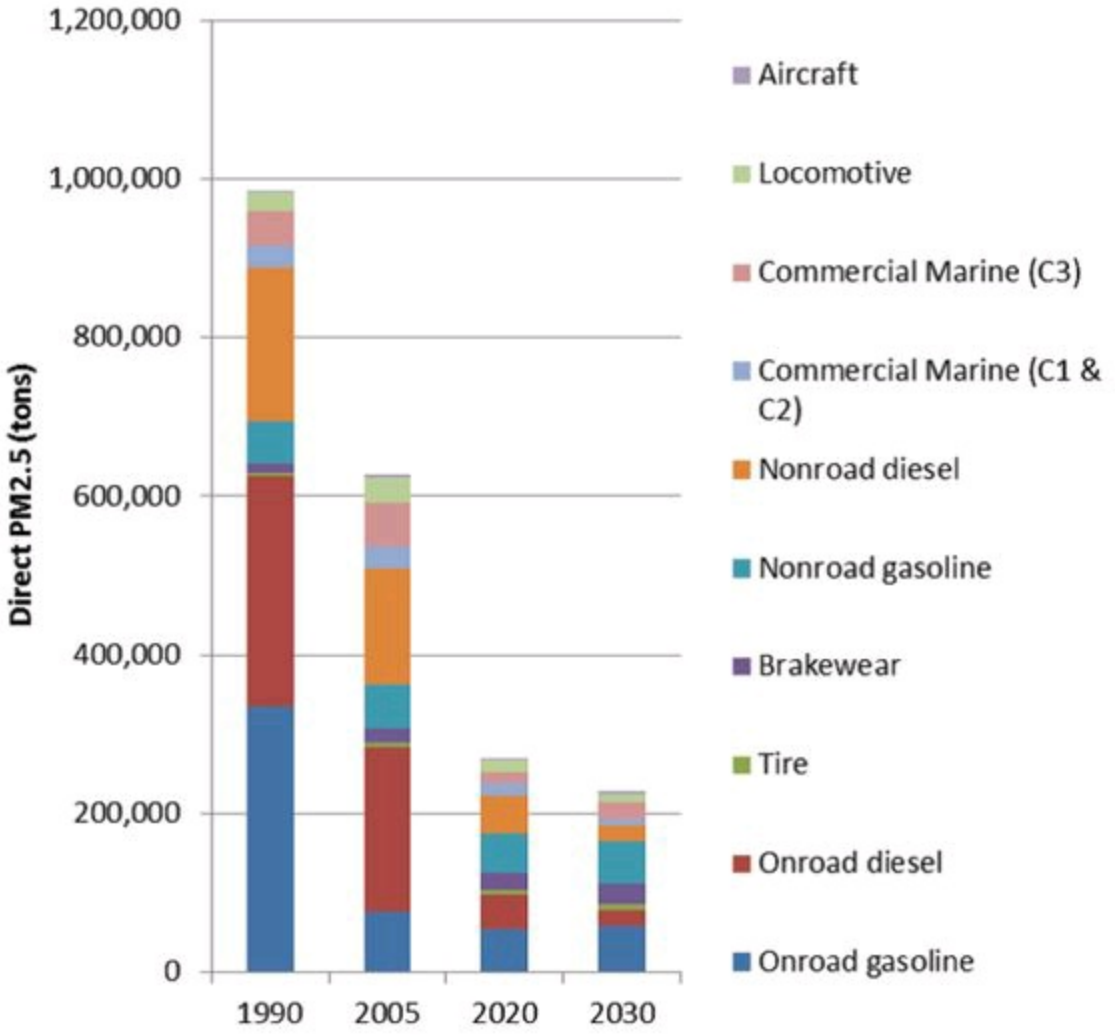


Figure 5.12. Substantial reductions in the mass and number of particles emitted from 2007-compliant heavy-duty diesel engines. Compiled from Khalek et al. (2011).

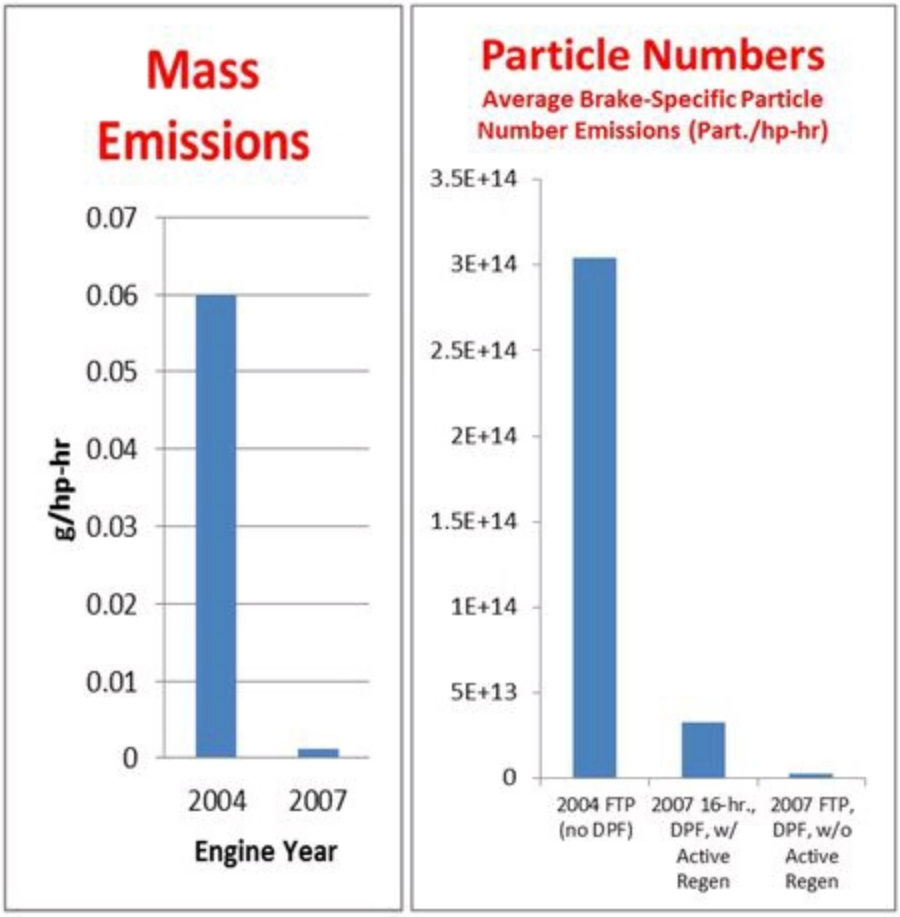
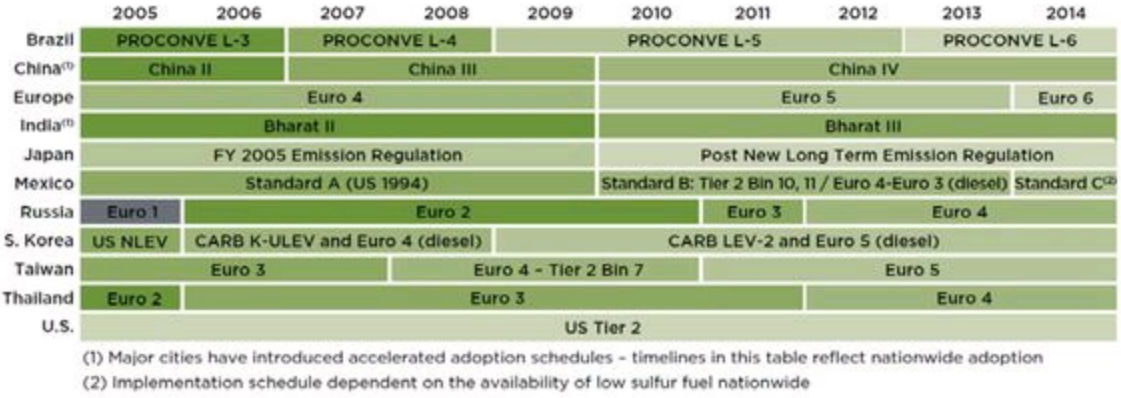


Figure 5.13. Current and planned requirements for light-duty vehicle emission standards in Asia and worldwide. Reproduced from Sanchez et al. (2012).



This progress in standards for new vehicles, however, is only possible in countries where the quality of fuel has been improved enough to implement the cleanest technologies (e.g. ultra-low-sulfur diesel). In most developing countries, that progress has slowed significantly as refineries, often government-owned, struggle with the costs of substantially reducing sulfur. This will inevitably slow the introduction of the newest, cleanest technologies (now available in the USA and soon to be available in Europe) and will result in continued and growing use of older diesel and gasoline technologies and the accompanying significant exposures.

In addition to standards for fuels and vehicle emissions using existing

technologies, increasing attention has focused on use of alternative fuels, such as ethanol and other plant sources (e.g. biodiesel), natural gas, alternative diesel fuels converting gas to liquid (e.g. the Fischer–Tropsch process), and hydrogen. Also, advanced and new vehicle technologies, which include natural gas vehicles, electric and electric hybrid vehicles, and fuel cell vehicles, are in development or beginning to appear on the market.

While these fuels and technologies may have certain air quality advantages, they have not all been subjected to rigorous assessment of their emissions benefits. For example, claims of emissions benefits for biodiesel have thus far exceeded the supporting data, and new health-related questions are emerging (e.g. the use of methanol to produce the hydrogen to power fuel cells). In emissions characterization tests of advanced diesel and natural gas bus technologies, conducted by the California Air Resources Board, the newest diesel technologies have appeared to have emissions characteristics that are comparable to, and in some cases better than, those of natural gas buses (Holmen and Ayala, 2002). These new fuels and technologies are also subject to the challenges of introducing a substantially different commodity. With a few exceptions–hybrids, natural gas (in urban areas), and ethanol–these new fuels and technologies are not currently in widespread use and are likely to take a long time to develop.

Even as emissions from conventional technologies have declined and more efficient technologies are being developed, continued growth in travel is expected to offset a portion of these reductions (Greenbaum, 1997). As a result, reducing emissions will remain a priority and will likely come about in three ways:

1. Financing, economic incentives, and some regulatory efforts to accelerate replacement and/or retrofitting of existing fleets of vehicles, especially older diesel vehicles;
2. Continued tightening of fuel and emissions standards for petrol and diesel vehicles, especially in developing countries; and
3. Policies to discourage growth in personal automobile use–potentially the most important and challenging future direction. Recent efforts in this area have included the London Congestion Charging Scheme, alternate day driving plans in European and Latin American cities, development of rapid transit systems (e.g. in Bangkok and Delhi), and efforts at growth planning and management to minimize vehicle travel (e.g. Portland, Oregon, USA, and several European cities).

In conclusion, the emissions of a variety of pollutants from vehicles account for approximately 20–40% of the ambient levels of air pollution (depending on the pollutant), with higher contributions in some microenvironments. These pollutants have been demonstrated to have a measurable negative effect on public health. As a result, the long-term trend towards reducing emissions from

motor vehicles is likely to continue, albeit at a slower pace in developing countries where fuel quality is a barrier to implementing the cleanest technologies now available elsewhere. In addition, continued growth in vehicle travel is likely to offset a portion of the expected reductions, suggesting the need for continued research on viable alternatives and strategies to reduce the emissions and their impact on public health.

Daniel S. Greenbaum is the president of the Health Effects Institute (HEI), which conducts research worldwide on the health effects of air pollution. HEI's core funding comes in equal part from the United States Environmental Protection Agency and the manufacturers of motor vehicles for sale in the USA.

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Chapter 6. Household use of biomass fuels

Isabelle Romieu and Astrid Schilmann

Household use of solid fuels (biomass fuels and coal) is the most widespread source of indoor air pollution worldwide; solid fuels are used extensively for cooking and home heating in developing countries, especially in rural areas (Perez-Padilla et al., 2010). Biomass fuel usually refers to solid fuels that are derived from plants and animals and that are intentionally burned by humans for household energy. The solid fuels primarily include wood, but also agricultural residue, animal waste (dung), charcoal, and even leaves and grass. These fuels are often collected from the local environment in rural areas and purchased through markets in urban areas. Traditional biomass represents 10% of the world's primary energy use, with almost 2.7 billion people worldwide using biomass fuels for their household energy needs. By 2030, the population projected to use biomass will be 2.8 billion, indicating that the use of solid fuels is anticipated to remain relatively constant in the future (IEA, 2010). The percentage of the population relying on household use of solid fuels for cooking varies significantly among countries (urban and rural areas) and regions. Recent estimates based on national surveys representing 85% of the world's population have shown a decline from 62% to 41% between 1980 and 2010. This decline occurred in all regions, with a slower decline in sub-Saharan Africa. Africa and South-East Asia have the highest proportion of households using solid fuels, with 77% and 61%, respectively. In the Western Pacific and Mediterranean regions, the proportion of use is estimated to 46% and 35%, respectively. (Bonjour et al., 2013). In Latin America and the Caribbean, 16% of households use solid fuels, with a large variation between countries. For example, in Guatemala 62% of the population uses solid fuels, with 88% in rural areas and 29% in urban areas, whereas in Mexico 15% of the population uses solid fuels, with 45% in rural areas and < 5% in urban areas. (WHO, 2012).

In the majority of industrialized countries, solid fuel use falls below the 5% mark. Greater use of solid fuels is associated with poverty in countries, in communities within a country, and in households within a community (Perez-Padilla et al., 2010; Lim and Seow, 2012).

The World Health Organization (WHO) identified indoor smoke from combustion of solid fuels as one of the top 10 risks for worldwide burden of disease, accounting for 2.7% of the global burden of disease and 2 million premature deaths annually from acute lower respiratory infections, chronic obstructive pulmonary disease, and lung cancer (for coal smoke only), mainly occurring in developing countries (WHO, 2009; Smith et al., 2004).

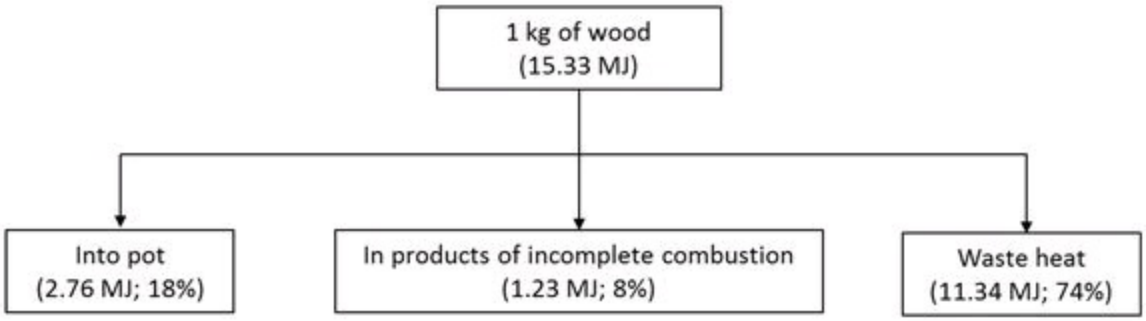
In this review, we will briefly address the component of exposure to indoor

smoke from burning biomass fuel, the mechanisms of carcinogenicity, and the epidemiological evidence on the relationship of biomass fuel to cancer.

Indoor smoke from burning biomass fuel

Cooking and heating with biomass fuels on open fires or with traditional stoves results in high levels of health-damaging pollutants. Combustion of biomass fuel in households often takes place in simple, poorly designed and maintained stoves with no chimney for removing emissions and with poor ventilation. Biomass combustion is typically inefficient because it is generally difficult to pre-mix solid fuels sufficiently with air to ensure complete combustion in simple, small-scale devices such as those traditionally used for household needs (Naeher et al., 2007). Even in households with chimneys, heavily polluting biomass fuel stoves can produce significant local outdoor pollution. This is particularly true in dense urban slums, where such neighbourhood pollution can be much higher than levels of average urban air pollution (Holdren and Smith, 2000) . Figure 6.1 shows the energy flow of a typical wood-fired cooking stove, in which a large fraction of the fuel energy is lost because of low combustion efficiency.

Figure 6.1. Energy flow in a typical wood-fired cooking stove. MJ, megajoules. Source: Holdren and Smith (2000); reproduced with permission from the United Nations Development Programme.



Although most biomass fuels are intrinsically free of contaminants, a substantial fraction of the fuel is converted to products of incomplete combustion. The smoke from burning biomass fuel contains thousands of chemicals, many of which have documented adverse health effects, including irritant, inflammatory, and carcinogenic properties. Few studies have been conducted to characterize detailed chemical speciation for biomass stoves in developing countries. The composition of the smoke varies with even minor changes in fuel quality, configuration of the cooking stove, or characteristics of the combustion. Although emission factors for specific compounds have been reported by different investigators, it is difficult to compare them as many of the reports are semiquantitative and the analytical methods used were not always

validated for each analysis. Furthermore, variable combustion conditions (fuel type, moisture content, combustion device) were used and emission factors were reported in a variety of units (Naeher et al., 2007). Some illustrative compounds of the different groups of pollutants generally present in the smoke are listed in Table 6.1.

Table 6.1. Pollutants present in biomass smoke

Group	Pollutants[a]	Emission rate (g/kg of wood burned)
Criteria pollutants	Inhalable particles PM_{10}	
	Fine particles $PM_{2.5}$	1.6–9.5
	Carbon monoxide Carbon monoxide	5.87-6.92 5.87–6.92
	Nitrogen oxides	1.16–2.78
Respiratory irritants	Phenols	
	Cresols	
	Acrolein	
Carcinogenic organic compounds	Acetaldehyde (IARC Group 2B)	0.041–0.371
	Benzene (IARC Group 1)	0.264–0.629
	Styrene (IARC Group 2B)	
	Formaldehyde HCHO (IARC Group 1)	0.042–0.261
	1,3-Butadiene (IARC Group 1)	0.0008–0.001
	Benzo[a]pyrene (IARC Group 1)	0.0004–0.0007

Polycyclic aromatic hydrocarbons	Benz[a]anthracene (IARC Group 2B)	0.0006–0.0008
	Dibenz[a,h]anthracene (IARC Group 2A)	0.0002–0.0006
	Chrysene (IARC Group 2B)	
	Pyrene	
	Fluorene	
	Phenanthrene	
	Naphthalene (IARC Group 2B)	0.004–0.039

[a] IARC Groups: Group 1, carcinogenic to humans; Group 2A, probably carcinogenic to humans; Group 2B, possibly carcinogenic to humans; Group 3, not classifiable as to its carcinogenicity to humans; Group 4, probably not carcinogenic to humans.

Adapted from Naeher et al. (2007); IARC (2010); Zhang et al. (2000).

Particles emitted from biomass combustion are fine and ultrafine in size (< 1 µm); some larger particles can result from resuspension of ash and debris. Particulate matter (PM) small in size is most damaging to health. The composition of the PM varies with the specific fuel being burned and with the combustion conditions, but it generally consists of elemental carbon, levoglucosan, and hundreds of distinct organic compounds. The measured range of PM concentrations has been quite wide, starting with tens of µg/m^3 and reaching into the hundreds or even thousands of µg/m^3 for peak exposures during cooking. Fine particulate exposure measurement has been proposed as the best single indicator of the health impacts of most combustion sources (Naeher et al., 2007). Carbon monoxide is the single most important contaminant emitted during combustion of wood (Viau et al., 2000). Both the International Agency for Research on Cancer (IARC) Monograph Volume 95 (IARC, 2010) and Naeher et al. (2007) present summaries of indoor air quality studies reporting household pollution levels.

Burning of biomass fuel is a major source of volatile organic compounds, some of which are known for their carcinogenic effects, as listed in Table 6.1. Table 6.2 shows the measured levels of some of these pollutants compared with the WHO indoor air quality guidelines (WHO, 2010). Another approach for exposure

assessment is the measurement of biological indicators or exposure biomarkers. Levels of biomarkers represent the absorbed dose of a chemical, integrated across all microenvironments and routes of exposure. Some biomarkers of exposure have been evaluated as metrics of biomass smoke exposures; for example, urinary polycyclic aromatic hydrocarbon (PAH) metabolites (Viau et al., 2000; Riojas-Rodriguez et al., 2011) and the benzene metabolite trans,trans-muconic acid (Roychoudhury et al., 2012).

Table 6.2. Measured indoor concentrations of organic pollutants present in biomass smoke

Study location and population	Benzene (μg/m^3)	Formaldehyde (μg/m^3)	Benzo[*a*]pyrene (ng/m^3)	Naphthalene (μg/m^3)
WHO indoor air quality guidelines (WHO, 2010)	1.7 annual average	100 short-term (30 minute)	0.12 annual average	10 annual average
Bangladesh (Khalequzzaman *et al.*, 2010), 42 urban households using biomass fuel, 24 hour kitchen monitoring	GM winter 54.2 GM summer 31.4	GM winter 9.9 GM summer 19.1		
India (Sinha *et al.*, 2006), 55 rural households, monitored during cooking hours	Kitchen with ventilation 31.2 Kitchen without ventilation 45.0			
Sweden (Gustafson *et al.*, 2007), 14 households, wood burning for space heating, 24 hour indoor monitoring	Median 2.6	Median 26		
Burundi (Viau *et al.*, 2000), 16 rural homes, 8–12 hour indoor monitoring			Mean 70	Mean 28.7 Other low-weight PAHs Fluorene mean 8.6 Phenanthrene mean 3.4

GM, geometric mean.

PAHs are important chemical components of combustion emissions. The smaller PAHs with 2 to 4 rings are volatile and are found in the gas phase to a higher degree than the 5- to 7-ring PAHs, which occur mainly or entirely as particles. Individual PAHs and specific PAH mixtures have been classified as carcinogenic by IARC. Benzo[a]pyrene (B[a]P), the most widely investigated PAH, has been classified as carcinogenic to humans (IARC Group 1). The lung

cancer risk from inhalation exposure to a PAH mixture can be estimated by summarizing the individual PAH concentrations and taking into account the toxic equivalency factors denoting the cancer potency relative to the cancer potency of B[a]P (Boström et al., 2002). As summarized in IARC Monograph Volume 95, the concentration of PAHs in wood smoke emissions is generally lower than that for coal emissions. Other components of wood smoke may also be important for the observed health effects and a potential area for future research (Reid et al., 2012).

Biomass fuel smoke can contaminate more than only the indoor air; it may also settle on the walls, floors, clothing, and food. PAHs can be absorbed through the respiratory tract, gastrointestinal tract (diet is the main route of exposure to PAHs in the general population), and skin. Most studies to date have not considered all routes of exposure (IARC, 2010; Reid et al., 2012).

Mechanisms of carcinogenesis

The main compounds of interest in biomass fuel smoke with regard to carcinogenicity are PM and PAHs. Fine particles are deposited in the central and peripheral airways, where they may exert toxic effects. When the inhaled concentration of PM is high, the mechanism of lung overload with impairment of particle clearance has been observed. The response to chronic lung overload is a sustained increase in neutrophilic inflammation and the subsequent release of reactive oxygen species (ROS). ROS within cells may damage DNA directly and induce mutations and also promote cell turnover and proliferation (Lim and Seow, 2012; IARC, 2010; ILSI Risk Science Institute Workshop Participants, 2000).

High-molecular-weight PAHs are clearly carcinogenic, as shown in both in vitro and in vivo studies. Activated PAH metabolites can form adducts with DNA and if these adducts are not repaired, misreplication converts them to mutations. Accumulation of additional mutations in key genes within stem cells, together with epigenetic and/or non-genetic changes, can result in tumour formation. Phase I and phase II enzymes are involved in the metabolic activation and detoxification of PAHs. Genetic polymorphism in these enzymes may confer susceptibility to individuals exposed to solid fuel smoke. Some gene–environment interactions have been explored, including CYP1A1, GSTM1, and GSTT1 genotypes and use of coal, but fewer studies have included such susceptibility biomarkers considering biomass smoke exposure (IARC, 2010). A multicentre case–control study of nonsmokers in eight countries evaluated the association between GSTM1 and GSTT1 and risk of lung cancer (Table 6.3). Compared with subjects with < 20 years of wood smoke exposure, subjects with > 20 years of

exposure had a higher risk of lung cancer among those with the GSTM1 null genotype (odds ratio [OR], 6.2; 95% confidence interval [CI], 1.5–25). No gene–environment interactions were observed for the GSTT1 null genotype (Malats et al., 2000).

Table 6.3. Summary of case–control studies on the risk of cancer associated with biomass smoke exposur

Location, period (Reference)	Study population (cases/controls)	Exposure assessment	Outcome	Odds ratio (95% CI)	Adjusted covariates and comments
Osaka, Japan 1986–1988 (Sobue, 1990)	144/731 nonsmoking women Hospital-based unmatched controls	Self-administered questionnaire Used straw or wood for cooking at age 15, at age 30, and at time of interview	Newly diagnosed lung cancer (78% ADC, 8% SCC, 5% small cell, 5% large cell, 4% other)	Straw or wood for cooking at age 30 1.77 (1.08–2.91)	Age, education, other household members smoked in adulthood, mother smoked in childhood Controls were younger with higher education Reference category was not clearly defined
Shanghai, China 1984–1986 (Gao *et al.*, 1987)	672/735 women Population-based controls	Oil used, frequency of stir-frying, deep-frying, boiling Type of fuel used for cooking	Newly diagnosed lung cancer, mainly ADC	Wood for cooking 1.0 (0.6–1.8)	Age, education, smoking Type of fuel used for cooking unrelated to risk
Guangzhou, China 1983–1984 (Liu *et al.*, 1993)	316/316 women and men Hospital-based matched (sex, age, residential district) controls	In-person interview Type of fuel (coal and wood) used for cooking during three periods of time	Newly diagnosed lung cancer	Wood for cooking 1.19 (0.46–3.11)	Smoking, passive smoking, education, occupation, history of tuberculosis and chronic bronchitis, family history of cancer, size of living area Very few wood users, mostly coal
Taiwan, China 1992–1993 (Ko *et al.*, 1997)	117/117 nonsmoking women Hospital-based matched (age) controls	In-person interview No cooking or use of gas, coal, or wood for cooking during three age-stages	Newly diagnosed lung cancer Information on histological type not provided	Wood or charcoal versus gas or none < 20 years old 2.5 (1.3–5.1) 20–40 years old 2.5 (1.1–5.7) > 40 years old 1.0 (0.2–3.9) After further	Socioeconomic status, education, residential area Use of fume extractor in the kitchen (protective), history of tuberculosis, vegetable consumption, living near industrial district

				adjustment	
				20–40 years old	
				2.7 (0.9–8.9)	
				Use of wood stove versus no use	
Brazil	784/1568 women (13%) and men (87%)	In-person interview	Newly diagnosed mouth, larynx, and pharynx cancer	All sites	Smoking, alcohol consumption, rural residence, schooling, ethnicity, income, consumption of smoked meat and other foods
1987–1989	Hospital-based matched (sex, age, hospital, admission) controls	Wood stove use for cooking and heating		2.45 (1.84–3.26)	
(Pintos *et al*., 1998)				Pharynx	
				3.82 (1.96–7.42)	
				All subjects	Sex, age, centre
Sweden, Germany, France, Italy, the Russian Federation, Romania, Poland, Brazil	122/121 nonsmoking women and men	In-person interview	Newly diagnosed lung cancer (69% ADC, 21% SCC, 6% small cell, 4% large cell)	> 20 years indoor wood combustion versus no wood use	Nonsmokers were defined as never-smokers and occasional smokers (up to 400 cigarettes in a lifetime)
	Population- and hospital-based controls	Use of wood or coal for cooking or heating, duration of exposure		2.5 (1.0–6.2)	Controls were not matched by age and sex
(Malats *et al*., 2000)				*GSTM1* null	Controls were younger than cases
				> 20 years indoor wood combustion versus no wood use	Study period not specified
				6.2 (1.5–25)	
Chandigarh, India				Cumulative exposure in women of > 45 years to indoor air pollution from use of coal or wood for cooking or heating	
1995–1997	265/525 women and men	In-person interview	Newly diagnosed lung cancer		Age, socioeconomic status, smoking, sex
(Gupta *et al*., 2001)	Hospital-based matched (sex, age) controls	Coal or wood for heating and cooking			Mixed coal and biomass use
				1.43 (0.33–6.30)	
		In-person interview		For women	Smoking, residential area (urban, suburban, rural), socioeconomic status, and education
Taiwan, China	527/805 women and men	No cooking or use of gas, coal, or wood for cooking when women were 20–40 years old	Newly diagnosed lung cancer (SCC and small cell 28.2%, ADC 47.7%)	Wood or charcoal versus gas or none	
1993–1999	Hospital-based matched (sex, age) controls			SCC 3.1 (1.0–9.2)	Long-term residence near industrial district increased lung
(Le *et al*., 2001)				ADC 3.0 (1.4–6.4)	

					cancer risk Fume extractor in the kitchen decreased lung cancer risk Only 7% of men reported cooking
Mexico City, Mexico 1986–1994 (Hernández-Garduño *et al.*, 2004)	113/273 nonsmoking women Hospital-based controls	Medical records Ever used wood fuel for cooking Years of exposure	Newly diagnosed ADC of the lung	Years of cooking with wood versus no use of wood fuel 1–20 years 0.6 (0.3–1.2) 21–50 years 0.6 (0.3–1.3) > 50 years 1.9 (1.1–3.5)	Age, ETS exposure, socioeconomic status, education Different control groups were used
Czech Republic, Hungary, Poland, Romania, the Russian Federation, Slovenia, United Kingdom 1998–2002 (Lissowska *et al.*, 2005)	2861/3118 women and men Multicentre study Population- and hospital-based matched (sex, age, and area) controls	In-person interview Fuels used for cooking and for heating	Newly diagnosed lung cancer	Ever used wood for cooking versus no solid fuel use 1.23 (1.00–1.52) Ever used wood for heating versus no solid fuel use 1.31 (1.06–1.61)	Age, sex, education, smoking, centre Coal was the most commonly used fuel for heating (50%) and cooking (44%) Associations due to mixed wood and coal exposures could not be ruled out
Montreal, Canada 1996–1997 (Ramanakumar *et al.*, 2007)	1205/1541 women and men Population-based matched (sex, age) controls	In-person or next-of-kin interview Fuels used for cooking and for heating and duration of exposure	Newly diagnosed lung cancer	In women versus never exposed Only traditional heating 1.8 (1.0–3.2) Only traditional cooking 1.2 (0.7–1.9)	Age, ethnic group, family income, smoking, place of birth, type of interview, schooling, occupational exposures, ETS Mixed coal and biomass use

					Both 2.5 (1.5–3.6)	
					Always wood use versus always modern fuels	
					Hypopharynx:	
					1.56 (1.09–2.25)	
					Larynx:	
	799 (lung)/718				1.06 (0.74–1.53)	
	1062 (upper digestive)/718					
India	Women and men	In-person interview	Newly diagnosed lung and hypopharyngeal/laryngeal cancer		Lung:	Centre, age, socioeconomic status, cumulative tobacco consumption
2001–2004	Multicentre study	Solid fuel use and duration of exposure			1.06 (0.77–1.47)	
(Sapkota *et al.*, 2008)	Hospital-based matched (sex, age, area of residence) controls (19% hospitalized, 81% visitors)				Years of wood usage	
					Hypopharynx	
					> 0–30: 0.85 (0.50–1.45)	
					> 30–50: 1.59 (1.06–2.38)	
					> 50: 1.45(0.96–2.19)	
					P_{trend} = 0.03	
North America, Europe, Asia	5105/6535	In-person interview	Newly diagnosed lung cancer		Wood use in Europe/North America versus nonsolid fuel user	Age, sex, education, smoking status, race/ethnicity, study centre
International Lung Cancer Consortium	Pooled analysis	Solid fuel use, wood use, coal use			All studies	Cases tended to be older and more educated
(Hosgood *et al.*, 2010)	Population- and hospital-based matched (at least age and sex) controls				1.21 (1.06–1.38)	

ADC, adenocarcinoma; CI, confidence interval; ETS, environmental tobacco smoke; SCC, squamous cell carcinoma.

PAH metabolites also increase cell proliferation through interaction with some signalling pathways, including the epidermal growth factor receptor pathway and the serine/threonine kinase Akt pathway (Lim and Seow, 2012). Compared with liquefied petroleum gas (LPG) users, women using biomass for cooking in India showed upregulation of phosphorylated Akt proteins in airway epithelial cells, suggesting that cumulative exposure to biomass smoke increases the risk

of carcinogenesis via oxidative stress-mediated activation of the Akt signal transduction pathway (Roychoudhury et al., 2012).

Whereas the indoor emissions from wood combustion contain lower levels of PAHs, available data suggest that the mechanisms described for the carcinogenicity of coal may also be plausible for the lung cancer risk associated with biomass fuel emissions. Data from coal smoke are consistent with a carcinogenic mechanism including at least six major pathways disrupted by a mixture of genetic and epigenetic changes for a normal cell to be transformed to a tumour cell. Lung tumours had mutations in the KRAS gene, affecting cell growth and signalling, and in the p53 gene, affecting cell growth and replication (IARC, 2010).

The genotoxicity of human exposure to biomass combustion emissions has been examined. Compared with LPG users, women using biomass for cooking in India had increased micronucleated buccal and airway epithelial cells, as well as comet tail% DNA and tail length in comet assay. The exposure to biomass fuel smoke stimulated the DNA repair mechanisms and increased ROS generation. A depletion of superoxide dismutase and total antioxidant status was also reported (Mondal et al., 2010).

Exposure to biomass fuel smoke and cancer (excluding coal smoke)

Indoor air pollution has been associated with cancers of the lung, upper aerodigestive tract, and cervix. Lung cancers are the most studied and well characterized. Although biomass fuel is much more widely used than coal, the adverse health effects, including the association between biomass smoke and lung cancer, have been less studied. Burning of coal appears to be a stronger risk factor for lung cancer than wood burning (Lim and Seow, 2012; IARC, 2010; Reid et al., 2012; Kurmi et al., 2012). But because exposure to biomass fuels is much more prevalent, the adverse health effects are likely large even if the risks associated are smaller than for coal.

As part of the Global Burden of Disease analysis, the literature relating solid fuel use exposure to different health outcomes was qualitatively evaluated (Desai et al., 2004). At that time, there was strong evidence of lung cancer from exposure to coal smoke in adult women, but only moderate evidence for this same association for biomass smoke exposure. Four investigations, one in Japan (Sobue, 1990), two in China (Gao et al., 1987; Liu et al., 1993), and one in Taiwan, China (Ko et al., 1997), assessing the relation between biomass fuel use and lung cancer in women, were considered and a relative risk of 1.5 (95% CI, 1.0–2.1) was obtained (Table 6.3).

In the evaluation of the carcinogenicity of biomass fuel by IARC (Straif et al., 2006), four new studies were considered. A study conducted in Taiwan, China, reported that women who burned wood for cooking had a 3-fold increase in risk of lung cancer after adjusting for potential confounders, reporting stronger associations with squamous cell carcinoma and adenocarcinoma than with other histological subtypes of lung cancer (Le et al., 2001). In a case–control study from Japan, smoke exposure from wood or from wood and straw was associated with lung cancer only among those exposed before the age of 30 years (Sobue, 1990). Exposure to wood smoke for 50 years or more was associated with adenocarcinoma in a case–control study from Mexico (Hernández-Garduño et al., 2004). In addition, a large multicentre European case–control study (Lissowska et al., 2005) recorded an adjusted 20–30% increased risk of lung cancer in people who burned wood but not coal, compared with people who never used solid fuels for cooking or heating. However, information on any exposure–response relationship could not be determined as data on duration and intensity of exposure were lacking. These studies, conducted across several geographical regions, supported the conclusion of the IARC Working Group that evaluated indoor emissions from household combustion of biomass fuel (mainly wood) as a possible carcinogen (Group 2A) (Straif et al., 2006; Table 6.3).

Since the IARC Working Group evaluated the evidence in 2006, a pooled analysis from the International Lung Cancer Consortium, including seven case–control studies from Europe, Asia, and the USA, reported a modest association between lung cancer and wood smoke exposure (OR, 1.2; 95% CI, 1.06–1.38) (Hosgood et al., 2010). More recently, a review listed 13 studies reporting lung cancer risk estimates for biomass fuels (Lim and Seow, 2012). A systematic review and meta-analysis including seven of these studies (Sobue, 1990; Ko et al., 1997; Lissowska et al., 2005; Hernández-Garduño et al., 2004; Le et al., 2001; Sapkota et al., 2008; Liu et al., 1991) estimated an overall OR of 1.50 (95% CI, 1.17–1.94) for biomass use (predominantly wood) and lung cancer (Kurmi et al., 2012), similar to the pooled estimate obtained previously.

Other types of cancer have also been related to biomass fuel. A study conducted in Brazil observed an increase in risk of upper aerodigestive tract cancer in women (Pintos et al., 1998). IARC Monograph Volume 95 mentions studies of nasopharyngeal cancer and other upper aerodigestive tract cancers, but the existing evidence precluded the Working Group from drawing conclusions about these cancers (IARC, 2010). A subsequent case–control study in India reported an association between the use of wood as a solid fuel and hypopharyngeal cancer, but not lung and laryngeal cancer (Sapkota et al., 2008).

A study conducted in Honduras suggested that wood burning could increase the risk of cancer among women infected with human papillomavirus (HPV) (Velema et al., 2002). Since the 2006 IARC review, a case–control study of Colombian women reported that the risk of cervical cancer was stronger among

HPV-infected women exposed to wood smoke in the kitchen for 16 or more years than in HPV-INFECTED women without wood smoke exposure (OR, 5.3; 95% CI, 1.9–14.7) (Sierra-Torres et al., 2006).

Interventions

The use of biomass fuels in developing countries is likely to remain stable in the near future. The fuel-switching approach has turned out to be too simplistic to describe the household fuel use, particularly within rural and suburban areas. Many households follow a multiple fuels strategy, taking advantage of both traditional and modern practices. Improved biomass cook stoves have been identified as an option to reduce negative impacts of cooking with traditional open fires (Masera et al., 2005; Ruiz-Mercado et al., 2011). Improvements to biomass stoves have focused on combustion efficiency and the venting of emissions outdoors. Reductions in concentrations of PM < 2.5 μm in diameter ($PM_{2.5}$) and carbon monoxide have been reported due to the use of improved stoves in Mexico (Zuk et al., 2007) and Guatemala (Smith et al., 2010). Despite being substantially lowered, the concentrations remain high compared with those in households using gaseous fuels and health-based guideline values (IARC, 2010). While an intervention study conducted in Mexico provides some evidence that lowering exposure to biomass fuel through clean stove intervention decreases lung function decline comparably to smoking cessation (Romieu et al., 2009), no data are available on the impact of stove intervention on the risk of lung cancer. After an intervention with an efficient biomass stove, a reduction of PAHs exposure biomarkers has been reported in Mexico and Peru (Riojas-Rodriguez et al., 2011; Li et al., 2011; Torres-Dosal et al., 2008). However, levels of these exposure biomarkers remained higher than those reported for the general population.

Conclusion

There is widespread use of biomass fuel, involving almost 40% of the human population. Exposure occurs during cooking or heating, typically in poorly ventilated and crowded spaces. Women and children are often most exposed to extremely high levels of health-damaging pollutants. This chronic exposure to toxic pollutants has severe health consequences and may increase the risk of cancer. Although further studies are needed, available data suggest that exposure to biomass fuel smoke increases the risk of lung cancer as well as

other types of cancer. One of the main limitations of the epidemiological studies reported so far has been the exposure duration and intensity assessment, precluding the demonstration of an exposure–response relationship. Considering information about household characteristics, such as room partitions and extent of ventilation (air exchange), could provide more accurate measurement of the exposure. Most of the studies controlled for confounding to a reasonable extent, but few considered the potential confounding by socioeconomic status, a determinant of both disease and fuel use. Intervention studies can provide strong evidence for causal inference, showing how the exposure cessation or reduction decreases the risk of cancer, but such studies have not been performed to date for biomass fuel smoke exposure and lung cancer (Perez-Padilla et al., 2010; Lim and Seow, 2012; IARC, 2010).

Opportunities for research on indoor air pollution (due to domestic use of biomass fuels) and cancer include studies of the effect on cancers, other than lung, and studies of genetic factors that modify susceptibility. Studies exploring gene–environment interaction have been performed among populations exposed to coal, but similar studies are needed in populations with exposure to smoke from wood and other biomass fuels. Such research areas could be incorporated into intervention studies to maximize the information that can be obtained and to identify susceptible subgroups (Reid et al., 2012).

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Chapter 7. Polycyclic aromatic hydrocarbons in ambient air and cancer

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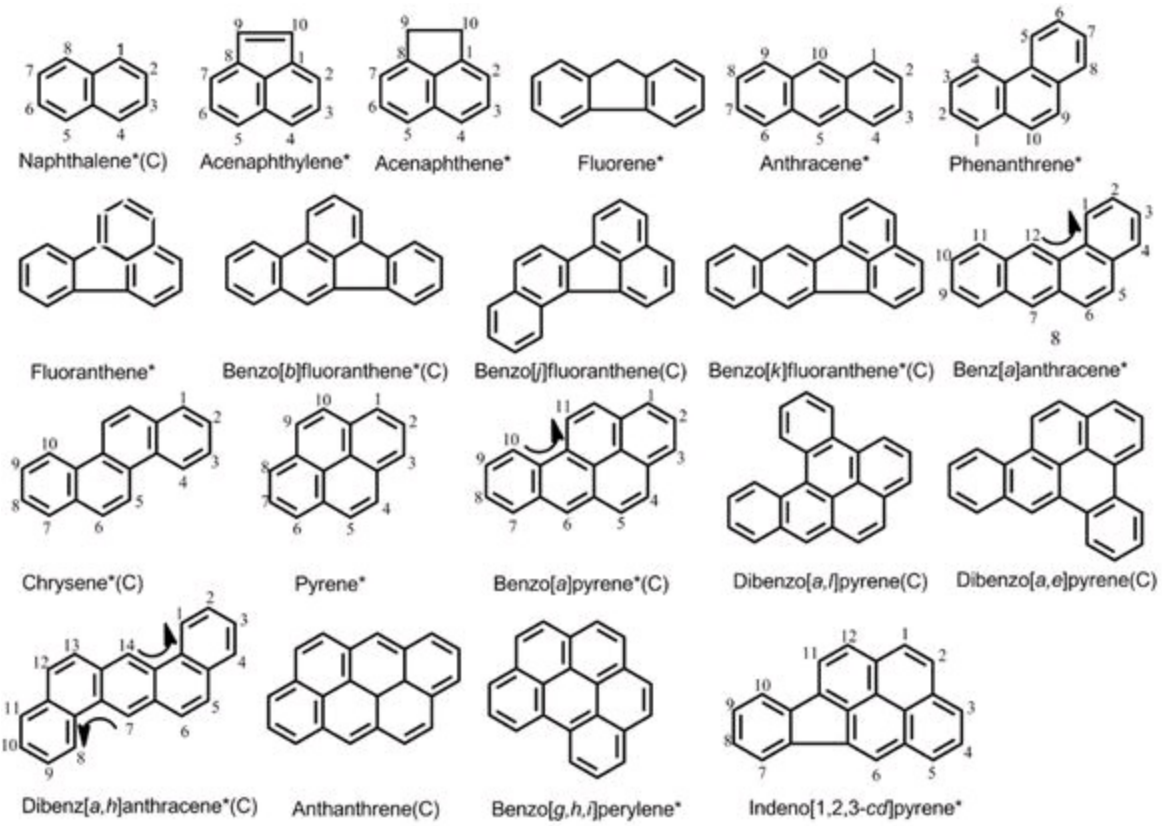
Polycyclic aromatic hydrocarbons (PAHs), which are generated from the incomplete combustion of organic (carbonaceous) material, are ubiquitous contaminants in ambient air (IARC, 1983, 1984a, 1984b, 1985, 2010; WHO, 1998). Their occurrence in the air we breathe has been substantial during the past centuries due to emissions from industrial processes and energy production, motor vehicular traffic, incineration of refuse, and residential heating.

PAHs consist of two or more fused aromatic rings made up of carbon and hydrogen atoms. The ring systems can be present in multiple configurations and may be unsubstituted or substituted. PAHs range from semivolatile molecules to molecules with high boiling points. Thus, they may be found both in the gas and the particulate phase of ambient air or in mixtures of both phases. About 500 different PAHs have been detected in air, but often the measurements focus on benzo[a]pyrene (B[a]P) as a representative of the whole PAH family (WHO, 1998; Boström et al., 2002). Many of the PAHs in ambient air are carcinogenic (IARC, 1983, 1984a, 1984b, 1985, 2010) (Figure 7.1), and a recent reassessment of their carcinogenic potential led to B[a]P being upgraded to a Group 1 known human carcinogen (IARC, 2010). Thus there is considerable concern about the relationship between PAH exposure in the ambient air and the potential to contribute to human cancer incidence. The United States Environmental Protection Agency (EPA) monitors 16 priority PAHs in air due to health concerns: naphthalene, acenaphthylene, acenaphthene, fluorene, anthracene, phenanthrene, fluoranthene, pyrene, chrysene, benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, B[a]P, indeno[1,2,3-cd]pyrene, benzo[g,h,i]-perylene, and dibenz[a,h]anthracene (in order of number of aromatic rings per structure) (Figure 7.1). Of particular note is that several PAHs (naphthalene, chrysene, benzo[b]fluoranthene, benzo[k]fluoranthene, B[a]P, dibenz[a,h]anthracene, dibenzo[a,e]pyrene and dibenzo[a,l]pyrene, and anthanthrene) have been found to be carcinogenic in experimental animals after inhalation or intratracheal ingestion, increasing concern about the levels of these carcinogens in ambient air (Figure 7.1).

Figure 7.1. PAHs in ambient air. An asterisk denotes a United States Environmental Protection Agency priority pollutant. (C) indicates that the compound is carcinogenic by inhalation or intratracheal

administration in experimental animals. Source: Park and Penning (2008); reproduced with permission from John Wiley & Sons.



PAH emissions in ambient air

A recent global atmospheric emission inventory of PAHs (Zhang and Tao, 2009) showed that the emission from the 16 priority PAHs listed by the EPA was 520 000 tonnes per year. Anthropogenic sources of total PAHs in ambient air emissions are greater than those that come from natural events such as forest fires and volcanic eruptions.

Apart from localized risk at or near the source of emission, PAHs can be dispersed regionally and intercontinentally through atmospheric long-range transport. For example, PAHs emitted from East Asia are transported to the west coast of the USA, and PAHs emitted in the Russian Federation influence atmospheric PAH concentrations in the Arctic (Zhang and Tao, 2009). The annual PAH emission from Asian countries is 290 000 tonnes (55% of the total); the amounts from China (114 000 tonnes per year) and India (90 000 tonnes per year) are the major contributors. The USA is the third largest emitter of PAHs, at 32 000 tonnes per year. By contrast, European countries account for only 9.5% of the total PAH emissions annually (Zhang and Tao, 2009). The contribution of the various anthropogenic sources of PAHs to the total emission profile can vary by country and region. The global sources of PAH emissions are shown in Table 7.1, and the main sources of PAHs in six European countries are

shown in Table 7.2.

Table 7.1. Main sources of emission for the United States Environmental Protection Agency 16 priority PAHs in China, India, and the USA

Source	Global	China	India	USA
Biofuel	56.7%	66.4%	92.5%	9.1%
Wild fire	17.0%	0%	0%	3.3%
Consumer product use	6.9%	0.9%	0.6%	35.1%
Traffic oil	4.8%	2.0%	IS	23.0%
Domestic coal	3.7%	10.7%	1.3%	IS
Coke production	3.6%	14.4%	IS	IS
Petroleum refining	2.4%	1.0%	IS	8.7%
Waste incineration	1.9%	IS	IS	9.5%
Aluminium electrolysis	1.4%	IS	IS	1.9%
Open straw burning	IS	2.0%	3.2%	IS
Gasoline distribution	IS	IS	IS	3.0%
Aerospace industry	IS	IS	IS	2.5%
Other	1.5%		2.7%	3.9%
Tonnes in thousands	530	114	90	32

IS: insignificant

Compiled from Zhang and Tao (2009).

Table 7.2. Main source sectors for PAHs in 1994 in six European countries (Austria, Denmark, Germany, Luxembourg, Norway, and the United Kingdom)

Sector	PAH emissions	
	Amount (tonnes per year)	Percentage of total
Combustion of energy and transformation industries	6.1	0.3
Non-industrial combustion plants plus wood burning	1120	60
Combustion in manufacturing industry	63	3.4
Production processes	248	13
Road transport	383	20
Other mobile sources	10	0.5
Waste incineration	30	1.6
Agriculture and forestry	1	< 0.1
Natural sources	8	0.4
Total (approximately)	1900	

Reproduced from Boström et al. (2002).

The largest emission of PAHs globally comes from incomplete combustion of organic material, and the largest single source is from the combustion of biofuels. Biofuel is a single type of primary solid biomass (e.g. animal dung or peat) (Zhang and Tao, 2009). Burning biomass fuels such as wood on indoor open-pit stoves is common in developing areas, leading to harmful exposures to particulate matter < 2.5 μm in diameter ($PM_{2.5}$), carbon monoxide (CO), and PAHs, which can be significantly reduced by the introduction of modern stoves (Li et al., 2011). Anthropogenic sources include PAHs that come from incomplete combustion processes (especially biofuels) and those that are made commercially, are by-products of industrial processes, or are generated from vehicle emissions, cooking, food preservation, and first- and second-hand

cigarette smoke.

Anthropogenic sources of PAHs in ambient air

Commercial production

PAHs produced commercially include naphthalene, acenaphthene, phenanthrene, fluoranthene, and pyrene; however, only naphthalene is used directly without further processing, as a moth repellent.

Industrial processes

Many PAHs are released into the atmosphere during industrial processes such as coal coking and petroleum refining. It is estimated that coal coking was responsible for the release of thousands of tonnes of PAHs per year in different countries during the 1980s and early 1990s. Reduced coke production and technical improvements have led to reductions in PAH emissions from this source. Little is known about the composition of these PAH emissions (WHO, 1998). In petroleum refining, most of the emissions consist of smaller two- and three-ring compounds (94–99%, depending on the process studied) (IARC, 1989). Thus, the composition of PAHs from combustion (pyrogenic) versus the composition of PAHs from petroleum refining (petrogenic) can be widely different. Other industrial sources with significant PAH emissions are carbon black plants, wood preservation (creosote) plants, the asphalt and bitumen industry, aluminium production (Söderberg electrodes), iron and steel production, foundries, tyre production, power plants, waste incinerators, and stubble burning (WHO, 1998). Further restrictions may lead to lower PAH emissions from these industries (CORINAIR, 1997).

Estimation of the PAH emissions for six European countries indicates that the industrial sources contribute PAHs in the same range as mobile sources (Table 7.2; data from CORINAIR, 1997).

Residential sources

Domestic heating with oil and wood stoves leads to considerable PAH emissions in northern European countries, and especially in Scandinavia (Boström et al., 2002). In Sweden, the emissions from wood-fired domestic heating are estimated to be about 100 tonnes per year, with minor contributions from oil combustion. Environmental tobacco smoke is also a considerable source of indoor air pollution and contamination within the home (Hoh et al.,

2012).

Motor vehicle emissions

The amount of PAHs released into the air from vehicles has been reduced considerably by the introduction of three-way converters. However, older diesel and gasoline cars with a catalytic converter of outmoded design have 5–10 times higher PAH emissions than modern cars. In addition, cold start at temperatures below the standardized cold start (23 °C), and especially at temperatures below 0 °C, results in a several-fold increase in PAH emissions. Several other technical variations lead to varying emissions, for example spark ignition engines (WHO, 1998). The total amounts of PAHs emitted from vehicles vary between countries; in the USA this can be as high as 6000 tonnes per year, and in six European countries the amount is about 400 tonnes per year (Tables 7.1 and 7.2).

As might be expected, not all PAHs contribute equally to the emissions into ambient air. Table 7.3 lists a typical PAH profile in ambient air arising from different sources.

Table 7.3. Mean profiles of individual PAHs in ambient air (relative to benzo[a]pyrene = 1.0)

Compound	Point source	Near mobile source	Home heating	Transport	Geometric mean
Anthracene	5.5	7.6	1.0	1.8	2.9
Phenanthrene	38	200	39	43	60
Fluoranthene	14	48	12	13	18
Pyrene	9.3	28	11	7.1	12
Benz[a]anthracene	1.4	0.82	1.0	0.78	0.97
Perylene	0.33	0.25	0.22	0.24	0.26
Benzo[e]pyrene	1.5	1.3	1.6	1.4	1.4
Benzo[g,h,i]perylene	1.4	1.5	2.4	1.3	1.6
Indeno[1,2,3-cd]pyrene	1.5	1.3	1.5	1.4	1.4

Anthanthrene	0.19	0.15	0.13	0.20	0.17
Chrysene and triphenylene	3.0	2.7	3.5	2.9	3.0
Benzofluoranthene	3.6	2.9	3.6	4.4	3.6

Source: WHO (1998); reproduced with permission from the publisher.

Human exposure

PAHs may be found in the gas and particulate phases (see Chapter 1). The levels given below frequently reflect the levels of discrete PAHs in the particulate phase and are often given as the sum of a limited number of PAH components. B[a]P is the traditional marker for PAH exposure. Several additional PAH components have been proposed as emission markers, for example fluoranthene, B[a]P, and benzo[b]fluoranthene. Boström et al. (2002) suggested the use of the following set of PAHs as emission and effect markers for monitoring air pollution: B[a]P, fluoranthene, phenanthrene, methylanthracenes/phenanthrenes, pyrene, benzo[b]fluoranthene, benzo[k]fluoranthene, indeno[1,2,3-cd]pyrene, benzo[g,h,i]-perylene, dibenz[a]anthracene, and dibenzo[a,l]pyrene. This list is quite similar to the 16 priority PAHs listed by the EPA (Figure 7.1). In some studies, the total PAH exposure is given as B[a]P toxic equivalency concentrations. In this approach, individual components are measured and ranked relative to B[a]P in terms of carcinogenicity. For example, chrysene has 1/1000th of the carcinogenicity of B[a]P and has a toxic equivalency concentration of 0.001. These calculations are used to estimate human health risk and can be used to calculate incremental lifetime cancer risk (ILCR). ILCR = exposure (µg/kg/day) × cancer slope factor (µg/kg/day). The ILCR is considered negligible when it is less than 1 in 10^5 (less than 1 additional cancer case per 100 000 persons), and the cancer slope factor is based on the extrapolation of a dose–response curve for tumorigenicity seen at high dose in experimental animals.

Background levels of PAHs in remote locations have been measured between 0.01 ng/m^3 and 0.1 ng/m^3 for individual PAH components (WHO, 1998). In rural districts the levels were approximately 10 times higher, whereas in city streets levels may amount to 50 ng/m^3 or more of the more abundant individual PAHs (Boström et al., 2002). Total PAHs in the centre of Stockholm, Sweden, ranged from below 100 ng/m^3 to 200 ng/m^3. The most abundant PAH was

phenanthrene. In other cities higher levels of individual PAHs have been measured (WHO, 1998; Binková et al., 2003). PAH was measured in the gas and particulate phase over summer and winter sampling periods in Kocaeli, Turkey. Σ_{13}PAH in the gas and particulate phases ranged from 6.2 ng/m^3 dibenz[a,h]anthracene to 98.6 ng/m^3 phenanthrene in the winter, and from 3.0 ng/m^3 benz[a]anthracene to 35.1 ng/m^3 phenanthrene in the summer. The most abundant PAH in both sampling periods was phenanthrene, followed by fluoranthene and pyrene. B[a]P toxic equivalency concentrations were found to be 3-fold higher in the winter months (Gaga et al., 2012). A similar outcome was observed in a study of children aged 5–6 years (n = 260) in New York City when measurements were conducted in the heating and non-heating seasons (Jung et al., 2010). In the United Kingdom, the Toxic Organic Micropollutants programme measured temporal trends in PAH in the atmosphere from 1991 to 2005 at six different sampling sites. Most showed a reduction in PAH levels and had concentrations that were lower than the new air quality standard of 0.25 ng/m^3. However, this value was exceeded in urban areas in the winter months (Meijer et al., 2008).

Indoor PAH levels usually range from 1 ng/m^3 to 50 ng/m^3 due to tobacco smoke and residential heating with wood, coal, and other materials (WHO, 1998). Environmental tobacco smoke is a major contributor to air pollution and dust, and surfaces remain contaminated long after the smoking has ceased (called third-hand smoke). Measurement of PAHs in settled household dust in 132 homes showed that total PAHs were 990 ng/g in smoking households versus 756 ng/g in nonsmoking households, and when corrected for loading (dust/m^3), the fold change was greater than 2-fold (Hoh et al., 2012).

PAHs in the ambient air can react with nitrates, hydroxyl radicals, or ozone, leading to the production of more water-soluble compounds. These compounds are rarely included in routine PAH measurements. However, nitro-PAHs have been detected on soot, and the formation of B[a]P-nitroquinone has been identified (Schauer et al., 2004). Exposure levels of nine different nitroarenes resulting from diesel and gasoline exhaust have recently been reviewed by the International Agency for Research on Cancer; diesel exhaust was ranked as a Group 1 known human carcinogen (Benbrahim-Tallaa et al., 2012).

Generally the mobile sources differ in their PAH profile, with the heavy diesel vehicles being characterized by lower-molecular-weight components than gasoline vehicles. However, per driven kilometre, total emissions from a gasoline-fuelled car are much lower than emissions from a diesel car. The three-way converter does not change the PAH profile of a gasoline-fuelled car significantly but reduces the total levels considerably. PAH levels vary with season, with higher levels being observed in the winter than in the summer. Data from Stockholm, Sweden, indicate that during the winter the levels of low-molecular-weight PAHs are increased compared with the summer (Prevedouros

et al., 2004).

Biomonitoring

Significant progress has been made in biomonitoring of human exposure to PAH. External dose can be measured using personalized air monitoring devices where PM is trapped on filters and then analysed for PAH content. Internal dose can be assessed by measuring blood and urinary biomarkers of exposure. Different analytes have been used as biomarkers of PAH exposure and effect. These include measuring PAH metabolites in the urine and intermediate biomarkers of effect (e.g. DNA and haemoglobin adducts). Analysis using urinary metabolites has given the most clear-cut results. Particulate pyrene is well correlated with total PAH in the breathing zone.

Urinary 1-hydroxypyrene may also reflect inter-individual variation in PAH metabolism. Occupational exposure has been found to lead to a 10–100 times greater urinary 1-hydroxypyrene content. Danish bus drivers excreted more 1-hydroxypyrene than mail carriers did, but outdoor working mail carriers had more PAH metabolites in their urine than those working indoors, indicating the impact of outdoor air pollution (Hansen et al., 2004). The use of 1-hydroxypyrene as a biomarker of PAH exposure has been criticized on the grounds that pyrene is not a carcinogenic PAH. This has led to the substitution of 3-hydroxy-B[a]P, but sensitive methods of detection have been a challenge. The detection of 3-hydroxy-B[a]P has also been criticized as a biomarker since this metabolite is not derived from any of the known pathways of B[a]P activation.

Measurements of urinary 1-hydroxypyrene-glucuronide, 2-naphthol, and malondialdehyde by synchronous fluorescence spectroscopy or high-performance liquid chromatography were used to evaluate seasonal and regional variations in PAH exposure and oxidative stress in Korean adults and women. Higher levels were found in individuals from industrialized areas and in the winter. Further elevation of 1-hydroxypyrene-glucuronide was observed in children exposed to environmental tobacco smoke (Yoon et al., 2012). In a study in Chinese children from polluted and non-polluted areas, the levels of nine urinary monohydroxylated PAH metabolites and 8-oxo-2′-deoxyguanosine (8-oxo-dG) were compared. Children from the polluted area had a higher PAH burden than those from the non-polluted area, but no significant difference in 8-oxo-dG levels was noted (Fan et al., 2012). The effect of involuntary tobacco smoke exposure on urinary levels of 23 monohydroxylated metabolites of PAH in 5060 subjects aged > 6 years was studied in the National Health and Nutrition Examination Survey (NHANES). After correcting for other confounders,

significant increases in urinary 1-hydroxypyerene, 2-hydroxyfluorene, 3-hydroxyfluorene, 9-hydroxyflourene, 1-hydroxypyrene, and 1-2-hydroxy-phenanthrene were observed. Increases of 1.1–1.4-fold for involuntary exposure were noted, which increased to 1.6–6.9-fold increases when children were actively exposed (Suwan-ampai et al., 2009).

As there is compelling evidence for the conversion of PAH to diol-epoxides as an activation pathway (see below), there have been recent advances in measuring their corresponding tetraol hydrolysis products in humans. Progress has been made in developing stable isotope dilution liquid chromatographic mass spectrometric methods to detect phenanthrene tetraols (Hecht et al., 2010; Zhong et al., 2011). Phenanthrene contains a bay region and undergoes similar metabolic transformation to B[a]P to form diol-epoxides, which hydrolyse to tetraols. The detection of phenanthrene tetraols has also been criticized, since it is not a carcinogenic PAH. Recently, methods have been developed to measure urinary B[a]P tetraols with femtomole sensitivity (Hecht et al., 2010), and these techniques can now be applied to biomonitoring studies.

Efforts have also been made to detect stable covalent diol-epoxide DNA and haemoglobin adducts in exposed humans. Repaired diol-epoxide DNA adducts in blood can be measured using ELISA and chemiluminescence-based methods, while unrepaired DNA adducts can be measured in lymphocytes by [^{32}P]-postlabelling methods. For example, (+)-7β,8α-dihydroxy-9α,10α-oxo-7,8,9,10-tetrahydro-B[a]P-N^2-deoxyguanosine [(+)-anti-B [a]PDE-N^2-dGuo] adducts have also been detected in human maternal and umbilical white blood cells after exposure to air pollution, using ELISA-based methods (Whyatt et al., 1998; Santella, 1999). Total DNA and B[a]P-like DNA adducts were measured by [^{32}P]-postlabelling in lymphocytes of nonsmoking policemen in Prague (n = 109) working 8 hour shifts. While there was no significant change in total DNA adducts, there was a marked increase in B[a]P-like DNA adducts correlated to personal exposure to PAHs collected on respirable particles (Topinka et al., 2007). Diol-epoxide DNA adducts are short-lived; therefore, attention has also focused on the development of methods to detect haemoglobin diol-epoxide adducts since the half-life of the red blood cell is 7–10 days (Day et al., 1990).

Toxicokinetics, including metabolic activation

Parent PAHs have low chemical reactivity and must be metabolically activated to electrophilic intermediates to exert their carcinogenic effects (Sims and Grover, 1974; Conney 1982; Thakker et al., 1985). Three pathways of PAH activation have been proposed in the literature and are best exemplified with B[a]P (Figure 7.2). In the first pathway, B[a]P is metabolically activated by

either P450 peroxidase or another peroxidase by acting as a co-reductant of complex-1 (Fe^{V}). This leads to a radical cation on the most electron-deficient C6 atom, which is highly reactive and capable of forming unstable C8-guanine [8-(benzo[a]pyren-6-yl)guanine)], N7-guanine [7-benzo [a]pyren-6-yl)guanine], and N7-adenine [7-benzo[a]pyren-6-yl)adenine] depurinating DNA adducts (Cavalieri and Rogan, 1995). Evidence for this pathway comes from in vitro reactions with B[a]P, microsomes, and a peroxide substrate, which has led to the trapping of DNA adducts, as well as from mouse skin studies (Cavalieri et al., 1990, 1991). Data exist that B[a]P and dibenzo[a,l]pyrene can exert their tumorigenicity through this mechanism in mouse skin and rat mammary gland (Cavalieri et al., 1991, 2005) In addition, trace amounts of B[a]P-depurinating DNA adducts have been detected in the urine of smokers and in women exposed to household smoke (Casale et al., 2001). However, apart from this single study, the evidence to support this mechanism due to inhalation exposure to PAH is not strong.

Figure 7.2. Pathways of PAH activation using benzo[a]pyrene as an example. Source: Park and Penning (2008); reproduced with permission from John Wiley & Sons.

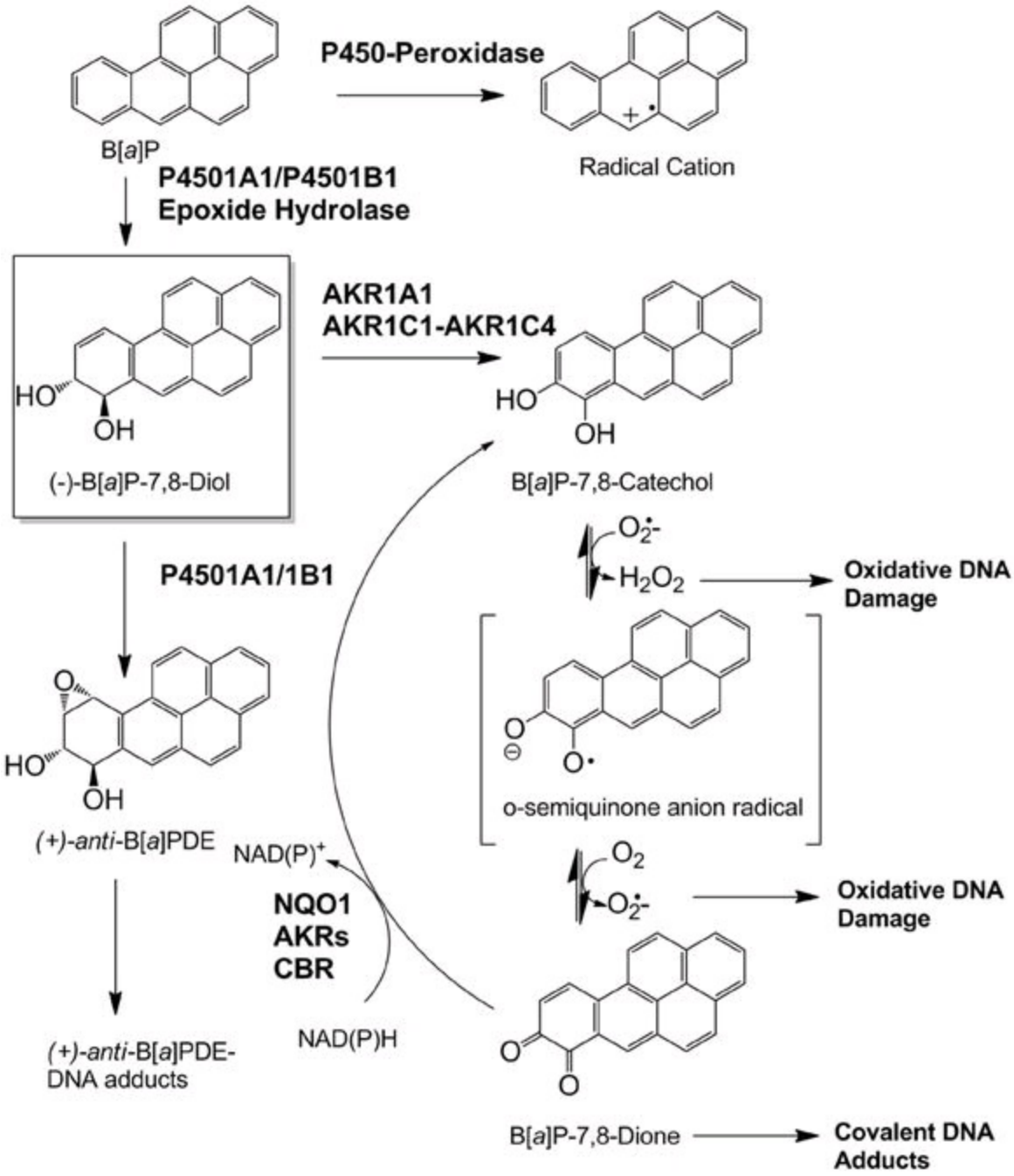


Figure 2

In the second pathway, B[a]P is metabolically activated to vicinal diol-epoxides (Jerina et al., 1991) formed through a three-step process involving oxidation and hydrolysis reactions (Figure 7.2). In the first step, B[a]P is converted preferentially in the lung by the cytochrome P450 isozyme P4501B1 to the major (+)-7R,8S-epoxide and minor (–)-7S,8R-epoxide. In the second step, the 7R,8R-trans-dihydrodiol is predominately formed by the action of epoxide hydrolase. In the third step, diol-epoxide diastereomers are generated by another oxidation reaction via various P450 enzymes, including P4501B1 (Thakker et al., 1985; Petruska et al., 1992; Guengerich, 1993; Constantin et al., 1994; Cavalieri and Rogan, 1995; Shimada et al., 1999, 2001).

Diol-epoxides have been studied in various animal carcinogenicity models. It has been revealed that the diol-epoxides with the highest carcinogenic activity are in general the anti-diastereomers and especially the enantiomers with R-

absolute configuration at the benzylic arene carbon (Thakker et al., 1985; Glatt et al., 1991). In studies of interactions of diol-epoxides with DNA, they demonstrate a high preference for the exocyclic amino group of deoxyguanosine and deoxyadenosine, where the major adduct derived from B[a]P is (+)-anti-B[a]PDE-N ^{2}-dGuo (Jeffrey, 1985; Gräslund and Jernström, 1989; Jerina et al., 1991; Geacintov et al., 1997). This pathway of metabolic activation has been observed for many PAHs in ambient air, including 5-methyl-chrysene (Melikian et al., 1983, Koehl et al., 1996), benz[a]anthracene (Cooper et al., 1980), benzo[b]fluoranthene (Ross et al., 1992), B[a]P (as outlined above), dibenz[a,h]anthracene (Platt et al., 1990), and dibenzo[a,l]pyrene (Luch et al., 1997, 1999), in in vitro systems (cell extracts, microsomes, and cell culture systems), and in some cases in in vivo studies in animals and humans. For example, PAHs within airborne $PM_{2.5}$ produced DNA bulky stable adducts in human lung cell co-cultures (Abbas et al., 2013).

In the third pathway, PAHs are metabolically activated to o-quinones by the action of aldo-keto reductases (AKRs) (Penning et al., 1999; Penning, 2004). For B[a]P, the sequence involves the NAD(P)$^{+}$-dependent oxidation of the 7R,8R-trans-dihydrodiol to a ketol catalysed by AKR1A1, AKR1C1–AKR1C4 (Figure 7.2). The ketol then spontaneously rearranges to a catechol, which undergoes air-oxidation to yield B[a]P-7,8-dione and reactive oxygen species (ROS) (Palackal et al., 2001, 2002; Penning et al., 1996). B[a]P-7,8-dione is both electrophilic (will react with DNA) and redox-active. In the presence of reducing equivalents and NQO1, AKRs themselves, and carbonyl reductase, the quinones can be reduced back to the corresponding catechols, and if they are not intercepted a futile redox cycle will ensue in which NADPH is depleted and ROS is amplified (Shultz et al., 2011). This pathway of metabolic activation has been observed for several PAHs in ambient air, including phenanthrene, chrysene, 5-methyl-chrysene, benz[a]anthracene, and B[a]P in in vitro systems (recombinant enzymes) and cultures of human lung cells (Palackal et al., 2001, 2002; Park et al., 2008b).

Efforts have been made to assess the contribution of each of these pathways to the metabolic activation of B[a]P in human lung cells. Using a stable isotope dilution liquid chromatographic mass spectrometric method, signature metabolites of each of the three pathways were measured: B[a]P-1,6-dione and B[a]-3,6-dione (radical cation metabolites), B[a]P-tetraol-1 (diol-epoxide metabolites), and B[a]P-7,8-dione (o-quinone metabolites) in human bronchoepithelial (H358) cells in the presence and absence of the aryl hydrocarbon receptor (AhR) agonist TCDD. It was found that each of the pathways contributed equally to B[a]P metabolism in the presence and absence of TCDD (Lu et al., 2011).

The rate of absorption of PAHs from the tracheobronchial epithelium after inhalation exposure is determined by their high lipophilicity (Gerde et al., 1993). For lipophilic carcinogens such as B[a]P, the delayed absorption in the airway

mucosa is a result of slow passage through the airway epithelium, yielding a very high dose to these target cells. Because of the long retention time, the metabolic activation can be considerable even at low enzyme activities (Bond et al., 1988).

Modes of action

Carcinogenic PAHs are generally positive in short-term tests for mutagenicity (Table 7.4), for example the bacterial Salmonella mutagenicity (Ames) assay and the HPRT-mammalian cell mutagenicity assay, provided a metabolic activation system is present (Malaveille et al., 1977; MacLeod et al., 1988; Chen et al., 1990; Wei et al., 1993). In the Ames assay, a rat liver S9 activation system is used; in the HPRT assay, recombinant P4501A1 and P4501B1 are co-expressed. The mutagenic species has been identified by comparing the mutagenic potency of different PAH metabolites, which demonstrates that of the known metabolites the diol-epoxides are the most potent mutagens (Malaveille et al., 1977). Treatment of a plasmid containing K-Ras with the (+)-anti-B[a]PDE followed by transfection into NIH3T3 cells led to cell transformation with increased foci in soft agar. Rescue of the plasmid showed that there were single point mutations of the 12th and 61st codons, which could explain the transformation potential of the diol-epoxide. The dominant mutation observed was a G → T transversion, consistent with DNA-adduct formation on deoxyguanosine (Marshall et al., 1984). One of the most compelling pieces of data has shown that by using ligation-mediated polymerase chain reaction, the (+)-anti-B[a]PDE preferentially forms DNA adducts in hot spots on the p53 tumour suppressor gene, which is one of the most mutated genes in human lung cancer. These hot spots correspond to the same codons that are mutated in tumours obtained from humans with lung cancer. The dominant mutation observed was again a G → T transversion, consistent with DNA adduct formation on deoxyguanosine (Denissenko et al., 1996; Hainaut and Pfeifer, 2001).

Table 7.4. Genotoxicity of individual PAHs that are carcinogenic in experimental animals after inhalation or intratracheal instillation

Compound	Results
Anthanthrene	Positive, limited database
Benzo [b] fluoranthene	Positive

Benzo[j]fluoranthene	Positive
Benzo[k]fluoranthene	Positive
Benzo[a]pyrene	Positive
Chrysene	Positive
Dibenz[a,h]anthracene	Positive
Dibenzo[a,i]pyrene	Positive
Indeno[1,2,3-cd]pyrene	Positive
Naphthalene	Negative for gene mutations, positive for clastogenicity in vitro

Source: WHO (1998); reproduced with permission from the publisher.

In a separate in vitro study, the mutagenic potency of (±)-anti-B[a]PDE and B[a]P-7,8-dione (AKR product) were compared in a yeast-reporter gene assay for p53 mutation. It was found that B[a]P-7,8-dione was 80-fold more mutagenic than the diol-epoxide provided it was permitted to redox cycle (Yu et al., 2002). In these experiments there was a linear correlation between (±)-anti-B[a]PDE mutagenicity and the formation of (+)-anti-B [a]PDE-N^2-dGuo adducts, and a linear correlation between B[a]P-7,8-dione mutagenicity and the formation of 8-oxo-dGuo adducts (Park et al., 2008a). In addition, B[a]P-78-dione gave predominately G → T transversions, consistent with the base mispairing of 8-oxo-dGuo with adenine. The position of the point mutations within p53 was quite random until there was biological selection for dominance, and then the spectrum of mutations was similar to that seen in lung cancer (Park et al., 2008b). These data suggest that B[a]P-7,8-dione formed by AKRs has the potential to contribute to the carcinogenic mode of action of B[a]P.

Planar PAHs can induce their own metabolism. Compounds such as B[a]P can bind to the AhR (Nebert and Jensen, 1979; Nebert et al., 1993, 2004). This leads to nuclear localization of the liganded AhR, where it can act as a transcription factor by binding to the xenobiotic response element to induce the CYP1A1 and CYP1B1 genes (Denison et al., 1988a, 1988b, 1989), which will result in enhanced monoxygenation of the parent PAH. PAH metabolism leads to the production of electrophiles (e.g. quinones), which can activate the Nrf2-Keap 1 system. Nrf2 acts as a transcription factor and binds to the antioxidant response element to induce γGCS, NQO1 and AKR1C1–AKR1C3, and AKR1B10 (Burczynski et al., 1999; Jin and Penning 2007; Penning and Drury, 2007).

Importantly, AKR1C1–AKR1C3 are involved in the metabolic activation of PAH trans-dihydrodiols to the electrophilic and redox active PAH o-quinones, which could further exacerbate PAH activation via induction of AKRs. The PAH o-quinones produced by this pathway are also ligands for the AhR (Burczynski and Penning, 2000). Thus, both the parent PAH and their downstream metabolites can lead to the metabolic activation of PAHs in ambient air.

PAHs may, in addition to initiating carcinogenesis via a genotoxic mechanism, exert promotional effects through various modes of action. Certain PAHs induce inflammatory processes (Casale et al., 1997). The binding of PAHs to the AhR also leads to transcriptional upregulation of genes involved in growth as well as biotransformation and differentiation (Nebert et al., 1993). Studies also indicate the ability of both PAHs and their metabolites to activate kinases involved in survival signalling, thus giving DNA-damaged cells a survival advantage (Burdick et al., 2003). At higher concentrations some PAHs induce apoptosis (Solhaug et al., 2004). In addition, PAHs show inhibitory effects on gap junctional intercellular communication (Upham et al., 1996; Weis et al., 1998).

Carcinogenicity studies in animals

Most investigations of PAH carcinogenesis by the respiratory route are intratracheal instillation studies (WHO, 1998). In all, 10 PAHs have been found to be carcinogenic in experimental animals after inhalation or intratracheal instillation (WHO, 1998; NTP, 2000) (Table 7.5). Only B[a]P and naphthalene have been studied by the inhalation route. In one inhalation study in hamsters, groups of 24 males were exposed to B[a]P condensed onto sodium chloride particles at concentrations of 2.2, 9.5, and 46.5 mg/m^3 for 4.5 hours per day, 7 days per week for the first 10 weeks, then for 3 hours per day for 2 years. Exposure was by nose breathing only. There were no tumours in the controls or in the low-exposure group. In the other two groups, exposure-related tumours were found in the nasal cavity, larynx, trachea, pharynx, oesophagus, and forestomach, but not in the lung (Thyssen et al., 1981). RIVM (1989) cites two other inhalation studies with B[a]P not found in the open literature: one in mice (Knizhnikow et al., 1982; see RIVM, 1989) and one in rats with co-exposure with sulfur dioxide (Laskin et al., 1970; see RIVM, 1989). In both studies malignant lung tumours were observed.

Table 7.5. Carcinogenicity of individual PAHs in experimental animals after inhalation or intratracheal instillation

Compound	Carcinogenicity (weight of evidence)	Species	No. of studies with positive, negative, and questionable results		
			+	–	±
Anthanthrene	Positive	Mouse	1		
Anthracene	Negative	Rat		1	
Benzo[*b*]fluoranthene	Positive	Rat	1		
		Hamster		1	
Benzo[*j*]fluoranthene	Positive	Rat	1		
Benzo[*k*]fluoranthene	Positive	Rat	1		
Benzo[*g,h,i*]perylene	Negative	Rat		1	
Benzo[*a*]pyrene	Positive	Mouse	1		
		Rat	9		
		Hamster	11	1	1
Benzo[*e*]pyrene	Negative	Rat		1	
Chrysene	Positive	Rat	1		
Dibenz[*a,h*]anthracene	Positive	Rat	1		
		Hamster	1	1	
Dibenzo[*a,i*]pyrene	Positive	Hamster	2		
Indeno[1,2,3-*cd*]pyrene	Positive	Rat	1		
Naphthalene	Positive	Mouse			2
		Rat	1		
Phenanthrene	Negative	Rat		1	
Pyrene	Negative	Hamster		1	

Source: WHO (1998); reproduced with permission from the publisher; IARC (2002).

In recent bioassay inhalation studies with naphthalene, Fischer 344/N rats developed neuroblastomas of the nasal olfactory epithelium after being exposed in inhalation chambers to 0, 10, 30, or 60 ppm (80, 52, 157, or 314 mg/m^3) for 6 hours per day, on 5 days per week, for 105 weeks (NTP, 2000). The observed rates in males were 0/49, 0/49, 4/48, and 3/48, respectively, and in females 0/49, 2/49, 3/49, and 12/49, respectively. In addition, adenomas of the nasal respiratory epithelium were observed in 0/49, 06/49, 8/48, and 15/48 males and in 0/49, 0/49, 4/49, and 2/49 females, respectively. In the study with B6C3F$_1$ mice subjected to whole-body exposure of 0, 10, or 30 ppm (0, 52, or 157 mg/m^3) naphthalene in inhalation chambers for 6 hours per day, 5 days per week, for 104 weeks, a statistically significant increase in the incidence of bronchioloalveolar adenomas in high-dose female mice was observed (NTP, 2000). Increased incidences of bronchioloalveolar adenomas and carcinomas were observed in the male mice, but the increases were not statistically significant.

PAHs and their metabolites will also cause lung cancer in animals when administered by other routes. Classically, the newborn mouse model of lung cancer was used to rank the tumorigenicity of different B[a]P metabolites, given that the developing lung is more susceptible to carcinogen exposure. Studies such as these showed that the (+)-anti-B[a]PDE was the most potent lung tumorigen of the known B[a]P metabolites (Buening et al., 1978; Kapitulnik et al., 1978). Similarly, in the A/J mouse lung model of B[a]P-induced

carcinogenesis, anti-B[a]PDE-DNA adducts were early lesions that could be detected in the initiation phase (Nesnow et al., 1998).

Carcinogenesis experiments with mixtures containing PAHs have also been reported. Heinrich et al. (1994) exposed groups of 72 female Wistar rats to a coal tar/pitch aerosol containing either 20 or 46 µg/m^3 B[a]P for 17 hours per day, 5 days per week, for 10 or 20 months, followed by a clear air period of up to 20 or 10 months, respectively. The cumulative doses of inhaled B[a]P of the four exposure groups were 71, 143, 158, and 321 mg B[a]P/m^3 hours, and the corresponding lung tumour rates were 4.2%, 33.3%, 38.9%, and 97.2%, respectively, whereas there were no tumours in the control group. In similar experiments in which rats were exposed to coal tar/pitch vapour condensed on the surface of fine carbon black particles, the resulting lung tumour rate was about twice as high.

Pott and Heinrich (1990) have also performed a lifelong inhalation study with rats exposed to diesel exhaust. In this study, tumour rates similar to those in the study with pitch pyrolysis vapours were induced, although the PAH content (measured as B[a]P) was 100–1000 times lower. This result indicates that diesel exhaust contains other potent carcinogenic or tumour-promoting compounds besides unsubstituted PAHs.

Numerous carcinogenicity studies have been performed using dermal application and subcutaneous and intramuscular injection (for overview, see WHO, 1998). An oral gavage study with B[a]P revealed tumour development in the liver, forestomach, auditory canal, oral cavity, skin, and intestines in both sexes of rats, and additionally the kidney in males and the mammary gland and oesophagus in females (RIVM, 2001). However, no lung tumours were observed after this route of administration. In a feeding study of B[a]P in mice, tumours in the tongue, oesophagus, forestomach, and larynx, but not lung, were observed (Culp et al., 1998).

Carcinogenicity studies in humans

Occupational exposures

A review and meta-analysis on the association between occupational exposure to PAHs and lung cancer development in 39 cohorts found an average relative risk of 1.20 per 100 µg/m^3 years cumulative B[a]P (Armstrong et al., 2004). For some occupations relative risks were considerably higher, but confidence intervals were very wide. For exposures in coke ovens, gas works, and aluminium industries, the risk is equivalent to a relative risk of 1.06 for a working lifetime of 40 years at 1 µg/m^3.

Ambient air exposures

Few studies have addressed the impact of exposure to PAHs in ambient air on human cancer. Studies using other exposure indicators (PM or NO_2) have shown associations between air pollution and lung cancer; however, no PAH exposure information was available (Pope et al., 2002; Hoek et al., 2002; Nafstad et al., 2003). An analysis of the United States data on lung cancer, PM exposure, and older PAH and metal air concentration data, supports the plausibility that known chemical carcinogens may be responsible for the lung cancer attributed to $PM_{2.5}$ exposure in the American Cancer Society study (Harrison et al., 2004). A study by Cordier et al. (2004) found an increased risk of childhood brain cancer associated with PAH exposure. Both paternal preconception occupational PAH exposure and paternal smoking were associated with increased risks for childhood brain tumours.

Human susceptibility

PAHs are metabolically activated by phase I P450 isozymes (CYP1A1, CYP1B1) in combination with epoxide hydrolase (EPHX) and phase I AKR isozymes (AKR1A1, AKR1C1-AKR1C4) and are detoxified by phase II enzymes including GSTs, UTGs, SULTs, and COMT. In addition, bulky covalent diol-epoxide DNA adducts can be repaired by nucleotide excision repair proteins (XPD [helicase], XPA, and XPC [damage recognition]), and oxidative DNA lesions can be repaired by base excision repair enzymes (hOGG1 and APE). Each of these genes is highly polymorphic in the human population. (A complete list of these variants is available at the NCBI database: http://www.ncbi.nlm.nih.gov/.) Many of these variants are non-synonymous single-nucleotide polymorphisms (nSNPs) that can affect enzyme activity. Combinations of these nSNPs rather than an individual SNP may affect human genetic susceptibility to PAH emissions in ambient air.

In a study of Prague policemen occupationally exposed to polluted air, B[a]P-like DNA adducts were detected and found to be positively associated with SNPs in XPD and GSTM1 (Binková et al., 2007). In another lung cancer case–control study, exposure to environmental tobacco smoke and polymorphisms in CYP1B1 Leu(432) Val was significantly associated with lung cancer susceptibility, with an odds ratio for at least one allele of 2.87 (95% confidence interval [CI], 1.63–5.07) (Wenzlaff et al., 2005a). Combinations of the polymorphism in this phase I enzyme gene along with those selected from either phase II enzyme genes (GSTM1 null, GSTP1 Ile(105)Val) or NADPH-quinone oxidoreductase (NQO1) C(609)T) were also evaluated. Here the combination of the CYP1B1 Leu(432)

Val allele and the NQO1 C(609)T allele was associated with the highest risk of lung cancer (odds ratio [OR], 4.14; 95% CI, 1.60–10.74) (Wenzlaff et al., 2005a). In the same study cohort, variants in GSTM1, GSTT1, and GSTP1 were examined to determine whether there was an association of the genotype with lung cancer incidence in never-smokers. Individuals who had been exposed to household environmental tobacco smoke for > 20 years, and who were carriers of either the GSTM1 null allele or the GSTP1 Val allele, were at a 4-fold increased risk of developing lung cancer (OR, 4.56; 95% CI, 1.21–17.21) (Wenzlaff et al., 2005b). In a lung cancer case–control study in China, women who were never-smokers were found to be at a significant increased risk of adenocarcinoma if they were carriers of the variants in the nucleotide excision repair variant XRCC1 399 Gln/Gln versus the Arg/Arg genotype (OR, 14.12; 95% CI, 2.14–92.95). The OR of lung adenocarcinoma for the XRCC1 399Gln allele with exposure to cooking oil smoke was 6.29 (95% CI, 1.99–19.85) (Li et al., 2005). DNA integrity was investigated in 50 bus drivers, 20 garage men, and 50 controls in the Czech Republic and associated with variants in the base excision repair gene hOGG1. Carriers of at least one variant (Cys allele) had a higher degree of DNA damage (Bagryantseva et al., 2010). To date, no molecular epidemiological study has been performed whereby combinations of polymorphic variants in phase I, phase II, and DNA repair genes have been pooled. However, based on the studies described, carriers of variants in all three classes of genes might be at higher risk of developing lung cancer from emissions of PAHs in ambient air.

Conclusions

PAHs generated from the incomplete combustion of organic material are ubiquitous contaminants in urban air. There are numerous unsubstituted PAHs (pyrogenic) and substituted PAHs (petrogenic). The pyrogenic PAHs may occur in the gas phase, particulate phase, or mixtures of both phases. The major worldwide source is the combustion of biofuels, while other sources such as combustion plants, various industrial and production processes, road transport, and waste incineration can contribute. Total PAH levels in some urban areas are in the range of 100–200 ng/m^3 but may be even higher in more polluted areas and can show distinct seasonal variation. However, measurements of total PAHs are relatively scarce. B[a]P is the traditional marker for PAHs, but various other individual PAHs have also been proposed, such as fluoranthene, B[a]P, and benzo[b]fluoranthene. Biomarkers of exposure include 1-hydroxypyrene, 3-hydroxy-B[a]P, and tetraols, but DNA and protein adducts can also be measured as intermediate cancer biomarkers. The major disease end-

point of interest is lung cancer, and approximately 10–15% of all lung cancer cases are seen in never-smokers. Parent PAHs must be metabolically activated to electrophilic intermediates (radical cations, vicinal diol-epoxides, and o-quinones) to act as lung carcinogens. All three routes have been observed in human lung cells. Various promotional effects of PAHs may contribute to their carcinogenic action. In all, 10 PAHs have been found to be carcinogenic in experimental animals after inhalation or intratracheal instillation. Naphthalene seems to be an exception compared with other carcinogenic PAHs as it appears to not be genotoxic. A meta-analysis of occupational cohort studies found a 20% increase in relative risk per 100 $\mu g/m^3$ years cumulative B[a]P exposure. Studies of ambient air pollution and cancer have demonstrated an association between carriers of polymorphic variants in phase I, phase II, and DNA repair enzyme genes.

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Chapter 8. Hazardous air pollutants: approaches and challenges in identifying assessment priorities

John J. Vandenberg

This chapter provides information to support decisions by the International Agency for Research on Cancer (IARC) on prioritizing hazardous air pollutant assessments. The decisions may be based on a variety of alternative approaches and criteria, some of which are presented here for consideration along with other methods. A key criterion influencing the methods described here is the necessary focus on agents that may present the greatest potential threat to human health. For agencies charged with the protection of public health, it is of primary importance to prioritize activities to ensure that resources are expended to address the largest public health risks and to seek optimal risk reduction as required, in many instances, by legislative direction or executive order.

In the conventional model of risk assessment (NRC, 1983, 1994), hazard identification is followed by the development of estimates of toxic potency and human exposure, which results in estimates of risk for the endpoints of concern. After this risk assessment, valuable resources can be allocated to research chemicals presenting the greatest risk instead of those with little or no potential for human exposure. Health risk assessment approaches provide insights on setting priorities for assessments and subsequent risk management activities. Here, selected data on risk potential are considered in the prioritization of chemicals for IARC review.

It is essential to recognize that a focus on only those chemicals for which toxicity and exposure data are available may fail to identify other chemicals that are highly important but for which data are scant or missing and the potential for risk is poorly understood. Identification of key missing information and priorities for toxicity testing and research may be a significant by-product of prioritization efforts as documentation of knowledge gaps can inform future prioritization efforts.

Scope of evaluation: hazardous air pollutants

Two major types of air pollutants are defined for regulatory purposes in the

USA. One type, criteria air pollutants, has historically been the primary focus of air quality management programmes. These pollutants accumulate in the atmosphere as a result of emissions from numerous and diverse mobile and stationary sources. They have widespread exposures and include tropospheric ozone, carbon monoxide, particulate matter (PM) (of various size classifications), lead, sulfur dioxide, and nitrogen dioxide. Of these, there is some evidence or suggestion of carcinogenic potential for tropospheric ozone (Bell et al., 2004), PM (Pope et al., 2002), and lead (NTP, 2003). There are widespread human exposures to ozone and PM, with current exposure levels for these pollutants exceeding ambient standards in some areas in the USA (EPA, 2003a) and elsewhere. For lead, exposures may occur due to the cumulative influence of air, water, and dietary routes of exposure. Timing of scientific and regulatory evaluation is also relevant. In the USA, the most recent evaluation of PM was completed in 2012, carbon monoxide in 2011, nitrogen dioxide and sulfur dioxide in 2010, and ozone and lead in 2008. Hence, PM, ozone, and lead may be reasonable candidates for IARC evaluation over the next several years to inform scientific and regulatory evaluations in the near future. Billions of dollars per year are being spent in the USA alone to achieve and maintain acceptable air quality related to these pollutants.

The second major type of air pollutant, the hazardous air pollutants (HAPs), has historically been a focus for source-specific emissions standards. In the USA, the 1970 Clean Air Act directed the United States Environmental Protection Agency (EPA) to identify and develop emissions standards to protect public health with an ample margin of safety. From 1970 to 1990, several HAPs were identified (e.g. mercury, benzene, beryllium, arsenic, coke oven emissions) and regulations were developed. Concerns about non-criteria pollutants increased substantially in the 1980s, due in part to the thousands of people killed and injured by a large accidental emission of methyl isocyanate from an industrial facility in Bhopal, India. It became evident that substantial public exposure could be occurring in the USA, through a toxics release inventory mandated by provisions of the Emergency Planning and Community Right-to-Know Act of 1986 and expanded by the Pollution Prevention Act of 1990. In 1990, the United States Congress identified 188 chemicals and compound groups as HAPs under Section 112 of the Clean Air Act. The list was developed from an evaluation of state and local agency efforts in the USA to control non-criteria pollutants, coupled with the potential for the agents to be present in ambient air, among other factors. This list has been the focus in the USA of technology-based emissions standards and, subsequently, residual risk evaluations intended to ensure protection of public health.

Prioritization approaches and data input

Four approaches and data are described and evaluated: (1) emissions data from the Toxics Release Inventory; (2) information from the Integrated Risk Information System; (3) potential risk data for a subset of HAPs based on emissions information evaluated in the United States National Air Toxics Assessment; and (4) a subjective evaluation.

Toxics Release Inventory

The Toxics Release Inventory (TRI) provides insights on the potential for human exposures (in the USA) to more than 650 chemicals emitted to the air, water, and waste sites from facilities that meet certain criteria (e.g. employ at least 10 workers, manufacture or use in excess of 10 000 pounds of a chemical in a year) (http://www.epa.gov/tri). Emissions from smaller facilities that also emit chemicals (e.g. dry cleaning facilities) are not included.

The most current TRI data indicate that for many chemicals the largest environmental releases are from fugitive and point-source air emissions. In addition, the quantity of emissions to the air of these various agents spans > 7 orders of magnitude; hence, the potential for human exposure is also highly variable among these agents. It is important to note, however, that emissions do not relate directly to exposure and risk.

Integrated Risk Information System

The EPA's Integrated Risk Information System (IRIS) collects information in support of prioritization efforts (http://www.epa.gov/iris). The IRIS programme reviews scientific information for priority environmental pollutants. It develops hazard characterization and dose–response evaluations for cancer and non-cancer health end-points through a process that includes internal and external expert peer review. Through IRIS, EPA provides the highest quality science-based human health assessments to support environmental decision-making by EPA and other organizations.

Since 1997, the IRIS programme has sought nominations for high-priority chemicals and other substances for assessment or reassessment from EPA regulatory and other programmes, regional offices, other United States federal agencies, and the public. The chemicals identified through this process reflect, in aggregate, priorities resulting from EPA programme activities.

The criteria used by the EPA Office of Research and Development to evaluate nominations include:

- Statutory, programmatic need for EPA
- Other stakeholder need
- Availability of scientific information
- Existing assessment available
- Widespread exposures, cross-media concern, and other factors.

Many of the IRIS assessments in progress at any time are for HAPs, and their presence on this list is an indicator of high priority to EPA. The chemicals nominated or being reviewed under the IRIS programme represent candidates for IARC evaluation.

National Air Toxics Assessment

The EPA conducted a National Air Toxics Assessment (NATA) for 1996 and again for 2005 (http://www.epa.gov/ttn/atw/natamain/). This national-scale assessment identified 33 air pollutants (a subset of 32 air toxics on the Clean Air Act list of 188 air toxics, plus diesel PM) of greatest potential concern in terms of their contribution to population risk.

Health effects tables support the NATA process by providing cancer hazard characterization and potency estimates, as well as non-cancer characterization. The web site includes a description of the information collected and cautions about the use of NATA summary information, which is subject to change.

Information from modelled population exposure, when coupled with health effects information on hazard and dose–response, has been used to estimate potential population health risks. The calculated distribution of lifetime cancer risk for the United States population, based on 1996 exposure estimates to all sources combined, is available at http://www.epa.gov/ttn/atw/nata/rcharts/figure06.pdf (along with important cautions about interpretation of modelling results). These results suggest that the lifetime cancer risks from individual pollutants range over several orders of magnitude, and in aggregate for the 29 chemicals or compound groups with cancer potency values, the lifetime cancer risks exceed 1 in 10 000 for a subset of the population most exposed to these chemicals.

A subjective synthesis

Analyses of information on emissions, health data, and health risk provide insights on potential priorities for IARC and other purposes. The information sources noted above present a means for looking across chemicals to evaluate their potential for risk and, to some extent, the possible availability of new information that might influence existing risk estimates. It must be cautioned that these analyses are limited and uncertain due to the methods used to collect the original data (TRI, NATA), evaluate existing data (IRIS), and conduct population modelling (NATA). In some ways, the most valuable information obtained from these analyses is that emissions and potential exposures vary widely and there are many gaps in our knowledge of health effects; therefore, looking at the emissions with the highest exposure potential is a reasonable approach.

Recognizing the chemicals that are most important to environmental

regulatory programmes may be useful as such perspectives reflect consideration of risk magnitude and confidence in the data used to support decision-making. The carcinogens most important to air toxics regulatory programmes include benzene, metals (arsenic, cadmium, chromium, beryllium, nickel), industrial chemicals or releases (1,3-butadiene, ethylene oxide, perchloroethylene, benzidine, hydrazine, 1,4-dioxane, acetaldehyde, naphthalene, polycyclic organic matter, ethylene dichloride, ethylene dibromide, p-dichlorobenzene, bis(2-ethylhexyl)phthalate, formaldehyde, acrylonitrile, methylene chloride, trichloroethylene and 1,1,2,2-tetrachloroethane, chloroprene, ethylbenzene, and vinyl acetate), and persistent chlorinated chemicals such as dioxin, polychlorinated biphenyls, and chlorinated pesticides. Although many of these chemicals have been evaluated numerous times, repeated evaluations are important as new information becomes available so that regulatory programmes have access to the most recent data and analyses. It is helpful to align the evaluations by IARC with new study data collected by the United States National Toxicology Program (http://ntp-server.niehs.nih.gov/) and with evaluations by IRIS and the Agency for Toxic Substances and Disease Registry (http://www.atsdr.cdc.gov/).

Some chemical groups such as the ketones, asbestos subgroups, various aldehydes, and phthalates are also obvious assessment candidates. Due to their relatively high cancer potency, metals as a group are generally of higher priority.

In addition, pollutant emissions from emerging or changing technologies are a priority, for example nanomaterials, emissions from new diesel engines, and gasoline PM. New information sources are also becoming available; the development of chemical dossiers by the Registration, Evaluation, Authorisation and Restriction of Chemical Substances (REACH) programme in Europe (http://ec.europa.eu/environment/chemicals/reach/reach_intro.htm) may provide information of substantial importance in identifying additional candidate chemicals for assessment.

There are many HAPs produced through atmospheric chemistry that may be important targets for IARC assessment. Claxton et al. (2004) reviewed the research on genotoxicity of ambient outdoor air and demonstrated that many compounds that would not be identified by TRI or NATA may be very important to public health. For example, they stated that the mutagenicity of PM organics is due to at least 500 identified compounds from varying chemical classes. These compounds present a challenge, and an opportunity, for assessment programmes.

It is important to keep in mind that available data focus on those pollutants we know the most about. There are many more chemicals emitted from industrial, residential, or commercial uses, emitted from gasoline and diesel engines, or produced through atmospheric chemistry, than we have satisfactory data for about emissions, exposures, and health effects. Recognition of these limitations

and staying vigilant to identify emerging health concerns is of significant value in prioritizing assessment activities.

Disclaimer

This document has been reviewed in accordance with United States Environmental Protection Agency policy. The views expressed in this chapter are those of the author and do not necessarily reflect the views or policies of the agency.

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Chapter 9. Household air pollution

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Household air pollution arising from the use of coal has long been recognized as a cause of lung cancer and possibly of cancers at other sites. Drawing on data from 19 studies in an unpublished review (unpublished review prepared for the Advisory Group to plan a series of IARC Monographs on air pollution and cancer, IARC, 2004), Tian and Smith investigated the risk of lung cancer associated with exclusive coal or mixed coal and biomass use for cooking and/or heating, from which they derived pooled, adjusted odds ratios (ORs) of 1.86 (95% confidence interval [CI], 1.48–2.35) for studies of men and women combined, 1.51 (95% CI, 0.97–2.46) for men only, and 1.94 (95% CI, 1.09–3.47) for women only. Tian and Smith also reviewed the prevalence of coal use, pointing out the extensive use in China and possible increases in rural areas, mechanisms of toxicity, tentative evidence for links with upper aerodigestive tract (UADT) cancers, and the presence of contaminants including arsenic (a known carcinogen for bladder, lung, and skin). The review concluded that tens of thousands of cancer deaths may be attributed to coal use in China, and that similar risks (although involving fewer households) were likely in other countries such as India and South Africa where coal is used in low-quality stoves for cooking and heating.

Since that review was conducted, several new studies and reports have become available that warrant updating this evidence. In 2010, the International Agency for Research on Cancer (IARC) published a Monograph on household use of solid fuels and high-temperature frying (IARC, 2010). Two new systematic reviews on coal and lung cancer have been published (Hosgood et al., 2011; Kurmi et al., 2012), one of which includes biomass and lung cancer (Kurmi et al., 2012), and another review has been initiated by Bruce et al. (unpublished work). Reviews carried out for the Global Burden of Disease (GBD) 2010 project's comparative risk assessment (CRA) included updating evidence on cancers of the UADT and uterine cervix, although evidence for these outcomes was not sufficient for inclusion in the GBD estimates. Results from this new CRA, which do include lung cancer from both coal and biomass use, were recently published (Lim et al., 2012). There is also concern about the health implications of kerosene use for cooking and lighting in developing countries, where simple stoves and lamps known to emit high levels of pollutants are often used. Currently, however, relatively few studies of cancer risk are available (Lam et al., 2012). Accordingly, this update reviews the existing

evidence on cancer risks associated with household use of both coal and biomass, with brief consideration of kerosene.

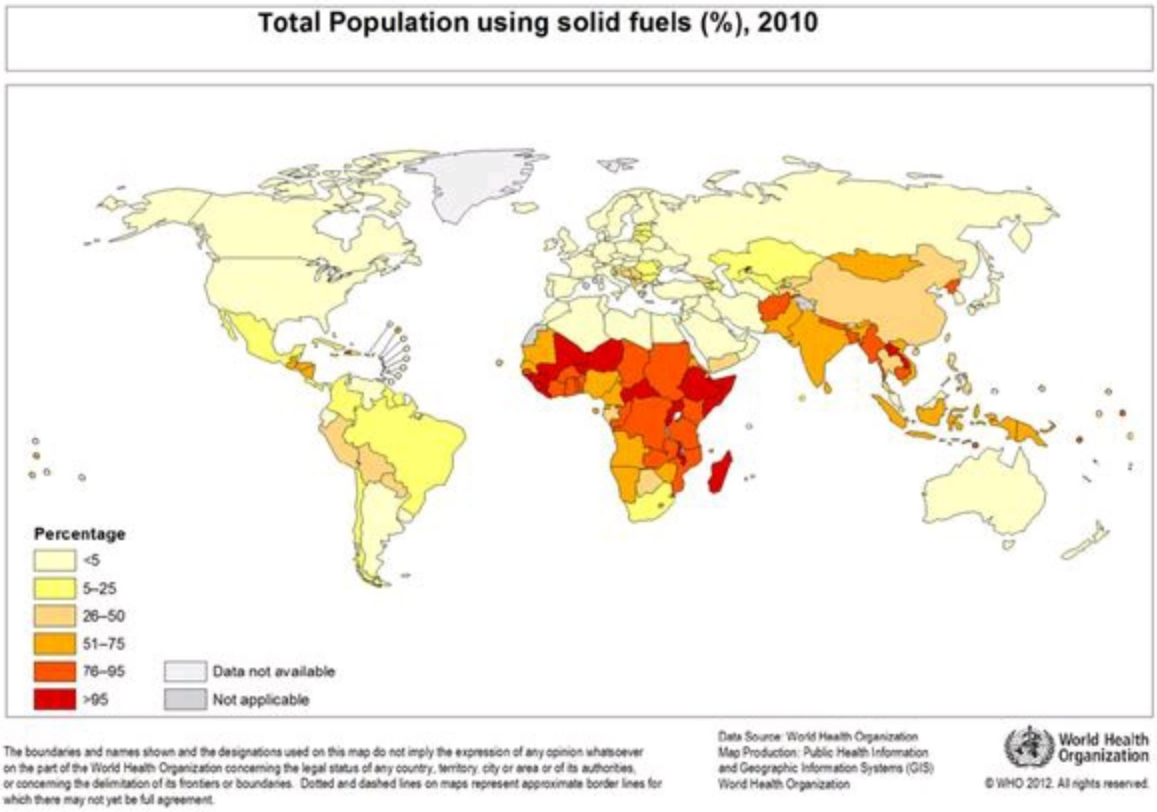
Trends in exposure

The World Health Organization (WHO) compiles data on household fuel use for cooking obtained through nationally representative surveys to assess risk from household air pollution exposure and to monitor trends (WHO, 2012a). Data from 586 surveys for 155 countries for 1974–2010 are available. The headline indicator percentage of homes using solid fuels as their primary cooking fuel is updated and published by WHO each year (WHO, 2012b), and a report on trends was recently published (Bonjour et al., 2013). Data on specific fuel type are available, and work is in progress to summarize these for cooking, heating, and lighting.

Solid fuel

Although the percentage of homes using solid fuels as the primary cooking fuel has fallen from 62% in 1980 to 41% in 2010, due to population growth the total number of people affected has remained steady at 2.8 billion (Bonjour et al., 2013). Prevalence is highest in Africa (77%) and South-East Asia (61%), but such fuels are still used by almost half (46%) of the population in the western Pacific region (Figure 9.1). The great majority of solid fuel use is biomass (i.e. wood, animal dung, crop waste, and charcoal), which is estimated to be used by approximately 2.4 billion people. Waste materials, including plastics, are also reportedly used as household fuels and may present cancer risks, but we are not aware of any reliable estimates of their use or of studies of health risks they impose.

Figure 9.1. Households using solid fuels as the primary cooking fuel, by country, 2010. Source: WHO (2012b); reproduced with permission from the World Health Organization.



Coal

Coal continues to be used by substantial numbers of households for cooking and heating, although data on heating use are sparse. Table 9.1 summarizes estimates for the percentage of homes (and equivalent populations) using coal for cooking in countries for which nationally representative surveys conducted since 2005 are available. China has the largest number of users, with 25% of homes still using coal in 2005, although several other countries have similar proportions of users. Even though only 2% of homes in India are thought to be using coal for cooking, given the population of 1.22 billion (2012) this figure translates into more than 20 million people at risk of exposure in homes that use coal for cooking, in addition to other residents of neighbourhoods where coal is used. While there has been a downward trend in some countries, as noted by Tian and Smith in their unpublished review, coal use may be increasing in rural China as biomass becomes scarcer.

Table 9.1. Recent estimates from national surveys of the proportion of households primarily using coal for cooking

Country	Year	Survey[a]	Proportion of households (%)	Population using coal[b]
Afghanistan	2010	MICS	< 1	–

Antigua and Barbuda	2007	National Survey	1	887
Bhutan	2010	MICS	< 1	–
Bosnia and Herzegovina	2005	MICS	1	37 601
Burkina Faso	2006	National Survey	1	164 687
China	2005	Census	25	335 333 800
Congo	2009	DHS	3	121 287
Democratic People’s Republic of Korea	2008	Census	46	11 199 270
Dominican Republic	2007	DHS	4	397 093
Guinea	2005	DHS	19	1 896 502
India	2006	National Survey	2	24 492 290
Kazakhstan	2005	MICS	15	2 403 955
Kenya	2008	DHS	1	405 127
Kyrgyzstan	2005	MICS	14	746 791
Lao People’s Democratic Republic	2006	MICS	21	1 302 188
Mongolia	2005	MICS	19	523 640
Montenegro	2005	MICS	4	25 260
Peru	2010	National Survey	3	872 295
Serbia	2010	MICS	< 1	–
Solomon Islands	2007	National Survey	2	10 763

South Africa	2010	National Survey	1	501 328
Sudan	2006	National Survey	14	6 097 272
Swaziland	2006	National Survey	< 1	–
Tajikistan	2005	MICS	1	68 786
Ukraine	2007	DHS	2	908 967
Viet Nam	2011	MICS	2	2 020 514

[a] DHS, Demographic Health Survey, USAID; MICS, Multi-Cluster Indicator Survey, UNICEF.

[b] Values are estimated by multiplying the percentage of households primarily using coal for cooking by the 2010 population figures.

Compiled from WHO (2012a).

Assuming that the percentage of homes relying on coal has changed minimally, if at all, since the most recent survey, the total number of people using coal for cooking in 2010 is estimated to be about 400 million, with more than 300 million in China alone (assuming that the percentage of households using coal on the most recent national survey [2005 or later] is equivalent to the percentage of the total 2010 national population). Currently, no useful estimates are available of the number of people using coal for heating because many homes using coal for cooking will also use it for heating, while others cooking with cleaner fuels will use coal for heating. Exposure levels resulting from coal heating can be expected to vary markedly between countries and settings, depending on the nature and quality of the stove, the coal, and the presence or absence and condition of the flue or chimney used.

Kerosene

The use of kerosene as the primary cooking fuel varies widely between developing countries, from zero to > 50% in urban areas of some countries, including Indonesia, Kenya, and Nigeria. Generally, use of kerosene for cooking is greater in urban than in rural areas. For most developing countries, the

proportion is < 10% in urban areas and < 5% overall (WHO, 2012a). The situation for lighting, however, is quite different as kerosene is the primary fuel for the great majority of homes where electricity is unavailable or unreliable, especially in sub-Saharan Africa. Use in rural areas is as great as, or greater than, that for urban homes, where electricity is more available. The majority of homes using this fuel for lighting do so with simple wick lamps.

IARC Monograph on household use of solid fuels and high-temperature frying

The IARC Monograph on household solid-fuel use, based on an expert group meeting held in 2006, reviewed the evidence from human epidemiological studies, animal studies, and mechanistic work and classified household coal use as carcinogenic (Group 1) and biomass use and high-temperature frying as probably carcinogenic (Group 2A) (IARC, 2010).

For coal, more than 20 case–control studies and one cohort study of lung cancer were reviewed, and those deemed to be most informative showed significant exposure–response relationships. Pooled estimates were not obtained as the purpose was to establish carcinogenicity, not effect size. For biomass, 13 case–control studies of lung cancer were reviewed. While many showed significantly increased risk with exposure, those deemed to be most informative did not provide data on duration of use or other measures from which exposure–response relationships could be assessed. Several other epidemiological studies of lung cancer that combined biomass and coal in the exposed groups or used proxies (such as years of cooking, perceived smokiness, reported fumes from cooking, and kitchen location) were also reviewed. Studies of other cancer sites including UADT and uterine cervix were reviewed, but no firm conclusions about causality could be reached (further details below).

In the overall evaluation of household coal use, the human epidemiological research was assessed as providing sufficient evidence of carcinogenicity, as was the animal evidence on carcinogenicity of emissions and of extracts from coal-derived soot. For biomass, the human epidemiological evidence was assessed as limited, as was the animal evidence on carcinogenicity of emissions, although the evidence for carcinogenicity of woodsmoke extracts was judged to be sufficient.

Reviews of household fuels and lung cancer since

Coal use

Sixteen English-language and nine Chinese-language case–control studies published through 2009 were reviewed using criteria that included specifying coal use distinct from biomass use (Hosgood et al., 2011). The intervention-based study that reported ORs of 0.59 (95% CI, 0.49–0.71) for men and 0.54 (95% CI, 0.4–0.65) for women (Lan et al., 2002) was not included in the meta-analysis by Hosgood et al. (2011), as this was restricted to case–control studies. The overall pooled OR for all studies was 2.15 (95% CI, 1.61–2.89), but this was associated with very substantial statistical heterogeneity (I^2 = 90.4%).

The majority of studies were from mainland China and Taiwan, China, and were used for more detailed sensitivity analysis focused on identifying estimates by sex and determining whether design issues affected the risk estimates in any substantive way. Pooled ORs were 2.50 (95% CI, 1.56–4.00) for women (eight studies) and 2.76 (95% CI, 1.44–5.27) for men (three studies). For nonsmoking women (three studies) the OR was 2.93 (95% CI, 1.40–6.12), but no studies were available for nonsmoking men. Various study design features did not produce very different effect estimates, other than for three rural studies with an OR of 3.28 (95% CI, 1.46–7.39). This finding may, however, have been confounded by geographical variations across China, analysis of which found the highest risk (OR > 2.5) among six studies in the south, south-eastern, and south-western parts of the country, including Xuan Wei. A key conclusion of the review was that while risks of lung cancer with household coal use may vary by location and type, elevated risks are seen with coal use across a wide range of settings.

The second systematic review, published by Kurmi et al. (2012), examined cancer risk with exposure to both coal and biomass (see below). For coal, 22 studies including Chinese-language studies were included. While all study designs were eligible, most were case–control in design and inclusion criteria required that effect estimates were adjusted. The overall pooled OR was 1.82 (95% CI, 1.60–2.06), with evidence of statistical heterogeneity (I^2 = 43.4%). Sensitivity analysis reported pooled ORs of 1.54 (95% CI, 1.25–1.88) for men (three studies) and 1.70 (95% CI, 1.40–2.06) for women (10 studies), and a larger effect in the studies combining men and women. Analysis by histological type found the largest risk for squamous cell carcinoma (five studies) (OR, 3.81; 95% CI, 1.37–10.58) compared with adenocarcinoma (four studies) (OR, 2.22; 95% CI, 1.60–3.08), but histology was not available for the majority (16 studies). Effect estimates for smoking-adjusted studies and nonsmokers were very similar. Notable among other methodological subgroup analyses was a larger effect for Chinese-language studies (which may relate to higher exposures in that country, or parts of it as identified by Hosgood et al., 2011)

and a trend of increasing effect estimates with lower quality exposure assessment (based on the Newcastle-Ottawa scale).

Conclusion: coal and lung cancer

Coal continues to be widely used as a cooking fuel by approximately 400 million people, with an additional unknown number using coal for heating. The 2010 IARC Monograph on household use of solid fuel and high-temperature frying found household use of coal to be a Group 1 carcinogen. Recent systematic reviews provide estimates of the increased risk of lung cancer associated with exposure to be about 2.0, with higher risk in women (> 2) reflecting their higher levels of exposure. The geographical variation in reported risk estimates, which are highest in southern China (> 2.5), may well reflect higher exposures as well as use of coal with greater carcinogenic potential. However, nearly all of the available studies lacked measurements of particulate matter (PM) or other indicators. Consequently, the exposure gradients within the studies cannot be quantified and also cannot be compared across studies; however, considerable variation in levels and exposure gradients across the studies is likely. Contaminants in coal, including arsenic, present additional risk. WHO estimated that coal used for cooking was responsible for 36 000 lung cancer deaths in 2004. Given the technological challenges in burning coal cleanly in homes (including removal of toxins such as arsenic), policy on household fuel use should aim for the complete substitution of coal with cleaner fuels and should closely monitor levels and trends in the household use of coal.

Biomass

Given that biomass is used by some 2.4 billion people for cooking, even a small elevated cancer risk would, if confirmed, have very important public health implications. As noted above, the human epidemiological evidence on biomass and cancer was assessed by IARC as limited, although some support for carcinogenicity was available from animal (limited) and mechanistic (sufficient) studies. The reviews published and in preparation since the 2006 IARC workshop provide some new and updated perspectives on the evidence.

The published review, part of the same paper that reported on coal and lung cancer risk, found seven studies, including one with separate estimates for males and females and one with estimates for squamous cell carcinoma and adenocarcinoma, but none in the Chinese language (Kurmi et al., 2012). Two other studies included mixed coal and biomass use in the exposed group. In a pooled analysis, there was marginally significant statistical heterogeneity (I^2 = 41.2%, P = 0.092) and an OR of 1.50 (95% CI, 1.17–1.94). A set of sensitivity analyses similar to those for coal were carried out, although the relatively small

number of studies limited the conclusions. The OR for females (five studies) was 1.98 (95% CI, 1.44–2.73), but there was only one estimate for males. Only two of the studies provided data by histological type. There was no assessment of exposure–response data.

The review by Bruce et al. (unpublished work) searched for studies on household use of biomass, but required estimates for cooking (separate from other uses such as heating) for the GBD 2010 analysis, and found 11 case–control studies eligible for meta-analysis. These included a re-analysis of data from the European study by Lissowska et al. (2005) carried out by IARC for this review in order to obtain sex-stratified estimates for cooking and to examine exposure–response relationships. There was no evidence of publication bias, moderate heterogeneity (I^2 = 41%), and a pooled OR of 1.23 (95% CI, 1.03–1.48), but with evidence of a larger but marginally nonsignificant effect for women of 1.31 (95% CI, 0.99–1.74), P = 0.06 when stratified by sex.

As noted previously, all of the studies used proxy descriptions for exposure measurements. Of crucial importance was the finding that seven (of the 11) studies did not specify the type of cooking fuel used in the unexposed group and, in at least one study, wood may have been compared with some solid fuel use including coal (Gupta et al., 2001). Sensitivity analysis of the studies for which the comparison group used cleaner fuel found stronger and significant ORs of 1.26 (95% CI, 1.04–1.52) for men (two studies) and 1.81 (95% CI, 1.07–3.06) for women (five studies). A recent report of a pooled analysis of previously unpublished data from four European and North American studies found a significant risk for wood use for cooking or heating of 1.21 (95% CI, 1.06–1.38) (Hosgood et al., 2010), but this report was excluded from the meta-analysis because wood use for heating and cooking were combined. Assessment of exposure–response data found no good evidence of such a relationship except in the re-analysis of Lissowska et al. (2005), which was based on duration of wood use for heating or cooking as a percentage of lifetime use. There was a significant (P < 0.01) adjusted trend for men but not for women; similar findings for use of coal for heating or cooking were reported.

Summary: biomass and lung cancer

Biomass is still used as the primary cooking fuel by approximately 2.4 billion people, while many more use wood for heating, including in rural areas of developed countries. Although the trend is generally downward for biomass as a cooking fuel, levels remain high in some countries, with little change in the past 10 years, notably in sub-Saharan Africa. Household use of biomass fuel was assessed as probably carcinogenic (Group 2A) by IARC. Since the 2006 IARC review, a few new studies of lung cancer and a re-analysis of one have strengthened the epidemiological evidence somewhat, but it is still hampered by poor definition of exposure comparisons and limited exposure–response data.

However, with pooled ORs only slightly less than those for coal, the presence of known carcinogens in wood smoke, and IARC's assessment of animal and mechanistic evidence, it seems highly probable that biomass smoke at the levels common across developing countries increases the risk of lung cancer. Further evidence comes from a recent analysis of the exposure–response relationship for combustion-derived fine PM ($PM_{2.5}$) and lung cancer, which includes estimates from both second-hand and active smoking, a form of exposure to pollutants from biomass combustion. This is consistent with the association of exposure to household-derived biomass smoke at the average levels typically recorded (several hundred g/m^3) being associated with an elevated lung cancer risk (Pope et al., 2011). Confirmation and further quantification of the risk of lung cancer from household biomass use with research designs that address current methodological limitations, including exposure assessment, should be a research priority.

Cancer of the upper aerodigestive tract

A systematic review carried out for the GBD 2010 project found 13 case–control studies of solid fuel use and cooking. Studies of nasopharyngeal cancer (nine studies) were analysed separately for those reporting on cancer of the larynx, oropharynx, and hypopharynx (four studies) as these have distinct risk factor profiles. Exposure was assessed as solid fuel since there was insufficient information to separate coal and wood.

Nasopharyngeal cancer

Five studies were considered for meta-analysis, although there was very substantial and significant statistical heterogeneity (I^2 = 89%) as well as wide variation in the methods of exposure assessment and generally weak designs. The pooled OR was 1.10 (95% CI, 0.98–1.24), but overall the evidence was determined to be inadequate to support a causal association.

Cancer of the larynx, oropharynx, and hypopharynx

The four studies included showed significant statistical heterogeneity (I^2 = 78%, P = 0.008) and a significant pooled OR of 1.90 (95% CI, 1.39–2.59). Again, exposure assessment was variable and unclear, and only one study compared solid fuel use against cleaner fuel. While these investigations suggest that there may well be increased risk of cancers of the larynx, oropharynx, and hypopharynx with solid fuel use in the home, further studies are required.

Cancer of the uterine cervix

A further systematic review conducted for the GBD 2010 project found three case–control studies of cancer of the uterine cervix for exposure to wood (Ferrera et al., 2000; Velema et al., 2002; Sierra Torres et al., 2006) and one for coal (Wu et al., 2004). For wood use, one study was of cervical dysplasia and carcinoma in situ, but all three found significantly elevated risks among human papillomavirus (HPV)-positive women, with ORs in the range of 3–7, but much smaller effects (not statistically significant) in HPV-negative women. Although neither of the two Honduran studies was adjusted for smoking, few women smoked; significant exposure–response relationships were reported based on duration of exposure (Ferrera et al., 2000; Velema et al., 2002). In the one study on coal exposure from Taiwan, China, a nonsignificant OR of 2.09 (95% CI, 0.86–5.10) comparing coal with gas was reported.

This limited set of studies does suggest that there may be an increased risk of cancer of the uterine cervix with household use of solid fuel, and this would be consistent with the well-established evidence from smoking, which is another form of exposure to pollutants from biomass combustion. Given the high incidence and mortality of cervical cancer, particularly in rural areas of developing countries where exposure to solid fuels in the homes is highest, further research on this risk should be a research priority.

Kerosene

A recently published systematic review on kerosene reported levels of pollutants and exposure and covered evidence on health implications (Lam et al., 2012). IARC has previously found inadequate evidence that kerosene is a human carcinogen; limited evidence is available for animals as well (IARC, 1989). Kerosene emissions include both formaldehyde and polycyclic aromatic hydrocarbons, both classified by IARC as Group 1 carcinogens. Levels of particulate pollution from widely used kerosene lamps were found to be high during use, reaching more than 6000 µg/m^3 for total suspended particulate with simple wick lamps, somewhat lower for hurricane lamps, and 40 µg/m^3 in one study of pressurized lamps. Studies of cooking with kerosene (stove type not stated in all studies) found indoor 24–48 hour average concentrations of PM_5 in the range of 590–1280 µg/m^3, while 24 hour personal PM_5 exposures were similar (450–1650 µg/m^3). Even allowing for the short averaging times (1–2 hours) and particle size fractions in the lighting studies, these levels far exceed

WHO air quality guideline levels for particulate matter (WHO, 2005).

Few studies on the risk of cancer from kerosene use are available. In their review, Lam et al. (2012) reported three case–control studies from the Hong Kong Special Administrative Region for which unadjusted ORs range between 0.75 (95% CI, 0.32–1.70) and 17.8 (95% CI, 6.2–7.0), but exposure comparisons are either not specified or include solid fuels. One other case–control study of lung cancer, from urban Cuba, found nonsignificant adjusted ORs for lung cancer among individuals using kerosene versus those using gas of 1.26 for women (95% CI, 0.81–0.95) and 1.14 for men (95% CI, 0.87–1.47) (Esquivel et al., 1996). A study of salivary gland cancer reported an OR of 3.0 (95% CI, 1.4–6.8) but was judged as hard to interpret because of few cases and many exposures (Lam et al., 2012).

Conclusions

The household use of solid fuels for cooking and heating remains prevalent across developing countries, and solid fuel is also widely used for heating in mainly rural areas of developed countries (usually in higher quality, vented stoves). While the majority of solid fuel use is biomass, coal remains important and its use may be increasing in some settings.

IARC has classified coal use as Group 1 (carcinogenic) and biomass as Group 2A (probably carcinogenic). Recent reviews find ORs for lung cancer with household coal use of about 2, higher for women and in southern China, while ORs for household biomass use are somewhat lower.

Household use of coal and biomass may also increase the risk of other cancers, including those of the UADT and uterine cervix (the latter is among the most common female cancers in developing countries where solid fuel use is greatest), but further research is needed to confirm these relationships.

When last estimated, the burden of cancer from solid fuel use was restricted to exposures and outcomes for which evidence was best established, namely coal use and lung cancer. About 36 000 deaths and 338 000 disability-adjusted life years were attributed to this exposure, the great majority in China (WHO, 2009).

Kerosene is widely used in developing countries, especially for lighting, and the simple wick stoves and lamps used by most households emit high levels of pollutants, including carcinogens. The few studies on cancer risk are limited by exposure assessment and adjustment for confounding, but do suggest that there may be an increased risk that warrants further investigation.

Air pollution from household coal use already results in a substantial cancer risk, and if the estimates reported here for biomass exposure and links with

kerosene use and other common cancers such as that of the uterine cervix are confirmed, this will further increase the cancer burden. These cancer risks add weight to the urgency of ensuring a rapid transition by all households to technologies and fuels that deliver clean household air, and the need to focus attention on the importance of substituting coal.

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Chapter 10. Using experimental data to evaluate the carcinogenicity of mixtures in air pollution

Joe Mauderly

It is well recognized that the air pollution encountered by humans is a mixture of pollutants that varies from place to place and with time. Acknowledgement of the full complexity of the mixture is an appropriate starting point to consider approaches to research the carcinogenicity of air pollution and evaluate the evidence. Current regulatory and research strategies tend to disregard the full complexity of the mixture. A small number of widespread pollutant species or classes that are known or thought to be of key health importance have been given highest priority for regulatory attention. In response, most research efforts have been directed towards these few pollutant groups. This situation is quite understandable; however, to move forward, it must first be recognized that the multipollutant dilemma (Mauderly et al., 2010) extends far beyond interactions among a few widely monitored species. In short, the carcinogenic hazard of air pollution cannot be understood by considering only those few pollutant species that are measured routinely and for which epidemiological evidence is available.

In the USA, for example, most regulatory and research energy is focused on the six criteria pollutants (carbon monoxide, lead, nitrogen dioxide, ozone, particulate matter [PM], and sulfur dioxide) named in the Clean Air Act (as amended in 1990), which leaves few resources to be directed towards the 33 urban air toxics designated as most important among the 188 hazardous air pollutants (HAPs) (EPA, 1999, 2001a, 2004), and fewer yet are directed towards the remaining 155 HAPs. HAPs exist in the particulate, vapour, and gas phases, and many are listed because of their known or suspected carcinogenicity. Very little attention is given to the myriad other natural and anthropogenic air contaminants that are not on these lists.

Air pollution is not only complex but also a mixture of mixtures that can vary considerably with time and location. A single example suffices to demonstrate the point. Diesel engine emissions constitute one of the embedded mixtures that receive considerable regulatory and research attention. There has been a tendency to treat diesel emissions as if they were a single material of some relatively constant composition. Very few health studies have characterized the exposure material beyond a few physical–chemical species, and many have reported only the PM mass concentration. Two reports described in detail the exposure atmospheres that resulted from dilution of emissions from two

different contemporary engines operated under different conditions and not equipped with emission reduction technologies. Both listed more than 100 physical–chemical parameters, acknowledged falling short of full speciation, and demonstrated that PM was only a small portion of the emitted mass. In one case (McDonald et al., 2004a) the mass concentration of volatile organic carbon species was approximately equal to the mass concentration of PM, and in the other (McDonald et al., 2004b) PM constituted only 1% of the total mass of measured emissions and was 5-fold less than the mass of volatile organic carbon species. A third report described the marked change in the composition of emissions from one of the engines that was equipped with a catalysed PM trap and burned a different fuel (McDonald et al., 2004c), demonstrating that diesel emissions have become even more heterogeneous during the current period of phase-in of progressive emission controls. Impacts of the striking evolution of the composition of diesel emissions on estimates of carcinogenic hazard from this source category were recently reviewed (McClellan et al., 2012). The diesel example illustrates challenges that international differences in source technologies and changes in source emissions with time present to summarizing carcinogenic hazards from source-based embedded air pollution mixtures.

Déjà vu: does air pollution present a unique mixture dilemma?

Perhaps not. The challenges presented by the experimental assessment of the carcinogenic hazards of air pollution are no different, for the most part, from those encountered in the assessment of the carcinogenic hazard of any physically and chemically complex mixture of known and potential mutagens, carcinogens, and promoting agents. The International Agency for Research on Cancer has dealt with complex mixtures in the past (e.g. tobacco smoke and diesel emissions, both of which are components of ambient air pollution) and is familiar with the difficulties involved in designing informative experiments and interpreting experimental evidence. The research challenges of selecting the material to study, the biological test system and response indicators, and the experimental design are considerable, but fundamentally no different for air pollution than for other complex mixtures of varying composition. The biological research tools, which range from chronic inhalation bioassays of whole mixtures to dosing cultured cells with specific chemical fractions, are no different for air pollution than for other mixtures (and are not reviewed in detail here). Accordingly, the interpretive challenges associated with these issues are similar for air pollution and other mixtures. This commonality, however, does not mean that the answers are straightforward; these fundamental issues have not been

fully resolved for any mixture. The two main lines of evidence for the carcinogenicity of air pollution are conceptually similar to those for the carcinogenicity of other mixtures. Epidemiology has demonstrated associations between common pollutants and cancer (e.g. fine PM and sulfur oxides) (Pope et al., 2002), and there is experimental evidence for the mutagenicity or carcinogenicity of individual compounds or components of air pollution (e.g. DeMarini, et al., 2000; Claxton et al., 2004). Similarly, there is suggestive epidemiological evidence for the carcinogenicity of engine emissions, and some individual components of emissions are proven carcinogens or mutagens (EPA, 2001b). These two lines of evidence suggest that there are two principal types of source material for studies of the carcinogenicity of air pollution and other mixtures: the mixture and components of the mixture.

There are additional issues on mixed exposure that are also conceptually similar for air pollution and other mixtures. The ratio of components could be important to the carcinogenicity of the mixture. A first-order index of hazard might be developed by adding the products of the concentrations and relative potencies of the known carcinogenic components. However, it must be remembered that non-carcinogenic components also probably influence the carcinogenicity of the mixture, such as by acting as promoters (Madden et al., 2000) or by creating mutagenic reaction products (Finlayson-Pitts and Pitts, 1997). The extent to which air pollution acts as a complete carcinogen undoubtedly depends on this factor. Moreover, issues on mixed exposure range beyond simply evaluating exposures to mixtures (reviewed in NIOSH, 2004). For example, the combination of exposure to ambient air pollutants and other factors (e.g. indoor air pollution, occupational carcinogens, and diet) could influence the relationship between ambient air pollution and cancer. It is also possible that the sequence of exposures to different pollutants, or to air pollution and other factors, may influence the risk of cancer.

Air pollution presents one dilemma that, while not strictly unique, is especially important in this case. Assuming that by air pollution we mean the complete mixture of ambient air contaminants, it must be recognized that there are very few complete physical–chemical characterizations of air pollution in any location, and certainly not in many locations or at many times. It can be assumed with confidence that cancer hazard is not limited to the species that are measured routinely. In contrast to at least limited detailed characterizations of embedded mixtures such as diesel emissions (cited above) and tobacco smoke (e.g. Guerin, 1987; Guerin et al., 1987; IARC, 2004), there are few, if any, exhaustive characterizations of ambient air. There have been a few detailed characterizations of air pollution in the conduct of individual studies (e.g. Klemm et al., 2004) and in monitoring programmes designed for that purpose (e.g. the United States Environmental Protection Agency PM Supersites Program, www.epa.gov/ttn/amtic/-supersites.html), but the scope of such data is small. This gap impairs the ability to select representative ambient sites and times to

use for real-time exposures, to model air pollution mixtures in the laboratory, and to place the composition of air pollution mixtures into context regarding the composition of the mixtures for which we have the greatest body of experimental data.

Pathways and pitfalls: what can we learn from prior use of experimental tools to assess carcinogenic hazards of complex mixtures?

It should be instructive to consider the experience gathered to date with using experimental data to evaluate the carcinogenicity of complex mixtures. A complete review is not attempted here, but two cases–cigarette smoke and diesel emissions–are offered as illustrative examples. These examples are examined by considering the different approaches (exposure and biological response models) that have been used and their outcomes. There is little reason a priori to expect better or worse success in using these approaches for air pollution.

There is epidemiological evidence for the carcinogenicity of both cigarette smoke and diesel emissions, but with very different degrees of certainty. Clearly a strong epidemiological link exists between cancer and tobacco smoke (reviewed in IARC, 2004), and although there is also a large body of experimental data that confirm the mutagenicity and carcinogenicity of tobacco smoke components, experimental data are not needed to confirm the cancer hazard or to assist in estimating risk. However, experimental data continue to be sought from cellular and animal models to understand carcinogenic mechanisms, to improve early detection and chemoprevention, and to develop safer smoking alternatives. In contrast, the epidemiological evidence for the cancer risk in humans from diesel emissions remains suggestive but uncertain. This is in large part due to the lack of exposure data (reviewed in IARC, 1989; EPA, 2001b; Bunn et al., 2002). As for tobacco smoke, there is a large body of data that demonstrate the mutagenicity and carcinogenicity of components of historic diesel emissions, primarily soot-borne organic compounds. Experimental data were initially sought to confirm a cancer hazard and, considering the uncertainty of the epidemiological database, to assist in estimating the risk of cancer in humans (CalEPA, 1988). Experimental data continue to be sought to understand carcinogenic mechanisms and to compare the hazards of different emissions.

Chronic inhalation bioassays of cancer using conventional

strains of rodents

For both cigarette smoke and diesel emissions, there is a long history of attempts to define carcinogenic hazard by chronic inhalation bioassays. The outcomes and interpretive challenges, however, have differed markedly between the two mixtures. Until recently, the many attempts to produce statistically significant increases in the incidence of lung tumours in rodents exposed chronically to tobacco smoke failed (reviewed in Mauderly et al., 2004). Probable reasons include the failure of intermittent, nose-only, puff-by-puff exposures to achieve lung doses that model those incurred by human heavy smokers and the statistical weakness of small treatment groups. Using larger treatment groups and a conventional whole-body exposure approach that was estimated to model lung doses received by smokers of more than three packs per day produced significant increases in the incidence of lung tumours in both Fischer 344 rats (Mauderly et al., 2004) and B6C3F1 mice (Hutt et al., 2005). Moreover, the studies demonstrated genetic changes in lung tumour cells of rodents that mirror those of cancers in human smokers. Thus, conventional (i.e. not selected for genetic susceptibility) strains of rats and mice can model the human carcinogenicity of cigarette smoke.

In contrast, the first wave of studies on diesel emissions demonstrated conclusively by the mid-1980s that chronic whole-body inhalation exposures of conventional strains of rats (Fischer 344 and Wistar) to extreme concentrations (2.2–7.0 mg/m^3 PM) of fresh emissions produced significant dose-related increases in the incidence of lung tumours and accompanying DNA adducts (reviewed in Mauderly, 1999). Identical exposures of Syrian hamsters or standard strains of mice were not carcinogenic. However, a second wave of studies demonstrated that the response in rats was not related to organic mutagens; clean carbon black, and even titanium dioxide, caused the same response (including the adducts) with the same exposure–response slope (Heinrich et al., 1995; Nikula et al., 1995). Moreover, the lung tissue responses to heavy exposures to poorly soluble PM were found to differ between rats and primates (Nikula et al., 1997). This experience led to awareness of the rat-specific particle lung overload phenomenon (Mauderly and McCunney, 1996) and an improved understanding of the utility of the rat for evaluating cancer hazard from PM and mixtures that contain PM (Mauderly, 1997). Finally, analysis of the results of multiple studies revealed a threshold for significant increases in the incidence of lung tumours in rats that was much higher than environmental exposures to diesel emissions (Mauderly, 1999; Valberg and Crouch, 1999). Recent technology on-road emissions contain very little PM, often in lower concentration than in ambient air (McClellan et al., 2012). These findings do not prove that there is no risk of cancer to humans from environmental exposures to diesel emissions; rather, they demonstrate some of the potential complexities and important precautions for high-dose studies of

poorly soluble PM.

The experiences with chronic inhalation bioassays of cancer of tobacco smoke and diesel emissions provide lessons that are relevant to the use of such approaches for complex mixtures of air pollutants. The approach may be more sensitive for some physical–chemical species than for others, but this is not readily predicted in advance. The general approach remains a standard for assessing lung cancer hazard, assuming that suitable exposure atmospheres can be identified, but careful attention must be given to the experimental design. Advantage is gained by using multiple species, multiple exposure concentrations, sufficient group sizes, and measures of genetic alterations, and by avoiding unrealistic exposure concentrations. The selection of exposure concentrations has been reviewed, and guidance is available (Lewis et al., 1989; Haseman and Lockhart, 1994).

Subchronic inhalation assays using genetically susceptible rodents

It would be desirable to have a sensitive bioassay that induced lung tumours but did not require near-lifetime exposures or large numbers of animals. Lung adenoma-prone mice have been used in attempts to develop such an assay, in which the increase in incidence and multiplicity of lung adenomas (nearly all benign) is examined in mice exposed subchronically (typically for 3–6 months) and then held for a few months after exposure. This assay is responsive to chemical mutagens and carcinogens (Stoner and Shimkin, 1982) and thus might be considered for use with atmospheres of complex air pollution.

This tumorigenicity assay has been used as an index of the cancer hazard of both cigarette smoke and diesel emissions. The experience with cigarette smoke has been variable. Increased incidences of adenomas have been produced in A/J, Balb/c, and SWR mice by simulated environmental cigarette smoke (D'Agostini et al., 2001; Witschi et al., 2002), but attempts using simulated mainstream smoke did not produce increases (Finch et al., 1996; D'Agostini et al., 2001). In a later study (Reed et al., 2004), A/J mice were exposed for 6 hours per day on 7 days per week for 6 months to old technology diesel emissions at multiple concentrations up to 1000 mg/m^3 PM and held for 6 months without exposure before lung adenomas were assessed. This protocol produced no dose-related increase in the incidence of adenomas, although the PM extracts had characteristic direct-acting mutagenicity in the Salmonella reverse mutation assay. Even if the results from this assay were consistent, there would be considerable uncertainty in extrapolating from tumorigenicity in genetically susceptible mice to human lung cancer hazard. However, the variable results with cigarette smoke and lack of response to high concentrations of old technology diesel emissions do not provide encouragement for using this approach to evaluate the carcinogenic hazard of air pollution.

Non-inhalation in vivo and in vitro assays

An alternative to direct experimental evaluation of the carcinogenicity of air pollution as a complete mixture is to evaluate the carcinogenic hazard of individual components of the mixture and thereby infer the cancer hazard of the mixture. A wide array of test systems is available to evaluate the mutagenicity, adduct-forming potential, clastogenicity, and carcinogenicity of components of air pollution and other complex mixtures. Examples are mutations in bacteria, mammalian cells, and intact animals, indices of chromosomal injury (e.g. sister chromatid exchange or micronuclei), indices of DNA injury (e.g. methylation or adduct formation), and tumour formation after instillation, injection, or implantation with extracted materials. No attempt is made to review these approaches in detail here as they all present the same set of fundamental advantages and disadvantages. Most of the common assays have been applied to components of both cigarette smoke (e.g. condensate) and diesel emissions (e.g. PM extract). For both mixtures, numerous assays have clearly demonstrated the presence of mutagenic, clastogenic, and carcinogenic components.

It has long since been demonstrated that components of air pollution are genotoxic. As an example, Seagrave et al. (2006) demonstrated marked differences in bacterial mutagenicity among ambient fine PM samples collected at different locations in the south-eastern USA. From such data, the plausibility of a cancer hazard from air pollution is already well established. Indeed, if demonstration of the plausibility of hazard without regard for dose or demonstration of carcinogenicity is sufficient, then little further work need be done.

There are several difficulties in using these approaches to estimate the actual human carcinogenic hazard presented by mixtures of air pollution. First, the relation between responses of these assays and cancer hazard for humans remains a perennial question, and the degree of confidence varies among the assays. Second, it is typically difficult to establish a relation between the cellular doses achieved in these assays and those incurred during real-world exposures of humans. Understanding the exposure–dose–response relationship is the key to extrapolating from hazard to human cancer risk. Third, the ability to extrapolate from the activity of individual components to the activity of the mixture is poor, even if we could assess the genotoxicity or carcinogenicity of each component of the mixture. The prevalent default assumption for estimating the cancer risk from mixtures is to assume that the cancer risks from individual components are additive (e.g. EPA, 1986, 1993). However, not only is it uncertain whether the activities of all genotoxic components are truly additive, it is also uncertain how the promoting activities of the many cytotoxic and inflammatory components of the air pollution mixture might influence the carcinogenicity of that mixture.

Identifying the culprit: what experimental designs can be used to disentangle the contributions of mixture components?

Assuming that a few typical air pollution mixtures could be defined and either located in the environment or reproduced for experimental study, the above approaches could be used to estimate the hazard of the mixtures. Reducing risk, however, requires knowledge of the components and sources that contribute most strongly to the hazard of the mixture. The fundamental approaches to evaluating the contributions of components to the effects of mixtures have been reviewed (Mauderly, 1993, 2004) and are summarized here. There are two fundamental approaches: study mixtures (top-down) and study components (bottom-up).

Top-down: the brute force approach

Clearly experiments cannot be conducted with every possible mixture of air pollutants; indeed, the number or nature of all air contaminants is not known. Studying realistically complex pollution mixtures requires selecting locations and times in the actual environment or simulating selected combinations of air contaminants in the laboratory. A study in the actual environment involves the challenges of the inability to predict detailed composition in advance, to hold composition constant for repeated exposures, or to concentrate all components identically to achieve (along with dilution) multiple exposure concentrations that exceed the highest ambient levels. Laboratory simulation necessarily falls short of the full spectrum of air contaminants and typically excludes many atmospheric reaction products. However, complex mixtures of key pollutants, such as representative combustion source emissions, can be (and have been) generated and studied experimentally.

There are two general top-down pathways for determining the causal components of complex mixtures. The most common is the physical–chemical dissection, or the bio-effect directed fractionation approach, in which the mixture is divided progressively and the fractions are tested until the most active ones are identified. A good example was the bio-effect directed fractionation of organic extracts of diesel PM to determine that certain nitro-aromatic compounds primarily drive the bacterial mutagenic activity (e.g. Schuetzle and Lewtas, 1986). This approach can potentially be used with any reproducible biological assay and is technically limited only by the ability to separate the different physical–chemical fractions of the mixture and satisfactorily expose the biological system. The study of concentrated ambient PM is a variant of this approach. With current methods, only the PM is

concentrated, which prevents a study of the complete mixture in its original ratio of components.

An alternative approach is to conduct identical evaluations of different mixtures and use multivariate statistical analysis to determine the components that co-vary most closely with the target biological response. This mathematical dissection strategy is amenable to any database that encompasses mixtures that have sufficient differences in both composition and toxicity. For example, combined principal component analysis and partial least-squares regression were applied to a database on the bacterial mutagenicity and lung toxicity of several combined PM and semivolatile organic compounds from gasoline and diesel emissions (McDonald et al., 2004c). This study demonstrated that certain, but not total, nitro-aromatic compounds co-varied most closely with mutagenicity (which was previously known and served to validate the approach) and that engine oil tracers co-varied most closely with inflammation of the lung (which was not previously known). In addition, multivariate analysis of PM components was used to determine that silica (assumed to arise from street dust) co-varied most closely with electrocardiographic changes in dogs exposed to concentrated PM (Wellenius et al., 2003). On a somewhat larger scale, the National Environmental Respiratory Center programme (http://www.nercenter.org) (McDonald et al., 2004b; Reed et al., 2004) followed this strategy by building a detailed database on the composition of several complex source emissions (e.g. diesel and gasoline emissions, wood smoke, road dust, and coal emissions) and a range of respiratory and cardiovascular responses. The identification of key components as the putative causes of pro-atherosclerotic vascular responses in mice (Seilkop et al., 2012) suggests that this general strategy may have utility for identifying key carcinogens in highly complex air pollution mixtures.

Bottom-up: paralysis by permutation

Interactions between mixture components to cause biological effects can also be explored using a factorial approach (i.e. effects of A, effects of B, effects of A + B). For example, this approach was used by Anderson et al. (1992) to examine the relative contributions of aerosolized carbon and sulfuric acid to the effects of the combined materials on the respiratory function of asthmatics. It was also used by Kleinman et al. (2000) to examine interactions between ozone, carbon black, and ammonium bisulfate that cause changes in lung inflammation, cell division, and collagen in rats, and this approach requires confidence that the key components have been identified. More importantly, although this approach is very useful for testing hypotheses about interactions between a few components, the number of permutations of combinations of exposure becomes overwhelmingly large beyond three components.

Choosing the right stuff: how do we select the exposure atmosphere?

Assuming that a suitable biological system and experimental design can be identified, selecting the exposure atmosphere is a critical issue. It is important to recognize that there is no correct air pollution mixture. The three basic choices are to (i) use actual ambient air at some location and over some time period and accept the inherent variations in composition and concentration; (ii) generate in the laboratory a simpler, but still complex, mixture of pollutants in some average ratio; or (iii) generate in the laboratory complex source emissions that are important components (embedded mixtures) of ambient pollution. The second and third approaches are commonly used, and examples are given above.

Only a few experimental exposures to ambient air have used the natural ratio of components. For example, Moss et al. (2001) exposed rats directly to air in Mexico City for up to 49 days and evaluated respiratory tissues; no histopathology was found compared with rats exposed to clean air. More relevant to carcinogenicity, Soares et al. (2003) exposed mice for 120 days to air in Sao Paulo, Brazil, and found greater frequencies of micronuclei in circulating blood in those mice than in mice exposed in a location with less pollution. Somers et al. (2004) exposed mice to ambient air with and without filtration and found that the PM fraction was chiefly responsible for the induction of heritable mutations. Although this approach is inherently challenging, these studies demonstrate that it is possible to expose animals directly to ambient air pollution, and the study of Somers et al. provides direct evidence of a clastogenic effect of air pollution. Exposures to ambient air cannot be controlled beyond selecting location, time, and dilution. Relating effects to the composition of the mixture is dependent on the level of characterization of the exposure, including both the number of analytes and the frequency of analysis.

Conclusions: what to do now?

There is no straightforward answer to the dilemmas faced in the experimental assessment of the carcinogenicity of air pollution. There is no single correct experimental approach, and the exposure material is extremely complex and variable. Certainly, experimental results have provided and will provide a basis for the plausibility of a risk of cancer by demonstrating both cancer hazards

from individual pollutants and evidence of genotoxicity from exposures to ambient air. The former presents no great advance because it has been known for some time that many individual pollutants are mutagenic or carcinogenic, and most major contributing sources can probably be identified. That line of investigation could be pursued to identify the principal genotoxic components of ambient pollution, the relative hazards presented by different pollution sources, and genotoxic interactions among pollutants. The results will not confirm or define actual cancer risk, but they will be useful, together with human exposure assessment and cancer epidemiology, in the overall assessment of risk and identification of its sources.

Chronic inhalation bioassays of ambient air can be conducted, but one has to be sceptical about their likely productivity because of their uncontrolled nature and the inability to exceed ambient exposure concentrations. It would be very challenging to conduct near-lifetime inhalation exposures of large numbers of animals to ambient air, but it is not impossible and may be valuable. Based on negative results from heavy exposures to source emissions that contain known mutagens and carcinogens (e.g. old technology diesel emissions at concentrations < 2 mg/m^3 PM), it is reasonable to assume this would be insufficient to cause increases in the incidence of lung tumours in standard strains of animals. The present high level of uncertainty in interpreting tumorigenicity results from genetically susceptible animals prevents giving substantial weight to results from their exposure to ambient air.

Overall, it must be decided whether there is value in the experimental demonstration of lung cancer in animals from chronic exposure to actual air pollution. If so, alternatives to designing a study of ambient air can then be explored, despite the challenges and limitations. If not, then there may not be a great need for further experimental work related solely to air pollution. It is known that components of air pollution are genotoxic and some are carcinogenic. The challenge therein, of course, is to determine whether to accept that evidence in view of the typically much lower long-term doses received from actual exposures to air pollution.

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Chapter 11. Mechanistic considerations for air pollution and lung cancer: genotoxicity and molecular biomarker data from experimental and human studies

Kirsti Husgafvel-Pursiainen

It has long been postulated that lung cancer may result from long-term exposure to ambient air pollution; the actual excess risk has nevertheless been estimated to be considerably less than that associated with tobacco smoking (Higgins, 1976; Pershagen, 1990). In confirmation of the early studies, recent epidemiological investigations have observed an association between outdoor air pollution and lung cancer mortality. It appears that particulate matter (PM), a complex mixture of airborne solid particles and aerosols, is the component causing serious health effects, for example mortality due to cardiovascular diseases and lung cancer (Dockery et al., 1993; Hemminki and Pershagen, 1994; Beeson et al., 1998; Abbey et al., 1999; Cohen, 2000; Pope et al., 2002; Vineis et al., 2004). In particular, long-term exposure to ambient fine particles (aerodynamic diameter < 2.5 μm [$PM_{2.5}$]) has been associated with lung cancer mortality (or incidence) in studies carried out in different parts of the world and among nonsmokers (Dockery et al., 1993; Beeson et al., 1998; McDonnell et al., 2000; Pope et al., 2002, 2004; Laden et al., 2006; Beelen et al., 2008; Katanoda et al., 2011; Turner et al., 2011; Raaschou-Nielsen et al., 2011). One extended follow-up study, the Harvard Six Cities Study from 1974–2009, demonstrated that the association between $PM_{2.5}$ exposure and lung cancer mortality was statistically significant, with a linear concentration–response relationship without a threshold observed down to the $PM_{2.5}$ level of 8 $\mu m/m^3$ (Lepeule et al., 2012). In terms of lung cancer deaths, the annual contribution from ambient air pollution to lung cancer mortality has been estimated to be responsible for more than 60 000 deaths worldwide, while more than 700 000 deaths are attributable to cardiac and non-malignant respiratory diseases (Cohen, 2003).

Sources and constituents of ambient air particulate matter

Airborne particulate pollution is emitted when organic material is burned. There are several major anthropogenic sources of this pollution, such as emissions from traffic (especially diesel-powered vehicles) and other sources such as industrial installations and power stations (see other chapters for more detail). Despite several decades of research, it is not well understood how and why various factors, such as emission site, source, type of emission and exposure concentration, non-particulate fractions and particulate extractable organic matter (e.g. volatile and semivolatile organic compounds), as well as atmospheric transformation products, contribute to the toxicity and biological effects of ambient air pollution (White, 2004; de Kok et al., 2006; Künzli et al., 2006; Claxton and Woodall, 2007; Lewtas, 2007; Steenhof et al., 2011; Benbrahim-Tallaa et al., 2012; also discussed in other chapters).

If one examines the major chemical constituents, then it appears that many complex mixtures from combustion emissions share qualitatively similar profiles; for example, a large number of well-known carcinogens and genotoxicants have been identified in all types of emissions (Claxton et al., 2004: Claxton and Woodall, 2007; Lewtas, 2007; see other chapters). Polycyclic aromatic hydrocarbons (PAHs), in particular mixtures of different PAH compounds, constitute an important class of established genotoxicants and carcinogens (IARC, 1989, 2004; Lewtas and Gallagher, 1990; Boffetta et al., 1997; Claxton et al., 2004; Armstrong et al., 2004; Claxton and Woodall, 2007; Lewtas, 2007; Benbrahim-Tallaa et al., 2012). It is known that genotoxicity and carcinogenicity can also be induced by other chemical components present in ambient air pollution in addition to PAHs (Heinrich et al., 1986; Claxton et al., 2004; Claxton and Woodall, 2007). Differences in the biological effects of these non-PAH components, including their genotoxic and pulmonary inflammatory properties, are to a larger extent dependent on physicochemical characteristics such as particle size and surface area. Moreover, adding to the complexity, the adverse effects of these agents can be mediated via different cellular pathways (Schins, 2002; Donaldson et al., 2002, 2003; Li et al., 2003; Knaapen et al., 2004; Künzli et al., 2006; de Kok et al., 2006; Claxton and Woodall, 2007).

Genetic alterations and epigenetic modifications in human lung cancer

Large proportions of human cancers are sporadic and have mostly an environmental etiology (Lichtenstein et al., 2000; Wogan et al., 2004). A complex, multifactorial disease, human cancer develops through a multistep process with genomic changes representing the driving force. Key oncogenes and tumour suppressor genes (the somatic driver genes) are frequent targets of

genetic alterations, in particular mutations (somatic driver mutations) that enable cells to escape growth control and to assume malignant features by disrupting central signalling pathways and networks (Hanahan and Weinberg, 2000; Wood et al., 2007; Hanahan and Weinberg, 2011; Hammerman et al., 2012; Imielinski et al., 2012).

During the past two decades or so, epigenetic modifications–the cancer epigenome–have emerged as another major class of molecular alterations involved in cancer development, with epigenetics taking on a role comparable in significance to that of genetics (Jones and Baylin, 2002; Baylin and Jones, 2011; Berger et al., 2011; Esteller, 2011). Evidence for a close link between the genomic and epigenomic changes has emerged; in other words, genes that directly control the epigenome are also frequent targets of inactivating mutations (You and Jones, 2012). Recent efforts applying exome and whole-genome sequencing have highlighted the importance of the histone modifier genes as one class of driver mutations in lung cancer (Hammerman et al., 2012; Imielinski et al., 2012).

Along with increasing knowledge of the central molecular features of human cancer, many of the key alterations have become recognized as biomarkers that can be used in translational clinical studies (Baylin and Jones, 2011; Heyn and Esteller, 2012), molecular epidemiology research (Olivier et al., 2010; Herceg and Vaissière, 2011; Schulte et al., 2011), and cancer chemoprevention (Huang et al., 2011). Also, given the fact that it is almost impossible to obtain direct mechanistic information, molecular biomarker data from human lung cancer associated with relevant exposures are of great value when evaluating the evidence for an association between ambient air pollution and the elevated lung cancer risk demonstrated in epidemiological studies.

Aim of the current review

There is wide-ranging and comprehensive literature extending over three decades on the many toxic and other adverse biological effects of exposure to ambient air pollution, including experimental studies conducted both in vitro and in vivo. There are several extensive and thorough reviews that have compiled and discussed the data and identified the major knowledge gaps that still exist (White, 2004; Claxton et al., 2004; de Kok et al., 2006; Claxton and Woodall, 2007; Benbrahim-Tallaa et al., 2012). Data from human molecular biomarker studies on cancer examining the mechanisms involved in lung carcinogenicity of airborne complex mixtures have focused primarily on TP53 gene mutations and aberrant DNA methylation of an array of cancer-related genes implicated in human lung cancer. Currently, much of the data on lung cancer originates from

smokers, with fewer studies describing lung cancer associated with combustion-related indoor exposure to PAHs. It is more challenging to elucidate the difficult and complex issue of outdoor air pollution and human lung cancer by using the same or similar approaches. This chapter briefly reviews some of those data as a way of providing a mechanistic foundation for the epidemiological findings on the association between air pollution and lung cancer (Vineis and Husgafvel-Pursiainen, 2005; Demetriou et al., 2012). However, no attempt is made to conduct an exhaustive review of the large and continuously growing body of relevant studies; that is beyond the scope of this chapter, and these enormous data sets have been comprehensively and systematically reviewed elsewhere (Claxton et al., 2004; Claxton and Woodall, 2007; Demetriou et al., 2012).

Genotoxicity, mutations, and related biomarkers

Experimental studies on genotoxicity

The properties of outdoor air pollution from anthropogenic, combustion-related sources have been tested for mutagenicity in various systems and experimental settings for many decades. There is now overwhelming evidence that the ambient air contains hundreds of genotoxic compounds. Genotoxicity has been detected in in vitro and in vivo assays for diesel exhausts, diesel exhaust particles, organic solvent extracts from diesel exhaust PM, urban air particulates, and gasoline exhausts (Ames, 1979; IARC, 1989; Claxton et al., 2004; DeMarini, 2004; de Kok et al., 2006; Claxton and Woodall, 2007; Lewtas, 2007; Benbrahim-Tallaa et al., 2012). However, many of the diverse biological mechanisms underlying the toxic, inflammatory, DNA damaging, and carcinogenic effects still remain unidentified (Krewski et al., 2003; Harrison et al., 2004; Claxton et al., 2004; de Kok et al., 2006; Claxton and Woodall, 2007; Lewtas, 2007).

The mutagenicity of airborne particulates is estimated to be attributable to at least 500 identified components in many different chemical classes (Claxton et al., 2004; Claxton and Woodall, 2007). Furthermore, the size range of airborne particles collected and the chemical reactions occurring in the atmosphere contribute to the complex nature of the genotoxic potential of the ambient air (Claxton et al., 2004; Claxton and Woodall, 2007). For instance, in many studies the quantity of extractable PM, the concentrations of carcinogenic PAHs, as well as the genotoxicity, appear to be higher in winter samples than in summer samples (Binková et al., 1999; Zhao et al., 2002; Farmer et al., 2003; Shi et al., 2003; Castaño-Vinyals et al., 2004; Ramgolam et al., 2009).

In addition to PAH-related damage to DNA, there are abundant data from cell-

free systems and experiments using cultured mammalian or human cells revealing that various types of particulates, including diesel exhaust, traffic-related PM/urban dust particles, and wood smoke, can all evoke oxidative stress and subsequent damage to DNA, mainly DNA single-strand breaks or 8-oxo-2′-deoxyguanosine (8-oxo-dG) (Risom et al., 2005, 2007; de Kok et al., 2006; Shi et al., 2006; Danielsen et al., 2011; Benbrahim-Tallaa et al., 2012). Animal experiments have demonstrated that besides diesel exhaust, ambient air can also induce oxidative DNA damage in rodent lung tissue, and some of these effects have been detected at low doses (Nagashima et al., 1995; Ichinose et al., 1997; Tsurudome et al., 1999; Iwai et al., 2000; Sato et al., 2000; Aoki et al., 2001; Risom et al., 2003, 2005, 2007; Dybdahl et al., 2004; Danielsen et al., 2010).

It has been proposed that the oxidative damage related to particulate air pollution is at least partially due to the particles per se–that is to say, the insoluble particle core (Schins, 2002; Donaldson et al., 2003; Karlsson et al., 2004; Knaapen et al., 2004; de Kok et al., 2006; Møller et al., 2010). According to much of the published data, it is both the particulates, in particular the fine dust fraction $PM_{2.5}$, and the soluble chemical substances that are involved in inducing oxidative DNA damage, with possible influences from other components present in the polluted air (Adamson et al., 1999; Bornholdt et al., 2002; Claxton et al., 2004; Risom et al., 2005; Karlsson et al., 2008; de Kok et al., 2005, 2006; Claxton and Woodall, 2007). In general, a crucial role of small PM size fractions (< PM_{10}) has also been recognized for toxicity and genotoxicity of ambient air and traffic-related PM (de Kok et al., 2006; Claxton and Woodall, 2007).

Carcinogenicity and mutations in rodent assays

The carcinogenicity of diesel exhaust has been extensively studied and documented in animal assays over several decades (Heinrich et al., 1986; Mauderly et al., 1987, 1994; IARC, 1989; Mauderly, 1994; Iwai et al., 1997; Pott and Roller, 2005; Lewtas, 2007; Benbrahim-Tallaa et al., 2012); however, only a few studies have applied in vivo cancer bioassays to actual ambient air samples (Claxton and Woodall, 2007). If one tries to assess the relative roles of chemical substances versus particulates in carcinogenicity in rats in vivo, then it would seem that only 1% of the carcinogenic potency can be explained by organic substances, with only a minimal concentration of adsorbed PAH (Pott and Roller, 2005; Roller, 2009). The strong carcinogenic effect of diesel engine exhaust particles observed in rat inhalation studies is postulated to be due to the small size of the particles (Roller and Pott, 2006; Roller, 2009).

An International Agency for Research on Cancer Monograph Working Group that convened in Lyon in June 2012 concluded that there was sufficient evidence in experimental animals for the carcinogenicity of whole diesel engine exhaust,

diesel engine exhaust particles, and extracts of diesel engine exhaust particles (Benbrahim-Tallaa et al., 2012). For gasoline exhaust, another significant contributor to urban air pollution, the Working Group concluded that there was sufficient evidence in experimental animals for carcinogenicity of condensates of gasoline engine exhaust (Benbrahim-Tallaa et al., 2012).

In vivo transgenic rodent assays have revealed both positive and negative results on the ability of diesel exhaust PM to induce transgene mutations in lung tissue (Sato et al., 2000; Dybdahl et al., 2004; Müller et al., 2004). In the earlier studies, lung tumours from rats exposed by inhalation to diesel exhaust exhibited a low frequency of Kras and p53 gene mutations (Swafford et al., 1995; Belinsky et al., 1997). A high rate of Kras mutations in adenomas and adenocarcinomas of the lung was reported after exposure by intratracheal instillation (Iwai et al., 1997).

The human TP53 knock-in (Hupki) mouse model represents another experimental approach for studying DNA damaging agents (Luo et al., 2001; Olivier et al., 2010; Kucab et al., 2012). This is based on a mouse model with a partial knock-in of the human TP53 gene and is designed for investigation of TP53 gene mutations (Luo et al., 2001; Liu et al., 2004). The in vitro assay uses immortalized embryonic fibroblasts from the Hupki mouse (HUFs) and has been shown to mimic mutagenesis of the human TP53 gene (Liu et al., 2004; Olivier et al., 2010). HUFs treated with a mutagen and a suspected human carcinogen present in diesel exhaust and urban ambient air, 3-nitrobenzanthrone (3-NBA), were found to harbour mutations in the human DNA-binding domain of the Hupki TP53 gene (vom Brocke et al., 2009; Kucab et al., 2010). The most frequently observed mutation was a G:C → T:A transversion, consistent with the presence of persistent 3-NBA-guanosine adducts in the DNA of the exposed cells, and in accordance with earlier studies on 3-NBA-induced mutations. Furthermore, six of these transversions have repeatedly been found in human lung tumours (vom Brocke et al., 2009). In the same manner, an earlier investigation revealed evidence for the induction of human TP53 gene mutations in HUFs after exposure to benzo[a]pyrene (B[a]P), another common pollutant in urban ambient air and tobacco smoke (Liu et al., 2005). The B[a]P-induced mutations detected in the human TP53 sequence in HUFs were mainly (41%) G:C → T:A transversions, again in concordance with the TP53 mutations observed in human lung tumours (Liu et al., 2005). The principal type of mutation (G:C → T:A) found in the human TP53 sequence in HUFs was also in keeping with the main class of mutations detected in the cII gene in the livers of lambda/lacZ transgenic mice (Muta Mouse) exposed intraperitoneally to 3-NBA (Arlt et al., 2004), as well as with the detection of the gpt gene mutations in the lungs of another transgenic (gpt delta) mouse strain after inhalation of diesel exhaust (Hashimoto et al., 2007).

Germline mutagenicity in animals

In addition to the genotoxicity observed in somatic cells, heritable mutations at repetitive DNA loci have been reported to occur in association with air pollution. A series of studies made use of both experimental and sentinel animals to investigate heritable effects after exposure to ambient air at industrial sites and at locations with air pollution from traffic (Somers et al., 2002, 2004; Somers and Cooper, 2009; Somers, 2011).

Laboratory mice were caged outdoors near two integrated steel mills and a major highway in Canada and examined for the presence of expanded simple tandem repeat (ESTR) mutations (Somers et al., 2004). After the mice were housed for 10 weeks at the site, the ESTR mutation rate was increased in comparison with offspring of the unexposed control mice, with the majority of mutations being transmitted through the paternal germline. However, the mutation rate was reduced by 50%, down to levels measured at a rural reference location, in those animals for whom the air was filtered through a high-efficiency particulate air (HEPA) filter, which removed practically all (> 99%) particles > 0.1 μm in diameter (Somers et al., 2004). The data from laboratory studies with individual chemicals have suggested that the cells sensitive to the induced DNA damage were pre-meiotic germ cells (Vilariño-Güell et al., 2003; Somers et al., 2004). A previous study described a 1.5–2-fold increase in the germline mutation rate at the same repetitive loci in laboratory mice housed at an industrial/urban site compared with rural controls, but the experimental setting did not allow for identification of either the causative agents or the fractions (Somers et al., 2002). Before these studies on laboratory mice housed outdoors in areas with air pollution, a series of experiments on long-lived, non-migratory birds (herring gulls) living near industrial areas consistently observed elevated rates of germline mutations (Yauk and Quinn, 1996; Yauk et al., 2000; Somers and Cooper, 2009).

In a continuation study, mice from an inbred strain (C57BL/CBA) (as opposed to the outbred mice used in the earlier investigation) were exposed in situ to ambient air at the same industrial/urban site as in the original study. This study quantified the induced ESTR mutations at three time points, evaluated mutations arising directly in sperm, and characterized DNA lesions (DNA adducts, strand breaks, and global methylation) in the exposed and control (HEPA-filtered air at the same site) animals (Yauk et al., 2008). A 1.6-fold increase in sperm ESTR mutation frequency was detected in mice exposed for 10 weeks, followed by a 6 week break, compared with the control animals, indicating that the mutations had been induced in spermatogonial stem cells. While no bulky adducts were detected in the testes DNA, lung DNA was positive for DNA adducts in the exposed mice compared with control mice caged with HEPA filters. However, strand breaks (at 3 and 10 weeks) were observed in sperm DNA, suggesting that oxidative rather than PAH-related chemical DNA damage had occurred in

the mice after the exposure to particles and the associated airborne pollutants. A persistent increase in epigenetic modification (global hypermethylation) in the sperm DNA was also found in mice exposed to ambient air (Yauk et al., 2008). The ESTR mutation induction observed in this study in the sperm of the exposed inbred mice was similar to that detected in the previous study in the offspring of the outbred mice (Somers et al., 2004).

These findings suggest that germline mutagenicity (i.e. induction of mutations that can be passed on to the unexposed next generation) due to air pollution is likely caused by the PM fraction of ambient air; in other words, by mutagens bound to the particles and/or the particles themselves. The central role of particles is supported by the positive findings of strand breaks in the sperm DNA but negative results on PAH-related adducts in the testes DNA in mice caged in a polluted area (Yauk et al., 2008). The mice studies further demonstrate a predominant effect on male germ cells, which is transmissible to the offspring (Somers et al., 2004; Somers and Cooper, 2009; Somers, 2011).

The described series of studies on germ cell mutagenicity of air pollution is supported by investigations demonstrating that tobacco smoke, both mainstream smoke and sidestream smoke, causes germ cell mutations in exposed mice (Yauk et al., 2007; Marchetti et al., 2011). Consequently, it has been postulated that air pollution and tobacco smoke should be classified as germ cell mutagens that may be active at concentrations and through mechanisms also relevant for humans (Demarini, 2012). However, it is of note that multiple mechanisms, not all comprehensively understood, are likely involved in tandem repeat mutagenesis, and, in field experiments, it was not possible to differentiate between true germline mutations that occurred during gametogenesis and mutations that may have affected early cell divisions in the developing embryos after fertilization (Samet et al., 2004; Somers and Cooper, 2009).

Biomarker studies on genotoxicity in exposed human subjects

Biomarker studies investigating genotoxic effects in various human populations (including studies in children and newborn infants) living in environments with air pollution have been conducted for decades, and many, but not all, have reported positive findings (Perera et al., 1992, 2002; Farmer et al., 1996; Srám et al., 1996; Hemminki and Veidebaum, 1999; Srám and Binková, 2000; Kyrtopoulos et al., 2001; Neri et al., 2006a, 2006b).

DNA damage measured as ^{32}P-postlabelled aromatic adducts has been identified in white cells from peripheral blood of individuals exposed to urban air pollution (Farmer et al., 1996; Peluso et al., 1998; Whyatt et al., 1998; Autrup et al., 1999; Palli et al., 2001; Ruchirawa et al., 2002; Perera et al., 2005; as reviewed in Castaño-Vinyals et al., 2004 and Demetriou et al., 2012). Similar to experimental studies, oxidative DNA damage (8-oxo-dG) and/or DNA single-

strand breaks have emerged as an important class of genotoxicity detected in lymphocyte DNA or nasal respiratory epithelium in groups of adults and children with exposure to outdoor air particulates (Calderon-Garciduenas et al., 1996; Valverde et al., 1997; Calderón-Garcidueñas et al., 1999; Loft et al., 1999; Sørensen et al., 2003a, 2003b).

DNA damage was measured by the comet assay in outdoor workers in Mexico City. These workers were found to exhibit significantly higher levels of DNA damage (tail length in comet assay) and a greater percentage of cells with high DNA damage compared with indoor workers (Tovalin et al., 2006). The magnitude of the DNA damage was found to be positively correlated with the exposure of the workers to $PM_{2.5}$ and ozone (Tovalin et al., 2006). In Denmark, nonsmoking bus drivers exposed to urban air pollution (i.e. mainly traffic exhaust fumes) exhibited increased urinary mutagenicity in the Salmonella mutagenicity assay compared with mail carriers (Hansen et al., 2004).

Cytogenetic effects (chromosome aberrations, micronuclei, and sister chromatid exchange) have been found in groups of healthy individuals in various geographical locations worldwide. In particular, cytogenetic damage has been observed among traffic policemen in many, but not all, studies. In addition, cytogenetic investigations that have taken into account in the analyses ambient exposure to PAHs, B[a]P, or ozone, or effect modification by various susceptibility genotypes have often reported positive findings (Chandrasekaran et al., 1996; Bolognesi et al., 1997a, 1997b; Zhao et al., 1998; Knudsen et al., 1999; Michalska et al., 1999; Burgaz et al., 2002; Carere et al., 2002; Leopardi et al., 2003; Huen et al., 2006; Ishikawa et al., 2006; Sreedevi et al., 2006, 2009; Rossnerova et al., 2009; Rossner et al., 2011). Special attention has been paid to the role of benzene exposure in this context (Hrelia et al., 2004). With regard to mutations, no increase in the frequencies of hypoxanthine-guanine phosphoribosyltransferase (HPRT) gene mutations in adults has been found in studies that have included this gene as one of the set of molecular markers being investigated (Farmer et al., 1996; Kyrtopoulos et al., 2001; Perera et al., 2002).

Biomarker studies on exposure of children and newborn infants to ambient air pollution from various urban and other locations, and in different study settings, have reported genotoxicity in a variety of ways, for example DNA adducts (aromatic or PAH–DNA adducts; 8-oxo-dG), protein adducts (albumin or haemoglobin adducts), other DNA damage such as DNA strand breaks, and chromosomal aberrations (Calderón-Garcidueñas et al., 1996, 1997, 1999; Bocskay et al., 2005; Neri et al., 2006a, 2006b; Huen et al., 2006; Orjuela et al., 2010). In particular, studies have investigated pregnant women living in areas with ambient air pollution, often from traffic. In Poland, cord blood samples from newborn infants of mothers living in heavily polluted areas exhibited significantly increased frequencies of aromatic DNA adducts and HPRT gene mutations, also seen after adjustment for maternal smoking,

suggesting transplacental genotoxicity (Perera et al., 2002). In all, several mother–newborn infant cohorts living in areas with heating- or traffic-related air pollution in Poland, the USA (New York City), and China have consistently reported B[a]P-related DNA damage in the newborn infant (leukocytes from umbilical cord blood) in association with maternal exposure to ambient air PAHs (most studies were conducted with nonsmoking mothers); this reflects increased susceptibility of the fetus to DNA damage due to prenatal PAH exposure (Perera et al., 2004, 2005; Jedrychowski et al., 2013; Perera, 2008).

Effects on reproductive health in humans

There are several studies linking exposure to high levels of air pollution with adverse effects on male reproductive health, although with somewhat variable results; mainly damage to sperm DNA, abnormal sperm morphology, and reduced sperm performance have been examined (Selevan et al., 2000; Rubes et al., 2005; Jurewicz et al., 2009; Somers, 2011; Demarini, 2012). There are also reports of a possible influence of genetic polymorphisms on susceptibility to the sperm DNA damage associated with exposure to air pollution (Rubes et al., 2010). In addition, numerous studies have investigated the associations between air pollution and female reproductive health, fecundability, and adverse pregnancy outcomes (Dejmek et al., 1999; Ritz et al., 2002, 2007; Liu et al., 2003; Perera et al., 2003; Srám et al., 2005; Slama et al., 2008; Wilhelm and Ritz, 2005; Wilhelm et al., 2012). One international collaborative study on air pollution and pregnancy outcomes noted the variability in results and study protocols used but reported that 6 (out of 14) studies had found a statistically significant adverse association between an increase in PM_{10} concentration and low birth weight (Parker et al., 2011).

Taken together, the current human biomarker data strongly suggest that genotoxicity (measured as DNA adducts, other DNA damage, cytogenetic effects, urinary mutagenicity) is one of the principal biological mechanisms associated with exposure to ambient air pollution in exposed healthy adults, children, and prenatally exposed newborn infants. There are, however, numerous qualifying issues, including those related to study design, characterization, and concentrations and sources of exposure, as well as issues of individual susceptibility to which attention needs to be paid when carrying out such studies. An accurate assessment of air particulate concentrations is needed to establish exposure–effect relationships. Some biomonitoring studies have included different levels of ambient pollution and carried out personal exposure measurements to overcome this problem (Kyrtopoulos et al., 2001; Sørensen et al., 2003a; Avogbe et al., 2005; Neri et al., 2006a, 2006b). In some studies a correlation has been reported between the extent of the biomarker damage and the level of personal exposure (Sørensen et al., 2003b; Tovalin et al., 2006).

TP53 mutations as a molecular biomarker in human lung cancer

The well-known and most frequently detected genetic alteration in human lung cancer, as in many other cancers, is mutation in the TP53 gene (Hollstein et al., 1991; Hainaut and Hollstein, 2000; Olivier et al., 2010). Some recent comprehensive efforts with exome and whole-genome sequencing have confirmed the key somatic driver mutation role of TP53 in lung cancer (Hammerman et al., 2012; Imielinski et al., 2012).

The spectrum and pattern of TP53 mutations encountered in human cancers have been widely used as a biomarker in the search for etiological factors involved in the carcinogenic process. As summarized in multiple reviews, there are several unique features that make TP53 gene mutations a well-suited molecular biomarker for monitoring DNA damage-related human carcinogenesis (Hussain and Harris, 1998; Pfeifer et al., 2002; Olivier et al., 2010; Meek, 2009).

Tobacco smoke (either directly inhaled by the smoker or second-hand smoke) and its various constituents are known to be genotoxic and mutagenic, as has been comprehensively documented (DeMarini, 2004; IARC, 2004; Husgafvel-Pursiainen, 2004). In keeping with this overwhelming evidence, an array of studies has demonstrated an association between mutations of the TP53 gene and exposure to tobacco smoke in human lung cancer (Hernandez-Boussard and Hainaut, 1998; Hussain and Harris, 1998; Pfeifer et al., 2002; Olivier et al., 2010). The data show that TP53 mutations occur more frequently in lung cancer among smokers than among never-smokers, and that the frequency of TP53 mutations is dependent on the daily amount of smoking (Pfeifer et al., 2002; DeMarini, 2004; Husgafvel-Pursiainen, 2004; IARC, 2004). Furthermore, the types and spectrum of mutations in TP53 are compatible with the presence of PAH-related bulky DNA adducts in the smokers' lung tissue, as well as with the type of DNA damage and mutations known to result from exposure to B[a]P and other PAH compounds (Hussain et al., 2001; Hainaut and Pfeifer, 2001; Pfeifer et al., 2002; DeMarini, 2004; Pfeifer and Besaratinia, 2009; Kucab et al., 2010).

Mutations in lung tumours from women exposed to PAHs

TP53 gene and Kras gene mutations have been investigated in lung tumours from Chinese (Xuan Wei County) nonsmokers exposed to domestic emissions from unvented firepits or stoves (DeMarini et al., 2001). The indoor combustion emissions from smoky coal contained high levels of PAHs. An exceptionally high mutation frequency (71%), in fact one of the highest frequencies ever reported for lung cancer, was found in the TP53 gene. The mutations primarily represented the types known to be related to PAH exposure in vitro (76% G:C →

T:A transversions, with 100% of the guanines involved being on the non-transcribed strand) (DeMarini et al., 2001). Similarly, the mutations in the Kras gene, although clearly lower in frequency (29%), were almost entirely G:C → T:A transversions (86%) (DeMarini et al., 2001). A follow-up of these findings in a larger set of lung cancer cases (n = 102), from nonsmoking women exposed to unvented coal smoke in their homes in Xuan Wei County, reported very similar findings (Keohavong et al., 2003) . Kras mutations were found in 9 women (21.9%), with G:C → T:A transversions accounting for 66.7% of the changes. The frequency and type of Kras mutations among the nonsmoking women were comparable to those found in smoking men from Xuan Wei and elsewhere in China (Keohavong et al., 2003). An extension of the study investigated sputum samples from individuals exposed to coal smoke but with no clinical signs of lung cancer. Of the 26 nonsmoking women included in the study, 2 (7.6%) had a TP53 mutation detected in the non-malignant epithelial cells present in sputum, whereas Kras mutations were absent (Keohavong et al., 2005).

There is an impressive amount of evidence proposing that indoor air exposure to PAHs can cause lung mutagenesis and carcinogenesis in nonsmoking women who use smoky coal for cooking and heating in their unvented homes in Xuan Wei. The lung cancer mortality rates in this county were among the highest for women in China (25.3/100 000; about 8 times the national average for women); almost all (> 99%) of the women were nonsmokers (Mumford et al., 1987). A long-term reduction was observed in the lung cancer incidence in Xuan Wei County after stoves for burning smoky coal were improved by adding chimneys (Lan et al., 2002). In a large retrospective cohort study, domestic use of coal in Xuan Wei County was demonstrated to be linked to highly elevated lung cancer risk, particularly in association with use of smoky coal compared with smokeless coal (hazard ratio for women, 99; 95% confidence interval, 37–266) (Barone-Adesi et al., 2012).

Biomarker studies and chemical analyses have provided further data for the etiological link between lung cancer in women in Xuan Wei and exposure to unvented smoky coal emissions with high levels of various carcinogenic PAH compounds (Mumford et al., 1987). Organic extracts of indoor air particles from smoky coal combustion exhibited tumorigenicity in a mouse skin assay (Mumford et al., 1990). Air measurement of B[a]P during cooking and measurements of urinary 9-hydroxy-B[a]P concentrations were indicative of high exposure to PAHs. PAH concentrations in indoor air during cooking using smoky coal indicated occupational levels of PAHs (mean concentration for B[a]P, 14.6 $\mu g/m^3$) (Mumford et al., 1995). The women were regularly exposed to emissions that contained 81% organic matter, of which 43% was PAHs (Granville et al., 2003).

DNA adducts were detected in peripheral blood white cells and placental samples from the exposed women (Mumford et al., 1993), and the presence and quantification of depurinated B[a]P-adducted DNA bases in the urine also

demonstrated damage due to PAH (B[a]P) exposure (Casale et al., 2001). When extracts of smoky coal emissions were tested in various Salmonella tester strains, they exhibited a mutagenicity profile that was consistent with that of PAHs (Granville et al., 2003). A prevalence of G:C → T:A transversions (78–86%) was observed that closely resembled those induced by cigarette smoke condensate (78%) and B[a]P (77%) (Granville et al., 2003). Again, the frequency of G:C → T:A transversions detected in Salmonella was in accordance with the frequencies for TP53 (76%) and Kras (86%) genes observed in lung tumours from the nonsmoking women who had been exposed to coal smoke (DeMarini et al., 2001).

The possible role of genetic variation in xenobiotic-metabolizing genes or in DNA repair genes was investigated in studies of 122 lung cancer patients and 122 individually matched controls from Xuan Wei. The results did point to some protective effects and some associations with elevated lung cancer risk but largely remained suggestive (Lan et al., 2000; Shen et al., 2005a, 2005b). A suggestion of the mechanisms and pathways involved was provided by a study indicating that the oxidative pathway of PAH metabolism is likely to be involved in the TP53 mutation spectrum and the risk of lung cancer among this population (Lan et al., 2004).

In conclusion, a central role of mutagenesis and carcinogenesis related to exposure to PM rich in PAHs is clear in the etiology of lung cancer among the nonsmoking women in Xuan Wei County, China, who were highly exposed to indoor emissions from combustion of smoky coal. The exceptionally large body of evidence from experimental studies, human biomarker investigations, and epidemiological studies lends support to this conclusion.

Epigenetic changes

Epigenetic modification and environmental exposure

Epigenetics can be defined as the activity of the inherited genome that does not depend on the naked DNA sequence, or as mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in the DNA sequence. Epigenetic mechanisms include DNA methylation, histone modification, chromatin remodelling, and non-coding RNAs. These processes have a fundamental function during development and organogenesis, and their abnormal modifications play an important role in cancer (Jones and Baylin, 2002; Baylin and Jones, 2011; Esteller, 2011; Heyn and Esteller, 2012). In addition to aberrant gene promoter hypermethylation, hypomethylation and site-specific demethylation are part of the machinery that may disrupt the normal

function of the epigenome (Bhutani et al., 2011; Toraño et al., 2012; You and Jones, 2012). Since the late 1990s, evidence has been accumulating for the role of external exposures in modification and deregulation of the epigenome in human cancer, particularly lung cancer (Belinsky, 2004). It has been proposed that epigenetic mechanisms may function as an interphase between environmental factors and the genome in the cancer process (Herceg and Vaissière, 2011).

In experimental studies, epigenetic alterations, typically altered DNA methylation or histone modification but also other classes of epigenetic modifications (e.g. microRNAs), have been observed in vitro in rodent and human cells, as well as in vivo in tumour or other tissue from mice and rats after exposure to chemical agents known to be toxic, genotoxic, or carcinogenic. Examples of such exposures include tobacco smoke, carbon black, diesel exhaust, wood smoke, endocrine disrupter chemicals such as bisphenol A and diethylstilbestrol, genotoxic and carcinogenic metals such as chromium, nickel, arsenic, and cadmium, and the tobacco-specific carcinogen NNK (4-[methylnitrosamino]-1-[3-pyridyl]-1-butanone) (Belinsky, 2005 ; Vuillemenot et al., 2006; Sood et al., 2010; Hou et al., 2012; Feil and Fraga, 2011). In terms of lung carcinogenesis, a crucial role of aberrant DNA methylation has been demonstrated in experimental work, which indicated that inhibition of DNA methylation and histone deacetylation prevent murine lung cancer (Belinsky et al., 2003). Overall, the data from animal experiments strongly support involvement of epigenomic changes in carcinogenesis related to environmental exposure (Fraga et al., 2004; Belinsky, 2005 ; Hou et al., 2012; Feil and Fraga, 2011).

DNA methylation, lung cancer, and smoking

Hypermethylation of cytosines in CpG-rich islands of gene promoter regions is one of the most studied epigenetic mechanisms (Jones and Baylin, 2002; Jones, 2012). In cancer, hypermethylation of the gene promoter regions is associated with transcriptional inactivation and loss of expression of tumour suppressor and other regulatory genes, thus constituting a mechanism of loss of gene function as an alternative to genetic alterations (Jones and Baylin, 2002; Herman and Baylin, 2003; Jones, 2012). In human cancer, aberrant promoter methylation and other epigenetic modifications occur in a tumour-type and gene-specific manner; in many cancers epigenetic modifications occur early in the tumorigenesis process and may affect a wide range of cellular pathways (Heyn and Esteller, 2012; Baylin and Jones, 2011; Jones, 2012).

Early work indicated that promoter hypermethylation occurs frequently in human lung cancer in the CDKN2A (p16) gene, as well as in a series of other genes important in the control of cellular growth and proliferation (Merlo et al., 1995; Belinsky et al., 1998; Esteller et al., 1999; Zöchbauer-Müller et al.,

2001). Subsequently, a significant association has been detected between tobacco smoking and aberrant promoter hypermethylation in one gene (CDKN2A), or multiple cancer-related genes, in lung tumours from cases with non-small cell lung cancer who were current smokers or former smokers. These studies reported significant associations between p16 methylation and various smoking characteristics such as duration, pack-years, time since quitting smoking, or smoking in adolescence (Kersting et al., 2000; Palmisano et al., 2000; Kim et al., 2001; Jarmalaite et al., 2003; Toyooka et al., 2003; Belinsky, 2004; Marsit et al., 2005; Vaissière et al., 2009; Heller et al., 2010). A series of studies have further established that tumour suppressor gene hypermethylation can be detected in non-malignant bronchial epithelium from smoking lung cancer patients, as well as in DNA from plasma, serum, or sputum samples from cancer-free smokers; promoter methylation in plasma and sputum increases with lung cancer risk; and promoter hypermethylation in multiple genes in sputum predicts lung cancer (Palmisano et al., 2000; Belinsky, 2004; Belinsky et al., 2005, 2006; Leng et al., 2012).

Recent studies have investigated differential DNA methylation using more epigenome-wide profiling approaches, with variable results. Paired samples of tumour and non-tumour lung tissue were examined for changes in methylation from a total of 146 cases of non-small cell lung cancer (Nelson et al., 2012). The results revealed more than 100 CpG loci with a > 2-fold increase and more than 40 loci with a > 2-fold decrease in methylation from the total studied set of more than 1400 autosomal CpG loci associated with close to 800 cancer-related genes. From these, two genes (HOXA9, SOX1) showed statistically significant, several-fold increases in methylation, and one gene (DDR1) exhibited a significant, several-fold decrease in the level of methylation (Nelson et al., 2012). Another study combined whole-genome DNA methylation analysis with gene expression profiling to investigate lung tumour samples from 50 squamous cell carcinoma cases (Kwon et al., 2012). Thirty hypermethylated and downregulated genes and 22 hypomethylated and upregulated genes were identified. After selection of candidate genes to be targeted, the study reported six genes that were regulated by DNA methylation as based on a demethylation assay; five of these (CCDC37, CYTL1, CDOI, SLIT2, LMO3) were hypermethylated, whereas one (SERPINB5) was hypomethylated (Kwon et al., 2012). Another genome-wide DNA methylation profiling study initially discovered more than 14 000 differentially methylated regions (DMRs) in seven tumour samples of non-small cell lung cancer. After 48 cases of non-small cell lung cancer were studied in more detail, 57 differently methylated regions between paired tumour–non-tumour tissue samples were identified, with some distinct differences between squamous cell carcinoma and adenocarcinoma (Carvalho et al., 2012). The hypomethylated DMRs did not correlate with any particular functional category of genes, while the hypermethylated DMRs were strongly associated with genes encoding transcriptional regulators (Carvalho et

al., 2012).

Global methylation has been studied in peripheral blood DNA in smokers, former smokers, and never-smokers. A recent scan of about 27 000 sites in more than 14 000 gene promoter regions in close to 200 individuals identified, with genome-wide significance, that one locus displayed showed lower methylation in smokers (Breitling et al., 2011). The finding was replicated in an independent set of samples analysed with different technologies. The single locus that was hypomethylated in smokers was found to reside in the F2RL3 (coagulation factor II receptor-like 3) gene region (Breitling et al., 2011).

In contrast to the impressive number of findings among smokers, there are fewer data available on the role of promoter methylation in lung cancer in nonsmokers. The present studies have reported varying frequencies of promoter methylation in nonsmokers (Belinsky et al., 2002; Pulling et al., 2003; Belinsky, 2004; Divine et al., 2005; Sun et al., 2007; Subramanian and Govindan, 2008). An association with exposure to second-hand smoke has been proposed in lung cancer in never-smokers (Scesnaite et al., 2012).

Air pollution and the epigenome

In experimental settings, various types of particulate exposures have been shown to evoke altered DNA methylation, primarily promoter hypermethylation, as briefly described above. With regard to ambient air pollution, a recent study reported that concentrated urban $PM_{2.5}$ increased p16 promoter methylation in the lungs of mice exposed via inhalation and in primary murine alveolar epithelial cells treated in vitro (Soberanes et al., 2012).

In humans, data on epigenetic modifications associated with air pollution have been accumulating during recent years (Christensen and Marsit, 2011; Hou et al., 2012; Jardim, 2011). The association between repetitive element DNA methylation and exposure to particulate emissions from traffic was investigated in blood DNA of more than 700 elderly people living in the Boston, Massachusetts, USA, area. Methylation of the genomic repetitive element LINE-1 was significantly decreased after recent exposure (for 0.5–7 days on average) to carbon black, a PM component of traffic exhaust, and ambient $PM_{2.5}$, with stronger effects observed for the longer time windows (Baccarelli et al., 2009). Among the same study population, prolonged exposure to carbon black and sulfate particles, but not to $PM_{2.5}$, was reported to be associated with hypomethylation of LINE-1 and Alu repeats (Madrigano et al., 2011). In urban traffic officers and gasoline filling station attendants, exposure to low levels of benzene was associated with a significant decrease in global methylation (LINE-1 and Alu repeats) in peripheral blood cell DNA (Bollati et al., 2007).

In the Southern California Children's Health Study, exposure to estimated ambient air PM (PM_{10} and $PM_{2.5}$) was investigated for association with

methylation in CpG sites on the three nitric oxide synthase genes (NOS1, NOS2A, and NOS3) in buccal cells from more than 900 children (Breton et al., 2012). $PM_{2.5}$ exposure was found to be associated with different levels of DNA methylation, depending on the NOS gene, the CpG site studied, and the length of exposure. Mostly, but not exclusively, lower methylation levels were observed in association with average 1 year $PM_{2.5}$ exposure (Breton et al., 2012). Another investigation of the same study population reported that an increased 7 day average $PM_{2.5}$ exposure was significantly associated with lower NOS2 gene (encoding inducible nitric oxide synthase, iNOS) promoter methylation, with some interrelated effects of $PM_{2.5}$, NOS2 promoter haplotypes, and NOS2 promoter methylation (Salam et al., 2012). In studies of newborn infants (white cells from umbilical cord blood) whose mothers were nonsmokers and lived in New York City, lower global DNA methylation was significantly associated with prenatal PAH exposure but positively linked with the presence of detectable PAH–DNA adducts in cord blood (Herbstman et al., 2012). In the same study population, increased promoter methylation (CpG islands) of the ACSL3 and INF-γ genes in cord blood white cells was associated with maternal PAH exposure (Perera et al., 2009; Tang et al., 2012).

Workers (n = 67) at an industrial estate in Thailand exhibited significantly lower LINE-1, TP53 gene, and IL-6 gene methylation, but higher HIC1 (hypermethylated-in-cancer) gene methylation in blood leukocyte DNA compared with rural residents (n = 45) (Peluso et al., 2012). For all these biomarkers, the residents of the industrial area exhibited methylation levels intermediate between those detected in the workers and in the rural resident controls. Bulky DNA adducts were also assessed and found to be negatively correlated with TP53 gene methylation (Peluso et al., 2012). In steel plant workers exposed to airborne metal-rich PM, significantly decreased methylation in the NOS2 gene promoter and the LINE-1 and Alu repeats was observed in peripheral blood cell DNA in association with long-term PM_{10} exposure (Tarantini et al., 2009). In yet another study, workers' exposure to metal-rich PM in a steel factory was associated with changes in microRNA expression in post-exposure samples of blood leukocytes (Bollati et al., 2010).

Overall summary and conclusions

There is a large body of experimental studies clarifying the mutagenicity, genotoxicity, and male germ cell effects associated with ambient air pollution. Similarly, numerous human biomarker investigations on exposed healthy subjects, both adults and children, have examined DNA damage, other genotoxic and mutagenic effects, and effects on reproductive health effects, as well as

epigenetic changes in association with air pollution, as summarized in Table 11.1. These various approaches have provided clear evidence linking air pollution to hazardous biological effects. Data from an abundant number of human lung cancer studies that have investigated mutations or epigenetic alterations in cancer-related genes, in relation to exposure to tobacco smoke or indoor emissions from smoky coal combustion, lend further mechanistic support for this evidence, due to the closely similar nature of these particulate exposures with ambient air pollution. Collectively, the published experimental and human biomarker data, only briefly reviewed in this chapter, clearly associate air pollution with mutagenicity, genotoxicity, and epigenetic modification.

Table 11.1. Summary and examples of positive findings from human biomarker studies investigating combustion-related outdoor or indoor air pollution

Type of damage	Excreta/cell type studied	Main type of particulate exposure	Reference
Bacterial mutagenicity	Urine (adults)	Outdoor air pollution (urban/traffic exhausts)	Hansen *et al.* (2004)
DNA damage			
Bulky/aromatic or PAH–DNA adducts	White blood cells/lymphocytes from peripheral blood, umbilical cord leukocytes (adults, newborn infants of mothers with exposure)	Outdoor air pollution (urban/traffic exhausts, industrial site, coal heating)	Farmer *et al.* (1996) Peluso *et al.* (1998) Whyatt *et al.* (1998) Autrup *et al.* (1999) Palli *et al.* (2001) Ruchirawa *et al.* (2002) Perera *et al.* (2005) Demetriou *et al.* (2012)
		Indoor air pollution (emissions from domestic smoky coal combustion)	Mumford *et al.* (1993)
	Placenta	Indoor air pollution (emissions from domestic smoky coal combustion)	Mumford *et al.* (1993)
Oxidative (8-oxo-2′-deoxyguanosine)	White blood cells/lymphocytes from peripheral blood, nasal epithelium (adults, children)	Outdoor air pollution (urban/traffic exhausts)	Calderon-Garciduenas *et al.* (1996, 1997, 1999) Loft *et al.* (1999) Sorensen *et al.* (2003a, 2003b) Demetriou *et al.* (2012)

DNA damage/strand breaks/tail length in comet assay	White blood cells from peripheral blood, nasal epithelium (adults, children)	Outdoor air pollution (urban/traffic exhausts, industrial site)	Valverdere *et al.* (1997) Calderon-Garciduenas *et al.* (1996, 1997, 1999)
DNA fragmentation (%)	Sperm cells	Outdoor air pollution (coal heating, industrial site)	Rubes *et al.* (2005)
Cytogenetic effects			
Chromosome aberrations, micronuclei, or sister chromatid exchanges	Lymphocytes from peripheral blood, buccal cells (adults, children)	Outdoor air pollution (urban/traffic exhausts, industrial site)	Chandrasekaran *et al.* (1996) Zhao *et al.* (1998) Michalska *et al.* (1999) Burgaz *et al.* (2002) Huen *et al.* (2006) Ishikawa *et al.* (2006) Sreedevi *et al.* (2006, 2009) Rossnerova *et al.* (2009)
Gene mutations			
HPRT gene	Lymphocytes from umbilical cord blood (newborn infants of mothers with exposure)	Outdoor air pollution (urban/traffic exhausts, heating), transplacental exposure	Perera *et al.* (2002)
TP53 gene	Lung tumour tissue (nonsmokers), lung epithelial cells in sputum from nonsmokers with no evidence of cancer	Indoor air pollution (emissions from domestic smoky coal combustion)	DeMarini *et al.* (2001) Keohavong *et al.* (2005)
K-ras (or *NRAS* or *HRAS*) gene	Lung tumour tissue (nonsmokers), lung epithelial cells in sputum from nonsmokers with no evidence of cancer	Indoor air pollution (emissions from domestic smoky coal combustion)	DeMarini *et al.* (2001) Keohavong *et al.* (2003) Keohavong *et al.* (2005)
Differential DNA methylation			
Increased methylation in gene promoter region (*ACSL3* gene, *INF-γ* gene)	Leukocytes from umbilical cord blood (newborn infants of mother with exposure)	Outdoor air pollution (urban/traffic exhausts)	Perera *et al.* (2009) Tang *et al.* (2012)

Decreased methylation of *NOS1*, *NOS2A*, or *NOS3* gene (various CpG loci or gene promoter)	Buccal cells (children)	Outdoor air pollution (urban/traffic exhausts, residential communities)	Breton *et al.* (2012) Salam *et al.* (2012)
Hypomethylation of LINE-1 and/or ALU repeats	White blood cells from peripheral blood (adults)	Outdoor air pollution (urban/traffic exhausts)	Baccarelli *et al.* (2009) Madrigano *et al.* (2011)
Decreased global DNA methylation	Leukocytes from umbilical cord blood (newborn infants of mothers with exposure)	Outdoor air pollution (urban/traffic exhausts)	Herbstman *et al.* (2012)

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Chapter 12. Biomarkers of air pollution: DNA and protein adducts

Paolo Vineis

Biomarkers were introduced in the epidemiology of chronic disease under the assumption that they could enhance research on the health effects of air pollution, and other exposures, by improving exposure assessment, increasing the understanding of mechanisms (e.g. by measuring intermediate biomarkers), and enabling the investigation of individual susceptibility.

Biomarkers used in the epidemiology of cancer are usually divided into three categories: markers of internal dose, markers of early response, and markers of susceptibility. In fact, each category includes subcategories. For example, protein adducts and DNA adducts are both markers of internal dose, but their biological significance differs. While protein adducts are not repaired (i.e. they reflect external exposure more faithfully), DNA adducts are influenced by an individual's repair capacity. If DNA adducts are not eliminated by the DNA repair machinery, they induce a mutation. Also, markers of early response are a heterogeneous category that encompasses DNA mutations and gross chromosomal damage. The main advantage of early response markers is that they are more frequent than the disease and can be recognized sooner, thus allowing researchers to identify earlier effects of potentially carcinogenic exposures. Finally, markers of susceptibility include several subcategories; in particular, a type of genetic susceptibility related to the metabolism of carcinogenic substances, and another type related to DNA repair. Biomarkers of exposure, such as DNA adducts, are described here, while markers of early damage are considered in a separate chapter.

DNA adducts and exposure to air pollution

Several studies have considered DNA damage as an end-point of the effects of air pollution, especially bulky DNA adducts that are related to exposure to aromatic compounds, including polycyclic aromatic hydrocarbons (PAHs).

A systematic review was performed to evaluate whether metabolites of pyrene and DNA adducts are valid markers of low-level environmental (not occupational) exposure to PAHs (Castano-Vinyals et al., 2004). Thirty five studies with more than 10 subjects were identified that evaluated environmental air pollution with PAHs in relation to metabolites of PAHs, PAH–DNA adducts,

or protein adducts. PAH metabolites and, to a lesser extent, PAH–DNA adducts correlated well among the groups with exposure to benzo[a]pyrene (B[a]P), even at low levels of pollution.

As Tables 12.1 and 12.2 suggest, studies in different countries have shown that the levels of white blood cell DNA adducts were higher among subjects who were more heavily exposed to air pollutants. This has been observed in different population categories, such as police officers in Italy and Thailand (Peluso et al., 1998; Ruchirawa et al., 2002), residents in highly industrialized areas in Poland (Perera et al., 1992), and bus drivers in Denmark (Nielsen et al., 1996a). In all of these cases, the differences in the levels of adducts between more heavily exposed or less exposed subjects were significant (Tables 12.1 and 12.2).

Table 12.1. Results on the association between air pollution and DNA adducts in exposed individuals–comparison of means analysis

Reference	Study location	Exposure	Controlled confounders	Group, sample size[a] (total: 1044)	Mean adducts/ 10^8 nucleotides ± SD (unless otherwise stated)	*P*
Perera *et al.* (1992)	Poland	Environmental air pollution	NA	Residents in industrial area, 20	30.4 ± 13.5	< 0.05
				Rural controls, 21	11.01 ± 22.6	
Hemminki *et al.* (1994)	Stockholm, Sweden	Traffic-related air pollution	Age, smoking	Bus drivers – urban routes, 26	0.9 ± 0.35	NS
				Bus drivers – suburban routes, 23	1.4 ± 0.48	< 0.001
				Taxi drivers – mixed routes, 19	1.6 ± 0.91	< 0.010
				Controls, 22	1.0 ± 0.32	
Nielsen *et al.* (1996a)	Denmark	Environmental air pollution	Smoking, PAH-rich diet	Bus drivers in central Copenhagen, 49	Median: 1.214	0.001
				Rural controls, 60	Range: 0.142–22.24	
					Median: 0.074	
					Range: 0.003–8.876	
Nielsen *et al.* (1996b)	Denmark and Greece	Environmental air pollution	Smoking, sex	Students at urban universities, 74	Median: 0.205	0.02
				Students at agricultural colleges, 29	Median: 0.152	
Yang *et al.* (1996)	Milan, Italy	Traffic-related air pollution	Sex, age, smoking habits	News stand workers in heavy traffic areas, 31	2.2 ± 1.0	0.27
				News stand workers in light traffic areas, 22	2.2 ± 1.2	
Topinka *et al.* (1997)	Teplice and Prachatice, North and South Bohemia, Czech Republic	Residence in industrial area	NA	Placenta samples – industrial polluted area (winter): *GSTM*– genotype, 15	1.49 ± 0.70	0.027
				Placenta samples – agricultural area (winter): *GSTM*– genotype, 17	0.96 ± 0.55	
Merlo *et al.* (1997)	Genoa, Italy	Ambient PAH concentrations	NA	Traffic police workers, 94	1.48 ± 1.35	0.007
				Urban residents, 52	1.01 ± 0.63	
Georgiadis *et al.* (2001)	Greece	Environmental air pollution	Smoking	Students in Athens (highest PAH concentration), 117	1.25 ± 1.19	< 0.001

				Students in Halkida (highest PAH concentration), 77	1.54 ± 1.19		
Ruchirawa *et al.* (2002)	Bangkok, Thailand	Environmental air pollution	Smoking, sex	Traffic policemen, 41	1.6 ± 0.9	0.03	
				Office duty policemen, 40	1.2 ± 1.0		
Marczynski *et al.* (2005)	Germany	PAHs in air (ambient and personal monitoring)	NA	Samples from 16 workers (increased PAH exposure)	Range: 0.5–1.19	< 0.0001	
				Samples from 16 workers[a] (reduced PAH exposure)	Range: < 0.5–0.09		
Topinka *et al.* (2007)	Prague, Czech Republic	c-PAH (personal exposure)	Smoking, occupational duration	109 policemen – January (highest exposure)	2.08 ± 1.60	< 0.0001	
				109 policemen – March	1.66 ± 0.65		
Tuntawiroon *et al.* (2007)	Bangkok and Chonburi, Thailand	c-PAH and B[*a*]P	Age and lifestyle (i.e. ETS, transportation, medication, diet, etc.)	Bangkok schoolchildren, 115	0.45 ± 0.03	< 0.0001	
				Provincial schoolchildren (group matching), 69	0.09 ± 0.00		
Ayi-Fanou *et al.* (2011)	Cotonou, Benin	Environmental air pollution	NA	Taxi-motorbike drivers, 13	24.6 ± 6.4	< 0.001	
				Intermediate-exposure suburban group, 20	2.1 ± 0.6		
		Environmental air pollution	NA	Street food vendors, 16	34.7 ± 9.8	< 0.001	
				Intermediate-exposure suburban group, 20	2.1 ± 0.6		
		Environmental air pollution	NA	Gasoline salesmen, 20	37.2 ± 8.1	< 0.001	
				Intermediate-exposure suburban group, 20	2.1 ± 0.6		
		Environmental air pollution	NA	Street-side residents, 11	23.78 ± 6.9	< 0.001	
				Intermediate-exposure suburban group, 20	2.1 ± 0.6		

B[*a*]P, benzo[*a*]pyrene; c-PAH, carcinogenic polycyclic aromatic hydrocarbon; ETS, environmental tobacco smoke; NA, not available; NS, not significant; PAH, polycyclic aromatic hydrocarbon; SD, standard deviation.

[a]The sample sizes reported in the summary tables refer to subjects with measurements available both before and after change in work conditions.

Compiled from Demetriou *et al.* (2012).

Table 12.2. Results on the association between air pollution and DNA adducts in exposed individuals–linear regression, logistic regression, and correlation analyses

Reference	Study location	Exposure	Controlled confounders	Effect measure	Sample size (total: 1787)	Subject description	*P*
Binkova *et al.* (1995)	Czech Republic	Outdoor air pollution, individual PAH	Age, active and passive smoking, consumption of fried or smoked food, job category	r: 0.541	21	Nonsmoking women working outdoors up to 8 hours – gardeners or postal workers	0.016
Whyatt *et al.* (1998)	Krakow, Poland	Ambient pollution at mother's place of residence	Smoking, dietary PAH, use of coal stoves, home or occupational exposures to PAH and other organics	β: 1.77	19	Mothers not employed away from home	0.05
		Ambient pollution at place of residence	Smoking, dietary PAH, use of coal stoves, home or occupational exposures to PAH and other organics	β: 1.73	23	Newborns of mothers (high-pollution/low-pollution group)	0.03
Sørensen *et al.* (2003)	Copenhagen, Denmark	Personal $PM_{2.5}$	Smoking, diet, season	β: –0.0035	75	Students monitored during four seasons in a year	0.31
Castaño-Vinyals *et al.* (2004)	Review	B[*a*]P (stationary measure)	N/A	r: 0.6	12	Pairs of data	0.038
Peluso *et al.* (2005)	10 European countries	O_3 levels	Age, gender, educational level, country, batch	β: 0.066	564	EPIC cohort subjects	0.0095
Neri *et al.* (2006)	Review	Environmental pollutants (including ETS exposure)	N/A	N/A	178	Newborn to age 17 years Two studies in total, both with statistically significant results	N/A
Pavanello *et al.* (2006)	Northeast Italy	B[*a*]P indoor exposure	Smoking, diet, area of residence, traffic near house, outdoor exposure	β: 0.973	457	Municipal workers (nonsmoking)	0.012
Palli *et al.* (2008)	Florence, Italy	PM_{10} (from heavy traffic stations)	Smoking	r: 0.562	16	Traffic-exposed workers	0.02
Peluso *et al.* (2008)	Thailand	Industrial estate residence	Smoking habits, age, gender	OR: 1.65	72	Industrial estate residents	< 0.05
					50	Control district residents	
			Smoking habits, age, gender	OR: 1.44	64	PAH-exposed workers	< 0.05

						72	Industrial estate residents	
Pavanello *et al.* (2009)	Poland	1-Pyrenol	NA	r: 0.67		92	Coke oven workers and controls	< 0.0001
Pedersen *et al.* (2009)	Copenhagen, Denmark	Residential traffic density	ETS, use of open fireplace, pre-pregnancy weight, folate levels, vitamin B12 levels, maternal education, season of delivery	β: 0.6/0.7		75/69	Women/umbilical cords	< 0.01
Garcia-Suastegui *et al.* (2011)	Mexico City, Mexico	$PM_{2.5}$	Various risk alleles	r: NR		92	Young adults living in Mexico City	0.013
		PM_{10}	Various risk alleles	r: NR		92	Young adults living in Mexico City	0.035
Herbstman *et al.* (2012)	USA	PAH exposure measured in both air and urine	NA	r: NR		NR	152 participants – prenatal exposure, DNA adducts in cord blood	NS

β, linear regression coefficient: change in DNA adduct levels (adducts/10^8 nucleotides) for every unit change in exposure; B[*a*]P, benzo[*a*]pyrene; ETS, environmental tobacco smoke; NA, not available; N/A, not applicable; NR, not reported; NS, not significant; O_3, ozone; OR, logistic regression odds ratio; PAH, polycyclic aromatic hydrocarbons; $PM_{2.5}$, particulate matter < 5 μm in diameter; PM_{10}, particulate matter < 10 μm in diameter; r, correlation coefficient

Compiled from Demetriou *et al.* (2012).

More recently, a group of 114 workers exposed to traffic pollution and a random sample of 100 residents were studied in Florence, Italy. Bulky DNA adducts were analysed in peripheral leukocytes donated at enrolment using ^{32}P-postlabelling. Adduct levels were significantly higher for traffic workers among never-smokers (P = 0.03) and light current smokers (P = 0.003). In both groups, urban residents tended to show higher levels than those living in

suburban areas, and a seasonal trend emerged of adduct levels being highest in summer and lowest in winter (Palli et al., 2001).

In a study in Greece, the levels of bulky DNA adducts were measured by ^{32}P-postlabelling in the lymphocytes of 194 nonsmoking students living in the city of Athens and the region of Halkida (Georgiadis et al., 2001). Personal exposures to PAHs were significantly higher among the subjects in Athens. However, the highest adduct levels were observed in a subgroup of students living in Halkida, with a minimal burden of urban air pollution. Among these (but not the remaining subjects), positive correlations were observed between DNA adducts and measured personal exposures to chrysene or B[a]P. A much clearer association of adducts with second-hand tobacco smoke was observed.

In Denmark, Sørensen et al. (2003) measured personal exposure to particulate matter (PM) < 2.5 μm in diameter and exposure to black smoke in 50 students four times during 1 year and analysed biomarkers of DNA damage. Personal exposure to PM was found to predict the presence of 8-oxo-2′-deoxyguanosine (8-oxo-dG) in lymphocyte DNA, with an 11% increase in 8-oxo-dG per 10 μg/m^3 increase in exposure to PM (P = 0.007).

In Europe, a case–control study nested in a large prospective study (European Prospective Investigation into Cancer and Nutrition [EPIC]) has been completed (Peluso et al., 2005). Cases included newly diagnosed lung cancer (n = 115), upper respiratory cancers (pharynx, larynx) (n = 82), bladder cancer (n = 124), and leukaemia (n = 166), and deaths from chronic obstructive pulmonary disease or emphysema (n = 77) that accrued after a median follow-up of 7 years among EPIC former smokers and never-smokers. Leukocyte DNA adducts were analysed blindly using the nuclease P1 modification of the ^{32}P-postlabelling technique. The intensity of adduct patterns was generally stronger in the chromatograms of healthy nonsmokers who developed lung cancer in the following years compared with the other samples. The observed adduct profile has been described previously among subjects environmentally exposed to air pollution. Adducts were associated with a subsequent risk of lung cancer with an odds ratio (OR) of 1.86 (95% confidence interval [CI], 0.88–3.93). The association with lung cancer was stronger in never-smokers (OR, 4.04; 95% CI, 1.06–15.42) and among the younger age groups. After exclusion of the 36 months preceding the onset of lung cancer, the OR was 4.16 (95% CI, 1.24–13.88). In addition, the authors found an association of adduct levels with ozone, suggesting a possible role for photochemical smog in determining DNA damage of nonsmokers in western Europe. This is consistent with the previous investigation in Florence that showed a significant relationship between cumulative exposure to ozone and bulky DNA adducts among nonsmokers (Palli et al., 2001). Ozone is a marker of photochemical smog. It is produced by a complex series of reactions involving hydrocarbons and nitrogen dioxide that are emitted primarily during combustion of fossil fuels by industry and transportation activities, and driven by ultraviolet (UV) radiation in sunlight.

Ozone may have biological effects directly and/or via free radicals that react with other air pollutants.

The conditions needed for the formation of ozone are generally present in modern large cities, and the average levels at the Earth's surface have more than doubled since pre-industrial times in western Europe. Summer months, characterized by high temperatures, strong UV radiation, long periods of solar radiation, and light winds, provide more favourable conditions for the production of ozone in the troposphere. Indeed, episodes with elevated concentrations of ozone generally occur during periods of warm sunny weather. Transformation reactions that occur in the troposphere during such episodes may induce the formation of highly reactive PAH and nitro-PAH compounds (Finlayson-Pitts et al., 1997). Soot aerosols are the main carriers of PAHs in outdoor air and can react rapidly on the surface with free radicals, such as those produced by ozone photolysis (Finlayson-Pitts et al., 1997). In addition, PAHs such as anthracene, benzo[a]anthracene, benzo[g,h,i]perylene, B[a]P, indeno[1,2,3-cd]pyrene, and pyrene may be transformed by UV irradiation, become directly mutagenic, and form highly reactive quinone products. After UV activation, PAHs may produce covalent adducts (e.g. benzo[a]anthracene, B[a]P, and 1-hydroxypyrene DNA adducts) (Prodi et al., 1984; Dong et al., 2000). UV irradiation has been also shown to synergize with B[a]P to enhance significantly the expression levels of the tumour suppressor gene p53 (* et al., 2003). Recently, an enhancement of the signature of mutations produced by B[a]P, i.e. G → T and C → A transversions, has been found after UV irradiation (Besaratinia and Pfeifer, 2003).

Firefighters and oil-well fires

Studies have also been conducted in populations with specific exposures–for example, forest firefighters and the United States troops exposed to oil-well fires in the Persian Gulf. Forest firefighters are exposed to a wide range of carcinogenic PAHs in forest fire smoke. PAH–DNA adducts were measured in 47 California firefighters at two time points, early and late in the 1988 forest fire season. PAH–DNA adduct levels were not associated with cumulative hours of recent firefighting activity. However, firefighters who had consumed charbroiled food within the previous week had elevated PAH–DNA adduct levels, which were related to the frequency of intake of such food. These findings suggest that dietary sources of PAH contribute to levels of PAH–DNA adducts in peripheral white blood cells (Rothman et al., 1993).

In addition, levels of PAH–DNA adducts were determined in a group of United States Army soldiers who were deployed after the Persian Gulf War and were

exposed to oil-well fires. The United States Army Environmental Hygiene Agency monitored air and soil for ambient PAHs. PAH–DNA adducts were measured from DNA samples in blood cells of 22 soldiers, and bulky aromatic adducts were measured by ^{32}P-postlabelling in blood cell DNA samples from 20 of the same soldiers. Urinary 1-hydroxypyrene-glucuronide levels were determined in a matched set of samples from 33 soldiers. Contrary to expectations, environmental monitoring showed low levels of ambient PAHs in the areas where these soldiers were working in Kuwait. Both DNA adducts and urinary 1-hydroxypyrene-glucuronide levels were lowest in Kuwait and highest in Germany, where the soldiers returned after the war (Poirier et al., 1998).

DNA adducts in children

Experimental evidence indicates that developing fetuses are more susceptible than adults to the carcinogenic effects of PAHs. To assess fetal versus adult susceptibility to PAHs and second-hand tobacco smoke, a study compared carcinogen–DNA adducts (a biomarker associated with an increased risk of cancer) and cotinine (a biomarker of exposure to tobacco smoke) in paired blood samples collected from mothers and newborns in New York City, USA. The authors enrolled 265 nonsmoking African-American and Latina mother–newborn pairs between 1997 and 2001. Despite the estimated 10-fold lower fetal dose, mean levels of B[a]P–DNA adducts were comparable in paired newborn and maternal samples (0.24 adducts per 10^8 nucleotides in newborns, with 45% of newborns with detectable adducts, vs 0.22 per 10^8 nucleotides in mothers, with 41% of mothers with detectable adducts). These results indicate an increased susceptibility of the fetus to DNA damage.

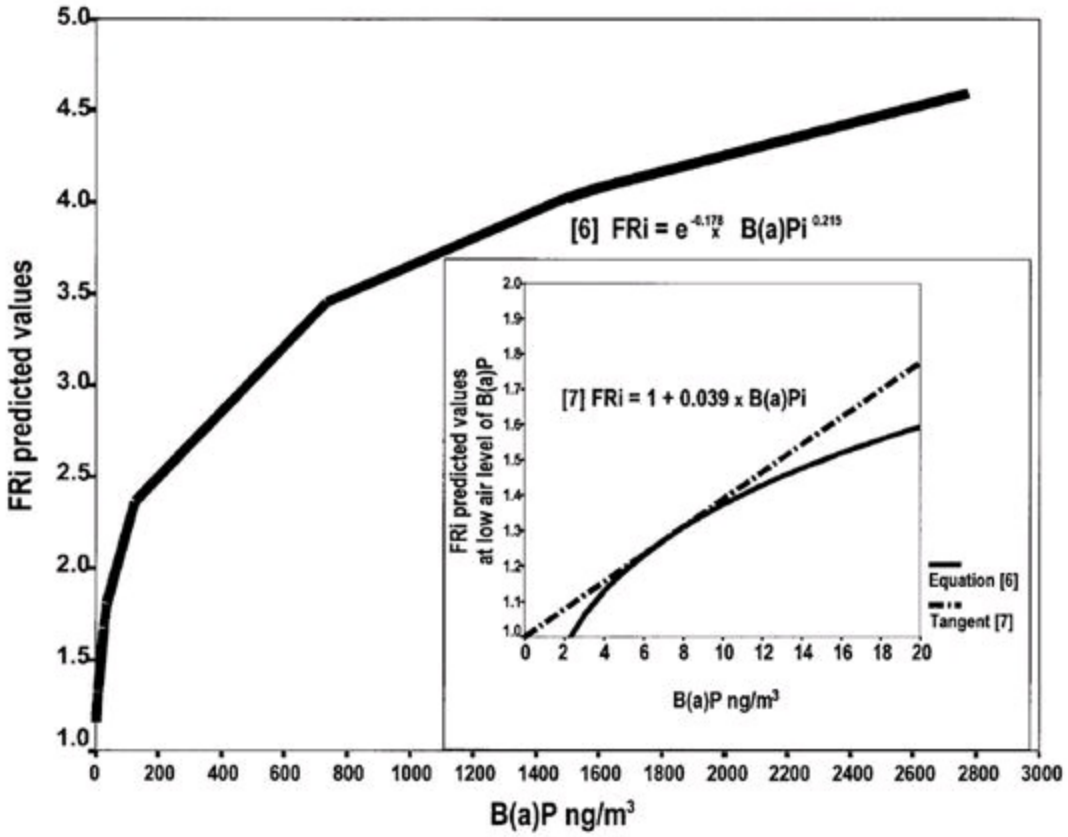
Protein adducts

Among newspaper vendors, Pastorelli et al. (1996) found a higher level of B[a]P–haemoglobin adducts, but the difference between these and levels in less exposed populations was not statistically significant. Richter et al. (2001) studied haemoglobin adducts formed by aromatic amines, including 4-aminobiphenyl, in groups of children, and found that children living in the most polluted cities had significantly higher levels of adducts than those living in less polluted cities.

Dose–response relationship

Lewtas et al. (1997) observed that human populations exposed to PAH via air pollution exhibit a nonlinear relationship between levels of exposure and white blood cell-DNA adducts. Among highly exposed subjects, the level of DNA adducts per unit of exposure was significantly lower than those measured after environmental exposures. The observation was confirmed in a meta-analysis of the epidemiological studies (Peluso et al., 2001) (Figure 12.1). The same exposure–dose nonlinearity was observed in lung DNA from rats exposed to PAHs. One interpretation proposed for such an observation is that saturation of metabolic enzymes or induction of DNA repair processes occurs at high levels of exposure (Lutz, 1990; Garte et al., 1997).

Figure 12.1. Dose–response relationship between frequency ratios and external concentrations of benzo[a]pyrene (B[a]P) in work environments in a meta-analysis of occupational exposure to air pollution. The inset shows an extrapolated dose–response curve at low exposure doses, assuming a linear dose–response relation, for B[a]P levels between 0 and 4.5 ng/m^3, the lowest value in the database. FRi: frequency ratio for the ith study. Source: Peluso et al. (2001); reproduced with permission from Oxford University Press.



Conclusions

On the basis of recent large cohort studies in the USA and Europe, there are reasonable grounds for concern that air pollution may increase the risk of lung cancer, especially in combination with other known risk factors such as voluntary and involuntary smoking and occupational exposures. Although there are examples of biomarkers contributing to the understanding of the health effects of air pollution, there are still many aspects that need clarification, such as the reliability of the markers (e.g. bulky DNA adducts have a considerable degree of variation by batch and between laboratories) (Peluso et al., 2005).

Production of DNA damage primarily reflects carcinogenic exposures, but is also regulated by inherited and acquired susceptibilities. Age, gender, body mass index, physical exercise, consumption of charcoal-broiled food, consumption of fresh fruit and vegetables, and seasonal variations have also been reported to influence the formation of aromatic DNA adducts. DNA adduct levels have been found to be dependent on polymorphisms in metabolic genes (i.e. the CYP1A1, MspI, and GSTM1 null genotypes) (Shields et al.,1993; Ryberg et al., 1997; Pastorelli et al., 1998; Butkiewicz et al., 2000; Rojas et al., 2000; Teixeira et al., 2002; Georgiadis et al., 2005). DNA damage may be repaired, but the ability of a person to remove aromatic DNA adducts may vary from individual to individual.

In conclusion, DNA and protein adducts seem to be valuable markers of exposure to air pollutants in spite of errors in measurement. Since DNA adducts express genetic and acquired susceptibility, they can usefully complement other measures of exposure in research on risks for cancer.

Chapter 12. Biomarkers of air pollution: DNA and protein adducts

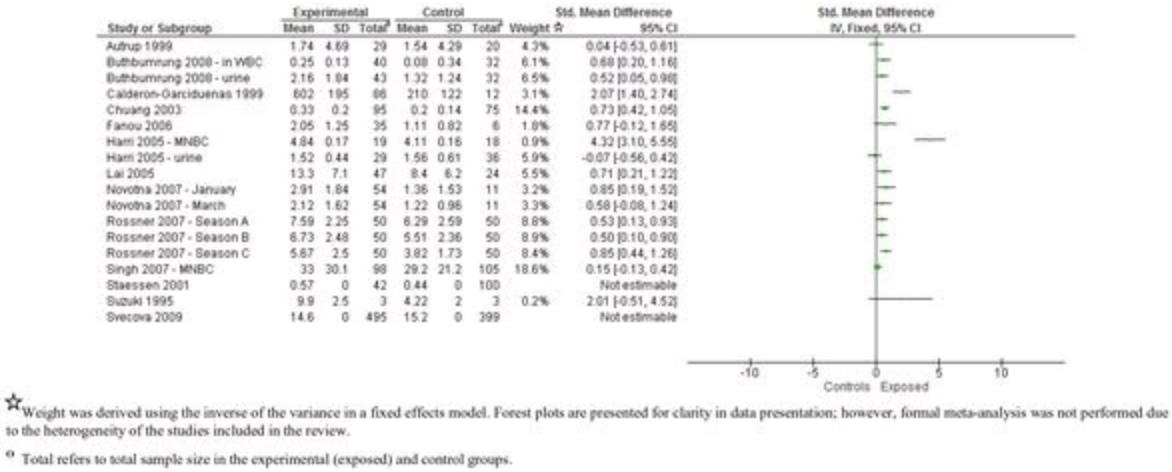
Addendum (2012 update)

Christiana Demetriou and Paolo Vineis

Numerous studies have considered DNA and protein adducts as biomarkers of exposure to genotoxic carcinogens, such as polycyclic aromatic hydrocarbons (PAHs), present in environmental air pollution.

The association between air pollution and DNA adducts was investigated in 26 studies. These are cross-sectional and case–control studies, some nested within prospective cohorts. Some studies (Perera et al., 1992; Hemminki et al., 1994; Nielsen et al., 1996b, 1996b; Yang et al., 1996; Topinka et al., 1997; Georgiadis et al., 2001; Merlo et al., 1997; Ruchirawa et al., 2002; Marczynski et al., 2005; Topinka et al., 2007; Tuntawiroon et al., 2007; Ayi-Fanou et al., 2011) compared the mean DNA adduct levels in individuals with estimated high or low external exposures (Table 12.1), while others (Binková et al., 1995; Whyatt et al., 1998; Sørensen et al., 2003; Castaño-Vinyals et al., 2004; Peluso et al., 2005; Neri et al., 2006; Pavanello et al., 2006; Palli et al., 2008; Peluso et al., 2008; Pavanello et al., 2009; Pedersen et al., 2009; García-Suástegui et al., 2011; Herbstman et al., 2012) carried out correlation and regression analyses on all subjects (Table 12.2). As illustrated in Figure 12.2, most studies (including two reviews) found positive associations between exposure to air pollution or chemicals in polluted air and the formation of DNA adducts in exposed individuals. Subjects in these studies included, among others, residents in an industrial area and rural controls in Poland (Perera et al., 1992), bus and taxi drivers in Stockholm (Hemminki et al., 1994), students in Denmark and in Greece (Nielsen et al., 1996b), bus drivers in Copenhagen (Nielsen et al., 1996a), policemen in Genoa (Merlo et al., 1997), policemen in Bangkok (Ruchirawa et al., 2002), and schoolchildren in Thailand (Tuntawiroon et al., 2007), as well as street vendors, taxi drivers, gasoline salesmen, and roadside residents in Benin (Ayi-Fanou et al., 2011). Fetal exposures were associated with DNA adducts in newborns (Topinka et al., 1997; Whyatt et al., 1998; Pedersen et al., 2009). Only two studies did not find an association (Yang et al., 1996; Sørensen et al., 2003). One study found that students in a rural area had higher DNA adduct levels than students in Athens, the most heavily polluted city; however, exposure to second-hand smoke (SHS) explains this paradoxical observation (Georgiadis et al., 2001).

Figure 12.2. Standardized mean difference forest plot of studies on DNA adducts reporting difference in means. Source: Demetriou et al. (2012); reproduced with permission from BMJ Publishing Group Ltd.



☆ Weight was derived using the inverse of the variance in a fixed effects model. Forest plots are presented for clarity in data presentation; however, formal meta-analysis was not performed due to the heterogeneity of the studies included in the review.

Ω Total refers to total sample size in the experimental (exposed) and control groups.

Protein adducts and exposure to air pollution

Far fewer studies (Hemminki et al., 1994; Pastorelli et al., 1996; Nielsen et al., 1996c; Richter et al., 2001) have examined the relationship between exposure to air pollution and protein adducts, and their results are inconsistent (Table 12.3). Only one study (Richter et al., 2001) shows a statistically significant association between exposure to air pollution and protein adducts, while another shows a significant association between exposure to diesel exhaust and protein adducts (Nielsen et al., 1996c). The other two studies show either no significant association (Pastorelli et al., 1996) or significant association only between certain subject groups (Hemminki et al., 1994).

Table 12.3. Results on the association between air pollution and protein adducts in exposed individuals

Reference	Study location	Exposure	Controlled confounders	Outcome measure	Group, sample size (total: 1044)	Protein adduct levels	*P*
Hemminki *et al.* (1994)	Stockholm, Sweden	Traffic-related air pollution	Age, smoking	Plasma protein (albumin) adducts	Bus drivers – urban routes, 26	Mean: 232 fmol./mg Ab (SD:108)	NS
					Bus drivers – suburban routes, 23	Mean:120 fmol./mg Ab (SD:102)	NS
					Taxi drivers – mixed routes, 19	Mean: 318 fmol./mg Ab (SD:180)	< 0.001
					Controls, 22	Mean: 119 fmol./mg Ab (SD:109)	
Pastorelli *et al.* (1996)	Italy	Traffic-related air pollution	Smoking	Benzo[*a*]pyrene–haemoglobin adducts	Newspaper vendors – high exposure, 30	Median: 0.3 fmol/mg Hb	0.09
					Newspaper vendors – low exposure, 23	Range: ≤ 0.1–3.3	
						Median: ≤ 0.1 fmol/mg Hb	
						Range: ≤ 0.1–0.41	

Nielsen *et al.* (1996a)	Copenhagen, Denmark	Diesel exhaust exposed workers	Smoking, sex	Haemoglobin adducts	Bus garage workers and mechanics, 10 Bus company administrative staff, 12	Median: 33.3 fmol./mg Hb Range: 25.4–58.8 Median: 22.1 fmol./mg Hb Range: 8.0–37.0	0.0038
Richter *et al.* (2001)	Germany	Environmental air pollution		4-ABP-haemoglobin adducts	Children from Munich, 34 Children from Eichstatt and Augsburg, 64 and 126	Mean: 30.7 pg/g Hb Mean: 20.7 pg/g Hb	< 0.001

Ab, albumin; ABP, aminobiphenyl; Hb, haemoglobin; NS, not significant; SD, standard deviation. Compiled from Demetriou *et al.* (2012).

Confounding

Of the studies on DNA adducts, only 14 adjusted for various potential confounders and only 7 of those 14 adjusted for PAHs in diet, indicating lack of adequate adjustment for confounding. Similarly, adjustment for confounders was minimal in the studies on protein adducts. Considering that PAHs in diet, smoking, and exposure to SHS are factors that have great impact on DNA adduct and protein formation, these exposures need to be accounted for when investigating the association between exposure to air pollution and DNA adducts.

Reversibility of changes and individual susceptibilities

A second issue is the plasticity and reversibility of protein and DNA adduct changes. Protein adducts cannot be repaired and thus better reflect exposure, whereas DNA adducts can be eliminated by DNA repair mechanisms and are therefore more transient indicators of external exposure. In addition, one needs to consider inherited and acquired individual susceptibilities, as DNA adduct levels have been found to be dependent on polymorphisms in metabolic genes (i.e. the CYP1A1, MspI, and GSTM1 null genotypes) (Shields et al., 1993; Ryberg et al., 1997; Pastorelli et al., 1998), which may determine an individual's ability to remove DNA adducts.

Intensity, duration, and timing of exposure

Furthermore, the issues of intensity, duration, and timing of exposure are of primary importance when evaluating the impact of air pollution. Studies show that developing fetuses are more susceptible than adults to the carcinogenic effects of PAHs (Topinka et al., 1997; Pedersen et al., 2009). Exposure at this critical developmental stage may cause subtle changes that may or may not be repaired. If not repaired, these changes can persist and lead to increased risk of dysfunction and disease later in life (Barouki et al., 2012). Studies also show that exposure to PAHs and DNA adduct formation are not linearly associated (Lewtas et al., 1997). Instead, as shown in Figure 12.1, among highly exposed subjects the level of DNA adducts per unit of exposure was significantly lower than those at lower exposures (Peluso et al., 2001). There is little evidence in the literature about the impact of duration of exposure on the formation of protein and DNA adducts.

Target versus surrogate tissues

Another important consideration is that most studies available to date use surrogate tissues, such as blood. Air pollution is more likely to have the largest

impact on sites of deposition where doses are highest, such as the upper aerodigestive tract and lung. If DNA and protein adducts are investigated in target tissues, the associations observed are likely to be much stronger, more reliable, and more accurate.

Conclusions

Despite these considerations, DNA adducts are undeniably a valuable biomarker of exposure to air pollution. A recent review (Demetriou et al., 2012) recognized DNA adducts, along with 1-hydroxypyrene (1-OHP), chromosomal aberrations (CAs), micronuclei (MN), and oxidative damage to nucleobases, as valid biomarkers of exposure to air pollution. These biological markers cover the whole spectrum of progression from external exposure to tumour formation. 1-OHP is an excellent marker of internal dose, and DNA adducts and oxidized nucleobases are markers of the biologically effective dose, whereas MN, CA, and DNA methylation are good markers of early biological effect. DNA adducts have also been suggested to be predictive for the risk of future cancer (Peluso et al., 2005; Veglia et al., 2008). This multilevel evidence adds to the plausibility of a causal association between exposure to ambient air pollution and lung cancer.

In conclusion, biomarkers, including DNA adducts, are without question a valuable tool in the investigation of the relationship between air pollution and cancer since they not only improve exposure assessment but also increase our understanding of mechanisms underlying this association.

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Chapter 13. Combined effect of air pollution with other agents

Jonathan M. Samet

Air pollution has been linked to several malignancies, including lung cancer, urinary bladder cancer, and acute leukaemia; the evidence is most abundant for lung cancer, for which several causal factors are well established (Samet and Cohen, 2006). Worldwide, tobacco use, and in particular cigarette smoking, is the dominant cause of lung cancer and accounts for the majority of cases; in fact, most cases in many countries (IARC, 2004). Other well-characterized causes of lung cancer include occupational agents and indoor radon (Alberg and Samet, 2003). When considering air pollution and its sources in the causation of lung cancer, its combined effects with these other causes of lung cancer are inevitably an issue. At present in the USA and some other developed countries, the relative risk of lung cancer in regular smokers compared with never-smokers ranges from 10 to > 20. These extremely high relative risk values indicate a need to consider the potential modification by tobacco smoking of the risk of lung cancer (and possibly other cancers) associated with air pollution, and to assess the potential for residual confounding by tobacco smoking to explain risks associated with air pollution in epidemiological studies. In addition, information on tobacco smoking and cancer is relevant to the collective body of evidence for an evaluation of air pollution by the International Agency for Research on Cancer (IARC), since some specific carcinogens in air pollution are also found in tobacco smoke, which similarly to ambient and indoor air pollution, is a complex mixture that contains a multitude of carcinogens, and, similarly to ambient air pollution, elicits an inflammatory response in the lung and systemically (Lewtas, 2007).

Conceptual issues

The combined effects of particular carcinogens with other carcinogens have been addressed in previous IARC Monographs, including those that covered asbestos (IARC, 1977), radon (IARC, 1988), man-made fibres (IARC, 1988), and tobacco smoking (IARC, 2004). The Monograph on tobacco smoking provides an extended conceptual framework, which is summarized below.

For many cancers, including lung cancer, multiple causal factors are relevant. Persons who are exposed to more than one risk factor may experience risks that

differ from those anticipated from the effects of the individual agents when they act alone. Epidemiologists refer to effect modification when effects of multiple agents are interdependent; the pattern of effect modification is termed synergistic when positive and antagonistic when negative. Statistical models test whether there is an interaction between independent determinants of cancer risk, and model-derived estimates of the degree of interaction are interpreted within the epidemiological framework. In the Monograph on tobacco smoking (IARC, 2004), standardization of the concepts and terminology of effect modification was introduced. Interdependence of effects was termed effect modification, and synergism and antagonism were used to describe the consequences of the interdependence of risk for disease when both factors are present (Rothman and Greenland, 1998). Interaction was a term reserved for the statistical approach of testing whether effect modification occurs.

In considering air pollution with other risk factors and the risk of cancer, many potential stages exist at which the biological consequences of other risk factors could affect a response to air pollution. Following a toxicological paradigm that extends from exposure through to dose and finally to biological effects, several different stages in the sequence exist at which tobacco smoking or other risk factors might influence the effect of an air pollutant or air pollution in general (Table 13.1). The levels of potential interaction between the agents are multiple and range from molecular to behavioural. Some of the likely points of interaction could have an impact on the level of exposure; others, including an exposure–dose relationship, could affect the dose–response relationship of exposure with risk, either for tobacco smoking or for air pollution. In assessing the presence of synergism or antagonism, a model is assumed to predict the combined effect from the individual effects. However, due to the lack of sufficient biological understanding to be certain of the most appropriate model, the choice is often made by convention or convenience.

Table 13.1. Levels of interaction between smoking and other agents

Exposure	• Work assignments of smokers and nonsmokers differ
	• Absenteeism rates differ for smokers and nonsmokers
	• Patterns of physical activity and ventilation differ for smokers and nonsmokers
	• Exposures of smokers and nonsmokers differ in activity size distribution
Exposure–dose	

relationships	• Patterns of lung deposition and clearance differ in smokers and nonsmokers • Morphometry of target cells differ in smokers and nonsmokers
Carcinogenesis	• Alpha particles and tobacco smoke carcinogens act at the same or different steps in a multistage carcinogenic process

Of interest is effect modification, which is reviewed and considered in IARC Monographs because of its implications for disease prevention and insights into mechanisms of carcinogenesis. In a multistage formulation of carcinogenesis, inferences as to the stages at which agents act can be made based on patterns of effect modification, particularly if data are available on the timing of the exposures (Doll, 1971; Whittemore, 1977; Thomas and Whittemore, 1988). In general, agents that act at the same step would be anticipated to have additive combined effects, whereas those that act at different steps are anticipated to have synergistic effects. While simplistic, this formulation offers a useful framework for considering joint exposures to air pollutant mixtures that have many of the components of tobacco smoke.

Epidemiological studies

In most epidemiological studies of air pollution and lung or other cancers, tobacco smoking has been treated as a potential confounding factor that has been controlled through stratification or modelling (Samet and Cohen, 2006). Only a few studies provide information on effect modification, since most do not have a sufficient sample size to estimate rates of lung cancer in smokers and never-smokers. In addition, some of the major cohort studies that provide relevant data have obtained information on smoking only at enrolment; therefore, misclassification of smoking over follow-up most likely occurred as some smokers successfully quit.

The American Cancer Society's Cancer Prevention Study II (CPS-II) is one of the few studies with sufficient data to assess the modification by cigarette smoking of the risk of lung cancer associated with air pollution. The cohort was established in 1982, and risks for mortality in relation to air pollution were described in two reports that were based on follow-up through 1989 (Pope et al., 1995) and through 1998 (Pope, 2000). Pope et al. (2002) described risks for

lung cancer in approximately 500 000 of the 1.2 million participants in relation to exposure to fine particles (particulate matter < 2.5 μm in diameter [$PM_{2.5}$]). Overall, mortality from lung cancer was estimated to increase by 14% (relative risk [RR], 1.14; 95% confidence interval [CI], 1.04–1.23) per 10 μg/m^3 $PM_{2.5}$ from enrolment through 1998. The authors presented the effect of $PM_{2.5}$ on mortality from lung cancer by smoking status in their Figure 4, which showed an increment in effect from current to former to never-smokers. Formal tests for effect modification were not provided. The picture of risk of lung cancer by smoking stratum was less clear in the earlier follow-up (Pope et al., 1995); risk of lung cancer was increased in association with ambient concentrations of sulfate (RR, 1.36; 95% CI, 1.11–1.66 for a 19.9 μg/m^3 increment) but not with $PM_{2.5}$ (RR, 1.03; 95% CI, 0.80–1.33 for a 24.5 μg/m^3 increment). Turner et al. (2011) followed the American Cancer Society cohort through 2008 and reported relative risks of lung cancer mortality of 1.15–1.27 for a 10 μg/m^3 increment in $PM_{2.5}$ among 188 000 never-smokers.

The Harvard Six Cities Study of Air Pollution and Mortality included a much smaller population (n = 8111) (Dockery et al., 1993). A report on the re-analysis (Krewski et al., 2000) included estimates of the effect of air pollution for ever- and never-smokers. The relative risk estimates for a $PM_{2.5}$ concentration difference of 18.6 μg/m^3 were 3.88 (95% CI, 0.44–34.18) for never-smokers and 1.40 (95% CI, 0.80–2.46) for ever-smokers.

Samet and Cohen (1999) made estimates of the effect of joint exposure to ambient air pollution and cigarette smoking based on several studies that provided the requisite data (Table 13.2). Although the studies were limited in scope, the results indicated that the joint contribution may be substantial.

Table 13.2. Proportion of lung cancer attributable to the joint effect of air pollution and tobacco smoking

Reference	Air pollution	Measure of smoking	Rate ratios relative to nonsmoking residents of low-pollution areas		Prop attrib to exp
			Air pollution	Air pollution/smoking	(E
Stocks and Campbell (1955)	Urban residents	1 pack per day	9.3	21.2	0

Haenszel et al. (1962)	Male residents of urban counties	> 1 pack per day	1.1	5.7	0
Vena (1982)	Lifetime residents of high- and medium-pollution areas	≥ 40 pack-years	1.1	4.7	0
Jedrychowski et al. (1990)	Residents of high-pollution areas	Ever-smokers	1.1	6.7	0
Barbone et al. (1995)	Residence in areas with high levels of particulate deposition (> 0.298 g/m^2/day)	≥ 40 cigarettes per day	3.7	59.6	0

[a] The EFI (etiological fraction due to interaction) provides an estimate of the proportion of disease among those exposed to both high air pollution and smoki (either former or current) that is attributable to their joint effect.

Conclusions

Assessment of the relatively modest effects of air pollution on risk of cancer has long been complicated by the high prevalence of tobacco smoking and the powerful effect that smoking has to increase the risk of cancer. To the extent possible, IARC Monographs on air pollutants will need to assess studies carefully with regard to their approach to tobacco smoking, to the potential for residual confounding, and also to an evaluation of any effect modification.

Synergism of air pollution with smoking would indicate that the burden of cancer associated with smoking may be far greater than that indicated by the estimated risk for smoking alone.

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