World Health Organization
REGIONAL OFFICE FOR Europe

Human health effects of polycyclic aromatic hydrocarbons as ambient air pollutants

Report of the Working Group on Polycyclic Aromatic Hydrocarbons of the Joint Task Force on the Health Aspects of Air Pollution

Abstract

Polycyclic aromatic hydrocarbons (PAHs) are a large group of organic compounds containing two or more fused aromatic (benzene) rings. The main anthropogenic sources of emission are the incomplete combustion or pyrolysis of organic material (i.e. emissions from vehicles, domestic heating or cooking) and the burning of agricultural waste. Human exposure to PAHs may occur from inhalation, dermal exposure or the ingestion of food contaminated with PAHs. PAHs in air pollution are primarily found bound to particulate matter; when PAHs are present in the gas phase, they have a duration of less than a day. Overall, the present scientific evidence suggests that the PAHs in ambient air are associated with increased cancer incidence in exposed populations. Positive associations have been reported between ambient PAHs and breast cancer, childhood cancers and lung cancer. Epidemiological studies have shown that PAHs are associated with reduced lung function, exacerbation of asthma, and increased rates of obstructive lung diseases and cardiovascular diseases. Limited epidemiological evidence also suggests adverse effects on cognitive or behavioural function in children. For several PAHs that are carcinogenic air pollutants, a lowest possible exposure should be aimed at to minimize the risk of cancer development in view of a no-effect threshold. It was not possible to establish whether current WHO guidelines for benzo[*a*]pyrene provide sufficient protection against diseases other than cancer. Therefore, the relevance of non-cancer health end-points of PAH exposure should be further explored.

Keywords

AIR POLLUTION
POLYCYCLIC AROMATIC HYDROCARBON
BENZO(A)PYRENE
CANCER
RESPIRATORY DISEASE
CARDIOVASCULAR DISEASE
NEURODEVELOPMENT OUTCOMES

ISBN: 978-92-890-5653-3

Suggested citation. Human health effects of polycyclic aromatic hydrocarbons as ambient air pollutants: report of the Working Group on Polycyclic Aromatic Hydrocarbons of the Joint Task Force on the Health Aspects of Air Pollution. Copenhagen: WHO Regional Office for Europe; 2021. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Cover image: © WHO/Helena Shkarubo

Design and layout: Imre Sebestyén / Unit Graphics

World Health Organization
REGIONAL OFFICE FOR Europe

Human health effects of polycyclic aromatic hydrocarbons as ambient air pollutants

Report of the Working Group on Polycyclic Aromatic Hydrocarbons of the Joint Task Force on the Health Aspects of Air Pollution

Contents

Acknowledgements

This report was prepared by the Working Group on Polycyclic Aromatic Hydrocarbons, established under the Joint Task Force on the Health Aspects of Air Pollution, which was formed in 1998 under the aegis of WHO and the United Nations Economic Commission for Europe's Convention on Long-range Transboundary Air Pollution. The Working Group is composed of the following experts from six Parties to the Convention (Canada, Finland, Norway, Sweden, Switzerland and the United Kingdom): Julie Bourdon-Lacombe, Bendik C. Brinchmann, Kristian Dreij, Alison M. Gowers, Marie-Ève Héroux,[1] Jørn A. Holme, Meltem Kutlar Joss, Titus Kyrklund, Marit Låg, Siiri Latvala, Lara Milena Lüthi, Johan Øvrevik, Magne Refsnes, Lamia Salmi, Raimo O. Salonen and Eleanor M. Sykes.

The development of this publication was coordinated by the WHO European Centre for Environment and Health, WHO Regional Office for Europe, with input from Fahad Alfahad, Pierpaolo Mudu, Román Pérez Velasco, Pilmu Ryu and Hanna Yang, under the supervision of Dorota Jarosińska and Francesca Racioppi.

The WHO Regional Office for Europe is grateful for comments received from seven representatives of the Joint Task Force on the Health Aspects of Air Pollution,[2] and from Alexey Gusev (EMEP Meteorological Synthesizing Centre – East, Moscow, Russian Federation), Martí Nadal Lomas (Laboratory of Toxicology and Environmental Health – TecnATox, Universitat Rovira I Virgili, Reus, Spain) and Mary Schubauer-Berigan (Evidence Synthesis and Classification Branch, International Agency for Research on Cancer, Lyon, France), who peer reviewed the document.

Thanks also go to Richard Ballaman (Swiss Federal Office for the Environment, Bern, Switzerland) for providing valuable input and suggestions for the Executive summary; Elisabeth Galarneau (Environment and Climate Change Canada, Toronto, Canada) for providing comments and suggestions for Chapter 2 on Emissions and ambient exposure to PAHs; and David Phillips (King's College, London, United Kingdom) for reviewing an early draft of section 4.3 on the effects of PAHs on neurodevelopment outcomes in children.

The WHO Regional Office for Europe is grateful for funding received from the German Federal Ministry for the Environment, Nature Conservation and Nuclear Safety and from the Swiss Federal Office for the Environment to support the work published in this report.

1 Of the Air Quality Assessment Section, Health Canada, Ottawa, Canada.

2 From whom comments were collected anonymously.

Authors

Titus Kyrklund
Air Quality Unit, Swedish Environmental Protection Agency, Stockholm, Sweden

Julie Bourdon-Lacombe
Air Quality Assessment Section, Health Canada, Ottawa, Canada

Bendik C. Brinchmann
Section of Air Quality and Noise, Department of Environmental Health, Norwegian Institute of Public Health, Oslo, Norway

Kristian Dreij
Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden

Alison M. Gowers
UK Health Security Agency, United Kingdom

Jørn A. Holme
Section of Air Quality and Noise, Department of Environmental Health, Norwegian Institute of Public Health, Oslo, Norway

Meltem Kutlar Joss
LUDOK Swiss Literature Database on Air Pollution and Health, Swiss Tropical and Public Health Institute, University of Basel, Switzerland

Marit Låg
Section of Air Quality and Noise, Department of Environmental Health, Norwegian Institute of Public Health, Oslo, Norway

Siiri Latvala
Environmental Pollutants Unit, Swedish Environmental Protection Agency, Stockholm, Sweden

Lara Milena Lüthi
Swiss Federal Office for the Environment, Bern, Switzerland

Johan Øvrevik
Section of Air Quality and Noise, Department of Environmental Health, Norwegian Institute of Public Health, and Department of Biosciences, Faculty of Mathematics and Natural Sciences, University of Oslo, Oslo, Norway

Magne Refsnes
Section of Air Quality and Noise, Department of Environmental Health, Norwegian Institute of Public Health, Oslo, Norway

Lamia Salmi
Air Quality Assessment Section, Health Canada, Ottawa, Canada

Raimo O. Salonen
Environmental Health Unit, National Institute for Health and Welfare, Kuopio, Finland

Eleanor M. Sykes
UK Health Security Agency, United Kingdom

Titus Kyrklund was the editor and the authors of specific chapters and sections were as follows: Julie Bourdon-Lacombe (Chapter 3, section 3.3), Bendik C. Brinchmann (Chapter 4, section 4.2), Kristian Dreij (Chapters 2, 5 and 6; Chapter 3, sections 3.1, 3.2 and 3.4), Alison M. Gowers (Chapters 5 and 6; Chapter 4, section 4.3), Jørn A. Holme (Chapters 5 and 6; Chapter 4, sections 4.1 and 4.2), Titus Kyrklund (Chapters 1, 2, 5 and 6), Meltem Kutlar Joss (Chapters 5 and 6; Annex 1), Marit Låg (Chapters 5 and 6; Chapter 4, sections 4.1 and 4.2), Siiri Latvala (Chapter 2), Lara Milena Lüthi (Chapters 2, 5 and 6), Johan Øvrevik (Chapter 4, sections 4.1 and 4.2), Magne Refsnes (Chapter 4, sections 4.1 and 4.2), Lamia Salmi (Chapters 2, 5 and 6; Chapter 3, section 3.3; Annex 2), Raimo O. Salonen (Chapters 2, 5 and 6; Annex 2) and Eleanor M. Sykes (Chapters 5 and 6; Chapter 4, section 4.3).

Abbreviations

8-OHdG	8-hydroxy-2'-deoxyguanosine
ADHD	attention deficit hyperactivity disorder
AhR	aryl hydrocarbon receptor
Air Convention	Convention on Long-range Transboundary Air Pollution
B[a]P	benzo[*a*]pyrene
β_2-AR	β_2-adrenergic receptor
CCCEH	Columbia Centre for Children's Environmental Health
CVD	cardiovascular disease
CXCL8	CXC motif chemokine ligand 8
CYP	cytochrome P450
EMEP	European Monitoring and Evaluation Programme (Co-operative Programme for Monitoring and Evaluation of the Long-range Transmission of Air Pollutants in Europe)
EU	European Union
IARC	International Agency for Research on Cancer
IL	interleukin
IQ	intelligence quotient
MPF	mixture potency factor
NABEL	National Air Pollution Monitoring Network
OH-PAH	hydroxylated polycyclic aromatic hydrocarbon
PAH	polycyclic aromatic hydrocarbon
PM	particulate matter
RPF	relative potency factor
Th	T helper (cells)
TNF-α	tumour necrosis factor alpha
UNECE	United Nations Economic Commission for Europe
US EPA	United States Environmental Protection Agency

Executive summary

Polycyclic aromatic hydrocarbons (PAHs) are a large group of organic compounds containing two or more fused aromatic (benzene) rings. The main anthropogenic sources of PAH emission are incomplete combustion or pyrolysis of organic material: emissions from fossil fuels, biofuels (e.g. wood or agricultural waste), automobile exhaust, emissions from domestic heating and cooking, and tobacco smoke. PAHs, including benzo[*a*]pyrene (B[*a*]P), represent an important set of indoor and outdoor air pollutants, both in Europe and globally. In the European Monitoring and Evaluation Programme (EMEP)[3] region, PAH emissions decreased by more than 30% between 1990 and 2005. However, no further improvement in PAH emissions was observed in the 2000–2012 period, in contrast to many other air pollutants. Human exposure to PAHs may occur from inhalation, dermal exposure or ingestion of food contaminated with PAHs. PAHs in air pollution are primarily found bound to particulate matter (PM); when PAHs are present in the gas phase, they have a duration of less than a day.

Overall, the present scientific evidence suggests that the PAHs in ambient air are associated with increased cancer incidence in exposed populations. Given that many PAHs are considered either carcinogenic or probably carcinogenic to humans and are assumed to cause direct DNA damage, it is reasonable to expect an association between exposure to PAHs in ambient air and the development of various types of cancers. Positive associations between ambient PAHs and breast cancer, childhood cancers and lung cancer have been reported. However, assessment of PAH exposure in the general population is difficult because of the length of time needed for cancer development and the possibility that exposure conditions may change over time. Since 2000, only a few epidemiological studies have focused on cancer in the general population. Additional studies will be needed to support a causal link between PAH exposures from ambient air and cancer in human populations. In particular, longitudinal studies on the potency of different PAHs in a mixture would be important.

Regarding the non-carcinogenic effects, epidemiological studies have found associations between ambient exposure to PAHs and adverse health effects, including reduced lung function, exacerbation of asthma, and increased morbidity and mortality of obstructive lung diseases. Human epidemiological studies, combined with experimental animal and in vitro studies, strongly suggest that exposure to combustion PM increases the risk of cardiovascular diseases (CVDs). The limited epidemiological evidence available suggests that prenatal and early life exposure to PAHs in ambient air affect cognitive or behavioural function in children. However, the specific role of PAHs is difficult to disentangle from those of other products of combustion processes, including combustion PM. Based on epidemiological data alone, it is also difficult to separate the effects of airborne PAHs from those of other PAHs sources.

From a policy perspective, PAHs are an important group of air pollutants that should receive more attention for regulating air pollution, in particular from combustion

3 The official name is the Co-operative Programme for Monitoring and Evaluation of the Long-range Transmission of Air Pollutants in Europe. The EMEP region covers not only Europe but also countries in central and western Asia and North America.

sources. Ambient PM is characterized by its physical properties upon sampling; in contrast, PAHs are chemically defined. For carcinogenic PAHs, the aim should be the lowest possible exposure to minimize the risk of cancer development in view of a no-effect threshold. However, within this group, individual PAHs may differ in carcinogenic potency by an order of magnitude. The current knowledge base is insufficient to determine whether B[*a*]P is a representative marker for exposure to a PAH mixture in ambient air or to permit the establishment of guidelines or standards for non-malignant effects of either B[*a*]P or other PAH species. Therefore, it is not possible to establish whether current WHO guidelines for B[*a*]P provide sufficient protection against diseases other than cancer. In addition, further exploration of non-cancer health end-points of PAH exposure is needed. Lastly, monitoring programmes should be optimized to support the protection of populations from PAH exposure. This could be achieved in hot-spot areas either by creating high-resolution monitoring networks or by high-resolution modelling of PAH concentrations.

1. Introduction

1.1 Background

Polycyclic aromatic hydrocarbons (PAHs) are a large group of organic compounds containing two or more fused aromatic (benzene) rings *(1)*. Anthropogenic sources that emit the highest number of these chemicals are incomplete combustion or pyrolysis of organic material: fossil fuels, biofuels (e.g. wood or agricultural waste), automobile exhaust and tobacco smoke. In nature, PAHs are formed, for example, by forest and other vegetation fires or volcanic activity. PAHs, including benzo[*a*]pyrene (B[*a*]P), are an important set of indoor and outdoor air pollutants, both in Europe and globally.

People may be exposed to PAHs via inhalation, dermal exposure or ingestion of food contaminated with PAHs. PAHs containing five or more aromatic rings are mainly found bound to particulate matter (PM), whereas PAHs containing up to four aromatic rings are predominantly found in the gas phase *(2,3)*. Nevertheless, owing to the considerably higher levels of low-molecular-weight PAHs in ambient air, three- and four-ring PAHs also tend to be the predominant group bound to PM. PAHs present in ambient air in the gas phase generally have durations of less than a day, whereas particle-associated PAHs may persist for weeks and undergo long-range atmospheric transport *(4)*.[4]

1.2 Context of WHO and the 1979 Convention on Long-range Transboundary Air Pollution

To improve air quality, Member States of the United Nations Economic Commission for Europe (UNECE), in particular the 51 Parties to the 1979 Convention on Long-range Transboundary Air Pollution (hereafter, referred to as the Air Convention) *(5)*, have been working successfully to reduce air pollution in the wider UNECE region. The Air Convention was the first international treaty to deal with air pollution on a regional basis. Entering into force in 1983, the Air Convention laid down the principles of international cooperation for air pollution abatement and set up an institutional framework combining research and policy with the aim to cut emissions of air pollution. It has since been extended by eight protocols, including the 1998 Aarhus Protocol on Persistent Organic Pollutants, which was ratified by 33 Parties *(6)*. The Protocol states that each Party shall reduce its total annual

4 The names of PAHs can vary by authority and source, and can change over time. The International Union of Pure and Applied Chemistry is the main authority on the matter. The names used in the present document reflect this source, but also take account of nomenclature that is familiar to the target readership.

emissions of substances listed in Annex III (including PAHs) from the level of the emission in 1990 (or an alternative year from 1985 to 1995 inclusive) by taking effective measures as outlined in Annex V and the guidance document, which identify the best available techniques to control emissions from stationary and mobile sources. For the purposes of emission inventories, the following four indicator compounds should be used: B[*a*]P, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene and indeno[1,2,3-*cd*] pyrene.

Additionally, Article 8 on research, development and monitoring specifies that:

The Parties shall encourage research, development, monitoring and cooperation related, but not limited, to:

(a) Emissions, long-range transport and deposition levels and their modelling, existing levels in the biotic and abiotic environment, the elaboration of procedures for harmonizing relevant methodologies;

(b) Pollutant pathways and inventories in representative ecosystems;

(c) Relevant effects on human health and the environment, including quantification of those effects.

To date, there is no international consensus on which PAH emissions or resulting exposure should be reported. However, WHO and UNECE have suggested suitable PAHs for reporting based on their abundance and toxicity to health and the environment *(7)*.

WHO issued the *Air quality guidelines for Europe* in 1987 *(8)*, which was updated in 2000 *(9,10)*. The update estimated the unit risk for lung cancer from PAHs as 8.7×10^{-5} per ng/m^3 B[*a*]P, and this value was also adopted by the 2010 *WHO guidelines for indoor air quality (11)*. For lifetime exposure, the concentrations producing excess lifetime cancer risks of one in 10 000, one in 100 000 and one in 1 million were approximately 1.2, 0.12 and 0.012 ng/m^3 B[*a*]P, respectively *(11)*. B[*a*]P was selected as an indicator for assessing the health risk of PAHs mainly because at the time it was the only PAH for which sufficient data were available to make a health risk assessment. Debate is continuing as to whether B[*a*]P is representative as a marker for exposure to other PAHs: "Evaluation of, for example, B[*a*]P alone will probably underestimate the carcinogenic potential of airborne PAH mixtures, since co-occurring substances are also carcinogenic" *(12)*. No threshold value could be determined and all indoor exposures were considered relevant to health *(11)*. The WHO *Air quality guidelines: global update 2005. Particulate matter, ozone, nitrogen dioxide and sulfur dioxide* did not provide a guideline value for PAHs *(13)*, although it referred to the carcinogenicity of PAHs. The WHO project, Review of evidence on health aspects of air pollution – REVIHAAP *(14)*, reviewed new evidence following the publication of *Air quality guidelines: global update 2005 (13)*. In addition to confirming that some PAHs are potent carcinogens, it found a new link between PAH exposure to cardiovascular outcomes. However, these effects could not be separated from the effects of PM and, therefore, could not serve as the basis for developing a guideline value. Nevertheless, WHO has developed AirQ+ software, which includes a module that allows the calculation of risks due to exposure to carcinogenic air pollutants, including B[*a*]P, based on the unit risk factor *(15,16)*.

1.3 Scope and objectives

Work on this report was initiated at the 20th meeting of the Joint Task Force on the Health Aspects of Air Pollution, Bonn, Germany, 16–17 May 2017 *(17)* in response to a suggestion from the Swiss representative, and was included in the 2018–2019 workplan of the Air Convention *(18,19)*. The initiative aimed to evaluate the current state of knowledge on the health risk of PAHs, identify critical gaps, and assess whether and to what extent such an evaluation could be continued by the Task Force on Health.

The initial deliverables of the workplan were:

- a proposal for a roadmap for how health risks of PAHs can be assessed in view of their relative carcinogenic potencies;
- an evaluation of the representativeness of B[*a*]P as an indicator for the PAH group; and
- an evaluation of how equivalence factors could be used in risk assessment of PAHs.

The work continued as part of the 2020–2021 workplan *(20)*, with further refinement of objectives to:

- review epidemiological findings on the relation between PAH exposure in ambient air and different health outcomes, including cancer and non-cancer end-points;
- review experimental studies that indicate selected important aspects of PAH toxicity;
- highlight the mechanistic background for the toxicity of PAHs and its relevance for risk assessment; and
- give policy-makers a short update of recent findings of the health effects of PAHs as air pollutants and of B[*a*]P as a relevant marker for toxicity.

This report provides a resource for those interested in the current state of the scientific discussion, knowledge gaps and ideas for future directions of work. It is not intended to provide a systematic and comprehensive review of airborne PAHs and health, but instead focuses on specific aspects relevant to health risk assessment. It includes selected studies on human health effects, emissions and sources of as well as exposure to PAHs, as well as current national work on PAHs in the countries of the Working Group on Polycyclic Aromatic Hydrocarbons of the Joint Task Force on the Health Aspects of Air Pollution. The methodology used to conduct the literature search is shown in Annex 1.

2. Emissions and ambient exposure to PAHs

2.1 Emission trends and ambient concentrations

In the European Monitoring and Evaluation Programme (EMEP)[5] region, PAH emissions decreased by more than 30% between 1990 and 2005, with Germany and the United Kingdom achieving the largest reductions. However, in contrast to many other air pollutants, no further improvement was observed in 2000–2012. Air pollution levels of PAHs and their trends, and population exposure within the UNECE region are discussed in reports published by Meteorological Synthesizing Centre – East *(1)* and EMEP *(22)*. The reports aimed to analyse the effectiveness of the Aarhus Protocol on Persistent Organic Pollutants and to support relevant bodies under the UNECE umbrella. The spatial distribution of emissions of PAHs in the EMEP region was also reported (Fig. 2.1).

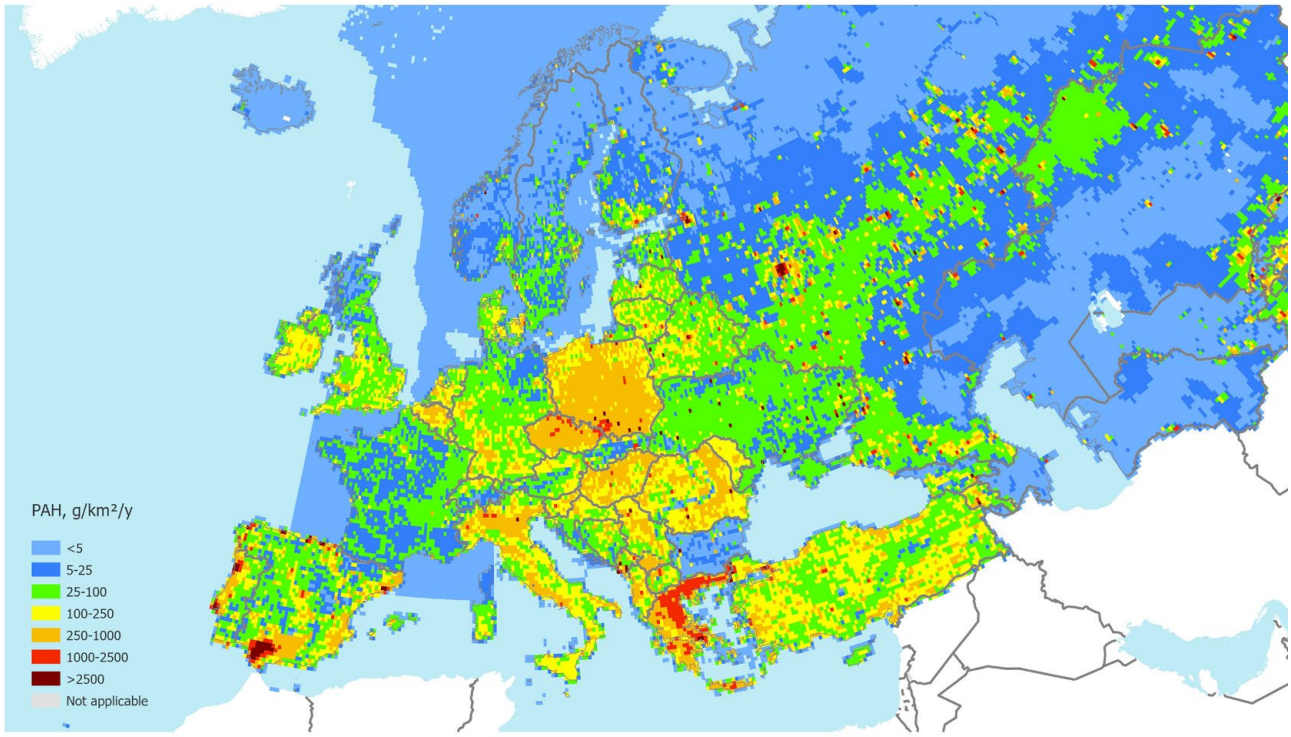
In the European Union (EU), PAH emissions from the commercial, institutional and household sectors are much greater than those from the industrial sector, which have decreased since 2000 *(23)*. However, the highest B[*a*]P concentrations were reported from countries in eastern Europe, where coal is a common fuel for domestic heating and energy production. Wood burning is another important source of B[*a*]P emissions, although the emissions are less well detected by monitoring networks in sparsely populated regions of northern Europe (Fig. 2.2). In the EU between 2007 and 2017, 65% of national monitoring sites reported decreasing B[*a*]P concentrations, although a significant number of sites showed increasing concentrations in Austria, Cyprus, Czechia, Ireland, Italy, Poland, Slovakia, Spain and the United Kingdom *(1)*. In some countries, mostly in southern Europe, agricultural waste burning is also a relevant source of B[*a*]P emissions *(23)*.

In Canada, data from the Air Pollutant Emission Inventory show that the national total emissions of selected PAHs decreased between 1990 and 2019 by 72%, primarily due to emission reductions in the aluminium, iron and steel industries resulting from the implementation of new production technologies *(24)*. Over the reporting period, PAH emissions decreased by almost 100% in both the aluminium and the iron and steel industries; and by 65% in the transportation and mobile equipment sector. In 2019 the Air Pollutant Emission Inventory attributed 87% of PAHs emitted in Canada to commercial/residential/institutional sources *(25)*. PAHs are sampled through several air monitoring stations located in different urban Canadian cities and monitoring data can be accessed through the National Air Pollution Surveillance Program *(26)*. Tevlin et al. (2021) reported the annual average B[*a*]P concentrations from 1989 to 2017 and compared them

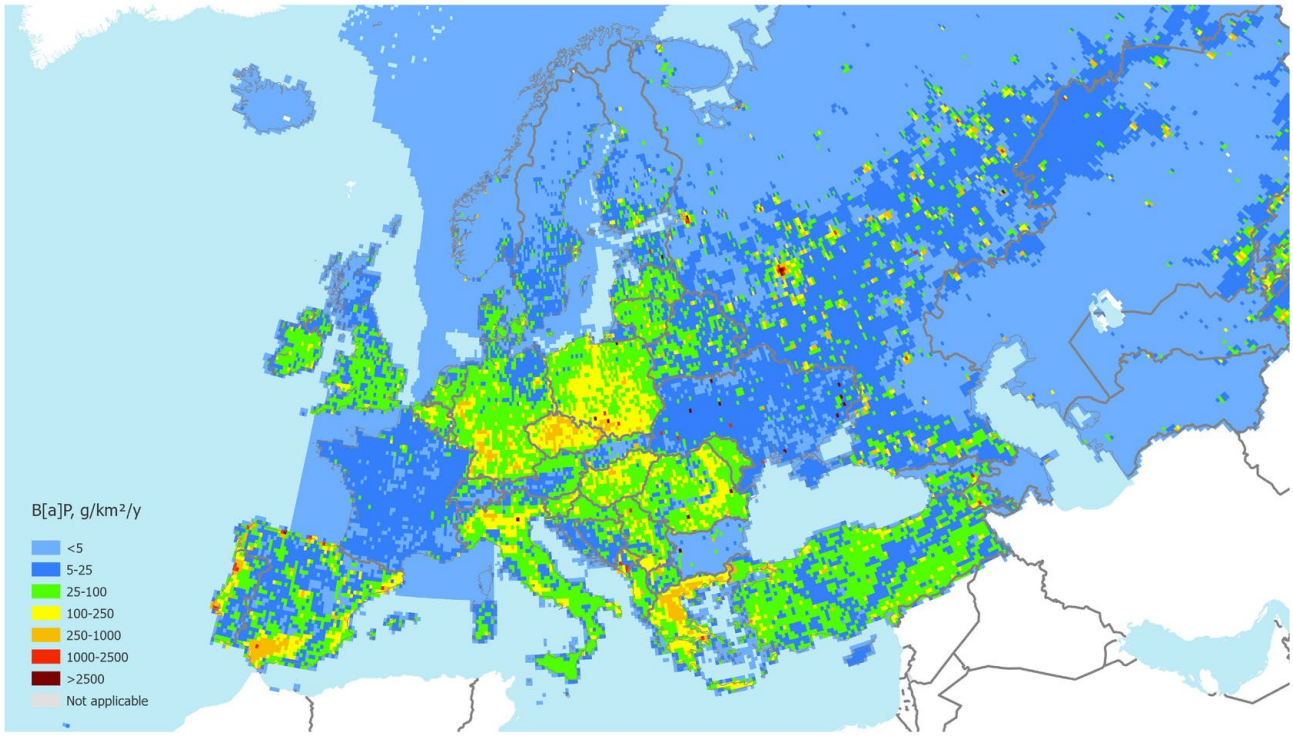
5 Officially called the Co-operative Programme for Monitoring and Evaluation of the Long-range Transmission of Air Pollutants in Europe *(21)*.

Fig. 2.1. Spatial distribution of PAH and B[*a*]P emissions in the EMEP region, 2017

(a)



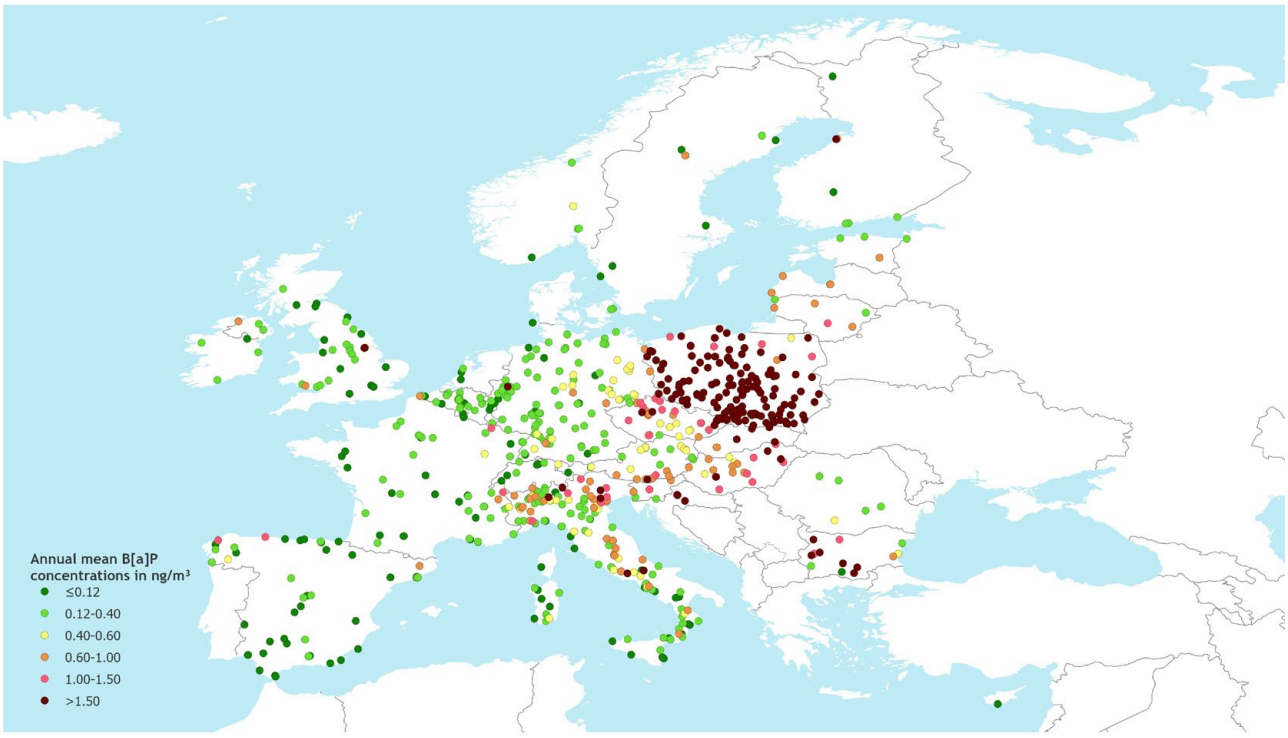
(b)



Notes: distributions of (a) emissions of the four indicator PAHs for which reporting is mandatory under UNECE (that is, B[*a*]P, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene and indeno[*1,2,3-cd*]pyrene) and of (b) B[*a*]P emissions. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement. Data source: Meteorological Synthesizing Centre - East (MSC-E); Map production: WHO GIS Centre for Health, DNA/DDI; Map creation date: 25 October 2021.

Source: Gusev A, Batrakova N. Assessment of PAH pollution levels, key sources and trends: contribution to analysis of the effectiveness of the POPs Protocol. Moscow: Meteorological Synthesizing Centre; 2020 *(1)*. Reproduced with permission.

Fig. 2.2. Distribution of B[*a*]P concentrations in ambient air in European countries, 2018



Notes: The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement. Data source: European Environment Agency; Map production: WHO GIS Centre for Health, DNA/DDI; Map creation date: 27 October 2021.

Source: European Environment Agency. Air quality in Europe: 2020 report. Luxembourg: Publications Office of the European Union; 2020 (European Environment Agency Report No. 9/2020) *(23)*. Reproduced with permission.

with guidelines from a few Canadian provinces *(27)*. The annual average thresholds for B[*a*]P were 0.01 ng/m^3 in Ontario, 0.3 ng/m^3 in Alberta and 0.9 ng/m^3 in Quebec. The guideline set by Ontario was exceeded at almost every location with more than five years of data. The Alberta and Quebec guidelines were also exceeded at specific locations such as downtown Montreal (Quebec) and downtown Hamilton (Ontario). However, it is important to note that such exceedances are less widespread in other urban Canadian cities *(27)*. For example, in 2018 the annual average levels of B[*a*]P in Canadian cities ranged between 0.01 ng/m^3 and 0.08 ng/m^3. The highest urban annual average level of B[*a*]P (0.08 ng/m^3) was observed in Toronto (the most populous city in Canada), near to highway 401, which comprises 18 lanes at its widest segment *(26)*. This indicates that traffic is an important source of PAH emissions. In contrast, Rivière-des-Prairies, a suburban borough located on the eastern tip of Montreal, has historically been associated with residential wood combustion emissions in winter, with higher PAH levels recorded there *(28)*. However, since 2018, the annual average level of B[*a*]P has been relatively low, at 0.06 ng/m^3 *(26)*. Furthermore, Montreal City Council established a regulation in 2018 that bans solid-fuel-burning appliances unless the emission rate is certified by the United States Environmental Protection Agency (US EPA) and does not exceed 2.5 g/h *(29)*.

2.2 Sources of outdoor air PAH emissions

Incomplete combustion of various solid or liquid organic fuels or materials produces PAHs. These fuels include various types of coal, crude oil, heavy fuel oil and other fossil fuels, biofuels such as firewood and agricultural and community waste, and tobacco smoke. The relative contribution to the different combustion sources of outdoor air PAHs has changed during the last 30–40 years. The European Environment Agency reported in 2020 that commercial, institutional and household sources account for 66% of total emissions, followed by agriculture (mostly in southern Europe), which accounts for 14% *(30)*. In Canada, wildfires are a major contributor to polycyclic aromatic compounds, among which PAHs are of environmental concern *(27,28)*. Regarding non-natural sources, household wood combustion and mobile sources are the two largest contributors, although these have declined by 25–65% since the 1990s. A small contribution from industrial sources, mainly aluminium production and iron/steel manufacturing, was reported owing to considerable reductions (90%) over the same period *(28)*. The most significant non-natural sources of PAH emissions in 2018 were commercial/residential/institutional sources, almost entirely due to household wood combustion, accounting for 90% of total emissions *(31)*. The relative contributions of PAHs from different sectors in the EU and Canada are summarized in Table 2.1.

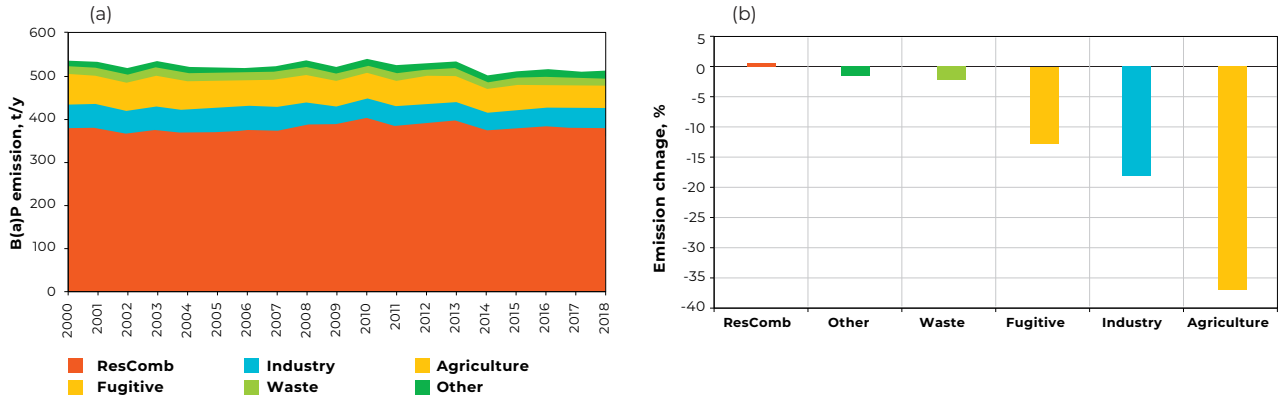
Total emissions of the four PAHs listed in the Aarhus Protocol (B[*a*]P, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene and indeno[1,2,3-*cd*]pyrene; section 1.2) in the EMEP region have not changed much since the early 2000s. However, decreases in emissions from the industrial and agricultural sectors of approximately 17% and 36%, respectively, during this period are balanced by a small relative increase in emissions from the domestic sector (Fig. 2.3).

Table 2.1. Relative contribution (%) of PAH emissions from various sources/sectors, EU and Canada, 2018

Geographical area	Sector						
EU *(30)*	**Commercial, institutional and households**	**Industrial processes and product use**	**Energy production and distribution**	**Energy use in industry**	**Agriculture**	**Road transport**	**Waste**
	66%	2%	6%	3%	14%	2%	7%
Canada *(31)*	**Commercial, residential, institutional**	**Industry, electric power generation, agriculture**				**Transportation and mobile equipment**	**Incineration, waste, fires**
	90%	1%				8%	1%

Sources: Data for the EU: European Environment Agency, 2020 *(30)*; data for Canada: Environment and Climate Change Canada, 2018 *(31)*.

Fig. 2.3. Long-term changes in sector-specific B[*a*]P emissions in EMEP countries, 2000–2018



ResComb: residential combustion.

Notes: (a) Changes in total emissions. t/y: tons per year. (b) Changes in relative percentage, by sector. Fugitive emissions are defined as those not caught by a capture system – they are often due to equipment leaks, evaporative processes and windblown disturbances *(32)*.

Source: Gusev A, Batrakova N. Assessment of PAH pollution levels, key sources and trends: contribution to analysis of the effectiveness of the POPs Protocol. Moscow: Meteorological Synthesizing Centre; 2020 *(1)*. Reproduced with permission.

2.3 Small-scale combustion for residential heating

In contrast to other sectors, strong progress has not been made in reducing PAH emissions from residential heating. Small-scale burning of wood, biomass waste or coal is still favoured in some countries owing to their availability and affordability but also to a lack of the infrastructure necessary to access gas or district heating. Wood is the commonest fuel, although coal predominates in some countries *(1)*.

In many countries, the development of emission standards for residential heating has been slow. However, automatically controlled low-emitting burners have been favoured in Austria and Germany *(33,34)*. Furthermore, emission standards for boilers and stoves have recently been adopted in the EU as a part of the Ecodesign Directive *(35,36)*.

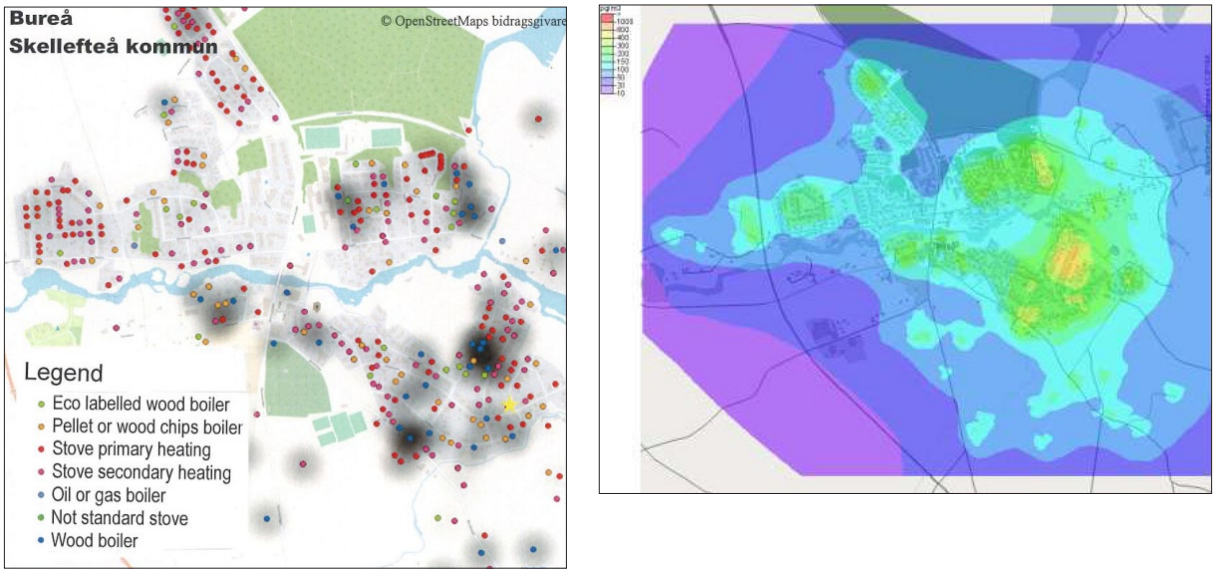
Case studies 1 and 2 illustrate the different characteristics of small-scale combustion for residential heating in Sweden and Switzerland, respectively.

Case study 1. Mapping B[*a*]P hotspots in Swedish towns

Andersson et al. (2019) estimated emissions from residential wood heating and calculated B[*a*]P levels in ambient air in the Swedish municipalities of Alingsås, Skellefteå and Strömsund *(37)*. These municipalities were chosen because they were suspected to have relatively high B[*a*]P concentrations in ambient air as a result of heating by small-scale wood burning and because they had emissions databases of sufficient quality for spatial modelling of B[*a*]P concentrations. Fig. 2.4 shows the types of wood-burning installation and modelled B[*a*]P concentrations in Bureå (in Skellefteå).

Fig. 2.4. Residential heating and emissions in Bureå, Skellefteå municipality, Sweden

(a) (b)



Notes: (a) Distribution of installations for residential heating. The monitoring station is marked by a yellow star. (b) Modelled B[*a*]P concentrations (pg/m³) from small-scale wood burning for heating in Bureå, northern Sweden. Green and light blue: > 0.1 ng/m³; yellow: > 0.4 ng/m³. Modelling is based on a scenario with site-specific burning habits and medium emission factors. Spatial resolution is 20 × 20 m.

Source: Andersson S, Arvelius J, Jones J, Kindell S, Leung W. Beräkningar av emissioner och halter av benso(a)pyren och partiklar från småskalig vedeldning: luftkvalitetsmodellering för Skellefteå, Strömsunds och Alingsås kommuner [Calculations of emissions and levels of benzo (a) pyrene and particles from small-scale wood burning: air quality modeling for the municipalities of Skellefteå, Strömsund and Alingsås]. Meteorologi 164. Norrköping: Swedish Meteorological and Hydrological Institute; 2019 *(37)* (in Swedish). Reproduced with permission.

The study showed that residential wood burning is the predominant source of B[*a*]P in all three municipalities. However, large variations in ambient B[*a*]P concentrations were observed, depending on the type and age of the installation and how it was used. The highest B[*a*]P concentrations were measured in the vicinity of old wood boilers that did not meet environmental quality standards (such as the EU Ecolabel) *(38)*. Furthermore, the quality of modelling data was highly dependent on having detailed knowledge of the type of installation and the burning habits of users.

Therefore, a very effective measure to reduce the levels of B[*a*]P would be to replace old wood boilers with modern boilers that meet stricter environmental quality standards.

Case study 2. Measuring B[*a*]P to monitor PAH emissions in Switzerland

Switzerland does not set emission limits for carcinogenic substances because the Swiss Ordinance on Air Pollution Control stipulates that carcinogenic emissions must be minimized regardless of the emissions that occur *(39)*. In order to obtain an overview of the emission concentrations of PAHs in PM_{10} (particulate matter with a diameter of < 10 µm) occurring in Switzerland, analyses have been conducted at selected National Air Pollution Monitoring Network (NABEL) stations since 2006. Data from monitoring stations have been aggregated for roadside or motorway traffic (Bern, Härkingen and Lausanne), urban locations (Basel, Dübendorf, Lugano and Zurich), rural locations (Payerne, Sion and Tänikon), and rural and wood-burning locations (Magadino and San Vittore; Fischer A, Hüglin C. Polyzyklische aromatische Kohlenwasserstoffe im PM_{10} an ausgewählten Stationen des NABEL sowie der Kantone: messbericht 2020 [Polycyclic aromatic hydrocarbons in PM10 at selected stations of NABEL and the cantons: measurement report 2020], Department of Air Pollutants and Environmental Technology, EMPA – Swiss Federal Laboratories for Materials Science and Technology, unpublished).

The study found that in 2019, as in previous years, the highest PAH concentrations were measured in San Vittore, which had an annual mean value of 0.77 ng/m^3 for B[*a*]P, meaning that the European target value for B[*a*]P of 1 ng/m^3 had been met at all measurement sites. At all other stations, the 2019 PAH exposure levels were significantly below the European target value (Fig. 2.5a). PAH levels at the rural sites were clearly influenced by emissions from wood combustion; therefore, the measured values were higher than at non-rural stations. The B[*a*]P load has decreased at all 12 of the investigated NABEL sites since measurements started in 2006 and is now significantly below the European target value at all stations (Fig. 2.5b). The long-term trend of quarterly values of B[*a*]P concentrations shows pronounced seasonality at all measuring stations, with high values in winter and significantly lower values in summer owing to biomass burning for heating purposes.

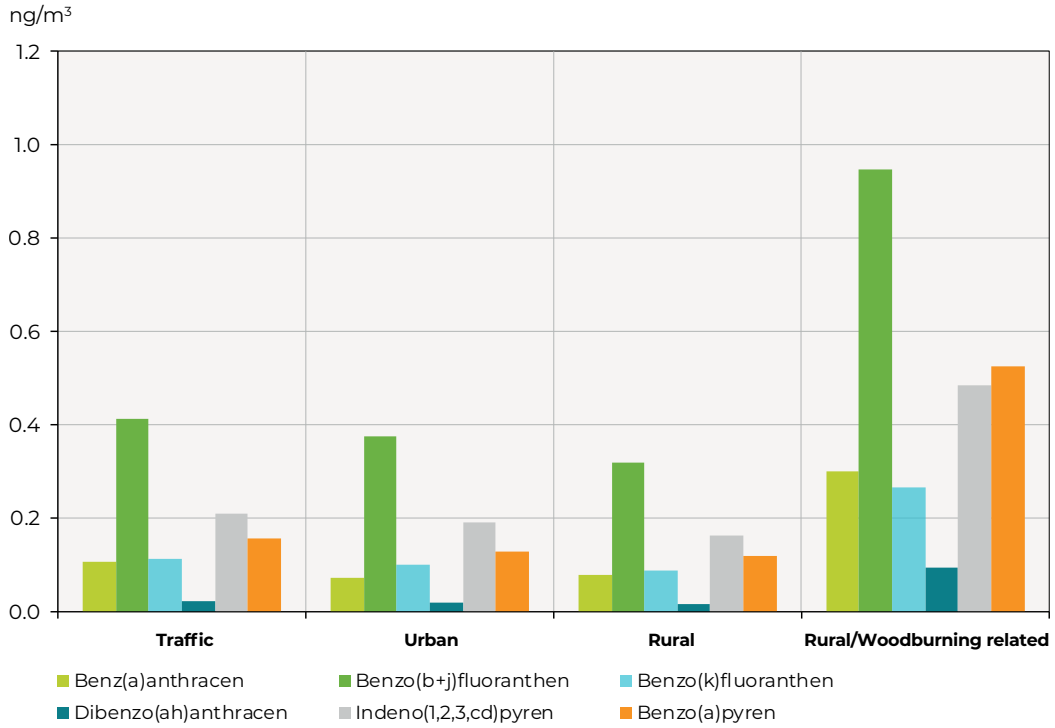
This clearly indicates the significant contribution of wood burning to PAH pollution in the winter months. Similarly, a study by Zotter et al. (2014) showed the major influence of biomass combustion based on measurement of the carbon-14 content of PM *(40)*. As early as 1995, a study of the cantons of Lucerne, Schaffhausen and Zurich found that emissions from wood-fired systems do indeed contain significant amounts of PAHs *(41)*. At that time, the highest B[*a*]P values were measured not at measuring stations exposed to traffic but during a winter measuring campaign at a rural station. A report in 2013 and 2014 in the province of Tyrol (Austria) also found that B[*a*]P levels were higher in residential areas than at sites exposed to heavy traffic *(42)*.

Data from monitoring stations do not differ significantly in the relative composition of the various PAHs. An evaluation of the relative toxicity of PAH concentrations measured in 2019 found that B[*a*]P alone was responsible for around 58% of the toxicity of PAHs in PM_{10} *(43)*. The relative contributions of the individual PAHs to the toxicity of PM_{10} were similar at all stations. A comparison of PAH-related toxicity of PM_{10} at the individual monitoring stations in 2019 found significantly greater toxicity values at rural monitoring stations in areas with high levels of wood combustion than at other stations.

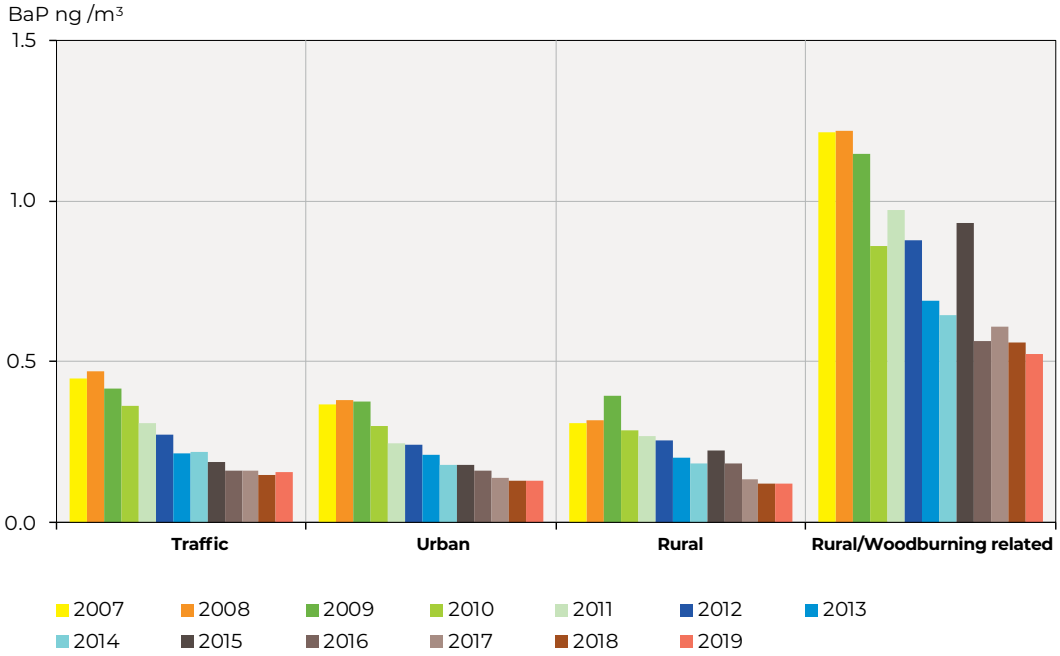
Case study 2 contd

Fig. 2.5. Average concentrations of selected PAHs at 12 NABEL stations, by emission source

(a)



(b)



Notes: (a) Average concentrations of six selected PAHs in 2019. (b) Average B[*a*]P concentration in 2006–2019.

Source: Fischer A, Hüglin C. Polyzyklische aromatische Kohlenwasserstoffe im PM_{10} an ausgewählten Stationen des NABEL sowie der Kantone: messbericht 2020 [*Polycyclic aromatic hydrocarbons in PM_{10} at selected stations of NABEL and the cantons: measurement report 2020*], Department of Air Pollutants and Environmental Technology, EMPA – Swiss Federal Laboratories for Materials Science and Technology, unpublished. Reproduced with permission.

2.4 Human exposure to PAHs

PAHs containing five or more aromatic rings are poorly water soluble and lipophilic; thus, they are mainly found adsorbed on black carbon in fine PM ($PM_{2.5}$ or PM_{10}[6]), whereas PAHs containing four or less aromatic rings are predominately found in the gas phase *(2,37)*. Nevertheless, owing to the considerably higher level of low-molecular-weight PAHs in outdoor air, three- and four-ring PAHs also tend to be the predominant PAHs adsorbed on fine and ultrafine PM. Levels of phenanthrene and pyrene bound to diesel exhaust and wood smoke particles typically exceed the B[*a*]P level by orders of magnitude *(2,3)*. This partly explains why phenanthrene and pyrene are so prominent in urban and suburban environments with a variable mixture of emission sources.

The relative amount of PAHs adsorbed to PM is also affected by temperature: a larger proportion of airborne PAHs (and relatively higher amounts of three- and four-ring PAHs compared with larger PAHs) are attached to PM in winter than in summer *(45)*.

Human exposure to PAHs may occur from inhalation, dermal exposure or ingestion of PAH-contaminated food. Food ingestion is a major source of PAH intake, especially for larger PAHs with four to six aromatic rings: daily intakes of PAHs are much smaller via inhalation to the respiratory tract than via food ingestion. Food crops can absorb PAHs from the soil or via atmospheric deposition through their root system *(3)*. Additional sources of PAHs in food are related to different cooking processes; for example, charbroiling, grilling, roasting, frying and baking may contribute to PAH formation. In addition, where PAH levels are elevated via contamination from coal tar coatings of water pipes, PAH intake from drinking water may equal or even exceed that from food.

PAH levels in blood and urine result from a mixture of compounds originating from a variety of sources and that have entered the body via multiple routes. However, urinary levels of metabolites of some of the more volatile PAHs (e.g. naphthalene, phenanthrene and pyrene) are often used as surrogates to assess PAH exposure via inhaled air *(46)*.

Annex 2 presents basic information on 16 high-priority PAHs.

6 Defined in European Commission Directive 2008/50/EC on ambient air quality and cleaner air for Europe *(44)*.

3. Carcinogenic effects and risk assessment of PAHs

3.1 Genotoxic and carcinogenic PAHs

Based on their environmental presence and toxicity, a number of priority PAHs have been identified by the US EPA *(47)* and the European Commission and its Scientific Committee on Food *(48)*, of which 24 PAHs have been prioritized for risk assessment. The US EPA has identified 16 priority PAHs, referred to as the PAH16 (acenaphthene, acenaphthylene, anthracene, B[*a*]P, benzo[*a*]anthracene, benzo[*b*] fluoranthene, benzo[*ghi*]perylene, benzo[*k*] fluoranthene, chrysene, dibenzo[*ah*]anthracene, fluoranthene, fluorene, indeno[1,2,3-*cd*] pyrene, naphthalene, phenanthrene and pyrene). As the PAH16 are perhaps the most relevant for measurements of airborne PAHs, the presence and environmental levels of these PAHs are well studied. In contrast, the presence and levels of other PAHs (such as dibenzopyrenes) that are more carcinogenic than B[*a*]P are less studied, which might impact the risk estimation for PAHs in ambient air (see section 3.3) *(49)*.

Despite the structural similarities of PAHs, the strength of evidence for their carcinogenicity varies greatly: PAHs are classified as possible (Group 2B), probable (Group 2A) or human (Group 1) carcinogens by the International Agency for Research on Cancer (IARC) *(4)*. In general, the strength of evidence for carcinogenicity is greater for larger PAHs (with more than four rings) than for smaller PAHs. B[*a*]P is currently the only PAH classified as Group 1 (carcinogenic to humans). To date, the most potent genotoxic and carcinogenic PAH is dibenzo[*al*]pyrene (Group 2A), but it has not yet been reported as a human carcinogen owing to a lack of studies. In vivo studies suggest its potency is up to 100-fold greater compared with B[*a*]P *(50)*. Dibenzo[*al*]pyrene (and the other dibenzopyrenes) is present in ambient air, as well as in vehicle exhaust, airborne PM, coal tar, fly ash and cigarette smoke *(49)*.

PAHs may also exist in substituted forms. For example, nitro- and oxy-PAHs have received increasing attention owing to their biological activity. These compounds are emitted from the same sources as PAHs, although they may also be formed through chemical, photochemical or biological oxidation of PAHs in the environment. Compared with the PAH16, substituted PAHs are frequently neglected, although their occurrence has often been documented and they have similar toxicities *(51,52)*. For example, nitroketone 3-nitrobenzanthrone, one of the most potent mutagens and deemed a possible human carcinogen (Group 2B) by IARC, was recently identified in diesel exhaust, where it was bound to airborne PM *(53)*.

PAH binding to DNA, leading to the formation of stable DNA adducts, is the major mechanism of PAH-induced mutagenesis and carcinogenesis. Like many carcinogens, PAHs require activation through a series of enzymatically catalysed reactions to form their active metabolites *(54)*. The cytochrome P450 (CYP) family of enzymes (in particular, CYP1A1, CYP1A2 and CYP1B1) are primarily involved in the bioactivation of PAHs to their reactive intermediates *(55)*. Many PAHs are ligands for the aryl hydrocarbon receptor (AhR), which has different metabolic roles, including in the regulation of different bioactivating and detoxifying enzymes *(56)*. An additional metabolic pathway is the aldo-keto reductase mechanism that activates PAHs to redox-active *ortho*-quinone derivatives, which might also have mutagenic and tumorigenic properties *(57)*.

3.2 Role of sources in the genotoxicity and mutagenicity of airborne PAHs

In the general population, inhaled PAHs mainly originate from airborne PM, grilling of food or cigarette smoke *(58,59)*. In air, PAHs exist in the atmospheric gas or particulate phase; therefore, PAH sampling should preferably be performed in both phases. Approximately 70–90% of ambient PAHs are bound to PM, most notably $PM_{2.5}$ *(60)*. Despite their low emissions, these PAHs (consisting of more than four rings) may induce harmful effects on human health *(61)*. According to IARC, average concentrations of individual PAHs in the ambient air of urban areas range from 1 ng/m^3 to 30 ng/m^3 *(4)*.

The major sources of global total atmospheric emissions of PAH16 have been identified as residential and commercial biomass burning (60.5%), open-field biomass burning (agricultural waste burning, deforestation, wildfires; 13.6%) and petroleum combustion by motor vehicles (12.8%) *(62)*. As discussed by IARC in evaluations of the carcinogenicity of outdoor air pollution and of diesel engine and gasoline engine exhaust, the contribution of the sources is likely to vary from location to location and with season; the same also applies to PAHs *(63,64)*. Since airborne PAHs are a complex mixture with contributions from different sources, the relative contribution of each source to the carcinogenicity of airborne PAHs is difficult to assess through epidemiological studies. Observations from experimental animal and in vitro experiments comparing the effects of PM samples or organic solvent extracts of PM samples from various emission sources in the same system are summarized below.

Results from studies based on mutagenicity assays using different *Salmonella* strains suggest that exhausts from biodiesel fuels may be more mutagenic than exhaust from fossil-based diesel, but the mutagenic potency does not correlate with PAH content *(65,66)*. Repeated inhalation exposure of rats to exhausts of fossil fuel diesel or rapeseed-supplemented biofuel induced similar levels of genotoxic stress, but fossil fuel diesel induced higher levels of bulky adducts in lung tissue *(67)*. Similarly, comparison of the genotoxic potential in human lung cells showed that diesel and biodiesel samples (organic extracts and native diesel exhaust particles) induced similar levels of DNA damage *(68,69)*. The disparity between the results from the *Salmonella* strains and the mammalian in vivo and in vitro experiments could be caused by differences in the testing systems or samples used. Comparison of wood smoke particles with PM from ambient air, diesel and gasoline emissions showed that, in general, the former have a higher PAH content and lower soluble metal content *(70,71)*. In vitro evaluation of genotoxicity in human lung cells showed that wood smoke particle extracts generate higher

levels of reactive oxygen species, DNA strand breaks and reactive oxygen species-induced 8-oxoguanine compared with extracts from ambient air. Neither study found a correlation between PAH content and toxicological end-points, suggesting that genotoxicity was driven by extractable organic compounds other than PAHs *(70,71)*. In agreement, several studies found that the main mutagenic components of PM extracts obtained from ambient air and diesel and gasoline engine exhaust were in the polar or moderately polar fractions *(72–75)*.

In conclusion, the role of emission sources in the carcinogenicity of airborne PAHs is still not well established. However, for all sources (i) there seems to be no direct correlation between PAH content and genotoxic or mutagenic potency and (ii) the major mutagenic components are present in the more polar fraction of airborne PAHs (containing oxy- and nitro-PAHs). These results are based on animal and in vitro studies; therefore, these findings need to be confirmed in epidemiological and mechanistic studies.

3.3 Effects of PAHs on the development of various types of cancer: review of epidemiological studies

3.3.1 Background

Since the early 2000s, epidemiological studies have examined the association between cancer and exposure to PAHs in ambient air. Most of these studies have investigated breast cancer and various childhood cancers *(76–82)*. In contrast, studies relating lung cancer to ambient PAHs in the general population are virtually non-existent.

A total of 14 epidemiological studies (six on childhood cancers, five on breast cancer, and one each on cervical, lung and bladder cancer) met the criteria for inclusion: that is, they linked cancer to exposure to ambient PAHs in the general population. Studies that used a proxy indicator of exposure to PAHs (e.g. vehicular traffic) or linked cancer to biomarkers of exposure to PAHs (e.g. PAH–DNA adducts) were excluded. Occupational studies linking cancer to ambient PAHs were also excluded. However, an exception was made for occupational meta-analysis studies examining the risk of lung cancer associated with ambient PAHs in different industrial workers, given that important literature on this topic has been published recently.

3.3.2 Lung cancer

Most epidemiological studies examining the associations between lung cancer and ambient PAHs were occupational. In fact, only one study from 1983 investigated the association between lung cancer and exposure to ambient B[*a*]P in the general population *(83)*. This ecological study reported no association between B[*a*]P and lung cancer incidence in the total population of Erie County, New York (United States of America; Table 3.1). However, the results from this study should be interpreted with caution because of the absence of a comparator population and the risk of ecological fallacy.[7] In addition, the design of an ecological study is mostly intended to generate a hypothesis, not a causal association.

7 Ecological fallacy is when ecological inferences about the nature of specific individuals are generated from aggregates to which individuals belong rather from individuals per se.

Table 3.1. Association between exposure to B[*a*]P in ambient air and lung cancer incidence

Reference, location	Study design	Study population	Exposure, mean/IQR concentration (ng/m³)	Adjusted risk estimates[a] (95% CI) for lung cancer incidence Single pollutant model
Vena, 1983 *(83)*: Erie County (NY), USA	Descriptive, ecological	Diagnosis: 2 201 lung cancer patients (all lung cancer cases from Erie County reported to the New York State tumour registry, 1973–1976)	Monitoring stations (1973–1974) Mean: 2.13 ng/m³ IQR: not reported	B[*a*]P Total population: β: **–0.286 (0.407)** Men: β: **–0.506 (0.435)**

CI: confidence interval; IQR: interquartile range.

[a] β coefficient.

Note: bold indicates a positive association.

Occupational studies relating PAH exposure to lung cancer are well documented in IARC monograph No. 92 *(4)*. In most cases, workers were exposed to very high concentrations of PAHs (up to 100 µg/m³), primarily by inhalation. One meta-analysis included in the IARC monograph report *(84)* and three other meta-analyses *(85–87)* captured findings from studies relating lung cancer to occupational exposure to PAHs. These studies showed a positive association between lung cancer in workers and exposure to PAHs. However, the associations were weak (i.e. low relative risks), making it difficult to attribute lung cancer to PAH exposure. Moreover, workers exposed to PAHs are also exposed to a large number of other carcinogenic or potentially carcinogenic compounds, such as asbestos, diesel exhaust, chromium and nickel. Furthermore, most of the individual studies did not control for smoking.

In summary, only one study has examined lung cancer following exposure to PAHs in ambient air. The meta-analyses of occupational exposure demonstrated positive but weak associations among workers exposed to high levels of PAHs in comparison to the general population, who are exposed to lower levels of PAHs.

3.3.3 Breast cancer

Breast cancer might be associated with exposure to ambient PAHs from various sources *(76,77,88,89)*. Five studies in the United States examined the association between breast cancer incidence and the sum of all measured PAHs (hereafter referred to as total PAHs) or individual PAHs in ambient air (Table 3.2). Of these, two case–control studies examined the association between exposure to B[*a*]P from traffic sources and breast cancer in premenopausal and postmenopausal women. In the study by Nie et al. (2007), the associations were often positive but not significant *(76)*, whereas no associations were found by Mordukhovich et al. (2016) *(77)*. Three ecological studies examined geographical variations in PAH emissions between urban/industrialized and less industrialized/less urbanized regions *(90–92)*. All three studies found significant positive associations between total or individual PAHs and breast cancer incidence in highly polluted areas (urban/industrialized). For example, Large and Wei reported that carcinogenic PAHs, including B[*a*]P, benzo[*b*]fluoranthene and dibenzo[*ah*]anthracene, increased the risk of breast cancer incidence in highly urbanized, industrialized and polluted north-eastern regions of the United States compared with less industrialized, less urbanized and, thus, less polluted south-eastern regions *(91)*. An important limitation of these studies is that they did not consider early life exposure, including in utero and in childhood, which are sensitive developmental periods. Although the limited literature supports an association between ambient air exposure to PAHs and increased breast cancer incidence, three of the five studies should be interpreted with caution

because of their ecological study design. In fact, through using aggregated data, in which the study sample is an entire population in a region, the findings are prone to ecological fallacy. Consequently, the results may not necessarily remain valid at individual level.

Overall, the limited epidemiological studies showed positive associations between exposure to PAHs and breast cancer.

Table 3.2. Association between exposure to PAHs or B[*a*]P in ambient air and breast cancer incidence

Reference and location	Study design	Study population	Exposure	Single pollutant model, adjusted risk estimates[a] (95% CI)		
				Premenopausal breast cancer	Postmenopausal breast cancer	All breast cancers
Nie et al., 2007 *(76)* Erie and Niagara Counties in western New York, the United States	Population-based case–control study	Diagnosis: 1996–2001 Age: 35–79 years Cases: 1 170 Controls: 2 116	Data beginning in 1960 (ambient exposure to PAHs in early life) Geographical traffic exposure model using B[*a*]P as a surrogate to estimate PAH exposure from traffic emissions Mean/IQR: not reported	Traffic B[*a*]P: Q3 vs Q1 at menarche: **OR = 2.14 (0.93–4.94)** Q3 vs Q1 at birth of first child: OR = 0.78 (0.33–1.86) Q3 vs Q1 at 20 years prior to the year of interview; **OR = 1.48 (0.74–2.99)** Q3 vs Q1 at 10 years prior to the year of interview: **OR = 1.41 (0.76–2.60)**	Traffic B[*a*]P: Q3 vs Q1 at first birth: **OR = 1.20 (0.52–2.77)** Q3 vs Q1 at 20 years prior to the year of interview: OR = 0.89 (0.64–1.24) Q3 vs Q1 at 10 years prior to the year of interview: **OR = 1.04 (0.74–1.45)**	NA
Mordukhovich et al., 2016 *(77)* Long Island, New York, the United States	Population-based case–control (LIBSCP)	Diagnosis: 1996–1997 Age: 20–98 years old Cases: 1 508 Controls: 1 556	Roadway emissions were translated into predicted residential ambient B[*a*]P concentrations Mean/IQR (ng/m^3): 1960–1990 (cumulative exposure): 227.42/125.31 1995: 1.03/0.62	Traffic B[*a*]P: 50th to < 75th percentile vs < 50th percentile: OR = 0.84 (0.42–1.66)	Traffic B[*a*]P: 50th to < 75th percentile vs < 50th percentile: OR = 1.00 (0.70–1.42)	Traffic B[*a*]P: 50th to < 75th percentile vs < 50th percentile: OR = 0.97 (0.66–1.42)
Parikh & Wei, 2016 *(90)* Metropolitan Atlanta area vs rural Georgia, the United States	Ecological (SEER programme)	Diagnosis: 1992–2011 SEER registry (metro Atlanta and rural Georgia)	Year: 2008 PAH emissions (urban vs rural) Mean/IQR: not reported	NA	NA	Total PAHs: **β = 0.568 (0.209–0.927)***

Table 3.2 contd

Reference and location	Study design	Study population	Exposure	Single pollutant model, adjusted risk estimates[a] (95% CI)		
				Premenopausal breast cancer	Postmenopausal breast cancer	All breast cancers
Large & Wei, 2017 *(91)* North-eastern and south-eastern states, the United States	Ecological, (SEER programme)	Diagnosis: 2000–2012 SEER registry (north-eastern and south-eastern)	Year: 2008 PAH emissions (highly industrialized and heavily polluted in the north-eastern compared with south-eastern states) Mean/IQR: not reported	NA	NA	Total PAHs: **β = 0.85 (0.35–1.35)*** B[*a*]P[b] **β = 58.37 (17.52–99.23)*** DB[*ah*]A[b] **β = 628.56 (309.79–947.33)*** B[*b*]F:[b] **β = 77.68 (38.13–117.23)***
Stults & Wei, 2018 *(92)* nationwide, the United States	Ecological (SEER programme)	Diagnosis: 1973–2013 SEER registry (more industrialized metropolitan SEER regions and less industrialized regions)	Year: 2008 PAH emissions nationwide geographical variation (more industrialized metropolitan SEER regions vs less industrialized regions) Mean/IQR: not reported	NA	NA	Total PAHs: From all emission sources: **β = 0.424 (0.278–0.570)*** From traffic sources: **β = 0.552 (0.278–0.826)***

B[*b*]F: benzo[b]fluoranthene; CI: confidence interval; DB[*ah*]A: dibenzo[*ah*]anthracene; IQR: interquartile range; NA: not applicable; LIBSCP: Long Island Breast Cancer Study Project; OR: odds ratio; SEER: Surveillance, Epidemiology, and End Results; *: $P \leq 0.05$ (significant association; Student *t*-test for continuous variables, χ^2 test for categorical variables).

[a] β coefficient or odds ratio.

[b] Belongs to the US EPA 16 priority ambient PAHs.

Note: bold indicates a positive association.

3.3.4 Childhood cancers

Although little is known about the etiology of childhood cancers, a significant proportion can be attributed to genetic factors *(93)*. Environmental risk factors such as ambient air pollution may contribute to the risk of developing these cancers.

To date, six case–control studies have examined the relationship between exposure to PAHs and childhood cancers in the United States. In most of these studies, the PAHs originated from road traffic, congested roadways in and around large urban areas, and industrial sites. The studies generally showed positive associations between PAH exposure during the prenatal or postnatal period and the development of various types of cancer in children, including brain tumours *(81)*, leukaemia *(79,82)*, nephroblastoma *(94)*, neuroblastoma *(78)* and retinoblastoma *(80)* (Table 3.3). However, some limitations were related to the experimental design of the six studies. Most were severely underpowered to detect modest odds ratios. In addition, none adjusted for parental smoking and only two adjusted for exposure to other air toxicants *(94)* or performed co-pollutant modelling *(82)*. Moreover, it is notable that only one epidemiological study per childhood cancer type (or two in the case of leukaemia) has been conducted to date. Therefore, more information is necessary to evaluate the role of ambient air PAHs in the development of various childhood cancers.

Table 3.3. Association between total exposure to PAHs and incidence of childhood tumours

Reference and location	Study design	Type of cancer	Study population	Exposure	Mean/IQR concentration (ng/m³)	Adjusted OR (95% CI) per IQR increase in pollutant	
						Prenatal exposure, single pollutant model (total PAH)	**Postnatal and infant exposure, single pollutant model (total PAH)**
Heck et al., 2013 *(78)* California, the United States[a]	Population-based case–control (California Cancer Registry records)	Neuroblastoma: 75 cases, 14 602 controls	Children aged < 6 years living within 2.5 km and 5 km of an air pollution monitor (1990–2007)	Home addresses were geocoded as listed on the birth certificate. Each geocoded residence area was linked to the closest air monitoring stations to obtain PAH exposure data (available from 1990)	Mean: 1.47 IQR: 1.09	Children living within 2.5 km of an air monitor Entire pregnancy: **OR = 1.39 (1.01–1.91)*** Children living within 5 km of an air monitor Entire pregnancy: **OR = 1.12 (0.86–1.46)**	NA
Heck et al., 2014 *(79)* California, the United States[b]	Population-based case–control (California Cancer Registry records)	Acute lymphoblastic leukaemia: 53 cases, 2 159 controls Acute myeloid leukaemia: 31 cases, 13 535 controls	Children aged < 6 years living within 2 km and 6 km of an air pollution monitor (1990–2007)	Home addresses were geocoded as listed on the birth certificate. Each geocoded residence area was linked to the closest air monitoring stations to obtain PAH exposure data (available from 1990)	Mean: 1.47 IQR: 1.09	Acute lymphoblastic leukaemia (for children living within 2 km of an air monitor) First trimester: OR = 0.95 (0.82–1.11) Second trimester: **OR = 1.04 (0.94–1.14)** Third trimester: **OR = 1.16 (1.04–1.29)*** Entire pregnancy: **OR = 1.17 (0.94–1.45)** Acute myeloid leukaemia (for children living within 6 km of an air monitor) First trimester: OR = 0.88 (0.63–1.21) Second trimester: OR = 0.96 (0.74–1.24) Third trimester: **OR = 1.13 (0.93–1.36)** Entire pregnancy: **OR = 1.07 (0.69–1.65)**	NA
Shrestha et al., 2014 *(94)* California, the United States[c]	Population-based case–control (California Cancer Registry records)	Nephroblastoma: 241 cases, 96 514 controls	Children aged < 6 years (1988–2008)	Home addresses were geocoded as listed on birth certificate. Each geocoded residence area was linked to the closest air monitoring stations to obtain PAH exposure data (1990–2008) Sources: industrial and road traffic	Mean: not reported IQRs: 2.43–2.61	First trimester: OR = 0.99 (0.88–1.12) Second trimester: **OR = 1.06 (0.98–1.15)** Third trimester: **OR = 1.10 (0.99–1.22)** Entire pregnancy: **OR = 1.15 (1.02–1.31)***	NA

Table 3.3 contd

Reference and location	Study design	Type of cancer	Study population	Exposure	Mean/IQR concentration (ng/m³)	Adjusted OR (95% CI) per IQR increase in pollutant	
Heck et al., 2015 *(80)* California, the United States[d]	Population-based case–control (California Cancer Registry records)	Retinoblastoma: 103 cases, 30 601 controls	Children aged < 6 years living within 5 km of an air pollution monitor (1990–2007)	Home addresses were geocoded as listed on the birth certificate. Each geocoded residence area was linked to the closest air monitoring stations (data available from 1990)	Mean: 1.44 IQR: 1.05	OR = 0.95 (0.71–1.27)	Child's first year: **OR = 1.09 (0.65–1.83)**
von Ehrenstein et al., 2016 *(81)* California, the United States[e]	Population-based case–control (California Cancer Registry records)	Brain tumours Medulloblastoma: 34 cases Primitive neuroectodermal tumour: 43 cases Astrocytoma: 106 cases All tumours: 183 cases, 30 569 controls	Children aged < 6 years living within 5 miles of an air pollution monitor (1990–2007)	Home addresses were geocoded as listed on the birth certificate. Each geocoded residence area was linked to the closest air monitoring stations to obtain PAH exposure data. (available from 1998; before 1998, only ZIP codes were available) Sources: industrial and road traffic sources	Mean: not reported IQR: 1.049	Medulloblastoma: **OR = 1.44 (1.15–1.80)*** Primitive neuroectodermal tumour: **OR = 1.06 (0.73–1.55)** Astrocytoma: **OR = 1.06 (0.85–1.33)**	Medulloblastoma (child's 1st year): **OR = 1.48 (0.85–2.57)** Primitive neuroectodermal tumour (child's 1st year): **OR = 1.03 (0.53–2.01)** Astrocytoma (child's 1st year): **OR = 1.17 (0.81–1.69)**

Reference and location	Study design	Type of cancer	Study population	Exposure	Mean/ IQR Concentration (µg/m³)	In utero and early life exposures		
Symanski et al., 2016 *(82)* Texas, the United States[f]	Population-based case–control (Texas Cancer Registry records)	Leukaemia: 1 248 cases, 12 172 controls	Children aged < 5 years (1995–2011)	Used maternal address at delivery and relied on data from the US EPA NATA (modelled estimates of air toxics, 1991–2002 and 2005) to obtain PAH exposure data. Sources: road traffic, petrochemical plants, petroleum refineries, active seaports	POM: Mean: 69 (1995), 8 (2002), 6 (2005) IQR: not reported	Single pollutant model[g], POM: Medium vs low levels: OR = 0.94 (0.79–1.12) Medium–high vs low levels: **OR = 1.18 (1.00–1.39)** High vs low levels: **OR = 1.11 (0.94–1.32)**	Co-pollutant model[f], POM + benzene: Medium vs low levels: OR = 0.89 (0.73–1.08) Medium–high vs low levels: **OR = 1.12 (0.91–1.38)** High vs low levels: **OR = 1.10 (0.86–1.39)**	Co-pollutant model[f], POM + 1,3-butadiene: Medium vs low levels: OR = 0.88 (0.73–1.06) Medium–high vs low levels: **OR = 1.05 (0.85–1.31)** High vs low levels: OR = 1.00 (0.78–1.28)

CI: confidence interval; IQR: interquartile range; NA: not applicable; NATA: National-Scale Air Toxics Assessment; OR: odds ratio; POM: particulate organic matter; *: $P \leq 0.05$ (significant association; Student *t*-test for continuous variables, χ^2 test for categorical variables).

[a] Benzo[*k*]fluoranthene, B[*a*]P, benzo[*b*]fluoranthene, indeno[*1,2,3-cd*]pyrene and dibenzo[*ah*]anthracene showed positive associations with neuroblastoma (within 5 km or 2.5 km of an air monitoring station).
[b] Benzo[*k*]fluoranthene, B[*a*]P, benzo[*b*]fluoranthene, indeno[*1,2,3-cd*]pyrene, dibenzo[*ah*]anthracene and benzo[*ghi*]perylene showed positive associations with leukaemia (within 2 km or 6 km of an air monitoring station).
[c] Adjusted for multiple air toxics.
[d] Exposure to indeno[*1,2,3-cd*]pyrene, B[a]P or benzo[*ghi*]perylene during a child's first year and to only benzo[*ghi*]perylene during the entire pregnancy showed a positive association with retinoblastoma.
[e] Significant positive associations were reported between medulloblastoma and prenatal exposure to individual PAHs included in the study: benzo[*k*]fluoranthene, benzo[*b*]fluoranthene, indeno[*1,2,3-cd*]pyrene, B[*a*]P, dibenzo[ah]anthracene and benzo[*ghi*]perylene.
[f] PAHs are the most common subclass of particulate organic matter.
[g] Levels not reported.

Note: bold indicates a positive association.

3.3.5 Other cancers

Information is limited on the association between exposure to PAHs in ambient air and other cancers. Although a few meta-analyses have reported an increased risk for bladder cancer, predominantly in aluminium production facilities and iron and steel foundries *(84–86,95)*, only one study has examined bladder cancer in the general population. A Spanish case–control study (1219 cases and 1271 controls) found a positive but non-significant association between bladder cancer and living in proximity to industrial sites emitting PAHs. However, it failed to control for other carcinogenic air toxicants *(96)* (Table 3.4). A cross-sectional study in the United States explored the association between outdoor residential exposure to traffic-related ambient PAHs and the development of cervical cancer in an urban population. The prevalence of cervical dysplasia was increased in highly exposed women after adjustment for age, race/ethnicity, education, smoking status and human papillomavirus status *(96)* (Table 3.5).

Table 3.4. Association between exposure to PAHs in ambient air and bladder cancer incidence

Reference and location	Study design	Study population	Exposure, mean/IQR concentration (ng/m³)	Adjusted risk estimate[a] (95% CI)
Castaño-Vinyals et al., 2008 *(96)* Vallès/Bages, Alicante, Tenerife and Asturias, Spain	Population-based case–control	Diagnosis: 1998–2001 Age: 21–80 years Cases: 1 219 Controls: 1 271	Year: 2000 Several indices were used to assess exposure among people with residences within 1 km of an industry with either PAH or diesel emissions (windows facing traffic and size of the city of residence were also considered) Mean: not reported IQR: not reported	Proximity to industries emitting PAHs **OR = 1.23 (0.98–1.55)**

CI: confidence interval; IQR: interquartile range; OR: odds ratio.

[a] Odds ratio and 95% confidence intervals were adjusted for age, gender, region, smoking, occupation, water contaminants and diet.

Note: bold indicates a positive association.

Table 3.5. Association between exposure to PAHs in ambient air and increased prevalence of cervical dysplasia

Reference and location	Study design	Study population	Exposure, mean/IQR concentration (ng/m³)	Adjusted risk estimates[a] (95% CI)
Scheurer et al., 2014 *(97)* Houston, Texas, the United States	Cross-sectional study	Diagnosis: 2000–2004 Sex: women Age: 21–80 years Cases: 173 Controls: 563	Annual concentration estimates of PAHs was obtained for each census tract from the US EPA 1999 ASPEN[b] Mean: 11 IQR: 6	Medium (25th–74th percentile) vs low (< 25th percentile) levels: **OR = 1.30 (0.77–2.20)** High (75th–89th percentile) vs low (< 25th percentile) levels: **OR = 2.46 (1.35–4.48)***

ASPEN: Assessment System for Population Exposure Nationwide; CI: confidence interval; IQR: interquartile range; OR: odds ratio;
*: $P \leq 0.05$ (significant association; Student *t*-test for continuous variables, χ^2 test for categorical variables).

[a] Multivariable logistic regression was used to estimate prevalence odds ratios and 95% confidence intervals adjusted for age, race/ethnicity, education, smoking status and human papillomavirus status.

[b] A computer simulation model used in the National-Scale Air Toxics Assessment conducted by the US EPA.

Note: bold indicates a positive association.

3.4 Cancer risk assessment for airborne PAHs

Three approaches are typically used for cancer risk assessment for PAHs: (i) use of B[*a*]P as a surrogate marker for complex mixtures; (ii) use of component-based potency factors with B[*a*]P as an index compound; and (iii) a comparative whole-mixture potency approach.

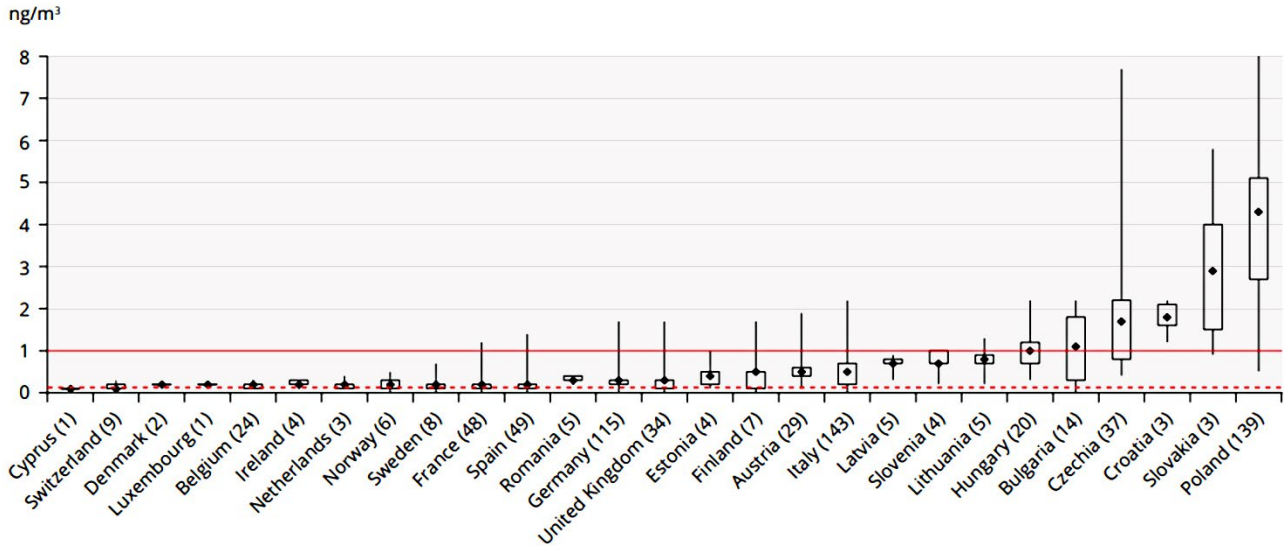
3.4.1 Use of B[*a*]P as a marker for complex mixtures

The first approach is based on the assumption that relative PAH concentrations will remain stable between different exposure scenarios and sources (e.g. rural vs urban). This assumption was invalid in a study conducted over an 18-year period from 1974 to 1992 in Sapporo (Japan), where ambient B[*a*]P levels decreased by 75–80%, while indirect-acting mutagenic activities declined by only 44–50% and direct-acting mutagenic activities did not change significantly *(98)*. The study suggested that the sole use of B[*a*]P as an indicator might not always be appropriate and could underestimate the risk. In addition, a large number of more polar PAHs (such as nitro- and oxy-PAHs) that are released from the same sources as PAHs or can be formed as decomposition products of PAHs in air might also contribute to the toxicological activity *(75)*. Indeed, both WHO and the European Food Safety Agency concluded that the surrogate marker approach is likely to misestimate the actual risk, as co-occurring substances are also carcinogenic *(9,99)*.

The main carcinogenic mode of action of B[*a*]P is the induction of DNA damage, leading to mutagenesis. However, many PAHs are suggested to contribute to carcinogenesis through non-genotoxic modes of action, including increased cell proliferation and inflammation, which could potentiate the effects of genotoxic PAHs *(2)*. Consequently, attributing the observed effects to B[*a*]P alone may be misleading, as exposure occurs in conjunction with other PAHs. Furthermore, using B[*a*]P as a surrogate marker or index compound assumes that there are no interactions between PAHs leading to antagonistic or synergistic toxic effects. This assumption might lead to the misestimation of risks and warrants a shift towards assessment of whole-mixture exposure and effects *(100,101)*.

The surrogate marker approach is currently used in EU regulatory processes to manage air quality and regulate the permissive levels of PAHs in ambient air *(9,102)*. The EU air quality target value for PAHs is 1 ng/m^3 B[*a*]P (representing the annual mean) and should have been achieved by the Member States by the end of 2012. According to the European Environment Agency, in 2018 five Member States, mostly in central and eastern Europe, reported yearly mean concentrations exceeding this value (Fig. 3.1) *(23)*. Both the EU target value (1 ng/m^3 B[*a*]P) and the estimated WHO reference level (0.12 ng/m^3 B[*a*]P) are based on the WHO lung cancer unit risk for PAH mixtures (8.7 × 10^{-5} per ng/m^3 B[*a*]P), and correspond to an additional lifetime cancer risk of approximately nine cases and one case in 100 000 exposed individuals, respectively *(9)*. The unit risk is based on an epidemiological study of coke oven workers active between 1953 and 1970 that observed a strongly increased risk of death from cancer of the respiratory system. Similar estimated unit risks based on other occupational settings have ranged between 1 × 10^{-5} per ng/m^3 and 43 × 10^{-5} per ng/m^3 B[*a*]P *(2)*. How well these unit risks can represent other sources such as diesel exhaust or biomass burning is not well known. Indeed, Pott and Heinrich concluded that, based on epidemiological and experimental data, a much smaller amount of B[*a*]P in diesel exhaust than in coke oven emissions was needed to induce a certain level of tumour incidence *(103)*. In addition, the B[*a*]P surrogate approach lacks the flexibility to be adapted to highly potent carcinogenic PAHs, such as dibenzopyrenes, which are now being discovered as technology is developed to detect higher numbers of PAHs present at lower levels *(104)*.

Fig. 3.1. Mean annual B[*a*]P concentration in European countries, 2018



Note: the graph is based on the annual mean concentration values. For each country, the number of stations considered (in brackets), and the lowest, highest and average values (in ng/m³) recorded at its stations are given. The rectangles mark the 25th and 75th percentiles. At 25% of the stations, levels are below the lower percentile; at 25% of the stations, concentrations are above the upper percentile. The upper horizontal line marks the concentration of 1.0 ng/m³. The lower horizontal line marks the estimated air quality reference level. The graph should be read in relation to Fig. 2.2 in the present document, as a country's situation depends on the number of stations considered. The highest value for Poland, 18.3 ng/m³, has not been included in the graph for representation purposes.

Source: European Environment Agency. Air quality in Europe: 2020 report. Luxembourg: Publications Office of the European Union; 2020 (European Environment Agency Report No. 9/2020) *(23)*. Reproduced with permission.

3.4.2 Use of component-based potency factors using B[*a*]P as an index compound

For the second approach, the US EPA has evaluated the use of relative potency factors (RPFs) for assessing the cancer risks of exposure to PAH mixtures, including airborne PAHs *(105)*. In this approach, the different components of the PAH mixtures are assigned RPFs relative to B[*a*]P (i.e. $RPF_{B[a]P} = 1$) and cancer risk estimates for PAH mixtures are derived from these factors. Firstly, the sum of B[*a*]P-equivalent values (B[*a*]Peq) for the different PAHs in the mixtures is determined:

$$B[a]P_{eq} = \sum ([PAH_i] \times RPF_i)$$

and then this value is used to estimate the risk:

$$Risk = B[a]P_{eq} \times \text{unit risk.}$$

However, a large range of RPFs exists for most PAHs, which might result in disparity between risk estimates based on different scales. For example, published RPF values for dibenzo[*ah*]anthracene range between 0.1 and 10. Since the US EPA priority list was determined, many highly potent PAHs have been identified in ambient air, including the dibenzopyrenes and benzo[*j*]aceanthrylene. Thus, although these PAHs have been assigned RPF values, they are rarely included in air monitoring programmes or health risk assessments because they have not been identified as priority PAHs. However, many studies have shown that, although present at relatively low levels in air compared with B[*a*]P, these PAHs make a considerable contribution to the cancer risk from air pollution *(106–109)*.

Another issue is that the RPF system requires a common mode of action and an assumption of additivity in the resulting toxicological effect. However, the different PAHs have heterogeneous mechanisms of action and many studies have demonstrated that interactions between PAHs have non-additive carcinogenic effects (both higher and lower) *(2,110)*. In summary, the lack of coherence between the different scales and the assumption of additivity are major limitations for risk assessments based on component-based potency factors. To overcome these, a whole-mixture approach has been recommended *(105,111)*.

3.4.3 Assessing the whole PAH mixture by estimating potency

The third approach assesses the whole PAH mixture by estimating the potency without the need to identify or quantify individual PAH compounds. It differs from the other two approaches in that it attempts to consider all compounds in a mixture such as air pollution (i.e. PAHs and others). Using a source-specific PAH mixture that has been thoroughly characterized in epidemiological and biological studies as a reference, a second sufficiently similar PAH mixture is ranked based on its comparative potency in a biological test. This approach has been suggested for a variety of complex PAH mixtures *(112,113)*, but has yet to be implemented by regulatory agencies. To use this approach, the carcinogenicity of the source mixtures that contribute to a given ambient environment must first be established. The levels of each source mixture must then be estimated for a given ambient environment (e.g. an industrial city) because contributing sources differ in their carcinogenicity. It would be costly and impractical to attempt to generate carcinogenicity data on many such PAH mixtures using traditional in vivo testing. However, both the European Commission and the US EPA have stated that risk assessment approaches based on toxicity evaluations of whole mixtures are preferable because they inherently address interaction effects among chemicals *(101,105)*. A whole-mixture approach would also remove uncertainties related to levels of known unknowns (e.g. dibenzopyrenes) in the mixture. The question of whether B[*a*]P is a suitable surrogate marker for airborne PAHs would also be redundant.

3.4.4 Alternative approaches: use of mixture potency factors

Although the component-based approach is recommended and mainly used by both United States and EU authorities, implementation of a whole-mixture approach is necessary to account for possible interaction effects. This has been recognized by the US EPA *(105,111)*. As discussed in section 3.4.3, this approach is not yet viable, mainly because of limited data for establishing reference mixtures and limited methods for determining sufficient similarity. A potential alternative would be to use mixture potency factors (MPFs). The MPF approach is similar to the comparative potency approach but differs from component-based approaches in that it does not rely on compound-specific potency values. Instead, it compares the effects of whole mixtures on a relevant biological end-point *(114)*. However, in contrast to the comparative potency approach, the MPF approach does not rely on a well-characterized and sufficiently similar reference mixture but instead uses a well-characterized single PAH, such as B[*a*]P. As B[*a*]P is already an established, well-studied marker for PAHs, it would be a suitable reference compound. Thus, potencies of whole-mixture samples would be expressed as MPFs relative to B[*a*]P.

As it is not possible to perform animal studies for every complex mixture, sensitive and relevant in vitro testing systems need to be developed. The potential of using DNA damage signalling in human cultured cells as a marker to develop in vitro MPFs has recently been suggested *(110,114,115)*. The applicability of DNA damage signalling as an in vitro marker for genotoxic potency of other groups of compounds is also supported by previous studies *(116–118)*. Dreij et al. (2017) recently showed that the relative potency of eight single PAHs to activate DNA damage signalling in vitro was in very good agreement with published RPFs based on in vivo studies *(114)*. The combination of in vitro-derived MPFs for urban whole-mixture air PAH samples with population exposure modelling in cancer risk assessment suggested that 6% of all lung cancer cases in Stockholm are caused by airborne PAHs, in agreement with estimations of lung cancer incidences due to outdoor air pollution in Europe *(119,120)*. The study concluded that an in vitro approach for establishing MPFs could be a novel method to test and assess whole-mixture samples of airborne PAHs to improve health risk assessment *(114)*.

3.5 Conclusions, knowledge gaps and remaining challenges

The review of epidemiological studies focused on epidemiological literature published up to November 2019 on the association between exposure to PAHs in ambient air and various cancers in the general population. Since the early 2000s, only a few epidemiological studies on breast, childhood, cervical and bladder cancer have been performed in the general population. The included studies assessed exposure to PAHs by collecting data from monitoring stations, where associations with cancer were examined using either total PAHs or B[*a*]P as a marker of PAHs. The evidence demonstrated a relationship between exposure to PAHs in ambient air, particularly from traffic emissions, and an increased risk of breast cancer. However, the number of studies investigating this effect was low and the quality of more than half was considered poor in terms of causality. A number of case–control studies investigated the effects of exposure to ambient PAHs on the occurrence of childhood cancers. The target populations primarily lived in urban areas where exposure to PAHs predominantly originates from traffic and industrial emission sources. Positive associations between ambient PAHs and each type of childhood cancer have been reported. Limited data linking PAHs from industrial and road traffic sources to bladder and cervical cancer were available. Since only one study from the 1980s was identified on the association between lung cancer and exposure to PAHs through ambient air in the general population, lung cancer findings were predominantly sourced from occupational meta-analyses. These showed modest positive associations between exposure to PAHs and lung cancer. Furthermore, most did not adjust for confounding factors such as smoking and co-exposure to other carcinogenic substances.

Lastly, it is notable that the epidemiological studies using total PAHs to link any type of cancer to ambient PAHs did not indicate whether any of the three approaches used in cancer risk assessment (see section 3.4) was considered when summing the carcinogenic potential of the individual PAHs. This may have resulted in overestimation or underestimation of the risk estimates.

Overall, the evidence suggests that PAHs in ambient air are associated with increased cancer incidence. Given that many PAHs are considered carcinogenic or probably carcinogenic to humans, and assuming that PAHs cause direct DNA damage, it seems reasonable to conclude that exposure to PAHs in ambient air is associated with various types of cancers. However, additional studies, especially those using a longitudinal design and considering the potency of different PAHs within a mixture to contribute to cancer development, are needed to determine causality for an increased cancer risk in human populations from exposure to PAHs in ambient air. An important change for the future will be to investigate the clinical effects of complex PAH mixtures, ideally those extracted from actual environmental samples (e.g. urban air), in order to reflect relevant sources. Risk assessment should focus on whole mixtures so as to take account of the effects of interactions between components. As the composition of PAH mixtures might change over time, this should be re-evaluated every 10 years or so. Identification of more of the chemical components of the mixtures would improve the understanding of human exposure to particulate and gaseous PAHs in a wide variety of environments.

4. Non-carcinogenic effects of PAHs

4.1 Effects of PAHs on respiratory disease

4.1.1 Background

Epidemiological studies have linked exposure to air pollution and PM to cancer and various non-malignant respiratory diseases *(121–126)*. PAHs are among the air pollutants of particular concern. They occur both in gas phase and bound to PM. Although many of the PAHs in ambient air have carcinogenic potential and may contribute to the occurrence of malignant diseases *(2)*, this section focuses on the potential role of airborne PAHs in non-malignant respiratory diseases. Evidence is derived from epidemiological studies showing associations between PAHs in ambient air pollution and respiratory diseases and by experimental in vivo and in vitro studies indicating a causal mechanistic link between exposure to PAHs and various health outcomes (for a detailed overview, see a recent review *(127)*).

4.1.2 Review of experimental and mechanistic studies

Exposure to combustion particles and PAHs may result in oxidative stress, redox imbalance, inflammation, smooth muscle constriction, epithelial and endothelial dysfunction, and dysregulated lung development. These symptoms and health outcomes have also been linked to various non-malignant respiratory diseases *(128–130)*, and may be initiated via various molecular triggering mechanisms. PAH metabolism by CYP enzymes may result in the formation of reactive oxygen species and reactive electrophilic metabolites with the potential to inactivate sulfhydryl groups important for the activity of many key signalling enzymes and transporters. The effects of PAHs may also be triggered through more specific binding of parent compounds to cellular receptors such as AhR, the β_2-adrenergic receptor (β_2-AR) and G protein-coupled receptors.

4.1.2.1 PAHs and AhR

AhR is a key sensor of aromatic compounds (such as PAHs); it is highly expressed in the main structural cells/tissues (epithelial layer, submucosal glands, fibroblasts and endothelial cells) of the lungs and in immune cells *(131,132)*. In the classical mode of action, ligand-activated AhR dimerizes with the AhR nuclear translocator and binds and induce expression of target genes such as those encoding the CYP enzymes. CYP-mediated metabolism of PAHs leading to formation of reactive oxygen species may have proinflammatory effects *(131,133)*. The binding of chemicals to AhR may also mediate inflammatory signals via non-classical pathways (independent of activation of the AhR nuclear translocator), including cross-talk with members of the nuclear factor

kappa B family of transcription factors as well as other transcription factors *(134,135)*. AhR ligand binding has also been suggested to mediate immunomodulatory effects via non-genomic signals, including by increasing intracellular calcium *(136,137)*. This pathway does not necessarily follow the classical activation mechanism: for example, pyrene binding activates AhR-dependent calcium signalling but also decreases B[*a*]P-induced CYP expression *(138)*. The immunomodulatory properties of AhR suggest that PAH exposure may alter respiratory immune responses and, thus, may be a causative factor in the development of respiratory diseases.

4.1.2.2 PAHs and β_2-AR

Activation of β_2-AR in the airways initiates smooth muscle relaxation and bronchodilation, partly through activation of intracellular calcium and cyclic adenosine monophosphate (cAMP) signalling *(139)*. For decades, β-agonists have been widely used as bronchodilators in treating asthma and chronic obstructive pulmonary disease. In vitro studies suggest that B[*a*]P at low concentrations may interact directly with the ligand binding pocket of the β_2-AR, leading to increased intracellular calcium and cAMP signalling, and desensitization of β_2-AR *(140–142)*. It is hypothesized that PAH interference with β-AR signalling in the airways may affect respiratory function in patients with asthma and chronic obstructive pulmonary disease *(127)*, as they seem to be particular sensitive to urban air PM *(124,126)*.

4.1.2.3 Pulmonary oxidative stress, inflammation and immunological effects of PAHs

The proinflammatory and AhR-immunomodulatory properties of PAHs may lead to the production of cytokines and chemokines, cell death and disruption of the epithelial barrier *(131,143)*. Such responses may include increased levels of neutrophils, eosinophils and macrophages and the production of reactive oxygen species, which are important components of pulmonary inflammation. Sustained inflammation may exacerbate or contribute to the development of lung diseases, such as asthma and chronic obstructive pulmonary disease *(143,144)*. Several studies have examined inflammatory responses in lung cells exposed to PAHs. B[*a*]P exposure is reported to induce CXC motif chemokine ligand 8 (CXCL8) via an AhR-dependent pathway in primary human macrophages *(145)*. In epithelial lung cells, B[*a*]P and other PAHs (e.g. pyrene and 1-nitropyrene) are reported to induce the expression of CXCL8 and other chemokines or cytokines *(146–148)*. However, the concentrations of pure PAHs required to induce cytokine responses in vitro appear to be several orders of magnitude higher than those reached in real-life exposure scenarios. Furthermore, ligand binding to AhR appears to induce both pro- and anti-inflammatory responses *(129)*. Consistent with the latter, B[*a*]P was reported to attenuate the proinflammatory phenotype of macrophages by inducing in AhR-dependent expression of the anti-inflammatory interleukin (IL), IL-10 *(149)*.

Oxidative stress plays a critical role in the pathogenesis of asthma and is regulated by protein phosphatases, nuclear factor-erythroid 2-related factor 2 and intracellular antioxidant molecules *(150)*. Reactive PAH metabolites and reactive oxygen species may interact with these systems. PAHs may also increase oxidative stress by binding to AhR *(131,151)*. Furthermore, studies suggest that PAHs may act through immunoglobulin E to stimulate inflammatory responses and enhance allergic reactions *(144)*. In vivo PAH exposure may influence the differentiation of B cells and T helper (Th) cells by skewing immune responses towards a Th2-specific profile favouring B cell production of immunoglobulin E and eosinophils, which are both hallmarks of allergic inflammation and allergic asthma *(144,152)*.

Other studies indicate that PAHs can act directly on AhR in T cells, leading to enhanced Th17 cell differentiation. As sources of IL17 and IL-22, Th17 cells are implicated in the pathogenesis of asthma *(153,154)*.

4.1.2.4 Lung epithelial barrier and respiratory infections

Disruption of the lung epithelial barrier due to cell death induced by reactive PAH species or reactive oxygen species may increase the probability of exposure to various pathogens *(155)*. Synergistic effects between PAH and particles, allergens and lung microbiota may increase the probability of lung infections *(131,143,156,157)*. Experimental data from mouse models indicate that AhR is involved (via non-classical genomic or non-genomic pathways) in orchestrating appropriate immune responses in barrier organs such as the lung *(131)*. As AhR has important functions in the development and differentiation of the immune system, ligand binding to AhR might affect vulnerability to respiratory infections. In addition to immune cells, both epithelial and endothelial cells are targets of AhR-mediated changes in immune function *(158)*. Notably, PAHs may increase susceptibility to respiratory infections by reducing lung function and exacerbating asthma (as discussed in section 4.1.2.3).

Both enhancement of and protection against infections have been reported after exposure to AhR ligands *(158–160)*. As they can bind to AhR and activate various AhR pathways, PAHs are among the environmental contaminants suggested to affect vulnerability to respiratory infections. Notably, as low-molecular-weight (non-carcinogenic) PAHs can bind to AhR and trigger non-classical pathways, it is tempting to speculate that they might also affect vulnerability to respiratory infections.

4.1.2.5 Respiratory neuronal reflexes and respiratory symptoms

Respiratory reflexes are responsible for symptoms such as cough and bronchospasm. They are regulated by vagal afferent nerves (or C-fibres), which innervate the airways. In a recent study, Robinson and co-workers showed that diesel exhaust particles (Standard Reference Material 2975) activate vagal C-fibres in guinea pigs *(161)*. An organic extract of diesel exhaust particles (including PAHs), and not the cleaned particles, evoked depolarization of vagal C-fibres in guinea pig and human. Interestingly, this effect was also seen after exposure to very low concentrations (1 nM) of phenanthrene, a non-carcinogenic PAH that is among the most abundant PAHs in urban air *(2)*. The mechanisms for these responses appear to involve AhR activation and the subsequent influx of calcium through transient receptor potential channels.

4.1.3 Review of epidemiological studies

Causality between air pollution exposure and respiratory diseases is well established *(121,122,124–126)*. As PAHs are important components of PM from combustion sources, it is difficult to discriminate between the impacts of combustion-derived PAHs and of PM on respiratory diseases from epidemiological data. Furthermore, people are also exposed to PAHs from other major sources, including food. Nevertheless, several epidemiological studies have associated airborne PAHs with the occurrence of different respiratory symptoms and diseases, such as asthma, impaired respiratory functions and chronic obstructive pulmonary disease. Inhaled PAHs are considered to have a greater impact on respiratory health outcomes compared with exposure from other sources.The following sections are based on a recent review of studies on the effects of PAH exposure on asthma and respiratory function *(127)*.

4.1.3.1 Childhood asthma

Studies have shown that PAH exposure is associated with asthma onset and increasing asthmatic symptoms in children *(144)*. A case–control study of 195 children identified a strong association between serum PAHs and biomarkers of childhood asthma *(162)*. Another case–control study in children found that exposure to PAHs (measured as urine 1hydroxypyrene) is associated with asthma *(163)*. The latter study suggested that the effect of PAH exposure on asthma was mediated by oxidative stress, based on measurement of the oxidative stress marker, 8-hydroxy-2'-deoxyguanosine (8-OHdG), in children's urine. However, it is difficult to determine which mechanisms are involved owing to the variety of PM components and the heterogeneous causes of asthma. Furthermore, 8OHdG may also be a direct effect of PAH exposure rather than indirectly produced by inflammatory reactions.

4.1.3.2 Respiratory function and symptoms in children

No association was reported between PAH exposure and respiratory symptoms in children living near an industrial complex and petroleum refineries in Canada *(164)* nor in an inner-city cohort in New York City (United States) *(165)*. An overall evaluation of the few studies that have examined this relationship reported only a slight or no association between PAH exposure and pulmonary function in children *(166)*.

4.1.3.3 Prenatal and postnatal exposure: effects on respiratory symptoms and morbidity

Several studies have indicated that in utero PAH exposure of the fetus dysregulates lung development and results in respiratory symptoms soon after birth *(144,167,168)*. In another study, epigenetic changes were significantly associated with transplacental PAH exposure and asthma symptoms in childhood *(169)*. These modifications are suggested to have the greatest consequences for asthma linked to prenatal and infant exposure to PAHs *(170)*. In addition, postnatal exposure to PAHs is suggested to affect respiratory function in children, with the possibility of both separate and joint effects of transplacental and postnatal PAH exposure *(167,171–173)*. In a longitudinal birth cohort study in New York City (United States), both prenatal and postnatal exposure to pyrene were associated with non-atopic asthma in urban children *(174)*.

4.1.3.4 Respiratory function and symptoms in adults

Changes in urinary PAH metabolites seem to be associated with significant decrements in lung function in the general population and in elderly people *(175,176)*. In occupational settings, associations between decreases in lung function parameters and increased levels of urinary PAH metabolites have also been observed *(177,178)*.

4.1.3.5 Obstructive lung diseases and mortality

Both ambient and occupational exposures to air pollution have been shown to induce exacerbation of, and increased mortality from, obstructive lung diseases *(123)*. However, it is uncertain whether particle-bound PAHs are associated with increased respiratory morbidity and mortality. A study of a large cohort of asphalt workers concluded that exposure to PAHs originating from coal tar, and possibly from bitumen fumes, might have contributed to mortality from obstructive lung diseases *(179)*.

4.1.4 Conclusions, knowledge gaps and remaining challenges

Human epidemiological studies combined with experimental studies support the hypothesis that exposure to PAHs linked to PM may at least partly explain the enhanced risk of non-malignant respiratory diseases observed after PM exposure *(127)*.

Epidemiological studies found that PAHs are associated with the adverse health effects observed after exposure to combustion particles, including reduced lung function, exacerbation of asthma, and increased morbidity and mortality from obstructive lung diseases. However, the specific role of PAHs is difficult to disentangle from the contribution from other components originating from combustion processes, including PM.

In support of these epidemiological associations, in vivo and in vitro experimental studies have provided possible mechanisms linking PAH exposure to various non-malignant respiratory diseases. The effects of PAHs on respiratory tissue or cells may be partly mediated by classical AhR-dependent mechanisms, including binding to AhR, increased gene expression and metabolic activation of PAHs to reactive metabolites. These events have been found to induce proinflammatory mediators and oxidative stress, along with more subtle effects, such as altered calcium signalling and cell membrane depolarization. Other experiments suggest that organic compounds attached to the carbonaceous core of combustion particles may mediate PAH-induced immunomodulation, although not necessarily via the classical AhR genomic pathway. However, a number of uncertainties remain, including concentration–response relationships, the mechanisms involved and the relative importance of different PAH species.

Clearly, further epidemiological and experimental studies are required to clarify the potential role of exposure to PAHs in ambient air in asthma and other non-malignant airway diseases. Current knowledge of the mechanisms for air-pollution-induced non-malignant respiratory diseases is insufficient to establish regulatory guidelines for B[*a*]P or other PAH species. Furthermore, it is not possible to conclude whether the current WHO guidelines for B[*a*]P, which are based on its carcinogenic potential, may provide sufficient protection against other respiratory diseases that may be affected by PAH exposure.

4.2 Effects of PAHs on cardiovascular diseasess

4.2.1 Background

Epidemiological studies combined with experimental studies strongly suggest that exposure to $PM_{2.5}$ may have vascular effects, leading to ischaemia, myocardial infarction, stroke and other cardiovascular diseases (CVDs) *(121,180,181)*. Most of the health impact of $PM_{2.5}$ is caused by its cardiovascular effects *(120,182)*, and there is no apparent effect threshold in the dose range to which humans are exposed *(183)*.

Combustion PM may contribute to CVD development via several mechanisms. Inhaled diesel exhaust is reported to trigger receptors in the autonomic nervous system of the respiratory tract, thereby affecting cardiac control *(184,185)*. Exposure of pulmonary macrophages and epithelial cells to combustion PM may cause oxidative stress and systemic inflammation, with harmful consequences for endothelial cells *(186,187)* or platelets and coagulation processes *(188–190)*. However, combustion particles or their constituents

may also have direct cardiovascular effects *(191–193)*.

The biological effects of combustion PM seem to largely depend on bound organic chemicals, although the carbonaceous cores may also be involved *(191,192,194,195)*. Animal studies have shown that after the removal of organic chemicals, diesel exhaust particles lose their potential to induce atherosclerosis *(196)*. This finding was further supported by in vitro studies suggesting that many of the biological effects of combustion PM relevant to CVD are linked to their extractable chemicals *(191,192,194,195,197–201)*. The complex composition of combustion PM means that a single chemical, chemical group or component is unlikely to be responsible for the various cardiovascular effects *(121,130,202)*. However, from a toxicological perspective, PAHs are clearly among the PM components of particular concern. Although only a small number of inhaled particles will reach the bloodstream *(195)*, PAHs may rapidly detach from particles deposited in the alveoli and diffuse into the bloodstream *(203,204)*. The following sections discuss the potential role of PAHs in the development or exacerbation of CVD from PM exposure. More detailed overviews can be found in two recent reviews *(128,205)*.

4.2.2 Review of experimental and mechanistic studies

4.2.2.1 Effects on the cardiovascular system via AhR and CYP

Most effects of PAHs are mediated via AhR and AhR-regulated xenobiotic metabolizing enzymes, which are abundantly expressed in the cardiovascular system. Particularly high levels are found in the endothelium of the aorta, coronary arteries and ventricles *(206)*. Disruption of the synthesis or metabolism of endogenous substances by PAH modulation of CYP1A1 levels may contribute to CVD pathogenesis via mechanisms such as cardiotoxicity and effects on development of the cardiovascular system *(206–209)*. In addition, PAH exposure may induce cardiac hypertrophy. However, experimental studies of PAHs with differing potentials to bind AhR or to form reactive metabolites have not unequivocally identified the mechanisms involved *(206,210–213)*.

4.2.2.2 Oxidative stress, inflammation and atherosclerosis

PAHs such as B[*a*]P are suggested to aggravate atherosclerosis via increasing oxidative stress *(151)*. For example, overexpression of antioxidant enzymes suppressed B[*a*]P-accelerated atherosclerosis in apolipoprotein E (ApoE)-deficient mice *(214)*. Some studies found that B[*a*]P and other AhR agonists increase the expression of chemokines and proinflammatory cytokines such as CXCL8 and tumour necrosis factor alpha (TNF-α), which may cause macrophage and neutrophil infiltration into the lungs *(145)*. Pulmonary oxidative stress and inflammation may result in systemic spillover, thereby contributing to vascular inflammation and CVD development *(121)*. Oxidative stress in the vascular endothelium will decrease the availability of nitric oxide, a key regulator of vascular tone and blood pressure. Oxidative stress may also lead to alteration in circulating lipids. Elevated serum cholesterol-associated triglyceride and low-density lipoproteins are regarded as the primary causative factors for the development of atherosclerosis. These pro-atherogenic molecules diffuse into the subendothelial space and cause further vascular dysfunction *(180)*. Atherosclerosis induced by PAHs has also been more directly linked to AhR-dependent effects on cholesterol synthesis *(215)*.

4.2.2.3 DNA damage and atherosclerosis

Environmental carcinogens, including PAHs, are suggested to be risk factors for atherosclerosis owing to their mutagenic effects

(216–218). PAHs are hypothesized to cause aberrant smooth muscle cell proliferation, a potential focal starting-point in the pathogenesis and progression of atherosclerosis *(219–221)*. However, in at least some models, PAHs seem to induce an inflammatory atherosclerotic plaque phenotype irrespective of their DNA- or AhR-binding properties *(222,223)*.

4.2.2.4 Endothelial dysfunction

In vitro studies on human endothelial cells have demonstrated that B[*a*]P can increase intercellular adhesion molecule 1 (ICAM-1) expression through a caveolae- and AhR-mediated pathway *(224)*. This indicates that PAHs may cause endothelial dysfunction, characterized by increased adhesiveness caused by cell surface presentation of cellular adhesion molecules, such as ICAM-1 and vascular cell adhesion molecule 1 (VCAM-1). Increased endothelial adhesiveness is an essential initiating event in numerous CVDs via the retention of macrophages and monocytes in the subendothelial space.

Endothelial dysfunction is also characterized by disruption of calcium homeostasis *(225,226)* and increased expression of proinflammatory markers *(227)*. Interestingly, in a human exposure study, the vasodilatory effect of the calcium blocker, verapamil, was reduced in volunteers exposed to diesel exhaust particles, indicating that exposure affects intracellular calcium ($[Ca^{2+}]_i$) regulation *(228)*. Recent in vitro studies suggest that various lipophilic organic chemicals extracted from diesel exhaust particles, as well as various PAHs, may increase $[Ca^{2+}]_i$ through mechanisms involving the AhR non-genomic pathway or β_2-AR-dependent responses *(138,140,229,230)*. These mechanisms may also affect the expression of proinflammatory marker proteins *(201,231)*. It should also be noted that pyrene binding to AhR reduces B[*a*]P-induced CYP expression but activates AhR-dependent non-genomic Ca^{2+} signalling *(138)*.

4.2.2.5 Blood pressure

In experimental animals, PAH exposure has produced equivocal effects on hypertension. Hypertension induced by 3-methylcholanthrene was associated with inactivation of endothelial nitric oxide synthase *(232)*. Atherosclerosis and hypertension are risk factors for the development of abdominal aortic aneurysms. Therefore, it is notable that B[*a*]P aggravates the development of abdominal aortic aneurysms in ApoE-knockout mice *(233)*. Furthermore, ischaemia-induced angiogenesis following B[*a*]P exposure was found to be AhR dependent in zebrafish (*Danio rerio*) *(234)*.

4.2.2.6 Foam cell development

Macrophages play a key role in atherosclerosis progression by releasing proinflammatory cytokines and forming lipid-loaded foam cells in subendothelial lesions. Combustion PM may increase foam cell formation from macrophages in vitro *(235)*. The study found that organic extracts from PM induce stronger inflammatory responses compared with the core particles. These responses and the associated cholesterol and lipid accumulation were also found after B[*a*]P exposure and seem to involve AhR *(235,236)*. Although foam cell formation is probably induced by several PM components, PAHs are good candidates.

4.2.2.7 Effects on embryonic development

Several studies indicate that in utero exposure to PAHs impairs cardiovascular development. In Long-Evans hooded rats, in utero exposure to B[*a*]P led to significantly elevated systolic blood pressure in the offspring *(237)*. Potential mechanisms include AhR activation because endogenous AhR signalling is thought to be important for the correct development and function of the cardiovascular system. AhR-deficient mice develop cardiac hypertrophy,

abnormal vascular structure in multiple organs and altered blood pressure, depending on the environmental conditions *(238)*. Several studies also found AhR-dependent effects of PM and various PAHs on cardiovascular development in zebrafish embryos *(234,239–243)*. Interestingly, the mechanism in zebrafish does not seem to involve classical AhR ligand binding or the formation of electrophiles.

4.2.3 Review of epidemiological studies

Accumulating evidence suggests that PM with the highest proportion of organic chemicals have the greatest effects on vascular outcomes *(180,191,192,244,245)*. In a recent review, most epidemiological studies found significant positive associations between PAH exposure and CVD as well as the major risk factors for CVD, including elevated blood pressure *(246)*. However, based on the epidemiological data, it is difficult to discriminate between the impacts on CVD of combustion-derived PAHs versus PM, or of airborne PAHs versus PAHs from other sources.

4.2.3.1 Heart disease and mortality

In some occupations, PM and PAH exposure may be one to three orders of magnitude higher than in environmental settings *(247)*. However, heart disease mortality rates in occupational cohorts (such as aluminium smelters) are typically lower than those in the general population *(248,249)*, probably due to the healthy worker effect bias.[8] The relationship between PAH exposure and mortality from ischaemic heart disease (418 deaths) was studied in a cohort of 12 367 male asphalt workers from several countries *(249)*. Both cumulative and average exposure indices for B[*a*]P were positively associated with mortality and demonstrated a consistent exposure–response relation for this association. Recent morbidity studies using biomarkers of CVD (e.g. systemic inflammation, blood pressure and altered heart rate variability) reported associations of PM and PAH exposure with adverse cardiovascular effects in aluminium smelters *(250)*. Ischaemic heart disease mortality was associated with B[*a*]P in the highest exposure category. Furthermore, a monotonic,[9] but non-significant, association was observed between chronic B[*a*]P exposure and acute myocardial infarction. However, these associations were stronger during employment, suggesting that CVD risk may not persist after occupational exposure stops.

A study of a cohort of automobile workers reported modest evidence that occupational exposure to PM containing PAHs may increase the risk of mortality from ischaemic heart disease *(251)*. In a population-based case–reference study of myocardial infarction and occupational exposure to motor exhaust and other combustion products, the relative risk of myocardial infarction was 2.11 for highly exposed individuals and 1.42 for those with intermediate exposure to combustion products from organic material (compared with a control population with matching demographic characteristics). Exposure–response patterns in terms of both maximum exposure intensity and cumulative dose were also found *(252)*.

Exposure to traffic increased the risk of myocardial infarction in susceptible people *(253)*. Increased onset of chest pain was observed immediately and up to 6 hours after traffic exposure. Exacerbated heart symptoms among myocardial infarction survivors have been linked to PM-associated organic compounds *(254)*. The study showed an association between PM-adhered organic chemicals and daily symptoms.

8 The healthy worker effect is a special type of selection bias, typically seen in observational studies of occupational exposures with an improper choice of comparison group (usually, the general population). Conversely, the health of people who stop working is generally worse than the health of a similar group of people who continue to work.

9 Monotonic functions are those that increase or decrease over their entire domain.

An association with symptom severity among myocardial infarction survivors suggests that PM-associated PAH concentrations have a major influence on cardiovascular health *(255)*. In the general population, cross-sectional studies found that the concentration of urinary monohydroxy (OH) metabolites of phenanthrene is significantly associated with self-reported CVD *(256)*. Individuals in the middle and highest tertiles for fluorene and phenanthrene metabolites had a significantly higher prevalence of peripheral arterial disease compared with those in the lowest tertile *(257)*. A Chinese multiprovincial cohort study found an association between the 10-year risk of atherosclerotic CVD and PAH exposure, measured as urinary hydroxylated PAH (OH-PAH) metabolites, specifically 2hydroxyfluorene, 9-hydroxyfluorene, 1-hydroxyphenanthrene and total OH-PAH levels *(258)*.

Occupational PAH exposure was associated with altered heart rate variability in boilermakers *(59,259)* and coke oven workers *(59)*. Recently, an association between background PAH exposure and heart rate variability in the general population was also reported. Increased urinary OH-PAH metabolites were associated with a decrease in heart rate variability (using Framingham Risk Scores) in an exposure–responsive manner *(260)*.

4.2.3.2 Inflammatory markers

Urinary 1-hydroxypyrene was higher in taxi drivers than in non-occupationally exposed people and correlated positively with levels of both proinflammatory cytokines (IL-1β, IL-6, IL10, TNF-α, interferon gamma and high-sensitivity C-reactive protein) and biomarkers of oxidative damage (serum levels of oxidized low-density lipoproteins, autoantibodies and homocysteine) and negatively with levels of antioxidants. As increased levels of inflammatory biomarkers and homocysteine are important predictors of cardiovascular events, these data suggest a possible link between occupational PAH exposure and CVD *(261)*. In support of this, urinary 1-hydroxypyrene levels were positively associated with both carotid intima–media thickness and serum homocysteine levels in taxi drivers *(262)*. Occupational exposure to soot (which is rich in PAH) has also been associated with an increased risk of CVD. A cross-sectional study found that chimney sweeps had up to sevenfold higher concentrations of PAH metabolites in their urine compared with controls, and the concentration of PAH metabolites correlated positively with the percentage of time spent sweeping soot *(263)*. Furthermore, early markers of CVD (i.e. cholesterol, homocysteine and reduced levels of high-density lipoproteins) were affected in serum from chimney sweeps. A study of school-aged children identified an association between increased oxidative stress biomarkers and urinary PAHs *(264)*. Increased serum levels of Creactive protein (indicating inflammation) have also been reported in people with elevated levels of urinary PAHs *(265)*.

4.2.3.3 Blood pressure

Coke oven workers are exposed to high levels of PAHs, and studies have shown an association between exposure to coke oven emissions and both hypertension and abnormal electrocardiography *(266–268)*. Levels of 2hydroxyphenanthrene, 3-hydroxybenzo[*a*]pyrene and 3-hydroxybenzo[*a*]anthracene in chimney sweeps were positively associated with diastolic blood pressure *(263)*. Contradictory findings were reported in a study of blood pressure and PAH exposure in outdoor workers: overall, levels of urinary 1-hydroxypyrene were negatively associated with systolic and diastolic blood pressure *(269)*. The authors suggest that occupational exposure to PAHs may significantly influence blood pressure, probably via the autonomic nervous system.

In a population of elderly people, oxy-PAHs (chrysene-5,6-dione and B[*a*]P-3,6-dione) were significantly associated with increased systolic

blood pressure and pulse pressure *(270)*. PAHs were also associated with hypertension in a study of younger adults, mostly women *(271)*. Another study investigated the association between PAH concentrations in housewives' hair and hypertension *(177)*. Of the seven PAHs measured, only acenaphthylene was associated with an increased risk of hypertension. A study in Saudi Arabia found that living close to an oil refinery was associated with increased PAH and PM exposure and prehypertension and in children *(272)*. However, urinary PAH metabolites (1-hydroxypyrene and hydroxyphenanthrene) were not associated with cardiovascular outcomes. A repeated measures study of 106 residents in China analysed eight urinary OH-PAH metabolites *(273)*. The study found an association of OH-PAHs with high blood pressure and increased risk of atherosclerotic CVD, which may have been partly mediated by obesity.

4.2.3.4 Embryonic development

Passive diffusion seems to control the transplacental transfer of PAHs from maternal serum to the fetal circulatory system *(274)*. Evidence from experimental systems shows that embryonic PAH exposure results in congenital heart defects *(234)*, as discussed in section 4.2.3.1. However, results from a large population-based study do not support an association between potential maternal occupational exposure to PAHs and congenital heart defects in children *(275)*.

4.2.4 Conclusions, knowledge gaps and remaining challenges

Human epidemiological studies, combined with experimental animal and in vitro studies, strongly suggest that exposure to combustion particles, specifically $PM_{2.5}$, increases the risk of CVDs, including atherosclerosis, hypertension, myocardial infarction and thrombosis. The available evidence suggests that organic compounds attached to these particles are significant triggers of CVD, of which PAHs may be important contributors. However, based on epidemiological data alone, it is difficult to separate airborne PAHs from other PAHs sources.

Potential mechanisms linking PAH exposure to CVD include AhR-induced changes in gene expression, changes in calcium homeostasis, and the formation of reactive oxygen species or reactive electrophilic metabolites. That is, they are not restricted to the classical mechanisms of PAH-induced mutagenesis and carcinogenesis, upon which the current PAH risk assessments and regulations are based. The current understanding of PAH mechanisms mainly derives from B[*a*]P exposure studies, but PAHs that lead to cardiovascular outcomes could differ from the classical carcinogenic PAHs. A limited number of studies indicate that three- and four-ring PAH species with low or no carcinogenic potential, such as pyrene and phenanthrene, could also affect the cardiovascular system. Owing to the high abundance of these PAHs in outdoor air (exceeding B[*a*]P levels by several orders of magnitude *(2)*), further clarification of their effects on CVD is needed. Moreover, the concentration–response relationship, mechanisms involved and importance of different PAH species are uncertain. Studies on the association between PAHs and CVD in the general population are also scarce.

4.3 Effects of PAHs on neurodevelopment outcomes in children

4.3.1 Review of experimental studies

The effects of B[*a*]P exposure during gestation or early life have been investigated in experimental animals (rodents). Reported effects of developmental toxicity include changes in embryonic or fetal survival, pup weight, blood pressure, fertility, reproductive organ weight and histology, and nervous system function *(276)*.

According to a review by US EPA, the results of neurodevelopmental studies in rodents have consistently demonstrated that B[*a*]P exposure, particularly during late gestation or early postnatal development, has persistent neurobehavioural effects *(276)*. These effects have been observed across several behavioural domains in multiple strains and both sexes of two rodent species. The review covered several types of neurodevelopmental outcomes, including cognitive function; neuromuscular function, coordination and sensorimotor development; anxiety and activity; and electrophysiological changes.

4.3.1.1 Cognitive function

B[*a*]P (lactational or administered through oral gavage) affected the performance of rodents in Y-maze (mice) and Morris water maze (rats) tests *(276)*. These responses probably reflect effects on spatial learning and memory, although other neurobehavioural alterations may also have contributed to the responses. Dose-dependent effects in rats persisted for weeks or months after the exposure.

4.3.1.2 Neuromuscular function, coordination and sensorimotor development

The US EPA review of available studies indicated that impaired performance in neuromuscular and sensorimotor tests (surface righting reflex test, negative geotaxis test and forelimb grip strength test) was consistently observed in mice lactationally exposed to B[*a*]P (≥ 2 mg/kg per day) and in rat pups exposed postnatally (≥ 0.02 mg/kg per day) by oral gavage *(276)*. The results suggested that the effects may be specific to exposure during particular developmental life stages.

4.3.1.3 Anxiety and activity

Decreased anxiety-like behaviour has been reported in both rats and mice tested in an elevated plus maze after postnatal (lactational) exposure to B[*a*]P *(276)*. The results suggested that effects were greater in older animals, that is, when the period was longer between exposure and testing.

4.3.1.4 Electrophysiological changes

Two studies on electrophysiological changes in rats following gestational exposure to B[*a*]P were undertaken by the same research group. One of the studies suggested that gestational exposure to B[*a*]P may have long-lasting effects on neuronal activity in response to sensory stimuli (whisker stimulation) *(276)*. However, data from the other study were difficult to interpret owing to maternal toxicity and ex vivo methodology.

Fish and in vitro models of toxicity have been used to explore the developmental neurotoxicity of PAH mixtures and of single PAHs other than B[*a*]P.

Geier, Chlebowski et al. (2018) assessed the neurobehavioural effects of 123 PAHs (parent, nitrated, oxygenated, hydroxylated, methylated, heterocyclic and aminated compounds) in a high-throughput assay in zebrafish embryos and larvae *(277)*. The photomotor response outcomes observed at these life stages suggested that a diverse range of PAH structures can elicit neurobehavioural effects. A number of PAHs induced larval photomotor responses but did not affect other end-points. Geier, Minick et al. (2018) also used a zebrafish model to investigate the developmental neurotoxicity of 10 PAHs, applied both individually and as a mixture *(278)*. Effects in the larval photomotor response assay were observed after exposure to most of the individual PAHs and to the PAH mixture. Embryos exposed to the mixture and then grown to adulthood in chemical-free water demonstrated learning and memory deficits, suggesting that developmental exposure can have long-term behavioural effects.

Brown et al. (2016) and Slotkin et al. (2017) investigated the effects of an environmentally derived PAH mixture in killifish (*Fundulus heteroclitus*) and cultured rodent cells, respectively *(279,280)*. Brown et al. (2016) found that embryonic exposure caused short-term and persistent locomotor and behavioural impairments in naive killifish, but not in PAH-adapted killifish *(279)*. Slotkin et al. (2017) investigated the effects of exposure in two in vitro cell models: neuronotypic PC12 cells and embryonic neural stem cells *(280)*. In PC12 cells, the PAH mixture was far less effective than B[*a*]P in impairing the transition from cell replication to neurodifferentiation. In contrast, neural stem cells were more sensitive to the PAH mixture than to B[*a*]P alone.

4.3.2 Review of epidemiological studies

Of the 26 epidemiological studies of neurodevelopmental effects of exposure to PAHs identified, many reported findings consistent with the effects of B[*a*]P observed in animal studies. Three research groups had published most of the epidemiological studies, and these had involved the same three cohorts (or subsets of these cohorts). Many studies had enrolled children at or before birth and most assessments were carried out in children aged 5 years or younger, but some were in older children. Several studies were based on the Columbia Centre for Children's Environmental Health (CCCEH) cohort in New York City (United States) *(281–292)*. Researchers from the CCCEH have also studied a cohort in Krakow (Poland) *(172,290,293–295)* and been involved in research in Tongliang County (China) *(296–301)*, focusing on a site where improvements in air quality were seen following the closure of a coal-fired power plant. In addition, Mortamais et al. (2017) studied schoolchildren in Barcelona (Spain) *(302)* and Abid et al. (2014) used information from the United States National Health and Nutrition Examination Survey (NHANES) *(303)*. The studies examined both cognitive development (such as intelligence quotient (IQ) or development quotient) and behavioural development and difficulties; a few examined brain physiology or biochemistry. The sample of children included in the studies was often small. Only three studies included more than 500 children; of these, only one included over 1000 children *(303)*. Therefore, the small sample sizes may have limited the power of the studies to detect associations.

Using NHANES data, Abid et al. (2014) found a statistically significant association between urinary fluorene metabolites (but not with urinary levels of several other PAH metabolites) and receipt of special education or early intervention services *(303)*. However, no association was found between urinary fluorene metabolites and attention deficit hyperactivity disorder (ADHD) or learning disability.

A 2014 summary of results from the CCCEH cohort by Perera, Weiland et al. *(304)* indicated that prenatal exposure to airborne PAH was associated with developmental delay at age

3 years *(283)*, reduced IQ at age 5 years *(285)* and behavioural problems at age 7 years *(286)*. Margolis et al. (2016) later reported that prenatal PAH exposure was associated with effects on social competence, mediated by the delayed development of self-regulatory capacity *(282)*. Perera, Phillips et al. (2015) found that cord blood PAH adducts were associated with reduced brain-derived neurotrophic factor (BDNF) at age 2 years, but not at age 3 years *(287)*. Results reported by Perera, Wheelock et al. (2018) and Vishnevetsky et al. (2015) suggest that PAH exposure has adverse effects on IQ or ADHD behaviour problems, respectively, in children who also suffered material hardship *(288,292)*.

In Poland, PAH exposure was found to be associated with adverse effects on non-verbal reasoning at the age of 5 years *(293)*, on IQ *(172)*, and on thought and behavioural problems *(294)*. In Tongliang County (China), decreased head circumference *(298,301)*, decrements in development quotients *(299,300)* and reduced levels of mature BDNF *(301)* were associated with either cord blood DNA adducts or exposure to emissions from a coal-fired power plant. The findings of Perera, Tang, Rauh et al. (2007) in New York City (United States) and Perera, Li et al. (2009) in China do not show that cognitive development is associated with exposure to PAH exposure *(284,285)*, but suggest an association with exposure to environmental tobacco smoke *(305)*.

A morphological study in New York City reported that PAH exposure is associated with a reduced white matter surface in the left hemisphere of the brain *(289)*. This reduction was associated with slower information processing during an intelligence test and with more severe externalizing behaviour problems, including ADHD symptoms and conduct disorder problems. In a study in Barcelona (Spain), Mortamais et al. (2017) found that PAH exposure was associated with decreased caudate nucleus volume *(302)*. A trend analysis indicated that ADHD symptoms and inattentiveness increased with increasing exposure to B[*a*]P, although the relative risks were not statistically significant. No significant relationships were reported between total PAH exposure and neurobehavioural effects.

However, although many studies adjusted for confounding factors, they did not adjust for the effects of other air pollutants, and none provided information on correlations between levels of PAHs with other pollutants. This limits confidence in identifying PAH exposure as the causal factor in the developmental outcomes reported. This is particularly relevant, given the emerging evidence from epidemiological studies of possible neurological effects associated with concentrations of other air pollutants *(306–308)*.

4.3.3 Review of other studies and mechanisms

The US EPA noted that limited data are available on the potential modes of action for the developmental effects of B[*a*]P *(276)*. Possible modes of action include genotoxicity, mutagenicity, altered cell signalling via AhR, cytotoxicity, and oxidative stress. Similarly, no clear modes of action have been demonstrated for the observed neurodevelopmental changes. The US EPA noted limited experimental support for a mechanism involving altered neurotransmission in the central nervous system. This might include altered neurotransmitter gene expression, neurotransmitter levels and neurotransmitter receptor signalling in relevant brain regions.

Mechanistic studies in rodents exposed to B[*a*]P as adults may be informative. Studies in developing and adult rodents suggest that changes in *N*-methyl-D-aspartate (NMDA) receptor signalling may lead to changes in spatial learning and memory processes that may cause behavioural effects in learning and memory tests *(276,309)*. The evidence suggests other plausible mechanisms, including increased oxidative stress in the in brain (perhaps from B[*a*]P metabolites) and

possible effects on monoamine neurotransmitter signalling (in particular serotonin and dopamine) *(276)*.

Studies into the neurodevelopmental effects of B[*a*]P and other PAHs should be considered in the wider context of the neurodevelopmental and neurodegenerative effects of air pollutants more generally, including PM (notably ultrafine particles) and ozone, with increasing focus on the involvement of neuroinflammation (via activation of glial cells) *(310,311)*.

4.3.4 Conclusions, knowledge gaps and remaining challenges

The limited epidemiological evidence suggests associations between prenatal and early life exposure to PAHs in ambient air and effects on cognitive or behavioural function in children. Experimental studies in laboratory animals indicate biological plausibility. However, a number of knowledge gaps and challenges remain, including:

- the extent to which PAHs are the causal agents of associations reported in epidemiological studies;
- whether developmental and neurodevelopmental effects are general to all PAHs or specific to some;
- the relative importance of inhalation exposure and dietary exposure to PAHs (and possible interactions);
- elucidation of the mechanisms involved in neurotoxicity; and
- differences in brain development stages between humans and the various animal models.

The US EPA's Integrated Risk Information System assessment uses neurodevelopmental (oral) and developmental (inhalation) toxicity in experimental animals (rodents) as sensitive end-points to derive a reference dose and reference concentration considered tolerable for public health *(276)*. However, large uncertainty factors have been applied, reflecting low–medium confidence levels in the studies and evidence base. More research is needed to address all of these issues.

5. Discussion

PAHs are widespread pollutants emitted into air from many different sources. People are exposed by inhalation but also by ingesting contaminated food (e.g. via the long-range atmospheric transport of air pollutants). Some PAHs are well-known carcinogens, with current policy focusing on lung cancer. However, other cancers must also be considered, such as breast cancer and childhood cancers in urban areas. In addition, PAH exposure is associated with several other health effects, including asthma development/exacerbation and CVD, and adverse effects on neurodevelopment in children.

In the general population, it is difficult to determine the relative contribution of different sources of PAHs and to assess exposure levels with sufficient resolution. One reason for this is that monitoring is often designed to meet requirements for checking compliance with standards and might be less suitable for determining PAH exposure at individual level. Monitoring specific PAH-emitting sources or modelling PAH emissions at local level might help to address this. B[*a*]P has been used widely as a marker for PAHs for regulatory purposes based on its documented carcinogenic effects. However, other highly potent carcinogenic PAHs and PAH mixtures should also be considered. PAHs are often emitted from the same sources as other common air pollutants. This is both a challenge and an advantage: the challenge is to disentangle the component-specific biological effects and exposure at the individual level of common pollutants such as PM, nitrogen oxides and polycyclic aromatic compounds (including PAHs); the advantage is the possibility of source-specific measures to combat pollution.

Experimental studies of PAHs and mixtures of PAHs support the epidemiological findings. The studies have elucidated the relative potency of individual PAHs and suggested possible mechanisms of action. Although DNA damage and mutation are probably essential steps, recent studies indicate that other non-genotoxic mechanisms may also be involved. However, the relative importance of the various processes involved in human cancer development following PAH exposure is not yet fully understood.

Experimental studies of PM, organic extracts from PM, and individual PAHs attached to PM support epidemiological studies on various non-cancerous diseases. The studies suggest a role for PAHs in respiratory diseases and CVDs, as well as in neurodevelopment, and have elucidated possible mechanisms of action. The effects of PAHs on many processes involved in the development or exacerbation of these diseases are mediated (at least in part) by AhR. Suggested mechanisms include AhR-induced changes in gene expression, changes in calcium homeostasis, and the formation of reactive oxygen species or reactive electrophilic metabolites. However, the dose–response relationships, mechanisms of action and relative importance of different PAH species remain uncertain.

6. Conclusions

PAHs are a group of chemical compounds emitted from combustion and some industrial processes, and often associated with PM in ambient air. In contrast to ambient PM, PAHs are chemically defined and are not characterized by their physical properties upon sampling. The monitoring networks for PAHs mainly report the yearly mean levels.

Exposure assessment of PAHs is difficult in the general population because cancer takes a long time to develop and exposure conditions may change over time. The number of monitoring stations reporting annual data on PAHs to the European Environment Agency is about one third of those reporting on PM_{10}. Therefore, it is difficult to obtain high-resolution exposure data for PAHs without the use of various modelling techniques. To address this, further studies are needed, especially longitudinal studies with high temporal and spatial resolution of exposure that consider the potency of different PAHs in a mixture to contribute to cancer development. An updated assessment based on more sophisticated epidemiological data on cancer outcomes in the general population is also needed. In classifying outdoor air pollution as carcinogenic, IARC based some of its conclusions on epidemiological studies of cancer related to PM exposure. As reported by Hamra et al. (2014), "The Group I classification raises questions regarding individual components in the air pollution mixture regarding, for example, the carcinogenic potential of each component as well as through what pathways they may contribute to cancer risk" *(312)*. As PAHs are well known for their carcinogenic properties, they may make a significant contribution to the carcinogenicity of pollutants in outdoor air.

Few epidemiological studies describing the effects on cancer of PAHs in ambient air have been published since the early 2000s. Overall, these studies suggest that PAHs in ambient air are associated with increased cancer incidence. In addition, organic compounds attached to PM are significant triggers for CVD and are at least partly responsible for the enhanced risk of various non-malignant respiratory diseases after exposure to polluted ambient air. Some evidence suggests associations between prenatal and early life exposure to PAHs in ambient air and adverse effects on lung development and on cognitive/behavioural function in children. Experimental studies of PAHs support the epidemiology and have elucidated the possible mechanisms of action, including AhR-induced changes in gene expression, changes in calcium homeostasis, and the formation of reactive oxygen species or reactive electrophilic metabolites.

The main findings of this review are as follows.

- For carcinogenic air pollutants, including several PAHs, the lowest possible exposure should be aimed at to minimize the risk of cancer development in view of a no-effect threshold.
- Of the carcinogenic PAHs, individual PAHs may differ in carcinogenic potency by an order of magnitude.
- Based on current knowledge, it is not possible to establish whether B[*a*]P is a representative marker for exposure to other PAHs.
- Current knowledge does not permit the establishment of regulatory guidelines for the non-malignant effects of B[*a*]P or other PAH species.
- It is not possible to establish whether current WHO guidelines for B[*a*]P provide

sufficient protection against diseases other than cancer.
- Non-cancer health end-points of PAH exposure should be further explored.
- Monitoring programmes should be optimized to support the protection of populations from PAH exposure, either by establishing high-resolution networks in hot spots or by high-resolution modelling of PAH concentrations.

References

1. Gusev A, Batrakova N. Assessment of PAH pollution levels, key sources and trends: contribution to analysis of the effectiveness of the POPs Protocol. Moscow: Meteorological Synthesizing Centre; 2020 (Progress report; https://en.msceast.org/reports/2_2020_tech.pdf, accessed 12 October 2021).

2. Bostrom CE, Gerde P, Hanberg A, Jernstrom B, Johansson C, Kyrklund T et al. Cancer risk assessment, indicators, and guidelines for polycyclic aromatic hydrocarbons in the ambient air. Environ Health Perspect. 2002;110(suppl 3):451–88. doi: 10.1289/ehp.110-1241197.

3. Srogi K. Monitoring of environmental exposure to polycyclic aromatic hydrocarbons: a review. Environ Chem Lett. 2007;5(4):169–95. doi: 10.1007/s10311-007-0095-0.

4. World Health Organization, International Agency for Research on Cancer. Some non-heterocyclic polycyclic aromatic hydrocarbons and some related occupational exposures. Lyon: International Agency for Research on Cancer; 2010 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans No. 92; https://inchem.org/documents/iarc/iarcmono/v92iarc.pdf, accessed 12 October 2021).

5. Conventions and protocols [website]. Geneva: United Nations Economic Commission for Europe; 2021 (https://unece.org/environment-policy/conventions-and-protocols, accessed 18 October 2021).

6. The 1998 Protocol on Persistent Organic Pollutants, including the amendments adopted by the Parties on 18 December 2009. Geneva: United Nations Economic Commission for Europe; 2010 (https://unece.org/environment-policy/air/protocol-persistent-organic-pollutants-pops, accessed 12 October 2021).

7. Guidelines for estimating and reporting emission data under the Convention on Long-range Transport of Air Pollution. Geneva: United Nations Economic Commission for Europe; 2003 (UNECE Air Pollution Studies No. 15; https://digitallibrary.un.org/record/517855?ln=en, accessed 12 October 2021).

8. Air quality guidelines for Europe. Copenhagen: WHO Regional Office for Europe; 1987 (https://apps.who.int/iris/handle/10665/107364, accessed 12 October 2021).

9. Air quality guidelines for Europe, second edition. Copenhagen: WHO Regional Office for Europe; 2000 (https://apps.who.int/iris/handle/10665/107335, accessed 12 October 2021).

10. Evolution of WHO air quality guidelines: past, present and future. Copenhagen: WHO Regional Office for Europe; 2017 (https://apps.who.int/iris/handle/10665/341912, accessed 12 October 2021).

11. WHO guidelines for indoor air quality: selected pollutants. Copenhagen: WHO Regional Office for Europe; 2010 (https://apps.who.int/iris/handle/10665/260127, accessed 12 October 2021).

12. Barrett K, Fiala J, de Leeuw F, Ward J. Air pollution by benzene, carbon monoxide, PAHs, and heavy metals. European Topic Centre on Air and Climate Change; 2008 (ETC/ACC Technical Paper 2008/12; https://www.eionet.europa.eu/etcs/etc-atni/products/etc-atni-reports/etcacc_tp_2008_12_aqstatus_benz_hm_co_pah, accessed 12 October 2021).

13. Air quality guidelines: global update 2005. Particulate matter, ozone, nitrogen dioxide and sulfur dioxide. Copenhagen: WHO Regional Office for Europe; 2005 (https://apps.who.int/iris/handle/10665/107823, accessed 12 October 2021).

14. Review of evidence on health aspects of air pollution: REVIHAAP project: technical report. Copenhagen: WHO Regional Office for Europe; 2013 (https://apps.who.int/iris/handle/10665/341712, accessed 12 October 2021).

15. AirQ+: software tool for health risk assessment of air pollution [website]. Geneva: World Health Organization: 2021 (https://www.euro.who.int/en/health-topics/environment-and-health/air-quality/activities/airq-software-tool-for-health-risk-assessment-of-air-pollution, accessed 12 October 2021).

16. AirQ+: carcinogenic pollutants and risk analysis. Copenhagen: WHO Regional Office for Europe; 2020 (https://apps.who.int/iris/handle/10665/337685, accessed 12 October 2021).

17. Effects of air pollution on health: report of the Joint Task Force on the Health Aspects of Air Pollution on its twentieth meeting. Geneva: United Nations Economic and Social Council; 2017 (https://unece.org/fileadmin/DAM/env/documents/2017/AIR/EMEP/_E__ECE_EB.AIR_GE.1_2017_17–ECE_EB.AIR_WG.1_2017_10.pdf, accessed 18 October 2021).

18. The Convention and its achievements: a common framework for transboundary cooperation on air pollution. Geneva: United Nations Economic Commission for Europe; 2021 (https://www.unece.org/environmental-policy/conventions/envlrtapwelcome/the-air-convention-and-its-protocols/the-convention-and-its-achievements.html, accessed 11 April 2021).

19. Report of the Executive Body on its thirty-seventh session. Addendum: 2018–2019 workplan for the implementation of the Convention. In: Economic Commission for Europe, Executive Body for the Convention on Long-range Transboundary Air Pollution, thirty-seventh session, Geneva, 11–14 December 2017. Geneva: United Nations Economic and Social Council; 2018 (ECE/EB.AIR/140/Add.1; https://www.unece.org/fileadmin/DAM/env/documents/2017/AIR/EB/_E__ECE_EB.AIR_140_Add_1.pdf, accessed 11 April 2021).

20. Report of the Executive Body on its thirty-ninth session. Addendum: 2020–2021 workplan for the implementation of the Convention. In: Economic Commission for Europe, Executive Body for the Convention on Long-range Transboundary Air Pollution, thirty-ninth session, Geneva, 9–13 December 2019. Geneva: United Nations Economic and Social Council; 2020 (ECE/EB.AIR/140/Add.2; https://www.unece.org/fileadmin/DAM/env/documents/2019/AIR/EB/ECE_EB.AIR_144_Add.2__Advance_version_.pdf, accessed 11 April 2021.

21. EMEP [website]. Geneva: United Nations Economic Commission for Europe; 2021 (https://emep.int/, accessed 18 October 2021).

22. Air pollution trends in the EMEP region between 1990 and 2012. Co-operative Programme for Monitoring and Evaluation of the Long-range Transmission of Air Pollutants in Europe (EMEP). Kjeller, Norway: Norwegian Institute for Air Research; 2016 (EMEP/CCC-Report 1/2016; http://nora.nerc.ac.uk/id/eprint/513779/, accessed 12 October 2021).

23. European Environment Agency. Air quality in Europe: 2020 report. Luxembourg: Publications Office of the European Union; 2020 (European Environment Agency Report No. 9/2020; www.eea.europa.eu/publications/air-quality-in-europe-2020-report, accessed 3 May 2020).

24. Canada's Air Pollutant Emission Inventory [database]. Ottawa (ON): Environment and Climate Change Canada, Government of Canada; 2021 (https://open.canada.ca/data/en/dataset/fa1c88a8-bf78-4fcb-9c1e-2a5534b92131, accessed 18 October 2021).

25. Canada's air pollutant emissions inventory report. Gatineau (QC): Environment and Climate Change Canada; 2019 (http://publications.gc.ca/site/eng/9.869731/publication.html, accessed 10 June 2021).

26. Integrated data. In: Environment and Climate Change Canada Data [website]. Gatineau (QC): Environment and Climate Change Canada; 2021 (http://data.ec.gc.ca/data/air/monitor/national-air-pollution-surveillance-naps-program/Data-Donnees/2016/IntegratedData-DonneesPonctuelles/?lang=en, accessed 14 April 2021).

27. Tevlin A, Galarneau E, Zhang T, Hung H. Polycyclic aromatic compounds (PACs) in the Canadian environment: ambient air and deposition. Environ Pollut. 2021;271:116232. doi: 10.1016/j.envpol.2020.116232.

28. Berthiaume A, Galarneau E, Marson G. Polycyclic aromatic compounds (PACs) in the Canadian environment: sources and emissions. Environ Pollut. 2021;269:116008. doi: 10.1016/j.envpol.2020.116008.

29. Solid fuel-burning stoves and fireplaces [website]. Montreal (QC): Ville de Montreal; 2019 (https://montreal.ca/en/topics/solid-fuel-burning-stoves-and-fireplaces, accessed 23 July 2021)

30. European Union emission inventory report 1990–2018 under the UNECE Convention on Long-range Transboundary Air Pollution (LRTAP). Copenhagen: European Environment Agency; 2020 (EEA report No. 05/2020; https://www.eea.europa.eu/publications/european-union-emission-inventory-report-1990-2018, accessed 18 October 2021).

31. Canada's air pollutant emissions inventory report. Gatineau (QC): Environment and Climate Change Canada; 2018 (http://publications.gc.ca/site/eng/9.869731/publication.html, accessed 1 May 2021).

32. Fugitive emission. In: EEA glossary [website]. Copenhagen: European Environment Agency; 2021 (https://www.eea.europa.eu/help/glossary/eea-glossary/fugitive-emission, accessed 18 October 2021).

33. Hoffman E, Weiss J, Hirschl B. Feasability study for new ecolabels for the product group: wood pellet firings. Berlin: Federal Environment Agency; 2003 (https://www.umweltbundesamt.de/sites/default/files/medien/publikation/long/2224.pdf, accessed 18 October 2021).

34. Amann M, Cofala J, Klimont Z, Nagl C, Schieder W. Measures to address air pollution from small combustion sources. Vienna: Umweltbundesamt; 2018 (https://ec.europa.eu/environment/air/pdf/clean_air_outlook_combustion_sources_report.pdf, accessed 18 October 2021).

35. Commission Regulation (EU) 2015/1185 of 24 April 2015 implementing Directive 2009/125/EC of the European Parliament and of the Council with regard to ecodesign requirements for solid fuel local space heaters. Brussels: European Commission; 2015 (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32015R1185, accessed 12 October 2021).

36. Commission Regulation (EU) 2015/1189 of 28 April 2015 implementing Directive 2009/125/EC of the European Parliament and of the Council with regard to ecodesign requirements for solid fuel boilers. Brussels: European Commission; 2015 (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.L_.2015.193.01.0100.01.ENG, accessed 12 October 2021).

37. Andersson S, Arvelius J, Jones J, Kindell S, Leung W. Beräkningar av emissioner och halter av benso(a) pyren och partiklar från småskalig vedeldning: luftkvalitetsmodellering för Skellefteå, Strömsunds och Alingsås kommuner [Calculations of emissions and levels of benzo(a)pyrene and particles from small-scale wood burning: air quality modelling for the municipalities of Skellefteå, Strömsund and Alingsås]. Meteorologi 164. Norrköping: Swedish Meteorological and Hydrological Institute; 2019 (in Swedish; https://www.smhi.se/publikationer/publikationer/berakningar-av-emissioner-och-halter-av-benso-a-pyren-och-partiklar-fran-smaskalig-vedeldning-1.144701, accessed 12 October 2021).

38. EU Ecolabel [website]. Brussels: Directorate-General for Environment, European Commission; 2021 (https://ec.europa.eu/environment/ecolabel/, accessed 18 October 2021).

39. Ordinance on Air Pollution Control (OAPC). Bern: Swiss Federal Council; 1985 (Regulation 814.318.142.1; https://www.fedlex.admin.ch/eli/cc/1986/208_208_208/en, accessed 18 October 2021).

40. Zotter P, Ciobanu VG, Zhang YL, El-Haddad I, Macchia M, Daellenbach KR et al. Radiocarbon analysis of elemental and organic carbon in Switzerland during winter smog episodes from 2008 to 2012, part 1: source apportionment and spatial variability. Atmos Chem Phys. 2014;14:15591–643. doi: 10.5194/acpd-14–15591–2014.

41. Schläpfer K. PAH-Immissionsmessungen in den Kantonen Zürich, Schaffhausen und Luzern (1994/1995). Zurich und Lucerne: Amtes für Technische Anlagen des Kant. Laboratoriums für Lebensmittelkontrolle und Umweltschutz Schaffhausen und des Amtes für Umweltschutz; 1995.

42. Krismer A. Benzo(a)Pyren und Hausbrand. Innsbruck: Forest Protection Department, Office of the Tyrolean Provincial Government; 2015 (https://www.tirol.gv.at/fileadmin/themen/umwelt/luftqualitaet/downloads/sonstige_Berichte/Benzo_a_pyren_und_Hausbrand.pdf, accessed 1 May 2021).

43. Fischer A, Hüglin C. Polyzyklische aromatische Kohlenwasserstoffe im PM10 an ausgewählten Stationen des NABEL sowie der Kantone: messbericht 2020 [Polycyclic aromatic hydrocarbons in PM_{10} at selected stations of NABEL and the cantons: measurement report 2020]. Department of Air Pollutants and Environmental Technology, EMPA – Swiss Federal Laboratories for Materials Science and Technology; 2019 (https://www.empa.ch/documents/56101/246436/PAK+Bericht+2019/95ac6e20-e72c-434a-ba4d-50653cdd2ffa, accessed 18 November 2021).

44. Directive 2008/50/EC of the European Parliament and of the Council of 21 May 2008 on ambient air quality and cleaner air for Europe. OJ. 2008;L152:1–44 (https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32008L0050&from=EN, accessed 18 October 2021).

45. Gualtieri M, Ovrevik J, Holme JA, Perrone MG, Bolzacchini E, Schwarze PE et al. Differences in cytotoxicity versus pro-inflammatory potency of different PM fractions in human epithelial lung cells. Toxicol In Vitro. 2010;24(1):29–39. doi: 10.1016/j.tiv.2009.09.013.

46. Sobus JR, Waidyanatha S, McClean MD, Herrick RF, Smith TJ, Garshick E et al. Urinary naphthalene and phenanthrene as biomarkers of occupational exposure to polycyclic aromatic hydrocarbons. Occup Environ Med. 2009;66(2):99–104. doi: 10.1136/oem.2008.041418.

47. Keith LH. The source of US EPA's sixteen PAH priority pollutants. Polycycl Aromat Compd. 2015;35(2–4):147–60. doi: https://doi.org/10.1080/10406638.2014.892886.

48. European Commission. Commission Recommendation of 4 February 2005 on the further investigation into the levels of polycyclic aromatic hydrocarbons in certain foods (2005/108/EC). OJ. 2005;L34/43 (https://www.fsai.ie/uploadedfiles/commission_recommendation_2005_108_ec.pdf, accessed 12 October 2021).

49. Andersson JT, Achten C. Time to say goodbye to the 16 EPA PAHs? Toward an up-to-date use of PACs for environmental purposes. Polycycl Aromat Compd. 2015;35(2–4):330–54. doi: 10.1080/10406638.2014.991042.

50. Luch A. On the impact of the molecule structure in chemical carcinogenesis. EXS. 2009;99:151–79. doi: 10.1007/978-3-7643-8336-7_6.

51. Achten C, Andersson JT. Overview of polycyclic aromatic compounds (PAC). Polycycl Aromat Compd. 2015;35(2–4):177–86. doi: 10.1080/10406638.2014.994071.

52. Lundstedt S, White PA, Lemieux CL, Lynes KD, Lambert IB, Oberg L et al. Sources, fate, and toxic hazards of oxygenated polycyclic aromatic hydrocarbons (PAHs) at PAH-contaminated sites. Ambio. 2007;36(6):475–85. doi: 10.1579/0044-7447(2007)36[475:sfatho]2.0.co;2.

53. Arlt VM. 3-Nitrobenzanthrone, a potential human cancer hazard in diesel exhaust and urban air pollution: a review of the evidence. Mutagenesis. 2005;20(6):399–410. doi: 10.1093/mutage/gei057.

54. Conney AH. Induction of microsomal enzymes by foreign chemicals and carcinogenesis by polycyclic aromatic hydrocarbons: GHA Clowes Memorial Lecture. Cancer Res. 1982;42(12):4875–917. PMID: 6814745

55. Shimada T, Fujii-Kuriyama Y. Metabolic activation of polycyclic aromatic hydrocarbons to carcinogens by cytochromes P450 1A1 and 1B1. Cancer Sci. 2004;95(1):1–6. doi: 10.1111/j.1349-7006.2004.tb03162.x.

56. Nebert DW, Dalton TP, Okey AB, Gonzalez FJ. Role of aryl hydrocarbon receptor-mediated induction of the CYP1 enzymes in environmental toxicity and cancer. J Biol Chem. 2004;279(23):23847–50. doi: 10.1074/jbc.R400004200.

57. Penning TM. Genotoxicity of ortho-quinones: reactive oxygen species versus covalent modification. Toxicol Res. 2017;6(6):740–54. doi: 10.1039/C7TX00223H.

58. Libalova H, Krckova S, Uhlirova K, Milcova A, Schmuczerova J, Ciganek M et al. Genotoxicity but not the AhR-mediated activity of PAHs is inhibited by other components of complex mixtures of ambient air pollutants. Toxicol Lett. 2014;225(3):350–7. doi: 10.1016/j.toxlet.2014.01.028.

59. Li X, Feng Y, Deng H, Zhang W, Kuang D, Deng Q et al. The dose-response decrease in heart rate variability: any association with the metabolites of polycyclic aromatic hydrocarbons in coke oven workers? PLOS One. 2012;7(9):e44562. doi: 10.1371/journal.pone.0044562.

60. Piekarska K. Mutagenicity of airborne particulates assessed by salmonella assay and the SOS chromotest in Wroclaw, Poland. J Air Waste Manag Assoc. 2010;60(8):993–1001. doi: 10.3155/1047-3289.60.8.993.

61. Kim KH, Jahan SA, Kabir E, Brown RJ. A review of airborne polycyclic aromatic hydrocarbons (PAHs) and their human health effects. Environ Int. 2013;60:71–80. doi: 10.1016/j.envint.2013.07.019.

62. Shen H, Huang Y, Wang R, Zhu D, Li W, Shen G et al. Global atmospheric emissions of polycyclic aromatic hydrocarbons from 1960 to 2008 and future predictions. Environ Sci Technol. 2013;47(12):6415–24. doi: 10.1021/es400857z.

63. Diesel and gasoline engine exhausts and some nitroarenes. Lyon: International Agency for Research on Cancer; 2014 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans No. 105; https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono105.pdf, accessed 12 October 2021).

64. Outdoor air pollution. Lyon: International Agency for Research on Cancer; 2016 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans No. 109; https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Outdoor-Air-Pollution-2015, accessed 12 October 2021).

65. Westphal GA, Krahl J, Munack A, Rosenkranz N, Schroder O, Schaak J et al. Combustion of hydrotreated vegetable oil and jatropha methyl ester in a heavy duty engine: emissions and bacterial mutagenicity. Environ Sci Technol. 2013;47(11):6038–46. doi: 10.1021/es400518d.

66. Andre V, Barraud C, Capron D, Preterre D, Keravec V, Vendeville C et al. Comparative mutagenicity and genotoxicity of particles and aerosols emitted by the combustion of standard vs. rapeseed methyl ester supplemented bio-diesel fuels: impact of after treatment devices: oxidation catalyst and particulate filter. Mutat Res Genet Toxicol Environ Mutagen. 2015;777:33–42. doi: 10.1016/j.mrgentox.2014.11.007.

67. Douki T, Corbiere C, Preterre D, Martin PJ, Lecureur V, Andre V et al. Comparative study of diesel and biodiesel exhausts on lung oxidative stress and genotoxicity in rats. Environ Pollut. 2018;235:514–24. doi: 10.1016/j.envpol.2017.12.077.

68. Cervena T, Rossnerova A, Sikorova J, Beranek V, Vojtisek-Lom M, Ciganek M et al. DNA damage potential of engine emissions measured in vitro by micronucleus test in human bronchial epithelial cells. Basic Clin Pharmacol Toxicol. 2017;121(suppl 3):102–8. doi: 10.1111/bcpt.12693.

69. Kowalska M, Wegierek-Ciuk A, Brzoska K, Wojewodzka M, Meczynska-Wielgosz S, Gromadzka-Ostrowska J et al. Genotoxic potential of diesel exhaust particles from the combustion of first- and second-generation biodiesel fuels: the FuelHealth project. Environ Sci Pollut Res Int. 2017;24(31):24223–34. doi: 10.1007/s11356-017-9995-0.

70. Danielsen PH, Moller P, Jensen KA, Sharma AK, Wallin H, Bossi R et al. Oxidative stress, DNA damage, and inflammation induced by ambient air and wood smoke particulate matter in human A549 and THP-1 cell lines. Chem Res Toxicol. 2011;24(2):168–84. doi: 10.1021/tx100407m.

71. Velali E, Papachristou E, Pantazaki A, Besis A, Samara C, Labrianidis C et al. In vitro cellular toxicity induced by extractable organic fractions of particles exhausted from urban combustion sources: role of PAHs. Environ Pollut. 2018;243(Pt B):1166–76. doi: 10.1016/j.envpol.2018.09.075.

72. Strandell M, Zakrisson S, Alsberg T, Westerholm R, Winquist L, Rannug U. Chemical analysis and biological testing of a polar fraction of ambient air, diesel engine, and gasoline engine particulate extracts. Environ Health Perspect. 1994;102(suppl 4):85–92. doi: 10.1289/ehp.94102s485.

73. DeMarini DM, Brooks LR, Warren SH, Kobayashi T, Gilmour MI, Singh P. Bioassay-directed fractionation and salmonella mutagenicity of automobile and forklift diesel exhaust particles. Environ Health Perspect. 2004;112(8):814–19. doi: 10.1289/ehp.6578.

74. Mutlu E, Warren SH, Matthews PP, King C, Linak WP, Kooter IM et al. Bioassay-directed fractionation and subfractionation for mutagenicity and chemical analysis of diesel exhaust particles. Environ Mol Mutagen. 2013;54(9):719–36. doi: 10.1002/em.21812.

75. Umbuzeiro GA, Franco A, Martins MH, Kummrow F, Carvalho L, Schmeiser HH et al. Mutagenicity and DNA adduct formation of PAH, nitro-PAH, and oxy-PAH fractions of atmospheric particulate matter from São Paulo, Brazil. Mutat Res. 2008;652(1):72–80. doi: 10.1016/j.mrgentox.2007.12.007.

76. Nie J, Beyea J, Bonner MR, Han D, Vena JE, Rogerson P et al. Exposure to traffic emissions throughout life and risk of breast cancer: the Western New York Exposures and Breast Cancer (WEB) study. Cancer Causes Control. 2007;18(9):947–55. doi: 10.1007/s10552-007-9036-2.

77. Mordukhovich I, Beyea J, Herring AH, Hatch M, Stellman SD, Teitelbaum SL et al. Vehicular traffic-related polycyclic aromatic hydrocarbon exposure and breast cancer incidence: the Long Island Breast Cancer Study Project (LIBCSP). Environ Health Perspect. 2016;124(1):30–8. doi: 10.1289/ehp.1307736.

78. Heck JE, Park AS, Qiu J, Cockburn M, Ritz B. An exploratory study of ambient air toxics exposure in pregnancy and the risk of neuroblastoma in offspring. Environ Res. 2013;127:1–6. doi: 10.1016/j.envres.2013.09.002.

79. Heck JE, Park AS, Qiu J, Cockburn M, Ritz B. Risk of leukemia in relation to exposure to ambient air toxics in pregnancy and early childhood. Int J Hyg Environ Health. 2014;217(6):662–8. doi: 10.1016/j.ijheh.2013.12.003.

80. Heck JE, Park AS, Qiu J, Cockburn M, Ritz B. Retinoblastoma and ambient exposure to air toxics in the perinatal period. J Expo Sci Environ Epidemiol. 2015;25(2):182–6. doi: 10.1038/jes.2013.84.

81. von Ehrenstein OS, Heck JE, Park AS, Cockburn M, Escobedo L, Ritz B. In utero and early-life exposure to ambient air toxics and childhood brain tumors: a population-based case–control study in California, USA. Environ Health Perspect. 2016;124(7):1093–9. doi: 10.1289/ehp.1408582.

82. Symanski E, Tee Lewis PG, Chen TY, Chan W, Lai D, Ma X. Air toxics and early childhood acute lymphocytic leukemia in Texas: a population based case control study. Environ Health. 2016;15(1):70. doi: 10.1186/s12940-016-0154-8.

83. Vena JE. Lung cancer incidence and air pollution in Erie County, New York. Arch Environ Health. 1983;38(4):229–36. doi: 10.1080/00039896.1983.10545808.

84. Armstrong B, Hutchinson E, Unwin J, Fletcher T. Lung cancer risk after exposure to polycyclic aromatic hydrocarbons: a review and meta-analysis. Environ Health Perspect. 2004;112(9):970–8. doi: 10.1289/ehp.6895.

85. Bosetti C, Boffetta P, La Vecchia C. Occupational exposures to polycyclic aromatic hydrocarbons, and respiratory and urinary tract cancers: a quantitative review to 2005. Ann Oncol. 2007;18(3):431–46. doi: 10.1093/annonc/mdl172.

86. Rota M, Bosetti C, Boccia S, Boffetta P, La Vecchia C. Occupational exposures to polycyclic aromatic hydrocarbons and respiratory and urinary tract cancers: an updated systematic review and a meta-analysis to 2014. Arch Toxicol. 2014;88(8):1479–90. doi: 10.1007/s00204-014-1296-5.

87. Singh A, Kamal R, Ahamed I, Wagh M, Bihari V, Sathian B et al. PAH exposure-associated lung cancer: an updated meta-analysis. Occup Med. 2018;68(4):255–61. doi: 10.1093/occmed/kqy049.

88. Parada H Jr, Steck SE, Bradshaw PT, Engel LS, Conway K, Teitelbaum SL et al. Grilled, barbecued, and smoked meat intake and survival following breast cancer. J Natl Cancer Inst. 2017;109(6):djw299. doi: 10.1093/jnci/djw299.

89. Terry PD, Rohan TE. Cigarette smoking and the risk of breast cancer in women: a review of the literature. Cancer Epidemiol Biomarkers Prev. 2002;11(10 Pt 1):953–71. PMID: 12376493.

90. Parikh PV, Wei Y. PAHs and $PM_{2.5}$ emissions and female breast cancer incidence in metro Atlanta and rural Georgia. Int J Environ Health Res. 2016;26(4):458–66. doi: 10.1080/09603123.2016.1161178.

91. Large C, Wei Y. Geographic variations in female breast cancer incidence in relation to ambient air emissions of polycyclic aromatic hydrocarbons. Environ Sci Pollut Res Int. 2017;24(21):17874–80. doi: 10.1007/s11356-017-9395-5.

92. Stults WP, Wei Y. Ambient air emissions of polycyclic aromatic hydrocarbons and female breast cancer incidence in US. Med Oncol. 2018;35(6):88. doi: 10.1007/s12032-018-1150-3.

93. Agha MM, Williams JI, Marrett L, To T, Zipursky A, Dodds L. Congenital abnormalities and childhood cancer. Cancer. 2005;103(9):1939–48. doi: 10.1002/cncr.20985.

94. Shrestha A, Ritz B, Wilhelm M, Qiu J, Cockburn M, Heck JE. Prenatal exposure to air toxics and risk of Wilms' tumor in 0- to 5-year-old children. J Occup Environ Med. 2014;56(6):573–8. doi: 10.1097/JOM.0000000000000167.

95. Armstrong B, Hutchinson E, Fletcher T. Cancer risk following exposure to polycyclic aromatic hydrocarbons (PAHs): a meta-analysis. Bootle: HSE Books; 2003 (Research report 3; https://www.hse.gov.uk/research/rrpdf/rr068.pdf, accessed 12 October 2021).

96. Castaño-Vinyals G, Cantor KP, Malats N, Tardon A, Garcia-Closas R, Serra C et al. Air pollution and risk of urinary bladder cancer in a case–control study in Spain. Occup Environ Med. 2008;65(1):56–60. doi: 10.1136/oem.2007.034348.

97. Scheurer ME, Danysh HE, Follen M, Lupo PJ. Association of traffic-related hazardous air pollutants and cervical dysplasia in an urban multiethnic population: a cross-sectional study. Environ Health. 2014;13(1):52. doi: 10.1186/1476-069X-13-52.

98. Matsumoto Y, Sakai S, Kato T, Nakajima T, Satoh H. Long-term trends of particulate mutagenic activity in the atmosphere of Sapporo. 1. Determination of mutagenic activity by the conventional tester strains TA98 and TA100 during an 18-year period (1974–1992). Environ Sci Technol. 1998;32(18):2665–71.

99. European Food Safety Agency. Polycyclic aromatic hydrocarbons in food: scientific opinion of the Panel on Contaminants in the Food Chain. EFSA J. 2008;724:1–114. doi: https://doi.org/10.2903/j.efsa.2008.724

100. Development of a relative potency factor (RPF) approach for polycyclic aromatic hydrocarbon (PAH) mixtures: in support of summary information on the Integrated Risk Information System (IRIS). Washington (DC): United States Environmental Protection Agency; 2010 (EPA/635/R-08/012A; https://www.federalregister.gov/documents/2010/02/26/2010-4082/development-of-a-relative-potency-factor-rpf-approach-for-polycyclic-aromatic-hydrocarbon-pah, accessed 12 October 2021).

101. Kortenkamp A, Backhaus T, Faust M. State of the art report on mixture toxicity: final report. Brussels: European Commission; 2009 (https://ec.europa.eu/environment/chemicals/effects/pdf/report_mixture_toxicity.pdf, accessed 12 October 2021).

102. Directive 2004/107/EC of the European Parliament and of the Council of 15 December 2004 relating to arsenic, cadmium, mercury, nickel and polycyclic aromatic hydrocarbons in ambient air. OJ. 2005;L23:3–16 (https://eur-lex.europa.eu/eli/dir/2004/107/oj, accessed 12 October 2021).

103. Pott F, Heinrich U. Relative significance of different hydrocarbons for the carcinogenic potency of emissions from various incomplete combustion processes. IARC Sci Publ. 1990;104:288–97. PMID: 1699890.

104. Pufulete M, Battershill J, Boobis A, Fielder R. Approaches to carcinogenic risk assessment for polycyclic aromatic hydrocarbons: a United Kingdom perspective. Regul Toxicol Pharmacol. 2004;40(1):54–66. doi: 10.1016/j.yrtph.2004.04.007.

105. EPA Risk Assessment Forum Technical Panel. Supplementary guidance for conducting health risk assessment of chemical mixtures. Washington (DC): United States Environmental Protection Agency; 2000 (EPA/630/R-00/002; https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=20533, accessed 12 October 2021).

106. Jia Y, Stone D, Wang W, Schrlau J, Tao S, Simonich SL. Estimated reduction in cancer risk due to PAH exposures if source control measures during the 2008 Beijing Olympics were sustained. Environ Health Perspect. 2011;119(6):815–20. doi: 10.1289/ehp.1003100.

107. Layshock J, Simonich SM, Anderson KA. Effect of dibenzopyrene measurement on assessing air quality in Beijing air and possible implications for human health. J Environ Monit. 2010;12(12):2290–8. doi: 10.1039/c0em00057d.

108. Lim H, Mattsson Å, Jarvis IW, Bergvall C, Bottai M, Morales DA et al. Detection of benz[j]aceanthrylene in urban air and evaluation of its genotoxic potential. Environ Sci Technol. 2015;49(5):3101–9. doi: 10.1021/es505458g.

109. Menichini E, Merli F. Dibenzopyrenes, other PAHs with molecular weight 302, and selected carcinogenic PAHs seldom determined: identification and one-year quantification in urban air. Int J Environ Anal Chem. 2012;92(14):1609–25. doi: https://doi.org/10.1080/03067319.2011.554979.

110. Jarvis IW, Dreij K, Mattsson A, Jernstrom B, Stenius U. Interactions between PAHs in complex mixtures and implications for cancer risk assessment. Toxicology. 2014;321:27–39. doi: 10.1016/j.tox.2014.03.012.

111. Flowers L, Rieth SH, Cogliano VJ, Foureman GL, Hertzberg R, Hofmann EL et al. Health assessment of polycyclic aromatic hydrocarbon mixtures: current practices and future directions. Polycycl Aromat Compd. 2002;22(3–4):811–21. doi: 10.1080/10406630290103960.

112. Albert RE. Comparative carcinogenic potencies of particulates from diesel engine exhausts, coke oven emissions, roofing tar aerosols and cigarette smoke. Environ Health Perspect. 1983;47:339–41. doi: 10.1289/ehp.8347339.

113. Lewtas J. Development of a comparative potency method for cancer risk assessment of complex mixtures using short-term in vivo and in vitro bioassays. Toxicol Ind Health. 1985;1(4):193–203. doi: 10.1177/074823378500100412.

114. Dreij K, Mattsson Å, Jarvis IWH, Lim H, Hurkmans J, Gustafsson J et al. Cancer risk assessment of airborne PAHs based on in vitro mixture potency factors. Environ Sci Technol. 2017;51(15):8805–14. doi: 10.1021/acs.est.7b02963.

115. Jarvis IW, Bergvall C, Bottai M, Westerholm R, Stenius U, Dreij K. Persistent activation of DNA damage signaling in response to complex mixtures of PAHs in air PM. Toxicol Appl Pharmacol. 2013;266(3):408–18. doi: 10.1016/j.taap.2012.11.026.

116. Audebert M, Zeman F, Beaudoin R, Pery A, Cravedi JP. Comparative potency approach based on H2AX assay for estimating the genotoxicity of PAHs. Toxicol Appl Pharmacol. 2012;260(1):58–64. doi: 10.1016/j.taap.2012.01.022.

117. Khoury L, Zalko D, Audebert M. Validation of high-throughput genotoxicity assay screening using gH2AX in-cell western assay on HepG2 cells. Environ Mol Mutagen. 2013;54(9):737–46. doi: 10.1002/em.21817.

118. Tsamou M, Jennen DG, Claessen SM, Magkoufopoulou C, Kleinjans JC, van Delft JH. Performance of in vitro gamma H2AX assay in HepG2 cells to predict in vivo genotoxicity. Mutagenesis. 2012;27(6):645–52. doi: 10.1093/mutage/ges030.

119. Lung cancer risk factors: outdoor air pollution [website]. Oxford: Cancer Research United Kingdom; 2021 (http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/risk-factors, accessed 25 August 2020).

120. Nyberg F, Gustavsson P, Järup L, Bellander T, Berglind N, Jakobsson R et al. Urban air pollution and lung cancer in Stockholm. Epidemiology. 2000;11(5):487–95. doi: 10.1097/00001648-200009000-00002.

121. Brook RD, Rajagopalan S, Pope CA 3rd, Brook JR, Bhatnagar A, Diez-Roux AV et al. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. Circulation. 2010;121(21):2331–78. doi: 10.1161/CIR.0b013e3181dbece1.

122. Burnett R, Chen H, Szyszkowicz M, Fann N, Hubbell B, Pope CA 3rd et al. Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. Proc Natl Acad Sci U S A. 2018;115(38):9592–7. doi: 10.1073/pnas.1803222115.

123. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1659–724. doi: 10.1016/S0140-6736(16)31679-8.

124. Kelly FJ, Fussell JC. Air pollution and airway disease. Clin Exp Allergy. 2011;41(8):1059–71. doi: 10.1111/j.1365-2222.2011.03776.x.

125. Loomis D, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L et al. The carcinogenicity of outdoor air pollution. Lancet Oncol. 2013;14(13):1262–3. doi: 10.1016/s1470-2045(13)70487-x.

126. Wen CP, Gao W. $PM_{2.5}$: an important cause for chronic obstructive pulmonary disease? Lancet Planet Health. 2018;2(3):e105–6. doi: 10.1016/S2542-5196(18)30025-1.

127. Låg M, Øvrevik J, Refsnes M, Holme JA. Potential role of polycyclic aromatic hydrocarbons in air pollution-induced non-malignant respiratory diseases. Respir Res. 2020;21:299. doi: 10.1186/s12931-020-01563-1.

128. Holme JA, Brinchmann BC, Le Ferrec E, Lagadic-Gossmann D, Ovrevik J. Combustion particle-induced changes in calcium homeostasis: a contributing factor to vascular disease? Cardiovasc Toxicol. 2019;19(3):198–209. doi: 10.1007/s12012-019-09518-9.

129. Ovrevik J, Refsnes M, Lag M, Holme JA, Schwarze PE. Activation of proinflammatory responses in cells of the airway mucosa by particulate matter: oxidant- and non-oxidant-mediated triggering mechanisms. Biomolecules. 2015;5(3):1399–440. doi: 10.3390/biom5031399.

130. Ovrevik J, Refsnes M, Lag M, Brinchmann BC, Schwarze PE, Holme JA. Triggering mechanisms and inflammatory effects of combustion exhaust particles with implication for carcinogenesis. Basic Clin Pharmacol Toxicol. 2017;121(suppl 3):55–62. doi: 10.1111/bcpt.12693.

131. Esser C, Rannug A. The aryl hydrocarbon receptor in barrier organ physiology, immunology, and toxicology. Pharmacol Rev. 2015;67(2):259–79. doi: 10.1124/pr.114.009001.

132. Stockinger B, Di Meglio P, Gialitakis M, Duarte JH. The aryl hydrocarbon receptor: multitasking in the immune system. Ann Rev Immunol. 2014;32:403–32. doi: 10.1146/annurev-immunol-032713-120245.

133. Miller KP, Ramos KS. Impact of cellular metabolism on the biological effects of benzo[a]pyrene and related hydrocarbons. Drug Metab Rev. 2001;33(1):1–35. doi: 10.1081/dmr-100000138.

134. Tian Y, Rabson AB, Gallo MA. Ah receptor and NF-kappaB interactions: mechanisms and physiological implications. Chem Biol Interact. 2002;141(1–2):97–115. doi: 10.1016/s0009-2797(02)00068-6.

135. Vogel CF, Matsumura F. A new cross-talk between the aryl hydrocarbon receptor and RelB, a member of the NF-kappaB family. Biochem Pharmacol. 2009;77(4):734–45. doi: 10.1016/j.bcp.2008.09.036.

136. Larigot L, Juricek L, Dairou J, Coumoul X. AhR signaling pathways and regulatory functions. Biochim Open. 2018;7:1–9. doi: 10.1016/j.biopen.2018.05.001.

137. Matsumura F. The significance of the nongenomic pathway in mediating inflammatory signaling of the dioxin-activated Ah receptor to cause toxic effects. Biochem Pharmacol. 2009;77(4):608–26. doi: 10.1016/j.bcp.2008.10.013.

138. Brinchmann BC, Le Ferrec E, Bisson WH, Podechard N, Huitfeldt HS, Gallais I et al. Evidence of selective activation of aryl hydrocarbon receptor nongenomic calcium signaling by pyrene. Biochem Pharmacol. 2018;158:1–12. doi: 10.1016/j.bcp.2018.09.023.

139. Barisione G, Baroffio M, Crimi E, Brusasco V. Beta-adrenergic agonists. Pharmaceuticals. 2010;3(4):1016–44. doi: 10.3390/ph3041016.

140. Mayati A, Le Ferrec E, Lagadic-Gossmann D, Fardel O. Aryl hydrocarbon receptor-independent up-regulation of intracellular calcium concentration by environmental polycyclic aromatic hydrocarbons in human endothelial HMEC-1 cells. Environ Toxicol. 2012;27(9):556–62. doi: 10.1002/tox.20675.

141. Mayati A, Levoin N, Paris H, N'Diaye M, Courtois A, Uriac P et al. Induction of intracellular calcium concentration by environmental benzo(a)pyrene involves a beta2-adrenergic receptor/adenylyl cyclase/Epac-1/inositol 1,4,5-trisphosphate pathway in endothelial cells. J Biol Chem. 2012;287(6):4041–52. doi: 10.1074/jbc.M111.319970.

142. Mayati A, Podechard N, Rineau M, Sparfel L, Lagadic-Gossmann D, Fardel O et al. Benzo(a)pyrene triggers desensitization of beta2-adrenergic pathway. Sci Rep. 2017;7(1):3262. doi: 10.1038/s41598-017-03646-4.

143. Li N, Wang M, Bramble LA, Schmitz DA, Schauer JJ, Sioutas C et al. The adjuvant effect of ambient particulate matter is closely reflected by the particulate oxidant potential. Environ Health Perspect. 2009;117(7):1116–23. doi: 10.1289/ehp.0800319

144. Karimi P, Peters KO, Bidad K, Strickland PT. Polycyclic aromatic hydrocarbons and childhood asthma. Eur J Epidemiol. 2015;30(2):91–101. doi: 10.1007/s10654-015-9988-6.

145. Podechard N, Lecureur V, Le Ferrec E, Guenon I, Sparfel L, Gilot D et al. Interleukin-8 induction by the environmental contaminant benzo(a)pyrene is aryl hydrocarbon receptor-dependent and leads to lung inflammation. Toxicol Lett. 2008;177(2):130–7. doi: 10.1016/j.toxlet.2008.01.006.

146. Bommel H, Haake M, Luft P, Horejs-Hoeck J, Hein H, Bartels J et al. The diesel exhaust component pyrene induces expression of IL-8 but not of eotaxin. Int Immunopharmacol. 2003;3(10–11):1371–9. doi: 10.1016/S1567-5769(03)00135-8.

147. Pei XH, Nakanishi Y, Inoue H, Takayama K, Bai F, Hara N. Polycyclic aromatic hydrocarbons induce IL-8 expression through nuclear factor kappaB activation in A549 cell line. Cytokine. 2002;19(5):236–41. PMID: 12393170.

148. Ovrevik J, Arlt VM, Oya E, Nagy E, Mollerup S, Phillips DH et al. Differential effects of nitro-PAHs and amino-PAHs on cytokine and chemokine responses in human bronchial epithelial BEAS-2B cells. Toxicol Appl Pharmacol. 2010;242(3):270–80. doi: 10.1016/j.taap.2009.10.017.

149. Fueldner C, Kohlschmidt J, Riemschneider S, Schulze F, Zoldan K, Esser C et al. Benzo(a)pyrene attenuates the pattern-recognition-receptor induced proinflammatory phenotype of murine macrophages by inducing IL-10 expression in an aryl hydrocarbon receptor-dependent manner. Toxicology. 2018;409:80–90. doi: 10.1016/j.tox.2018.07.011.

150. Cho YS, Moon HB. The role of oxidative stress in the pathogenesis of asthma. Allergy Asthma Immunol Res. 2010;2(3):183–7. doi: 10.4168/aair.2010.2.3.183.

151. Yang L, Wang WC, Lung SC, Sun Z, Chen C, Chen JK et al. Polycyclic aromatic hydrocarbons are associated with increased risk of chronic obstructive pulmonary disease during haze events in China. Sci Total Environ. 2017;574:1649–58. doi: 10.1016/j.scitotenv.2016.08.211.

152. Riedl MA, Nel AE. Importance of oxidative stress in the pathogenesis and treatment of asthma. Curr Opin Allergy Clin Immunol. 2008;8(1):49–56. doi: 10.1097/ACI.0b013e3282f3d913.

153. Brandt EB, Kovacic MB, Lee GB, Gibson AM, Acciani TH, Le Cras TD et al. Diesel exhaust particle induction of IL-17A contributes to severe asthma. J Allergy Clin Immunol. 2013;132(5):1194–204.e2. doi: 10.1016/j.jaci.2013.06.048.

154. van Voorhis M, Knopp S, Julliard W, Fechner JH, Zhang X, Schauer JJ et al. Exposure to atmospheric particulate matter enhances Th17 polarization through the aryl hydrocarbon receptor. PLOS One. 2013;8(12):e82545. doi: 10.1371/journal.pone.0082545.

155. Brugha R, Grigg J. Urban air pollution and respiratory infections. Paediatr Respir Rev. 2014;15(2):194–9. doi: 10.1016/j.prrv.2014.03.001.

156. Nemmar A, Holme JA, Rosas I, Schwarze PE, Alfaro-Moreno E. Recent advances in particulate matter and nanoparticle toxicology: a review of the in vivo and in vitro studies. BioMed Res Int. 2013;279371. doi: 10.1155/2013/279371.

157. Hauptmann M, Schaible UE. Linking microbiota and respiratory disease. FEBS Lett. 2016;590(21):3721–38. doi: 10.1002/1873-3468.

158. Head JL, Lawrence BP. The aryl hydrocarbon receptor is a modulator of anti-viral immunity. Biochem Pharmacol. 2009;77(4):642–53. doi: 10.1016/j.bcp.2008.10.031.

159. Vorderstrasse BA, Bohn AA, Lawrence BP. Examining the relationship between impaired host resistance and altered immune function in mice treated with TCDD. Toxicology. 2003;188(1):15–28. doi: 10.1016/s0300-483x(02)00749-7.

160. Wang T, Wyrick KL, Pecka MR, Wills TB, Vorderstrasse BA. Mechanistic exploration of AhR-mediated host protection against *Streptococcus pneumoniae* infection. Int Immunopharmacol. 2012;13(4):490–8. doi: 10.1016/j.intimp.2012.05.008.

161. Robinson RK, Birrell MA, Adcock JJ, Wortley MA, Dubuis ED, Chen S et al. Mechanistic link between diesel exhaust particles and respiratory reflexes. J Allergy Clin Immunol. 2018;141(3):1074–84. doi: 10.1016/j.jaci.2017.04.038.

162. Al-Daghri NM, Alokail MS, Abd-Alrahman SH, Draz HM, Yakout SM, Clerici M. Polycyclic aromatic hydrocarbon exposure and pediatric asthma in children: a case–control study. Environ Health. 2013;12:1. doi: 10.1186/1476-069X-12-1.

163. Wang IJ, Karmaus WJ, Yang CC. Polycyclic aromatic hydrocarbons exposure, oxidative stress, and asthma in children. Int Arch Occup Environ Health. 2017;90(3):297–303. doi: 10.1007/s00420-017-1198-y.

164. Smargiassi A, Goldberg MS, Wheeler AJ, Plante C, Valois MF, Mallach G et al. Associations between personal exposure to air pollutants and lung function tests and cardiovascular indices among children with asthma living near an industrial complex and petroleum refineries. Environ Res. 2014;132:38–45. doi: 10.1016/j.envres.2014.03.030.

165. Miller RL, Garfinkel R, Lendor C, Hoepner L, Li Z, Romanoff L et al. Polycyclic aromatic hydrocarbon metabolite levels and pediatric allergy and asthma in an inner-city cohort. Pediatr Allergy Immunol. 2010;21(2 Pt 1):260–7. doi: 10.1111/j.1399-3038.2009.00980.x.

166. Padula AM, Balmes JR, Eisen EA, Mann J, Noth EM, Lurmann FW et al. Ambient polycyclic aromatic hydrocarbons and pulmonary function in children. J Expo Sci Environ Epidemiol. 2015;25(3):295–302. doi: 10.1016/j.envres.2014.03.030.

167. Jedrychowski W, Galas A, Pac A, Flak E, Camman D, Rauh V et al. Prenatal ambient air exposure to polycyclic aromatic hydrocarbons and the occurrence of respiratory symptoms over the first year of life. Eur J Epidemiol. 2005;20(9):775–82. doi: 10.1007/s10654-005-1048-1.

168. Jedrychowski WA, Perera FP, Maugeri U, Mrozek-Budzyn D, Mroz E, Klimaszewska-Rembiasz M et al. Intrauterine exposure to polycyclic aromatic hydrocarbons, fine particulate matter and early wheeze: prospective birth cohort study in 4-year olds. Pediatr Allergy Immunol. 2010;21(4 Pt 2):e723–32. doi: 10.1111/j.1399-3038.2010.01034.x.

169. Perera F, Tang WY, Herbstman J, Tang D, Levin L, Miller R et al. Relation of DNA methylation of 5'-CpG island of ACSL3 to transplacental exposure to airborne polycyclic aromatic hydrocarbons and childhood asthma. PLOS One. 2009;4(2):e4488. doi: 10.1371/journal.pone.0004488.

170. Klingbeil EC, Hew KM, Nygaard UC, Nadeau KC. Polycyclic aromatic hydrocarbons, tobacco smoke, and epigenetic remodeling in asthma. Immunol Res. 2014;58(2–3):369–73. doi: 10.1007/s12026-014-8508-1.

171. Jedrychowski WA, Perera FP, Majewska R, Camman D, Spengler JD, Mroz E et al. Separate and joint effects of transplacental and postnatal inhalatory exposure to polycyclic aromatic hydrocarbons: prospective birth cohort study on wheezing events. Pediatr Pulmonol. 2014;49(2):162–72. doi: 10.1002/ppul.22923.

172. Jedrychowski WA, Perera FP, Camann D, Spengler J, Butscher M, Mroz E et al. Prenatal exposure to polycyclic aromatic hydrocarbons and cognitive dysfunction in children. Environ Sci Pollut Res Int. 2015;22(5):3631–9. doi: 10.1007/s11356-014-3627-8.

173. Jedrychowski WA, Perera FP, Maugeri U, Majewska R, Mroz E, Flak E et al. Long term effects of prenatal and postnatal airborne PAH exposures on ventilatory lung function of non-asthmatic preadolescent children: prospective birth cohort study in Krakow. Sci Total Environ. 2015;502:502–9. doi: 10.1016/j.scitotenv.2014.09.051.

174. Jung KH, Yan B, Moors K, Chillrud SN, Perzanowski MS, Whyatt RM et al. Repeated exposure to polycyclic aromatic hydrocarbons and asthma: effect of seroatopy. Ann Allergy Asthma Immunol. 2012;109(4):249–54. oi: 10.1016/j.anai.2012.07.019.

175. Cakmak S, Hebbern C, Cakmak JD, Dales RE. The influence of polycyclic aromatic hydrocarbons on lung function in a representative sample of the Canadian population. Environ Pollut. 2017;228:1–7. doi: 10.1016/j.envpol.2017.05.013.

176. Zhou Y, Sun H, Xie J, Song Y, Liu Y, Huang X et al. Urinary polycyclic aromatic hydrocarbon metabolites and altered lung function in Wuhan, China. Am J Respir Crit Care Med. 2016;193(8):835–46. doi: 10.1164/rccm.201412-2279OC.

177. Wang B, Li Z, Ma Y, Qiu X, Ren A. Association of polycyclic aromatic hydrocarbons in housewives' hair with hypertension. Chemosphere. 2016;153:315–21. doi: 10.1016/j.chemosphere.2016.03.067.

178. Zhang LP, Zhang X, Duan HW, Meng T, Niu Y, Huang CF et al. Long-term exposure to diesel engine exhaust induced lung function decline in a cross sectional study. Ind Health. 2017;55(1):13–26. doi: 10.2486/indhealth.2016-0031.

179. Burstyn I, Boffetta P, Heederik D, Partanen T, Kromhout H, Svane O et al. Mortality from obstructive lung diseases and exposure to polycyclic aromatic hydrocarbons among asphalt workers. Am J Epidemiol. 2003;158(5):468–78. doi: 10.1093/aje/kwg180.

180. Lee KK, Miller MR, Shah ASV. Air pollution and stroke. J Stroke. 2018;20(1):2–11. doi: 10.5853/jos.2017.02894.

181. Lelieveld J, Klingmuller K, Pozzer A, Poschl U, Fnais M, Daiber A et al. Cardiovascular disease burden from ambient air pollution in Europe reassessed using novel hazard ratio functions. Eur Heart J. 2019;40(20):1590–6. doi: 10.1093/eurheartj/ehz135.

182. Pope CA 3rd, Turner MC, Burnett RT, Jerrett M, Gapstur SM, Diver WR et al. Relationships between fine particulate air pollution, cardiometabolic disorders, and cardiovascular mortality. Circ Res. 2015;116(1):108–15. doi: 10.1161/CIRCRESAHA.116.305060.

183. Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Lancet. 2017;389(10082):1907–18. doi: 10.1016/S0140-6736(17)30505-6.

184. Carll AP, Hazari MS, Perez CM, Krantz QT, King CJ, Winsett DW et al. Whole and particle-free diesel exhausts differentially affect cardiac electrophysiology, blood pressure, and autonomic balance in heart failure-prone rats. Toxicol Sci. 2012;128(2):490–9. doi: 10.1093/toxsci/kfs162.

185. Kodavanti UP. Stretching the stress boundary: linking air pollution health effects to a neurohormonal stress response. Biochim Biophys Acta. 2016;1860(12):2880–90. doi: 10.1016/j.bbagen.2016.05.010.

186. Van Eeden S, Leipsic J, Paul Man SF, Sin DD. The relationship between lung inflammation and cardiovascular disease. Am J Respir Crit Care Med. 2012;186(1):11–16. doi: 10.1164/rccm.201203-0455PP.

187. Pope CA 3rd, Bhatnagar A, McCracken JP, Abplanalp W, Conklin DJ, O'Toole T. Exposure to fine particulate air pollution is associated with endothelial injury and systemic inflammation. Circ Res. 2016;119(11):1204–14. doi: 10.1161/CIRCRESAHA.116.309279.

188. Mills NL, Törnqvist H, Gonzalez MC, Vink E, Robinson SD, Soderberg S et al. Ischemic and thrombotic effects of dilute diesel-exhaust inhalation in men with coronary heart disease. N Engl J Med. 2007;357(11):1075–82. doi: 10.1056/NEJMoa066314.

189. Mills NL, Törnqvist H, Robinson SD, Gonzalez M, Darnley K, MacNee W et al. Diesel exhaust inhalation causes vascular dysfunction and impaired endogenous fibrinolysis. Circulation. 2005;112(25):3930–6. doi: 10.1161/CIRCULATIONAHA.105.588962.

190. Lucking AJ, Lundback M, Mills NL, Faratian D, Barath SL, Pourazar J et al. Diesel exhaust inhalation increases thrombus formation in man. Eur Heart J. 2008;29(24):3043–51. doi: 10.1093/eurheartj/ehn464.

191. Araujo JA, Barajas B, Kleinman M, Wang X, Bennett BJ, Gong KW et al. Ambient particulate pollutants in the ultrafine range promote early atherosclerosis and systemic oxidative stress. Circ Res. 2008;102(5):589–96. doi: 10.1161/CIRCRESAHA.107.164970.

192. Araujo JA, Nel AE. Particulate matter and atherosclerosis: role of particle size, composition and oxidative stress. Part Fibre Toxicol. 2009;6:24. doi: 10.1186/1743-8977-6-24.

193. Borm PJ, Robbins D, Haubold S, Kuhlbusch T, Fissan H, Donaldson K et al. The potential risks of nanomaterials: a review carried out for ECETOC. Part Fibre Toxicol. 2006;3:11. doi: 10.1186/1743-8977-3-11.

194. Scheer V, Kirchner U, Casati R, Vogt R, Philippin S, Wiedensohler A et al. Composition of semi-volatile particles from diesel exhaust. In: SAE 2005 World Congress & Exhibition, Detroit, 11–14 April 2005 (SAE Technical Paper 2005-01-0197). doi:10.4271/2005–01–0197.

195. Miller MR, Raftis JB, Langrish JP, McLean SG, Samutrtai P, Connell SP et al. Inhaled nanoparticles accumulate at sites of vascular disease. ACS Nano. 2017;11(5):4542–52. doi: 10.1021/acsnano.6b08551.

196. Keebaugh AJ, Sioutas C, Pakbin P, Schauer JJ, Mendez LB, Kleinman MT. Is atherosclerotic disease associated with organic components of ambient fine particles? Sci Total Environ. 2015;533:69–75. doi: 10.1016/j.scitotenv.2015.06.048.

197. Kawasaki S, Takizawa H, Takami K, Desaki M, Okazaki H, Kasama T et al. Benzene-extracted components are important for the major activity of diesel exhaust particles. Am J Respir Cell Mol Biol. 2001;24(4):419–26. doi: 10.1165/ajrcmb.24.4.4085.

198. Bonvallot V, Baeza-Squiban A, Baulig A, Brulant S, Boland S, Muzeau F et al. Organic compounds from diesel exhaust particles elicit a proinflammatory response in human airway epithelial cells and induce cytochrome p450 1A1 expression. Am J Respir Cell Mol Biol. 2001;25(4):515–21. doi: 10.1165/ajrcmb.25.4.4515.

199. Totlandsdal AI, Herseth JI, Bolling AK, Kubatova A, Braun A, Cochran RE et al. Differential effects of the particle core and organic extract of diesel exhaust particles. Toxicol Lett. 2012;208(3):262–8. doi: 10.1016/j.toxlet.2011.10.025.

200. Ma JY, Ma JK. The dual effect of the particulate and organic components of diesel exhaust particles on the alteration of pulmonary immune/inflammatory responses and metabolic enzymes. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 2002;20(2):117–47. doi: 10.1081/GNC-120016202.

201. Brinchmann BC, Skuland T, Rambol MH, Szoke K, Brinchmann JE, Gutleb AC et al. Lipophilic components of diesel exhaust particles induce pro-inflammatory responses in human endothelial cells through AhR dependent pathway(s). Part Fibre Toxicol. 2018;15(1):21. doi: 10.1186/s12989-018-0257-1.

202. Gutleb AC. Potential of in vitro methods for mechanistic studies of particulate matter-induced cardiopulmonary toxicity. Crit Rev Environ Sci Technol. 2011;41(22):1971–2002. https://doi.org/10.1080/10643389.2010.495641

203. Penn A, Murphy G, Barker S, Henk W, Penn L. Combustion-derived ultrafine particles transport organic toxicants to target respiratory cells. Environ Health Perspect. 2005;113(8):956–63. doi: 10.1289/ehp.7661.

204. Gerde P, Muggenburg BA, Lundborg M, Dahl AR. The rapid alveolar absorption of diesel soot-adsorbed benzo[a]pyrene: bioavailability, metabolism and dosimetry of an inhaled particle-borne carcinogen. Carcinogenesis. 2001;22(5):741–9. doi: 10.1093/carcin/22.5.741.

205. Holme JA, Brinchmann BC, Refsnes M, Låg M, Ovrevik J. Potential role of polycyclic aromatic hydrocarbons as mediators of cardiovascular effects from combustion particles. Environ Health. 2019;18(1):74. doi: 10.1186/s12940-019-0514-2.

206. Korashy HM, El-Kadi AO. The role of aryl hydrocarbon receptor in the pathogenesis of cardiovascular diseases. Drug Metab Rev. 2006;38(3):411–50. doi: 10.1080/03602530600632063.

207. Rifkind AB, Gannon M, Gross SS. Arachidonic acid metabolism by dioxin-induced cytochrome P-450: a new hypothesis on the role of P-450 in dioxin toxicity. Biochem Biophys Res Commun. 1990;172(3):1180–8. doi: 10.1016/0006-291x(90)91573-b.

208. Annas A, Brunstrom B, Brandt I, Brittebo EB. Induction of ethoxyresorufin *O*-deethylase (EROD) and endothelial activation of the heterocyclic amine Trp-P-1 in bird embryo hearts. Arch Toxicol. 1998;72(7):402–10. doi: 10.1007/s002040050520.

209. Quilley CP, Rifkind AB. Prostaglandin release by the chick embryo heart is increased by 2,3,7,8-tetrachlorodibenzo-p-dioxin and by other cytochrome P-448 inducers. Biochem Biophys Res Commun. 1986;136(2):582–9.

210. Aboutabl ME, Zordoky BN, El-Kadi AO. 3-Methylcholanthrene and benzo(a)pyrene modulate cardiac cytochrome P450 gene expression and arachidonic acid metabolism in male Sprague Dawley rats. Br J Pharmacol. 2009;158(7):1808–19. doi: 10.1111/j.1476-5381.2009.00461.x.

211. Huang L, Xi Z, Wang C, Zhang Y, Yang Z, Zhang S et al. Phenanthrene exposure induces cardiac hypertrophy via reducing miR-133a expression by DNA methylation. Sci Rep. 2016;6:20105. doi: 10.1038/srep20105.

212. Kopf PG, Huwe JK, Walker MK. Hypertension, cardiac hypertrophy, and impaired vascular relaxation induced by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin are associated with increased superoxide. Cardiovasc Toxicol. 2008;8(4):181–93. doi: 10.1007/s12012-008-9027-x.

213. Kerley-Hamilton JS, Trask HW, Ridley CJA, DuFour E, Lesseur C, Ringelberg CS et al. Inherent and benzo[a]pyrene-induced differential aryl hydrocarbon receptor signaling greatly affects life span, atherosclerosis, cardiac gene expression, and body and heart growth in mice. Toxicol Sci. 2012;126(2):391–404. doi: 10.1093/toxsci/kfs002.

214. Yang H, Zhou L, Wang Z, Roberts LJ 2nd, Lin X, Zhao Y et al. Overexpression of antioxidant enzymes in ApoE-deficient mice suppresses benzo(a)pyrene-accelerated atherosclerosis. Atherosclerosis. 2009;207(1):51–8. doi: 10.1016/j.atherosclerosis.2009.03.052.

215. Iwano S, Nukaya M, Saito T, Asanuma F, Kamataki T. A possible mechanism for atherosclerosis induced by polycyclic aromatic hydrocarbons. Biochem Biophys Res Commun. 2005;335(1):220–6. doi: 10.1016/j.bbrc.2005.07.062.

216. Pulliero A, Godschalk R, Andreassi MG, Curfs D, Van Schooten FJ, Izzotti A. Environmental carcinogens and mutational pathways in atherosclerosis. Int J Hyg Environ Health. 2015;218(3):293–312. doi: 10.1016/j.ijheh.2015.01.007.

217. Penn A. International Commission for Protection Against Environmental Mutagens and Carcinogens. ICPEMC Working Paper 7/1/1. Mutational events in the etiology of arteriosclerotic plaques. Mutat Res. 1990;239(3):149–62. doi: 10.1016/0165-1110(90)90003-t.

218. Zhang YJ, Weksler BB, Wang L, Schwartz J, Santella RM. Immunohistochemical detection of polycyclic aromatic hydrocarbon-DNA damage in human blood vessels of smokers and non-smokers. Atherosclerosis. 1998;140(2):325–31. doi: 10.1016/s0021-9150(98)00136-1.

219. Ou X, Ramos KS. Proliferative responses of quail aortic smooth muscle cells to benzo[a]pyrene: implications in PAH-induced atherogenesis. Toxicology. 1992;74(2–3):243–58. doi: 10.1016/0300-483x(92)90143-3.

220. Ramos KS, Parrish AR. Growth-related signaling as a target of toxic insult in vascular smooth muscle cells: implications in atherogenesis. Life Sci. 1995;57(7):627–35. doi: 10.1016/0024-3205(95)00314-v.

221. Ramos KS, Zhang Y, Sadhu DN, Chapkin RS. The induction of proliferative vascular smooth muscle cell phenotypes by benzo(a)pyrene is characterized by up-regulation of inositol phospholipid metabolism and c-Ha-ras gene expression. Arch Biochem Biophys. 1996;332(2):213–22. doi: 10.1006/abbi.1996.0335.

222. Curfs DMJ, Lutgens E, Gijbels MJJ, Kockx MM, Daemen MJAP, van Schooten FJ. Chronic exposure to the carcinogenic compound benzo[a]pyrene induces larger and phenotypically different atherosclerotic plaques in ApoE-knockout mice. Am J Pathol. 2004;164(1):101–8. doi: 10.1016/S0002-9440(10)63101-X.

223. Curfs DMJ, Knaapen AM, Pachen DMFA, Gijbels MJJ, Lutgens E, Smook MLF et al. Polycyclic aromatic hydrocarbons induce an inflammatory atherosclerotic plaque phenotype irrespective of their DNA binding properties. FASEB J. 2005;19(10):1290–2. doi: 10.1096/fj.04-2269fje.

224. Oesterling E, Toborek M, Hennig B. Benzo[a]pyrene induces intercellular adhesion molecule-1 through a caveolae and aryl hydrocarbon receptor mediated pathway. Toxicol Appl Pharmacol. 2008;232(2):309–16. doi: 10.1016/j.taap.2008.07.001.

225. Sandow SL, Haddock RE, Hill CE, Chadha PS, Kerr PM, Welsh DG et al. What's where and why at a vascular myoendothelial microdomain signalling complex. Clin Exp Pharmacol Physiol. 2009;36(1):67–76. doi: 10.1111/j.1440-1681.2008.05076.x.

226. Sandow SL, Senadheera S, Grayson TH, Welsh DG, Murphy TV. Calcium and endothelium-mediated vasodilator signaling. Adv Exp Med Biol. 2012;740:811–31. doi: 10.1007/978-94-007-2888-2_36.

227. Kelly FJ, Fussell JC. Linking ambient particulate matter pollution effects with oxidative biology and immune responses. Ann N Y Acad Sci. 2015;1340:84–94. doi: 10.1111/nyas.12720.

228. Barath S, Mills NL, Lundback M, Törnqvist H, Lucking AJ, Langrish JP et al. Impaired vascular function after exposure to diesel exhaust generated at urban transient running conditions. Part Fibre Toxicol. 2010;7:19. doi: 10.1186/1743-8977-7-19.

229. Mayati A, Le Ferrec E, Holme JA, Fardel O, Lagadic-Gossmann D, Ovrevik J. Calcium signaling and beta2-adrenergic receptors regulate 1-nitropyrene induced CXCL8 responses in BEAS-2B cells. Toxicol In Vitro. 2014;28(6):1153–7. doi: 10.1016/j.tiv.2014.05.012.

230. Brinchmann BC, Le Ferrec E, Podechard N, Lagadic-Gossmann D, Holme JA, Ovrevik J. Organic chemicals from diesel exhaust particles affects intracellular calcium, inflammation and β-adrenoceptors in endothelial cells. Toxicol Lett. 2018;302:18–27. doi: 10.1016/j.toxlet.2018.11.009.

231. Brinchmann BC, Le Ferrec E, Podechard N, Lagadic-Gossmann D, Shoji KF, Penna A et al. Lipophilic chemicals from diesel exhaust particles trigger calcium response in human endothelial cells via aryl hydrocarbon receptor non-genomic signalling. Int J Mol Sci. 2018;19(5):1429. doi: 10.3390/ijms19051429.

232. Chang CC, Hsu YH, Chou HC, Lee YG, Juan SH. 3-Methylcholanthrene/aryl-hydrocarbon receptor-mediated hypertension through eNOS inactivation. J Cell Physiol. 2017;232(5):1020–9. doi: 10.1002/jcp.25497.

233. Prins PA, Perati PR, Kon V, Guo Z, Ramesh A, Linton MF et al. Benzo[a]pyrene potentiates the pathogenesis of abdominal aortic aneurysms in apolipoprotein E knockout mice. Cell Physiol Biochem. 2012;29(1–2):121–30. doi: 10.1159/000337593.

234. Incardona JP, Collier TK, Scholz NL. Defects in cardiac function precede morphological abnormalities in fish embryos exposed to polycyclic aromatic hydrocarbons. Toxicol Appl Pharmacol. 2004;196(2):191–205. doi: 10.1016/j.taap.2003.11.026.

235. Vogel CFA, Sciullo E, Wong P, Kuzmicky P, Kado N, Matsumura F. Induction of proinflammatory cytokines and C-reactive protein in human macrophage cell line U937 exposed to air pollution particulates. Environ Health Perspect. 2005;113(11):1536–41. doi: 10.1289/ehp.8094.

236. Podechard N, Le Ferrec E, Rebillard A, Fardel O, Lecureur V. NPC1 repression contributes to lipid accumulation in human macrophages exposed to environmental aryl hydrocarbons. Cardiovasc Res. 2009;82(2):361–70. doi: 10.1093/cvr/cvp007.

237. Jules GE, Pratap S, Ramesh A, Hood DB. In utero exposure to benzo(a)pyrene predisposes offspring to cardiovascular dysfunction in later-life. Toxicology. 2012;295(1–3):56–67.

238. Zhang N. The role of endogenous aryl hydrocarbon receptor signaling in cardiovascular physiology. J Cardiovasc Dis Res. 2011;2(2):91–5. doi: 10.4103/0975-3583.83033.

239. Zhang H, Yao Y, Chen Y, Yue C, Chen J, Tong J et al. Crosstalk between AhR and wnt/β-catenin signal pathways in the cardiac developmental toxicity of $PM_{2.5}$ in zebrafish embryos. Toxicology. 2016;355–6:31–8. doi: 10.1016/j.tox.2016.05.014.

240. Yue C, Ji C, Zhang H, Zhang LW, Tong J, Jiang Y et al. Protective effects of folic acid on $PM_{2.5}$-induced cardiac developmental toxicity in zebrafish embryos by targeting AhR and Wnt/β-catenin signal pathways. Environ Toxicol. 2017;32(10):2316–22. doi: 10.1002/tox.22448.

241. Massarsky A, Prasad GL, Di Giulio RT. Total particulate matter from cigarette smoke disrupts vascular development in zebrafish brain (*Danio rerio*). Toxicol Appl Pharmacol. 2018;339:85–96. doi: 10.1016/j.taap.2017.12.003

242. Zhang Y, Wang C, Huang L, Chen R, Chen Y, Zuo Z. Low-level pyrene exposure causes cardiac toxicity in zebrafish (*Danio rerio*) embryos. Aquat Toxicol. 2012;114–15:119–24. doi: 10.1016/j.aquatox.2012.02.022.

243. Zhang Y, Huang L, Wang C, Gao D, Zuo Z. Phenanthrene exposure produces cardiac defects during embryo development of zebrafish (*Danio rerio*) through activation of MMP-9. Chemosphere. 2013;93(6):1168–75. doi: 10.1016/j.chemosphere.2013.06.056.

244. Ntziachristos L, Froines JR, Cho AK, Sioutas C. Relationship between redox activity and chemical speciation of size-fractionated particulate matter. Part Fibre Toxicol. 2007;4:5. doi: 10.1186/1743-8977-4-5.

245. Pope CA 3rd, Dockery DW. Health effects of fine particulate air pollution: lines that connect. J Air Waste Manag Assoc. 2006;56(6):709–42. doi: 10.1080/10473289.2006.10464485.

246. Poursafa P, Moosazadeh M, Abedini E, Hajizadeh Y, Mansourian M, Pourzamani H et al. A systematic review on the effects of polycyclic aromatic hydrocarbons on cardiometabolic impairment. Int J Preventive Medicine. 2017;8:19. doi: 10.4103/ijpvm.IJPVM_144_17.

247. Liu B, Jia C. Effects of profession on urinary PAH metabolite levels in the US population. Int Arch Occup Environ Health. 2016;89(1):123–35. doi: 10.1007/s00420-015-1057-7.

248. Ronneberg A. Mortality and cancer morbidity in workers from an aluminium smelter with prebaked carbon anodes. Part III: mortality from circulatory and respiratory diseases. Occup Environ Med. 1995;52(4):255–61. doi: 10.1136/oem.52.4.255.

249. Burstyn I, Kromhout H, Partanen T, Svane O, Langård S, Ahrens W et al. Polycyclic aromatic hydrocarbons and fatal ischemic heart disease. Epidemiology. 2005;16(6):744–50. doi: 10.1097/01.ede.0000181310.65043.2f.

250. Friesen MC, Demers PA, Spinelli JJ, Eisen EA, Lorenzi MF, Le ND. Chronic and acute effects of coal tar pitch exposure and cardiopulmonary mortality among aluminum smelter workers. Am J Epidemiol. 2010;172(7):790–9. doi: 10.1093/aje/kwq208.

251. Costello S, Garcia E, Hammond SK, Eisen EA. Ischemic heart disease mortality and PM(3.5) in a cohort of autoworkers. Am J Industrial Medicine. 2013;56(3):317–25. doi: 10.1002/ajim.22152.

252. Gustavsson P, Plato N, Hallqvist J, Hogstedt C, Lewné M, Reuterwall C et al. A population-based case-referent study of myocardial infarction and occupational exposure to motor exhaust, other combustion products, organic solvents, lead, and dynamite: Stockholm Heart Epidemiology Program (SHEEP) Study Group. Epidemiology. 2001;12(2):222–8. doi: 10.1097/00001648-200103000-00015.

253. Peters A, von Klot S, Heier M, Trentinaglia I, Hormann A, Wichmann HE et al. Exposure to traffic and the onset of myocardial infarction. N Engl J Med. 2004;351(17):1721–30. doi: 10.1056/NEJMoa040203.

254. Kraus U, Breitner S, Schnelle-Kreis J, Cyrys J, Lanki T, Ruckerl R et al. Particle-associated organic compounds and symptoms in myocardial infarction survivors. Inhal Toxicol. 2011;23(7):431–47. doi: 10.3109/08958378.2011.580471.

255. Schnelle-Kreis J, Kupper U, Sklorz M, Cyrys J, Briede JJ, Peters A et al. Daily measurement of organic compounds in ambient particulate matter in Augsburg, Germany: new aspects on aerosol sources and aerosol related health effects. Biomarkers. 2009;14(suppl 1):39–44. doi: 10.1080/13547500902965997.

256. Xu X, Cook RL, Ilacqua VA, Kan H, Talbott EO, Kearney G. Studying associations between urinary metabolites of polycyclic aromatic hydrocarbons (PAHs) and cardiovascular diseases in the United States. Sci Total Environ. 2010;408(21):4943–8. doi: 10.1016/j.scitotenv.2010.07.034.

257. Xu X, Hu H, Kearney GD, Kan H, Sheps DS. Studying the effects of polycyclic aromatic hydrocarbons on peripheral arterial disease in the United States. Sci Total Environ. 2013;461–2:341–7. doi: 10.1016/j.scitotenv.2013.04.089.

258. Hu C, Hou J, Zhou Y, Sun H, Yin W, Zhang Y et al. Association of polycyclic aromatic hydrocarbons exposure with atherosclerotic cardiovascular disease risk: a role of mean platelet volume or club cell secretory protein. Environ Pollut. 2018;233:45–53. doi: 10.1016/j.envpol.2017.10.042.

259. Lee MS, Magari S, Christiani DC. Cardiac autonomic dysfunction from occupational exposure to polycyclic aromatic hydrocarbons. Occup Environ Med. 2011;68(7):474–8. doi: 10.1136/oem.2010.055681.

260. Feng Y, Sun H, Song Y, Bao J, Huang X, Ye J et al. A community study of the effect of polycyclic aromatic hydrocarbon metabolites on heart rate variability based on the Framingham risk score. Occup Environ Med. 2014;71(5):338–45. doi: 10.1136/oemed-2013-101884.

261. Brucker N, Moro AM, Charão MF, Durgante J, Freitas F, Baierle M et al. Biomarkers of occupational exposure to air pollution, inflammation and oxidative damage in taxi drivers. Sci Total Environ. 2013;463–4:884–93. doi: 10.1016/j.scitotenv.2013.06.098.

262. Brucker N, Charão MF, Moro AM, Ferrari P, Bubols G, Sauer E et al. Atherosclerotic process in taxi drivers occupationally exposed to air pollution and co-morbidities. Environ Res. 2014;131:31–8. doi: 10.1016/j.envres.2014.02.012.

263. Alhamdow A, Lindh C, Albin M, Gustavsson P, Tinnerberg H, Broberg K. Early markers of cardiovascular disease are associated with occupational exposure to polycyclic aromatic hydrocarbons. Sci Rep. 2017;7(1):9426. doi: 10.1038/s41598-017-09956-x.

264. Bae S, Pan XC, Kim SY, Park K, Kim YH, Kim H et al. Exposures to particulate matter and polycyclic aromatic hydrocarbons and oxidative stress in schoolchildren. Environ Health Perspect. 2010;118:579–83. doi: 10.1289/ehp.0901077.

265. Everett CJ, King DE, Player MS, Matheson EM, Post RE, Mainous AG 3rd. Association of urinary polycyclic aromatic hydrocarbons and serum C-reactive protein. Environ Res. 2010;110(1):79–82. doi: 10.1016/j.envres.2009.09.010.

266. Liang JJ, Yi GL, Mao GS, Wang DM, Dai XY. [Influence of coke oven emissions on workers' blood pressure and electrocardiographic findings]. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 2016;34(9):667–9 (in Chinese). doi: 10.3760/cma.j.issn.1001-9391.2016.09.007.

267. Sroczyński J, Biskupek K, Podolecki A, Schneiberg P. [Effect of work in the coke-producing plant on the circulatory system of workers]. Med Pr. 1990;41(2):99–107 (in Polish). PMID: 2215207

268. Yang K, Jiang X, Cheng S, Chen C, Cao X, Tu B. Effects of coke oven emissions and benzo[a] pyrene on blood pressure and electrocardiogram in coke oven workers. J Occup Health. 2017;59(1):1–7. doi: 10.1539/joh.15-0264-OA.

269. Sancini A, Caciari T, Sinibaldi F, Sacco C, Boscolo P, Giubilati R et al. Blood pressure changes and polycyclic aromatic hydrocarbons in outdoor workers. Clin Ter. 2014;165(4):e295–303. doi: 10.7417/CT.2014.1746.

270. Jacobs L, Buczynska A, Walgraeve C, Delcloo A, Potgieter-Vermaak S, Van Grieken R et al. Acute changes in pulse pressure in relation to constituents of particulate air pollution in elderly persons. Environ Res. 2012;117:60–7. doi: 10.1016/j.envres.2012.05.003.

271. Bangia KS, Symanski E, Strom SS, Bondy M. A cross-sectional analysis of polycyclic aromatic hydrocarbons and diesel particulate matter exposures and hypertension among individuals of Mexican origin. Environ Health. 2015;14:51. doi: 10.1186/s12940-015-0039-2.

272. Trasande L, Urbina EM, Khoder M, Alghamdi M, Shabaj I, Alam MS et al. Polycyclic aromatic hydrocarbons, brachial artery distensibility and blood pressure among children residing near an oil refinery. Environ Res. 2015;136:133–40. doi: 10.1016/j.envres.2014.08.038

273. Yin W, Hou J, Xu T, Cheng J, Li P, Wang L et al. Obesity mediated the association of exposure to polycyclic aromatic hydrocarbon with risk of cardiovascular events. Sci Total Environ. 2018;616–17:841–54. doi: 10.1016/j.scitotenv.2017.10.238.

274. Zhang X, Li X, Jing Y, Fang X, Zhang X, Lei B et al. Transplacental transfer of polycyclic aromatic hydrocarbons in paired samples of maternal serum, umbilical cord serum, and placenta in Shanghai, China. Environ Pollut. 2017;222:267–75. doi: 10.1016/j.envpol.2016.12.046.

275. Lupo PJ, Symanski E, Langlois PH, Lawson CC, Malik S, Gilboa SM et al. Maternal occupational exposure to polycyclic aromatic hydrocarbons and congenital heart defects among offspring in the national birth defects prevention study. Birth Defects Res A Clin Mol Teratol. 2012;94(11):875–81. doi: 10.1002/bdra.23071.

276. Toxicological review of benzo[a]pyrene. Washington (DC): Integrated Risk Information System, United States Environmental Protection Agency; 2017 (EPA/635/R-17/003Fa; https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0136tr.pdf, accessed 12 October 2021).

277. Geier MC, Chlebowski AC, Truong L, Massey Simonich SL, Anderson KA, Tanguay RL. Comparative developmental toxicity of a comprehensive suite of polycyclic aromatic hydrocarbons. Arch Toxicol. 2018;92(2):571–86. doi: 10.1007/s00204-017-2068-9.

278. Geier MC, Minick DJ, Truong L, Tilton S, Pande P, Anderson KA et al. Systematic developmental neurotoxicity assessment of a representative PAH Superfund mixture using zebrafish. Toxicol Appl Pharmacol. 2018;354:115–25. doi: 10.1016/j.taap.2018.03.029.

279. Brown DR, Bailey JM, Oliveri AN, Levin ED, Di Giulio RT. Developmental exposure to a complex PAH mixture causes persistent behavioral effects in naive *Fundulus heteroclitus* (killifish) but not in a population of PAH-adapted killifish. Neurotoxicol Teratol. 2016;53:55–63. doi: 10.1016/j.ntt.2015.10.007.

280. Slotkin TA, Skavicus S, Card J, Di Giulio RT, Seidler FJ. In vitro models reveal differences in the developmental neurotoxicity of an environmental polycyclic aromatic hydrocarbon mixture compared to benzo[a]pyrene: neuronotypic PC12 cells and embryonic neural stem cells. Toxicology. 2017;377:49–56. doi: 10.1016/j.tox.2016.12.008.

281. Lovasi GS, Eldred-Skemp N, Quinn JW, Chang HW, Rauh VA, Rundle A et al. Neighborhood social context and individual polycyclic aromatic hydrocarbon exposures associated with child cognitive test scores. J Child and Family Studies. 2014;23(5):785–99. doi: 10.1007/s10826-013-9731-4.

282. Margolis AE, Herbstman JB, Davis KS, Thomas VK, Tang D, Wang Y et al. Longitudinal effects of prenatal exposure to air pollutants on self-regulatory capacities and social competence. J Child Psychol Psychiatry. 2016;57(7):851–60. doi: 10.1111/jcpp.12548.

283. Perera FP, Rauh V, Whyatt RM, Tsai WY, Tang D, Diaz D et al. Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children. Environ Health Perspect. 2006;114(8):1287–92.

284. Perera FP, Tang D, Rauh V, Tu YH, Tsai WY, Becker M et al. Relationship between polycyclic aromatic hydrocarbon-DNA adducts, environmental tobacco smoke, and child development in the World Trade Center cohort. Environ Health Perspect. 2007;115(10):1497–502. doi: 10.1289/ehp.9084.

285. Perera FP, Li Z, Whyatt R, Hoepner L, Wang S, Camann D et al. Prenatal airborne polycyclic aromatic hydrocarbon exposure and child IQ at age 5 years. Pediatrics. 2009;124(2):e195–202. doi: 10.1542/peds.2008-3506.

286. Perera FP, Tang D, Wang S, Vishnevetsky J, Zhang B, Diaz D et al. Prenatal polycyclic aromatic hydrocarbon (PAH) exposure and child behavior at age 6–7 years. Environ Health Perspect. 2012;120(6):921–6. doi: 10.1289/ehp.1104315.

287. Perera F, Phillips DH, Wang Y, Roen E, Herbstman J, Rauh V et al. Prenatal exposure to polycyclic aromatic hydrocarbons/aromatics, BDNF and child development. Environ Res. 2015;142:602–8. doi: 10.1016/j.envres.2015.08.011.

288. Perera FP, Wheelock K, Wang Y, Tang D, Margolis AE, Badia G et al. Combined effects of prenatal exposure to polycyclic aromatic hydrocarbons and material hardship on child ADHD behavior problems. Environ Res. 2018;160:506–13. doi: 10.1016/j.envres.2017.09.002.

289. Peterson BS, Rauh VA, Bansal R, Hao X, Toth Z, Nati G et al. Effects of prenatal exposure to air pollutants (polycyclic aromatic hydrocarbons) on the development of brain white matter, cognition, and behavior in later childhood. JAMA Psychiatry. 2015;72(6):531–40. doi: 10.1001/jamapsychiatry.2015.57.

290. Wang S, Chanock S, Tang D, Li Z, Edwards S, Jedrychowski W et al. Effect of gene-environment interactions on mental development in African American, Dominican, and Caucasian mothers and newborns. Ann Hum Genet. 2010;74(1):46–56. doi: 10.1111/j.1469-1809.2009.00550.x.

291. Weiland K, Neidell M, Rauh V, Perera F. Cost of developmental delay from prenatal exposure to airborne polycyclic aromatic hydrocarbons. J Health Care Poor Underserved. 2011;22(1):320–9. doi: 10.1353/hpu.2011.0012.

292. Vishnevetsky J, Tang D, Chang HW, Roen EL, Wang Y, Rauh V et al. Combined effects of prenatal polycyclic aromatic hydrocarbons and material hardship on child IQ. Neurotoxicol Teratol. 2015;49:74–80. doi: 10.1016/j.ntt.2015.04.002.

293. Edwards SC, Jedrychowski W, Butscher M, Camann D, Kieltyka A, Mroz E et al. Prenatal exposure to airborne polycyclic aromatic hydrocarbons and children's intelligence at 5 years of age in a prospective cohort study in Poland. Environ Health Perspect. 2010;118(9):1326–31. doi: 10.1289/ehp.0901070.

294. Genkinger JM, Stigter L, Jedrychowski W, Huang TJ, Wang S, Roen EL et al. Prenatal polycyclic aromatic hydrocarbon (PAH) exposure, antioxidant levels and behavioral development of children ages 6–9. Environ Res. 2015;140:136–44. doi: 10.1016/j.envres.2015.03.017.

295. Jedrychowski W, Whyatt RM, Camann DE, Bawle UV, Peki K, Spengler JD et al. Effect of prenatal PAH exposure on birth outcomes and neurocognitive development in a cohort of newborns in Poland: study design and preliminary ambient data. Int J Occup Med Environ Health. 2003;16(1):21–9. PMID: 12705714.

296. Lee J, Kalia V, Perera F, Herbstman J, Li T, Nie J et al. Prenatal airborne polycyclic aromatic hydrocarbon exposure, LINE1 methylation and child development in a Chinese cohort. Environ Int. 2017;99:315–20. doi: 10.1016/j.envint.2016.12.009.

297. Perera F, Li TY, Zhou ZJ, Yuan T, Chen YH, Qu L et al. Benefits of reducing prenatal exposure to coal-burning pollutants to children's neurodevelopment in China. Environ Health Perspect. 2008;116(10):1396–400. doi: 10.1289/ehp.11480.

298. Tang D, Li TY, Liu JJ, Chen YH, Qu L, Perera F. PAH–DNA adducts in cord blood and fetal and child development in a Chinese cohort. Environ Health Perspect. 2006;114(8):1297–300. doi: 10.1289/ehp.8939.

299. Tang D, Li TY, Liu JJ, Zhou ZJ, Yuan T, Chen YH et al. Effects of prenatal exposure to coal-burning pollutants on children's development in China. Environ Health Perspect. 2008;116(5):674–9. doi: 10.1289/ehp.10471.

300. Tang D, Lee J, Muirhead L, Li TY, Qu L, Yu J et al. Molecular and neurodevelopmental benefits to children of closure of a coal burning power plant in China. PLOS One. 2014;9(3):e91966. doi: 10.1371/journal.pone.0091966.

301. Tang D, Li TY, Chow JC, Kulkarni SU, Watson JG, Ho SS et al. Air pollution effects on fetal and child development: a cohort comparison in China. Environ Pollut. 2014;185:90–6. doi: 10.1016/j.envpol.2013.10.019.

302. Mortamais M, Pujol J, van Drooge BL, Macià D, Martínez-Vilavella G, Reynes C et al. Effect of exposure to polycyclic aromatic hydrocarbons on basal ganglia and attention-deficit hyperactivity disorder symptoms in primary schoolchildren. Environ Int. 2017;105:12–19. doi: 10.1016/j.envint.2017.04.011.

303. Abid Z, Roy A, Herbstman JB, Ettinger AS. Urinary polycyclic aromatic hydrocarbon metabolites and attention/deficit hyperactivity disorder, learning disability, and special education in U.S. children aged 6 to 15. J Environ Public Health. 2014;2014:628508. doi: 10.1155/2014/628508.

304. Perera F, Weiland K, Neidell M, Wang S. Prenatal exposure to airborne polycyclic aromatic hydrocarbons and IQ: estimated benefit of pollution reduction. J Public Health Policy. 2014;35(3):327–36. doi: 10.1057/jphp.2014.14.

305. Perera F, Li TY, Lin C, Tang D. Effects of prenatal polycyclic aromatic hydrocarbon exposure and environmental tobacco smoke on child IQ in a Chinese cohort. Environ Res. 2012;114:40–6. doi: 10.1016/j.envres.2011.12.011.

306. Guxens M, Sunyer J. A review of epidemiological studies on neuropsychological effects of air pollution. Swiss Med Wkly. 2012;141(1):w13322. doi: 10.4414/smw.2011.13322.

307. Suades-González E, Gascon M, Guxens M, Sunyer J. Air pollution and neuropsychological development: a review of the latest evidence. Endocrinology. 2015;156(10):3473–82. doi: 10.1210/en.2015-1403.

308. Clifford A, Lang L, Chen R, Anstey KJ, Seaton A. Exposure to air pollution and cognitive functioning across the life course: a systematic literature review. Environ Res. 2016;147:383–98. doi: 10.1016/j.envres.2016.01.018.

309. Chepelev NL, Long AS, Bowers WJ, Gagne R, Williams A, Kuo B et al. Transcriptional profiling of the mouse hippocampus supports an NMDAR-mediated neurotoxic mode of action for benzo[a]pyrene. Environ Mol Mutagen. 2016;57(5):350–63. doi: 10.1002/em.22020.

310. Heusinkveld HJ, Wahle T, Campbell A, Westerink RHS, Tran L, Johnston H et al. Neurodegenerative and neurological disorders by small inhaled particles. Neurotoxicology. 2016;56:94–106. doi: 10.1016/j.neuro.2016.07.007.

311. Croze ML, Zimmer L. Ozone atmospheric pollution and Alzheimer's disease: from epidemiological facts to molecular mechanisms. J Alzheimers Dis. 2018;62(2):503–22. doi: 10.3233/JAD-170857.

312. Hamra GB, Guha N, Cohen A, Laden F, Raaschou-Nielsen O, Samet JM et al. Outdoor particulate matter exposure and lung cancer: a systematic review and meta-analysis. Environ Health Perspect. 2014;122(9):906–11. doi: 10.12 89/ehp/1408092.

Annex 1. Search strategy

Literature search

An initial screening of the literature was conducted in March 2018 *(1)* to identify which health outcomes to consider. This was used to understand the breadth of the literature on the health effects of PAHs and to define the relevant health outcomes. The latter comprised:

- different types of cancers
- CVDs
- respiratory diseases
- cognitive end-points, for example cognitive development in children
- reproductive outcomes.

Following the initial screening, a search strategy was developed for each outcome *(2)*. To ensure the efficient use of time and resources, a simple search of specific keywords in the PubMed/Medline database (i.e. MeSH terms) was conducted to identify relevant epidemiological literature. This literature was added to the recent reviews identified in the initial step. Search terms were tested against a number of relevant references found in LUDOK.[10] Reference lists on PAHs from Health Canada and the US EPA were also consulted to identify other possibly relevant documents. This iterative process enabled search terms to be optimized in order to find relevant epidemiological studies on health effects of ambient PAH exposure. The search terms, process of quality assurance and results of the literature search have been published *(1,2)*. Searches of PubMed/Medline were conducted on all five health outcomes in June 2018. An additional broader, more sophisticated search for cancer end-points was conducted in February 2019. These were combined with a complementary search of Embase by Health Canada, yielding a total of 1342 potentially relevant studies published up to November 2019 *(3)*. Following title and/or abstract screening, 14 epidemiological studies (six on childhood cancer, five on breast cancer, one on cervical cancer, one on lung cancer and one on bladder cancer) met the inclusion criteria (i.e. the study linked cancer to PAH exposure in the general population). Studies that used a proxy indicator of PAH exposure, such as living close to high levels of vehicular traffic, were excluded.

After duplicate removal, a title/abstract screening of 901 studies from the PubMed/Medline and LUDOK searches and 614 studies from the additional search on cancer end-points was conducted to differentiate between epidemiological studies, reviews and supporting evidence from studies that used proxy measures for PAH exposure (such as urinary metabolites), occupational studies, and animal or in vitro studies (Table A1.1). Where relevance was not clear from titles/abstracts, the full text was assessed for relevance.

10 The Swiss Literature Database on Air Pollution and Health, which is managed by the Swiss Tropical and Public Health Institute on behalf of the Swiss Federal Office for the Environment.

Table A1.1. Results from literature search for epidemiological studies on PAH exposure in humans

Outcome	Studies screened	Studies selected				
		Epidemiological studies	Reviews	Occupational studies	Studies using proxy measures	Others (e.g. animal, in vitro)
Cancer	1 013	23	30	63	25	–
CVD	123	7	0	9	6	3
Respiratory disease	89	19	6	6	14	3
Cognitive end-points	146	10	6	0	15	8
Reproductive outcomes	144	14	9	4	15	7

Additional literature

According to their areas of expertise, authors added literature on the biological mechanisms of the adverse effects of PAH exposure based on experimental studies and snowball searching of identified articles.

References

1. Kutlar Joss M. Short literature search on reviews on health effects of polycyclic aromatic hydrocarbons (PAH). Basel: Swiss Tropical and Public Health Institute; 2018 (https://swisstph.ch/fileadmin/user_upload/SwissTPH/Institute/Ludok/Sonstiges/TFH_PAH_Report/KutlarJoss2018_PAHReviewsOnHealthEffects_Search.pdf, accessed 16 April 2021).

2. Kutlar Joss M. Development of a search strategy for the review on health effects of polycyclic aromatic hydrocarbons (PAH). Basel: Swiss Tropical and Public Health Institute; 2018 (https://www.swisstph.ch/fileadmin/user_upload/SwissTPH/Institute/Ludok/KutlarJoss2018_PAHLiterature_Search.pdf, accessed 16 April 2021).

3. Kutlar Joss M. Development of a search strategy for the review on health effects of polycyclic aromatic hydrocarbons (PAHs): additional searches for (lung) cancer. Basel: Swiss Tropical and Public Health Institute; 2019 (https://www.swisstph.ch/fileadmin/user_upload/SwissTPH/Institute/Ludok/KutlarJoss2019_PAHLiterature_Search_CancerPlus_HealthCanada.pdf, accessed 16 April 2021).

Annex 2. Information on high-priority PAHs

Since 1976 the US EPA has published a list of priority PAH compounds (originally 15 and later increased to 16) as a reference for those who want to gain a wider knowledge of common atmospheric PAH compounds *(1,2)*. The EU (Directive 2004/107/EC) recommends that six PAH compounds should be measured in addition to the overall indicator, B[*a*]P, from the atmospheric particulate phase PAH mixture *(3)*.

The emissions, sedimentation to the ground or sea, and atmospheric background concentrations of four five- or six-benzene-ring PAH compounds in the particulate phase have been monitored for decades by EMEP[11] and the Arctic Monitoring and Assessment Programme of the Arctic Council *(5)*. Both organizations produce scientific support to implement the Aarhus Protocol on Persistent Organic Pollutants under the UNECE Convention on Long-range Transboundary Air Pollution, and other forums. The four PAH compounds selected for this purpose were B[*a*]P, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene and indeno[1,2,3-*cd*]pyrene (Table A2.1).

References

1. Keith LH. The source of US EPA's sixteen PAH priority pollutants. Polycycl Aromat Compd. 2015;35(2–4):147–60. doi: https://doi.org/10.1080/10406638.2014.892886.

2. Gusev A, Batrakova N. Assessment of PAH pollution levels, key sources and trends: contribution to analysis of the effectiveness of the POPs Protocol. Moscow: Meteorological Synthesizing Centre; 2020 (Progress report; https://en.msceast.org/reports/2_2020_tech.pdf , accessed 12 October 2021).

3. Directive 2004/107/EC of the European Parliament and of the Council of 15 December 2004 relating to arsenic, cadmium, mercury, nickel and polycyclic aromatic hydrocarbons in ambient air. OJ. 2005;L23:3–16 (https://eur-lex.europa.eu/eli/dir/2004/107/oj, accessed 12 October 2021).

4. EMEP [website]. Geneva: United Nations Economic Commission for Europe; 2021 (www.emep.int, accessed 12 October 2021).

5. AMAP and the Arctic Council [website]. Tromsø: AMAP secretariat; 2021 (www.amap.no, accessed 12 October 2021).

6. Cheruiyot NK, Lee WJ, Mwangi, JK, Wang LC, Lin NH, Lin YC et al. An overview: polycyclic aromatic hydrocarbon emissions from the stationary and mobile sources and in the ambient air. Aerosol Air Qual Res. 2015;15:2730–62. doi: https://doi.org/10.4209/aaqr.2015.11.0627.

7. IARC Working Group on the Evaluation of Carcinogenic Risk to Humans. Some non-heterocyclic polycyclic aromatic hydrocarbons and some related occupational exposures. Lyon: International Agency for Research on Cancer Press; 2010 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans No. 92; https://inchem.org/documents/iarc/iarcmono/v92iarc.pdf, accessed 12 October 2021).

11 The official name is the Co-operative Programme for Monitoring and Evaluation of the Long-range Transmission of Air Pollutants in Europe *(4)*.

Table A2.1. Basic information on the 16 high-priority PAH compounds, as issued by the US EPA

Compound name	Abbreviation	No. of rings	Molecular formula	Molecular mass	Vapour pressure[a] (Pa) at 25 °C
Naphthalene	Nap	2	$C_{10}H_8$	128	1.4
Acenaphthylene	Acy	3	$C_{12}H_8$	152	8.8×10^{-1}
Acenaphthene	Ace	3	$C_{12}H_{10}$	154	2.9×10^{-1}
Fluorene	Fl	3	$C_{13}H_{10}$	166	8.0×10^{-2}
Phenanthrene	Phe	3	$C_{14}H_{10}$	178	1.6×10^{-2}
Anthracene	Ant	3	$C_{14}H_{10}$	178	8.0×10^{-4}
Fluoranthene	Flu	4	$C_{16}H_{10}$	202	1.2×10^{-3}
Pyrene	Pyr	4	$C_{16}H_{10}$	202	6.0×10^{-4}
Benzo[*a*]anthracene[b]	BaA	4	$C_{18}H_{12}$	228	2.8×10^{-5}
Chrysene[b]	Chr	4	$C_{18}H_{12}$	228	8.4×10^{-5}
Benzo[*b*]fluoranthene[b,c]	BbF	5	$C_{20}H_{12}$	252	6.7×10^{-5}
Benzo[*k*]fluoranthene[b,c]	BkF	5	$C_{20}H_{12}$	252	1.3×10^{-5}
B[*a*]P[d]	BaP	5	$C_{20}H_{12}$	252	7.3×10^{-7}
Dibenzo[*ah*] anthracene[e]	DBA	5	$C_{22}H_{14}$	278	1.3×10^{-8}
Indeno[1,2,3-*cd*]pyrene[b]	IDP	6	$C_{22}H_{12}$	276	1.3×10^{-8}
Benzo[*ghi*]perylene	BghiP	6	$C_{22}H_{12}$	276	1.4×10^{-8}

Note: PAHs in bold are recommended to be measured in the EU (Directive 2004/107/EC) *(3)*, whereas those in the shaded rows are also included in Arctic Monitoring and Assessment Programme and EMEP monitoring protocols.

[a] Data obtained from a review by Cheruiyot et al. (2015) *(6)*.

[b] Group 2B: possibly carcinogenic to humans *(7)*.

[c] Benzo[*j*]fluoranthene is the sixth PAH compound recommended to be voluntarily measured in the Member States of the European Union (2004/107/EC) *(2)*, but it is difficult to separate from the closest isomer benzo[*k*]fluoranthene in chemical analysis. It is not on the US EPA list and, in practice, the sum of both isomers is often given as benzo[*k*]fluoranthene.

[d] Group 1: Carcinogenic to humans *(7)*.

[e] Group 2A: probably carcinogenic to humans *(7)*.

The WHO Regional Office for Europe
The World Health Organization (WHO) is a specialized agency of the United Nations created in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

Member States

Albania
Andorra
Armenia
Austria
Azerbaijan
Belarus
Belgium
Bosnia and Herzegovina
Bulgaria
Croatia
Cyprus
Czechia
Denmark
Estonia
Finland
France
Georgia
Germany
Greece
Hungary
Iceland
Ireland
Israel
Italy
Kazakhstan
Kyrgyzstan
Latvia
Lithuania
Luxembourg
Malta
Monaco
Montenegro
Netherlands
North Macedonia
Norway
Poland
Portugal
Republic of Moldova
Romania
Russian Federation
San Marino
Serbia
Slovakia
Slovenia
Spain
Sweden
Switzerland
Tajikistan
Turkey
Turkmenistan
Ukraine
United Kingdom
Uzbekistan

ISBN 978-92-890-5653-3

WHO European Centre for Environment and Health
Platz der Vereinten Nationen 1
D-53113 Bonn, Germany

Tel.: +49 228 815 0400
Fax: +49 228 815 0440
E-mail: euroeceh@who.int
Website: www.euro.who.int