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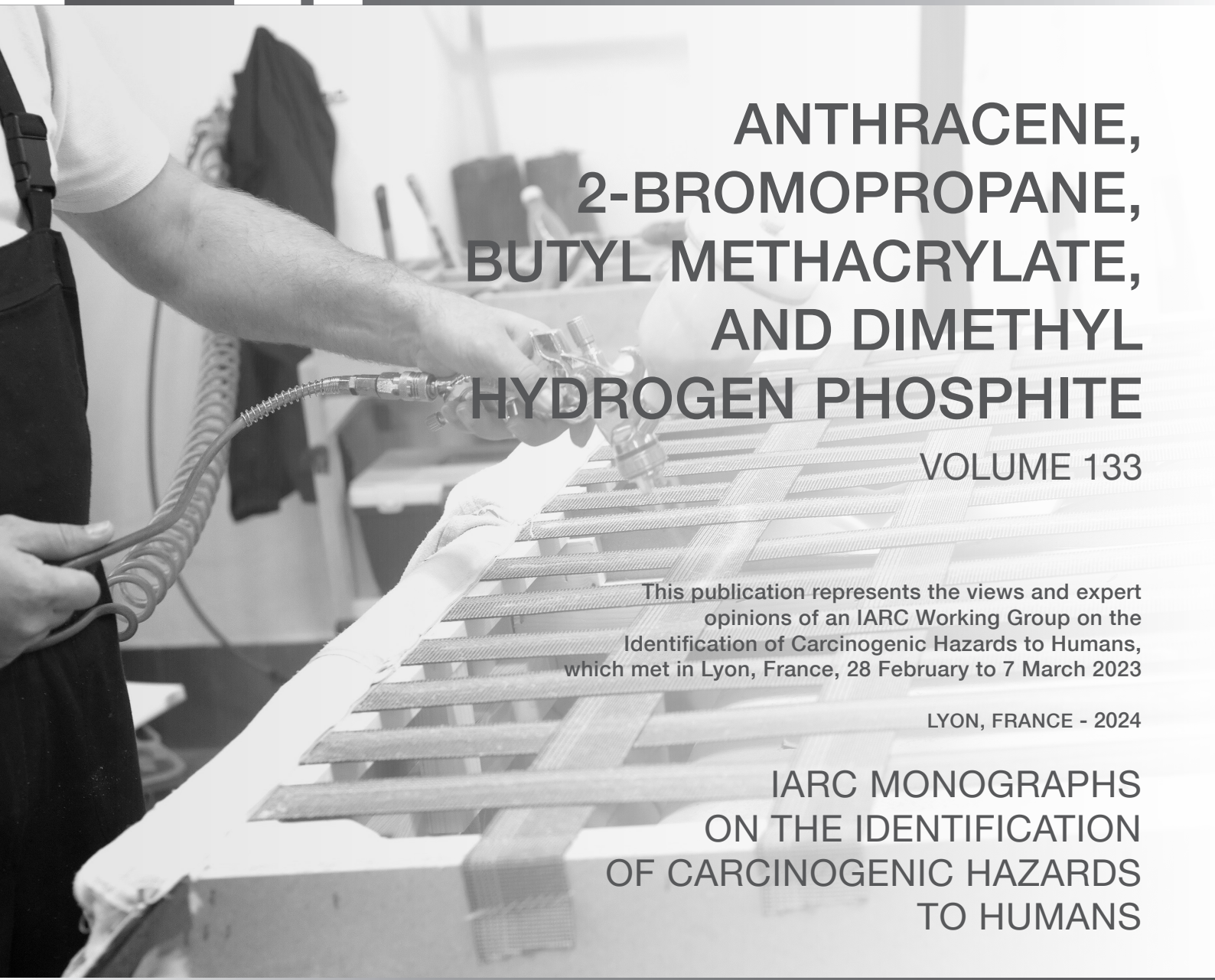

ANTHRACENE, 2-BROMOPROPANE, BUTYL METHACRYLATE, AND DIMETHYL HYDROGEN PHOSPHITE

VOLUME 133

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IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

World Health Organization

ANTHRACENE

1. Exposure Characterization

1.1 Identification of the agent

1.1.1 Nomenclature

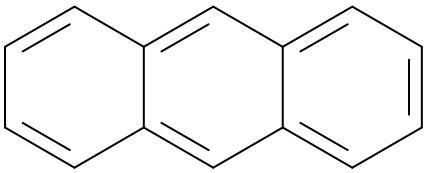
Chem. Abstr. Serv. Reg. No.: 120-12-7 (NCBI, 2022)

EC/List No.: 204-371-1 (NCBI, 2022)

IUPAC systematic name: anthracene (NCBI, 2022)

Synonyms: paranaphthalene; anthracin; Green Oil; Tetra Olive N2G (NCBI, 2022)

1.1.2 Structural and molecular information



Molecular formula: $C_{14}H_{10}$ (NCBI, 2022)

Relative molecular mass: 178.23 (NCBI, 2022).

1.1.3 Chemical and physical properties of the pure substance

Description: tablets or monoclinic prisms (from alcohol recrystallization) with weak aromatic odour. When pure, it is colourless with violet fluorescence; if impure (due to the presence of tetracene or naphthacene), it is yellow with green fluorescence (NCBI, 2022).

Boiling-point: 340–342 °C (NCBI, 2022; Royal Society of Chemistry, 2022)

Melting-point: 214 °C [the melting point of anthracene ranges from 208 °C to 218 °C, mainly depending on the grade of purity] (NCBI, 2022; Royal Society of Chemistry, 2022; ECHA, 2023)

Flash-point: 121 °C at 101.3 kPa (NCBI, 2022; Royal Society of Chemistry, 2022; ECHA, 2023)

Density: 1.25 g/mL at 20 °C (NCBI, 2022; Royal Society of Chemistry, 2022)

Vapour pressure: 9.4×10^{-4} Pa at 25 °C (ECHA, 2008a)

Solubility: 4.34×10^{-5} g/L in water at 24 °C; 14.93 g/L in ethanol; 14.29 g/L in methanol; 16.13 g/L in benzene; 11.76 g/L in chloroform; 5 g/L in ether; 32.36 g/L in carbon disulfide; 11.63 g/L in carbon tetrachloride; 8 g/L in toluene (IARC, 1983; NCBI, 2022; Royal Society of Chemistry, 2022).

Octanol/water partition coefficient (P): log K_{ow} = 4.45 (NCBI, 2022; Royal Society of Chemistry, 2022)

Octanol/air partition coefficient (P): log K_{oa} = 7.55 (Royal Society of Chemistry, 2022)

Stability: Darkens in sunlight. Strongly triboluminescent and triboelectric; forms molecular addition products with nitrogen compounds (NCBI, 2022).

[The Working Group used a conversion factor of 1 ppm ≈ 7.29 mg/m^3 at 25 °C in air.]

1.1.4 Technical grade and impurities

A commercial grade (purity, 90–95% by weight), higher-purity reagent grade (purity, 97%), and sublimed anthracene (purity, ≥ 99%) are available (IARC, 1983; ECHA, 2008a; NCBI, 2022).

Reported impurities include phenanthrene, carbazole, naphthothiophene, dibenzo[*b*,*c*]thiophene, acridine, acetophenone, and chrysene (ECHA, 2008a). Anthracene was reported to be available until 1982 from one producer in the USA, as refined anthracene with the following specifications: purity, 90–95% by weight; carbazole, 3% maximum; sublimation residue, 0.5% maximum; pyridine, 0.2% maximum; ash, 0.1% maximum; and iron, 0.03% maximum (IARC, 1983). Typical properties of this refined anthracene were: melting-point, 216 °C; boiling-point, 340 °C; specific gravity, 1.25; and vapour pressure, < 3 × 10^{-4} mm Hg (20 °C) (IARC, 1983).

1.2 Production and use

1.2.1 Production process

Anthracene can be synthesized from benzyl chloride in a two-step reaction (Friedel–Crafts reaction); from *ortho*-methylbenzophenone (Elbs reaction); from 2,3-dihydronaphthalene-1,4-dione (Diels–Alder reaction); from benzene and phthalic anhydride (Haworth synthesis); from the reaction between two molecules of benzene with 1,1,2,2-tetrabromoethane in the presence of aluminium chloride; and from phthalic anhydride and substituted benzene (Sahoo et al., 2020; Baviera & Donate, 2021). However, anthracene is not generally synthesized industrially and is usually recovered from coal tar, specifically from one of its distillate fractions (known as anthracene oil or green oil), through the application of a set of sequential separation and purification techniques, namely vacuum distillation (concentration to about 50% anthracene), salting out, recrystallization in polar solvents (yielding > 95% anthracene) and sublimation or azeotropic distillation (ECHA, 2008a, 2022b; Chemicalbook, 2021; NCBI, 2022). [The Working Group noted that anthracene oil is a complex mixture containing anthracene and other two- to four-ring aromatic compounds, and is not the agent under evaluation in the present monograph.] Anthracene, as a polycyclic aromatic hydrocarbon (PAH; a compound that is exclusively composed of fused aromatic rings that share a pair of carbon atoms), is also involuntarily produced during combustion and in some industrial processes (see Section 1.4.1) and is, in these processes, included in the respective tailings.

1.2.2 Production volume

Anthracene has been classified by the Organisation for Economic Co-operation and Development (OECD) as a High Production Volume chemical (OECD, 2023). Estimates of the world production of anthracene from coal tar range from 10 000 to 20 000 tonnes per year (Collin et al., 2011; Chemicalbook, 2021), which are almost exclusively used in the manufacture of anthraquinone (Collin et al., 2011). On the basis of the available data, two active suppliers were identified in the European Union (EU) (ECHA,

2022a). Few data were available, but production volumes of < 2000 tonnes per year have been reported for Europe between 1995 and 2001 (European Chemicals Bureau, 2007). Under the Toxic Substances Control Act, the United States Environmental Protection Agency (US EPA) reported a nationally aggregated production volume of < 1 000 000 pounds [453.6 tonnes] in 2016, 2017, 2018, and 2019, with no obvious differences when compared with data from 1986, 1998, and 2002 (10 000–500 000 pounds [4.54–226.8 tonnes]) (US EPA, 2020; NCBI, 2022).

1.2.3 Uses

Anthracene is reported to be mainly used as an intermediate in the manufacture of dyes (anthraquinone-based products and alizarin dyes), wood preservatives, and pesticides (see also Section 1.4.1(c) for uses of anthracene in consumer products) (NCBI, 2022). The US EPA classifies industrial use of anthracene as a chemical ingredient in the composition of propellants, e.g. in the manufacture of pyrotechnics; no information on anthracene was presented in the database on consumer and commercial uses (US EPA, 2020). In the European Economic Area, anthracene is registered under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulations for use as an intermediate in the manufacture of bulk, large-scale chemicals (including petroleum products), and fine chemicals, laboratory chemicals, and pharmaceuticals (ECHA, 2022b). In Nordic countries, anthracene was reported to be used during 2000–2003 in Denmark in rust inhibitors and anti-corrosion products, and during 2016–2017 in Finland in the manufacture of chemicals and chemical products (SPIN, 2022). Worldwide, anthracene is also used in research laboratories in the fields of polymers and semiconductor materials, including as a core component to obtain saturated deep blue organic light-emitting diodes to be used in flat-panel displays and lighting source technology (Park et al., 2012; Baviera & Donate, 2021).

Anthracene is likely to exist, simultaneously with additional PAHs, in commercial products such as coal tar, creosote, and asphalt (bitumen), and in their respective derived products (Government of Canada, 2022a).

1.3 Detection and quantification

Since anthracene is part of a complex mixture of PAHs that commonly occur as products of combustion/pyrolysis processes, it is usually detected and quantified together with other PAHs. A selection of methods used to detect and quantify anthracene in various matrices is reported in Table 1.1.

1.3.1 Air

Anthracene is a three-ring PAH and is therefore expected to be found mostly in the vapour phase in air, together with two-ring PAHs. A smaller proportion is found in the particle phase (Oliveira et al., 2016). The sampling of airborne PAHs requires the use of pumping systems in which adsorbent materials (for gaseous PAHs) are connected to filters for particle-phase PAHs. After collection, PAHs are desorbed from the adsorbents using various organic solvents (including dichloromethane, methanol, acetone, cyclohexane, and benzene). Chromatographic separation, either by gas chromatography (GC) or high-performance liquid chromatography (HPLC), is necessary to separate the different PAHs, usually followed by detection using universal methods such as mass spectrometry (MS) and fluorescence detection (FLD).

The sampling of anthracene in air is usually performed by means of an adsorbent material (including XAD-2 resins and polyurethane foam) placed downstream from the filter used to collect high-molecular-weight PAHs (National

Table 1.1 Analytical methods for the measurement of anthracene

Sample matrix	Sample preparation	Analytical method (LOD)	Comments	Reference
Air	Filter (glass fibre) + adsorption on sorbent material (XAD-7), extraction with methylene chloride in ultrasonic bath	GC-MS SIM (0.08 µg/sample)	NIOSH method 5528	NIOSH (1984)
Air	Filter (PTFE) + adsorption on sorbent material (XAD-2), extraction with acetonitrile	HPLC-FLD or UV (0.0010–0.090 µg/sample)	NIOSH method 5506	NIOSH (1998)
Air	Adsorption on sorbent material (XAD-2), extraction with alternate organic solvents depending on the sample matrix in ultrasonic bath	GC-FID (0.3–0.5 µg/sample)	NIOSH method 5515	NIOSH (1994)
Air	Adsorption on sorbent material (glass fibre filters), extraction with benzene	LC-FLD or UV (0.028 µg/m^3)	OSHA method 58	OSHA (1986)
Solid waste matrices, soils, and groundwater	Extraction with methylene chloride	GC-MS (ground water,10 µg/L; soil/sediment, 660 µg/kg)	US EPA method 8270D	US EPA (2014a)
Municipal and industrial discharge	Extraction with methylene chloride	HPLC-FLD (0.66 µg/L)	US EPA method 610	US EPA (1984)
Soil and sediments	Pressurized solvent extraction using a water/isopropyl alcohol mixture followed by SPE	GC-MS (11.9 µg/kg)	Method prepared by the United States Geological Survey Office of Water Quality	Zaugg et al. (2006)
Consumer products (polymer samples)	Extraction with toluene	GC-MS (0.2 mg/kg)	Method in the awarding of the GS mark	AfPS (2020)
Cosmetics	Extraction with acetone:hexane	GC-MS/MS (0.1 mg/kg)		Wang et al. (2019)
Edible fats and oils	Purification by donor–acceptor complex chromatography	HPLC-FLD (0.1 µg/kg)	Standard method ISO 22959	ISO (2009)
Seafood	Extraction with ethyl acetate followed by silica SPE clean-up	GC-MS (LOD not reported)	AOAC International	Mastovska et al. (2015)
Urine	HS-SPME	GC-MS (2.2 ng/L)		Campo et al. (2009)
Urine	SPME	GC-MS/MS (0.2 ng/L)		Campo et al. (2016)
Blood (serum)	Extraction with organic solvents, followed by silica SPE clean-up	GC-MS/MS (191 ng/L)		Yin et al. (2017)
Saliva	LLE-PTV	GC-MS (91 ng/L)		Santos et al. (2019)

Table 1.1 (continued)

Sample matrix	Sample preparation	Analytical method (LOD)	Comments	Reference
Saliva	HS-SPME	GC-MS/MS (13.4 ng/L)		Martín Santos et al. (2020)
Breast milk	Extraction with acetonitrile and filtration	HPLC-FLD (0.23 μg/L)		Oliveira et al. (2020)

AOAC, Association for Official Analytical Collaboration; GC-FID, gas chromatography-flame-ionization detection; GC-MS, gas chromatography-mass spectrometry; GC-MS/MS, gas chromatography-tandem mass spectrometry; GS, Geprüfte Sicherheit ("tested safety"), licensed by the German government for consumer products; HPLC-FLD, high-performance liquid chromatography method-fluorescence detection; HS-SPME, headspace solid-phase microextraction; LLE-PTV, liquid–liquid extraction and programmed temperature vapourizer; LOD, limit of detection; MS, mass spectrometry; MS/MS, tandem mass spectrometry; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Safety and Health Administration; PTFE, polytetrafluoroethylene; SIM, selected ion monitoring; SPE, solid-phase extraction; SPME, solid-phase microextraction;; US EPA, United States Environmental Protection Agency; UV, ultraviolet.

Institute for Occupational Safety and Health, NIOSH methods 5528, 5506, 5515; Occupational Safety and Health Administration (OSHA) method 58) (NIOSH, 1984, 1994, 1998; OSHA 1986; see Table 1.1). For NIOSH method 5528, which uses gas chromatography-mass spectrometry (GC-MS) in the selected ion monitoring (SIM) mode, the limit of detection (LOD) for anthracene (LOD, 0.08 µg/sample) is comparable to that for NIOSH method 5506, which uses HPLC-FLD (LOD, 0.010–0.090 µg/sample). For other PAHs, the LODs for NIOSH method 5528 are on average twice as low as for NIOSH method 5506. Moreover, NIOSH method 5528 is similar to NIOSH method 5515, the primary differences including a more efficient sampling device and the use of GC-MS SIM rather than GC-FID, thus leading to a lower LOD (0.08 µg/sample versus 0.3–05 µg/sample) and a higher specificity. OSHA method 58 is used in the assessment of exposure to coal tar pitch volatiles and coke-oven emissions. Analytes, including anthracene, are collected with glass fibre filters and desorbed with benzene. The LOD for OSHA method 58 is 0.028 µg/m^3, but the reliable limit of quantification (LOQ) is 0.066 µg/m^3.

1.3.2 Water and soil

In aqueous media (including municipal and industrial discharge), anthracene is extracted using solvents such as methylene chloride (US EPA methods 610 and 8270D, see Table 1.1) (US EPA, 1984, 2014a). In method EPA 610 (LOD, 0.66 µg/L), the extract is concentrated and then separated by HPLC or GC, but the GC procedure does not adequately resolve the pair anthracene/phenanthrene, so HPLC should be preferred (US EPA, 1984). Moreover, both FLD and ultraviolet (UV) detection coupled to HPLC could be used, but FLD is recommended for the determination of anthracene (US EPA, 1984). A less sensitive method is US EPA method 8270D, which uses GC-MS to quantify a series of semivolatile organic compounds (including PAHs) in extracts prepared from different types of matrix, including groundwater samples (LOD, 10 µg/L), sediment and soil matrices (LOD, 660 µg/kg), and wastes (LOD, 1–200 mg/kg, depending on matrix and method preparation) (US EPA, 2014a). For sediment and soil matrices, an extraction procedure consisting of pressurized solvent extraction using a water/isopropyl alcohol mixture followed by solid-phase extraction is described by the United States Geological Survey Office of Water Quality. Anthracene, together with 38 other PAHs and semivolatile organic compounds, is detected by GC-MS, with an LOD of 11.9 µg/kg (Zaugg et al., 2006), making this method more sensitive than US EPA method 8270D.

1.3.3 Consumer products

A method to test and assess anthracene (together with 14 other PAHs) in the awarding of the GS mark (the "Geprüfte Sicherheit" or "tested safety" mark licensed by the German government for consumer products) has been proposed by the German Federal Institute for Occupational Safety and Health (AfPS, 2020). Products (polymer samples) are extracted with toluene (a further purification step using silica gel columns may be necessary) and quantified by GC-MS. The LOD (0.2 mg/kg) achieved with this procedure meets the maximum PAH limits for materials with relevant contact/grip and operating surfaces (i.e. materials intended to be placed in the mouth, or materials coming into long-term contact with skin (more than 30 seconds) during the intended use according to EU legislation Directive 2009/48/EC for toys (European Parliament and Council, 2009a). A validated method to quantify PAHs in cosmetics has been proposed: anthracene is extracted, together with 17 other PAHs, by means of an acetone:hexane mixture and quantified by gas chromatography coupled to tandem mass spectrometry (GC-MS/

MS) with an LOQ as low as 0.1 mg/kg (Wang et al., 2019).

1.3.4 Food

ISO 15753 focuses on the determination of 16 PAHs (including anthracene) in animal and vegetable fats and oils, and has an LOD of 0.2 µg/kg (ISO, 2016). This method cannot be used for the determination of PAHs in palm oil and olive pomace oil. The standard method, ISO 22959, which enables the quantification of 17 PAHs in edible fats and oil, is more sensitive and has an LOD of 0.1 µg/kg (ISO, 2009). Both ISO methods are based on HPLC-FLD. In a method using GC-MS, focused on the determination of PAHs in seafood and published by the Association for Official Analytical Collaboration (AOAC) International, anthracene is quantified together with 18 other PAHs (Mastovska et al., 2015). Several analytical methods for the determination of PAHs in various food products and with different extraction and clean-up procedures and analytical techniques have been published in the scientific literature. A review of analytical methods for PAHs in food can be found in Zelinkova & Wenzl (2015), and a review focusing on the determination of PAHs in olive oils can be found in Bertoz et al. (2021).

1.3.5 Biological samples

Some analytical methods have been developed to quantify anthracene in urine, blood, saliva, and hair. The validation of these methods is not always described appropriately. In urine, a method based on headspace solid-phase microextraction (HS-SPME) coupled to GC-MS, with an LOQ of 2.28 ng/L, has been developed and validated by Campo et al. (2009). The method has been further improved by using direct immersion solid-phase microextraction (SPME) instead of HS-SPME and GC coupled to triple quadrupole mass spectrometer (GC-MS/MS), obtaining a lower LOQ for anthracene (0.2 ng/L) (Campo et al., 2016).

In blood, a method based on extraction with organic solvents followed by clean-up using silica solid-phase extraction and analysis by GC-MS/MS (LOD, 191 ng/L) was applied to umbilical cord serum samples (Yin et al., 2017) and to blood samples from firefighters (Ekpe et al., 2021).

For saliva, Santos et al. developed and validated a method based on liquid–liquid extraction and programmed temperature vapourizer-GC-MS (LLE-PTV-GC-MS), with an LOQ for anthracene of 91 ng/L (Santos et al., 2019), and a more sensitive method (LOQ, 13.4 ng/L) based on headspace solid-phase microextraction (HS-SPME) and GC-MS/MS (Martín Santos et al., 2020).

For breast milk, Oliveira et al. developed a method using HPLC-FLD to detect anthracene together with other PAHs after solvent extraction and filtration (LOQ, 0.23 µg/L) (Oliveira et al., 2020).

1.4 Occurrence and exposure

1.4.1 Environmental occurrence

Anthracene releases or disposal into the environment take place due to industrial use or unintended formation during production processes. Anthracene, as a PAH, is also a ubiquitous environmental pollutant since it is formed during the incomplete combustion or pyrolysis of organic matter (IARC, 2010). Thus, sources can be of both natural (e.g. forest fires, volcanic eruptions and seepage of petroleum or coal deposits) and anthropogenic (industrial, domestic, traffic, etc.) origins, with a predominance of the latter (Santonen et al., 2019). Several hundred PAHs exist, and they usually occur as complex mixtures that are produced during the combustion or pyrolysis processes. The US EPA (2005) has established a list of 16 PAHs, including anthracene, that are classified

Table 1.2 Total annual releases of anthracene to air, water, land disposal, or off-site disposal, in the USA, 2010–2020

	Releases (in pounds[b])										
	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Air	8 647	8 509	6 985	5 850	5 604	5 376	4 556	5 971	9 390	8 792	7 479
Land[a] (placed in a disposal facility on site)	[487]	[57 556]	[99 883]	[1 364]	[1 848]	[42 853]	[46 906]	[25 342]	[18 937]	[1 301]	[731]
Off-site disposal (transferred off-site) or other releases	58 493	24 969	15 179	7 578	7 978	9 541	6 529	22 053	12 351	55 805	20 603
Water	400	981	136	155	135	143	169	214	240	1 317	272
Total	68 027	92 015	122 183	14 947	15 565	57 913	58 161	53 579	40 918	67 215	29 085

[a] Release to land was calculated by the Working Group by subtracting all other releases from the total releases.
[b] To convert pounds into kilograms, multiply by 0.4536.
From US EPA (2023).

as priority pollutants on the basis of their representativeness and frequency of (co)occurrence in environmental samples (IARC, 2010; Keith, 2015). The total releases of anthracene per year to air, water, land (placed in disposal, defined as any underground injection, placed in landfills or surface impoundments, land treatment, or other intentional land disposal), or transferred off-site for disposal (or other releases not quantified elsewhere) in the USA during 2010–2020 are presented in Table 1.2 (US EPA, 2023). [The mean total is 56 328 pounds (25.57 tonnes) per year, with variations of –48% to +19% in the later years (2015–2020).] According to these data, the lowest emissions have been consistently to water (except for 2010 and 2019) and the highest to land (2011–2012, 2015–2018) or off-site disposal (2010, 2013–2014, 2019–2020). Emissions to air have been the second highest when off-site disposal was predominant (US EPA, 2023). The Toxics Release Inventory data from the 2019 national analysis in the USA (US EPA, 2023) show that releases by industry sector were, in descending order, petroleum (87.1%), chemical manufacturing (8.5%), primary metals (2.4%), electrical equipment (1.8%), petroleum bulk terminals (0.16%), electric utilities (0.03%), and non-metallic mineral products (0.009%); data from 2020 generally follow the same order (US EPA, 2023).

(a) Air

(i) Ambient air

Anthracene in the air originates mainly from incomplete combustion and industrial processes such as coking and primary aluminium production (Ravindra et al., 2008; Shen et al., 2014; Government of Canada, 2022b; US EPA, 2022). Since anthracene is a low-molecular-weight PAH, the majority of airborne anthracene is present in the gas phase, with a small fraction adsorbed on particles. Anthracene in the gas phase is degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals, and nitrate radicals and ozone (half-lives ranged from 2.1 to 10 hours) (Atkinson et al., 1989; ECHA, 2008a).

Anthracene is ubiquitous in the atmosphere and has even been detected at several global background sites, including the High Arctic (Norwegian Institute for Air Research 2022). There are numerous studies on measurements of anthracene in ambient air (selected references are listed in Table 1.3). Relatively high

Table 1.3 Occurrence of anthracene in ambient air

Location and collection date	No. of samples	Mean (range)	Median (IQR)	Analytical method (LOD)	Comments	Reference
Chicago, USA, 1995	12	14.1 ng/m³ (NR)	NR	HPLC-MS (NR)	Active sampling, 39 L/minute, QFF medium, gas and particle	Odabasi et al. (1999)
Gandy Bridge, USA, 2002	7–9	0.5 ng/m³ (NR)	NR	GC-MS (0.002 ng/m³)	Passive sampling, QFF, gas	Poor et al. (2004)
Baltimore, USA, 1997	1	0.332 ng/m³ (NR)	NR	GC-MS (NR)	Passive sampling, QFF-PUF, gas and aerosol	Dachs et al. (2002)
Adjacent to Chesapeake Bay, USA, 1997	1	0.185 ng/m³ (NR)			Summer, passive sampling, QFF-PUF, gas and aerosol	
Adjacent to Chesapeake Bay, USA, 1997	1	0.145 ng/m³ (NR)			Winter, passive sampling, QFF-PUF, gas and aerosol	
Bursa, Turkey, 2004–2005	25	6.09 ng/m³ (NR)	NR	GC-MS (0.5–201 ng)	Winter, filters and PUFs	Vardar et al. (2008)
		0.30 ng/m³ (NR)			Summer, filters and PUFs	
Boston, USA, 1991	NR	2.1 ng/m³ (NR)	NR	GC-MS	Average of the four seasons	US EPA (1992)
Houston, USA, 1991	NR	1.5 ng/m³ (NR)			Average of the four seasons	
Brisbane, Australia, 1998	6	4.3 (1.2–8.8) ng/m³	NR	GC-ITD (0.01 ng/m³)	Urban, winter, gas and particle	Müller et al. (1998)
	1	1.0 ng/m³ (NR)			Urban, summer, gas and particle	
Flanders, Belgium, 2001	6	6.22 ng/m³ (NR)	NR	HPLC-FLD (NR)	Active sampling, urban site, QF + PUF, winter	Du Four et al. (2005)
	6	2.5 ng/m³ (NR)			Active sampling, industrial site, QF + PUF, winter	
	6	6.1 ng/m³ (NR)			Active sampling, rural site, QF + PUF, winter	
Indigenous Nations' Park, Brazil, 2003	8	0.39 (0.05–1.77) ng/m³	NR	NR	Urban, active sampling, PUF, gas	Ströher et al. (2007)
Indubrasil, Brazil, 2003	9	0.51 (0.02–1.66) ng/m³			Industry, active sampling, PUF, gas	
Ary Coelho Square, Brazil, 2003	8	0.22 (0.03–0.87) ng/m³			Active sampling, square downtown, PUF, gas	
São Paulo City, Brazil, 2000	41	[0.021] (0.007–0.031) ng/m³		GC-MS (0.6 µg/mL)	Passive sampling, gas and particle	Vasconcellos et al. (2003)
Porto Alegre, Brazil, November 2001 to November 2002	73	[0.131] (0.010–5.120) ng/m³	NR	GC-MS (LOQ, 0.01 µg/mL)	Active sampling, gas and particle	Dallarosa et al. (2005b)
Metropolitan Area of Porto Alegre (MAPA), Brazil, 2002 and 2005	69	[0.056] (0.005–0.474) ng/m³	NR	GC-MS (0.001 ng/mL)	Traffic, active sampling, HV and dichotomous, PM_{10}	Dallarosa et al. (2008)

Table 1.3 (continued)

Location and collection date	No. of samples	Mean (range)	Median (IQR)	Analytical method (LOD)	Comments	Reference
Candiota region, Brazil, 2001	19	0.25 (0.010–2.420) ng/m³	0.060 ng/m³ (NR)	GC-MS (0.011 ng/m³)	Industry, active sampling, particle	Dallarosa et al. (2005a)
Santiago, Chile, 1997	60	NR (0.00–0.04) ng/m³	NR	GC-MS (NR)	Background, active sampling, particle	Kavouras et al. (1999)
Guangzhou, China, April 2001 to March 2002	NR	30 ng/m³	NR	GC-MS	Active sampling GFF-PUF, total in vapour and particle	Li et al. (2006)
Beijing, China, December 2005 to January 2006	30	1.15 ng/m³	NR	GC-MS (NR)	Active sampling (NR), GFF, particle $PM_{2.5}$	Wang et al. (2008)
Nanjing, urban, China, 2001–2002	40	0.52 (ND–1.83) ng/m³ 0.41 (ND–1.49) ng/m³	NR	GC-MS	Urban, active sampling, PM_{10} Urban, active sampling, $PM_{2.5}$	Wang et al. (2006)
Guangzhou, China, 2004	10	0.06 ng/m³ (NR)	NR	GC-MS (NR)	Active sampling, MOUDI, aerosol	Duan et al. (2007)
Seine estuary, France, 2001	26	[9.98] ng/m² per week (NR)	NR	HPLC-FLD-UV	Active sampling, GFF bulk atmospheric deposition, gas and particle	Motelay-Massei et al. (2007)
Marseilles, France, 2004	12	0.767 (0.003–4.343) ng/m³	NR	HPLC-FLD-UV	Urban, active sampling, gas and particle	Albinet et al. (2007)
	14	0.998 (ND–6.595) ng/m³		(NR)	Rural, active sampling, gas	
Essen, Germany, 1981	NR	About 10 ng/m³ (NR)	NR	Glass-capillary-GC	Winter, gas	Grimmer et al. (1981)
	NR	6.7 ng/m³ (NR)		Glass-capillary-GC	Summer, gas	
Athens, Greece, 2006	7	35.6 ng/m³ (NR)		HPLC-FLD (NR)	Winter, GFF, particle	Valavanidis et al. (2006)
	7	26.5 ng/m³ (NR)			Summer, GFF, particle	
Greater Athens area, 2001–2002	58	0.079 ng/m³ (NR)	NR	HPLC-FLD (NR)	Urban, active sampling, particle	Mantis et al. (2005)
	64	0.246 ng/m³ (NR)			Downtown, active sampling, particle	
	35	0.206 ng/m³ (NR)			Industry, active sampling, particle	
	29	0.01 ng/m³(NR)			Background, active sampling, particle	
Heraklion, Greece, 2000–2002	16	3.3 ng/m³ (NR)	NR	GC-MS (0.001 ng/m³)	Passive sampling, GFF-PUF, gas and particle	Tsapakis & Stephanou (2005)
Athens, Greece, 2003	55	3.18 ng/m³ (NR)	NR	GC-MS (NR)	Passive sampling, Koropi, gas and particle	Vasilakos et al. (2007)
	55	3.19 ng/m³ (NR)			Passive sampling, Spata, gas and particle	
Delhi, India, January 2002 to December 2003	24	63.6 ng/m³ (NR)	NR	GC-FID (NR)	Winter, particle	Sharma et al. (2007)
	24	17.1 ng/m³ (NR)			Summer, particle	

Table 1.3 (continued)

Location and collection date	No. of samples	Mean (range)	Median (IQR)	Analytical method (LOD)	Comments	Reference
Prato, Italy, 2002	11	4.48 ng/m³ (NR)	NR	HPLC-UV/FLD (NR)	Industry, active sampling, PUF-QFF, gas and particle	Cincinelli et al. (2007)
Nagasaki city, Japan, 1997–1998	42	0.09 ng/m³ (NR)	NR	HPLC-FLD (NR)	Traffic, active sampling, particle	Wada et al. (2001)
Higashi, Hiroshima, Japan, 2006–2007	21	0.035 ng/m³ (NR)	NR	GC-MS	Active sampling, particle	Tham et al. (2008)
Shimizu, Japan, 2000	NR	0.93 ± 0.88 (0.12–3.9 as min. and max.) ng/m³ [a] 0.51 ± 1.9 ng/m³	NR	HPLC-FLD (NR)	Summer, gas, and particle	Ohura et al. (2004)
Shimizu, Japan, 2001	NR	0.39 ± 0.26 (0.12–1.0 as min. and max.) ng/m³ [a] 0.31 ± 1.4 ng/m³			Winter, gas, and particle	
Sarajevo, (former) Jugoslavia, 2004	30	1.38 (0.50–2.39) ng/m³	NR	GC-MS (2.5 pg/m³)	Industry, active sampling, the average urban and rural areas, light industry, GFF-PUF, gas and particle	Škarek et al. (2007)
Tuzla, (former) Jugoslavia, 2004	30	4 ng/m³ (2.38–5.87) ng/m³			Industry, active sampling, the average urban and rural areas, heavy industrial, GFF-PUF, gas and particle	
Inchon, Seoul, Yangsuri, and Yangpyoung, Republic of Korea, 2002	NR	2.07 ng/m³ (NR)	NR	GC-MS (NR)	Active sampling, particle	Chang et al. (2006)
Changwon–Masan, Republic of Korea, 2004	18	NR (0.101–0.859) ng/m³	NR	HPLC-UV (NR)	Active sampling, particle, range of mean values	Lee & Lee (2008)
Daeyeon-dong, Republic of Korea, 2002–2004	NR	1.79 ng/m³ (NR)	NR	GC-MS (NR)	Urban, active sampling, GFF, particle	Moon et al. (2006)
Gijang-gun, Republic of Korea, 2002–2004	NR	1.23 ng/m³ (NR)			Suburban, active sampling, GFF, particle	
Seoul, Republic of Korea, 1998–1999	5	2.7 ng/m³ (NR)	NR	GC-MS	Passive sampling, gas and particle	Park et al. (2002)
Mount Halla site, Jeju Island, Republic of Korea, 1999–2002	36	0.004 (0.001–0.0185) ng/m³	NR	GC-MS (NR)	Passive sampling, QFF, particle	Lee et al. (2008)
Kuala Lumpur, Malaysia, 2001	19	0 ng/m³ (NR)	NR	GC-MS	Passive sampling, particle	Omar et al. (2006)

Table 1.3 (continued)

Location and collection date	No. of samples	Mean (range)	Median (IQR)	Analytical method (LOD)	Comments	Reference
Lahore, Pakistan, 1992–1993	62	4.99 ng/m³ (NR)	NR	HPLC-UV/FLD (NR)	Active sampling, city, QM/A QFF, particle	Smith et al. (1996)
	62	4.6 ng/m³ (NR)			Active sampling, industrial site, particle	
	62	2.93 ng/m³ (NR)			Active sampling, rural site, particle	
	62	4.17 ng/m³ (NR)			Traffic, active sampling, autumn, gas	
Balagtas, Bulacan, Philippines, 2005	2	1.631 ng/m³ (NR)	NR	GC-MS (0.24 ng/m³)	Rural, passive sampling, spring, gas	Santiago & Cayetano (2007)
	2	2.093 ng/m³ (NR)			Rural, passive sampling, summer, gas	
	2	3.719 ng/m³ (NR)			Rural, passive sampling, autumn, gas	
	2	8.574 ng/m³ (NR)			Rural, passive sampling, winter, gas	
Manila, Philippines, 2005	2	2.032 ng/m³ (NR)			Urban site, passive sampling, spring, gas	
	2	2.182 ng/m³ (NR)			Urban site, passive sampling, summer, gas	
	2	3.211 ng/m³ (NR)			Urban site, passive sampling, autumn, gas	
	2	7.318 ng/m³ (NR)			Urban site, passive sampling, winter, gas	
Rizal, Philippines, 2005	2	2.971 ng/m³ (NR)			Rural, passive sampling, spring, gas	
	2	2.635 ng/m³ (NR)			Rural, passive sampling, summer, gas	
	2	2.805 ng/m³ (NR)			Rural, passive sampling, autumn, gas	
	2	12.008 ng/m³ (NR)			Rural, passive sampling, winter, gas	
Laguna, Philippines, 2005	2	3.709 ng/m³ (NR)			Rural, passive sampling, spring, gas	
	2	2.907 ng/m³ (NR)			Rural, passive sampling, summer, gas	
	2	6.116 ng/m³ (NR)			Rural, passive sampling, autumn, gas	
	2	8.672 ng/m³ (NR)			Rural, passive sampling, winter, gas	
Errenteria, Spain, 1996–1997	167	0.05 ng/m³ (NR)	NR	GC-MS (0.02 ng/m³)	Traffic, active sampling (500 L/minute), particle	Mazquiarán & Cantón Ortiz de Pinedo (2007)
Valencia, eastern Spain, 2004–2005	126	0.03 ng/m³ (NR)	NR	NR	Active sampling, hospital, $PM_{2.5}$	Viana et al. (2008)
	120	0.03 ng/m³ (NR)			Local Sport Centre, $PM_{2.5}$	
	58	0.01 ng/m³ (NR)			Emergency Control Centre, $PM_{2.5}$	
	72	ND			School, $PM_{2.5}$	
	42	0.04 ng/m³ (NR)			Youth centre, $PM_{2.5}$	
	59	0.03 ng/m³ (NR)			Swimming pool, $PM_{2.5}$	

Table 1.3 (continued)

Location and collection date	No. of samples	Mean (range)	Median (IQR)	Analytical method (LOD)	Comments	Reference
Gothenburg, Sweden, 2000	NR	12 ng/m³ (NR)	NR	GC-FID (NR)	Active sampling (433 L/minute), gas and particle	Wingfors et al. (2001)
Hagfors, Sweden, 2003	8	1.2 (0.42–2.4) ng/m³	1.1 ng/m³ (NR)	GC-MS (NR)	Outdoors, gas and particle	Gustafson et al. (2008)
Thailand, Thailand, 2000	NR	0.21 ng/m³ (NR)	NR	GC-FID	Traffic, active sampling, particle	Chang et al. (2006)
Merinos, Turkey, 2004–2005	20	7 ng/m³ (NR)	NR	GC-MS (NR)	Industry, active sampling (161 L/minute), industrial residential area, gas and particle	Tasdemir & Esen (2007)
Bursa, Turkey, 2004–2005	20	120.6 ng/m³ (NR)	NR	GC-MS	Active sampling (9.8 m³/hour), gas and particle	Esen et al. (2008)
Aliaga industrial region, Turkey, 2004–2005	60	0.5 ng/m³ (NR)	NR	GC-MS (NR)	Industry, passive sampling, seasonal variation, summer, gas and particle	Bozlaker et al. (2008)
	60	1.5 ng/m³ (NR)			Industry, passive sampling, winter, gas and particle	
Bursa, Turkey, 2004–2005	25	6.09 ng/m³ (NR)	NR	GC-MS (NR)	Passive sampling, winter, GFF-PUF, gas and particle	Vardar et al. (2008)
	25	0.3 ng/m³ (NR)			Passive sampling, summer, GFF-PUF, gas and particle	
Birmingham, UK, 1996	NR	4.5 ng/m³ (NR)	NR	HPLC-UV/FLD (NR)	Winter, PUF, gas and particle	Harrison et al. (1996)
	NR	0.6 ng/m³ (NR)			Summer, PUF, gas and particle	
London, UK, 1992	26	5 ng/m³ (1.20-9.54 ng/m³)	NR	GC-MS (0.002 ng/m³)	PUF, gas and particle	Halsall et al. (1994)
Alert, High Arctic, Canada, 2004–2015	NR	3.78 pg/m³ (0.072–882 pg/m³ as min. and max.)	NR	GC-MS (NR)	GFF-PUF, gas and particle	Yu et al. (2019)

FID, flame ionization detection; FLD, fluorescence detection; GC-ITD, gas chromatography-ion trap detection; GC, gas chromatography; GC-MS, gas chromatography-mass spectrometry; GFF, glass microfibre filter; HPLC-FLD, high-performance liquid chromatography method-fluorescence detection; HPLC-UV, high-performance liquid chromatography method-ultraviolet detection; HV, high volume; IQR, interquartile range; LOD, limit of detection; max., maximum, min., minimum; LOQ, limit of quantification; MS, mass spectrometry; ND, not detected; NR, not reported; $PM_{2.5}$, particulate matter with diameter ≤ 2.5 µm; PM_{10}, particulate matter with diameter ≤ 10 µm; PUF, polyurethane foam; QF, quartz filter; QFF, quartz fibre filter; QFF-PUF, quartz fibre filter-polyurethane foam; UV, ultraviolet.

[a] Geometric mean.

concentrations of anthracene have been found in east Asia and south Asia. For example, measurements showed annual average concentrations of [40.3] ng/m^3 and [30.0] ng/m^3 in Delhi, India, and in Guangzhou, China, respectively, which can be one or more orders of magnitude higher than those in the USA [0.26] ng/m^3 (measurements only in July) and the United Kingdom [2.5] ng/m^3 (Harrison et al., 1996; Dachs et al., 2002; Li et al., 2006; Sharma et al., 2007) [Averages were calculated by the Working Group.] High seasonal levels of anthracene were also reported in the Philippines (up to 12 ng/m^3) and some European cities, including Essen, Germany (about 10 ng/m^3) and Athens, Greece (35.6 ng/m^3 in total suspended particulate) (Grimmer et al., 1981; Dachs et al., 2002; Mantis et al., 2005; Tsapakis & Stephanou, 2005; Valavanidis et al., 2006; Santiago & Cayetano, 2007; Vasilakos et al., 2007). The levels vary spatially, depending on the source proximity and long-range transport (Shen et al., 2014; Shrivastava et al., 2017). Based on a collection of measurements listed in Table 1.3, concentrations measured at urban (range, 0.021–120 ng/m^3) and industrial (range, 0.2–30 ng/m^3) sites or near road traffic (range, 0.05–4.17 ng/m^3) tended to be higher than those measured at regional background sites (range, 0.01–6.0 ng/m^3). Concentrations at rural sites (range, 0.11–12.0 ng/m^3), however, are comparable with or even higher than concentrations at urban sites (Table 1.3), mainly because of indoor and open burning of biomass, which frequently occurs in rural areas (Shen et al., 2013). Concentrations detected in the High Arctic are very low, in the order of 0.1–1000 pg/m^3 (Hung et al., 2005; Yu et al., 2019). Airborne anthracene shows seasonal variation, with some reported concentrations in winter being more than four times as high as those in summer (Sharma et al., 2007; Akyüz & Çabuk, 2010; Ma et al., 2010).

(ii) Indoor air

Cooking, heating, and smoking are the main indoor sources of anthracene (Liu et al., 2001; Ohura et al., 2004). Infiltration of air from the outside environment also contributes to indoor anthracene levels (Ali, 2019). Examples of measured levels of anthracene in indoor air can be found in Table 1.4. Indoor air quality was assessed in a residential area in Sweden, and levels were compared in households that did or did not use wood burning as a heating system; anthracene concentrations in the air were found to be higher in the wood-burning homes (median, 1 ng/m^3 versus 0.40 ng/m^3) (Gustafson et al., 2008). In China, in rural households using solid fuels for cooking, the highest concentrations of anthracene tend to be found in kitchens [mean ± standard deviation, 198 ± 96 ng/m^3] (Ding et al., 2012). In a study on different indoor microenvironments in Saudi Arabia, higher concentrations were also reported in kitchens (mean, 0.7 μg/m^3) than in other rooms (range of means, 0.3–0.6 μg/m^3) (Ali, 2019). In a study that evaluated exposure from indoor smoking in public bars in Enerhen Warri, Nigeria, the mean concentration in multiple samples collected in six different bars was 0.30 ng/m^3 (Adesina et al., 2021).

Seasonal variations in measured indoor anthracene concentrations are not consistent among studies, with some measurements indicating higher concentrations in autumn or winter (Ding et al., 2012; Chen et al., 2022; Florencia et al., 2022), whereas others suggested that concentrations were higher in summer (Liu et al., 2001; Ohura et al., 2004).

(b) Water

During 2010–2020 (Table 1.2), the annual amounts released from industry to water in the USA varied from 9047 pounds [4.10 tonnes] in 2010 to 135 pounds [0.06 tonnes] in 2014, demonstrating a marked reduction since 2013 (US EPA,

Table 1.4 Occurrence of anthracene in indoor air

Location and collection date	No. of samples	Mean (range)	Median (IQR)	Analytical method (LOD)	Comments	Reference
Hong Kong Special Administrative Region, China, 2014–2016	63	0.25 ± 0.17 (SD) ng/m³	NR	TD-GC-MS (0.48 ng/sample)	Average, air samples were taken in 26 non-smoking homes, 25% did not cook at home; $PM_{2.5}$-bound anthracene; 95th percentile, 0.60 ng/m³	Chen et al. (2022)
		0.20 ± 0.13 (SD) ng/m³			Summer	
		0.31 ± 0.19 (SD) ng/m³			Winter	
A rural household in Zhuanghu, Hebei, China, 4 days in winter (16, 17, 19, and 20 January) and 3 days in summer (13–15 June) in 2010	6	120 ± 48 (SD) ng/m³	NR	GC-MS	Winter, kitchen	Ding et al. (2012)
		42 ± 27 (SD) ng/m³			Winter, outdoors	
		19 ± 7.2 (SD) ng/m³			Winter, bedroom	
		58 ± 45 (SD) ng/m³			Summer, kitchen	
		3.7 ± 3.6 (SD) ng/m³			Summer, outdoors	
		18 ± 2.0 (SD) ng/m³			Summer, bedroom	
	4	11 ± 3.6 (SD) ng/m³			Winter, control	
		18 ± 7.1 (SD) ng/m³			Winter, cooking	
		16 ± 12(SD) ng/m³			Summer, control	
		17 ± 23 (SD) ng/m³			Summer, cooking	
Hangzhou, China, 1999	56	0.234 (0.019–0.683) μg/m³	NR	HPLC (3.58 pg)	Summer, smoking and non-smoking homes, air samples were taken in bedroom, balcony, kitchen, and living room.	Liu et al. (2001)
		0.220 (0.063–0.437) μg/m³			Autumn	
Qujiang District, south-eastern Xi'an, China, 2011–2012	18	95.1 (30.2–177.0) ng/m³	NR	HPLC (NR)	Measurements were taken in six different restaurants, under low ventilation conditions in wintertime	Dai et al. (2018)
Stockholm, Sweden, 2016–2017	5	2.01 (ND–10.9) pg/m³	NR	LC-GC-MS (0.027 pg/m³)	Preschool, indoor, PM_{10}	Lim et al. (2021)
Hagfors, Sweden, 2003	13	1.3 (ND–2.8) ng/m³	1.0 ng/m³	GC-MS (0.15 ng/m³)	Winter, wood-burning homes	Gustafson et al. (2008)
	10	0.41 (ND–0.84) ng/m³	0.40 ng/m³		Reference homes	
Shimizu, Japan, 2000–2001	25	0.94 (0.23–4.0) ng/m³	NR	HPLC-FLD (NR)	Homes, summer, industrial area	Ohura et al. (2004)
	22	0.31 (0.12–1.4) ng/m³			Homes, winter, industrial area	

Table 1.4 (continued)

Location and collection date	No. of samples	Mean (range)	Median (IQR)	Analytical method (LOD)	Comments	Reference
Preschools, Porto and Chaves, Portugal, May to June 2015	152 (8-hour)	NR	0.191 (0.00 471–0.665) ng/m³ 0.507 (0.336–0.638) ng/m³	LC-PAD (1 pg/m³)	Oporto city school Chaves city school	Oliveira et al. (2017b)
Jeddah, Saudi Arabia	20 10 15 10	0.6 (0.1–5.2) µg/m³ 0.4 (0.2–0.6) µg/m³ 0.7 (0.2–1.8) µg/m³ 0.3 (0.2–0.5) µg/m³	NR	GC-MS (NR)	Homes Hotel Kitchen Office Measurement of anthracene in PM_{10}	Ali (2019)
Urban area, Enerhen Warri, Nigeria, 2021	6	0.30 (0.15–0.44) ng/m³	NR	PUF passive samplers, GC-MS (NR)	Indoor smoking, bars in city with high petroleum activities	Adesina et al. (2021)
Urban–suburban, Cordoba, Argentina, winter and summer 2015	12 urban homes	0.31 ± 0.05 (SD) µg/m³ 0.52 ± 0.38 (SD) µg/m³ 0.25 ± 0.08 (SD) µg/m³ 0.63 ± 0.34 (SD) µg/m³	NR	HPLC	Summer, urban, TSP, passive collection for 28 days, non-smokers Winter, urban, TSP Summer, suburban, TSP Winter, suburban, TSP	Florencia et al. (2022)

GC-MS, gas chromatography-mass spectrometry; HPLC, high-performance liquid chromatography; HPLC-FLD, high-performance liquid chromatography method-fluorescence detection; IQR, interquartile range; LC-PAD, pulsed amperometric detection for liquid chromatography; LOD, limit of detection; MS, mass spectrometry; ND, not detected; NR, not reported; $PM_{2.5}$, particulate matter with diameter ≤ 2.5 µm; PM_{10}, particulate matter with diameter ≤ 10 µm; PUF, polyurethane foam; SD, standard deviation; TD-GC-MS, thermal desorption-gas chromatography-mass spectrometry; TSP, total suspended particulate matter.

2023). During 2013–2020, releases to water in the USA were < 1% of total industry releases and disposal of anthracene, except in 2019 (1.96%; 1317 pounds [0.60 tonnes] of the total of 67 215 pounds [30.49 tonnes]) (US EPA, 2023). The Canadian National Pollutant Release Inventory reported releases to water varying from 0.91 kg (2018; 0.009% of the total of 9956 kg released) to 2.39 kg (2019; 0.022% of the total of 10 757 kg released) during 2017–2021 (Government of Canada, 2022b). Besides industrial effluent discharge, other sources that contribute to the transfer of anthracene into water are municipal sewage, atmospheric deposition, surface runoff, and oil spills (IARC, 2010). Anthracene is not expected to hydrolyse in water, but its direct photolytic degradation to anthraquinone can be significant (half-lives in the range of 20 minutes to 125 hours), particularly under sunlight in shallow surface waters (half-lives, < 1 hour) (ECHA, 2008a; NCBI, 2022). Volatilization from water surfaces can also occur, but it is reduced by anthracene sorption to suspended particulate matter from the water column (NCBI, 2022).

Studies have shown the ubiquitous occurrence of anthracene in the aquatic environment worldwide, i.e. in seawater, surface water, groundwater, drinking-water, and wastewater (Table 1.5). Overall, levels for uncontaminated sites and drinking-water are the lowest, within the range of "not detected" picograms per litre to low nanograms per litre (< 10 ng/L). However, the median anthracene concentration in drinking-water was reported to be 28.76 ng/L in Nanjing, China, in 2007–2008 (Wu et al., 2010). Moreover, despite the very low solubility of anthracene in water, levels up to the microgram per litre range and as high as 14.14 µg/L and 14.89 µg/L in Algoa Bay, South Africa (Adeniji et al., 2019a), and 35.5 µg/L in Agbabu, Nigeria (Olajire et al., 2007), were reported for surface water or bottom water from geographical regions strongly affected by anthropogenic activities (Table 1.5). Groundwater is poorly characterized with regard to the presence of anthracene across continents, but the few available data also suggest that there is a high impact of industrial activities on groundwater contamination with anthracene (up to 5 µg/L in Sydney, Australia, and up to 3900 µg/L in Minnesota, USA, at old industrial sites) (Coffey Geotechnics Pty Ltd, 2016; Minnesota Department of Health, 2019). The levels in groundwater in the vicinity of non-industrial areas are typically in the low to tens of nanograms per litre range (e.g. 1.61–58.6 ng/L in the Grand Canal from Hangzhou to Beijing, east China) (Li et al., 2015), although higher concentrations were detected in Nigeria (0.010–2.91 µg/L) (Adekunle et al., 2017). Industrial and municipal wastewater displays the highest levels of anthracene, even after treatment, when compared with river water and other environmental waters from the same geographical area, e.g. not detected in river water and 16.4 ng/L in treated wastewater (Pena et al., 2009; Domínguez et al., 2018).

(c) Soil

Anthracene in soil can come from natural sources, such as oil spills, wildfires, and weathering of rocks, and from anthropogenic sources, including emissions from combustion of fossil fuel and biomass, and coking through atmospheric deposition (Tsibart & Gennadiev, 2013; Schlaback et al., 2016; Government of Canada, 2022b; US EPA, 2022). A large fraction of anthracene in the atmosphere is first accumulated in plants before being introduced into soils (Simonich & Hites, 1994). In soil, anthracene mainly undergoes sorption, leaching, and biodegradation processes and can be re-emitted into the atmosphere, representing part of the dynamic surface–air exchanges. The biodegradation of anthracene is influenced by the soil type and the resident microbial communities; half-lives ranging from 19 to 134 days have been reported (NCBI, 2022). The occurrence and concentrations of anthracene in soil are thus determined by source proximity, vegetation coverage, and

Table 1.5 Occurrence of anthracene in environmental waters

Sample type	Location and collection date	No. of samples	Mean (range)	Median (IQR)	Analytical method (LOD)	Comments	Reference
Africa							
Seawater: Surface microlayer (< 1 mm)	Alexandria coast, Egypt, 2002	21	24 (ND–69) ng/L	NR	GC-MS (0.2 µg/L)	12 sites	El Nemr & Abd-Allah (2003)
Subsurface water (0.5 cm)		51	3.8 (0.3–12.49) ng/L	NR			
Surface water: Raw water	Nile River, Greater Cairo, Egypt, 2018	96	ND–496 (ND–672) ng/L	NR	GC-MS (NR)	8 sites; drinking-water supply	Fouad et al. (2022)
Treated water		96	NR	NR			
Surface water	Estuaries and lagoons, coastal belt, Ghana, 2007	60	ND–1.2 µg/L	NR	GC-FID (0.001 µg/L)	6 sites	Essumang (2010)
Subsurface water (0.5 m)	Agbabu, Nigeria, NR	6	ND–35.5 µg/L	NR	GC-FID (1 ng/L)	Sampling in the vicinity of a bitumen exploration	Olajire et al. (2007)
Lagoon: Surface microlayer (< 1 mm)	Lagos Lagoon, Nigeria, NR	72	ND–0.2 µg/L	NR	GC-ECD (NR)	6 sites	Benson et al. (2014)
Subsurface water (15–20 cm)		72	ND–0.1 µg/L	NR			
Groundwater: Wet season Dry season	Ife North Local Government Area of Osun State, Nigeria, 2014	72	 0.51 (0.01–2.91) µg/L 0.10 (0.01–0.19) µg/L	 NR NR	GC-TOMS (NR)	Non-industrial area site; sampling done in wet and dry season	Adekunle et al. (2017)
Bay: Surface water (10 cm depth)	Algoa Bay, South Africa, 2015–2016	250	5.61 (ND–14.14) µg/L	NR	GC-FID (NR)	5 sites; the bay (only 30 m depths) receives large influx of wastes from Swartkops and Sundays Rivers	Adeniji et al. (2019a)
Bottom water (30 m depth)		250	6.87 (ND–14.89) µg/L	NR			
River Surface water (2.40–6.16 m)	Buffalo River Estuary, East London city, South Africa, 2015–2016	60	1.97 (ND–7.81) µg/L	NR	GC-FID (NR)	5 sites	Adeniji et al. (2019b)
Groundwater (12–30 m)	Bwaise and Wobulenzi, Uganda, 2018–2020	NR	ND–340.0 ng/L	NR	GC-MS (0.9 ng/L)	12 sites	Twinomucunguzi et al. (2021)

Table 1.5 (continued)

Sample type	Location and collection date	No. of samples	Mean (range)	Median (IQR)	Analytical method (LOD)	Comments	Reference
North America							
Lake, surface water Urban (basins with > 15% urban land cover)	Minnesota, Wisconsin, Michigan, Indiana, Ohio, and New York, USA, 2010–2013	196	0.016 (ND–0.14) µg/L	NR	GC-MS (0.01 µg/L)	Means computed using left-censored data methods	Baldwin et al. (2016)
Non-urban (samples from basins with < 15% urban land cover)		513	0.005 (ND–0.03) µg/L	NR			
Drinking-water wells	Minnesota, USA, 2018	NR	3900 µg/L	NR	NR	Wells near known contamination sites	Minnesota Department of Health (2019)
Drinking-water	Texas, Rhode Island, USA, 2017–2019	NR	0.00259–0.00407 µg/L	NR	NR		EWG (2022)
River water	South Dakota, USA, 2001–2004	NR	0.082 to < 0.5 µg/L (dissolved) 0.06 to < 0.5 µg/L (whole water)	NR	NR		USGS (2006)
Drinking-water			0.082 µg/L (dissolved) 0.06 to < 0.5 µg/L (whole water)				
Wastewater treatment plant effluent			0.082 to < 0.5 µg/L (dissolved)				
South America							
Surface water	São Paulo, Brazil	6	< 0.036 µg/L	NR	HPLC (NR)		Pereira et al. (2017)
Groundwater		3	< 0.036 µg/L				
Lake (5 m)	North Patagonian lake, Chile, 2017	13	10.1 (0.42–58.3) pg/L	NR	GC-MS (NR)	13 sampling events	Tucca et al. (2020)
River (15–30 cm)	Cauca River, Colombia, 2010–2011	NR	ND–431.1 ng/L	NR	HPLC-UV-FLD, GC-MS (NR)	8 sites; 3 campaigns	Sarria-Villa et al. (2016)
Asia							
Groundwater	Grand Canal from Hangzhou to Beijing, east China, 2014	50	1.61–58.6 ng/L	NR	GC-MS (0.24 ng/L)	8 sites	Li et al. (2015)
Drinking-water	Nanjing China, 2007–2008	32	28.80 (ND–79.82) ng/L	28.76 ng/L	GC-MS (NR)		Wu et al. (2010)

Table 1.5 (continued)

Sample type	Location and collection date	No. of samples	Mean (range)	Median (IQR)	Analytical method (LOD)	Comments	Reference
Lakes Surface water	Northern China, 2014	66	(0.05–6.82) ng/L	0.95 (1.7) ng/L	GC-MS (0.5 ng/mL)	44 lakes	He et al. (2020)
Lake	China, 2006–2018	NR	ND–1410 ng/L	NR	NR	Data retrieved from literature; 14 lakes	Meng et al. (2019)
Lakes and rivers (1 m)	China, 2013	NR	0.06–0.46 ng/L	NR	GC-MS (NR)	42 sites; the concentration in South Lake (27 ng/L), Wuhan, exceeded the water quality guidelines of the Canadian Council of Ministers of the Environment (12 ng/L)	Yao et al. (2017)
Reservoir Surface water (0.5–1 m)	Jilin, China, 2014	12	0.510 (0.120–0.760) µg/L	NR	GC-FID (NR)	12 sites	Sun et al. (2015)
Rivers, river basin, river estuary, reservoir, water body in city, drinking-water resource Surface water	China, 1999–2009	NR	71.235 (ND–2063.96) ng/L	5.225 (NR) ng/L	NR	Data retrieved from literature	Wu et al. (2011)
River Water	Jilin Province to the Russian Federation along Songhua River, China, 2007–2008	42	16.39 (9.68–70.68) ng/L	NR	GC-MS (NR)		Zhao et al. (2014)
River, surface water	Hun River, Liaoning Province, China, 2009				HPLC-FLD (NR)	14 sites	Zhang et al. (2013)
Dry period (April)		28	3.11 (0.33–8.24) ng/L	NR			
Flood period (July)		28	105.25 (ND–187.99) ng/L	NR			
Level period (November)		28	106.45 (62.38–233.3) ng/L	NR			
River	Tianjin, China, 2014				GC-MS (1 ng/L)	7 sites (surface water)	Cao et al. (2005)
Surface water (0–10 cm)		NR	< 1 ng/L	NR			
Reclaimed water (from secondary treated wastewater)		NR	< 1 ng/L	NR			

Table 1.5 (continued)

Sample type	Location and collection date	No. of samples	Mean (range)	Median (IQR)	Analytical method (LOD)	Comments	Reference
River Surface water	Tianjin, China, NR	30	0.006 (1.0–22.2) µg/L GM, 0.0051 µg/L	NR	GC-MS (NR)		Yang et al. (2006)
River, subsurface water (0.5 m)	Shenyang, China, 2015–2016	480	0.01 µg/L [a]	NR	HPLC-UV-FLD (NR)	10 sites	Li et al. (2017)
River (0.50 m)	Xihe River, Shenyang, China, 2005	NR	5–10 ng/L [a]	NR	GC-MS (NR)	7 sites	Guo et al. (2011)
River Surface water (0.5 m)	Middle China, 2005–2006	NR	1.1–128.1 ng/L	NR	GC-MSD (NR)	26 sites	Sun et al. (2009)
Seawater Surface water	Liaodong Bay, China, 2009	5	NR	3 (5) ng/L[a]	GC-MS (0.2 ng/L)		Wang et al. (2016a)
Drinking-water	Southern Jharkhand, east India, 2019	120	1.50–4.83 (ND–9.01) ng/L	NR	GC-FID with MS (0.13 ng/L)	6 districts, 60 locations; hand pumps and groundwater wells	Ambade et al. (2021)
River Surface water	Cuttack city, India, 2019	14	1.77 (ND–3.36) µg/L	1.5 (2) µg/L[a]	GC-FID (NR)	14 sites	Kurwadkar et al. (2022)
River Surface water (30 cm)	Gomti River, India, 2004–2006	48	0.03–0.09 (ND–0.86) µg/L	ND–0.01 µg/L	HPLC-UV-VIS (1 ng/L)	8 sites	Malik et al. (2011)
Drinking-water	Misan Governorate, Iraq, 2015	15	ND–70.79 ng/L	NR	HPLC-FLD (NR)	15 stations, 1 sample per station	Jazza et al. (2016)
Drinking-water	Tehran, Islamic Republic of Iran, 2011–2012	99	NR	NR	GC-MS (NR)	6 districts, 4 samples per district in each season	Karyab et al. (2013)
Tap water	Tehran, Islamic Republic of Iran, 2014	36	ND	NR	GC-MS (NR)	6 regions, 6 samples per region	Sadeghi et al. (2016)
Seawater (1.3–12.2 m)	Tokyo Bay and Suruga Bay, Japan, 2003	8	ND–4.7 ng/L	NR	GC-MS (0.2 ng/L)	8 sites	Kurihara et al. (2005)
Groundwater Surface water	Mongolia	22 11	0.81 ng/L	NR	GC-MS (NR)		Zhang et al. (2022)
River Surface water	Soan River, Kurang River, Ling Stream, Nallah lai Potohar, Pakistan, 2013	30	17.7 (8.7–28.0) ng/L	NR	GC-MS (NR)	10 sites	Aziz et al. (2014)

Table 1.5 (continued)

Sample type	Location and collection date	No. of samples	Mean (range)	Median (IQR)	Analytical method (LOD)	Comments	Reference
Europe							
River and lake	Strymonas River, Greece, 2013					7 sites	Terzopoulou & Voutsa (2017)
Active sampling		33	ND	ND	GC-MS/MS (NR)		
Passive sampling		12	0.039 µg/sample	ND	SPMD (NR)		
River Surface water	Nestos River, Greece, 2008–2009	NR	ND–0.062 µg/L	NR	GC-MS (NR)	16 sites	Gikas et al. (2020)
River Surface water (0.3 m)	Rackevei-Soroksari Danube Branch, Hungary, 2002–2004	240	13.2 (0.9–96.2) ng/L	6.9 (NR)	HPLC-UV-FLD (0.5 ng/L)	10 sites	Nagy et al. (2007)
River Surface water (30 cm)	Raba River, Hungary, 2008–2012	54	0.50–2.25 (ND–8) ng/L	NR	GC-MS (1 ng/L)	4 sites	Nagy et al. (2013)
Lake (1 m)	Headwater lake catchments, Ireland, 2009–2010	15	7.59 (ND–38.0) pg/L	NR	GC-LRMS (NR)	5 sites	Scott et al. (2012)
Tap	Galicia (north-western Spain), NR	9	ND	NR	HPLC-FLD (0.2 ng/L)		Pena et al. (2009)
Bottled			ND				
Fountain			ND				
Well waters			8.1 ng/L				
Rainwater			ND				
River waters			ND				
Treated wastewater			16.4 ng/L				
Urban wastewater	Sevilla, Spain, 2016–2017	18			GC-HRMS (NR)	18 sites; LOQ, 0.07 ng/L	Domínguez et al. (2018)
Influents			119.89–177.21 ng/L	NR			
Effluents			3.62–158.43 ng/L	NR			
Oceania							
Groundwater	Sydney, Australia, 2016	3	< 1–5 µg/L	NR	NR	3 sites near fuel bunkers	Coffey Geotechnics Pty Ltd (2016)

GC-ECD, gas chromatography-electron capture detection; GC-FID, gas chromatography-flame ionization detection; GC-HRMS, gas chromatography-high-resolution mass spectrometry; GC-LRMS, gas chromatography-low-resolution mass spectrometry; GC-MS, gas chromatography-mass spectrometry; GC-MS/MS, gas chromatography-tandem mass spectrometry; GC-TOMS, time-of-flight-mass spectrometry; GM, geometric mean; HPLC, high-performance liquid chromatography; HPLC-FLD, high-performance liquid chromatography method-fluorescence detection; HPLC-UV-FLD, high-performance liquid chromatography-ultraviolet detection-fluorescence detection; HPLC-UV-VIS, high-performance liquid chromatography-ultraviolet detection-visible light detection; IQR, interquartile range; LOD, limit of detection; LOQ, limit of quantification; MS, mass spectrometry; ND, not detected; NR, not reported; SPMD, semipermeable membrane device.

[a] Estimated value extracted from a graph.

soil properties, and show large spatial variation. Levels of soil anthracene are reported to be higher in city centres and residential areas than in urban green spaces (Ciarkowska et al., 2019). Levels of anthracene are typically lower in forest soils than in urban soils. Anthracene concentrations are higher in forest soils than in rural agricultural soils in temperate zones, and lower in tropical zones (Amazon basin) (Wilcke, 2000) than in temperate zones. Globally, south and east Asia show relatively high levels of soil anthracene (in the order of 1.0–100 µg/kg) (Table 1.6), primarily due to high levels of anthropogenic emissions (Tao et al., 2004; Liu et al., 2016). For example, anthracene concentrations of up to 448.1 µg/kg have been reported in severely contaminated agricultural soils in Tianjin, China (Tao et al., 2004). High levels of anthracene have been also detected in Europe and North America, especially in urban settings (Mielke et al., 2004; Ciarkowska et al., 2019). For example, it was reported that, in metropolitan New Orleans, USA, the median level of soil anthracene was 42 µg/kg at an inner-city site, whereas anthracene was not detected at a suburban site (Mielke et al., 2004).

(d) Food

Anthracene is detected in foodstuffs because of environmental contamination (via water, soil and/or air) and/or unintended formation during food processing. Smoking, barbecuing, grilling, broiling, roasting, frying, and other high-temperature heating processes are responsible for the highest levels of contamination, e.g. 0.01–0.02 and 13.23 ng/g fresh weight (fw) in raw and smoked meat, respectively (Golzadeh et al., 2021); 9.52 and 12.15–157.41 µg/kg dry weight (dw) in raw and smoked sausage, respectively (Roseiro et al., 2011); 0.2187–4.2340 and 0.9901–9.5054 µg/kg fw in uncooked and grilled meat products, respectively (Samiee et al., 2020) (Table 1.7). Data retrieved from several food surveys show that the lowest anthracene concentrations are always present in the raw food, independently of the category (Table 1.7). Also, in general, higher levels are found in animal-based raw or processed foodstuffs (predominantly in meat and meat products, and fish and shellfish) and the lowest levels are found in fruit and vegetables, e.g. 0.01–1.18 µg/kg fw in fresh fruit; 0.01–2.65 µg/kg fw in fish and fish products; and 0.01–7.84 µg/kg fw in meat and meat products (Cirillo et al., 2010); 0.018 µg/kg fw in fruit; 0.110 µg/kg fw in fish and shellfish; and 0.180 µg/kg fw in meat and meat products (Falcó et al., 2003; Domingo & Nadal, 2015; Aamir et al., 2021) (Table 1.7). [The Working Group noted the variation in precision of the reported values in the literature. Values are stated as reported in the original publications.] Since anthracene has low hydrophilicity, it mainly accumulates in lipophilic matrices such as fat animal or fish tissues and high-fat foodstuffs, such as fish oil (Table 1.7). When applicable, the contamination level of fat or oil introduced into the commercial formulations should be considered as a potential anthracene source in the final foodstuff (Santonicola et al., 2017). Moreover, when released into water, anthracene adsorbs to suspended particle matter and sediments, which can be ingested and promote bioaccumulation in aquatic organisms, particularly predators, in species that occupy higher trophic positions, in bottom-dwelling fish species, and in bivalves (filter feeders). Moderate to very high bioconcentration factors (162–9200) have been reported for anthracene (NCBI, 2022). Bivalves, molluscs, crustaceans, and cephalopods seem to be unable to significantly metabolize PAHs, including anthracene, resulting in higher concentrations in these species than in finfish, when collected from the same polluted site (Perugini et al., 2007; Ramalhosa et al., 2012; Semedo et al., 2014) (Table 1.7).

(e) Consumer products

Anthracene has been mostly detected in the particulate phase emitted from different products or uses such as tobacco

Table 1.6 Occurrence of anthracene in soil

Location and collection date	No. of samples	Mean (range)	Median	Analytical method (LOD)	Comments	Reference
Agra, India, 2003	319	1.29 ± 1.12 µg/g (mean ± SD)	NR	HPLC-UV (NR)	Industrial	Masih & Taneja (2006)
	319	1.02 ± 0.66 µg/g			Roadside	
	319	0.57 ± 0.39 µg/g			Residential	
	319	0.36 ± 0.21 µg/g			Agricultural	
Ulsan, Republic of Korea, July 2010	5	26 (14–52) µg/kg	20 µg/kg	GC-ITMS (1.2 µg/kg)	Rural area	Kwon & Choi (2014)
	10	19 (2.3–61) µg/kg	17 µg/kg		Urban area	
	10	50 (3.0–330) µg/kg	15 µg/kg		Industrial area	
	25	33 (2.3–330) µg/kg	16 µg/kg		Total	
Hong Kong Special Administrative Region, China, 2003	39	13.5 (ND–389) µg/kg	2.5 µg/kg	GC-MS (10 µg/kg)	Urban park	Chung et al. (2007)
	14	4.6 (ND–14.4) µg/kg	3.2 µg/kg		Greening area	
	9	1.4 (ND–4.3) µg/kg	1.0 µg/kg		Country park	
	19	2.4 (ND–10.0) µg/kg	1.0 µg/kg		Rural area	
	11	3.8 (ND–26.3) µg/kg	1.0 µg/kg		Restored landfill	
	9	1.5 (ND–5.08) µg/kg	1.0 µg/kg		Agricultural farmland	
	5	1.9 (ND–5.59) µg/kg	1.0 µg/kg		Orchard farm	
	10	1.0 (ND–ND) µg/kg	1.0 µg/kg		Crematorium	
	18	7.0 (ND–87.8) µg/kg	1.0 µg/kg		Industrial area	
	4	31.1 (2.2–56.1) µg/kg	33.1 µg/kg		Nearby highway	
Krakow, Poland, 2016	4	531 ± 740 (63.2–1628) µg/kg	NR	GC-MS (2 µg/kg)	City central	Ciarkowska et al. (2019)
Zakopane, Poland, 2016	3	45.2 ± 41.1 (ND–84.5) µg/kg			City central	
Krakow, Poland, 2016	3	34.8 ± 7.7 (25.9–40.2) µg/kg			Residential	
Zakopane, Poland, 2016	3	43.7 ± 47 (ND–94.9) µg/kg			Residential	
Krakow, Poland, 2016	3	12.1 ± 6.6 (6.0–19.1) µg/kg			Green area	
Zakopane, Poland, 2016	3	10.2 ± 9.8 (ND–21.2) µg/kg			Green area	
Republic of Korea, 2000	126	8.0 (0.30–43.1) µg/kg		GC-MS (NR)	Paddy soil	Nam et al. (2003)
	100	6.88 (0.30–33.7) µg/kg			Upland soil	
Temperate topsoil	14	2.4 (ND–11) µg/kg	1.6	GC-MS (NR)	Arable, temperate topsoil	Wilcke (2000)
	33	1.6 (ND–4.3) µg/kg	1.5		Grassland, temperate topsoil	
	54	8.6 (ND–75) µg/kg	3.4		Forest, temperate topsoil	
	94	58 (ND–1400) µg/kg	18		Urban, temperate topsoil	
Bangkok, Thailand, 1996	4	1.5 (1.3–1.9) µg/kg	1.4	GC-MS (NR)	Rural agricultural and forest	Wilcke et al. (1999a)
	30	1.2 (0.1–5.0) µg/kg	0.7		Urban	

Table 1.6 (continued)

Location and collection date	No. of samples	Mean (range)	Median	Analytical method (LOD)	Comments	Reference
Uberlândia, Brazil, 1996	18	1.0 (0.0–6.2) µg/kg	0.8	GC-MS (NR)	Urban	Wilcke et al. (1999b)
Amazonian, Brazil, 1997	6	0.8 (0.3–2.6) µg/kg	0.4	GC-MS (NR)	Forest	Wilcke (2000)
Bangkok, Thailand, 1996	4	1.2 (0.1–5.0) µg/kg	0.7	GC-MS (NR)	Rural agricultural and forest	Wilcke et al. (1999a)
Shanghai, China, 2007	36	6.4 ± 6.4 (1.0–36.6) µg/kg		GC-MS (NR)	Agricultural	Jiang et al. (2011)
Tianjin, China, 2006	105	36.2 ± 47.3 (ND–261) µg/kg	21.5	GC-MS (2.9 µg/kg)	Industrial	Jiao et al. (2009)
Shanxi, China, 2014	32	281.68 ± 347.07 (ND–1892.51) µg/kg	165.80	GC-MS (NR)	Agricultural soils in the vicinity of a chemical plant	Liu et al. (2016)
Beijing, China, 2008	127	12.5 ± 17.6 (ND–124.8) µg/kg GM, 6.4 µg/kg	NR	GC-MS (NR)	Urban	Liu et al. (2010)
Xiangfen, Shanxi, China, 2012	128	20.62 ± 29.79 (ND–287.25) µg/kg	14.01	GC-MS (NR)	County average	Pan et al. (2015)
Beijing, China, 2010	162 73	5.7 ± 8.8 (0.5–55.3) µg/kg 3.8 ± 4.6 (0.7–21.8) µg/kg	2.8 2.1	GC-MS (0.10 µg/kg)	Suburban Rural	Peng et al. (2016)
Yangtze River Delta, China, 2004	138	4.7 (ND–34.7) µg/kg	1.6	HPLC-FLD (0.35 µg/kg)		Ping et al. (2007)
Xianyang, China,	59	1.61 ± 4.07 (ND–20.61) µg/kg	NR	HPLC-FLD (NR)	Vegetable soil from suburbs	Wang et al. (2016a)
New Orleans, USA, 2001	38 38	NR (2–163) µg/kg NR (ND–45) µg/kg	42 ND	GC-MS (NR)	Inner city Suburban	Mielke et al. (2004)
Tianjin, China	4 4	42.4 µg/kg 448.1 µg/kg	NR	GC-MS (NR)	Agricultural Agricultural	Tao et al. (2004)

GC, gas chromatography; GC-ITMS, gas chromatography-ion trap-mass spectrometry; GM, geometric mean; HPLC, high-performance liquid chromatography; HPLC-FLD, high-performance liquid chromatography-fluorescence detection; IT-MS, ion trap-mass spectrometry; LOD, limit of detection; ND, not detected; NR, not reported; SD, standard deviation; UV, ultraviolet detection.

Table 1.7 Occurrence of anthracene in food and beverages

Sample type	Location and collection date	No. of samples	Mean (range)	Median (IQR)	Analytical method (LOD)	Comments	Reference
Africa							
Meat	Zagazig city, Egypt, 2017				HPLC-FLD (0.03 ng/g)	Beef	Darwish et al. (2019)
Raw		25	0.19 (0.12–0.28) ng/g fw	0.17 (NR) ng/g fw			
Boiled		25	0.31 (0.08–0.55) ng/g fw	0.29 (NR) ng/g fw			
Pan-fried		25	0.55 (0.35–0.78) ng/g fw	0.53 (NR) ng/g fw			
Grilled		25	1.24 (0.25–2.25) ng/g fw	1.13 (NR) ng/g fw			
Raw cocoa beans	Ghana; Côte d'Ivoire; Dominican Republic; Ecuador; Nicaragua; Venezuela, date of collection, NR	9 of each origin and variety	0.26–1.1 µg/kg dw	NR	HPLC-FLD (0.07 µg/kg)		Ciecierska (2020)
Roasted cocoa beans			0.40–1.48 µg/kg dw				
Cocoa mass			0.62–2.85 µg/kg dw				
Cocoa butter			1.35–5.54 µg/kg dw				
Chocolate			0.29–1.33 µg/kg dw				
North America							
Meat	Chicago, USA	15	2 µg/kg fw	NR	UV-FLD (NR)	Charcoal-broiled steak meat	Lijinsky & Shubik (1964)
Meat	Alberta, Canada, 2015			NR	GC-LRMS (NR)	Raw meat: grouse muscle, moose muscle, bear muscle; Raw fish muscle; Plants: berry, rat root, old man's beard	Golzadeh et al. (2021)
Raw		17	0.01–0.02 ng/g fw				
Smoked		5	13.23 ng/g fw				
Fish		6	0.04 ng/g fw				
Plants		21	0.03–0.67 ng/g fw				
Fish (*Megalops atlanticus*) (raw)	Lagoon of Terminos, Mexico, NR	NR	0.1 (0–1.2) ng/g dw	NR	GC-FID (NR)		Canedo-Lopez et al. (2020)
Fish oil from Menhaden fish	New Jersey, USA, 2010	NR	90–130 ng/g fw	NR	GC-MS (1 ng/g)		Chopra et al. (2019)
South America							
Liquid smoke flavour	São Paulo, Brazil, NR	22	ND–600.4 µg/kg fw	NR	HPLC-FLD- (0.6 µg/kg)	Ox rib, bacon, loin, ham, sausage	Yabiku et al. (1993)
Smoked meat and meat products		88	ND (ham) – 83.6 (ox rib) µg/kg fw				

Table 1.7 (continued)

Sample type	Location and collection date	No. of samples	Mean (range)	Median (IQR)	Analytical method (LOD)	Comments	Reference
Gastropods (*Buccinanops globulosus*)	Patagonia, Argentina, NR	50	ND–174 µg/kg dw	NR	GC-FID, GC-MS (5 µg/kg)	2 locations	Primost et al. (2018)
Hybrid corn grains No drying (no heat) Drying (firewood and direct fire)	Rio Grande do Sul, Brazil, NR	88	 ND 10.90–16.09 µg/kg dw	NR	GC-MS (2.3 µg/kg)		de Lima et al. (2017)
Asia							
Kebabs (grilled foods)	Kermanshah Province, Islamic Republic of Iran	50	NR	15.91 (3.5) µg/kg fw	GC–MS (NR)		Gholizadah et al. (2021)
Meat products Sausage (all cooking methods) Burger (all cooking methods) Uncooked Fried Grilled	Tehran, Islamic Republic of Iran, NR	50	 2.21 (0.56–4.20) µg/kg fw 5.05 (0.21–14.21) µg/kg fw 1.82 (0.219–4.23) µg/kg fw 4.86 (1–14.24) µg/kg fw 4.82 (0.99–9.51) µg/kg fw	NR	GC-MS (NR)	Sausages and burgers; fried in sunflower oil; grilled on charcoal (just burgers)	Samiee et al. (2020)
Fish: mackerel (*Scomber japonicas*); Alaska pollock (*Theragra chalcogrammus*); yellow croaker (*Larimichthys polyactis*); hair tail (*Trichiurus lepturus*); flatfish	Republic of Korea, NR	100	ND (mackerel, Alaska pollock, hair tail, flatfish) – 0.01 (yellow croaker) µg/kg fw	NR	GC-MS (0.01 µg/kg)	7 locations; raw	Hwang et al. (2012)

Table 1.7 (continued)

Sample type	Location and collection date	No. of samples	Mean (range)	Median (IQR)	Analytical method (LOD)	Comments	Reference
Shellfish: shortneck clam (*Tapes phillipinarum*); oyster (*Crassostrea gigas*); sea mussel (*Mytilus coruscus*); granular ark clam (*Tegillarca granosa*)		80	ND				Hwang et al. (2012) (cont.)
Cephalopod: cuttlefish (*Todarodes pacificus*); whip-arm octopus (*Octopus variabilis*); common octopus (*Octopus dofleini* [*vulgaris*])		60	ND				
Crustacea: crab (*Portunus trituberculatus*); shrimp (*Exopalaemon orientis Holthuis*)		40	ND (shrimp) –0.1 (crab) µg/kg fw				
Bread	Tehran city, Islamic Republic of Iran, NR	47	14.59 (ND–20.77) ng/g fw	NR	GC-MS (0.561 ng/g)	Iranian traditional Sangak bread	Peiravian et al. (2021)
Wheat grain	Shaanxi and Henan Provinces, China, 2015	51	4.04–5.22 (2.40–9.56) µg/kg fw	4.19–5.26 µg/kg (NR)	HPLC-UV-FLD (NR)	4 locations	Tian et al. (2018)
Coffee beans (*Coffea canephora*)	Chumphon Province, Thailand, NR	NR		NR	GC-MS (NR)		Rattanarat et al. (2021)
Hot air			0.09–0.34 µg/kg dw				
Superheated steam			0.10–0.21 µg/kg dw				

Table 1.7 (continued)

Sample type	Location and collection date	No. of samples	Mean (range)	Median (IQR)	Analytical method (LOD)	Comments	Reference
Natural mineral water	China, NR	3	ND (NR)	NR	HPLC-FLD (liquid, 0.6 ng/L; solid, 0.05 ng/g)	Beverages: natural, litchi juice, white grape juice, jasmine tea Solid: ginseng, milkvetch, Maojian tea, honeysuckle, Anji white tea	Deng et al. (2021)
Beverages		9	ND (NR)	NR			
Honey		3	37.86 (NR) ng/L	NR			
Plants		15	1.24 (ginseng) – 27.39 (Anji white tea) ng/g dw	NR			
Yogurt	Tehran, Islamic Republic of Iran, 2018–2019	48	0.02 (0.02–0.02) µg/kg fw	NR	GC-MS (0.040 µg/kg)	Yogurt	Kiani et al. (2021)
Butter		48	0.02 (0.02–0.02) µg/kg fw				
Europe							
Smoked fish	Denmark, Scotland, Norway, Italy, France	10	25.6 (ND) (salmon, swordfish, eel) to 51.8 (herring) ng/g fw	NR	HPLC-FLD (NR)	Salmon, swordfish, herring, eel, bluefin tuna	Storelli et al. (2003)
Mollusk (*Haliotis tuberculat*)	Italy, 2014	60	0.23–0.86 (ND–2.41) µg/kg fw	ND–0.30 (0.11–1.38) µg/kg fw	HPLC-FLD (0.30 µg/kg fw)	3 locations; raw	Conte et al. (2016)
Smoked dry-cured ham (prosciutto)	Herzegovina, Bosnia and Herzegovina, 2019	34	1.39 (0.50–5.06) µg/kg dw	NR	GC-MS (0.30 µg/kg)		Mastanjević et al. (2020)
Smoked seafood: Automatic smoking kilns	Northern Germany, NR	35	0.4 (salmon cold smoked) to 25 (belly flaps of spurdog) (ND (salmon cold smoked) to 29 (belly flaps of spurdog)) µg/kg fw	0.4 (salmon cold smoked) – 25 (belly flaps of spurdog) (NR) µg/kg fw	HPLC-FLD (1 µg/kg) GC-MS (NR)	8 locations; mackerel fish, eel, belly flaps of spurdog (Schillerlocke), salmon cold smoked, salmon hot smoked, herring, halibut cutlets, red-fish, sprat	Karl & Leinemann (1996)
Tradition smoking kilns		27	14 (eel) – 30 (sprat) (2 (eel) – 60 (sprat)) µg/kg fw	15 (eel) – 29 (sprat) (NR) µg/kg fw	NR		
Frankfurter-type sausages, smoked under different experimental conditions	Germany, NR	50	4.8–36.3 µg/kg dw	NR	GC-HRMS (0.1 µg/kg)		Zastrow et al. (2019)

Table 1.7 (continued)

Sample type	Location and collection date	No. of samples	Mean (range)	Median (IQR)	Analytical method (LOD)	Comments	Reference
Sausage (dry-cured fermented), raw	Alentejo, Portugal, NR		9.52 µg/kg dw	NR	HPLC-UV-FLD (NR)		Roseiro et al. (2011)
Sausage (dry-cured fermented), smoked (modern/ industrial)			12.15–157.41 µg/kg dw	NR			
Sausage (dry-cured fermented), smoked (traditional)			46.47–297.32 µg/kg dw	NR			
Smoked sausage	Spain, NR	32	9.96–15.39 µg/kg dw	NR	HPLC-FLD (NR)	16 locations	Lorenzo et al. (2011)
Milk	Naples, Italy, NR	80	(0.04–3.58) µg/kg fw	0.34 µg/kg fw	HPLC-UV-FLD (0.03 ng/g)		Cirillo et al. (2010)
Cakes, biscuits, pastries, etc.		120	0.01–4.00) µg/kg fw	0.21 µg/kg fw			
Cereal (cornflakes)		81	(0.11–2.24) µg/kg fw	0.58 µg/kg fw			
Fruit juices		65	(0.01–1.11) µg/kg fw	0.30 µg/kg fw			
Ham or salami sandwiches		67	(0.01–2.24) µg/kg fw	0.24 µg/kg fw			
Chocolate		67	(0.01–8.29) µg/kg fw	0.46 µg/kg fw			
Candies		28	(0.11–2.25) µg/kg fw	0.22 µg/kg fw			
Pasta/rice with tomatoes sauce/legumes		203	(0.01–4.48) µg/kg fw	0.18 µg/kg fw			
Meat and meat products		126	(0.01–7.84) µg/kg fw	0.26 µg/kg fw			
Fish and fish products		58	(0.01–2.65) µg/kg fw	0.22 µg/kg fw			
Dairy products		75	(0.01–1.66) µg/kg fw	0.21 µg/kg fw			
Egg-based products		79	(0.01–1.68) µg/kg fw	0.25 µg/kg fw			
Pizza		57	(0.01–1.12) µg/kg fw	0.24 µg/kg fw			
Fresh or cooked vegetables		91	(0.01–11.95) µg/kg fw	0.20 µg/kg fw			
Bread, crackers, bread sticks, rusks		42	(0.01–6.15) µg/kg fw	0.22 µg/kg fw			
Fresh fruit		88	(0.01–1.18) µg/kg fw	0.31 µg/kg fw			

Table 1.7 (continued)

Sample type	Location and collection date	No. of samples	Mean (range)	Median (IQR)	Analytical method (LOD)	Comments	Reference
Meat and meat products	Catalonia, Spain, 2000	30	0.180 µg/kg fw	NR	HPLC-UV-FLD (0.2 µg/kg)	7 locations	Falcó et al. (2003)
Fish and shellfish		16	0.110 µg/kg fw				
Vegetables		16	0.015 µg/kg fw				
Tubers		4	0.069 µg/kg fw				
Fruits		12	0.018 µg/kg fw				
Eggs		4	0.023 µg/kg fw				
Milk		4	0.011 µg/kg fw				
Dairy products		4	0.056 µg/kg fw				
Cereals (bread, pasta, rice)		8	0.131 µg/kg fw				
Pulses (lentils, beans)		4	0.045 µg/kg fw				
Oils and fats		6	0.185 µg/kg fw				
Meat and meat products	Catalonia, Spain, 2008	3120	3.38–32.00 µg/kg fw	NR	GC-HRMS (NR)	48 locations	Martorell et al. (2010)
Fish			0.12 µg/kg fw				
Squid			< 0.16 µg/kg fw				
Clam			< 0.16 µg/kg fw				
Mussel			0.42 µg/kg fw				
Shrimp			< 0.16 µg/kg fw				
Vegetables			0.06 µg/kg fw				
Tubers			0.05 µg/kg fw				
Fruits			0.05 µg/kg fw				
Eggs			0.24 µg/kg fw				
Milk			0.03 µg/kg fw				
Dairy product			0.13 µg/kg fw				
Cereals			0.08 µg/kg fw				
Pulses			0.10 µg/kg fw				
Oils and fats			1.23 µg/kg fw				
Industry bakery			0.08 µg/kg fw				
Honey	Serbia, 2017	61	NR (ND–6.51) µg/kg fw	2.11–2.38 µg/kg fw	GC-MS (1.10 µg/kg fw)	4 types	Petrović et al. (2019)
Wheat	Poland, 2017–2018	200	0.32 (NR–0.87) µg/kg fw	0.28 (NR) µg/kg fw	GC-MS (0.015 µg/kg fw)	16 locations	Roszko et al. (2020)

Table 1.7 (continued)

Sample type	Location and collection date	No. of samples	Mean (range)	Median (IQR)	Analytical method (LOD)	Comments	Reference
Milk infant formula	Italy, NR	30	32.22 (ND–72.88) µg/kg fw	NR	HPLC-FLD (NR)		Santonicola et al. (2017)
Breast milk		30	39.07 (ND–89.55) µg/kg fw				
Yogurt	Italy, 2014	20		NR	HPLC-FLD (0.01 µg/kg fw)		Battisti et al. (2015)
Low fat			0.08 (ND–0.20) µg/kg fw				
High fat			0.15 (ND–0.30) µg/kg fw				
Cheese	Vitoria, Spain, NR			NR	GC-MS (NR)		Guillén et al. (2011)
Unsmoked		2	0.03 µg/kg fw				
Smoked		24	1.33–7.13 µg/kg fw				
Olive oil	Bari, Italy, NR	NR	ND	NR	GC-MS (0.30 ng/g)		Cotugno et al. (2021)

dw, dry weight; fw, fresh weight; GC-FID, gas chromatography-flame ionization detection; GC-HRMS, gas chromatography-high-resolution mass spectrometry; GC-LRMS, gas chromatography-low-resolution mass spectrometry; GC-MS, gas chromatography-mass spectrometry; HPLC-FLD, high-performance liquid chromatography-fluorescence detection; HPLC-UV-FLD, high-performance liquid chromatography-ultraviolet and fluorescence detection; IQR, interquartile range; LOD, limit of detection; ND, not detected; NR, not reported.

(< 0.5–2.3 µg/mainstream smoke of 100 cigarettes), marijuana (< 0.5–3.3 µg/mainstream smoke of 100 cigarettes) (Graves et al., 2020; NCBI, 2022), incense burning (3.63–11.37 pg/µg particle mass) (Yang et al., 2017), exhausts of automotive diesel fuel and low concentration biodiesel blends (1.93–9.24 µg/km emissions) (Karavalakis et al., 2010) (Table 1.8), and exhausts of wood-, coal-, or other biomass-burning stoves and fireplaces (IARC, 2010). It has also been identified in smokeless tobacco traditionally consumed in north Africa, although no quantitative data were reported (Guezguez et al., 2021). Anthracene has also been detected in herbicides (< 2–26.5 mg/L) (Seralini & Jungers, 2020), wood vinegars (4.5–115.0 µg/L) (Zhang et al., 2021) (prepared from the condensation of biomass pyrolysis, and may be used as fungicides or biocides, among other uses), and in creosote wood preservatives (Table 1.8). Although the latter cannot be sold for domestic uses in Europe, some creosote-treated wood products may be placed on the secondhand market for reuse (building of fences, agricultural stakes, etc.); concentrations have been reported in the range of 4–2573 µg/g wood (Ikarashi et al., 2005). Coal tar can be used at levels of 0.5–5% in the USA and in Japan in over-the-counter products for the treatment of chronic skin diseases, but its use (as crude and refined) in Europe in cosmetic products is prohibited (Cosmetic Ingredient Review Expert Panel, 2008). European cosmetic products may only include pitch/coal tar-petroleum, low/high temperature pitch/coal tar, and residues (coal tar) of creosote oil distillation if these contain < 0.005% w/w benzo[*a*]-pyrene (B[a]P, a surrogate marker of exposure to carcinogenic PAHs) (European Parliament and Council, 2009b, regulation (EC) No. 1223/2009). These ingredients are likely to contain anthracene as part of a complex mixture (Mariani et al., 1997; Wang et al., 2019), predictably at ultra-trace levels, but there is a general lack of data on anthracene concentrations in these consumer products.

1.4.2 Occupational exposure

According to the National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 (NIOSH, 1988), workers potentially exposed to anthracene in the USA were almost exclusively roofers, a few construction workers, and workers from the health services (janitors and cleaners) and business services (physicists, astronomers, and chemists) (NIOSH, 1983). [Considering the 2304 exposed workers that were reported, the Working Group estimated a confidence interval of 1500–3100; however, the Working Group considered the numbers to be underestimated because of the lack of representation of industries with known exposure, such as coking industries and road paving (see *IARC Monographs* Volume 103, IARC, 2013).]

Like other PAHs, occupational exposure to anthracene is likely to occur primarily through inhalation and dermal absorption (IARC, 2010). As anthracene is a low-molecular-weight PAH with three aromatic rings, it is expected to be found predominantly in the gas phase in ambient air (see Section 1.4.1a). Exposure to anthracene occurs in general in combination with exposure to other PAHs, which occurs mainly in the following occupational settings: the production and use of coal tar and coal tar-derived products, coke production and coke ovens, use of asphalt for paving and roofing, carbon-electrode manufacture, aluminium production, creosote use, chimney sweeping, firefighting, and others (IARC, 2010). Consequently, most scientific papers report exposure to the sum of several PAH congeners (usually six carcinogenic PAHs, eight high-molecular-weight PAHs, or other combinations of compounds), and exposure to single PAHs (including anthracene) is seldom reported. A selection of studies reporting occupational exposure to anthracene considered through different exposure assessment methods is shown in Table 1.9.

Table 1.8 Occurrence of anthracene in consumer products

Sample type	Location and collection date	No. of samples	Mean (range)	Median (IQR)	Analytical method (LOD)	Comments	Reference
Fuels							
Biodiesel blends	Greece, date of collection NR	5 fuel blends with 2 samples per blend	NR (1.93–9.24) µg/km emissions	NR	GC-MS (NR)	The methyl esters incorporated (10% v/v) in the automotive diesel fuel (EN590) originated from soybean oil, used frying oil, palm oil, sunflower oil, and rapeseed oil.	Karavalakis et al. (2010)
Incense							
Smoke-free incense Binchotan charcoal incense Traditional incense	Taiwan, China and Japan, date of collection is NR	3 of each type	3.63 pg/µg particle mass (NR) 11.37 pg/µg particle mass (NR) 8.95 pg/µg particle mass (NR)	NR	GC-MS (NR)	The total suspended matter originated from incense burning was analysed.	Yang et al. (2017)
Preservatives and pesticides							
Creosote wood preservatives Creosote-treated woods	Japan (new railway sleepers and stakes) and China (used railway sleepers), date of collection NR	9 6	NR (7168–18 391) µg/g NR (4–2573) µg/g	NR	GC-MS (40 mg/g for paints and 4 mg/g for wood)	Wood placed on the secondhand market for reuse.	Ikarashi et al. (2005)
Herbicides without glyphosate	Commercially available in France, Poland, and Germany, 2019	14	4.7 (< 2–26.5) µg/L	NR	GC-MS		Seralini & Jungers (2020)
Wood vinegars (liquid product obtained from biomass pyrolysis)	Liaoning Province, Heilongjiang Province, China, date of collection NR	9	NR (4.5–115.0) µg/L	NR	GC-MS (0.01 µg/L)	9 different types of biomass were characterized. Wood vinegars are used as biocides, feed additives, and preservatives.	Zhang et al. (2021)
Tobacco and related products							
Smokeless tobacco (neffa)	Sousse, Tunisia, date of collection NR	7	NR	NR	HPLC-FLD (NR)	Thinly sliced tobacco leaves are inhaled by the nose or kept in the mouth. Anthracene was detected but no values are presented.	Guezguez et al. (2021)

Table 1.8 (continued)

Sample type	Location and collection date	No. of samples	Mean (range)	Median (IQR)	Analytical method (LOD)	Comments	Reference
Particulate phase of mainstream tobacco smoke	Kentucky, USA, 2019	NR	< 0.5 µg (NR)	NR	GC × GC-TOFMS (0.5 µg)	Reference products that represent tobacco products of US consumers were used. Comparison of smoke produced from a filtered tobacco cigarette with a nonfiltered marijuana joint.	Graves et al. (2020)
Particulate phase of marijuana smoke		NR	< 0.5 µg (NR)				
Aerosol of cigarettes	China, 2005–2006	7 brands with 3–4 cigarettes per brand	NR (0.02–0.2 µg)/(m^3 g tobacco)	NR	GC-MS and GC-C-IRMS		Zhang et al. (2009)
Particulate phase of mainstream cigarette smoke	USA, date of collection is NR	3 randomly selected from 5 different packs of each brand	NR (5.8–86.1) ng/cigarette		GC-MS (7 ng)	30 cigarette domestic brands.	Ding et al. (2005)
Tobacco smoke condensate	Tobacco cigarettes commercially available, Mexican marijuana, England, date of collection NR	2000	2.3 µg/100 cigarettes (NR)	NR	GC-MS (NR)		Lee et al. (1976)
Marijuana smoke condensate		2000	3.3 µg/100 cigarettes (NR)				

GC-C-IRMS, gas chromatography-combustion-isotope ratio mass spectrometry; GC × GC-TOFMS, two-dimensional gas chromatography with time-of-flight mass spectrometric detection; GC-MS, gas chromatography-mass spectrometry; HPLC-FLD, high-performance liquid chromatography-fluorescence detection; IQR, interquartile range, LOD, limit of detection; ND, not detected; NR, not reported; v/v, volume per volume.

Table 1.9 Measurement of anthracene in occupational settings

Occupational group/ job type/industry, location and date	Monitoring method	No. of samples	Analytical method (LOD)	Mean (range)	Median (IQR)	Comments	Reference
Stationary air monitoring							
Carbon black-manufacturing plant, Taiwan, China, date NR	Air measurements	16	GC-MS (NR)	NR (1.23–1976.34) ng/m^3	NR		Tsai et al. (2002)
Butchers burning scrap tyres, Nigeria, date NR	Air measurements	3	NR	50 ± 0.00 g/m^3	NR		Okonkwo et al. (2018)
Refractory-brick manufacturing, Italy, date NR	Air measurements	18	HPLC-FLD (0.10 µg/m^3)	Production area, 1.0 ± 0.16 µg/m^3 Packaging area, 0.51 ± 0.33 µg/m^3 External area, 0.65 ± 0.32 µg/m^3	Production area, 1.1 µg/m^3 Packaging area, 0.41 µg/m^3 External area, 0.50 µg/m^3	NIOSH method 5506.	Sartorelli et al. (2020)
Firefighters, Australia, 2017–2018	Air measurements	15	GC-MS/MS (0.050 ng/m^3)	NR	0.81 (0.45–2.3) ng/m^3		Banks et al. (2020)
Firefighters in incident command post, California, USA, 2015	Air measurements	2 (12 days of measurements each)	GC-MS (NR)	1 ng/m^3	1 (< 1–2) ng/m^3 (GM, min. to max.)		Navarro et al. (2019)
Surface contamination							
Refractory-brick manufacturing, Italy, date NR	Wipe test	17	HPLC-FLD (0.006 ng/cm^2)	Production area, clean surfaces, 7.4 ± 8.2 ng/cm^2 Production area, dirty surfaces, 601 ± 296 ng/cm^2 Packaging area, 1.1 ± 1.3 ng/cm^2 External area, 1.5 ± 0.46 ng/cm^2	Production area, clean surfaces, 5.1 ng/cm^2 Production area, dirty surfaces, 589 ng/cm^2 Packaging area, 0.61 ng/cm^2 External area, 1.2 ng/cm^2	Technique complies with the ASTM.	Sartorelli et al. (2020)
Settled dust measurements							
Automobile workshop, Jeddah, Saudi Arabia, 2016	Indoor settled dust	18	GC-MS/MS (10 ng/g)	0.410 ± 0.490 µg/g	0.235 (0.085–2.070) µg/g		Ali et al. (2017)
Firefighters, Australia, 2017–2018	Dust	49	GC-MS/MS (0.012 µg/g)	NR	0.032 (< LOD–0.17) µg/g		Banks et al. (2020)

Table 1.9 (continued)

Occupational group/ job type/industry, location and date	Monitoring method	No. of samples	Analytical method (LOD)	Mean (range)	Median (IQR)	Comments	Reference
Personal monitoring: air measurements							
Hazardous waste disposal facility, Baton Rouge, Louisiana, USA, 1980	Workers' breathing zone	36	HPLC (0.1 µg/sample)[a]	5 (1–18) µg/m³			NIOSH (1982a)
Coal-tar pitch roof tear-off and application of hot asphalt, Lancaster, Ohio, USA, 1981	Workers' breathing zone	16	HPLC (NR)[a]	Tear-off, 0.2–6.7 µg/m³ Application, 0.1–0.6 µg/m³			NIOSH (1982b)
Coal-tar pitch roof tear-off and application of hot asphalt, USA, 1987	Workers' breathing zone	10	HPLC-FLD (NR)	1.5 ± 0.6 µg/m³ (day 1) 0.5 ± 0.2 µg/m³ (day 2)	NR	NIOSH method 5506.	Wolff et al. (1989)
Impregnation and handling of creosote-impregnated wood, Finland [a]	Workers' breathing zone	Impregnation plants, 23 Handling, 11	GC-FID (NR)	Workers of the impregnation plants, 1.0 µg/m³ Openings, 19 µg/m³ Cleaning of chamber, 6.0 µg/m³ Handling during switch element assembly, 0.5 µg/m³ Manual metal-arc welding, 1.8 µg/m³	NR		Heikkilä et al. (1987)
Bitumen paving, Switzerland, 1992	Workers' breathing zone	9	GC-MS (1 ng/m³)	0.073 µg/m³ (GM)	NR		Petry et al. (1996a)
Shipbuilding, steel-pipe manufacturing, and paint-manufacturing workplaces handling coal-tar painting, 2001	Workers' breathing zone	106 workers from 10 workplaces	GC-MS (NR)	GM, 8 µg/m³ (range, 0–8230 µg/m³)	NR		KOSHA (2001)

Table 1.9 (continued)

Occupational group/ job type/industry, location and date	Monitoring method	No. of samples	Analytical method (LOD)	Mean (range)	Median (IQR)	Comments	Reference
Asphalt workers and construction workers, Milan, Italy, 2003	Workers' breathing zone	100 (asphalt) 47 (construction)	HPLC-FLD (0.4 ng/m^3)		Asphalt, 0.7 (< 0.4–97.7) ng/m^3 Construction, 0.4 (< 0.4–2.5) ng/m^3 (median, min. to max.)		Campo et al. (2006a)
Asphalt workers, north Italy, 2014–2015	Workers' breathing zone	7 workers (3 pavers, 3 ground operators and 1 roller)	HPLC-UV (0.10 ng)	20.39 ± 2.69 ng/m^3 (GM ± GSD)	NR	NIOSH method 5506.	Fostinelli et al. (2018)
Carbon anode plant, Switzerland, 1992	Workers' breathing zone	30	GC-MS (1 ng/m^3)	0.894 µg/m^3 (GM)	NR		Petry et al. (1996a)
Carbon anode plant, Switzerland	Workers' breathing zone	6	GC-MS (1 ng/m^3)	Range, 0.420–5.510 µg/m^3	NR		Petry et al. (1996b)
Graphite production, Switzerland, 1992	Workers' breathing zone	16	GC-MS (1 ng/m^3)	GM, 0.042 µg/m^3	NR		Petry et al. (1996a)
Silicon carbide production, Switzerland, 1992	Workers' breathing zone	14	GC-MS (1 ng/m^3)	GM, 0.006 µg/m^3	NR		Petry et al. (1996a)
Metal recycling process, Switzerland, 1992	Workers' breathing zone	5	GC-MS (1 ng/m^3)	GM, 0.04 µg/m^3	NR		Petry et al. (1996a)
Coke-oven workers, Germany, date NR	Workers' breathing zone	11	HPLC-UV (NR)	Topside, 14.34 (1.30–57.38) µg/m^3 Bench-side, 1.10 (< LOD–2.90) µg/m^3	NR	NIOSH method 5506	Strunk et al. (2002)
Coke-oven workers, Taiwan, China, July–November, 2003	Workers' breathing zone	17 (top-oven) 35 (side-oven)	GC-MS (NR)	Top-oven, 31.18 ± 5.72 ng/m^3 Side-oven, 10.35 ± 4.16 ng/m^3	NR		Lin et al. (2006)
Coke-oven workers, southern Taiwan, China, date NR	Workers' breathing zone	17 (top-oven) 25 (side-oven)	GC-MS (NR)	Top-oven, 43.29 ± 64.86 ng/m^3 Side-oven, 5.54 ± 6.81 ng/m^3	NR		Jeng et al. (2011)

Table 1.9 (continued)

Occupational group/ job type/industry, location and date	Monitoring method	No. of samples	Analytical method (LOD)	Mean (range)	Median (IQR)	Comments	Reference
Coke-oven workers, southern Taiwan, China[a]	Workers' breathing zone	31 (top-oven) 23 (side-oven)	GC-MS (NR)	Top-oven, 353.54 ± 93.33 ng/m³ Side-oven, 340.98 ± 66.58 ng/m³	NR		Jeng et al. (2023)
Coke-oven workers, Upper Silesia, Poland, 2005–2010	Workers' breathing zone	162	HPLC-FLD (11–113 ng/m³)		0.042 (0.014–0.653) µg/m³		Bieniek & Łusiak (2012)
Coke-oven workers, Taranto, Italy, 2005	Workers' breathing zone	45	HPLC-FLD (4.3 ng/m³)	3.184 (0.278–34.348) µg/m³	NR	NIOSH method 5506.	Campo et al. (2012)
Coke-oven workers, Anshan, China, 2002	Workers' breathing zone	57	GC-MS (0.05 ng/m³)	NR	0.01 (< LOQ–28.35) µg/m³	US EPA	Yamano et al. (2014)
Fire-proof materials production plants, Germany, 1999–2004	Workers' breathing zone	117	HPLC-DAD (NR)	NR	1.36 (< LOD–69.01) µg/m³	NIOSH method 5506.	Preuss et al. (2006)
Traffic police officers, Beijing, China, winter 2005	Workers' breathing zone	30	GC-MS (NR)	Vapour phase, 18.2 ± 10.6 ng/m³ Particulate phase, 21.0 ± 27.7 ng/m³	NR		Liu et al. (2007)
Firefighters in non-fire work environments (fire stations), northern Portugal, 2014	Workers' breathing zone	54	HPLC-FLD (NR)	0.223–0.330 ng/m³ (mean range in 5 stations) 0.223–0.551 (min. to max. in 5 stations)	NR		Oliveira et al. (2017a)
Firefighters during emergency fire suppression, Canada, 2015	Workers' breathing zone	29	GC-MS (0.71 ng/m³)	50.91 (0.03–746.85) µg/m³	NR		Keir et al. (2020)
Workers from an iron ore mine exposed to diesel and renewable diesel exhaust, northern Sweden, 2019	Workers' breathing zone	12	HRGC/LRMS after passive sampling (NR)	NR	2.78 (8–103) ng/m³		Gren et al. (2022)

Table 1.9 (continued)

Occupational group/ job type/industry, location and date	Monitoring method	No. of samples	Analytical method (LOD)	Mean (range)	Median (IQR)	Comments	Reference
Dermal contamination measurements							
Manufactured-gas plants, Paris, France, 1997	Dermal pads	29	HPLC-FLD (10 ng/cm^2)	NR	Neck, < LOD–13 ng/cm^2 Shoulder, < LOD ng/cm^2 Wrist, < LOD–100 ng/cm^2 Groin, < LOD ng/cm^2 Ankle, < LOD–12 ng/cm^2 (range)	Dermal pad locations: neck and wrist (uncovered), shoulder, groin, and ankle under the clothes.	Dor et al. (2000)
Asphalt workers, Finland, 1999–2000	Dermal pads	22	HRGC-MS (0.01 ng/cm^2)	NR (< 0.01–0.75) ng/cm^2	NR	Wrist contamination.	Väänänen et al. (2005)
Asphalt workers, Milan, Italy, 2003	Dermal pads	24	PTV-GC-MS (0.020 ng/cm^2)	NR	Wrist, 0.385 (< 0.02–6.455) ng/cm^2 Total body, 10.86 (3.86–142.19) µg (min. to max.)	Wrist contamination and total body contamination.	Fustinoni et al. (2010)
Biological monitoring							
Asphalt workers and construction workers, Milan, Italy, 2003	Urine	100 (asphalt) 47 (construction)	HS-SPME-GC-MS (2 ng/L)	NR	Asphalt workers: BS, 2 (< 2–16) ng/L ES, 5 (< 2–28) ng/L Construction workers: BS, < 2 (< 2–15) ng/L ES, 3 (< 2–9) ng/L (median, min. to max.)		Campo et al. (2007)
Coke-oven workers, Poland, 2000	Urine	55 (all smokers)	HS-SPME-GC-MS (2 ng/L)	NR	49 (9–319) ng/L (5th to 95th)		Campo et al. (2010)
Coke-oven workers, Poland, 2006	Urine	49 workers (non-smokers) 49 controls (non-smokers)	SPME-GC-MS (0.8 ng/L)	NR	Workers, 13 (< LOD–69.4) ng/L Controls, 1.3 (< LOD–3.7) ng/L (5th to 95th percentile)		Campo et al. (2014)

Table 1.9 (continued)

Occupational group/ job type/industry, location and date	Monitoring method	No. of samples	Analytical method (LOD)	Mean (range)	Median (IQR)	Comments	Reference
Electric steel-foundry workers, Menzel Bourguiba, Tunisia, 2013	Urine	93	SPME-GC-MS/ MS (0.2 ng/L)	NR	Steel smelter workshop, 1.97 (1.02–6.64) ng/L Rolling mill and galvanization workshop, 2.17 (1.18–6.30) ng/L Engine maintenance, 2.58 (1.17–11.43) ng/L		Campo et al. (2016)
Beauty salons workers, Islamic Republic of Iran[a]	Urine	50 women (workers) 35 women (controls)	SPME-GC-MS (NR)	Workers: BS, 14.51 ± 12.52 ng/L ES, 17.31 ± 15.01 ng/L Controls, 1.57 ± 0.62 ng/L (morning sample)	NR		Arfaeinia et al. (2022)
Firefighters, Korea, 2019	Serum	92 firefighters 70 controls	GC-MS/MS (NR)	Firefighters, 0.675 (< LOD–23.9) ng/g lipid weight Controls, < LOD	NR		Ekpe et al. (2021)
Coal-fired power plant workers, Shandong Province, China, 2021	Serum	125 men 32 women	GC-MS/MS (NR)	Men, 50 ± 48 ng/g lipid weight Women, 37 ± 10 ng/g lipid weight	NR		Zhao et al. (2022)
Sanitation workers, Guangzhou, China, 2020	Serum	115 sanitation workers working on roads 81 office employees and workers working in parks (controls)	GC-MS/MS (NR)	Workers, 2.13 ± 2.38 (< LOD–17.0) ng/mL Controls, 1.64 ± 2.04 (< LOD–10.08) ng/mL	Workers, 2.32 ng/mL Controls, 1.67 ng/mL		Lv et al. (2022)

Table 1.9 (continued)

Occupational group/ job type/industry, location and date	Monitoring method	No. of samples	Analytical method (LOD)	Mean (range)	Median (IQR)	Comments	Reference
Firefighters, Spain [a]	Saliva	45 firefighters working in firefighting activities 10 firefighters not working in firefighting activities (controls)	GC-MS (0.091 µg/L)	Exposed, < LOD–0.379 µg/L Controls, < LOD	NR		Santos et al. (2019)

ASTM, American Society for Testing and Materials; BS, before shift; ES, end of shift; GC-FID, gas chromatography-flame ionization detection; GC-MS, gas chromatography-mass spectrometry; GC-MS/MS, gas chromatography-tandem mass spectrometry; GM, geometric mean; GM ± GSD, geometric mean ± standard deviation; HPLC, high-performance liquid chromatography; HPLC-DAD, high-performance liquid chromatography-diode array detection; HPLC-FLD, high-performance liquid chromatography-fluorescence detection; HPLC-UV, high-performance liquid chromatography-ultraviolet detection; HRGC/LRMS, high-resolution gas chromatography/low-resolution mass spectrometry; HRGC-MS, high-resolution-gas chromatography-mass spectrometry; HS-SPME-GC-MS, headspace solid-phase microextraction-gas chromatography; IQR, interquartile range; LOD, limit of detection; LOQ, limit of quantification; min. to max., minimum to maximum; NIOSH, National Institute for Occupational Safety and Health; NR, not reported; PTV-GC-MS, programmable temperature vaporizer-gas chromatography-mass spectrometry; SPME-GC-MS, solid-phase microextraction-gas chromatography-mass spectrometry; SPME-GC-MS/MS, solid-phase microextraction-gas chromatography-tandem mass spectrometry; US EPA, United States Environmental Protection Agency; UV, ultraviolet.

[a] The detector used in this application was not indicated.

(a) Stationary air monitoring

Anthracene has been reported in the air of carbon black-manufacturing plants in Taiwan, China (range, 1.23–1976.34 ng/m^3) (Tsai et al., 2002) and in refractory-brick manufacturing in Italy (Sartorelli et al., 2020). In the latter, higher levels were found in the production area (mean, 1.0 μg/m^3) than in other areas of the plant (mean levels, < 1.0 μg/m^3). The presence of anthracene was reported at very high levels in sporadic measurements taken in the ambient air of an abattoir in Nigeria where burning tyres were used to remove the fur of slaughtered animals (mean, 0.05 μg/cm^3 [50 g/m^3]) (Okonkwo et al., 2018). In studies involving firefighters, anthracene was measured in the ambient air at the incident command post, (mean, 1 ng/m^3) (Navarro et al., 2019), and similar values were measured in the living quarters of fire stations (median levels, 0.81 ng/m^3) (Banks et al., 2020).

[Overall, according to the data reported above, the Working Group considered that the highest exposure to airborne anthracene may be in the industrial setting of carbon black-manufacturing plants.]

(b) Settled dust measurements

Anthracene was measured in dust samples from fire stations in Australia, including samples collected from living quarters, firefighter ensemble storage areas, and fire engine cabins, at levels up to 0.17 μg/g (Banks et al., 2020), and similar values were measured in indoor settled dust from automobile workshops in Saudi Arabia (median levels, 0.235 μg/g) (Ali et al., 2017). [The Working Group noted that the detection of anthracene on surfaces indicates a potential further source of worker exposure via hand-to-mouth involuntary behaviour, even if this possibility has not yet been studied.]

(c) Personal monitoring

Personal exposure to anthracene in the workplace has been studied by means of air samples collected by active samplers placed near the worker's breathing zone. Exposure to anthracene was evaluated for 36 workers from a hazardous waste disposal facility in Louisiana, USA (NIOSH, 1982a). Unit operations at this site included incineration, biological stabilization and treatment, landfilling, and landfarming. Anthracene was detected in samples from five workers (four operation and one maintenance personnel), and mean exposure to anthracene was 5 μg/m^3 (range, 1–18 μg/m^3). This exposure was probably a result of the previous mixing of anthracene-containing waste sludge with soil in the area (NIOSH, 1982a). Two studies evaluated the personal exposure of workers during the tear-off of old coal-tar roofs and the application of hot asphalt in the USA (NIOSH, 1982b; Wolff et al., 1989); mean exposure levels ranged from 0.2 to 6.7 μg/m^3 during tear-off operations, whereas levels were lower during hot asphalt application. Much lower anthracene levels (median, 0.7 ng/m^3) were found in asphalt workers laying asphalt at low temperature in Italy (Campo et al., 2006a), in a small group of asphalt workers laying hot-mix asphalt containing modified bitumen in Italy (mean, 20.39 ng/m^3) (Fostinelli et al., 2018), and in construction workers potentially exposed to diesel exhaust (median, 0.4 ng/m^3) (Campo et al., 2006a). Much higher mean levels (73 μg/m^3) were reported for workers employed in bitumen paving in Switzerland, but no details were given on the bitumen type (Petry et al., 1996a). Exposure to anthracene may occur during the manufacture of creosote or creosote-containing products. Heikkilä et al. reported exposure to creosote in two bulk impregnation plants and during the handling of creosote-treated wood in Finland; mean personal exposure to airborne anthracene ranged from 0.5 μg/m^3 (operators in the switch element assembly) to 19 μg/m^3 (peak values for

operators during the openings of cylinders in the impregnation plant) (Heikkilä et al., 1987). In a plant producing carbon anodes for aluminium electrolysis in Switzerland, airborne anthracene exposure was measured (i) in the personal air of 6 workers employed in different tasks – levels ranged from 420 ng/m^3 (foreman) to 5510 ng/m^3 (floor worker with operating and maintenance functions at the paste plant) (Petry et al., 1996b); and (ii) in the personal air of 30 workers – the mean level was 894 ng/m^3 (Petry et al., 1996a). Several studies assessed anthracene exposure in coke-oven workers; mean levels were up to 14.34 µg/m^3 (Strunk et al., 2002; Lin et al., 2006; Jeng et al., 2011, 2023; Bieniek & Łusiak., 2012; Campo et al., 2012; Yamano et al., 2014) when different sites in the coke plants were sampled; exposure levels were higher in top-side workers than in side-oven workers (Strunk et al., 2002; Lin et al., 2006; Jeng et al., 2011). Personal exposure to anthracene has also been reported for workers from fire-proof material production plants in Germany (median, 1.36 µg/m^3) (Preuss et al., 2006), workers from a graphite production plant (mean, 42 ng/m^3), workers involved in silicon-carbide production (geometric mean, 6 ng/m^3) and metal-recycling processes in Switzerland (geometric mean, 40 ng/m^3) (Petry et al., 1996a), and in workers from an iron ore mine in northern Sweden who were exposed to diesel and renewable diesel exhaust (median, 2.78 ng/m^3) (Gren et al., 2022). In firefighters, mean anthracene levels ranging from 0.223 to 0.330 ng/m^3 were reported for firefighters in non-fire work environments (fire stations) in northern Portugal (Oliveira et al., 2017a), whereas much higher values were found during emergency fire suppression (mean, 50.91 µg/m^3) in Canada (Keir et al., 2020). In a study that assessed anthracene exposure for traffic police officers during winter in Beijing, China, anthracene mean concentrations were reported to be much lower than those reported for industrial settings, and values were similar in the vapour phase and the particulate phase (mean, 18.2 and 21.0 ng/m^3, respectively) (Liu et al., 2007).

In 2001, the Korea Occupational Safety and Health Agency (KOSHA) in the Republic of Korea investigated workplaces with exposure to PAHs, including anthracene. In 106 workers from 10 workplaces (shipbuilding, steel-pipe manufacturing, and paint manufacturing) at which coal-tar paint was handled, mean personal exposure to anthracene was 8 µg/m^3 (assessed according to NIOSH method 5515) (KOSHA, 2001).

The COLCHIC database, which contains workplace exposure results for chemical samples collected by the prevention network in France from 1987 to 2020, identified 662 measures of occupational exposure to anthracene. The median levels for personal exposure were 2740 ng/m^3 before the year 2000 and below the LOD after the year 2000; median levels for ambient measures were below the LOD both before and after the year 2000 (INRS, 2022). Among the three most frequent workplace activities (road construction and highways; collection, treatment, and distribution of water; and manufacture of rubber articles), the highest median levels for personal exposure were found in the sector "collection, treatment, and distribution of water" (6322 ng/m^3, 24 measures). Among the three most frequent occupations, the highest median level for personal exposure was measured for "railway maintenance" (5732 ng/m^3, 26 measures). Among the three most frequent tasks, the highest median level for personal exposure was measured for the job task "machining by mechanical abrasion: cutting, sawing, filing, sharpening" (3438 ng/m^3, 22 measures) (INRS, 2022).

Overall, the highest personal exposure to anthracene via air is likely to be for asphalt workers dealing with the tear-off of old coal-tar roofs, firefighters in emergency situations, coke-oven workers, and workers employed in the production of carbon anodes.

Personal dermal exposure to anthracene has been studied in asphalt workers in Finland (Väänänen et al., 2005) and in Italy (Fustinoni et al., 2010). In the first study, in workers in Finland laying stone mastic asphalt containing coal fly ash or limestone, or using remixed asphalt, dermal contamination (evaluated only at the wrist using polypropylene pads) was between 0.20 and 0.42 ng/cm^2 (Väänänen et al., 2005). Higher concentrations were reported for asphalt workers laying hot asphalt in Italy, for whom a median wrist contamination of 0.385 ng/cm^2 and a median total body contamination of 10.86 µg were reported (Fustinoni et al., 2010). In workers from manufactured-gas plants in France, detectable levels of anthracene, at concentrations of up to 100 ng/cm^2, were found only in 3% of dermal pads (Dor et al., 2000).

(d) Biomonitoring

No biological marker for evaluating the internal dose of anthracene has been validated to date, and biological monitoring of occupational exposure to anthracene has very seldom been performed. The measurement of anthracene metabolites in the urine has not been reported. Anthracene has been quantified in urine samples from asphalt workers and construction workers in Italy (Campo et al., 2007), two groups of coke-oven workers in Poland (Campo et al., 2010, 2014), and in electric steel-foundry workers in Tunisia (Campo et al., 2016); median levels were ≤ 5 ng/L in all settings, except for coke-oven workers (see below). These values were higher than those found in the general population in Italy (median, 2.1 ng/L; 95th percentile, 3.5 ng/L) (Gatti et al., 2017). In asphalt workers, an association between personal exposure to anthracene and urinary levels was reported; levels were higher in end-shift samples than in before-shift samples (Campo et al., 2007). In coke-oven workers, median concentrations were 13.0 ng/L in the group of non-smokers but as high as 49 ng/L in the group of smokers. However, anthracene concentrations in the non-smokers were about 10-fold those in non-smokers from the general population living in the same area as the plant (median, 13 ng/L versus 1.3 ng/L) (Campo et al., 2014). Anthracene in the urine has also been reported for beauticians in the Islamic Republic of Iran, for whom values were 10-fold those for women not working in beauty salons (mean, 17.31 ng/L versus 1.57 ng/L) (Arfaeinia et al., 2022).

Sporadic measurements of anthracene in the serum and saliva have been reported. Anthracene was detected in 5.2% of serum samples from firefighters from the Republic of Korea, with a mean concentration of 0.675 ng/g lipid weight, but was below the LOD in all samples from the general population (Ekpe et al., 2021). In workers from a coal-fired power plant in China, mean concentrations of anthracene in serum were higher in men than in women (50 ng/g lipid weight versus 37 ng/g lipid weight) (Zhao et al., 2022). In sanitation workers from Guangzhou, China, mean concentrations of anthracene in serum samples from workers on busy roads were higher than in office employees or in sanitation workers working in parks (2.13 ng/mL versus 1.61 ng/mL), with the highest concentrations attributed to exposure to exhaust emissions (Lv et al., 2022). In saliva, anthracene was detected in 50% of samples taken from firefighters immediately after firefighting activities ceased (concentrations in the range of < 0.091 to 0.329 µg/L), but was always below the LOD in samples from firefighters not involved in firefighting activities (Santos et al., 2019).

1.4.3 Exposure of the general population

(a) Exposure data

Exposure of the general population to anthracene can occur via multiple routes, i.e. inhalation, ingestion of food and beverages, and skin absorption.

The most significant sources of polluted air for the general population are tobacco smoke

(mainstream and sidestream smoke), wood burning (indoors or outdoors, including forest fires) and high-traffic or highly industrialized urban locations. The average daily intake of anthracene from inhalation has been estimated to be approximately 11 ng in the USA (considering a background environmental level of 0.54 ng/m^3) (US EPA, 1987), and the maximum daily intake in Europe was estimated to be 680 ng (based on the measured maximum of 34 ng/m^3) (ECHA, 2008b).

Ingestion from contaminated food (contaminated as a result of environmental pollution – soil, water or atmospheric deposition – and/or processing) is the major route of anthracene intake by the non-smoking and non-occupationally exposed population. Intakes vary depending on diet (Falcó et al., 2003; Cirillo et al., 2010; Martorell et al., 2010) (see Table 1.2 in Section 1.4.1) but were estimated to be 45 ng/kg bw per day, i.e. 3.1 µg/day, in the United Kingdom; 10 µg/day (maximum conservative estimate) in Europe (ECHA, 2008b); and 0.96 µg/day in autumn to 2.53 µg/day in winter (median values) in China (Duan et al., 2016), based on occurrence in food and beverages. However, higher intakes may be observed for population groups that grill or bake using biomass as fuel, or whose diets are based on smoked products or foodstuff from highly contaminated agricultural lands (Li et al., 2018). Human milk can be an exposure source for infants and young children (Santonicola et al., 2017). Ingestion of soil and dust can be also a potential route of exposure for children because of behavioural differences from adults (e.g. playing on the floor indoors or outdoors, and hand-to-mouth behaviour) (see Table 1.6, Section 1.4.1) (US EPA, 2009, 2014b, 2017; Islam et al., 2018; Gao et al., 2019). Levels of anthracene have been reported in the range of < 0.001–10.0 µg/g in household dust from different countries (Canada, China, Nepal, Portugal, Saudi Arabia, Sweden) (Vicente et al., 2019; Alamri et al., 2021; Lim et al., 2021).

Dermal absorption in non-occupationally exposed individuals may take place mainly through contact with contaminated soils, wood treated with creosote and related products and used in secondhand goods (see Table 1.6 and Table 1.7 in Section 1.4.1), and with coal tar-based pharmaceuticals or cosmetic products (over-the-counter shampoos, skin and hair care products for the treatment of seborrheic dermatitis and psoriasis) (IARC, 2010). Because of their biological and physiological characteristics, as well their different behavioural patterns (e.g. playing on the ground), skin absorption can be also relevant for children (US EPA, 2014b, 2017). The amount of absorption is influenced by the concentration of anthracene, duration of contact, the individual's skin-specific properties (hydration, thickness, and fat), and temperature (US EPA, 2014b).

(b) Biomonitoring

The determination of anthracene in human biological fluids and tissues has been reported in several population groups, mostly in Asia and Europe (Table 1.10).

A survey conducted in Italy (2010; 2012–2013) showed that urinary levels of anthracene in participants living and working within 4 km of a municipal solid-waste incinerator were markedly influenced by the incinerator emissions, even when these complied with the European regulations (Ranzi et al., 2013; Gatti et al., 2017). Exposure of adults with pulmonary ailments, e.g. pulmonary cancer, in Romania (Cioroiu et al., 2013) and chronic obstructive pulmonary disease, in China (Che et al., 2020), was also described. Statistically higher levels of anthracene were observed in lung and in bronchoalveolar lavage fluid from patients living in polluted urban areas (Table 1.10). The same pattern of variation was described for anthracene in hair samples from urban inhabitants and/or smokers when compared with rural inhabitants and/or non-smokers in two regions of China (Palazzi et al., 2018; Wang et al., 2020; Table 1.10).

Table 1.10 Measurement of anthracene in human matrices

Compound or metabolite and sample type	Location, population group, and collection date	No. of samples	Mean (range)	Median (IQR)	Relevant percentiles	Analytical method (LOD)	Comments	Reference
Anthracene in blood (venous)	Owerri city, Imo State, Nigeria, children (age, 4–14 yr), date NR	36	0.06 (0.051–0.064) µg/dL	NR	NR	GC-MS	Boys (50%) and girls (50%).	Wirnkor et al. (2019)
Blood (venous)	Lucknow, India, children (age, 2–12 yr), 2005–2006	56	NR	3.6 (5.54) ng/mL	25th percentile, 1.45 ng/mL 75th percentile, 6.99 ng/mL	HPLC-UV-FLD (0.015 µg/L)	Average exposure time near kitchen: 31.57 minutes; residence distance from highway/traffic: 805.20 m.	Singh et al. (2008b)
Anthracene in blood serum (venous)	Nantong, China, pregnant women (age, 18–40 yr), 2018–2019	48	ND	NR	25th, 50th and 75th percentiles, ND	HPLC-UV-FLD (0.02 ng/mL)	Healthy pregnant women, non-smokers, no drinking habit, no history of occupational exposure to PAHs, no family genetic history of lung cancer, stomach cancer or asthma.	Guo et al. (2021)
Anthracene in serum	State of Tennessee, autopsied individuals, USA, 2001–2003	650	NR	NR	NR	GC-MS		Ramesh et al. (2014)

Table 1.10 (continued)

Compound or metabolite and sample type	Location, population group, and collection date	No. of samples	Mean (range)	Median (IQR)	Relevant percentiles	Analytical method (LOD)	Comments	Reference
Anthracene in maternal serum	Asaluyeh port (petrochemical and gas area) and Bushehr port (urban area), Islamic Republic of Iran, pregnant women (37–42 wk gestation; age, 18–37 yr) and fetuses, 2018–2019 Petrochemical and gas area	99	2.12 (ND–23.9) µg/L	ND 1.80 µg/L	25th percentile, ND 75th percentile, 1.75 µg/L	GC-MS (0.76 ng/L)	6 h between the collection of the maternal and cord blood. Pregnant healthy women that lived at least 1 yr in the sampling areas. Smoking/ passive smoking, alcoholism, mothers who had infants with congenital malformations and multiple gestations were excluded.	Khalili Doroodzani et al. (2021)
	Urban area	100	2.90 (ND–18.3) µg/L		25th percentile, 0.10 µg/L 75th percentile, 4.60 µg/L			
Anthracene in urine	Modena, Italy, participants (mean age, 48.1 yr) living and working within and outside 4 km of the solid waste incinerators, 2010					GC-MS (NR; LOQ, 0.5 ng/L)	Spot sampling in the morning. Smokers and non-smokers.	Ranzi et al. (2013)
	Exposed	65	0.9 ng/L	0.8 ng/L	5th percentile, < 0.5 ng/L 95th percentile, 2.3 ng/L			
	Unexposed	103	0.6 ng/L	< 0.5 ng/L	5th percentile, < 0.5 ng/L 95th percentile, 1.9 ng/L			
Anthracene in urine	Owerri city, Imo State, Nigeria, children (age, 4–14 yr), date NR	36	0.55 (0.51–0.62) µg/dL	NR	NR	GC-MS	Boys (50%) and girls (50%).	Wirnkor et al. (2019)

Table 1.10 (continued)

Compound or metabolite and sample type	Location, population group, and collection date	No. of samples	Mean (range)	Median (IQR)	Relevant percentiles	Analytical method (LOD)	Comments	Reference
Anthracene in urine	Modena, Italy, adults (age, 18–69 yr) living and working within 4 km of a municipal solid waste incinerator, 2012–2013	488	2.2 ng/L	2.1 ng/L	5th percentile, 0.9 ng/L 95th percentile, 3.5 ng/L	GC-MS/MS (NR; LOQ, 0.4 ng/L)	First morning void.	Gatti et al. (2017)
Anthracene in breast milk	Baltimore and North Carolina, nursing mothers (age, 15–25 yr), USA, 2015	12	ND	NR	NR	GC-MS (0.04 ng/g fat; 0.001 ng/mL milk)	Non-smoking women.	Kim et al. (2008)
Anthracene in breast milk	Italy, pregnant (age, 25–35 yr), women, NR	30	39.07 (0.00–89.55) µg/kg	NR	HPLC-FLD (NR)	NR	Non-smokers.	Santonicola et al. (2017)
Anthracene in breast milk	Aveiro, Coimbra, Lisboa, Viseu and Vila Real, Portugal, nursing mothers (age, 21–40 yr), 2019–2020	65	NR (0.044–2.04) ng/mL	0.050 ng/mL	25th percentile, 0.049 ng/mL milk 75th percentile, 0.087 ng/mL milk	HPLC-DAD-FLD (0.07 µg/L)	Healthy and non-smoking mothers.	Oliveira et al. (2020)

Table 1.10 (continued)

Compound or metabolite and sample type	Location, population group, and collection date	No. of samples	Mean (range)	Median (IQR)	Relevant percentiles	Analytical method (LOD)	Comments	Reference
Anthracene in placental tissue	Agra, India, pregnant women (age, 18–40 yr), 2016–2017			NR	NR	GC-FID (NR)	Tobacco usage: 45.45% in full-term; 58.62% in preterm. Higher values of anthracene in the preterm group but no significant difference ($P < 0.05$) between the control and the study group. High contribution of rural women (62%) in the preterm group that used biomass fuel as a cooking source.	Agarwal et al. (2018)
	Control group (gestational age, > 36 wk (full-term delivery, undergoing spontaneous labour at term)	55	0.027 µg/L					
	Case group (gestational age, < 36 wk (preterm delivery, undergoing preterm labour)	29	0.134 µg/L					
Anthracene in placental tissue	Agra, India, pregnant women (age, 18–32 yr), 2017–2018	110 (14.28% detection)	0.25 (ND–7.87) µg/L	NR	NR	GC-FID (NR)	Healthy pregnant women; smokers, having the previous history of serious chronic disease or pregnancy complications were excluded. Chewing tobacco and alcohol usage, 35.45%.	Agarwal et al. (2022)
Anthracene in placental tissue	Lucknow, India, pregnant women (age, 20–35 yr), 2005–2006			NR	NR	HPLC-FLD (0.03 µg/L)	Healthy, non-smokers.	Singh et al. (2008a)
	Full term (normal deliveries at term)	31	25.81 ppb [ng/g]					
	Preterm labour (gestational age, < 36 wk)	29	33.26 ppb [ng/g]					

Table 1.10 (continued)

Compound or metabolite and sample type	Location, population group, and collection date	No. of samples	Mean (range)	Median (IQR)	Relevant percentiles	Analytical method (LOD)	Comments	Reference
Anthracene in umbilical cord blood	La Palma, Canary Islands, Spain, pregnant women (age, 16–42 yr), 2015–2016	447	0.181 (ND–0.181) ng/mL	NR	NR	GC-MS (NR)	Smokers, 11.18%. Anthracene was only detected in 1 sample.	Cabrera-Rodríguez et al. (2019)
Anthracene in cord serum	Asaluyeh port (petrochemical and gas area) and Bushehr port (urban area), Islamic Republic of Iran, pregnant women (gestation, 37–42 wk; age, 18–37 yr) and fetuses, 2018–2019					GC-MS (0.76 ng/L)	6 h between the collection of the maternal and cord blood. Pregnant healthy women that lived at least 1 yr in the sampling areas. Smoking/passive smoking, alcoholism, mothers who had infants with congenital malformations and multiple gestations were excluded.	Khalili Doroodzani et al. (2021)
	Petrochemical and gas area	99	2.07 (ND–26.5) µg/L	ND	25th percentile, ND 75th percentile, 1.75 µg/L			
	Urban area	100	3.21 (ND–14.5) µg/L	2.85 µg/L	25th percentile, 0.05 µg/L 75th percentile, 5.25 µg/L			

Table 1.10 (continued)

Compound or metabolite and sample type	Location, population group, and collection date	No. of samples	Mean (range)	Median (IQR)	Relevant percentiles	Analytical method (LOD)	Comments	Reference
Anthracene in hair	Baoding and Dalian, healthy women (age, 25–45 yr), China, 2016					GC-MS/MS (NR)	Baoding as polluted city and Dalian as less polluted city. Subjects living for at least 15 yr in the same city.	Palazzi et al. (2018)
	Baoding	102	10.31 (0.06–40.9) pg/mL	8.63 pg/mL	25th percentile, 5.13 pg/mL 75th percentile, 12.6 pg/mL			
	Dalian	102	6.20 (0.06–29.7) pg/mL	5.8 pg/mL	25th percentile, 2.27 pg/mL 75th percentile, 8.86 pg/mL			
1-Hydroxy-anthracene in hair	Baoding	102	1.44 (0.24–10.9) pg/mL	0.92	25th percentile, 0.68 pg/mL 75th percentile, 1.48 pg/mL			
	Dalian	102	1.22 (0.24-3.71) pg/mL	1.05	25th percentile, 0.9 pg/mL 75th percentile, 1.47 pg/mL			
Anthracene in hair	Nanjing and Ningbo, general population, China, 2018	NR	NR	NR	NR	GC-MS (NR)	No hair dying in the past 2 yr. The first 12 cm of hair was used.	Wang et al. (2020)
	By region:							
	Nanjing (urban)	33	209 (ND–271) pg/mg	208 pg/mg				
	Ningbo (rural)	33	65.7 (ND–98.6) pg/mg	77.8 pg/mg				
	By region and smoking:							
	Nanjing							
	Smokers	9	270.9 pg/mg					
	Non-smokers	12	48.9 pg/mg					

Table 1.10 (continued)

Compound or metabolite and sample type	Location, population group, and collection date	No. of samples	Mean (range)	Median (IQR)	Relevant percentiles	Analytical method (LOD)	Comments	Reference
Anthracene in hair	Ningbo							Wang et al. (2020) (cont.)
	Smokers	9	20.6 pg/mg					
	Non-smokers	12	NR					
Anthracene in hair	Kanazawa, Japan, general population (age, 21–47 yr, 6 females and 14 males), date NR	20		NR	NR	HPLC-FLD (1.6 pg/injection)	Statistically significant differences between smokers and non-smokers.	Toriba et al. (2003)
	Smokers		8.2 (2.9–22.6) pg/mg hair					
	Non-smokers		3.5 (0.8–8.7) pg/mg hair					
Anthracene in forensic samples:	Murcia, Spain, cadavers (age, 29–80 yr), date NR			NR	NR	GC-MS (0.050 ng/g)		Pastor-Belda et al. (2019)
Brain		8 (87.5% of detection)	0.256 (0–0.601) ng/g					
Liver		8 (62.5%)	0.145 (0–0.597) ng/g					
Lung		8 (75%)	0.214 (0–0.469) ng/g					
Kidney		8 (62.5%)	0.152 (0–0.491) ng/g					
Heart		8 (75%)	0.178 (0–0.332) ng/g					
Fat		8 (62.5%)	2.774 (0–19.093) ng/g					
Spleen		8 (100%)	0.069 (0–0.176) ng/g					

Table 1.10 (continued)

Compound or metabolite and sample type	Location, population group, and collection date	No. of samples	Mean (range)	Median (IQR)	Relevant percentiles	Analytical method (LOD)	Comments	Reference
Anthracene in lung tissue	Moldavia, Romania, pulmonary cancer patients (mean age, 59.48 yr), 2008–2009	31			NR	HPLC-UV-FLD (NR)	Smokers (90%) and non-smokers (10%), mean level of 30 cigarettes per day.	Cioroiu et al. (2013)
	By location:							
	Urban donors	16	4.83 (0.12–30.59) ng/g wet tissue	2.72 ng/g wet tissue				
	Rural donors	15	1.89 (0.08–15.27) ng/g tissue	0.77 ng/g wet tissue				
	By blood type:							
	Group A	6	3.28 (0.15–12.84) ng/g wet tissue	0.81 ng/g wet tissue				
	Group O	7	4.41 (0.49–15.27) ng/g wet tissue	2.44 ng/g wet tissue				
	Group B	17	3.01 (0.08–30.59) ng/g wet tissue	0.79 ng/g wet tissue				
Anthracene in bronchoalveolar lavage fluid	Harbin, China, patients with chronic obstructive pulmonary disease (age, > 40 yr), 2017–2018			NR	NR	GC-MS (NR)	Non-smoking and non-secondhand smoking. Statistically higher levels of anthracene in the group with high risk of $PM_{2.5}$ inhalation.	Che et al. (2020)
	High-risk group of fine PM inhalation	13	0.78 ng/mL					
	Low-risk group of fine PM inhalation	19	0.35–0.40 ng/mL					

GC-FID, gas chromatography-flame ionization detection; GC-MS, gas chromatography-mass spectrometry; GC-MS/MS, gas chromatography-tandem mass spectrometry; h, hour(s); HPLC-DAD-FLD, high-performance liquid chromatography-diode array-fluorescence detection; HPLC-FLD, high-performance liquid chromatography-fluorescence detection; HPLC-UV-FLD, high-performance liquid chromatography method with ultraviolet and fluorescence detectors; IQR, interquartile range; LOD, limit of detection; LOQ, limit of quantification; ND, not detected; NR, not reported; $PM_{2.5}$, particulate matter with diameter ≤ 2.5 μm; PAH, polycyclic aromatic hydrocarbon; ppb, parts per billion; wk, week(s); yr, year(s).

1-Hydroxyanthracene in hair samples was additionally analysed to assess total exposure to anthracene in women from areas with different pollution levels and the same trend was observed; there were significantly higher concentrations in the hair samples collected from women living in the most polluted city (Palazzi et al., 2018).

Anthracene was also one of the low-molecular-weight PAHs that predominated in forensic biological samples (brain, liver, lung, kidney, heart, adipose tissue, and spleen) retrieved during autopsies in Spain (Pastor-Belda et al., 2019); mean tissue levels ranged from 0.069 ng/g (range, 0–0.176 ng/g) in the spleen to 2.774 ng/g (range, 0–19.093 ng/g) in fat (Table 1.10).

In one study, urine and blood were simultaneously collected from children. Concentrations of anthracene were 0.55 µg/dL (range, 0.51–0.62 µg/dL) [5.5 ng/mL (range, 5.1–6.2 ng/mL)] in the urine and 0.06 µg/dL (range, 0.051–0.64 µg/dL) [0.6 ng/mL (range, 0.51–6.4 ng/mL)] in the blood (Wirnkor et al., 2019).

Exposure of pregnant women (smokers or non-smokers, living in industrial or urban areas) and their fetuses and infants have been characterized through the analysis of venous maternal blood and serum, placental tissues, cord blood and serum, and breast milk (Table 1.10). Anthracene can cross the human placental barrier. Mean levels detected in placental tissue ranged from 0.027 µg/L (Agarwal et al., 2018) to 33.26 ppb [33.26 µg/kg] (Singh et al., 2008a) in two studies in India. Mean values measured in maternal venous serum ranged from < 0.02 µg/L in China to 2.9 µg/L (range, < 0.76–18.3 µg/L) in the Islamic Republic of Iran. In a study in Spain, anthracene was detected in only 1 out of 447 umbilical cord blood samples (0.181 ng/mL) (Cabrera-Rodríguez et al., 2019) [the LOD was not reported]. In a study from Iran (Khalili Doroodzani et al., 2021), the mean concentration of anthracene in cord serum was 3.21 µg/L (range, < 0.76–14.5 µg/L) (Table 1.10).

Anthracene can be transferred to breast milk. Reported levels of anthracene in human breast milk varied between < 0.04 ng/g fat (< 0.001 ng/mL, the LOD) in the USA (Kim et al., 2008), 0.05 ng/mL (median, range, 0.044–2.04 ng/mL) in Portugal (Oliveira et al., 2020) and 39.07 µg/kg (mean, range, not detected to 89.55 µg/kg) in Italy (Santonicola et al., 2017).

Overall, smoking habits, living or working in industrial or urban polluted areas, and cooking using biomass as fuel were the main exposure determinants of anthracene concentrations measured in the general population.

1.5 Regulations and guidelines

Available regulations and guidelines are reported in Table 1.11.

An occupational limit value specifically aimed to regulate the exposure of workers to anthracene was not available to the Working Group.

The EU Water Environmental Quality Standards Directive 2008/105/EC set an emission limit value of 0.1 µg/L for anthracene emissions into inland surface waters and other surface waters (encompassing rivers and lakes, and related to artificial or heavily modified water bodies) as an annual average (European Parliament and Council, 2008).

The US EPA suggested the reference dose 0.3 mg/kg day as the level not expected to cause adverse effects to human health when drinking-water or eating seafood from contaminated surface water (US EPA, 2015).

In the EU, anthracene is in the list of Hazardous Substances for Purposes of Council Directive 90/385/EEC on active implantable medical devices, 20 July 1990 (European Council, 1990), amended by Directive 2007/47/EC, 21 September 2007 (European Parliament and Council, 2007). This list contains hazardous substances particularly as regards Article 3 and Annex I, concerning essential requirements

Table 1.11 Regulatory and guideline values for anthracene

Regulatory or guideline value	Country, location	Description, applicability	Value and units	Comments	Reference
Environment					
Water	EU	Water environmental quality standards directive for anthracene emission into surface water (encompassing rivers and lakes and related artificial or heavily modified water bodies)	0.1 µg/L		European Parliament and Council (2013)
Soil	Canada	Environmental Quality Guidelines (Soil Quality Guidelines) for anthracene	2.5 µg/kg	Contact exposure – agricultural and residential land use soil.	CCME (2010)
			32 µg/kg	Contact exposure – commercial and industrial land use soil.	
			61.5 µg/kg	Soil and food ingestion for the protection of livestock and wildlife.	
Food and drinking-water					
Food and water	USA	Reference dose for human health when drinking water or eating seafood from contaminated surface water	0.3 mg/kg day	Level not expected to cause adverse effects to human health.	US EPA (2015)

EU, European Union

and the choice of materials used, particularly as regards toxicity aspects (ECHA, 2024).

In the EU and in the scope of the REACH regulations, anthracene is specified in the REACH candidate list of substances of very high concern for authorization (IFA, 2023). Also in the EU, and in the context of Directive 2012/18/EU (Seveso III), the substance is subject to the hazard categories of the Hazardous Incident Ordinance (E1 hazardous to the aquatic environment, category acute 1 or chronic 1).

1.6 Quality of exposure assessment in key mechanistic studies in humans

The Working Group reviewed five cross-sectional studies and one case–control study that contributed to mechanistic evidence related to exposure to anthracene (see Sections 4.2.1 and 4.2.4). Four studies were focused on relatively small groups of workers (roofers, steel-foundry workers, and coke-oven workers in a steel plant; fewer than 100 exposed individuals) and involved exposure to multiple PAHs, including anthracene (Herbert et al., 1990; Hanchi et al., 2017; Jeng et al., 2022, 2023). One cross-sectional study concerned exposure to PAHs from indoor (biofuel cooking, smoking) and environmental (traffic) sources among children aged 2–10 years in India (Singh et al., 2008c). The case–control study, also from India, concerned the reproductive health effects (risk of preterm delivery) of environmental (indoors, outdoors and via food consumption) exposure to PAHs, which were measured in placental tissue (Agarwal et al., 2018).

Details on the exposure assessments employed in the five studies are summarized in

Table S1.12 (see Annex 1, Supplementary material for Section 1, Exposure Characterization, online only, available from: https://publications.iarc.who.int/631).

In the three studies performed in occupational settings, the different assessment methods used included air monitoring, skin wipes, and urinary biomonitoring.

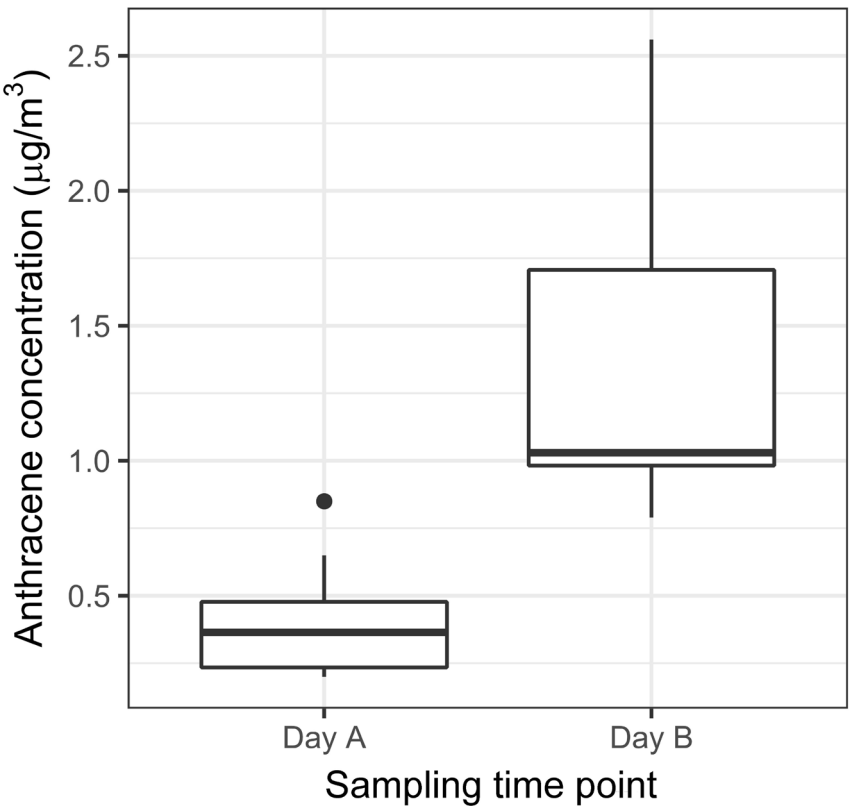
In a small study in the USA in 12 exposed workers involved in the removal of sequential sections of an old (coal-tar) pitch roof followed by replacement with a new asphalt (bitumen) roof (Herbert et al., 1990), inhalation and dermal exposure to anthracene, fluoranthene, pyrene, benzanthracene, B[a]P, benzo[*b*]-fluoranthene, benzo[*ghi*]perylene and benzo[*k*]-fluoranthene was measured on 2 days during 1 week. Inhalation samples were taken on two occasions (Thursday and Monday), and pre- and post-shift dermal wipes were only taken on the second measurement day (Monday). On the subsequent day (Tuesday), blood samples were collected for DNA adduct assessment. The reference group comprised employees of Mount Sinai Medical Center or patients from the Mount Sinai Occupational Health Clinical Center who were matched on age, sex, and smoking status. The inhalation and dermal samples were analysed according to standard NIOSH method 5506 (NIOSH, 1998) and inhalation measurements involved collection of PAHs on a filter and with a sorbent tube (for the more volatile PAHs).

The repeated measurement design and reporting of the results of individual measurements (Table 1 in Herbert et al., 1990) allowed the assessment of exposure variability. As expected among outdoor workers, temporal (day-to-day) variability in exposure outweighed the difference in average exposure for anthracene (see Fig. 1.1) within this group of workers in the same location. Analysis of variance showed that 100% of the variability was due to day-to-day changes in exposure concentrations, and therefore the roofers could be considered a uniformly exposed group. The total variability was relatively low (geometric standard deviation, 1.40 and 1.24 for anthracene and total PAH, respectively). Although not collected repeatedly, the forehead wipe samples showed slightly higher total variability than did the inhalation samples. A statistically significant tenfold difference in total PAH concentrations on forehead skin between wipe samples taken before and after work was apparent; however, anthracene was not detected in the wipe samples, most probably because most of the anthracene would have been in the gaseous phase.

The study among coke-oven workers from a steel plant in Taiwan, China (Jeng et al., 2022, 2023) focused on sperm oxidative DNA damage and semen quality and associations with inhalation exposure to 16 PAHs. One study included 38 coke-oven workers and 24 controls (Jeng et al., 2022), and a second study included 31 topside-oven workers and 23 side-oven workers but no controls (Jeng et al., 2023). PAH samples were collected on filters and XAD-2 sorbent tubes and analysed by GC-MS. No assessment of dermal exposure to PAHs was conducted, although this is considered to be the major route of exposure in coke-oven workers (VanRooij et al., 1993).

Median exposure to anthracene of the workers was reported as 337 (median of log transformed values, 5.82), no units provided, and an interquartile range (IQR) of 296–380. Also, the IQRs for all other PAHs reported were similar and improbably small (see Table 3 in Jeng et al., 2022). [Given that the reported LODs ranged between 6.1 and 9.8 ng for the PAHs analysed, the Working Group assumed that the units were reported in ng/m^3.] In another study by the same authors (Jeng et al., 2023), presumably performed in the same steel plant, similar levels of exposure were reported, but again the reporting was of very poor quality given that the actual statistical parameters were not specified, but simply reported as 353.54 ± 93.33 ng/m^3 and 340.98 ± 66.58 ng/m^3 for top-side oven and

Fig. 1.1 Inhalation exposure to anthracene and total PAHs for 12 roofers on two measurement days



PAH, polycyclic aromatic hydrocarbon.
Created by the Working Group using data from Table 1 in Herbert et al. (1990).

side-oven workers, respectively. [Given that the study results were poorly reported and dermal exposure was not assessed, the Working Group considered that this study could not be confidently interpreted with regard to exposure to anthracene.]

Details of a study among electric steel-foundry workers in Tunisia (Hanchi et al., 2017) were found in a separate paper (Campo et al., 2016). The study focused on biological monitoring of exposure to PAHs via spot urine samples collected at the end of an 8-hour work shift. No repeated samples were collected, and no inhalation or dermal exposure measurements were conducted. The 16 US EPA two- to six–ring unmetabolized PAHs and eight hydroxylated PAH metabolites were analysed by GC-MS/MS and liquid chromatography-triple quadrupole tandem mass spectrometry (LC-MS/MS). Multiple linear regression models showed that job title was a significant determinant for several unmetabolized PAHs but not for anthracene. Urinary levels of unmetabolized anthracene were similar among the three exposure groups, with median values of 1.97 ng/L, 2.17 ng/L, and 2.58 ng/L for workers from the steel smelter workshop ($n = 30$), workers near the fuel furnaces ($n = 43$), and workers involved in a variety of different tasks away from the furnaces ($n = 20$), respectively (Campo et al., 2016). The exposure

assessment in the study resulted in very limited contrasts in exposure to anthracene. In a multivariable analysis of the biomarker 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG), measuring oxidative DNA damage, the job title grouping and the actual biomonitoring values were used simultaneously as independent variables, but this would most probably have resulted in multicollinearity.

In a case–control study on risk of preterm delivery and exposure to PAHs via the environment and food in India, placental levels of PAHs were measured at the time of delivery (Agarwal et al., 2018). Placental samples were analysed for the 16 US EPA-classified PAHs using gas chromatography-flame ionization detection (GC-FID). For further confirmation, a few samples from each batch were randomly analysed by GC-MS. Levels of individual PAHs and several PAH sum measures were presented for cases and controls, and means and standard deviations were reported. No insight was given into the actual distributions of the individual PAH concentrations.

The cross-sectional study in 50 children (aged 2–10 years) concerned exposure to PAHs, as assessed in blood, and associations with indices of oxidative stress. Concentrations of naphthalene, acenaphthylene, phenanthrene, anthracene, benzo[*k*]fluoranthene, benzo[*b*]fluoranthene, and B[a]P were measured in blood samples collected on one occasion at the time of enrolment (Singh et al., 2008c). Blood levels of PAHs were determined by HPLC-FLD-UV. The results of anthracene were not reported, which precludes the assessment of an association between anthracene exposure and the outcome.

[The Working Group noted that all studies dealt with simultaneous exposure to multiple PAHs. Only one of the three industrial studies measured both inhalation and dermal exposure (Herbert et al., 1990). The reporting of exposure results was very poor in the coke-oven workers study (Jeng et al., 2022).]

2. Cancer in Humans

No epidemiological studies were available that investigated the association between exposure to anthracene and cancer in humans. One case report of a cancer of the scrotum after dermal exposure to anthracene oil was considered uninformative by the Working Group, since anthracene oil is a mixture containing anthracene and other two- to four-ring aromatic compounds obtained from coal tar (Weissenbach, 1952).

3. Cancer in Experimental Animals

In previous evaluations, the *IARC Monographs* programme concluded that there was *inadequate evidence* in experimental animals regarding the carcinogenicity of anthracene (IARC, 1987, 2010).

Studies of carcinogenicity with anthracene in experimental animals are summarized in Table 3.1 and Table 3.2.

3.1 Mouse

See Table 3.1.

3.1.1 Oral administration (feed)

In a well-conducted chronic toxicity and carcinogenicity study that complied with Good Laboratory Practice (GLP) (JBRC, 1998; also reported by Takeda et al., 2022), groups of 50 male and 50 female Crj:BDF1 mice (age, 6 weeks) were treated with feed containing anthracene (purity, 99.8–99.9%) at 0, 3200, 8000, or 20 000 ppm (weight per weight, w/w) for males and 0, 8000, 20 000, or 50 000 ppm (w/w) for females, 7 days per week for 104 weeks. On the basis of feed consumption, the estimated doses were 0, 459, 1178, and 3076 mg/kg body weight (bw) per day for male mice at 0, 3200, 8000, and

Table 3.1 Studies of carcinogenicity in mice exposed to anthracene

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Results	Significance	Comments
Full carcinogenicity Mouse, Crj:BDF_1 (M) 6 wk 104 wk JBRC (1998)	Oral administration (feed) Purity, 99.8–99.9% Feed 0, 3200, 8000, 20 000 ppm (w/w), continuous dosing 49, 50, 50, 50 41, 41, 37, 42	Any tumour type: no significant increase in incidence		*Principal strengths*: well-conducted GLP study; covered most of the lifespan; multiple dose study; males and females used; adequate number of animals per group; adequate duration of exposure and observation.
Full carcinogenicity Mouse, Crj:BDF_1 (F) 6 wk 104 wk JBRC (1998)	Oral administration (feed) Purity, 99.8–99.9% Feed 0, 8000, 20 000, 50 000 ppm (w/w), continuous dosing 50, 50, 50, 50 35, 31, 34, 34	*Liver* Hepatocellular adenoma 2/50 (4%), 3/50 (6%), 6/50 (12%), 20/50* (40%) Hepatocellular carcinoma 0/50, 2/50 (4%), 5/50* (10%), 12/50** (24%)	$P < 0.0001$, Peto prevalence method test $P < 0.0001$, Cochran–Armitage test; NC, Peto standard method test, Peto combined analysis test *$P = 0.0003$, Fisher exact test $P < 0.0001$, Peto prevalence method test $P < 0.0001$, Peto combined analysis $P < 0.0001$, Cochran–Armitage test; NS, Peto standard method test *$P = 0.036$, Fisher exact test; **$P = 0.0005$, Fisher exact test	*Principal strengths*: well-conducted GLP study; covered most of the lifespan; multiple dose study; males and females used; adequate number of animals per group; adequate duration of exposure and observation. *Historical controls*: hepatocellular adenoma, 45/899 (5.0%); range, 2–10%; hepatocellular carcinoma, 20/899 (2.2%); range, 0–8%; hepatocellular adenoma or carcinoma (combined), 65/899 (7.2%); range, 2–12%; histiocytic sarcoma (all organs), 199/899 (22.1%); range, 12–30%.

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Results	Significance	Comments
Full carcinogenicity Mouse, Crj:BDF_1 (F) 6 wk 104 wk JBRC (1998) (cont.)		Hepatocellular adenoma or carcinoma (combined) 2/50 (4%), 5/50 (10%), 11/50* (22%), 26/50** (52%)	$P < 0.0001$, Peto prevalence method test $P < 0.0001$, Peto combined analysis test $P < 0.0001$, Cochran–Armitage test; NS, Peto standard method test *$P = 0.0170$, Fisher exact test **$P = 0.0001$, Fisher exact test	
		All organs (uterus, liver, subcutis, salivary gland, urinary bladder) Histiocytic sarcoma 6/50 (12%), 18/50 (36%)*, 11/50 (22%), 11/50 (22%)	*$P = 0.0222$, Fisher exact test	
Initiation–promotion (tested as initiator) Mouse, Crl:CD/1 (ICR)BR (F) 50–55 days 24 wk La Voie et al. (1985)	Skin application Purity, > 99% Acetone 0, 100 µg 100 µg in 100 µL acetone, once every other day for a total of 10 doses, followed by 2.5 µg TPA in 100 µL acetone, 3×/wk, for 20 wk 20, 20 20, 20	*Skin* Tumours 2/20, 3/20	NS	*Principal limitations*: limited reporting; macroscopic evaluation of skin tumours only.

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Results	Significance	Comments
Initiation–promotion (tested as initiator) Mouse, CD-1 (F) 7 wk 32 wk Wislocki et al. (1982)	Skin application Purity, "sufficiently pure for use" Acetone 0, 400, 1000 nmol Single application of 400 or 1000 nmol in 200 µL of acetone, followed 1 wk later by promotion with 10 µg TPA, 2×/wk for 31 wk; mice were examined for skin papillomas, and tumours were counted when they were > 2 mm in diameter and present for 2 wk 30, 30, 30 29, 29, 29	*Skin (site of application)* Papilloma Tumour incidence: 13%, 11%, 21% Tumour multiplicity: 0.23, 0.18, 0.27	[Tumour incidence was reported as percentages. It was unclear how many tumour-bearing mice (numerator) or how many mice in total (denominator) were used for calculation of these percentages.]	*Principal limitations*: limited reporting; uncertainty regarding purity; uncertainty regarding the number of animals examined; macroscopic evaluation of skin tumours only.
Co-carcinogenicity Mouse, Skh: hairless-1 (M) 6 wk 38 wk Forbes et al. (1976)	Skin application Purity, 99% Methanol 4 µg/day, 5 days/wk, for 38 wk Daily skin application (in 40 µL of methanol solution, 0.1 g/L), 5 days/wk (Monday through Friday only), followed by 2 h of UV light after each application 24 NR	Skin: tumours Incidence, NR		*Principal limitations*: use of one sex only; limited reporting of histopathology. *Other comments*: tumour incidence was not reported although, on the basis of the final tumour prevalence, incidence did not seem to differ between the anthracene- and UV-treated group and the control group; the time to 50% prevalence of skin tumours did not differ significantly between anthracene treatment (28.2 wk) and methanol vehicle-control treatment (27.2 wk) by Wilcoxon rank-sum test statistics.

F, female; GLP, Good Laboratory Practice; h, hour(s); M, male; ppm, parts per million; NC, not calculable; NR, not reported; NS, not significant; TPA, 12-*O*-tetra-decanoylphorbol-13-acetate; UV, ultraviolet; wk, week(s); w/w, weight per weight.

20 000 ppm, respectively, and 0, 1459, 3711, and 9725 mg/kg bw per day for female mice at 0, 8000, 20 000, or 50 000 ppm, respectively. The survival rate for all dosed groups of males and females was similar to that of controls. At study termination, survival was 41/49, 41/50, 37/50, and 42/50 in males, for the groups at 0 (control), 3200, 8000, 20 000 ppm, respectively, and 35/50, 31/50, 34/50, and 34/50 in females, for the groups at 0 (control), 8000, 20 000, and 50 000 ppm, respectively. Body weights of the males at 20 000 ppm male and females at 50 000 ppm were significantly decreased throughout the administration period, compared with their respective controls. All mice underwent complete necropsy, and all organs and tissues were sampled for histopathology in all the animals.

In female mice, there was a significant positive trend ($P < 0.0001$, Peto trend test, prevalence method; $P < 0.0001$, Cochran–Armitage trend test) in the incidence of hepatocellular adenoma – 2/50 (4%), 3/50 (6%), 6/50 (12%), and 20/50 (40%) for the groups at 0 (control), 8000, 20 000, and 50 000 ppm, respectively – with the incidence being significantly increased at the highest dose ($P = 0.0003$, Fisher exact test), and exceeding the upper bound of the range observed for historical controls from the same laboratory – 45/899 (5.0%); range, 2–10%. [The Working Group noted that several Peto trend tests were conducted in this study, with the Peto test standard method being referred to as "death analysis", the Peto test prevalence method being referred to as "incidental tumour test", and the Peto test combined analysis being referred to as "death analysis plus incidental tumour test". A significant *P* value in any Peto test was considered relevant for the detection of treatment-related increases in tumour incidence.] There was a significant positive trend ($P < 0.0001$, Peto trend test, prevalence method and combined analysis; $P < 0.0001$, Cochran–Armitage trend test) in the incidence of hepatocellular carcinoma – 0/50, 2/50 (4%), 5/50 (10%), and 12/50 (24%) for the groups at 0 (control), 8000, 20 000, and 50 000 ppm, respectively – with the incidence being significantly increased at the intermediate and highest dose ($P = 0.036$, Fisher exact test; $P = 0.0005$, Fisher exact test, respectively), and exceeding the upper bound of the range observed for historical controls from the same laboratory – 20/899 (2.2%); range, 0–8%. There was a significant positive trend ($P < 0.0001$, Peto trend test (prevalence method and combined analysis); $P < 0.0001$, Cochran–Armitage trend test) in the incidence of hepatocellular adenoma or carcinoma (combined) – 2/50 (4%), 5/50 (10%), 11/50 (22%), and 26/50 (52%) for the groups at 0 (control), 8000, 20 000, and 50 000 ppm, respectively – with the incidence being significantly increased at the intermediate and highest dose ($P = 0.017$, Fisher exact test; $P = 0.0001$, Fisher exact test, respectively), and exceeding the upper bound of the range observed in historical controls from the same laboratory – 65/899 (7.2%); range, 2–12%. The incidence of histiocytic sarcoma of all organs (uterus, liver, subcutis, salivary gland, and urinary bladder) – 6/50 (12%), 18/50 (36%), 11/50 (22%), and 11/50 (22%) for the groups at 0 (control), 8000, 20 000, and 50 000 ppm, respectively – was significantly increased ($P = 0.0222$, Fisher exact test) at the lowest dose; and exceeded the upper bound of the range for historical controls from the same laboratory – 199/899 (22.1%); range, 12–30%.

In male mice, dietary administration of anthracene did not cause a significant increase in the incidence of any type of neoplasm.

Regarding the non-neoplastic lesions, anthracene caused hyaline droplet degeneration in superficial cells of the transitional epithelium of the urinary bladder in all treated groups of male and female mice. Significant treatment-related increases in the incidence of clear cell and basophilic cell foci in the liver of female mice were also observed (JBRC, 1998; also reported in Takeda et al., 2022). [The Working Group noted that this was a well-conducted GLP study that

had a duration of exposure and observation of most of the lifespan, used multiple dose groups, both sexes, and an adequate number of animals per group.]

3.1.2 Subcutaneous injection

A group of 40 male and female NMRI mice (age, 2 days) received a single subcutaneous injection of 71.3 µg (400 nmol) of anthracene (purity, 99.9%) dissolved in 50 µL of an aqueous solution (1% gelatin, 0.9% saline, 0.4% Tween 20) (Platt et al., 1990). A control group of 49 male and female mice was treated with the solvent alone. After 40 weeks, all mice underwent necropsy and the lung tissues were analysed by histopathology. There was no increase in the incidence of lung tumours: 2/17 treated male mice developed lung adenoma compared with 1/14 male mice from the solvent control group, and 1/12 treated female mice developed lung adenoma compared with 1/19 female mice from the solvent control group. [The Working Group noted that this study was limited because the numbers of male mice and female mice at the start of treatment were not reported (40 was reported for males and females combined in the anthracene group and 49 was reported for males and females combined in the control group), the use of a single dose, only lung tissue was examined, necropsy observations were not reported for animals that did not survive to the end of the experiment, and histopathology was not reported. Therefore, this study was judged to be inadequate for the evaluation of the carcinogenicity of anthracene in experimental animals.]

A group of 40–50 male and female C57BL mice [age not reported] were given a single subcutaneous injection of 5 mg of anthracene [purity not reported] dissolved in 0.5 mL of tricaprylin (Steiner, 1955). The number of mice surviving at 4 months was used to calculate tumour incidence. At study termination (between months 22 and 28), none of the anthracene-treated mice (0/26) developed sarcoma at the injection site. [The Working Group noted that the study was limited by the lack of untreated or solvent controls, the use of a single dose, the lack of information on anthracene purity, and the use of males and females in one group. Therefore, the study was judged to be inadequate for the evaluation of the carcinogenicity of anthracene in experimental animals.]

3.1.3 Intraperitoneal injection

A group of 20 male and female SPF Kun Ming mice [age not reported] were given 10 daily intraperitoneal injections of anthracene [purity not reported] at a dose of 50 mg/kg bw dissolved in dimethyl sulfoxide (DMSO) at 0.1 mL/g bw (Wang & Xue, 2015). Histological examinations were performed on the liver, kidney, stomach, and lung tissues, 3 months after exposure. There was a significant increase in the incidence of hepatocellular carcinoma (control, 0/20; anthracene, 5/18; $P < 0.05$, Fisher exact test). No tumours were observed in the kidney, stomach, or lung tissues in anthracene-treated or control animals. [The Working Group noted that this study was limited by the short duration, the combination of males and females in one group, the lack of information on anthracene purity, and the limited histological examination. Therefore, the study was judged to be inadequate for the evaluation of the carcinogenicity of anthracene in experimental animals.]

A group of five male Swiss mice (age, 2.0–2.5 months) were given a single intraperitoneal injection of 25 mg of anthracene [purity not reported] in ~750 µL olive oil (Shubik & Della Porta, 1957). Five months after the injection, no tumours were observed in the four surviving mice in the group treated with anthracene or the four surviving mice treated with olive oil. [The Working Group noted that this study was limited by the short duration, the small number of animals used, the use of a single dose and a single

sex, the lack of information on anthracene purity, and the limited reporting on histological examination. The study was judged to be inadequate for the evaluation of the carcinogenicity of anthracene in experimental animals.]

3.1.4 Skin application

A group of 20 male C3H/HeJ mice (age, 8–10 weeks) were given skin applications of 0.1% anthracene (purity, 99.5%) in 50 µL of toluene solution twice per week for 104 weeks (Warshawsky et al., 1993). Fifty male C3H/HeJ mice were given toluene as the solvent control. Only tumours at the application site were examined. No skin tumours were observed in the anthracene-treated or control group (control, 0/39; anthracene, 0/14). [The Working Group noted that this study was limited by the use of a single dose and a single sex, and the limited reporting of the histological examination. The study was judged to be inadequate for the evaluation of the carcinogenicity of anthracene in experimental animals.]

A group of five female Swiss mice [age not reported] received skin applications of anthracene [purity not reported] as a 10% solution in acetone, three times per week for up to 20 months (Wynder & Hoffmann, 1959). By 20 months, all five mice were dead, and no tumours were observed. [The Working Group noted that this study was limited by the lack of information on purity, the small number of animals used, the lack of information on the age of animals, the lack of control, and the use of a single unknown dose. Therefore, the study was judged to be inadequate for the evaluation of the carcinogenicity of anthracene in experimental animals.]

A group of 41 albino mice [strain, sex, and age not specified] were treated with an unknown amount of anthracene [purity not reported], diluted in water, benzene, or sesame oil, by intrascapular skin painting (Pollia, 1939). The average lifespan of all mice in the study (including mice receiving chemicals other than anthracene) was 133 days after skin painting. At 10 months, none of the surviving mice that received anthracene had developed any skin tumours. [The Working Group noted that this study was limited by the lack of information on purity, the lack of information on the strain, sex, and age of animals, the lack of control, and the use of a single unknown dose. The study was judged to be inadequate for the evaluation of the carcinogenicity of anthracene in experimental animals.]

Two groups of 100 mice [strain, sex, and age not specified] were treated via skin application with 40% anthracene (a tar derivative, purity not reported) in either a lanolin suspension or an ether solution (Kennaway, 1924a, b). No tumours developed in the group receiving anthracene in the lanolin suspension, and one mouse from the group receiving anthracene in the ether solution developed a papilloma after 131 days. [The Working Group noted that this study was limited by the lack of information on purity and probable contamination by other PAHs in tar, the lack of information on the strain, sex, and age of the animals, the lack of control, and the use of a single unknown dose. Therefore, the study was judged to be inadequate for the evaluation of the carcinogenicity of anthracene in experimental animals.]

3.1.5 Initiation–promotion

A group of 20 female Crl:CD-1(ICR)BR mice (age, 50–55 days) received skin applications of 100 µg of anthracene (purity, > 99%) in 100 µL of acetone, once every other day, for a total of 10 applications (total dose, 1 g). Ten days after the last exposure to anthracene, the mice were given skin applications of 2.5 µg of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) in 100 µL of acetone, three times per week, for 20 weeks (La Voie et al., 1985). The control group received acetone during the initiation phase and TPA during the promotion phase. The incidence

of skin tumours was 3/20 in the anthracene-initiated group, 2/20 in the control group, and 1/20 in a repeated control group. [The Working Group noted that this study was limited by the lack of survival data and the macroscopic evaluation of skin tumours only.]

Groups of 30 female CD-1 mice (age, 7 weeks) were given a single skin application of anthracene (purity reported as "sufficiently pure for use in the experiment") at doses of 400 and 1000 nmol in 200 µL acetone. One week after exposure to anthracene, the mice were given 10 µg of TPA in 200 µL of acetone, twice per week for 31 weeks (Wislocki et al., 1982). The control mice received acetone and TPA. The mice were examined for skin papillomas every other week. The incidence of skin papilloma was reported as follows: 13%, 11%, and 21% for the groups at 0 (control), 400, and 1000 nmol, respectively. Tumour multiplicity (number of tumours per mouse) was reported as follows: 0.23, 0.18, and 0.27 for the groups at 0 (control), 400, and 1000 nmol, respectively. [The Working Group noted that this study was limited by uncertainty regarding anthracene purity and the number of animals examined, and the macroscopic evaluation of skin tumours only.]

A group of 30 female CD-1 mice (age, 8 weeks) were given a single skin application of 10 µmol of anthracene (purity reported as "purified by preparative thin-layer chromatography") in benzene. One week later, the mice were treated with 5 µmol of TPA, twice per week for 34 weeks (Scribner, 1973). A control group of 30 mice were treated with 10 µmol of TPA only, twice per week for 34 weeks. [The Working Group noted that it was unclear whether the controls received solvent or no treatment during the initiation phase.] At week 35, 30, and 28 of the animals from the control group and the anthracene-initiated group, respectively, were alive. The incidence of skin papilloma was 0/30 in the control group and 4/28 in the anthracene-initiated group [P = 0.0483, Fisher exact test]. [The Working Group noted that this study was limited by uncertainty regarding anthracene purity, the use of benzene as a solvent, and the use of different doses of the promoter in the controls and the anthracene-treated animals. Therefore, the study was judged to be inadequate for the evaluation of anthracene in experimental animals.]

A group of 20 strain "S" mice [sex and age not reported] were given 20 skin applications of 0.5% anthracene [purity not reported] in acetone solution, twice per day (with a 30-minute interval), 3 days per week, for a total dose of 30 mg (Salaman & Roe, 1956). Starting on day 25 after the first application of anthracene, the mice were treated with 18 applications of 0.3 mL of croton oil in acetone solution (one application of 0.17% solution, two applications of 0.085% solution, and 15 further applications of 0.17% solution at weekly intervals). A group of 20 control mice received only croton oil according to the same protocol. The incidence of skin papilloma was 4/19 in the control and 3/17 in the anthracene-initiated group. [The Working Group noted that this study was limited by the lack of information on purity, and the lack of information on the sex and age of animals. Therefore, the study was judged to be inadequate for the evaluation of anthracene in experimental animals.]

3.1.6 Co-exposures

Two groups of 87 white mice [sex, strain, and age not reported] were given 10% anthracene (reported as "pure anthracene") ointment in olive oil and Vaseline (petroleum jelly) by skin application, immediately followed by ultraviolet (UV) radiation 5 hours per session, three sessions per week (Heller, 1950). One group received anthracene and long-wave UV-A, while the other group received anthracene, long-wave UV-A, and visible light. In the group that received anthracene and long-wave UV-A, carcinomas were first observed after 39 days and reached 100% incidence after 5–6 weeks, whereas no tumours were observed in the control group [group size not reported]

at up to 12 months. In the group that received anthracene, long-wave UV-A, and visible light, 100% of mice developed carcinoma within 7–8 weeks, whereas no tumours were observed in the control group (5 mice) at up to 12 months. [The Working Group noted that this study was limited by the use of a single unknown dose, and uncertainty regarding anthracene purity and the number of animals for each group. Therefore, the study was judged to be inadequate for the evaluation of the carcinogenicity of anthracene in experimental animals.]

Three groups of mice [strain, sex, and age not reported] were given 5% anthracene (reported as "pure anthracene") in a mixture of olive oil and petroleum jelly by skin application to the ears, three times per week for 9–11 months (Miescher, 1942). Two of the groups also received UV light irradiation 2 hours after anthracene treatment (one group received irradiation for 40 or 60 minutes, another group for 90 minutes), three times per week. A fourth group received UV light only, three times per week, for 40 minutes per session during the first 12 treatments then increased to 60 minutes per session afterwards. At the end of the experiments, high mortality rates were reported for all four groups. No skin tumours were observed (anthracene only, 0/44; anthracene and 40 or 60 minutes of UV, 0/44; anthracene and 90 minutes of UV, 0/100; 40 or 60 minutes of UV only, 0/44). [The Working Group noted that this study was limited by the lack of information on strain, the age and sex of the animals, the use of a single unknown dose, and uncertainty regarding purity. Therefore, the study was judged to be inadequate for the evaluation of the carcinogenicity of anthracene in experimental animals.]

A group of 24 male Skh: hairless-1 mice (age, 6 weeks) were given 40 µL of anthracene (purity, 99%) dissolved in methanol (concentration, 0.1 g/L; daily dose, 4 µg) by skin application, followed by 2 hours of UV radiation (Forbes et al., 1976). Anthracene and UV exposure were given once daily, 5 days per week for 38 weeks. Control mice received methanol by skin application followed by UV radiation once daily, 5 days per week for 38 weeks. The time to 50% prevalence of skin tumours was not significantly different between the groups treated with anthracene (28.2 weeks) or methanol vehicle control (27.2 weeks), according to Wilcoxon rank-sum test statistics. Tumour incidence was not reported but did not seem to differ between the anthracene- and UV-treated group and the control group on the basis of final tumour prevalence. [The Working Group noted that this study was limited by the use of one sex only and the limited reporting of histopathology.]

3.2 Rat

See Table 3.2.

3.2.1 Oral administration (feed)

In a well-conducted chronic toxicity and carcinogenicity study that complied with GLP (JBRC, 1998; also reported by Takeda et al., 2022), groups of 50 male and 50 female F344/DuCrj rats (age, 6 weeks) were treated with feed containing anthracene (purity, 99.8–99.9%) at 0 (control), 8000, 20 000, or 50 000 ppm (w/w), 7 days per week for 104 weeks. On the basis of feed consumption, the estimated dose for male rats was 0, 377, 957, and 2483 mg/kg bw per day, and for female rats was 0, 468, 1209, and 3122 mg/kg bw per day, for the groups at 0 (control), 8000, 20 000, and 50 000 ppm, respectively. Survival analysis did not show differences between the anthracene-treated groups and the respective control groups. At study termination, survival was: 33/50, 43/50, 43/50, and 38/50 in males, and 40/50, 40/50, 40/50, and 37/50 in females, for the groups at 0 (control), 8000, 20 000, and 50 000 ppm, respectively. Body weights in all groups of treated females were significantly decreased throughout the study, compared with controls. Body weights

Table 3.2 Studies of carcinogenicity in rats and rabbits exposed to anthracene

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Results	Significance	Comments
Full carcinogenicity Rat, F344/DuCrj (M) 6 wk 104 wk JBRC (1998)	Oral administration (feed) Purity, 99.8–99.9% Feed 0, 8000, 20 000, 50 000 ppm (w/w), continuous dosing 50, 50, 50, 50 33, 43, 43, 38	*Liver* Hepatocellular adenoma 0/50, 4/50 (8%), 9/50* (18%), 9/50* (18%)	$P = 0.0032$, Peto prevalence method test $P = 0.0056$, Cochran–Armitage test; NC, Peto standard method test, Peto combined analysis test *$P = 0.0029$, Fisher exact test	*Principal strengths*: well-conducted GLP study; covered most of the lifespan; multiple dose study; males and females used. *Historical controls*: hepatocellular adenoma, 18/949 (1.9%); range, 0–6%; hepatocellular carcinoma, 3/949 (0.3%); range, 0–2%; hepatocellular adenoma or carcinoma (combined), 21/949 (2.2%); range, 0–6%; transitional cell papilloma or carcinoma (combined) of the urinary bladder, 1/949 (0.1%); range, 0–2%; transitional cell carcinoma of the urinary bladder, 0/949; transitional cell papilloma of the urinary bladder, 1/949 (0.1%); range, 0–2%.
		Hepatocellular carcinoma 0/50, 0/50, 5/50* (10%), 5/50* (10%)	$P = 0.0158$, Peto prevalence method test $P = 0.0056$, Peto combined analysis test $P = 0.0081$, Cochran–Armitage test; NS, Peto standard method test *$P = 0.0360$, Fisher exact test	
		Hepatocellular adenoma or carcinoma (combined) 0/50, 4/50 (8%), 13/50* (26%), 13/50* (26%)	$P = 0.0003$, Peto prevalence method test $P = 0.0001$, Peto combined analysis test $P = 0.0002$, Cochran–Armitage test; NS, Peto standard method test *$P = 0.0003$, Fisher exact test	

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Results	Significance	Comments
Full carcinogenicity Rat, F344/DuCrj (M) 6 wk 104 wk JBRC (1998) (cont.)		*Urinary bladder* Transitional cell papilloma 0/50, 0/50, 2/50 (4%), 0/50 Transitional cell carcinoma 0/50, 1/50 (2%), 4/50 (8%), 3/50 (6%) Transitional cell papilloma or carcinoma (combined) 0/50, 1/50 (2%), 6/50 (12%)*, 3/50 (6%)	NS NS *P = 0.0190, Fisher exact test	
Full carcinogenicity Rat, F344/DuCrj (F) 6 wk 104 wk JBRC (1998)	Oral administration (feed) Purity, 99.8–99.9% Feed 0, 8000, 20 000, 50 000 ppm (w/w), continuous dosing 50, 50, 50, 50 40, 40, 40, 37	*Kidney* Renal cell adenoma 0/50, 3/50 (6%), 6/50 (12%)*, 4/50 (8%) Renal cell carcinoma 0/50, 0/50, 0/50, 1/50 (2%) Renal cell adenoma or carcinoma (combined) 0/50, 3/50, 6/50*, 5/50**	*P = 0.0190, Fisher exact test NS P = 0.0441, Peto combined analysis test; NS, Peto standard method test; NS, Peto prevalence method test *P = 0.0190, Fisher exact test **P = 0.0360, Fisher exact test	*Principal strengths*: well-conducted GLP study; covered most of the lifespan; multiple dose study; males and females used. *Historical controls*: renal cell adenoma or carcinoma (combined), 1/948 (0.1%); range, 0–2%; renal cell carcinoma, 0/948; renal cell adenoma, 1/948 (0.1%); range, 0–2%; transitional cell carcinoma of the urinary bladder, 0/948; endometrial stromal sarcoma of the uterus, 3/948 (0.3%); range, 0–2%; fibroadenoma of the mammary gland, 92/948 (9.7%); range, 0–20%; adenoma of the mammary gland, 44/948 (4.6%); range, 0–18%; adenoma or fibroadenoma (combined) of the mammary gland, 136/948 (14.3%); range, 4–24%; adenocarcinoma of the mammary gland, 14/948 (1.5%); range, 0–6%; adenocarcinoma, adenoma or fibroadenoma (combined) of the mammary gland, 150/948 (15.8%); range, 4–26%.

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Results	Significance	Comments
Full carcinogenicity Rat, F344/DuCrj (F) 6 wk 104 wk JBRC (1998) (cont.)		*Urinary bladder* Transitional cell carcinoma 0/50, 2/50, 3/50, 2/50	NS	
		Uterus Endometrial stromal sarcoma 0/50, 0/50, 0/50, 3/50 (6%)	$P = 0.0164$, Peto standard method test $P = 0.0032$, Peto combined analysis test $P = 0.0051$, Cochran–Armitage test; NS, Peto prevalence method test	
		Mammary gland Adenoma 0/50, 2/50 (4%), 0/50, 1/50 (2%)	NS	
		Fibroadenoma 3/50, 2/50, 3/50, 9/50 (18%)	$P = 0.0172$, Peto standard method test $P = 0.0299$, Peto prevalence method test $P = 0.0057$, Peto combined analysis test $P = 0.0094$, Cochran–Armitage test	

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Results	Significance	Comments
Full carcinogenicity Rat, F344/DuCrj (F) 6 wk 104 wk JBRC (1998) (cont.)		Adenoma or fibroadenoma (combined) 3/50, 4/50, 3/50, 10/50 (20%) Adenocarcinoma 0/50, 0/50, 2/50 (4%), 0/50 Adenocarcinoma, adenoma or fibroadenoma (combined) 3/50, 4/50, 5/50, 10/50 (20%)	$P = 0.0221$, Peto prevalence method test $P = 0.0077$, Peto combined analysis test $P = 0.0122$, Cochran–Armitage test; NS, Peto standard method test NS $P = 0.0242$, Peto prevalence method test $P = 0.0098$, Peto combined analysis test $P = 0.0157$, Cochran–Armitage test; NS, Peto standard method test	
Carcinogenicity with other modifying factor Rat, Sprague-Dawley Hras128 (M) 7 wk 20 wk Ohnishi et al. (2007)	Oral administration (gavage) Purity, > 99.9% Olive oil 0, 200 mg/kg bw 1×/wk for 3 wk 12, 7 12, 7	*Mammary gland* Adenoma or adenocarcinoma (combined) 0/12, 3/7*	*$P < 0.05$, Dunnett *t*-test *[$P = 0.0361$, Fisher exact test]	*Principal limitations*: limited number of dose groups; limited exposure duration; small number of rats per group. *Other comments*: inadequate use of χ^2 test for statistical analysis of tumour incidence.

Table 3.2 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Results	Significance	Comments
Carcinogenicity with other modifying factors Rat, Sprague-Dawley Hras128 (F) 7 wk 12 wk Ohnishi et al. (2007)	Oral administration (gavage) Purity, > 99.9% Olive oil 0, 200 mg/kg bw 1×/wk for 3 wk 11, 7 11, 7	*Mammary gland* Adenoma or adenocarcinoma (combined) 2/11, 4/7	**P* < 0.05, Dunnett *t*-test [NS, Fisher exact test]	*Principal limitations*: limited number of dose groups; limited exposure duration; small number of rats per group. *Other comments*: inadequate use of χ^2 test for statistical analysis of tumour incidence.
Full carcinogenicity Rat, Sprague-Dawley (M) 7 wk 20 wk Ohnishi et al. (2007)	Oral administration (gavage) Purity, > 99.9% Olive oil 0, 200 mg/kg bw 1×/wk for 3 wk 10, 6 10, 6	*Mammary gland* Adenoma or adenocarcinoma (combined) 0/10, 0/6	NA	*Principal limitations*: limited number of dose groups; limited exposure duration; small number of rats per group.
Full carcinogenicity Rat, Sprague-Dawley (F) 7 wk 12 wk Ohnishi et al. (2007)	Oral administration (gavage) Purity, > 99.9% Olive oil 0, 200 mg/kg bw 1×/wk for 3 wk 12, 8 12, 8	*Mammary gland* Adenoma or adenocarcinoma (combined) 0/12, 0/8	NA	*Principal limitations*: limited number of dose groups; limited exposure duration; small number of rats per group.

bw, body weight; F, female; GLP, Good Laboratory Practice; M, male; NA, not applicable; NC, not calculable; NS, not significant; ppm, parts per million; wk, week(s); w/w, weight per weight.

of males in all treatment groups were significantly decreased compared with controls at certain time points. Food consumption of all treated males and females was similar to that of their respective controls. All rats underwent complete necropsy. All organs and tissues were sampled for histopathology in all the animals.

In male rats, there was a significant positive trend (P = 0.0032, Peto trend test, prevalence method; P = 0.0056, Cochran–Armitage trend test) in the incidence of hepatocellular adenoma – 0/50, 4/50 (8%), 9/50 (18%), 9/50 (18%) at 0 (control), 8000, 20 000, and 50 000 ppm, respectively – and the incidence was significantly increased at 20 000 and 50 000 ppm (P = 0.0029, Fisher exact test), exceeding the upper bound of the range observed in historical controls from the same laboratory – 18/949 (1.9%); range, 0–6%. [The Working Group noted that several Peto trend tests were conducted in this study, with the Peto test standard method being referred to as "death analysis", the Peto test prevalence method being referred to as "incidental tumour test", and the Peto test combined analysis being referred to as "death analysis plus incidental tumour test". A significant P value in any Peto test was considered relevant for the detection of treatment-related increases in tumour incidence.] There was a significant positive trend (P = 0.0158, Peto trend test, prevalence method; and P = 0.0056, Peto trend test, combined analysis; P = 0.0081, Cochran–Armitage trend test) in the incidence of hepatocellular carcinoma – 0/50, 0/50, 5/50 (10%), and 5/50 (10%) at 0 (control), 8000, 20 000, and 50 000 ppm, respectively – and the incidence was significantly increased at 20 000 and 50 000 ppm (P = 0.036, Fisher exact test), exceeding the upper bound of the range observed in historical controls from the same laboratory – 3/949 (0.3%); range, 0–2%. There was a significant positive trend (P = 0.0003, Peto trend test, prevalence method; P = 0.0001, Peto trend test, combined analysis; P = 0.0002, Cochran–Armitage trend test) in the incidence of hepatocellular adenoma or carcinoma (combined) – 0/50, 4/50 (8%), 13/50 (26%), and 13/50 (26%) at 0 (control), 8000, 20 000, and 50 000 ppm, respectively – and the incidence was significantly increased at 20 000 and 50 000 ppm (P = 0.0003, Fisher exact test). The incidence in all treated groups exceeded the upper bound of the range observed in historical controls from the same laboratory – 21/949 (2.2%); range, 0–6%. The incidence of transitional cell papilloma or transitional cell carcinoma (combined) of the urinary bladder – 0/50, 1/50 (2%), 6/50 (12%), and 3/50 (6%) at 0 (control), 8000, 20 000, and 50 000 ppm, respectively – was significantly increased (P = 0.0190, Fisher exact test) at 20 000 ppm. The incidence at 20 000 and 50 000 ppm exceeded the upper bound of the range observed in historical controls from the same laboratory – 1/949 (0.1%); range 0–2%. The incidence of transitional cell papilloma at 20 000 and 50 000 ppm exceeded the upper bound of the range observed in historical controls from the same laboratory – 1/949 (0.1%); range, 0–2%. The incidence of transitional cell carcinoma at 20 000 ppm exceeded the incidence observed in historical controls from the same laboratory (0/949).

In female rats, the incidence of renal cell adenoma – 0/50, 3/50 (6%), 6/50 (12%), and 4/50 (8%) at 0 (control), 8000, 20 000, and 50 000 ppm, respectively – was significantly increased (P = 0.0190, Fisher exact test) in the group at the intermediate dose, exceeding the upper bound of the range observed in historical controls from the same laboratory – 1/948 (0.1%); range, 0–2%. There was a significant positive trend (P = 0.0441, Peto trend test, combined analysis) in the incidence of renal cell adenoma or renal cell carcinoma (combined) of the kidney – 0/50, 3/50 (6%), 6/50 (12%), 5/50 (10%)) at 0 (control), 8000, 20 000, and 50 000 ppm, respectively – and the incidence was significantly increased at 20 000 (P = 0.0190, Fisher exact test) and 50 000 ppm (P = 0.0360, Fisher exact test). The incidence in all treated groups exceeded the upper bound of

the range observed in historical controls from the same laboratory – 1/948 (0.1%); range, 0–2%. There was a significant positive trend ($P = 0.0164$, Peto trend test, standard method; $P = 0.0032$, Peto trend test, combined analysis; $P = 0.0051$, Cochran–Armitage trend test) in the incidence of endometrial stromal sarcoma of the uterus – 0/50, 0/50, 0/50, and 3/50 (6%) at 0 (control), 8000, 20 000, and 50 000 ppm, respectively – and the incidence at the highest dose exceeded the upper bound of the range observed in historical controls from the same laboratory – 3/948 (0.3%); range, 0–2%. There was a significant positive trend ($P = 0.0172$, Peto trend test, standard method; $P = 0.0299$, Peto trend test, prevalence method; $P = 0.0057$, Peto trend test, combined analysis; $P = 0.0094$, Cochran–Armitage trend test) in the incidence of fibroadenoma of the mammary gland – 3/50 (6%), 2/50 (4%), 3/50 (6%), 9/50 (18%) at 0 (control), 8000, 20 000, and 50 000 ppm, respectively. There was a significant positive trend ($P = 0.0221$, Peto trend test, prevalence method; $P = 0.0077$, Peto trend test, combined analysis); $P = 0.0122$, Cochran–Armitage trend test) in the incidence of adenoma or fibroadenoma (combined) of the mammary gland – 3/50 (6%), 4/50 (8%), 3/50 (6%), and 10/50 (20%) at 0 (control), 8000, 20 000, and 50 000 ppm, respectively. [The Working Group noted that mammary gland adenoma and mammary gland fibroadenoma should not be combined, because they are thought to arise from different parts of the mammary gland (see Brix et al., 2010). The only exception might occur when an adenoma or carcinoma arises from a fibroadenoma, and then it should be combined with other adenomas and carcinomas of the mammary gland. The conditions for this exception were not reported for the study by JBRC (1998). Therefore, the Working Group did not consider combination of adenomas and fibroadenomas of the mammary gland, or of adenomas, fibroadenomas, and adenocarcinomas of the mammary gland, to be appropriate for the detection of increases in tumour incidence.] The incidence of transitional cell carcinoma of the urinary bladder – 0/50, 2/50 (4%), 3/50 (6%), and 2/50 (4%) – at all dose levels exceeded the incidence observed in historical controls (0/949) in this laboratory.

Regarding the non-neoplastic lesions, in both males and females, anthracene caused an increased incidence of clear cell foci and acidophilic foci in the liver at all dose levels. In the kidney, the incidence of eosinophilic droplets in proximal tubules was increased at all dose levels in both males and females, and the incidence of atypical tubule hyperplasia was increased at all dose levels in females (JBRC, 1998; also reported by Takeda et al., 2022). [The Working Group noted that this was a well-conducted GLP study, with a duration of most of the lifespan, using multiple dose groups, both sexes, an adequate number of animals per group, and an adequate duration of exposure and observation.]

In a study of BDI and BDIII rats [sex and age not reported], anthracene (reported as "pure") was administered orally (in the feed) at a dose of 4.5 g in oil (not otherwise specified) for 91 weeks (5 mg/day then 15 mg/day, 6 days per week) (Druckrey & Schmähl, 1955; Schmähl, 1955). At the end of the study (median survival, 700 days), 1/28 rats had liver sarcoma and 1/28 rats had uterine adenocarcinoma. [The Working Group noted that this study was limited by the incomplete details regarding post mortem examination and histopathology, the lack of information on sex and age, the lack of details on anthracene purity, and the lack of controls. Therefore, the Working Group judged this study to be inadequate for the evaluation of the carcinogenicity of anthracene in experimental animals.]

3.2.2 Oral administration (gavage)

Anthracene was evaluated in a medium-term study using transgenic Hras128 rats (human c-Ha-*ras* proto-oncogene as the transgene) and non-transgenic rats (Ohnishi et al., 2007). These

rats were generated by pronucleus injection of Sprague-Dawley female rat embryos and maintained as a heterozygous line by breeding transgenic and non-transgenic offspring to produce transgenic and non-transgenic (wildtype) littermates, as described by Asamoto et al. (2000) and cited by Ohnishi et al. (2007). Groups of male and female, transgenic and non-transgenic littermates (age, 7 weeks) (number at start not reported) were treated with three consecutive weekly intragastric doses of anthracene (purity, 99.9%) at a dose of 200 mg/kg bw, dissolved in olive oil. Control rats were treated with olive oil alone (Ohnishi et al., 2007). After 12 weeks (females) or 20 weeks (males), all transgenic and non-transgenic rats underwent necropsy to determine the presence of mammary tumours, which were analysed by histopathology.

There was a significant increase ($P < 0.05$, Dunnett *t*-test; [$P < 0.05$, Fisher exact test]) in the incidence of mammary adenoma or adenocarcinoma (combined) in male transgenic rats (controls, 0/12; anthracene-treated, 3/7). In female transgenic rats, the incidence of mammary adenoma or adenocarcinoma (combined) was 2/11 for controls, and 4/7 for the anthracene-treated group. [The Working Group noted that the effect of anthracene treatment on tumour incidence in male rats was statistically significant according to the Fisher exact test, and reportedly statistically significant according to the chi-squared test. However, it was not statistically significant in female rats according to either the chi-squared or the Fisher exact test, although it was reported in the publication as statistically significant by the chi-squared test.] Anthracene administered by oral gavage did not cause any mammary tumours (adenomas or adenocarcinomas, combined) in non-transgenic male or female rats. [The Working Group noted the use of a transgenic rat model carrying the c-Ha-*ras* proto-oncogene as the transgene, the small and unbalanced group sizes used, the lack of survival and body-weight data, and the use of a single dose level. The Working Group also noted that the Fisher exact test was more relevant than the chi-squared test for tumour incidence. The Working Group further noted that a comparison of the group means for mammary tumour multiplicity (tumours/rat) and incidence data indicated that each of the rats in the anthracene-treated and control groups had ≤ 1 tumour, therefore analysis of multiplicity data was inappropriate for these data.]

3.2.3 Subcutaneous injection

A group of 10 rats [strain and sex not reported] were treated with 1 mg of anthracene in 2 mL of aqueous colloidal solution [purity not reported], injected into alternating subcutaneous and intraperitoneal sites, once per week for 103 weeks (Boyland & Burrows, 1935). No control group was reported. Sites of injection were evaluated for tumours at necropsy. Only 2/10 of the treated rats were alive at 18 months. No tumours were observed. [The Working Group noted the small group size, lack of controls, lack of information on anthracene purity, age, and sex, and incomplete experimental details. Therefore, the Working Group judged this study to be inadequate for the evaluation of the carcinogenicity of anthracene in experimental animals.]

A group of five Wistar rats [sex not reported] (age, 6–8 weeks) were treated with 5 mg of anthracene (purity not reported) in sesame oil by subcutaneous injection of 0.5 mL in the right flank once per week for 6–7 weeks (Pollia, 1941). No tumours were observed at the injection site in 4 of 5 treated mice surviving for 10 months. [The Working Group noted the small number of treated animals, the lack of a control group, the lack of information on anthracene purity, the lack of histopathological examination, and the limited duration because of the poor condition of the treated animals. Therefore, the Working Group judged this study to be inadequate for the

evaluation of the carcinogenicity of anthracene in experimental animals.]

In a study of 10 BDI and BDIII rats [sex and age not reported], anthracene [purity not reported] was administered by subcutaneous injection at a dose of 20 mg in oil (not otherwise specified), once per week for 33 weeks (Druckrey & Schmähl, 1955; Schmähl, 1955). After being followed for a lifetime, 1/9 rats had myxosarcoma and 4/9 rats had fibroma at the site of injection. [The Working Group noted the small number of animals and the lack of information on age and sex, the lack of controls and the lack of information on anthracene purity. Therefore, the Working Group judged this study to be inadequate for the evaluation of the carcinogenicity of anthracene in experimental animals.]

3.2.4 Intraperitoneal injection

In a study of 10 BDI and BDIII rats (sex and age not reported), anthracene (purity not reported) was administered by intraperitoneal injection at a dose of 20 mg in oil, once per week for 33 weeks (Schmähl, 1955). After being followed for a lifetime, 1/10 rats had a spindle cell sarcoma at the site of injection. [The Working Group noted the small number of animals and the lack of information on age and sex, the lack of controls, and the lack of information on anthracene purity. Therefore, the Working Group judged this study to be inadequate for the evaluation of the carcinogenicity of anthracene in experimental animals.]

3.2.5 Implantation in the liver and lung

A group of 60 female Osborne-Mendel rats (age, 3–6 months) were treated with anthracene [purity not reported] at a dose of 0.5 mg, formulated in pellets each composed of 0.05 mL of bees wax:tricaprylin (1:1), and administered by one-time surgical implantation in the lower left lung (Stanton et al., 1972). Controls were implanted with pellets that were identical except that they lacked anthracene. No lung tumours were observed at necropsy in 28 rats examined at 43–55 weeks post-implantation (23 additional rats were still alive at 120 weeks and were not examined). [The Working Group noted the lack of necropsy data for nearly half of the treated animals, and the lack of information on anthracene purity. Therefore, the Working Group judged this study to be inadequate for the evaluation of the carcinogenicity of anthracene in experimental animals.]

A group of 11 male rats of the Holtzman strain (age reported as "weanling") were treated with anthracene [purity not reported] at a dose of 61–78 mg administered as a single pellet by surgical implantation in the liver (Aterman, 1987). Control rats received a similar pellet composed of cholesterol. Survival was similar in anthracene-treated rats (490–631 days) and control rats (496–563 days). In anthracene-treated rats, 1/11 developed a fibrosarcoma that was found in a different non-implanted lobe of the liver. In control rats, 0/11 developed any tumour of the liver. [The Working Group noted the lack of information on anthracene purity, the use of one sex only, and the small number of animals used. Therefore, the Working Group judged this study to be inadequate for the evaluation of the carcinogenicity of anthracene in experimental animals.]

3.3 Rabbit

See Table 3.2.

A group of nine rabbits [strain, sex, and age not reported] were given a single injection of anthracene pellets [purity not reported] at a dose of 10, 12, or 20 mg into the brain (cerebrum or cerebellum), or 4 or 5 mg into the eye (Russell, 1947). Survival of 20–54 months (after brain injection) or 54 months (after eye injection) was reported. No tumours were observed by histological examination of the injection site

(brain, 0/7; eye, 0/2). [The Working Group noted the small number of animals used, the lack of controls, the lack of information on age, sex and strain, and the lack of information on anthracene purity. Therefore, the Working Group judged this study to be inadequate for the evaluation of the carcinogenicity of anthracene in experimental animals.]

3.4 Evidence synthesis for cancer in experimental animals

The carcinogenicity of anthracene has been assessed in one well-conducted GLP study in male and female Crj:BDF_1 mice treated by oral administration (in the feed) (JBRC, 1998; also reported in Takeda et al., 2022), and in one well-conducted GLP study in male and female F344/DuCrj rats (JBRC, 1998; also reported in Takeda et al., 2022) treated by oral administration (in the feed). The carcinogenicity of anthracene has also been evaluated in studies that did not comply with GLP. Specifically, there were studies of oral administration (feed) in BDI and BDIII rats [sex not reported] (Druckrey & Schmähl, 1955; Schmähl, 1955), oral administration (gavage) in male and female transgenic Hras128 and non-transgenic Sprague-Dawley rats (Ohnishi et al., 2007); in male and female C57BL mice (Steiner, 1955), in male and female NMRI mice (Platt et al., 1990), in rats [strain and sex not reported] (Boyland & Burrows, 1935), in Wistar rats [sex not reported] (Pollia, 1941), and in BDI and BDIII rats [sex not reported] (Druckrey & Schmähl, 1955; Schmähl, 1955) treated by subcutaneous injection; in male and female SPF Kun Ming mice (Wang & Xue, 2015), male Swiss mice (Shubik & Della Porta, 1957), and BDI and BDIII rats [sex not reported] (Schmähl, 1955) treated by intraperitoneal injection; in male C3H/HeJ mice (Warshawsky et al., 1993), female Swiss mice (Wynder & Hoffmann, 1959), albino mice [sex and strain not reported] (Pollia, 1939), and mice [strain and sex not reported] (Kennaway, 1924a, b) treated by skin application; in female Osborne-Mendel rats treated by implantation in the lung (Stanton et al., 1972); in male rats of the Holtzman strain treated by implantation in the liver (Aterman, 1987); and in rabbits [strain and sex not reported] treated by injection of anthracene pellets into the brain or the eye (Russell, 1947). In addition, four initiation–promotion studies in female Crl:CD/1 (ICR) BR mice (La Voie et al., 1985), female CD-1 mice (Scribner, 1973; Wislocki et al., 1982), and strain "S" mice [sex not reported] (Salaman & Roe, 1956); and co-exposure studies in mice [sex and strain not reported] (Miescher, 1942; Heller, 1950), and in male Skh: hairless-1 mice (Forbes et al., 1976) were available.

In the dietary study that complied with GLP in male and female Crj:BDF1 mice (JBRC, 1998; also reported in Takeda et al., 2022), a significant positive trend in the incidence of hepatocellular adenoma was observed in females, and the incidence was significantly increased at the highest dose. There was a significant positive trend in the incidence of hepatocellular carcinoma, and the incidence was significantly increased at the intermediate and highest dose. There was a significant positive trend in the incidence of hepatocellular adenoma or carcinoma (combined), and the incidence was significantly increased at the intermediate and highest dose. The incidence of histiocytic sarcoma of all organs was significantly increased at the lowest dose. In male mice, dietary administration of anthracene did not cause a significant increase in the incidence of any type of neoplasm (JBRC, 1998; also reported in Takeda et al., 2022).

In the dietary study that complied with GLP in male and female F344/DuCrj rats (JBRC, 1998; also reported in Takeda et al., 2022), there was a significant positive trend in the incidence of hepatocellular adenoma in males, and the incidence was significantly increased at the intermediate and highest dose. There was a significant positive trend in the incidence of hepatocellular

carcinoma, and the incidence was significantly increased at the intermediate and highest dose. There was a significant positive trend in the incidence of hepatocellular adenoma or carcinoma (combined), and the incidence was significantly increased at the intermediate and highest dose. The incidence of transitional cell papilloma or transitional cell carcinoma (combined) of the urinary bladder was significantly increased at the intermediate dose. In female rats, the incidence of renal cell adenoma was significantly increased at the intermediate dose. A significant positive trend in the incidence of renal cell adenoma or renal cell carcinoma (combined) of the kidney was observed, and the incidence was significantly increased at the intermediate and highest dose. There was a significant positive trend in the incidence of endometrial stromal sarcoma of the uterus. There was a significant positive trend in the incidence of fibroadenoma of the mammary gland (JBRC, 1998; also reported in Takeda et al., 2022).

In the study in male and female transgenic Hras128 and non-transgenic Sprague-Dawley rats treated by oral administration (gavage) (Ohnishi et al., 2007), there was a significant increase in the incidence of mammary adenoma or adenocarcinoma (combined) in male but not female transgenic rats. No mammary tumours (adenoma or adenocarcinoma) were observed in non-transgenic male or female rats.

Studies in BDI and BDIII rats [sex not reported] treated by oral administration (feed) (Druckrey & Schmähl, 1955; Schmähl, 1955); in male and female C57BL mice (Steiner, 1955), male and female NMRI mice (Platt et al., 1990), rats [sex not reported] (Boyland & Burrows, 1935), Wistar rats [sex not reported] (Pollia, 1941), and BDI and BDIII rats [sex not reported] (Druckrey & Schmähl, 1955; Schmähl, 1955) treated by subcutaneous injection; in male and female SPF Kun Ming mice (Wang & Xue, 2015), male Swiss mice (Shubik & Della Porta, 1957), and BDI and BDIII rats [sex not reported] (Schmähl, 1955) treated by intraperitoneal injection; in male C3H/HeJ mice (Warshawsky et al., 1993), female Swiss mice (Wynder & Hoffmann, 1959), albino mice [sex not reported] (Pollia, 1939), and mice [sex not reported] (Kennaway, 1924a, b) treated by skin application; in female Osborne-Mendel rats treated by implantation in the lung (Stanton et al., 1972); in male rats of the Holtzman strain treated by implantation in the liver (Aterman, 1987); and in rabbits [sex not reported] treated by injection of anthracene pellets into the brain or eye (Russell, 1947), the two initiation–promotion studies in female CD-1 mice (Scribner, 1973) and in strain "S" mice (Salaman & Roe, 1956); and the two co-exposure studies in mice [sex not reported] treated by skin application (Miescher, 1942; Heller, 1950) were judged to be inadequate for the evaluation of the carcinogenicity of anthracene in experimental animals.

4. Mechanistic Evidence

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Absorption, distribution, and excretion

(a) Humans

The absorption, distribution, and excretion of anthracene administered via different routes of exposure were reported in several studies in humans.

Storer et al. (1984) demonstrated that anthracene can penetrate the skin. Five non-smoking adult volunteers, presenting no skin alterations or diseases, were exposed topically to a petrolatum solution of coal tar (85 mL) containing anthracene (190 µg/mL) for two periods of 8 hours. In the blood samples collected, no anthracene was detected before exposure, but anthracene levels were 4.7, 0.1, 0.0, 0.5, and 1.6 ng/mL (mean,

1.4 ng/mL) in each of the five volunteers after the second period of exposure (Storer et al., 1984).

Indirect evidence for the absorption and distribution of anthracene in the human body was provided by measuring levels of PAHs in the urine. In several groups of road pavers and construction workers, anthracene concentrations in the urine were between < 2 and 30 ng/L (medians, 2–9 ng/L) (Campo et al., 2006b). In a similar study, urinary concentrations of anthracene in 55 coke-oven workers in Poland were between 7 and 899 ng/mL (median, 49 ng/mL) (Rossella et al., 2009). More data on urinary concentrations of anthracene assessed in various groups of workers are presented in Section 1.4.2. Anthracene was also determined in several human tissues, e.g. blood (Singh et al., 2008b; Drwal et al., 2017; Wirnkor et al., 2019), serum (Al-Daghri et al., 2014), placenta (Singh et al., 2008a; Drwal et al., 2017; Agarwal et al., 2018), maternal milk (Oliveira et al., 2020), hair (Palazzi et al., 2018; Wang et al., 2020), cord blood (Cabrera-Rodríguez et al., 2019), bronchoalveolar lavage fluid (BALF) (Che et al., 2020), lung cancer tissue (Cioroiu et al., 2013), and brain, liver and spleen (Pastor-Belda et al., 2019). [The Working Group considered the above evidence as proof of the wide distribution of anthracene within the human body.]

(b) Experimental systems

The absorption of anthracene was also assessed in the skin, lungs, and gastrointestinal tract in various experimental systems in various species.

Percutaneous absorption of [^{14}C]-anthracene was investigated in female Sprague-Dawley rats (Yang et al., 1986). In the in vivo study, a single topical dose of 9.3 µg/cm^2 was applied on the rat dorsal area and radioactivity was measured in the urine, faeces, and tissues. In vitro absorption was assessed by measuring radioactivity penetration of a similar dose of anthracene through excised dorsal skin preparations (consisting of stratum corneum, epidermis, and the top portion of the dermis, total thickness of 350 µm) into the receptor fluid of the diffusion cell. Within 6 days after application, 52.3% and 55.9% of the radioactivity administered in vivo and in vitro, respectively, was absorbed, demonstrating the penetration of anthracene through rat skin. Nevertheless, the increase in accumulated radioactivity in the rat excreta proceeded notably slower than did the in vitro penetration of anthracene through excised skin into the receptor fluid. The delay was caused by distribution, metabolism, and elimination in the rat body. Of the anthracene applied in vivo, 29.1% and 21.9% was recovered in the urine and faeces, respectively, during 6 days. At termination of the experiment, 1.3% of anthracene remained in the tissues, mainly the liver and kidney.

Percutaneous absorption of anthracene was also assessed in blood-infused pig ears onto which coal tar containing anthracene (3.7%) was applied at a dose of 11 mg/cm^2 per 24 cm^2. The mean cumulative absorption of anthracene was 138 pmol/cm^2 as measured for 200 minutes after the application of coal tar. [The Working Group noted that this amount accounted for 0.006% of the applied amount of anthracene.] Mean absorption flux at 200 minutes was 110 pmol/hour per cm^2 (VanRooij et al., 1995).

The absorption of anthracene after the administration by gavage of contaminated soil (about 0.5 g) or a solution of the pure compound in sunflower oil (2 mL, containing 2.1 µg of anthracene, 17.5 µg of pyrene, and 7.6 µg of B[a]P) was studied in male Lewis rats. In whole blood, two maximum concentrations (at 1–2 hours and at 3–4 hours) were observed, perhaps because of enterohepatic recycling. Plasma concentration–time curves (area under the curve, AUC) for anthracene during the first 7 hours after administration of the soil sample or of the pure anthracene solution differed in a ratio of 3:1, respectively. No significant difference was observed in the total amount of anthracene excreted in the faeces after treatment with soil

(about 0.5% of the administered dose) or the pure anthracene solution (about 0.4% of the administered dose) (van Schooten et al., 1997).

The bioavailability of anthracene after oral administration was assessed in female Landrace cross pigs treated daily, for 7 days, with artificial soil, solid food (a dough ball), or corn oil, all spiked with anthracene, or with a certified reference material (CRM) soil (natural clay soil collected from a PAH-contaminated area in the USA) (Peters et al., 2015). Several blood samples were collected within 1–24 hours post-exposure on days 1 and 7. For the CRM soil, peak serum concentrations of anthracene occurred at 2 hours post-exposure, followed by a second peak at 8 hours, accounted for by enterohepatic cycling. By far the highest bioavailability of anthracene was observed after ingestion of CRM soil, and then corn oil; no absorption was detected from spiked food and soil. In a separate group of pigs, uptake of anthracene to the stomach, jejunum, ileum, proximal colon, and liver was studied after ingestion of CRM soil. Anthracene was detected in these tissues 4 hours post-exposure at concentrations that continued to increase until 12 hours post-exposure, indicating that these tissues were acting as a repository for anthracene after systemic circulation in the blood and before elimination.

Elimination of [^{14}C]-anthracene from the lung was reported in female F344/Crl rats treated with [^{14}C]-anthracene (1 nmol; in 10% DMSO) by intratracheal instillation. Biphasic clearance was observed: a rapid component with a half-time of 0.1 hour, resulting in removal of 99.7% of the radiolabel, followed by a slower component with a half-time of 25.6 hours (Bond et al., 1985). [The Working Group noted that the 10% DMSO concentration used was too high and was potentially cytotoxic.]

In an in vitro model using full-thickness monkey skin (abdomen of *Cercopithecus aetiops*), percutaneous absorption of anthracene was characterized by a permeability constant (K_p) of $3.44 \pm 3.09 \times 10^{-3}$ cm/hour (Sartorelli et al., 1998).

The uptake of [^{14}C]-anthracene was also measured in a rabbit ocular lens model in vitro by using direct incubation in glutathione-buffered Ringer medium. A concentration ratio of 10:1 (lens:medium) was observed after a 24-hour incubation (Tang-Liu et al., 1992).

4.1.2 Metabolism

(a) Humans

Data on the metabolism of anthracene in humans were sparse. In the majority of studies assessing levels of urinary metabolites after environmental or occupational exposures to various PAH mixtures, anthracene metabolites were neither measured nor reviewed. In one study assessing concentrations of PAHs and a wide array of their metabolites in hair samples from women living in urban environments, 1-hydroxyanthracene concentrations were determined (mean, 1.33 pg/mg), but no correlation was observed with anthracene concentrations (mean, 8.26 ng/g) (Palazzi et al., 2018).

(b) Experimental systems

(i) Non-human mammals in vivo

In urine from rats or rabbits fed a diet containing 5% anthracene, two isomers of free dihydroxydihydroanthracene were found (Boyland & Levi, 1935). The corresponding glucuronic acid conjugates were identified as (+)-1,2-dihydro-1,2-dihydroxy-1-anthracene-glucuronic acid in the rabbit urine and its (–)-analogue in the rat urine. Whereas the concentration of the glucuronic acid conjugate predominated over that of the free compound in the rabbit urine, a much lower concentration of the conjugate was excreted in the rat urine (Boyland & Levi, 1936). [The Working Group noted that the rat and rabbit strains were not reported.]

A systematic analysis of the metabolism of anthracene was carried out in male Chester Beatty rats fed a diet containing 5% anthracene (Sims, 1964). Urine was fractionated into four main fractions that were further analysed to identify metabolic products as follows: (±)-*trans*-1,2-dihydro-1,2-dihydroxyanthracene (major product), 1,2-dihydroxyanthracene (partly conjugated with sulfuric and glucuronic acids), *trans*-9,10-dihydro-9,10-dihydroxyanthracene, and 9,10-dihydroxyanthracene. The latter is further hydroxylated to 2,9,10-trihydroxyanthracene, anthrone, and 1,2-dihydro-2-hydroxy-1-anthrylmercapturic acid (Fig. 4.1). [The Working Group noted that none of the above compound structures was assigned rigorously.]

Three monohydroxy metabolites of anthracene (isomerism not assigned) were tentatively identified for the first time in the urine of female Long-Evans rats treated by gavage with a mixture of PAHs at repeated doses equal to or greater than 0.01–0.20 mg/kg bw. The highest rate of urinary excretion occurred at 6–8 hours post-exposure. Metabolite concentrations strongly correlated (R^2, 0.86–0.95) with the level of exposure (Grova et al., 2017b). Moreover, three tetrahydroxyanthracenes (isomerism not assigned) were found in rat hair from the same experiment (Grova et al., 2017a).

Methylation of anthracene at positions 9 and 10 and subsequent oxidation of these methyl groups was investigated in male Sprague-Dawley rats dosed subcutaneously with anthracene (0.4 µmol in 200 µL of sesame oil) (Myers et al., 1988). The animals were killed 24 hours after dosing, and tissues in contact with anthracene were removed and further extracted with ethyl acetate. HPLC analysis of the dorsal subcutaneous tissue extract revealed the presence of the metabolites 9-methylanthracene (30%), 9,10-dimethylanthracene (7.2%), 9-formylanthracene (36.7%), 9-hydroxymethylanthracene (9.6%), 9-hydroxymethyl-10-methylanthracene (12.2%), and 9,10-dihydroxymethylanthracene (4.2%).

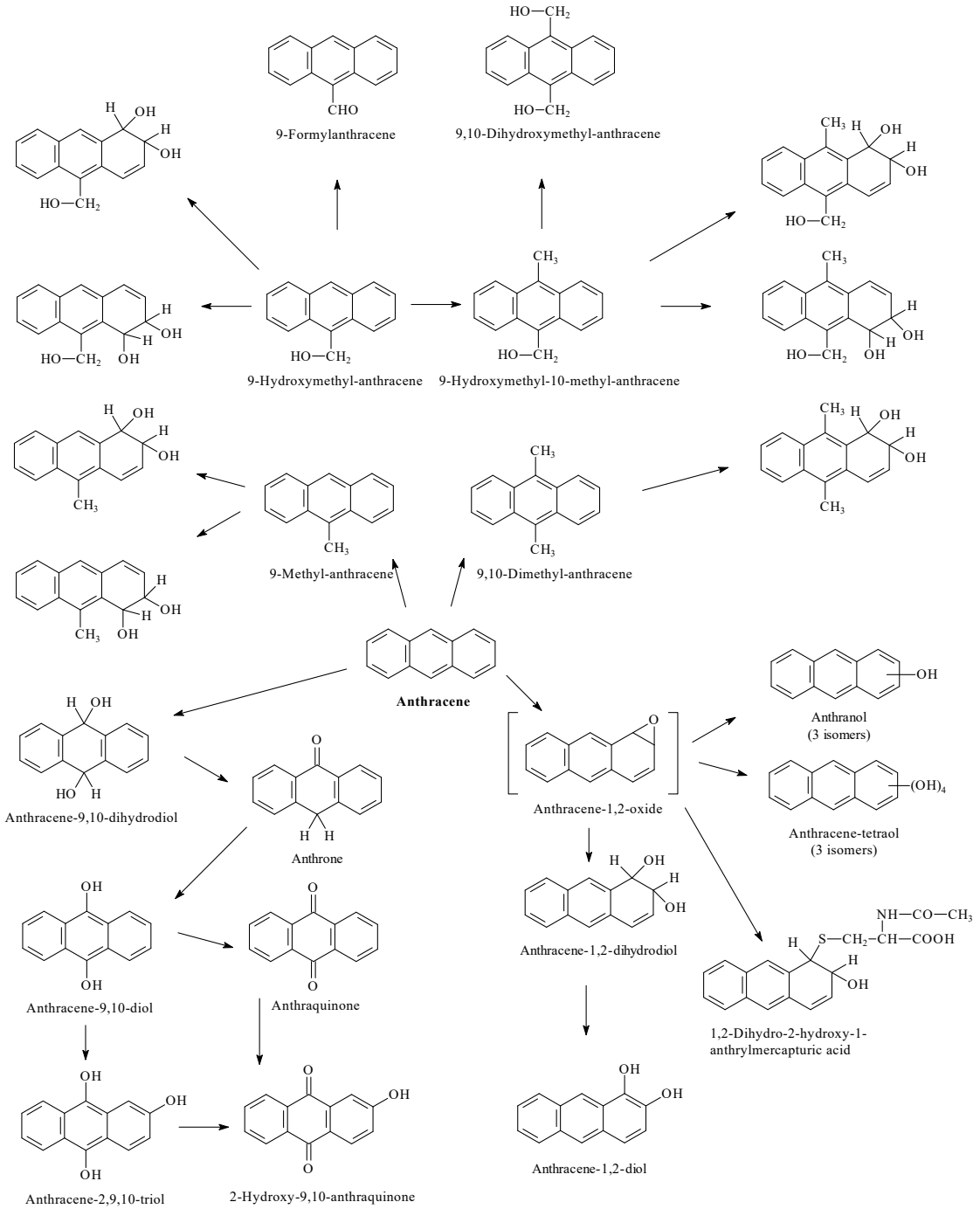
(ii) Non-human mammalian cells in vivo

In vitro metabolism of [^{14}C]-anthracene with liver microsomes from untreated and phenobarbital- or 3-methylcholanthrene (3-MC)-treated Sprague-Dawley rats resulted in retention of > 95% of radioactivity as *trans*-1,2-dihydro-1,2-dihydroxyanthracene; metabolites at the 9,10-position of anthracene were not detected (Akhtar et al., 1979). [The Working Group noted that if metabolites at the 9,10-position of anthracene were to be found in vivo, they might not be of hepatic origin.] The absence of anthrols in the incubate was accounted for by the high activity of epoxide hydrolase in hydrating anthracene 1,2-oxide, combined with the unusual stability of this arene oxide towards isomerization to phenols.

As the formation of 1,2-dihydroxyanthracene metabolites proceeds via the respective anthracene 1,2-oxides, the absolute configuration of the latter has been studied using [^{3}H]-anthracene in the liver monooxygenase system containing cytochrome P450c (CYPc) (current name, CYP1A1) obtained from immature Long-Evans rats treated with Aroclor 1254. In this system, the (+)-(1*R*,2*S*)-oxide form was found to predominate (van Bladeren et al., 1984). On the other hand, oxidation of anthracene in a reconstituted system containing cytochrome P450b (CYPb) (current name, CYP2B1) resulted in predominant formation of (–)-(1*S*,2*R*)-oxide (van Bladeren et al., 1985). In contrast to in rats, incubation of [^{14}C]-anthracene with microsomal fractions from the liver and aural epidermis of male New Zealand White rabbits resulted predominantly in the formation of the anthracene dihydrodiol 1*S*,2*S* enantiomer (Hall & Grover, 1987).

In addition to the studies with rats in vivo (Myers et al., 1988), methylation of anthracene at positions 9 and 10 and subsequent oxidation of these methyl groups was also investigated

Fig. 4.1 Metabolic scheme for anthracene



The scheme is based on studies in rats in vivo and rat liver microsomes in vitro. In this scheme, the enantiomeric composition of the metabolic products (although available for several) has been disregarded. Some hydroxyderivatives are excreted in the urine as glucuronic acid and sulfuric acid conjugates (not shown).
Compiled by the Working Group from Sims (1964), Akhtar et al. (1979), Lamparczyk et al. (1984), La Voie et al. (1985), Myers et al. (1988), and Grova et al. (2017a, b).

in rat liver cytosol preparations fortified with *S*-adenosyl-L-methionine. Identical metabolite patterns in both types of study were observed. The sum of the above metabolites produced in vitro for 1 hour accounted for 10–20% of the initial amount of anthracene. [The Working Group noted that the presence of methyl substituents at positions 9 and 10 of anthracene is associated with mutagenic potency and tumour-initiating activity, which is strongest in 9,10-dimethylanthracene (La Voie et al., 1985).] The biotransformation of anthracene itself and its 9-methyl and 9,10-dimethyl derivatives in rat liver microsomes was studied by La Voie et al. (1985). In this study, the major metabolites of anthracene were 1,2-dihydro-1,2-dihydroxydiol and anthraquinone. The metabolites of 9-methylanthracene were identified as *trans*-1,2-dihydro-1,2-dihydroxy- and *trans*-3,4-dihydro-3,4-dihydroxy-9-methylanthracenes, and 9-hydroxymethylanthracene and its 1,2- or 3,4-dihydrodiols. The microsomal metabolism of 9,10-dimethylanthracene resulted in *trans*-1,2-dihydro-1,2-dihydroxy-9,10-dimethylanthracene (major product), 9-hydroxymethyl-10-methylanthracene, and its 1,2- or 3,4-dihydrodiols. In a similar type of study with rat liver microsomes, 9,10-dihydroxymethylanthracene was identified in addition to the above metabolites (Lamparczyk et al., 1984).

Considering that numerous mouse pulmonary toxicants (including naphthalene) are metabolized by CYP2F2, the potential involvement of this isozyme in the metabolism of anthracene was investigated by Shultz and co-workers (Shultz et al., 2001). Incubation of mouse liver microsomes or recombinant mouse CYP2F2 in presence of glutathione/glutathione transferase with anthracene or [^{14}C]-anthracene, respectively, resulted in both cases in the formation of a tentative glutathione conjugate, most likely hydroxy-glutathionyl-1,2-dihydroanthracene, thus confirming formation of the reactive anthracene-1,2-epoxide as mediated by CYP2F2 (Shultz et al., 2001). [The Working Group, however, noted that metabolic formation of diol epoxides, known to be associated with mutagenicity and carcinogenicity of some PAHs, was not reported for anthracene.]

4.2 Evidence relevant to key characteristics of carcinogens

This section summarizes the evidence for the key characteristics of carcinogens (Smith et al., 2016), including whether anthracene is electrophilic or can be metabolically activated to an electrophile; is genotoxic; induces epigenetic alterations; induces oxidative stress; induces chronic inflammation; is immunosuppressive; modulates receptor-mediated effects; causes immortalization; or alters cell proliferation, cell death, or nutrient supply. No data were available for the evaluation of whether anthracene alters DNA or causes genomic instability.

4.2.1 Is electrophilic or can be metabolically activated to an electrophile

(a) Humans

(i) Exposed humans

One study in exposed workers was available to the Working Group. The ^{32}P-postlabelling assay was used to measure adducts in DNA isolated from peripheral leukocytes from roofers exposed to a mixture of PAHs and from non-occupationally exposed participants matched on age, sex, and smoking status (Herbert et al., 1990). [The Working Group considered this study to be of little relevance and excluded it because of the small sample size and the lack of analysis of anthracene-induced DNA adducts.]

(ii) Human primary cells

Only one study examined the potential for anthracene to form DNA adducts in human cells. Exposure of freshly isolated human lymphocytes from healthy volunteers to anthracene at 30 µM

did not result in the formation of DNA adducts (Gupta et al., 1988). Numerous carcinogenic PAHs were assessed in this study and compared with anthracene. No metabolic activation was used. [The Working Group noted that the lack of a metabolic activation system might result in underestimation of the formation of DNA adducts. Only one dose was tested, and the replicates were not listed.]

(b) Experimental systems

(i) Non-human mammals in vivo

Tetra-hydroxylated anthracene (0.01–0.8 mg/kg, three times per week for 90 days) released by the hydrolysis of DNA adducts was used as an indirect measure of DNA adduct formation and as a biomarker of exposure in a study that measured tetra-hydroxylated anthracene in the hair of Long-Evans rats exposed orally to a mixture of PAHs including anthracene (Grova et al., 2017a) (see also Section 4.1). Tetra-hydroxylated PAH metabolites, but not anthracene-specific metabolites, were identified by GC-MS/MS. [A reference standard for anthracene was not included in the study, and the exact dose that led to a detectable level of tetra-hydroxylated anthracene metabolites was unclear (between 0.01 and 0.8 mg/kg, orally, for 90 days); thus, the Working Group considered the results as weak evidence for electrophilic activity of anthracene and only an indirect measure of DNA adduct formation.]

(ii) Acellular systems

See Table 4.1.

PAHs are normally metabolized (e.g. by CYPs and/or epoxide hydrolases), and the resulting oxy-derivative products can actively bind to different biomolecules. [Since PAH–DNA adducts and PAH–protein adducts directly affect cellular functions, the Working Group also considered studies investigating anthracene–DNA or anthracene–protein adduct formation in acellular systems.] Two studies measured the formation of human serum albumin adducts after exposure to anthracene, with conflicting results. At a single concentration (60 μM) of anthracene, UV irradiation induced the formation of human serum albumin adducts via covalent crosslinking (Sinha & Chignell, 1983). By contrast, in a more recent study, no significant adduct formation was observed at low concentrations of anthracene (highest concentration used, 2.8 μM) by albumin fluorescence quenching, with sufficient replicates (Skupińska et al., 2006). [The Working Group noted that some PAHs could bind to specific tryptophan residues on albumin, which could result in the quenching of the albumin fluorescence, and that some oxy-derivatives of anthracene have quenching effects, suggesting that the specific location of residues on the anthracene structure is critical. The Working Group also noted that numerous studies (e.g. Kochevar et al., 1982; Oris et al., 1984) have demonstrated the phototoxic potential of anthracene in various species, for example, erythema in the skin of guinea-pigs, and toxicity in daphnia (*Daphnia pulex*) and mosquito larvae (*Aedes aegypti*), supporting the results observed by Sinha & Chignell (1983).] In another study (Sun et al., 2020), a change in DNA structure caused by groove binding by anthracene was demonstrated at a large range of anthracene concentrations (0–10 μM) and validated using molecular modelling. The Working Group considered that the available evidence for electrophilicity was inconclusive.]

4.2.2 Is genotoxic

(a) Humans

(i) Exposed humans

No data were available to the Working Group.

(ii) Human primary cells

See Table 4.2.

In a study in lymphocytes, anthracene caused a significant increase in DNA strand breaks at several time points, as measured by the phosphorylated histone γH2AX test (Bhargava et al.,

Table 4.1 Reactions of anthracene with proteins or DNA in acellular systems

End-point	Detection method	Results[a]	Concentration (LEC or HIC)	Comments	Reference
HSA protein concentration	Albumin fluorescence quenching	–	Dose range, 0.003–2.793 µM; 5 measurements		Skupińska et al. (2006)
HSA-crosslinking adducts	Binding of [^{14}C]-anthracene to HSA in the presence of light	(+)	60 µM	No justification of dose or dose–response relation.	Sinha & Chignell (1983)
DNA adduct, ct-DNA	UV-induced covalent DNA binding	(+)	56 µM	No justification of dose or dose–response relation.	Sinha & Chignell (1983)
Change in DNA structure by groove binding, ct-DNA	Resonance light scattering spectra	+	Large dose range, 0–10 µM	Validated using molecular modelling.	Sun et al. (2020)

ct-DNA, calf thymus DNA; HIC, highest ineffective concentration; HSA, human serum albumin; LEC, lowest effective concentration; UV, ultraviolet.

[a] +, positive; –, negative; (+) positive in a study of limited quality.

Table 4.2 Genetic and related effects of anthracene in human cells in vitro

End-point	Assay	Tissue, cells	Results[a] Without metabolic activation	Concentration (LEC or HIC)	Comments	Reference
DNA strand breaks	γH2AX	Primary peripheral blood lymphocytes	(+)	10 µM [1.78 µg/mL]	Study quality was poor; only one dose; cell species not reported but assumed to be human. Significant at 30 minutes, 3 h and 6 h; comparable to B[a]P; $n = 3$ but not clear whether replicated more than once.	Bhargava et al. (2020)
DNA strand breaks	Comet assay	Human keratinocyte (HaCaT) cells Human lymphocyte (A3) cells	– –	10 µM [1.78 µg/mL]	Study quality was good; doses, 0–10 µM; no detail about method or replicates.	Hu et al. (2009)
DNA repair	Unscheduled DNA synthesis	Human cervical cancer (HeLa S3) cells in the presence or absence of a rat liver mixed-function oxidase preparation	–	100 µg/mL	Study quality was good; dose range, 0.1–100 µg/mL, for 2.5 h. No response in presence or absence of metabolic activation.	Martin et al. (1978); Martin & McDermid (1981)
Micronucleus formation	Cytokinesis blocked cells (binucleated cells)	Human lymphoblastoid $TK^{+/-}$ (MCL-5) cells	–	10 µg/mL	Study quality: good; 0–10 µg/mL doses for 24 h followed by cytochalasin B; micronuclei/500 cells; 2 replicates; vehicle control.	Crofton-Sleigh et al. (1993)
Mutagenesis	Selection of DT-resistant mutants	Human embryo skin and muscle explant epithelial-like (EUE) cells	–	10 µM [0.178 µg/mL]	Study quality: poor; only one dose for chronic toxicity, 10^{-7} M (continuous exposure); acute dose, 10^{-6} M (24 h); few DT mutants ($< 7 \times 10^{-6}$); duration of chronic exposure not reported.	Rocchi et al. (1980)
DNA damage	ADP ribosyl transferase-mediated decrease in cellular NAD content	Human amnion FL cells	–	NR	Study quality: good; 24-h exposure at 4.58×10^{-3} to 10^{-7} mol/L; no clear information on number of replicates.	Yu et al. (1990)

B[a]P, benzo[*a*]pyrene; DT, diphtheria toxin; h, hour(s); γH2AX, phosphorylated histone 2AX; HIC, highest ineffective concentration; LEC, lowest effective concentration, NT, not tested; TK, thymidine kinase.

[a]–, negative; (+), positive in a study of limited quality. None of these studies used metabolic activation.

2020). Phosphorylation of γH2AX with anthracene at 10 μM was higher than with B[a]P at an equimolar concentration, although no statistical analysis was conducted (Bhargava et al., 2020). [The Working Group considered that the evidence was weak because of various study limitations: only one dose was tested, and there was no clear description of the biological replicates and of the species origin of the lymphocytes, presumably human.]

(iii) Human cell lines

DNA damage after exposure to anthracene was assessed in human keratinocyte (HaCaT) and human lymphocyte (A3) cell lines by the comet assay (Hu et al., 2009). Anthracene (up to 10 μM) did not elicit any increase in comet tail moment in either cell type, compared with controls (Hu et al., 2009). [The Working Group noted that no details regarding methodology or replicates were provided.]

An assay for unscheduled DNA synthesis (UDS) was used to detect excision or removal of damaged DNA in a human cervical cancer cell line (HeLa S3) exposed to anthracene. No changes in UDS were observed with anthracene at any concentration tested (range, 0.1–100 μg/mL) (Martin et al., 1978; Martin & McDermid, 1981).

The frequency of micronuclei was measured in human lymphoblastoid $TK^{+/-}$ (MCL-5) cells blocked in cytokinesis by cytochalasin B and exposed to anthracene at several concentrations for 24 hours. The average number of micronuclei was not increased above that in the vehicle (DMSO) controls in replicate analyses (Crofton-Sleigh et al., 1993).

In a quantitative mutagenesis study in human embryo skin and muscle explant epithelial-like cells (EUE) that are sensitive to diphtheria toxin, the number of mutant cells that were resistant to diphtheria was measured after either acute or chronic exposure to anthracene (Rocchi et al., 1980). The maximum recovery of mutants was observed after an expression time of 3 weeks, corresponding to 10 cell generations. Anthracene did not induce any increase in the number of mutant cells (mutation frequency, $< 7 \times 10^{-6}$) after 10 or 20 cell doublings, in comparison with controls or other known carcinogens (Rocchi et al., 1980).

Lastly, in human amnion cells (FL), exposure to anthracene at concentrations of up to 10^{-3} mol/L for 24 hours did not induce an ADP ribosyl transferase (ADPRT)-mediated decrease in cellular nicotinamide adenine dinucleotide (NAD) content, whereas exposure to B[a]P, the positive control, at concentrations of 10^{-3} to 10^{-5} mol/L, resulted in a significant reduction in NAD content (Yu et al., 1990).

(b) Experimental systems

(i) Non-human mammals in vivo

See Table 4.3.

The genotoxic potential of anthracene was investigated in several in vivo studies in rodent tissues.

When transgenic Sprague-Dawley rats carrying the human c-Ha-*RAS* proto-oncogene Hras128 (which are prone to spontaneous tumours of the mammary gland) were treated with anthracene at 200 mg/kg in oil administered orally by gavage once per week for 7–9 weeks, mutations of transgene *Hras128* were found in 2 of 3 tumours in females and in 2 of 3 tumours in males (Ohnishi et al., 2007). [The Working Group noted that these data were uninformative since no tumours were identified in the control group, thus there was no estimation of mutation frequency in the negative controls.]

In a study in female and male Chinese hamsters exposed to anthracene at a dose of 450 mg/kg as two intraperitoneal injections, the number of sister-chromatid exchanges (SCEs) per metaphase was not increased, compared with controls, in contrast to the results observed for similar experiments with B[a]P or benzanthracene (Roszinsky-Köcher et al., 1979).

Table 4.3 Genetic and related effects of anthracene in non-human mammals in vivo

End-point	Assay	Tissue, cell Species, strain (sex)	Results[a]	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Mutation analysis of Ha-*Ras* codons 12 and 61	PCR-RFLP	Mammary tumours Transgenic Sprague-Dawley rats with human c-Ha-*RAS* (Hras128)	+	200 mg/kg bw	Gastric intubation (in oil) to Hras128 rats (age, 7 wk), 1×/wk, for 3 wk	Study was inadequate – there was no negative control group for mutation frequency estimation.	Ohnishi et al. (2007)
Micronucleus formation	In vivo micronucleus assay	Bone marrow, PCE Mouse, B6C3F_1	–	Phase 1: 80% of LD_{50} Phase 2: 40% and 80% of LD_{50}	Phase 1: double i.p. injection at 0 h and 24 h, and analysis at 48 h, 72 h, and 96 h Phase 2 (if the result of phase 1 was negative): single i.p. injection, analysis at 30 h, 72 h, and 96 h	10 mice per group; 500 PCE from each animal; positive controls, B[a]P, DMBA.	Salamone et al. (1981)
Micronucleus formation	In vivo micronucleus assay	Bone marrow, PCE Mouse, C57BL/6 or BALB/c, DBA/2, and BDF_1 and CDF_1	–	100 mg/kg bw	Single i.p. injection	Analysis was performed at 48 h, 72 h and 96 h; 3 mice per group, 1000 erythrocytes from each animal; positive controls, B[a]P, DMBA.	Sato et al. (1987)
Sister-chromatid exchange	In vivo sister-chromatid exchange	Bone marrow Chinese hamsters, (M, F), age 8–12 wk	–	450 mg/kg bw	Two i.p. injections at 0 h and 24 h	Analysis at 48 h after first injection, 8 animals per group; 50 well-stained metaphases were analysed from each animal; positive controls, B[a]P and benzanthracene.	Roszinsky-Köcher et al. (1979)
Inhibition of DNA synthesis	[^{3}H]thymidine uptake into DNA	Testes Swiss mice (M), (25–35 g)	–	125 mg/kg bw	Single i.p. injection of anthracene and i.p. injection of [^{3}H]thymidine 3 h later	Positive controls, 3-methylcholanthrene or diethylnitrosamine. Analysis was performed 30 minutes after [^{3}H]thymidine injection, 3 or 4 mice per group.	Friedman & Staub (1976)

Table 4.3 (continued)

End-point	Assay	Tissue, cell Species, strain (sex)	Results[a]	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Mutagenicity of urine	Ames test	Urine Mouse, ICR (M), (age, 5 wk) Tested in *Salmonella typhimurium* TA100, TA98	– +	400 mg/kg bw alone 400 mg/kg bw with NO_2	Single i.p. injection dissolved in tri-*n*-caprylin were used alone or with 20 ppm NO_2; at a flow rate of 350 mL/min	Number of animals per group was not reported. Treatment with anthracene alone or with NO_2 alone did not have an effect. Positive controls, fluoranthene and the combination of fluoranthene with NO_2. Urine samples were treated with β-glucuronidase and arylsulfatase. Ames test performed with and without S9 fraction from rats treated with phenobarbital or 5,6-benzoflavone.	Miyanishi et al. (1996)

B[a]P, benzo[*a*]pyrene; bw, body weight; DMBA, 7,12-dimethylbenz[*a*]anthracene; F, female; h, hour(s); HID, highest ineffective dose; i.p. intraperitoneal; LD_{50}, median lethal dose; LED, lowest effective dose, M, male; NO_2, nitrogen dioxide; PCE, polychromatic erythrocyte; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; wk, week(s).
[a] +, positive; –, negative.

No change in DNA synthesis, as measured by [^{3}H]thymidine uptake into testicular DNA, was observed in male Swiss mice exposed to anthracene at a dose of 125 mg/kg bw by intraperitoneal injection, in contrast to mice exposed to the known carcinogenic PAHs 3-MC and diethylnitrosamine (Friedman & Staub, 1976). Likewise, anthracene at 100 mg/kg bw, when injected intraperitoneally, did not induce micronuclei in the bone marrow erythrocytes of B6C3F$_1$ mice (Salamone et al., 1981), or in C57BL/6, BALB/c, DBA/2, C57BL/6 × DBA/2, or BALB/c × DBA/2 hybrid mice (Sato et al., 1987).

Elevated mutagenicity was shown in urine samples from ICR mice treated with anthracene (400 mg/kg bw, by intraperitoneal injection) in combination with nitrogen dioxide (NO_2; 20 ppm) according to the Ames test in *Salmonella typhimurium* strains TA100 and TA98, (Miyanishi et al., 1996). [The Working Group noted that this finding showed that anthracene, when co-administered with inhaled NO_2, might be nitrated in vivo and possibly converted to mutagenic compounds.]

(ii) Non-human mammalian cells in vitro

See Table 4.4.

Genotoxicity was not observed in in vitro studies in non-human mammalian cells.

No DNA damage, as analysed by the comet assay, was observed in V79 Chinese hamster lung fibroblasts exposed to anthracene (1–50 μM) both with and without the presence of S9 (9000 × *g* supernatant) from the liver of Aroclor-induced rats. However, DNA damage was observed when anthracene-treated cells were also exposed to white fluorescent lamps (Platt et al., 2008).

In the pseudodiploid Chinese hamster cell line D-6, SCE and chromosomal aberrations were not induced after treatment with anthracene (1 mM) (Abe & Sasaki, 1977).

Genotoxic activity was not observed in anthracene-treated rat liver epithelial cells ARL 18, which have an intrinsic capacity for the metabolic activation of a broad spectrum of mutagens and carcinogens. Sister-chromatid exchange was not induced by anthracene in ARL 18 cells, although it was induced in cells treated with the positive control, B[a]P (Tong et al., 1981a).

Anthracene did not induce UDS in primary cultures of hepatocytes from adult male Fischer 344 rats (Williams, 1977; Tong et al., 1981b), although the positive controls 7,12-dimethylbenz[*a*]anthracene (DMBA) and B[a]P did so efficiently. Similarly, anthracene did not affect UDS in primary cultures of adult hepatocytes from male Fischer 344 rats, either without metabolic activation or with S9 derived from the livers of Aroclor 1254-treated rats, whereas the positive control, 2-acetylaminofluorene (2-AAF), demonstrated a strong increase in UDS in these cells (Probst et al., 1981).

Anthracene (20–60 μM), when activated with S9 from C57BL/6J mice, clearly increased the frequency of gene mutation in L5178Y/*Tk*$^{+/-}$ cells, as did the promutagenic positive controls, 2-AAF and B[a]P. Anthracene was marginally mutagenic when S9 from Aroclor-induced rats was used (Amacher & Turner, 1980). In the presence of Aroclor-induced rat S9, mutants were revealed with anthracene only at a high toxic concentration, 71.2 μM (Amacher et al., 1980).

In contrast to 2-AAF and B[a]P, anthracene (3–20 μg/mL) did not induce *Hprt* gene mutations in Chinese hamster ovary (CHO) cells in the presence of rat S9 microsome mix; only low levels of sporadic mutation (1/10 replicates) occurred, in a non-dose-dependent manner (Oshiro et al., 1988). Higher concentrations of anthracene (50 and 125 μg/mL) induced gene mutagenicity, as measured by the *Hprt* mutation assay, in V79 Chinese hamster lung fibroblasts pre-treated with methylazoxymethanol acetate, but not without pre-treatment (Knaap et al., 1985).

Table 4.4 Genetic and related effects of anthracene in non-human mammalian cells in vitro

End-point	Species Tissue, cells	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
DNA strand breaks Comet assay	Chinese hamster Lung (V79) fibroblasts	– +	– NT	50 µM 50 µM + white light	Positive control, DMBA. Cells treated with anthracene were also exposed to white fluorescent lamps exhibiting emission maxima at 334.1, 365.0, 404.7, and 435.8 nm.	Platt et al. (2008)
Unscheduled DNA synthesis	Rat Primary (HPC) hepatocytes	–	NT	1 mM	Positive control, DMBA.	Williams (1977)
Unscheduled DNA synthesis	Rat, Fischer 344 (M) Primary hepatocytes	–	NT	1 mM	Positive controls, DMBA and B[a]P. Source of the chemical was not reported.	Tong et al. (1981b)
Unscheduled DNA synthesis	Rat, Fischer 344 (M) Primary hepatocytes	–	–	100 nmol/mL (100 µM)	Positive controls: 2-AAF and MNNG. S9 fraction, derived from the livers of rats pre-treated with Aroclor 1254, was used.	Probst et al. (1981)
Gene mutation (*Hprt*)	Chinese hamster ovary (CHO) cells	–	+/–	LEC, 3 µg/mL (+S9) Range, 3–20 µg/mL	Positive controls, 2-AAF and B[a]P. Source of the chemical was not reported; some low-frequency mutations (1/10 experimental samples) were found when S9 activation was used with anthracene at concentrations of 3, 4, 5 µg/mL, but without dose-dependency.	Oshiro et al. (1988)
Gene mutation (*Hprt*)	Chinese hamster lung (V79) fibroblasts	–	–	125 µg/mL	Positive control, methylazoxymethanolacetate. Source of the chemical was not reported.	Knaap et al. (1985)
Gene mutation (*Tk* locus)	Mouse L5178Y/*Tk*$^{+/-}$ lymphoma cells	–	+	LEC, 20 µM Range, 0–60 µM	Positive control: B[a]P and 2-AAF. S9 from C57BL/6J mice clearly activated anthracene to a mutagenic substance; Aroclor-induced rat S9 produced marginal activation.	Amacher & Turner (1980)
Gene mutation (*Tk* locus)	Mouse L5178Y/*Tk*$^{+/-}$ lymphoma cells	–	+/–	LEC, 0.5 µM Range, 0–127 µM	Positive controls, B[a]P and 2-AAF. Mutants appeared only at a highly toxic concentration.	Amacher et al. (1980)
Chromosomal aberrations	Chinese hamster (D-6) cells	–	NT	1 mM	Positive control, DMBA.	Abe & Sasaki (1977)

Table 4.4 (continued)

End-point	Species Tissue, cells	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Sister-chromatid exchange	Chinese hamster (D-6) cells	–	NT	1 mM	Positive control, DMBA.	Abe & Sasaki (1977)
Sister-chromatid exchange	Rat, adult Liver, epithelial (ARL 18) cells	–	NT	1 mM	Positive control, B[a]P.	Tong et al. (1981a)

2-AAF, 2-acetylaminofluorene; B[a]P, benzo[*a*]pyrene; CHO, Chinese hamster ovary; DMBA, 7,12-dimethylbenz[*a*]thracene; HIC, highest ineffective concentration; HPRT, hypoxanthine-guanine phosphoribosyl transferase; LEC, lowest effective concentration; M, male; MNNG, methylnitronitrosoguanidine; NT, not tested; S9, 9000 × *g* supernatant; Tk, thymidine kinase.

[a] +, positive; –, negative; +/–, equivocal (variable response in several experiments within an adequate study).

(iii) Non-mammalian test systems

See Table 4.5.

Exposure to anthracene (20 ppm) for 12 days did not induce any increase in micronuclei frequency in the erythrocytes of *Pleurodeles waltl* larvae (1000 cells were analysed for every larva and every group contained 15 larvae). Micronuclei were clearly observed in B[a]P-treated cells (Djomo et al., 1995).

In contrast to the mutagenic effects observed with B[a]P, anthracene did not induce chromosomal aberrations in rainbow trout gonads (RTG-2) and bluegill fry (BF-2) (Kocan et al., 1982). Anthracene (50 ppb) caused DNA damage, as demonstrated by the comet assay, in blood cells of the flounder *Paralichthys olivaceus*; B[a]P also demonstrated a significant effect (Woo et al., 2006).

Anthracene was mutagenic in the *Drosophila melanogaster* wing spot test both in the standard cross (at two concentrations, 1 and 10 mM), and in the high bioactivation cross (at four concentrations, 1, 5, 10, and 20 mM). DMBA was also mutagenic in this test system (Delgado-Rodriguez et al., 1995). However, there was no mutagenic effect with anthracene at 2 mM in the *D. melanogaster* eye mosaic spot test, although the positive control represented by DMBA was very efficient (Vogel & Nivard, 1993).

An increase in DNA damage of > 2-fold induced by anthracene (3 µg/L) when activated by sunlight was also demonstrated, by the comet assay, in grass shrimp (*Palaemonetes pugio*) embryos (Lee & Kim, 2002).

In the mussel, *Mytilus galloprovincialis*, the frequency of micronuclei per 1000 cells (gills or erythrocytes) increased significantly after treatment for 7 days with anthracene (0.1 µg/mL) in sterile seawater with a 14:10 hour light:dark photoperiod ratio (Giannapas et al., 2012; Grintzalis et al., 2012). [The Working Group noted that, according to OECD guidelines, these studies analysed insufficient numbers of gills and erythrocytes.]

Treatment with anthracene at 0.6–1.0 µM induced significant DNA damage, measured by the comet assay, in coelomocytes of the earthworm *Eisenia fetida* (Sun et al., 2020).

In vitro assays with *Saccharomyces cerevisiae* D3 did not reveal any recombinogenic activity for anthracene, although such activity was shown for *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG) (Simmon, 1979b). Reverse mutations were not detected when *Cunninghamella elegans* cultures incubated with anthracene for 48 hours were tested in *S. typhimurium* strains TA98 and TA100, with and without S9 fraction from the liver of Aroclor 1254-treated rats (Cerniglia et al., 1985).

Anthracene (450 µg/plate) induced mutagenicity in *S. typhimurium* strain TA100 in the presence of the hamster metabolic activation system (S9) for procarcinogen activation (Carver et al., 1986). However, anthracene was not mutagenic, compared with the relevant positive controls, in other studies in the presence of S9 liver fraction from Aroclor 1254-induced rats, in *S. typhimurium* strains TA100 and TA98 (La Voie et al., 1985); TA100 and TA98 (La Voie et al., 1979); TA100-lux and TA98-lux (Ackerman et al., 2009); TA1535 and TA1538 (Rosenkranz & Poirier, 1979); TA100, TA1535, TA98, TA1538, TA1537 (Liberman et al., 1982); TA100, TA1535, TA98, TA1538, TA1537 (Ho et al., 1981); TA100, TA1535, TA98, TA1538, TA1536, TA1537 (McCann et al., 1975; Simmon, 1979a); and TM677 (Kaden et al., 1979). Anthracene was also not mutagenic in *S. typhimurium* strains TA100, TA1535, TA98, TA1538, and TA1537 in the presence of S9 liver fraction from 3-MC-induced guinea-pigs (Baker et al., 1980). In a collaborative validation study, which used *S. typhimurium* strain TA98 and TAMIX (a mixture of strains TA7001, TA7002, TA7003, TA7004, TA7005, and TA7006), anthracene was mutagenic in results from 2 out of 15 independent laboratories in the presence of S9

Table 4.5 Genetic and related effects of anthracene in non-mammalian experimental systems in vivo and in vitro

Test system (species, strain)	End-point	Results[a]		Concentration (LEC, HIC) or dose (LED or HID)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Pleurodeles waltl (Amphibia, Salamandridae)	Micronucleus formation in larvae erythrocytes	–	NA	20 ppm (minimum toxic concentration, 20 µg per 100 g of the larvae mixture)	Positive control, B[a]P. Pleurodeles larvae were treated with anthracene for 12 days. Every group contained 15 larvae and 1000 erythrocytes were analysed for every larva.	Djomo at al. (1995)
Rainbow trout gonad cells (RTG-2) and bluegill fry cells (BF-2)	Chromosomal aberrations	–	NA	5–20 µg/mL	Positive control, B[a]P. At each time and concentration, ≥ 200 anaphases were analysed.	Kocan et al. (1982)
Flounder (*Paralichthys olivaceus*)	DNA strand breaks, comet assay, blood cells	+	NT	LED, 50 ppb (range, 0–100 ppb)	Positive control, B[a]P. After treatment for 2 h with anthracene at 50 ppb, DNA damage as measured by tail length in the comet assay increased from 58 µm to 90 µm.	Woo et al. (2006)
Drosophila melanogaster, *flr*^{3}/*In(3LR)TM3*, *ri p*^{p} *sep l(3)89Aa bx*^{34e} *e Bd*^{s} females mated to *mwh* males	SMART, wing spots	+/–	NA	1, 5, 10, 20 mM	Positive control, DMBA. Clone formation frequency per 10^5 cells was calculated.	Delgado-Rodriguez et al. (1995)
Drosophila melanogaster, *ORR/ORR*; *flr*^{3}/*In(3LR) TM3*, *ri p*^{p} *sep l(3)89Aa bx*^{34e} *e Bd*^{s} females mated to *mwh/mwh* males.	SMART, with high bioactivation cross	+	NA	1, 5, 10, 20 mM		
Drosophila melanogaster: *y* (*yellow*) females × *w* (*white*) males, Leiden Standard (LS)	Interchromosomal mitotic recombination, eye mosaic spots	–	NA	2 mM	Positive control, DMBA. Source of anthracene was not provided.	Vogel & Nivard (1993)
Palaeomonetes pugio (grass shrimp) embryos	DNA strand breaks (comet assay)	+	NA	3 µg/L	A positive control was not included in the study. Source of anthracene was not provided. DNA damage increased more than twice when anthracene treatment was combined with sunlight, whereas sunlight alone did not cause a significant effect.	Lee & Kim (2002)

Table 4.5 (continued)

Test system (species, strain)	End-point	Results[a]		Concentration (LEC, HIC) or dose (LED or HID)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Mussel (*Mytilus galloprovincialis*), gills	Micronucleus formation	+	NA	0.1 µg/mL	A positive control was not included in the study. After treatment for 7 days with anthracene at 0.1 µg/mL in sterile sea water with a 14 h:10 h light:dark photoperiod, the frequency of micronucleus abnormalities per 1000 cells increased from 4.3 to 8.4 (this < 2-fold change and use of only 1000 cells were limitations of the experiment).	Grintzalis et al. (2012)
Mussel (*Mytilus galloprovincialis*), haemocytes	Micronucleus formation	+	NA	0.1 µg/mL	A positive control was not included in the study. After treatment for 7 days with anthracene at 0.1 µg/mL in sterile sea water with 14 h:10 h light: dark photoperiod, the relative increase in micronucleus frequency was 2.8.	Giannapas et al. (2012)
Earthworm (*Eisenia fetida)*, coelomocytes	DNA strand breaks, comet assay	+	NT	0.6 µM Range, 0–1 µM	No positive control was included in the study. Increase of 10-fold in DNA damage after cell treatment for 24 h.	Sun et al. (2020)
Saccharomyces cerevisiae D3	Mitotic recombinants	–	–	5% (w/v)	Positive control, MNNG. S9 obtained from rats induced with Aroclor 1254.	Simmon (1979b)
Culture medium from *Cunninghamella elegans* tested in *Salmonella typhimurium* TA98, TA100	Reverse mutation	–	–	125 µg/plate	Positive control, B[a]P.	Cerniglia et al. (1985)
Salmonella typhimurium, TA100	Reverse mutation	–	+/–	450 µg/plate	Positive control, B[a]P. Anthracene was genotoxic only with S9 from hamster liver.	Carver et al. (1986)
Salmonella typhimurium, TA98 and TA100	Reverse mutation	–	–	100 µg/plate	Positive control, 1,9-dimethylfluorene. Source of anthracene was not reported; S9 from the livers of rats pre-treated with Aroclor 1254.	La Voie et al. (1979)

Table 4.5 (continued)

Test system (species, strain)	End-point	Results[a]		Concentration (LEC, HIC) or dose (LED or HID)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Salmonella typhimurium, TA98 and TA100	Reverse mutation	–	–	200 µg/plate Range, 5–200 µg/plate	Positive control, 2,9-dimethylanthracene. S9 from the livers of rats pre-treated with Aroclor 1254.	La Voie et al. (1985)
Salmonella typhimurium, TA98-lux and TA100-lux	Reverse mutation	–	–	10 mg/plate	Positive control, B[a]P. Negative results were obtained by bioluminescent *Salmonella* reverse mutation assay performed in five independent laboratories.	Ackerman et al. (2009)
Salmonella typhimurium, TA98, TA100, TA1535, TA1537, and TA1538	Reverse mutation	–	–	20 µg/plate	Positive control, B[a]P.	Liberman et al. (1982)
Salmonella typhimurium, TA98, TA100, TA1535, TA1537, and TA1538	Reverse mutation	–	–	1000 µg/plate	Positive control, B[a]P. S9 from methylcholanthrene-induced guinea-pigs.	Baker et al. (1980)
Salmonella typhimurium, TA1535, TA1537, TA1538, TA98 and TA100	Reverse mutation	–	–	500 µg/plate Range, 1–500 µg/plate	Positive control, B[a]P. Purity was checked by thin-layer chromatography, gas chromatography, and mass spectrometry; S9 from the livers of rats pre-treated with Aroclor 1254.	Ho et al. (1981)
Salmonella typhimurium, TA98, TA100, TA1535, TA1536, TA1537, and TA1538	Reverse mutation	–	–	250 µg/plate	Positive control, B[a]P. S9 from Sprague-Dawley rats pre-treated with Aroclor 1254.	Simmon (1979a)
Salmonella typhimurium, TA98, TA100, TA1535, TA1537, and TA1538	Reverse mutation	–	–	HIC, 1000 µg/plate Range, 10–1000 µg/plate	Positive control, B[a]P. S9 from livers of rats pre-treated with Aroclor 1254.	McCann et al. (1975)
Salmonella typhimurium, TM677	Reverse mutation	–	–	225 µM [40 µg/mL]	Positive control, B[a]P. S9 from livers of rats pre-treated with phenobarbital and Aroclor 1254.	Kaden et al. (1979)
Salmonella typhimurium, TA98 and TAMix (TA7001–7006)	Reverse mutation	NT	+/–	4–5000 µg/mL	Positive control, B[a]P. Positive results at 100 µg/mL in 2 out of 15 laboratories.	Flückiger-Isler et al. (2004)

Table 4.5 (continued)

Test system (species, strain)	End-point	Results[a]		Concentration (LEC, HIC) or dose (LED or HID)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Salmonella typhimurium, TA98	Reverse mutation	NT NT	– +	50 µg/plate 20 µg/plate + 1 µg/plate B[a]P	Anthracene significantly increased the genotoxic effect of B[a]P at 1 µg/plate; S9 from rat liver.	Hermann (1981)
Salmonella typhimurium, TA102	Reverse mutation	– ++	– –	5 nmol/plate 0.11 nmol/plate under light	Under light exposure (1.1 J/cm² UVA + 2.1 J/cm² visible) –S9, anthracene increased its photomutagenic effect in a dose-dependent manner over a range of 0.11–0.54 nmol/plate.	Yan et al. (2004)
Salmonella typhimurium, TA1535/ pSK1002	umuC test; expression of the reporter transgene of β-galactosidase activated by umu-related proteins	+ (for photoproducts only)	–	20 µg/mL, anthracene and its photoderivatives	Analysis was performed +S9 and –S9, according to International Organization for Standardization (ISO) 13 829. S9 removed genotoxic activity; 1-hydroxyanthracene-9,10-dione and 1,4-dihydroxyanthracene-9,10-dione were identified and confirmed as genotoxic photoderivatives.	Brack et al. (2003)
Salmonella typhimurium, TA1535, TA1538	Reverse mutation	–	–	250 µg/plate	Positive control, MNNG. S9 from livers of rats induced with Aroclor 1254.	Rosenkranz & Poirier (1979)
Escherichia coli, pol A⁺ and pol A⁻ strains	DNA-modifying capacity	NT	–	250 µg/plate	Positive control, B[a]P.	
Escherichia coli, RT7h-RT18h with the reversible his-4 locus	Reverse mutation	–	NT	10 µg/mL + NUV 0–100 kJ m^{-2}	Genotoxicity occurred in the presence of cytotoxicity and cell membrane damage.	Tuveson et al. (1990)
Haemophilus influenzae	Decrease in DNA transforming activity	+	NT	10 µg/mL + NUV 0–100 kJ m^{-2}		
Plasmid pBR322 supercoiled DNA	Nicking of DNA	+	NT	10 µg/mL		
Bacillus subtilis, H17 and M45	Reverse mutation	–	–	62 µg/plate	Positive control, MNNG. S9 (crude extract, ISO 13 829) was obtained from rats after induction with Aroclor 1254.	McCarroll et al. (1981)

B[a]P, benzo[*a*]pyrene; DMBA, 7,12-dimethylbenz[*a*]anthracene; h, hour(s); HIC, highest ineffective concentration; HID, highest ineffective dose; LEC, lowest effective concentration; LED, lowest effective dose; MNNG, methylnitronitrosoguanidine; NA, not applicable; NT, not tested; NUV, near-ultraviolet light, 320–400 nm; ppb, parts per billion; ppm, parts per million; S9, 9000 × *g* supernatant; SMART, somatic mutation and recombination test; UV, ultraviolet; w/v, weight/volume.

[a] +, positive; –, negative; +/–, equivocal (variable response in several experiments within an adequate study).

liver fraction from rats induced with Aroclor 1254 (Flückiger-Isler et al., 2004).

Anthracene increased the mutagenicity of B[a]P in *S. typhimurium* strain TA98 (Hermann, 1981). Also, anthracene (≥ 0.11 nmol/plate) demonstrated strong photomutagenicity in *S. typhimurium* strain TA102, which is auxotrophic for histidine, under UV-A and light exposure (1.1 J/cm^2 UV-A + 2.1 J/cm^2 visible light) and without S9 activation. No mutagenicity was observed when UV-A was not applied, either with or without S9 activation (Yan et al., 2004). The *umuC* test for genotoxicity in *S. typhimurium* strain TA1535/pSK1002 revealed significant activity for anthracene and its photoderivatives, which decreased in the presence of Aroclor-induced rat S9 (Brack et al., 2003).

Anthracene did not possess a DNA-modifying capacity in normal and DNA polymerase-deficient *Escherichia coli* strains *polA*$^+$ and *polA*$^-$ (Rosenkranz & Poirier, 1979).

Anthracene was inert in the micro-suspension assay for reverse mutations in *Bacillus subtilis* strains H17 and M45, with and without metabolic activation by S9 (McCarroll et al., 1981). An *E. coli* strain deficient in *katF* (which is involved in catalase synthesis) was sensitive to its inactivation by anthracene plus near-visible ultraviolet irradiation, but when histidine independence was used as the end-point, no mutations were detected in experiments with *E. coli* strains RT7h, RT8h, RT10h, RT13h, or RT15h over the complete range of survival levels investigated. Anthracene plus near-visible ultraviolet irradiation inactivated *Haemophilus influenza* transforming DNA, leading to the nicking of supercoiled plasmid pBR322 DNA in vitro (Tuveson et al., 1990).

[The Working Group noted that the genotoxicity of anthracene was shown in several studies performed in mammalian cells and in several non-mammalian systems only in the presence of metabolic activation by mouse or hamster microsomal monooxygenases, photoactivation, or structure modification through interaction with NO_2. DNA damage was not shown in studies performed without photoactivation or in the presence of rat liver microsomal monooxygenases. The need for pre-activation, i.e. photoactivation, provided some explanation for the mixed results across studies of different end-points and in different experimental systems.]

4.2.3 Induces epigenetic alterations

The evidence on whether anthracene might exhibit the key characteristic of "induces epigenetic alterations" was scarce. No data in exposed humans were available to the Working Group. In addition, anthracene, either in a single study in isolated lymphocytes or in yeast, engineered to express human DNMT-1 and DNMT-3B genes, induced no alterations in target genes (Sugiyama et al., 2016; Bhargava et al., 2020). Bhargava et al. (2020) examined the epigenetic effects of treatment with the PAHs, anthracene and B[a]P (10 μM) in isolated lymphocytes [The Working Group noted that the cells appeared to be of human origin but this was not clearly stated in the manuscript.] Anthracene failed to modulate the expression levels of three of four microRNAs (miR-24, miR-34a, miR-150), known to be associated with carcinogenesis, as compared with B[a]P. [The Working Group noted that no statistics were provided for these changes.] In addition, anthracene did not alter the miRNA-related target genes (*MYC*, *P53*, *NFKB*) that were down-regulated by B[a]P or the epigenetic markers *DNMT1*, *HDAC1*, *HDAC7*, *KDM3a*, *EZH2*, and *P300*, which were also significantly altered by B[a]P at up to 72 hours of treatment. Finally, anthracene did not affect mitochondrial DNA methylation.

A yeast engineered to express human DNMT-1 and DNMT-3B genes was shown to respond to DNA methyltransferase inhibitors or the histone deacetylase inhibitor trichostatin A with increased flocculation behaviour (Sugiyama

et al., 2016). Trichostatin A also increased expression of the flocculin-encoding gene *FLO1*, a gene linked to nonsexual flocculation in the yeast. The natural product alizarin, derived from anthracene and considered to be a carcinogenesis promoter, promoted flocculation in this assay and enhanced *FLO1* mRNA expression, but anthracene (4.0–400 μM) was inactive.

4.2.4 Induces oxidative stress

Alterations in the generation of reactive oxygen species (ROS) or reactive nitrogen species and their interactions with biological macromolecules (i.e. lipids, DNA, RNA, and proteins), and alterations in the antioxidant defence capacity can both have a relevant role in neoplastic development (Klaunig et al., 2011; Smith et al., 2016; Suman et al., 2016). Studies investigating the formation of DNA oxidative bioproducts, i.e. 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG); the reaction of ROS combined with polyunsaturated fatty acids (PUFA) in the lipid membranes to generate malondialdehyde (MDA) through lipid peroxidation (Klaunig et al., 2011); the downregulation of antioxidant pathways, such as those downstream of the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) (Klaunig et al., 2011), including glutathione reductase (GSR), catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx); or other signalling pathways, such as AP-1, which are downstream of MAP kinases (JNK, p38) and are implicated in the regulation of pro-oxidative stress responses (Klaunig et al., 2011) were reviewed here (see details in Table 4.6, Table 4.7, Table 4.8, and Table 4.9).

(a) Humans

(i) Exposed humans

See Table 4.6.

Five studies investigating the potential association of anthracene with oxidative stress in exposed humans were available to the Working Group (Singh et al., 2008b; Hanchi et al., 2017; Agarwal et al., 2018; Jeng et al., 2022, 2023). However, in Agarwal et al. and Singh et al., the contribution of anthracene to the overall effects of the PAH mixture on oxidative stress was not clearly assessed and these studies were excluded.

Among coke-oven workers from a steel factory in Taiwan, China, the association between exposure to individual PAHs (including anthracene) and oxidative stress end-points was evaluated in a dose–response analysis. PAHs were measured in personal breathing-zone air samples, and levels were quantified by GC-MS; time-weighted concentrations of each PAH were calculated and used to estimate exposure. Compared with the controls, the coke-oven workers had significantly higher levels of sperm 8-oxodG, seminal MDA, and seminal ROS. Individual PAH associations with 8-oxodG, ROS, and malondialdehyde were determined in sperm from the same individuals (Jeng et al., 2022). Thirty-eight workers (18 top-side oven workers and 20 side-oven workers) and 22 office workers (reference controls) were evaluated. Levels of 8-oxodG were measured by LC-MS with an electrospray ion source (ESI) using established procedures. An increase in anthracene exposure was not associated with oxidative damage to DNA as assessed by 8-oxodG (Jeng et al., 2022). In addition, there were no positive associations between anthracene and ROS levels. However, increases in MDA levels were positively associated with increases in exposure to all the PAHs evaluated, including anthracene (Jeng et al., 2022), but not anthracene individually.

In a follow-up study from the same group (Jeng et al., 2023), oxidative damage to DNA was assessed in 54 of the workers (31 top-side oven workers and 23 side-oven workers) from the same factory in Taiwan, China. Levels of 8-oxodG were assessed as described above. However, no office worker controls were included in the study. Anthracene exposure did not correlate with oxidative damage to DNA as measured by 8-oxodG. [The Working Group considered

Table 4.6 End-points relevant to oxidative stress with anthracene in exposed humans

End-point	Assay Biospecimen	Location Setting, study design	Exposure level and no. of exposed and controls	Response (significance)	Covariates controlled	Comments	Reference
8-oxodG	GC-MS/MS and LC-MS/MS Urine	Tunisia Workers at an electric steel foundry, cross-sectional study	2.86 ng/L; 93 healthy male workers; 3 categories: SSW, $n = 30$; RGC, $n = 43$; MIX, $n = 20$	(↑), $r = 0.357$	Smoking	Limitations: PAH measurements including anthracene; a linear calibration curve was done for 8-oxodG and cotinine; small sample size. The exposure assessment was appropriate.	Hanchi et al. (2017)
8-oxodG	Triple quadrupole mass spectrometer Sperm DNA	Taiwan, China Workers ($n = 38$) from a coke-oven mill, 22 office workers, cross-sectional study	Median, 347 ng; log = 5.82	No alteration	Adjusted for age, education, smoking, drinking, BMI, and job site	Not very informative. Limitations: small sample size; no units provided for the PAHs measured, only log transformed; dermal exposure was not assessed; low confidence in the interpretation of anthracene exposure.	Jeng et al. (2022)
Malondialdehyde	Thiobarbituric acid Seminal plasma			(↑), association with PAHs only			
ROS	Chemiluminescence (by luminol) Seminal plasma			No alteration			
8-oxodG	Triple quadrupole mass spectrometer Sperm	Taiwan, China Workers from a coke-oven mill, cross-sectional study	54 exposed participants (31 topside-oven workers and 23 side-oven workers)	No alteration	Adjusted for age, BMI, education, smoking status, drinking status, and job site of the participants	Not very informative. Limitations: small sample size; the exposure assessment was appropriate, even though the description was not complete.	Jeng et al. (2023)

BMI, body mass index; GC-MS/MS, gas chromatography-tandem mass spectrometry; LC-MS/MS, liquid chromatography-tandem mass spectrometry; MIX, maintenance and quality control workers; 8-oxodG, 8-oxo-7,8-dihydro-2′-deoxyguanosine; PAH, polycyclic aromatic hydrocarbon; RGC, rolling, galvanization, and cable fibre workers; ROS, reactive oxygen species; SSW, steel smelter workers.
(↑), increase in a study of limited quality.

Table 4.7 End-points relevant to oxidative stress with anthracene in human cells in vitro

End-points	Assay	Tissue, cells	Results	Concentration (LEC or HIC)	Comments	Reference
Primary cells						
ROS	CellROX Deep Red Flow Cytometry assay	Human primary peripheral blood lymphocytes	↑	10 µM, 30 min to 6 h	Limitations: only one concentration; cell species not noted but assumed to be human, measured with ELISA; $n = 3$; unclear if technical or biological replicates.	Bhargava et al. (2020)
NRF2 activity	ELISA	Human primary peripheral blood lymphocytes	↑	10 µM, 1–24 h	Limitations: only one concentration;, measured with ELISA; $n = 3$, unclear if technical or biological replicates.	
$O_2^{\bullet}$	Photosensitized reduction of NBT to NBF, measured spectrophotometrically	Human peripheral blood leukocytes	↑, $r^2 = 0.83$; $P < 0.05$	0.05–0.25 µM for 24 h	Informative: correlation analysis determined that the association was significant; dose range not clear.	Uribe-Hernández et al. (2008)
$O_2^{\bullet}$	Superoxide dismutase-inhibitable cytochrome c reduction	Human peripheral blood monocytes	No change	10 µg/mL for 24 h	Limitations: one concentration tested.	Fabiani et al. (1999)
Human cell lines						
ROS	DCFH-DA	Human alveolar basal epithelial (A549) cells	↑, association with $PM_{2.5}$ anthracene and ROS; $r = 0.81$	Mixture of emission factors; dose not clear (100 or 200 µg/mL); 24 h exposure	Limitations: only association measured; not individual PAHs tested; $PM_{2.5}$ extracts may include other agents.	Sun et al. (2018)
ROS	DCFH-DA	Human keratinocyte (HaCaT) cells	↑ with UV only	0.01–0.5 µg/mL	Informative; sunlight, UV-A and UV-B were used to activate anthracene; no anthracene only or UV only controls; tested with replicates.	Mujtaba et al. (2011)
Radicals $O_2^{\bullet}$ and $^{\bullet}OH$	$O_2^{\bullet}$: photosensitized reduction of NBT to NBF, measured spectrophotometrically; $^{\bullet}OH$: measured by ascorbic acid–iron-EDTA system.	Human keratinocyte (HaCaT) cells	↑ with UV only	0.01–0.5 µg/mL		

DCFH-DA, 2′,7′-dichlorofluorescein diacetate; EDTA, ethylenediaminetetraacetic acid; ELISA, enzyme-linked immunosorbent assay; h, hour(s); HIC, highest ineffective concentration; NBF, nitro-blue diformazan; NBT, nitro-blue tetrazolium; NRF2, nuclear factor erythroid 2–related factor 2; $O_2^{\bullet}$, superoxide anion radical; $^{\bullet}OH$, hydroxyl radical; LEC, lowest effective concentration; min, minute; $PM_{2.5}$, particulate matter with diameter ≤ 2.5 µm; ROS, reactive oxygen species; UV, ultraviolet.
↑, increase.

Table 4.8 End-points relevant to oxidative stress with anthracene in non-human mammalian systems in vitro

End-point	Assay	Species, strain (sex), cell line	Tissue	Results[a]	Concentration (LEC or HIC)	Route, duration, dosing regimen	Comments	Reference
ROS	DCFH-DA	Rat, Sprague-Dawley, primary cardiomyocytes	Heart	(↑)	0–10 µM	Treated after cell isolation; dose–response relation.	Semi-quantitative study; not clear if exposure was 1 h.	Ju et al. (2020)
Protein carbonyls	Protein carbonylation colourimetric assay	Rat, Sprague-Dawley, primary cardiomyocytes	Heart	↑	0–10 µM for 24 h	Treated after cell isolation; $n = 4$, repeated 3 times.		
Malondialdehyde	Thiobarbituric acid	Rat, Sprague-Dawley, primary cardiomyocytes	Heart	↑	10 µM, significant response	Treated after cell isolation, dose–response relation over 0–10 µM for 24 h time point; $n = 4$, repeated 3 times.	Significant increases in phosphorylated ERK1/2 and AKT.	
ROS	DCFH-DA	Rat, Sprague-Dawley, vascular smooth muscle cells	Aorta	(↑)	0–10 µM for 1 h	Treated after cell isolation; $n = 3$.	Semi-quantitative study; only 1 experiment; MMP2 also significant; reversed with NAC, but no information about concentration. An increase in MMP2 was also observed.	Ju et al. (2022)
ROS	DCFH-DA	Mouse, hippocampal neuronal cells (HT-22)	Brain	↑	125 µM	Dose–response relation over 0–125 µM for 48 h; repeated 3 times.		Olasehinde & Olaniran (2022)
Antioxidants	CAT activity	Mouse, hippocampal neuronal cells (HT-22)	Brain	↑	25 µM	Dose–response relation over 0–125 µM for 48 h; repeated 3 times.		
Antioxidants	GST activity	Mouse, hippocampal neuronal cells (HT-22)	Brain	↑	25 µM	Dose–response relation over 0–125 µM for 48 h; repeated 3 times.		
Antioxidants	GSH	Mouse, hippocampal neuronal cells (HT-22)	Brain	↑	25 µM	Dose–response relation over 0–125 µM for 48 h; repeated 3 times.		

AKT, protein kinase B; CAT, catalase; DCFH-DA, 2′,7′-dichlorofluorescein diacetate; ERK1/2, extracellular signal-regulated kinase 1/2; GSH, glutathione; GST, glutathione-*S*-transferase; h, hour(s); HIC, highest ineffective concentration; LEC, lowest effective concentration; MMP2, matrix metalloproteinase 2; NAC, *N*-acetyl cysteine; ROS, reactive oxygen species.

[a] ↑, increase; (↑) increase in a study of limited quality.

Table 4.9 End-points relevant to oxidative stress with anthracene in non-mammalian systems in vivo

Assay	Species, strain (sex), cell line	Tissue	Results[a]	Dose (LED, HID) or concentration (LEC, HIC)[b]	Route[c], duration, dosing regimen	Comments	Reference
DTT (oxidative potential)	*Danio rerio*, zebrafish larvae	Whole fish	No change	20 µg/L (HID)	1, 2, 4, 6 h time points; exposure group, *n* = 15; repeated 3 times	In the article text, it was suggested that UV increased oxidative potential but not significantly; fish were laboratory-raised.	St Mary et al. (2021)
GST activity[d]	*Pomatoschistus microps*, common goby, juveniles	Liver	↓	0.5 µg/L	27 animals/dose; exposed for 96 h to 500 mL of anthracene (0.25–4 µg/L)	Naturally caught.	Vieira et al. (2008)
CAT activity	*Pomatoschistus microps*, common goby, juveniles	Liver	↑	2 µg/L	27 animals/dose; exposed for 96 h to 500 mL of anthracene (0.25–4 µg/L)	Naturally caught.	
SOD activity	*Pomatoschistus microps*, common goby, juveniles	Liver	↑	1 µg/L	27 animals/dose; exposed for 96 h to 500 mL of anthracene (0.25–4 µg/L)	Naturally caught.	
LPO (TBARs)	*Chanos chanos*, milkfish	Head, gill, and dorsal fin muscles	↑, all sites	0.011 mg/L	*n* = 3 per treatment; dose–response relation over 0–0.176 mg/L	Naturally caught.	Palanikumar et al. (2012)
CAT activity	*Chanos chanos*, milkfish	Head, gill, and dorsal fin muscles	↑, all sites	0.011 mg/L	*n* = 3 per treatment; dose–response relation over 0–0.176 mg/L	Naturally caught.	
GST activity	*Chanos chanos*, milkfish	Head, gill, and dorsal fin muscles	↑, all sites	0.011 mg/L (head only); 0.022 mg/L for others	*n* = 3 per treatment; dose–response relation over 0–0.176 mg/L	Naturally caught.	
LPO (malonaldehyde)	*Lepomis macrochirus*, bluegill sunfish	Liver microsomes	No change unless +UV light (2 h)	3.015 µg/mL	Exposed the microsomes to anthracene (3 h at 30 °C) and UV (20 min at 37 °C); *n* = 3, no clarity on number of replicate experiments; anthracene alone and UV alone controls were carried out	From hatchery.	Choi & Oris (2000b)
$O_2^{\bullet}$	*Lepomis macrochirus*, bluegill sunfish	Liver microsomes	No change unless +UV light (2 h)	3.015 µg/mL			

Table 4.9 (continued)

Assay	Species, strain (sex), cell line	Tissue	Results[a]	Dose (LED, HID) or concentration (LEC, HIC)[b]	Route[c], duration, dosing regimen	Comments	Reference
LPO (malonaldehyde)	*Poeciliopsis lucida*, top minnow hepatoma cell line (PLHC-1)	Cell line	No change unless +UV light (2 h)	Up to 5 mg/L; +UV light ~2.5 mg/L	$n = 4$ per treatment/dose; dose–response over 0–5 mg/L; 3 h with anthracene.		Choi & Oris (2000a)
LPO (TBARS)	*Palaemon serratus*, common prawn	Digestive gland	↑	32 µg/L	Dose range, 16–1024 µg/L in seawater for 96 h; $n = 9$ per treatment		Gravato et al. (2014)
GST activity			No change	1024 µg/L (HID)			
CAT activity			↑	1024 µg/L			
GPx activity			↑	256 µg/L			
GST activity	*Daphnia magna*, water flea	Whole animal	↓	0.25 µM	10 animals/treatment; 96 h exposure to anthracene; dose range, 0.0625–5 µM; repeated 3 times		Feldmannová et al. (2006)
GPx activity			↓	0.5 µM			
SOD activity	*Ruditapes decussatus*, Mediterranean clam	Gill and digestive gland	↑, gill; no change in digestive gland	100 µg/L	5 animals/treatment for 48 h exposure	No replicates.	Sellami et al. (2015a)
CAT activity			↑, gill; no change in digestive gland	100 µg/L			
GPx activity			↑, gill; no change in digestive gland	100 µg/L			
GST activity			↑, gill; no change in digestive gland	100 µg/L			
GSR activity			↑, gill; no change in digestive gland	100 µg/L			

Table 4.9 (continued)

Assay	Species, strain (sex), cell line	Tissue	Results[a]	Dose (LED, HID) or concentration (LEC, HIC)[b]	Route[c], duration, dosing regimen	Comments	Reference
Protein carbonyls			↑ observed; probably actin	100 µg/L			Sellami et al. (2015a) (cont.)
SOD activity	*Venerupis decus*[e], Mediterranean clam	Gill and digestive gland	↑, gill; no change in digestive gland	100 µg/L	5 pooled animals/replicate, $n = 3$; sea water used as medium; 48 h exposure	Appropriate replicates run.	Sellami et al. (2015b)
CAT activity			↑, gill; no change in digestive gland	100 µg/L			
GST activity			↑, gill; no change in digestive gland	100 µg/L			
LPO (malonaldehyde)	*Mytilus galloprovincialis*, mussel	Isolated haemocytes (immune system cells)	↑	100 µg/L	7-day exposure; 3 replicates/group		Giannapas et al. (2012)
$O_2^{\bullet}$	*Mytilus galloprovincialis*, mussel	Isolated haemocytes (immune system cells)	↑	100 µg/L	7-day exposure; 3 replicates/group	Response correlated to micronuclei frequency increase	
GSH content	*Mytilus galloprovincialis*, mussel	Digestive gland	↓	0.15 µg/L, 2 days 0.05 µg/L, 4 days 0.05 µg/L, 8 days	Dose range, 0.05–0.4 µg/L, for exposures of 2, 4, or 8 days; 39 mussels/group		Badreddine et al. (2017)
LPO (malonaldehyde)	*Mytilus galloprovincialis*, mussel	Digestive gland	↑	0.15 µg/L, 2 days 0.05 µg/L, 4 days 0.05 µg/L, 8 days	Dose range, 0.05–0.4 µg/L, for exposure of 2, 4, or 8 days; 39 mussels/group		

Table 4.9 (continued)

Assay	Species, strain (sex), cell line	Tissue	Results[a]	Dose (LED, HID) or concentration (LEC, HIC)[b]	Route[c], duration, dosing regimen	Comments	Reference
LPO (malonaldehyde)	*Mytilus edulis*, blue mussel	Gills and digestive glands	↑, gills; 18, 21 days ↑, digestive gland; 3, 6 days	0.25 µg/L	0.25 and 2.5 µg/L, 21-day exposures; 0–21 days, time course done; *n* = 3; replicated 3 times		Mengqi et al. (2017)
$O_2^{\bullet}$	*Mytilus edulis*, blue mussel	Gills and digestive glands	↑, gills; several days ↑, digestive gland; a few days	0.25 µg/L	0.25 and 2.5 µg/L, 21-day exposures; 0–21 days, time course done; *n* = 3; replicated 3 times	Lower increases for this end-point in the digestive gland.	
GST activity	*Mytilus edulis*, blue mussel	Gills and digestive glands	↑, in both tissues	0.25 µg/L for several days	0.25 and 2.5 µg/L, 21-day exposures; 0–21-day time course done; *n* = 3; replicated 3 times; days 3 and 9, some decreases		
GSH content	*Mytilus edulis*, blue mussel	Gills and digestive glands	↓, in gills ↑, digestive gland	0.25 µg/L	0.25 and 2.5 µg/L, 21-day exposures; 0–21-day time course done; *n* = 3; replicated 3 times		
GPx activity	*Mytilus edulis*, blue mussel	Gills and digestive glands	↑, in both tissues	0.25 µg/L, for several days	0.25 and 2.5 µg/L, 21-day exposures; 0–21-day time course done; *n* = 3; replicated 3 times; some reductions in the gills at 12 and 15 days		
GSR activity	*Mytilus edulis*, blue mussel	Gills and digestive glands	↑ in both tissues	0.25 µg/L for gills several days; 2.5 µg/L for digestive gland	0.25 and 2.5 µg/L, 21-day exposures; 0–21-day time course done; *n* = 3; replicated 3 times; some reductions at 3 and 9 days		

Table 4.9 (continued)

Assay	Species, strain (sex), cell line	Tissue	Results[a]	Dose (LED, HID) or concentration (LEC, HIC)[b]	Route[c], duration, dosing regimen	Comments	Reference
SOD activity	*Acropora tenuis*, scleractinian coral	Larvae	↓	4 µg/L	4 and 17 µg/L; 200 larvae per dose; *n* = 4 per control and treatment; *n* = 2 solvent controls	This study also assessed phototoxicity, which was found not to be a major influence on any oxidative stress biomarkers.	Overmans et al. (2018)
CAT mRNA expression	*Acropora tenuis*, scleractinian coral	Larvae	↑	17 µg/L	4 and 17 µg/L; 200 larvae per dose; *n* = 4 per control and treatment; *n* = 2 solvent controls	4 µg/L was variable for gene expression.	
MnSOD mRNA expression	*Acropora tenuis*, scleractinian coral	Larvae	No change	17 µg/L	4 and 17 µg/L; 200 larvae per dose; *n* = 4 per control and treatment; *n* = 2 solvent controls	4 µg/L was variable for gene expression.	
Hsp70 mRNA expression	*Acropora tenuis*, scleractinian coral	Larvae	↑	17 µg/L	4 and 17 µg/L; 200 larvae per dose; *n* = 4 per control and treatment; *n* = 2 solvent controls	4 µg/L was variable for gene expression.	
Hsp90 mRNA expression	*Acropora tenuis*, scleractinian coral	Larvae	↑	17 µg/L	4 and 17 µg/L; 200 larvae per dose; *n* = 4 per control and treatment; *n* = 2 solvent controls	4 µg/L was variable for gene expression.	
DCFH-DA	*Caenorhabditis elegans*	Whole body	↑ at 12 h	8 µg/L	Exposures, 6–12 h; dose range, 4–8 µg/L	No. of replicates was unclear.	Roh et al. (2018)
SOD activity	*Caenorhabditis elegans*	Whole body	↑ at 12 h	8 µg/L	Exposures, 6–12 h; dose range, 4–8 µg/L		
LPO (TBARS)	*Caenorhabditis elegans*	Whole body	No change	8 µg/L	Exposures, 6–12 h; dose range, 4–8 µg/L		
GSH content	*Caenorhabditis elegans*	Whole body	↑ at 3 h	400 µg/L	Exposures, 3 h		
Sod1 mRNA expression	*Caenorhabditis elegans*	Whole body	↑ at 6 h	8 µg/L	Exposures, 6–12 h; dose range, 4–8 µg/L		
Sod2 mRNA expression	*Caenorhabditis elegans*	Whole body	No change	8 µg/L	Exposures, 6–12 h; dose range, 4–8 µg/L		

Table 4.9 (continued)

Assay	Species, strain (sex), cell line	Tissue	Results[a]	Dose (LED, HID) or concentration (LEC, HIC)[b]	Route[c], duration, dosing regimen	Comments	Reference
Sod3 mRNA expression	*Caenorhabditis elegans*	Worm	No change	8 µg/L	Exposures, 6–12 h; dose range, 4–8 µg/L		Roh et al. (2018) (cont.)
DCFH-DA	*Eisenia fetida*, earthworm	Coelomocytes	↑	1 nM	Dose range tested, 0, 1, 300, 600, 1000 nM; significant result for all doses tested		Sun et al. (2020)
GSH activity	*Eisenia fetida*, earthworm	Coelomocytes	No change	60 nM	Dose range tested, 0–60 nM		
CAT activity	*Eisenia fetida*, earthworm	Coelomocytes	↑	6 nM	Dose range tested, 0–300 nM		
SOD activity	*Eisenia fetida*, earthworm	Coelomocytes	↑	3 nM	Dose range tested, 0–1000 nM		
LPO (malonaldehyde)	*Eisenia fetida*, earthworm	Coelomocytes	Upward trend; not significant	100 nM	Dose range tested, 0–100 nM		
TAOC	*Eisenia fetida*, earthworm	Coelomocytes	↑	3 nM	Dose range tested, 0–300 nM; only significant at 3 nM		
DCFH-DA staining	*Marchantia polymorpha* L., liverwort	Thallus	↑	280 µM	Exposure, 30 days; $n = 4$; unclear if there were replicates	Concentrations of anthracene resembled those observed in soil.	Spinedi et al. (2021)
LPO (malonaldehyde)		Whole plant	↑	280 µM			
SOD activity		Whole plant	No change	280 µM			
CAT activity		Whole plant	No change	280 µM			
POD activity		Whole plant	↑	50 µM			
APx activity		Whole plant	↑	280 µM			

Table 4.9 (continued)

Assay	Species, strain (sex), cell line	Tissue	Results[a]	Dose (LED, HID) or concentration (LEC, HIC)[b]	Route[c], duration, dosing regimen	Comments	Reference
LPO (TBARS)	*Sinapis alba*, *Triticum aestivum*, *Phaseolus vulgaris*	Whole plant	No change	2 µM	5–7 seeds/Petri dish; 6 Petri dishes/concentration; exposure, 96 h.		Paková et al. (2006)
GPx activity	*Sinapis alba*, *Triticum aestivum*, *Phaseolus vulgaris*	Whole plant	No change	2 µM			
GSH activity	*Sinapis alba*	Whole plant	No change	0.2 µM, 0.02 µM			
	Triticum aestivum		↑				
	Phaseolus vulgaris		↑				
GST activity	*Sinapis alba*	Whole plant	No change	0.2 µM			
	Triticum aestivum		No change				
	Phaseolus vulgaris		↑				
GSR activity	*Sinapis alba*	Whole plant	No change	0.2 µM			
	Triticum aestivum		↑				
	Phaseolus vulgaris		No change				
LPO[f]	*Glomus irregulare*, arbuscular mycorrhizal fungi	Extraradical hyphae	↑	280 µM	Two doses based on previous study in 2009; 6-week exposure to anthracene; 5 replicates.		Debiane et al. (2011)
SOD activity	*Desmodesmus obliquus*	Algal cells	↑	250 µg/L	Exposure, 1–24 h; dose was EC_{50} for growth; $n = 4$, unclear if replicated.		Pokora & Tukaj (2010)
	D. microspina		No change				
	D. subspicatus		No change				
SOD activity	*Scenedesmus armatus*, green alga	Algal cells	↑	0.5 mg/L	Exposure, 1–24 h; 3 replicates.		Aksmann & Tukaj (2004)
mRNA expression: Fds1 (FeSOD isoform)	*Chlamydomonas reinhardtii*, green alga	Algal cells	↑ at 12 and 24 h	5 µM	Exposures, 3–24 h; $n = 4$; unclear if replicated.		Aksmann et al. (2014)
Msd3 (MnSOD isoform)			↓ at 24 h				
Msd5 (MnSOD isoform)			↑ at 12 and 24 h				

Table 4.9 (continued)

Assay	Species, strain (sex), cell line	Tissue	Results[a]	Dose (LED, HID) or concentration (LEC, HIC)[b]	Route[c], duration, dosing regimen	Comments	Reference
CAT activity			↑ only at 24 h	5 µM			Aksmann et al. (2014) (cont.)
Cat1 mRNA expression			↑ only at 24 h				
APx activity			↓	5 µM			
Apx1 mRNA expression			No change				
H_2O_2			↑	5 µM			
H_2O_2			↑	5 µM	Exposures, 0–72 h; repeated 3 times.		González et al. (2021)
$O_2^{\bullet}$			↑	5 µM			
LPO			↑	5 µM			
SOD activity			↑	5 µM			
CAT activity			↑	5 µM			
GSR activity			↑	5 µM			
GPx activity			↑	5 µM			
APx activity			↑	5 µM			
DHAR			No change	5 µM			

APx, ascorbate peroxidase; DHAR, dehydroascorbate reductase; CAT, catalase; DCFH-DA, 2,7-dichlorofluorescein diacetate, DHAR, dehydroascorbate reductase; DMSO, dimethyl sulfoxide; DTT, dithiothreitol; EC_{50}, half-maximal effective concentration; GST, glutathione-*S*-transferase; GPx, glutathione peroxidase; GSH, glutathione; GSR, glutathione reductase; h, hour(s); HIC, highest ineffective concentration; HID, highest ineffective dose; H_2O_2, hydrogen peroxide; Hsp, heat-shock protein; LEC, lowest effective concentration; LED, lowest effective dose; LPO, lipid peroxidation; min, minute(s); MnSOD, manganese superoxide dismutase; NAC, *N*-acetyl cysteine; $O_2^{\bullet}$, superoxide anion radical; POD, peroxidase; SOD, superoxide dismutase; TAOC, total antioxidant capacity; TBARS, thiobarbituric acid reactive substances; UV, ultraviolet.

[a] ↑, increase; ↓, decrease. An arrow (↑ or ↓) indicates a significant difference compared with controls.

[b] If there was a response, the LEC or LED is not listed; if there were no changes, the HIC or HID is listed.

[c] Route for all marine or fresh-water animals was either in seawater or in fresh water. Anthracene was diluted in DMSO or acetone and then in the medium (water/solvent) used.

[d] For CAT, GPx, SOD, GST, and GSR, total protein was used for normalization in all studies and determined using routine assays, such as the Bradford protein assay.

[e] Same species of clam as *Ruditapes decussatus*.

[f] Malondialdehyde–thiobarbituric acid adducts measured; LPO was measured by TBARS.

that these two studies were not informative due to various limitations: small sample size, poor exposure assessment to anthracene, and no adequate adjustments for co-exposures (see also Section 1.6).]

Urinary concentrations of 8-oxodG and several PAHs, including anthracene, were measured in 93 healthy male workers from an electric steel foundry in Tunisia (Hanchi et al., 2017). Cotinine was also measured as a biomarker for smoking and used as an additional predictor variable alongside job title, body mass index, age, and creatinine. Measurement of 8-oxodG and cotinine was performed using LC-MS. Three PAHs were predictors of 8-oxodG: anthracene, phenanthrene, and naphthalene. For anthracene, it was estimated that for each 10-fold increase in urinary anthracene excreted, there was an approximately 2-fold (186%) increase in 8-oxodG excretion (Hanchi et al., 2017). [The Working Group deemed the study of low informativeness because of the lack of longitudinal exposure measurements.]

(ii) Human primary cells

See Table 4.7.

In one study in human primary peripheral blood lymphocytes exposed to increasing concentrations of anthracene (0.05–0.25 μM) for 24 hours, superoxide anion radicals significantly correlated with exposure (r^2 = 0.83, P < 0.05) (Uribe-Hernández et al., 2008). Bhargava et al. (2020), in addition to epigenetic alterations (as reported in Section 4.2.3), also examined the potential of 10 μM anthracene to induce oxidative stress in mitochondria of isolated lymphocytes. Anthracene induced a significant increase in ROS production with a time–response relation from 30 minutes to 3 hours, that levelled off at 6 hours, as measured by CellROX assay. It also induced an increase in NRF2 protein levels (pg/mL; measured by ELISA) and a significant alteration in mitochondrial integrity, with a maximum at 6 hours, attested by an increase in mitochondrial membrane potential (measured with MitoProbe DilC1) (Bhargava et al., 2020).

Conversely, there was no production of superoxide anion radicals in human primary peripheral blood monocytes exposed to anthracene at 10 μg/mL for 24 hours (Fabiani et al., 1999).

[The Working Group considered the study from Uribe-Hernández et al. (2008) to be the most informative of those investigating the effects of anthracene in human primary cells, as it examined the effects of multiple concentrations and made use of the most relevant assays.]

(iii) Human cell lines

The potential effects on oxidative stress of particulate matter with diameter of ≤ 2.5 μm ($PM_{2.5}$) extracts from stoves in the rural Guanzhong Plain, China, were investigated. Levels of individual PAHs (including anthracene) were measured by GC-MS, and $PM_{2.5}$ extracts were used to treat A549 cells (human alveolar basal epithelial cells). ROS were measured by 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA) assay. The levels of anthracene measured in different samples of $PM_{2.5}$ ranged from 0.01 to 1.6 mg/kg. Associations between ROS and PAHs were determined using Pearson correlation coefficients. Exposure to $PM_{2.5}$ extracts caused a concentration-dependent decline in cell viability but an increase in ROS. The correlation values (R) for pyrene, anthracene, and benzo[*a*]anthracene exceeded 0.80 (R = 0.85, 0.81, and 0.80, respectively). Inflammatory tumour necrosis factor alpha (TNFα) and interleukin 6 (IL-6) also exhibited better correlations with these three species than with other PAH species (P < 0.05 for acenaphthylene and acenaphthene, P > 0.05 for the others), demonstrating that the inflammatory response was induced by oxidative stress (Sun et al., 2018). [The Working Group noted that, although $PM_{2.5}$ extracts include several compounds, there was a positive association between anthracene and ROS increase.]

As observed with genotoxicity end-points, anthracene can be activated and modified by sunlight or UV-A or UV-B exposure to two photoproducts, anthrone and 9,10-anthracenedione, leading to phototoxicity (Mujtaba et al., 2011). Significant levels of oxidative stress, measured by DCFH-DA assay, were observed in a human skin epidermal cell line (HaCaT) after exposure to anthracene at all doses tested (0.01–0.5 μg/mL) followed by sunlight or UV-A exposure (Mujtaba et al., 2011). Also, superoxide anion ($O_2^{\bullet}$) and hydroxyl ($^{\bullet}OH$) radical generation were both significantly increased in these cells after anthracene exposure (0.1–1 μg/mL) combined with sunlight, UV-A, or UV-B, further supporting the phototoxicity of anthracene and its potential to elicit significant oxidative stress. Phototoxicity was also observed in non-mammalian models, as described below (Choi & Oris, 2000a, b). [The Working Group considered that the study from Mujtaba et al. (2011) was relevant, based on the evidence for increased oxidative stress induction.]

(b) Experimental systems

(i) Non-human mammalian cells in vitro

See Table 4.8.

The effects of anthracene exposure on several oxidative stress-associated end-points, including DCFH-DA, protein carbonyls, and MDA were assessed in rat cardiomyocytes in vitro. Treatment with anthracene at 10 μM induced a significant increase in protein carbonyls and MDA when compared with controls (Ju et al., 2020). Ju et al. also observed a significant increase in ROS, as measured with DCFH-DA staining, in rat aortic vascular smooth muscle cells exposed to anthracene at 10 μM (Ju et al., 2022).

In another study, significant increases in DCFH-DA, catalase activity, glutathione *S*-transferase (GST) activity, and total glutathione (GSH) were observed after exposure to anthracene at concentrations ranging from 25 to 125 μM in a murine hippocampal neuronal cell line (HT-22) (Olasehinde & Olaniran, 2022).

(ii) Non-mammalian test systems

See Table 4.9.

Several studies investigating the association between anthracene and oxidative stress biomarkers in non-mammalian species were available to the Working Group.

In the common goby, *Pomatoschistus microps*, anthracene (at concentrations ranging from 0.5 μg/L to 4 μg/L) induced significant increases in antioxidant enzyme activity, namely CAT, SOD, and phase II biotransformation markers GPx and glutathione reductase (GSR) in the liver, and decreases in GST (Vieira et al., 2008). In the milkfish, *Chanos chanos* (Forsskal), lipid peroxidation markers (LPO, MDA, and CAT) and phase II biotransformation markers (GST and GSH) were also significantly altered in a dose- and time-dependent manner in various tissues (e.g. gill, head, and dorsal fin) (Palanikumar et al., 2012). Conversely, anthracene treatment did not induce lipid peroxidation in a topminnow (*Poeciliopsis lucida*) hepatoma cell line (PLHC-1) and in a bluegill sunfish (*Lepomis machrochirus*) liver microsome model (Choi & Oris, 2000a, b), except in the presence of UV light. In addition, anthracene exposure did not elicit oxidative stress in a zebrafish (*Danio rerio*) model (St Mary et al., 2021).

Anthracene (at doses ranging from 256 to 1024 μg/L, or 1.44–5.75 μM) induced significant increases in the antioxidant enzymes SOD, CAT, and GPx but not GST in a prawn (*Palaemon serratus*) model; LPO was also significantly increased at 32 μg/L (Gravato et al., 2014). Similarly, anthracene exposure induced significant alterations in numerous antioxidant enzyme activities, as well as superoxide production and LPO markers such as protein carbonyls, in the gills, digestive glands, and haemocytes of molluscs (various Bivalvia). Species differences were observed in the degree of the responses

(dose and time) and tissue sensitivity, with the gill representing the most sensitive tissue tested (Giannapas et al., 2012; Sellami, et al., 2015a, b; Badreddine et al., 2017; Mengqi et al., 2017). Increased gene expression of several antioxidant and heat-shock stress biomarkers (*Cat*, *Hsp70*, *Hsp90*, *MnSod*) was observed in response to anthracene treatment in coral larvae. However, this was followed by a decrease in SOD activity (Overmans et al., 2018). In the microcrustacean water flea (*Daphnia magna*), GST and GPx activities were decreased after anthracene treatment (Feldmannová et al., 2006). Overall increases in ROS, SOD activity, CAT activity, and total antioxidant capacity were also reported in *C. elegans* and *Eisenia fetida* (earthworm) models (Roh et al., 2018; Sun et al., 2020). [The Working Group considered that the doses for these studies in worms to be low but relevant (8–400 µg/L for *C. elegans*; 1–1000 nM for *Eisenia fetida*).]

In several plants (*Marchantia polymorpha* L.*; Sinapis alba*, *Triticum aestivum*, and *Phaseolus vulgaris*), oxidative stress end-points (such as ROS, LPO, peroxidase, and ascorbate peroxidase) were altered, at least one of them significantly, after anthracene exposure (Paková et al., 2006; Spinedi et al., 2021).

Exposure to anthracene at a high concentration (280 µM) also increased LPO in the arbuscular mycorrhizal fungi *Glomus irregulare* (Debiane et al., 2011). Numerous biomarkers were also altered in several algae species, including *Desmodesmus obliquus*, *D. microspina*, *D. subspicatus*, *Scenedesmus armatus*, *Chlamydomonas reinhardtii*, and *Ulva lactuca* (a marine macroalga) (Aksmann & Tukaj, 2004; Pokora & Tukaj, 2010; Aksmann et al., 2014; González et al., 2021).

[The Working Group considered that all the non-mammalian test systems reported above, despite representing different species, environments, or dose regimens, were relevant bioindicators for toxicities that may elicit adverse human health effects. The doses used (especially in studies in molluscs and crustaceans) were highly relevant to human exposures of 0.05–1024 µg/L. The Working Group also considered that phototoxicity is a concern for exposure to anthracene, given that common exposures are from air pollution outdoors and in the sunlight, therefore anthracene photo-modifications should not be overlooked with regard to the carcinogenic potential of anthracene when combined with sunlight.]

4.2.5 Induces chronic inflammation

(a) Humans

(i) Exposed humans

No data were available to the Working Group.

(ii) Human primary cells and cell lines

Two in vitro studies in human cells were available to the Working Group (Lin et al., 2012; Oostingh et al., 2015). In the first study on endothelial dysfunction (Lin et al., 2012), the effects of particles from incense burning in temples were investigated in normal human coronary artery endothelial cells (HCAEC). Cells were treated with extracts of particulate matter (PM) in three size ranges – $PM_{0.1}$ (diameter < 0.1 µm), $PM_{1.0–0.1}$ (diameter between 1.0 and 0.1 µm), and $PM_{10–1.0}$ (diameter between 10 and 1.0 µm) – at a concentration of 50 µg/mL for 4 hours, and concentrations of IL-6, endothelin-1 (ET-1), and nitric oxide (NO) in the medium were measured. Depending on the particle size and parameter analysed, different effects were observed. $PM_{1.0–0.1}$ stimulation resulted in significantly higher IL-6 and ET-1 production than did $PM_{0.1}$ or $PM_{10–1.0}$. Exposure of cells to $PM_{1.0–0.1}$ markedly reduced NO formation, whereas $PM_{10–1.0}$ and $PM_{0.1}$ activated cells to synthesize higher levels of NO than did the controls. Anthracene was more abundant in $PM_{1.0–0.1}$ and $PM_{10–1.0}$ than in $PM_{0.1}$ (ultrafine particles). This study found that the size and composition of these particles were both important factors in inducing cytokine production and reducing NO formation in HCAEC cultures. In

the correlation of PAHs in $PM_{1.0–0.1}$ with NO, a statistically significant inverse correlation (–0.97) was found for anthracene. Anthracene, naphthalene, acenaphthylene, and acenaphthene in $PM_{1.0–0.1}$ were all highly correlated with NO reduction. No significant correlation was observed between PAHs and the other biological end-points. [The Working Group considered that, although the study was well-conducted, the individual components of the PM extracts were not tested alone, therefore, the contribution of anthracene is unknown.]

In the other study (Oostingh et al., 2015), the immunomodulatory effects of nine different PAHs at aqueous solubility in human alveolar basal epithelial cells (A549 cell line) were determined by analysing the cytokine promoter expression of three different inflammatory cytokines (IL-8, TNFα, IL-6) and NF-κB in stably transfected recombinant A549 cell lines. Anthracene did not affect TNFα or IL-6, and caused only a moderate non-statistically significant increase in IL-8 promoter induction. [The Working Group considered that the study was well conducted; however, release of the selected pro-inflammatory cytokines was not measured.] Anthracene did not induce pro-inflammatory cytokine (IL-8, TNF-α, IL-6) transcription activity in A549 cells. [The Working Group considered that, on the basis of these in vitro studies, it is not clear whether anthracene has inflammatory potential in vitro.]

(b) Experimental systems

Six studies in experimental systems were available to the Working Group (Forbes et al., 1976; Brune et al., 1978; JBRC, 1994a, b, c, d).

In the study by Forbes et al. (1976), anthracene (0.1 g/L, diluted in methanol, 40 µL) did not induce any alterations when applied to the skin (20 cm^2) of Skh: hairless-1 outbred mice. When the same mice were irradiated with solar-simulator radiation after exposure to anthracene (0.1 g/L in methanol; 40 µL per 20 cm^2) (see Section 3, Cancer in Experimental Animals), there was a more severe skin response than in mice whose skin had been pre-treated with the irradiated vehicle; inflammatory changes (oedema and redness) were visible by 6 hours, but no longer visible after 48 hours. Under the above experimental conditions, anthracene in the absence of solar irradiation did not induce skin inflammation (Forbes et al., 1976).

Brune et al. (1978) compared the inflammatory, tumour-initiating, and tumour-promoting activities of several compounds, including anthracene, applied to the NMRI mouse ear. The ID_{50} (irritant dose required to produce a discernible irritant reaction in 50% of the population; as assessed by standard methods at 24 hours after the administration of anthracene) was 6.6×10^{-4} mmol/ear, that is, anthracene was 10 times less potent than the other aromatic hydrocarbons tested (DMBA and B[a]P) and did not have an irritant effect. There was no detectable production of prostaglandin E_2 (PGE_2) or initiation–promotion activity (in a standard experiment with TPA as promoter). [The Working Group considered this study to be of low informativeness since many details were missing, including the supplier and the purity of the chemicals used (which were obtained from commercial sources and purified by recrystallization), and the sex and number of animals tested.]

Two dose-finding studies for carcinogenicity tests that complied with GLP were conducted by the Japan Bioassay Research Center (JBRC, 1994a, b, c, d). Groups of 5 (2-week study) or 10 (13-week study) male and female Crj:BDF_1 mice or F344/DuCrj rats (age, 5 weeks) were treated with feed containing anthracene (purity, ≥ 97.9%) at a dose of 0, 80, 400, 2000, 10 000, or 50 000 ppm for 2 or 13 weeks (JBRC, 1994a, b, c, d). In both studies, there was no significant increase in histopathology findings suggesting chronic inflammation. [The Working Group considered that the results from these studies were not sufficient

to show a chronic inflammatory potential for anthracene in experimental systems.]

4.2.6 Is immunosuppressive

(a) Humans

(i) Exposed humans

No data in exposed humans were available to the Working Group.

(ii) Human cell lines

Two in vitro studies using human cells were available to the Working Group (Zhao et al., 1996; Oostingh et al., 2015). Zhao et al. (1996) investigated the effect of several PAHs, including anthracene, on cloned Ca^{2+}-ATPases (SERCA1, SERCA2a, and SERCA3, which are involved in Ca^{2+}-dependent pathways of T-cell and B-cell activation) that were transiently expressed in human embryonic kidney (HEK) cells. The purpose of the study was to determine whether PAHs directly inhibited cloned SERCA enzymes and whether there was any selectivity for certain isoforms. All PAHs tested, including anthracene, had little inhibitory effect on any of the SERCA enzymes tested, indicating that metabolism might be required for PAH-induced inhibition, or that other cellular elements not present in the HEK transfection model might be required for activity. Davila et al. (1996) and Krieger et al. (1994) had previously published a study on the immunotoxicity of several PAHs (7,12-dimethylbenz[*a*]anthracene, B[a]P, dibenz-[*a*,*h*]anthracene, and 9,10-dimethylanthracene) in murine and human lymphocytes as well as in B- and T-cell lines. In all studies, anthracene gave negative results.

In a study by Oostingh et al. (2015), anthracene showed either no effects or a moderate, not statistically significant increase in IL-8 promoter induction in A549 cells. [The Working Group considered that this study was well conducted; however, it was noted that A549 cells are not immune system cells; also, the model was considered not relevant to address immunosuppression. The Working Group considered that the in vitro studies did not show immunosuppressive effects with anthracene.]

(b) Experimental systems

(i) Non-human mammals in vivo

White et al. (1985) investigated the immunotoxic potential of several PAHs, including anthracene (160 µmol/kg per day by subcutaneous injection, in corn oil), in female B6C3F_1 mice, using a well-established protocol (14-day exposure followed by injection of sheep erythrocytes and assessment of splenic antibody-forming cells at day 4). Anthracene did not reduce the antibody response; on the contrary, an increase of 37% was observed. No changes in thymus weight or body weight were observed. [The Working Group considered this study to be informative; however, no signs of immunosuppression were observed.]

Silkworth et al. (1995) investigated the immunotoxic potential of 15 PAHs by assessing their ability to suppress the antibody response to sheep erythrocytes. In C57BL/6 ($Ah^{+/+}$) mice immunized 12 hours after a single oral dose of anthracene at 0.1, 1, 10, or 100 mg/kg, anthracene had no effect on the immune response to sheep erythrocytes. [The Working Group considered this study to be informative, and the end-point (antibody response to T-cell-dependent antigen) to be very relevant for the measurement of immunotoxicity, specifically immunosuppression. However, the results did not support an immunosuppressive effect of anthracene.]

The study by Wang & Xue (2015) (also reviewed in Section 3, Cancer in Experimental Animals) investigated the ability of several PAHs, including anthracene, to induce solid tumours (e.g. in the liver, stomach, and kidney) and the roles of these PAHs in immune response regulation via the assessment of serum IL-2 and IL-6 levels. These two cytokines were selected

because the effect of PAHs on their production is largely unknown. IL-2 is a T-cell growth factor that enhances the cytotoxic activity of T-cells, and IL-6 is a multi-effect cytokine produced by endothelial cells, monocytes/macrophages, and lymphoid cells. In cancer, the predominant role of IL-6 is the promotion of tumour growth. SPF Kun Ming mice were randomly divided into groups of 10 males and 10 females and intraperitoneally injected with 10 daily doses of DMSO (control) or anthracene (50 mg/kg). The mice were examined once daily for 3 months. There were no changes in serum IL-6 levels, and a decrease in serum IL-2 levels was not statistically significant – control group ($n = 20$), 360 ± 16 ng/L; anthracene-treated group ($n = 18$), 154 ± 5 ng/L. [The Working Group considered that this study showed a slight reduction in serum IL-2, which may be supportive of immunosuppressive effects. However, the study had several drawbacks that limited the relevance of the findings, including that there was no blind assessment of the slides, the qualifications of the pathologist were not mentioned, the results were not separated according to sex, and it was not specified whether results were expressed as mean ± standard deviation or standard error.]

In the dose-finding studies for a carcinogenicity test reported in the previous section, few changes in immune status parameters were observed (JBRC, 1994a, b, c, d).

In the 2-week study in male mice, there was a significant decrease in erythrocyte count and an increase in platelet count after exposure to anthracene at concentrations of ≥ 10 000 ppm (approximately equal to 1823 mg/kg bw), and there were decreases in haemoglobin and haematocrit at 50 000 ppm (approximately equal to 9725 mg/kg bw). In female mice, there was a decrease in leukocyte count after exposure to anthracene at 50 000 ppm (approximately equal to 7690 mg/kg bw), an increase in platelet count at ≥ 10 000 ppm (approximately equal to 1472 mg/kg bw), and decreases in haemoglobin and haematocrit.

In the 13-week study in mice, no changes in leukocyte count were found in males, but there were significant decreases in erythrocyte count, haemoglobin, and haematocrit, and increases in mean corpuscular volume and platelets in males exposed to anthracene at concentrations of ≥ 10 000 ppm. In females, there was a decrease in leukocyte count at 10 000 ppm, a significant decrease in erythrocytes at ≥ 2000 ppm (approximately equal to 287 mg/kg bw), an increase in platelets at ≥ 10 000 ppm, and decreases in haemoglobin and haematocrit. In addition, there was a significant increase in absolute and relative weights of the spleen in males at 50 000 ppm. There was also an increase in the incidence of extramedullary haematopoiesis in the spleen of males at ≥ 400 ppm (approximately equal to 73 mg/kg bw) and females at ≥ 10 000 ppm.

In the 2-week study in rats, there were significant decreases in erythrocyte count, haemoglobin, and haematocrit in males exposed to anthracene at ≥ 2000 ppm and in females at ≥ 400 ppm. There was a significant increase in absolute and relative weights of spleen in males and females at ≥ 400 ppm.

In the 13-week study in male rats, there were significant decreases in erythrocyte count and haemoglobin and increases in mean corpuscular volume and platelet count at ≥ 400 ppm, and a decrease in haematocrit at ≥ 10 000 ppm. In females, there were significant decreases in erythrocyte count, haemoglobin, and mean corpuscular haemoglobin concentration, and increases in mean corpuscular volume and platelet count at ≥ 400 ppm, and a decrease in haematocrit at ≥ 2000 ppm. There was a significant decrease in absolute and relative weights of the thymus in males at 50 000 ppm, and a significant increase in absolute and relative weights of the spleen in males and females at ≥ 400 ppm. There was also a significant increase in the incidence of engorgement of erythrocytes in the spleen of males and females at ≥ 400 ppm, and a significant increase in the incidence of haematopoiesis in the bone

marrow of males at ≥ 2000 ppm and of females at ≥ 400 ppm (JBRC, 1994a, b, c, d). [The Working Group noted that changes in immune status parameters were observed only occasionally. These changes were inconsistent between species and sexes, with no dose–response relation, and were thus not supportive of immunosuppression.]

(ii) Non-human mammalian cells in vitro

Sonnenfeld et al. (1984) investigated the effects of several aromatic compounds, including anthracene, on polyriboinosinic:polyribocytidylic acid (poly I:C)-induced production of interferon alpha or beta (IFNα, IFNβ) (important in body defences against viral infection and with antitumour effects). Primary mouse fibroblasts were exposed in vitro for 24 hours to anthracene (10 or 100 μM) and then treated with poly I:C. At non-cytotoxic concentrations, anthracene did not affect IFNα and IFNβ production; non-statistically significant decreases of 17% and 27% were observed at 10 and 100 μM, respectively (Sonnenfeld et al., 1984). [The Working Group noted that fibroblasts are not immune cells and considered that the model was not relevant to address immunosuppression.]

[Overall, the Working Group noted that results from studies in experimental systems did not support a potential immunosuppressive effect for anthracene.]

4.2.7 Modulates receptor-mediated effects

(a) Humans

(i) Exposed humans

No data in exposed humans were available to the Working Group.

(ii) Human cell lines

See Table 4.10.

The effects of anthracene on the activation of estrogen receptor (ER), androgen receptor (AR), glucocorticoid receptor (GR), early growth response protein 1 (EGR-1), peroxisome proliferator-activated receptor alpha and beta/delta (PPARα, PPARβ/δ), constitutive androstane receptor (CAR), and the aryl hydrocarbon receptor (AhR) were investigated.

Two studies investigated the effect of anthracene on ER activation in a human breast carcinoma cell line (MCF-7) (Vondrácek et al., 2002; Gozgit et al., 2004). In the study by Vondrácek et al. (2002), several PAHs, including anthracene, were found to act as very weak inducers of ER-mediated activity in MCF-7 cells stably transfected with a luciferase reporter gene. The induction of luciferase was statistically significant at 6 hours with anthracene at ≥ 5 μM but not sufficient to calculate the induction equivalent factor (the ratio between the concentration of 17β-estradiol that was 25% effective and the concentration of PAH inducing the same level of luciferase activity). [The Working Group considered that the two studies above were informative and of good-quality design.]

Gozgit et al. (2004) investigated the estrogenicity of PAHs in the MCF-7 cell line, testing 14 PAHs for their ability to bind to either the ER or the AhR and to activate target gene expression. PAHs were tested at concentrations of 0.01–5 μM. PAHs that caused induction of estrogen-response element (ERE)-mediated luciferase expression were further studied using quantitative reverse transcription-polymerase chain reaction (qRT-PCR) to evaluate the expression of estrogen-responsive genes (HEM45, progesterone receptor, and pS2) and an aryl hydrocarbon-responsive gene (*CYP1A1*) in MCF-7 cells. Under conditions permissive of metabolism, anthracene was a weak inducer of ER-reporter luciferase activity (mean fold increase, 1.85) but did not induce mRNA expression of the three estrogen-responsive genes (HEM45, progesterone receptor, and pS2) or CYP1A1 mRNA expression, suggesting that the ER-reporter gene assay may detect concentrations of toxicants that are not physiologically active.

Table 4.10 End-points relevant to modulation of receptor-mediated effects with anthracene in human cells in vitro

End-point	Assay	Species, strain (sex), cell line	Tissue	Results	Dose or concentration	Route, duration, dosing regimen	Comments	Reference
CAR	Cell-based luciferase reporter assay	HepG2 cells	Liver	No differences	25 and 50 μM	24 h		
ER	[^{3}H]estradiol displacement	MCF-7 cells	Breast, adenocarcinoma	No differences	0–2 mM	10 min	Sigma; recrystallization and HPLC to ensure purity.	Chang & Liao (1987)
ERα	Luciferase reporter gene	MVLN cell line	Mammary gland, adenocarcinoma	No differences	Up to 400 μg/mL	72 h	Purity, 99%.	Villeneuve et al. (2002)
ERα	ERα CALUX	VM7Luc4E2 cell line	Mammary gland, adenocarcinoma	Weak activator, EC_{50} = 0.12 ± 0.02 mM	Up to 10 mM	19–22 h	Sigma, purity not reported.	Boonen et al. (2020)
PPARγ	PPARγ CALUX	U2OS cells	Osteosarcoma	Weak activator, EC_{50} = 0.13 ± 0.8 mM	Up to 10 mM	24 h	Sigma, purity not reported.	Boonen et al. (2020)

CALUX, chemical activated luciferase gene expression; CAR, constitutive androstane receptor; EC_{50}, half-maximal effective concentration; ER, estrogen receptor; h, hour(s); HPLC, high-performance liquid chromatography; min, minute(s); PPARγ, peroxisome proliferator-activated receptor gamma.

Concerning effects on other receptors, two studies were available: Kizu et al. (2003) and Kim et al. (2005). In the study by Kizu et al. (2003), the role of AhR on the anti-androgenic effects of PAHs was studied in human prostate carcinoma cells (LNCaP). The aims of the study were to determine whether AhR is involved in the anti-androgenicity of PAHs, and to obtain information on the molecular mechanisms of AhR-mediated anti-androgenic effects. Contrary to other PAHs, anthracene (1 μM) did not act as an AhR agonist, did not show anti-androgenic effects, and did not inhibit binding of the AR (in nuclear extracts) to oligonucleotide probes containing the AR-responsive element.

Kim et al. (2005) evaluated the ability of 15 PAHs to activate the EGR-1 gene and binding to PPARα and PPARβ/δ in cultures of human lung adenocarcinoma cells (A549) and human colorectal adenocarcinoma cells (HCT-116). The luciferase reporter gene was used to measure the activity of PPARs and transactivation of the EGR-1 promoter. Anthracene at 10 μM caused a significant increase in luciferase activity mediated by EGR-1, PPARα, and PPARβ/δ, which may be relevant in tumour progression and inflammation.

[The Working Group noted that, overall, data suggest that anthracene has weak estrogenic activity; however, this was not sufficient to calculate the induction equivalent factor or to induce mRNA expression of estrogen-responsive genes or CYP1A1 mRNA expression, suggesting that the ER-reporter gene assay may detect anthracene effects that do not result in biological activity. Concerning other receptors, anthracene caused a significant increase in EGR-1, PPARα, and PPARβ/δ luciferase activity, but no activation of AhR or activation/inhibition of AR was observed.]

(b) *Experimental systems*

See Table 4.11.

(i) *Non-human mammals in vivo*

Three studies were available to the Working Group (Chaloupka et al., 1994; Shimada et al., 2002; Yang et al., 2019). The study by Chaloupka et al. (1994) investigated the effect of several tricyclic hydrocarbons on hepatic microsomal methoxyresorufin *O*-demethylase (MROD) activity, Cyp1A2 and Cyp1A1 mRNA expression, and AhR binding in $B6C3F_1$ mice. Male $B6C3F_1$ mice were treated intraperitoneally with anthracene (0, 50, 100, 200, 300 mg/kg), and hepatic microsomal MROD activity was determined fluorimetrically 24 hours after treatment. Although it induced dose-dependent hepatic microsomal MROD activity and CyP1A2 expression without co-induction of CyP1A1, anthracene did not competitively displace radiolabelled 2,3,7,8-tetrachlorodibenzo-*p*-dioxin or B[a]P ([^{3}H]TCDD or [^{3}H]benzo[*a*]pyrene) from the mouse hepatic cytosolic AhR or the 4S carcinogen-binding protein. These data indicate that the induction of Cyp1A2 is independent from AhR activation. [The Working Group noted that this study was well conducted and informative.]

Shimada et al. (2002) investigated the effects of several PAHs and polychlorinated biphenyls on the induction of CYP1A1, 1A2, and 1B1 mRNA in the liver and lung of $AhR^{(+/+)}$ and $AhR^{(-/-)}$ mice of strain C57BL/6J. PAHs, including anthracene, and polychlorinated biphenyls were intraperitoneally injected at a dose of 100 mg/kg (olive oil was used as vehicle control). The mice were killed after 72 hours. Anthracene weakly induced expression of CYP1A1, 1A2 and 1B1 mRNA in the liver of $AhR^{(+/+)}$ mice. In $AhR^{(-/-)}$ mice, no induction was observed, indicating that the induction of CYP1A1, 1A2, and 1B1 occurred through an AhR-dependent mechanism. [The Working Group judged this study to be of low relevance because the number of animals investigated and statistical significance were not reported.]

Yang et al. (2019) investigated the effects of exposure to phenanthrene and anthracene on

Table 4.11 End-points relevant to modulation of receptor-mediated effects with anthracene in non-human mammalian systems in vivo and in vitro

End-point	Assay	Species, strain (sex), cell line	Tissue	Results[a]	Dose or concentration	Route, duration, dosing regimen	Comments	Reference
AhR	[^{3}H]TCDD or [^{3}H]-benzo[*a*]pyrene displacement	Mouse, B6C3F$_1$ (M)	Liver	No differences	50, 100, 200, 300 mg/kg	i.p., 24 h, single	Purity, 99%	Chaloupka et al. (1994)
MROD activity		Mouse, B6C3F$_1$ (M)	Liver	↑	50, 100, 200, 300 mg/kg	i.p., 24 h, single	Purity, 99%	
CYP1A2	Northern blot	Mouse, B6C3F$_1$ (M)	Liver	↑	50, 100, 200, 300 mg/kg	i.p., 24 h, single	Purity, 99%	
CYP1A1	Northern blot	Mouse, B6C3F$_1$ (M)	Liver	No differences	50, 100, 200, 300 mg/kg	i.p., 24 h, single	Purity, 99%	
CYP1A1, 1A2, 1B1	RT-PCR	Mouse, C57BL/6	Liver	(↑), weak induction only in AhR$^{(+/+)}$ mice	100 mg/kg	i.p., 72 h, single	Highest purity. Limitations: small sample size; no statistics reported.	Shimada et al. (2002)
CYP2B10	Real-time-PCR	Mouse, C57BL/6	Liver	No differences	350 mg/kg	Oral, 4 days, animals were killed 24 h after the last dose	From NTP repository. Limitations: lack of randomization, lack of blinding assessment for the animal studies, and the number of independent experiments performed for the in vitro experiments was not reported.	Yang et al. (2019)
AhR	Luciferase reporter gene	Rat, H4IIE-Luc hepatoma cell line	Hepatocarcinoma	No differences	Up to 400 µg/mL	72 h	Purity, 99%.	Villeneuve et al. (2002)
AhR	Luciferase reporter gene	Mouse, H1L1.1c2 hepatoma cell line	Hepatocarcinoma	No differences	Up to 10 µM	3 h	Sigma; purity, NR.	Ziccardi et al. (2002)
AhR	[^{3}H]TCDD displacement from AhR	Mouse, liver cytosol from C57BL/6N	Liver	+, 50 ± 8% displacement	1 µM	1 h	Sigma; purity, NR.	Bigelow & Nebert (1982)

Table 4.11 (continued)

End-point	Assay	Species, strain (sex), cell line	Tissue	Results[a]	Dose or concentration	Route, duration, dosing regimen	Comments	Reference
CYP1A1	Western blot	Rat, Fischer 344	Hepatocytes	No differences	10 µM	48 h	Purity, > 99%. Western blot not quantifiable.	Safa et al. (1997)
CYP2C11	Western blot	Rat, Fischer 344	Hepatocytes	+, ↓ 37%	10 µM	48 h		
AhR	[^{3}H]TCDD displacement	Rat, Fischer 344	Liver cytosol	Weak activator (IC_{50} binding affinity, > 100 µM AhR activation, 570 µM	Various concentrations tested	1 h		
AhR	AhR-CALUX	Mouse, H1L77.5c1	Hepatocarcinoma	Weak activator (no EC calculable, a fold induction of 1.60 ± 0.19 was calculated)	Up to 10 mM	48 h	Sigma; purity, NR.	Boonen et al. (2020)
AR	[^{3}H]R1881 displacement	Rat, Sprague-Dawley, tissue homogenate	Ventral prostate	No differences	0–2 mM	10 min	Sigma, recrystallization and HPLC to ensure purity.	Chang & Liao (1987)
GR	[^{3}H]dexamethasone displacement	Rat, Sprague-Dawley, tissue homogenate	Liver	No differences	0–2 mM	10 min	Sigma, recrystallization and HPLC to ensure purity.	
AhR	Yeast-based bioassay	*Saccharomyces cerevisiae* strain, YCM3	Yeast	Weak activator (< 25% of the maximal β-NF activity)	10 µM	18 h	Purity, > 99%.	Alnafisi et al. (2007)
ER	Yeast two-hybrid system	Y190	Yeast	No differences	Up to 1 mg/mL	NR	Purity, 99%.	Kurihara et al. (2005)

AhR, aryl hydrocarbon receptor; AR, androgen receptor; CALUX, chemical activated luciferase gene expression; CYP, cytochrome P450; EC, effective concentration; ER, estrogen receptor; GR, glucocorticoid receptor; h, hour(s); HPLC, high-performance liquid chromatography; IC_{50}, half-maximal inhibitory concentration; i.p., intraperitoneal; min, minute(s); MROD, methoxyresorufin *O*-demethylase; β-NF, beta-naphthoflavone; NR, not reported; NTP, National Toxicology Program; RT-PCR, reverse transcription-polymerase chain reaction; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

[a] +, positive; ↑, increase; ↓, decrease; (↑), decrease, not quantitated.

the liver, and the underlying mechanisms. In the study, C57BL/6 mice and human hepatocytes (HepG2 cells and primary human hepatocytes) were used. Phenanthrene or anthracene (350 mg/kg per day) was orally administered daily to groups of 5–6 C57BL/6 male mice (age, 8 weeks) for four consecutive days. Corn oil was used as the vehicle. This study demonstrated that phenanthrene, but not anthracene, effectively activates both human and mouse nuclear receptor CAR and induces promoter activity and gene expression of human CYP2B6 and mouse CYP2B10, and that CAR is essential for mediating phenanthrene-induced hepatotoxicity. [The Working Group identified some limitations, including the lack of randomization, lack of blinding assessment for the animal studies, and the fact that the number of independent experiments performed for the in vitro experiments was not reported.]

[The Working Group noted that the role of AhR in anthracene-induced hepatic enzymes in vivo remains unclear since contradictory results were reported. Both studies, however, demonstrated the induction of CYP1A2. No CAR activity was observed.]

(ii) Non-human mammalian cells in vitro

Six studies investigated the effect of anthracene on AhR activation. Two studies showed no activation (Villeneuve et al., 2002; Ziccardi et al., 2002), whereas the other studies reported weak or very poor activation (Bigelow & Nebert, 1982; Safa et al., 1997; Alnafisi et al., 2007; Boonen et al., 2020). In the study by Alnafisi et al. (2007), anthracene caused very weak AhR signalling (less than 25% of the maximal activity of β-naphthoflavone) at a high concentration (10 μM). In the study by Boonen et al. (2020), anthracene showed weak AhR agonist activity (effective concentration, EC_{50}, not determined; induction, 1.60 ± 0.19-fold) in the AhR-CALUX bioassay. [The Working Group noted that, overall, in vitro data indicate that anthracene has no effect on AhR activation or very modest effects that are observed only at high concentrations, compared with other polycyclic hydrocarbons.]

Four studies investigated the effect of anthracene on ER activation. Three studies showed no activation (Chang & Liao, 1987; Villeneuve et al., 2002; Kurihara et al., 2005), whereas Boonen et al. (2020) reported weak ER activation. In the study by Boonen et al. (2020), anthracene had weak ERα agonist activities (EC_{50} = 1.21 ± 0.62 × 10^{-5} M; induction, 1.62 ± 0.10-fold) in the ERα-CALUX bioassay. In the PPARγ-CALUX bioassay, anthracene showed weak agonistic activity (EC_{50} = 1.27 ± 1.8 × 10^{-4} M; induction, 1.36 ± 0.22-fold).

Jung et al. (2001) investigated the effects of several nitrated PAHs and azoarenes in a fish hepatoma cell line (PLHC-1). Anthracene was tested only in one experiment, and no induction in ethoxyresorufin-*O*-deethylase (EROD) activity was observed. [The Working Group noted that this study, although relevant for ecotoxicological evaluation, was not considered to be relevant since the transferability of results to humans is questionable.]

[The Working Group noted that, overall, there was no strong consensus in the literature on the effects of anthracene on AhR, ER, and other nuclear receptors. Some results suggested that anthracene may have multiple modes of action and may activate or inhibit multiple receptor-signalling pathways known to play critical roles in mediating endocrine disruption. However, where observed, these effects were shown at high concentrations, several orders of magnitude higher than for other PAHs.]

4.2.8 Causes immortalization

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

See Table 4.12.

(i) Non-human mammals in vivo

Three studies evaluated the effects of anthracene on the morphological transformation of embryo cells derived from pregnant animals. In the study by DiPaolo et al. (1972), cloned Balb/3T3 embryonic fibroblast cell lines were exposed to 0.1% anthracene in vitro for 48 hours; transformed colonies were counted and reseeded. To assess for tumourigenicity, transformed cells were injected subcutaneously into X-irradiated and non-irradiated weanling Balb/c mice and assessed after 13–35 days. The same group treated pregnant Syrian Golden hamsters with 0.5 mL of anthracene (1.0–3.0 mg/100 g maternal weight) by intraperitoneal injection on days 10–11 of gestation. Embryos were excised 48–72 hours after the injection and cells from the whole embryo were cultured in vitro. Derived transforming colonies were finally injected into X-irradiated weanling male hamsters and tumourigenicity was assessed (DiPaolo et al., 1973). In a third study (Evans & DiPaolo, 1975), growth in soft agar was assessed for primary embryonic fibroblast-like cells derived from pregnant inbred syngeneic strain 2 Sewall Wright guinea-pigs on day 32 of gestation and exposed to anthracene at a dose of 0.5 µg/mL in medium. Finally, transformed colonies were injected into X-irradiated guinea-pigs and assessed for tumourigenicity. All three studies gave negative results.

(ii) Non-human mammalian cells in vitro

The Working Group identified 21 relevant original in vitro studies related to morphological transformation and immortalization. Of these, four studies investigated tumorigenicity in addition to morphological transformation (DiPaolo et al., 1972; Evans & DiPaolo, 1975; Pienta et al., 1977; Laaksonen et al., 1986). Three studies used fetal cells (DiPaolo et al., 1972; Evans & DiPaolo, 1975; Pienta et al., 1977), and one study used newborn mouse skin fibroblasts, treated in vitro (Laaksonen et al., 1986). [The Working Group noted that in all four studies, anthracene gave negative results (no morphological transformation, no tumours), whereas several other chemicals, such as B[a]P, 3-MC, or DMBA, gave positive results.]

In a series of studies, Laaksonen et al. (1983, 1984, 1986) found anthracene to give negative results in cell transformation assays. Foci formation in nude mouse fibroblasts was increased by B[a]P, 3-MC, and benz[*a*]anthracene (Laaksonen et al., 1983), and 3-MC increased SV40-induced cell transformation (Laaksonen et al., 1984, 1986), whereas anthracene gave negative results in all these studies. Similarly, in a study by Lubet et al. (1983), anthracene gave negative results whereas B[a]P, DMBA, and 3-MC gave positive results in the C3H/10T1/2 clone 8 cell transformation assay.

The Bhas 42 cell transformation assay (carried out in BALB/c 3T3 murine cells transfected with v-Ha-*ras*) was used by Asada and co-workers (Asada et al., 2005) to compare the initiation and promotion capacity of several PAHs. Anthracene gave negative results. The Bhas 42 cell transformation assay was also used in a validation study conducted by three laboratories (Sakai et al., 2011). Anthracene gave negative results in the initiation assay in three laboratories, but positive results in the promotion assay in one laboratory. [The Working Group noted that in the laboratory in which the positive result was obtained, the solvent control (DMSO, 0.5%) gave 1.8 ± 1.3 foci/well, and there was a dose-dependent and statistically significant increase in the number of foci in wells treated with anthracene (1.25 µg/mL, 5.5 ± 2.3 foci/well; 2.5 µg/mL, 6.7 ± 2.3 foci/well; 5 µg/mL, 6.7 ± 4.4 foci/well; 10 µg/mL, 9.8 ± 4.4 foci/well; and 20 µg/mL, 10.2 ± 3.5 foci/well). The solvent control gave somewhat higher results in the other two laboratories, where it was 2.3 ± 1.0 and 2.3 ± 1.2 foci/well. The positive controls, 3-MC for the initiation assay and TPA for the promotion assay, gave clearly positive results (> 14 foci/well). However, the purity of anthracene (from Aldrich) was not reported. The

Table 4.12 End-points relevant to immortalization with anthracene in non-human mammals in vivo and in vitro

End-point	Assay or method	Species, strain (sex), cells	Study design, culture time	Dose or concentration	Results[a]	Comments	Reference
Morphological transformation	Visual assessment	Mouse, Balb/3T3, clones of embryonic fibroblasts Mouse, Balb/3T3 (F), irradiated weanling mice	Cells treated for 48 h and cultured for 8 days (n = 5) Tumourigenicity, subcutaneous inoculation of 10^6 transformed (30 colonies) or non-transformed (20 colonies) cells Mice (10/point), maintained for 180 days	10 µg/mL	–	Source and purity of chemicals, NR; solvent (acetone, ≤ 0.1% in medium); anthracene used as negative control.	DiPaolo et al. (1972)
Tumourigenicity of inoculated cells	Palpation, histology						
Morphological transformation Tumourigenicity	Visual assessment Palpation, histology	Hamster, Syrian Golden (F), pregnant Hamster, Syrian Golden (M), weanling	Pregnant animals (n = 4) at days 10–11 of gestation were injected intraperitoneally Cells from embryos prepared for culture on day 13 10^7 cells from colonies injected subcutaneously into irradiated male hamsters Hamsters were observed for tumour development for 1 yr	1–3 mg/100 g	–	Purity, NR; treatment of pregnant hamsters varied from 48 to 72 h; solvent (70% ethanol, DMSO, or trioctanoin) control and several positive-control chemicals included (e.g. B[a]P, DMBA).	DiPaolo et al. (1973)

Table 4.12 (continued)

End-point	Assay or method	Species, strain (sex), cells	Study design, culture time	Dose or concentration	Results[a]	Comments	Reference
Morphological transformation Immortalization Tumourigenicity	Visual assessment; microscopy Growth of colonies in soft agar NR	Guinea-pig (F), pregnant; and guinea-pig fetal cells; days 32–49 of gestation Guinea-pig, irradiated syngeneic newborns	Anthracene was administered in utero (32-day fetus), or during in vitro culture of fetal cells, passage 68; 4–24 mo of continuous culture; $n = 6$ Inoculation of 10^8 cells; guinea-pigs were observed for 1 year for tumour development; $n = 6$	0.5 µg/mL medium	–	Synthetic-grade anthracene, purity, NR; under similar conditions, DMBA gave positive results; negative control, acetone (solvent).	Evans & DiPaolo (1975)
Morphological transformation Tumourigenicity	Stereomicroscopy after Giemsa staining Palpation, histology	Hamster, Golden Syrian, embryo cells, cryopreserved primary cultures Non-immuno-suppressed suckling hamsters	Cells were previously tested with 3-MC; anthracene treatment, 8 days; $n = 6$ 10^6 cells inoculated; animals were followed for ≥ 6 mo	1, 5, 10, 25, 50 µg/mL medium	–	Purity, NR; solvent control, 0.2% DMSO; other tested chemicals induced transformation.	Pienta et al. (1977)
Morphological transformation	Visual assessment after Giemsa staining	Mouse, NMRI nu/nu (nude) newborn, skin fibroblasts	Incubation for 25 days after treatment	14, 28, 56, 112 µM; 16 dishes/dose	–	Purity, NR; positive controls, PAHs; negative control, DMSO (solvent).	Laaksonen et al. (1983)
Morphological transformation	Scoring after Giemsa staining	Mouse, NMRI nu/nu (nude) newborn, skin fibroblasts	Anthracene for 72 h, SV40 for 2 h, follow-up for 25 days	14 and 28 µM +/–SV40	–	Purity, NR; 3-MC positive; negative controls, DMSO + SV40 and medium + SV40.	Laaksonen et al. (1984)

Table 4.12 (continued)

End-point	Assay or method	Species, strain (sex), cells	Study design, culture time	Dose or concentration	Results[a]	Comments	Reference
Morphological transformation Tumourigenicity	Counting foci after Giemsa staining Inspection	Mouse, NMRI nu/nu (nude) newborn, skin fibroblasts Adult nude mice (F) (10/group)	SV40 for 2 h followed after 24 h by treatment with PAH for 3 days 10×10^6 cells from transformed foci were inoculated; mice were followed for their lifetime	Concentration, NR	–	Purity, NR; very poor data about anthracene experiments (concentration and time, NR); 3-MC gave a positive result.	Laaksonen et al. (1986)
Morphological transformation	Scoring after Giemsa staining	Mouse, C3H 101/2 clone 8	24 h treatment, 4–6 wk culture for foci	3, 10, 30 µg/mL medium	–	Purity, NR; solvent controls gave negative results; some tested chemicals induced transformation.	Lubet et al. (1983)
Morphological transformation	Visual assessment after Giemsa staining	Mouse, v-Ha-*ras*-transfected BALB/c 3T3 (Bhas 42) cells	Initiation assay (2-day treatment): cells were treated with anthracene until day 3 and fixed on day 24 Promotion assay (12-day treatment): fresh medium containing anthracene was applied on days 3, 7, and 10; fresh medium without chemical was applied on day 14; cells were fixed on day 21	0–10 µg/mL	–	Purity, NR; negative control, solvent; B[a]P was the positive control in the initiation assay, TPA was the positive control in the promotion assay.	Asada et al. (2005)

Table 4.12 (continued)

End-point	Assay or method	Species, strain (sex), cells	Study design, culture time	Dose or concentration	Results[a]	Comments	Reference
Morphological transformation	Visual assessment after Giemsa staining (criteria for positivity defined)	Mouse, v-Ha-*ras*-transfected BALB/c 3T3 cell line (Bhas 42)	Validation study in 6 (anthracene in 3) laboratories from 3 countries Initiation assay: treatment for 72 h, cells were fixed on day 21 Promotion assay: treatment on days 4, 7, and 11, fresh medium on day 14	0–50 µg/mL	–, In 3 of 3 laboratories in initiation assay +, In 1 of 3 laboratories in promotion assay (dose-dependent, statistically significant increase)	Purity, NR; negative control, solvent; positive controls, 3-MC for the initiation assay and TPA for the promotion assay.	Sakai et al. (2011)
Morphological transformation Immortalization	Stereomicroscopy after staining Growth of transformed cells in soft agar	Hamster, Syrian, kidney cells (BHK 21/Cl 13)	Anthracene treatment for 18 h, S9 mix added; centrifuged cells cultured for 6 days	0.025, 0.25, 2.5, 10, 25, 250 µg/mL	+, Increase in transformation rate at LC_{50} (25 µg/mL), 1.4, but no dose–response relation; results of growth in soft agar, NR	Purity, NR; negative control, DMSO; B[a]P, chrysene, and 3-MC gave the highest positive results.	Greb et al. (1980)
Morphological transformation	Infrared spectroscopy scoring	Hamster, Syrian, embryo cells (SHE)			+, Transformation rates: anthracene, 5.58%; D-mannitol, 3.36%; and B[a]P, 17.2%	B[a]P and 3-MC as positive controls; D-mannitol as negative control.	Ahmadzai et al. (2012)
Morphological transformation	Microscopy; transformation score based on size of colonies	Rat, Wistar, kidney cells (BRK) from baby rats aged 9 days	Co-transforming ability of PAHs; cells transfected with HPV16E7-t and plasmid pEJ6.6, which carries the H-*ras* oncogene and treated with anthracene; cells fixed 18 days after transfection	1 µM	+, Colony-forming index was increased (but not statistically significantly; high variation; $n = 3$) for anthracene, and was higher than that for fluoranthene or benzo[*ghi*]perylene (statistically significant increase)	Purity, NR; total duration of PAH treatment was unclear; negative control, NR; many PAHs included that gave positive results.	Zhang et al. (2019)

Table 4.12 (continued)

End-point	Assay or method	Species, strain (sex), cells	Study design, culture time	Dose or concentration	Results[a]	Comments	Reference
Morphological transformation	Stereomicroscopy after Giemsa staining	Hamster, Syrian Golden, embryo cells (SHE)	Incubation for 7 days	2.5–100 µg/mL	–	Chemicals of the highest purity available, generally > 97%; solvent controls gave negative results; B[a]P and DMBA gave clearly positive results; validation study; interlaboratory comparison.	Tu et al. (1986)
Morphological transformation	Microscopy after Giemsa staining	Hamster, Syrian, embryo cells (SHE)	After chemical treatment (approximately 20 h), the cells were subcultured and assayed for viability and enhancement of virus transformation (simian adenovirus SA7 transformation enhancement assay)	0–1100 µM	–	Purity, NR; negative control undefined, (solvent, acetone); B[a]P and DMBA gave positive results; doses up to the limit of solubility; validation study; two laboratories.	Schechtman et al. (1986)
Morphological transformation	Scoring for foci after Giemsa staining	Mouse, C3H/10T1/2 clone 8, embryo cells	Cells treated for 24 h, and cultured for 4–6 wk with or without subculture; method development to amplify expression of phenotypical transformation; amplification by replating (and rat S9 mix)	3, 10, and 30 µg/mL	–	Purity, NR; negative control, solvent (acetone); several PAHs induced transformation.	Schechtman et al. (1987)

Table 4.12 (continued)

End-point	Assay or method	Species, strain (sex), cells	Study design, culture time	Dose or concentration	Results[a]	Comments	Reference
Morphological transformation	Counting only type II and III foci (degree of morphological aberration); criteria for transformation established	Mouse, C3H/10T1/2, embryo cells	Comparison between two laboratories	0.8–100 µg/mL; 12–25 plates/dose	–, in both laboratories (in one laboratory, anthracene was not tested at a dose level giving 25% cytotoxicity as the highest dose level)	Chemicals from NCI Chemical Repository, purity, NR; anthracene coded before assay, not when delivered; negative control, solvent (acetone or DMSO); positive control, 3-MC.	Dunkel et al. (1988)
Morphological transformation	Visual assessment of transformed (according to set criteria) colonies	Hamster, Syrian, embryo cells (SHE)	Enhanced transformation assay (pH 7.35 or pH 6.7, culture for 7 days); comparison between two laboratories	0.63, 1.25, 2.5, 5, 10 µg/mL for each pH	–	Purity, NR; negative controls included separately for each chemical (different solvents); B[a]P gave a positive result.	LeBoeuf et al. (1989)
Morphological transformation	Stereomicroscopy after staining	Hamster, Syrian, embryo cells (SHE)	Syrian hamster embryo cell transformation assay, pH 6.7	Concentration, NR, only that concentrations were based on cytotoxicity assay	–	Purity, > 99%; solvent as negative control; B[a]P as positive control.	LeBoeuf et al. (1996)
Morphological transformation	Stereomicroscopy after Giemsa staining; morphological transformation defined	Hamster, Syrian, embryo cells (SHE)	Prevalidation study; 4 laboratories; 6 chemicals including anthracene, B[a]P, and 3-MC	0.001–100 µg/mL	–	Purity, NR; negative control, DMSO; positive control, B[a]P (positive in all laboratories).	Maire et al. (2012)
Morphological transformation	Stereomicroscopy after Giemsa staining	Hamster, Syrian, embryo cells (SHE)	Prevalidation study; 3 laboratories; 6 chemicals including anthracene, B[a]P, 3-MC; treatment for 7 days after which cells were fixed	0, 2.5, 5, 10, 25, 50, 100 µg/mL	–	Purity, NR; negative control, DMSO; positive control, B[a]P (positive in all laboratories).	Pant et al. (2012)

Table 4.12 (continued)

End-point	Assay or method	Species, strain (sex), cells	Study design, culture time	Dose or concentration	Results[a]	Comments	Reference
Morphological transformation	Visual assessment; only type III foci recorded (morphological criteria given)	Mouse, BALB/c 3T3, two different lineages of the A31-1-1 clone were used (ECVAM and HRI)	Prevalidation study; 3 laboratories; 6 chemicals including anthracene, B[a]P, and 3-MC; treatment for 72 h, cells fixed on day 24 or 25	0, 1, 10, 100, 1000 µg/mL	–	Purity, NR; negative control, solvent; positive control, 3-MC (positive in all laboratories).	Tanaka et al. (2012)

B[a]P, benzo[*a*]pyrene; DMBA, dimethylbenz[*a*]anthracene; DMSO, dimethyl sulfoxide; F, female; h, hour(s); HPV, human papilloma virus; 3-MC, 3-methylcholanthrene; LC_{50}, median lethal dose; M, male; mo, month(s); NCI, National Cancer Institute; NR, not reported; PAH, polycyclic aromatic hydrocarbon; SHE, Syrian hamster embryo; SV40, simian virus 40; S9, 9000 × *g* supernatant; TPA, 12-*O*-tetra-decanoylphorbol-13-acetate.

[a] –, negative; +, positive.

chemicals to be tested were coded before being distributed to the test laboratories.]

Three in vitro studies showed that anthracene did not induce cell transformation (Greb et al., 1980; Ahmadzai et al., 2012; Zhang et al., 2019); however, some inconsistencies in the results were observed. In the study by Greb et al. (1980), anthracene (with metabolic activation by S9 mix from Aroclor-treated rats) induced an increase of only 1.4-fold in the transformation rate at the LC_{50} (concentration that is lethal to 50% of cells) in Syrian Golden hamster kidney fibroblasts (BHK 21/CL 13) cells. The increase was higher than that induced by B[a]P without metabolic activation (0.9-fold) or phenanthrene with metabolic activation (0.9-fold); however, it was less than 2-fold and with no dose–response relation, and thus did not fulfil either of the set criteria for positivity.

Ahmadzai et al. (2012) determined the cell transformation rate for anthracene, B[a]P, and 3-MC, and other chemicals using a new type of scoring by infrared spectroscopy in Syrian hamster embryo cells. The rate of transformation for anthracene (5.58%) was higher than that induced by the negative control D-mannitol (3.36%), and lower than that for B[a]P (17.2%). Zhang et al. (2019) found that in kidney cells from Wistar rats (age, 9 days), anthracene exhibited a higher mean colony-forming unit index (not statistically significant compared with controls) than did either fluoranthene or benzo[*ghi*]-perylene (both statistically significant).

Negative results for morphological cell transformation were reported in six studies in Syrian hamster embryo cells (Schechtman et al., 1986; Tu et al., 1986; LeBoeuf et al., 1989, 1996; Maire et al., 2012; Pant et al., 2012), in two studies in C3H/10T1/2 mouse embryo cells (Schechtman et al., 1987; Dunkel et al., 1988), in one study in v-Ha-*ras*-transfected murine BALB/c 3T3 cells (Bhas 42) (Asada et al., 2005), and in one study in two clones of BALB/c 3T3 cells (ECVAM and HRI) (Tanaka et al., 2012). [The Working Group noted that, despite these negative results, the potential tumour-promoting activity of anthracene should not be dismissed. Few studies examined the promotion potential of anthracene; different transformation results might be obtained if, for example, an initiator was used first, followed by anthracene. In addition, the Working Group noted that the effects of UV light in combination with anthracene were not evaluated in these cell transformation assays.]

4.2.9 Alters cell proliferation, cell death, or nutrient supply

See Table 4.13.

No data for the key characteristic "alters cell proliferation, cell death, or nutrient supply" in exposed humans were available to the Working Group. Most of the available literature evaluated specific end-points, i.e. cell junctions, cell proliferation, and calcium signalling in vitro in various cell types, and the evidence was organized accordingly. Of note, dysregulated gap junction intercellular communication (GJIC) and related connexin proteins can lead to alterations in cell survival, proliferation, and calcium and other cell signalling pathways (Goodson et al., 2015; Sinyuk et al., 2018; Siegrist et al., 2019). The integrity of cell junctions (tight junctions, adherens junctions, gap junctions) and their complex crosstalk is vital for maintaining tissue homeostasis (Naser et al., 2022).

(a) Cell junctions

(i) Human primary cells and cell lines

Wu et al. (2022) showed that anthracene of high purity (99%), at concentrations found in human blood, disrupted endothelial barrier function via disruption of cell junctions in human umbilical vein endothelial cells (HUVEC). There was an increase of 1.15–1.42-fold in fluorescein leakage and a dose-dependent and statistically significant decrease in trans-endothelial electrical resistance. Paracellular gap formation was

Table 4.13 End-points relevant to cell proliferation, cell death, or nutrient supply with anthracene in human cells in vitro and non-human mammalian experimental systems in vitro

End-point	Assay or method	Species, strain, cells	Study design, culture time	Dose or concentration	Results[a]	Comments	Reference
Cell junctions							
Endothelial barrier function	Permeability (FITC-dextran fluorescence in Transwell monolayer, TER); barrier protein (immunoblotting) and mRNA (qPCR) expression (VE-cadherin, ZO-1, occludin) Morphology (TEM); VE-cadherin internalization (immunofluorescence)	Human umbilical vein endothelial cells (HUVEC)	Treatment for 24 h (VE-cadherin mRNA, 12 h);	0.01–1 µM [1.78 ng/mL–178 ng/mL] (anthracene in human whole blood, 79 ng/mL)	↑ FITC-dextran fluorescence ↓ TER (dose-dependent) ↓ mRNA expression of VE-cadherin and occluding ↓ Protein expression ZO-1 and occludin ↑ Intracellular gaps formation	Purity, 99%; EDTA, 2.5 mM, as positive control; DMSO (solvent), as negative control; $n = 3$ (except for immunoblotting, $n = 1$).	Wu et al. (2022)
GJIC inhibition	SL/DT assay	Human bronchial epithelial (HBE1) cell line	Exposure, 1 h, 24 h	0–100 µM	No differences	Purity, NR; for 1- and 9-methylanthracene, there was a dose-dependent, statistically significant decrease.	Brózman et al. (2020)
MAPK activation	Immunoblotting	Human bronchial epithelial (HBE1) cell line	Exposure, 1 h, 24 h	100 µM	Increased p38 phosphorylation at 1 h		
Connexin 43 protein	Immunoblotting	Human bronchial epithelial (HBE1) cell line	Exposure, 1 h, 24 h	100 µM	No differences		
GJIC inhibition	SL/DT assay	Rat liver WB-F344 epithelial cells	Treatment, 90 min; $n = 2$	5–20 mg/L	↓, 40% decrease compared with controls	Purity, NR; solvent control (acetonitrile); 9-methylanthracene and fluoranthene gave positive results. No statistical analysis provided.	Upham et al. (1994)

Table 4.13 (continued)

End-point	Assay or method	Species, strain, cells	Study design, culture time	Dose or concentration	Results[a]	Comments	Reference
GJIC inhibition	SL/DT assay	Rat liver WB-F344 epithelial cells	Treatment, 30 min; *n* = 3	0–350 µM	No differences	Purity, NR; solvent control (acetonitrile); 1- and 9-methylanthracene gave positive results.	Upham et al. (1996)
GJIC inhibition	SL/DT assay	Rat liver WB-F344 epithelial cells	Treatment, 10 min; *n* = 3	0–350 µM	No differences	Purity, NR; solvent control (acetonitrile); several positive chemicals. high variation at the highest concentrations.	Weis et al. (1998)
GJIC inhibition	SL/DT assay	Rat liver WB-F344 epithelial cells	Treatment, 15 min; *n* = 3	100–350 µM	No differences	Purity, NR; solvent control (acetonitrile); concentrations used based on Rummel et al. (1999); high variation at the highest concentrations.	Rummel et al. (1999)
GJIC inhibition	SL/DT assay	Rat liver WB-F344 epithelial cells	Treatment, 30 min; *n* = 3	0–100 µM	No differences	Purity, NR; DMSO as solvent control; 1- and 9-methylanthracene gave clearly positive results.	Vondrácek et al. (2007)
Connexin 43 phosphorylation	Immunoblotting (western blotting), densitometry	Rat liver WB-F344 epithelial cells	Treatment, up to 30 min.	60 µM	No differences	Purity, NR; TPA clearly inhibited.	Upham et al. (2008)
GJIC inhibition	SL-DT assay	Mouse testicular Leydig TM3 cells and Sertoli TM4 cells	Treatment, 0.5 h; *n* = 3	0–200 µM	Dose-dependent trend decrease from 50 µM but not statistically significant.	Purity, > 98.5%; vehicle controls, DMSO (maximum, 1% v/v in medium); TPA as positive control.	Kubincová et al. (2019)

Table 4.13 End-points (continued)

End-point	Assay or method	Species, strain, cells	Study design, culture time	Dose or concentration	Results[a]	Comments	Reference
Cell proliferation and cell death							
Cell proliferation	Alamar Blue	Human placental choriocarcinoma BeWo and JEG-3 cell lines	Anthracene dissolved in methanol (< 0.1% in medium); doses determined by in vivo levels; treatment, 24 h and 72 h; $n = 3$	10 and 80 ng/mL	No differences	Purity, NR; negative controls not defined; no positive control.	Drwal et al. (2017)
Cyclin D1 Cyclin A2; Cdk2, Cdk4; Bax; Bcl-xl; caspase-3	Immunoblotting	Human placental choriocarcinoma BeWo and JEG-3 cell lines	Anthracene dissolved in methanol (< 0.1% in medium); doses determined by in vivo levels; treatment, 24 h and 72 h; $n = 3$	10 and 80 ng/mL	JEG-3: ↑ Bax; ↑ cyclinA2; ↓ cyclin D1; ↑ cdk2 BeWo: ↑Bax; ↑ caspase	Purity, NR; negative controls not defined; no positive control.	
Cell viability	XTT assay	Human placental choriocarcinoma BeWo and JEG-3 cell lines	anthracene dissolved in methanol (< 0.1% in medium); doses determined by in vivo levels; treatment 24 h and 72 h; $n = 3$	10 and 80 ng/mL	↑ after 72 h JEG-3: 80 ng/mL BeWo: 10 ng/mL	Purity, NR; negative controls not defined; no positive control.	Drwal et al. (2017)
Cell death	Annexin-V-FITC apoptosis detection kit, flow cytometry; DNA ladder kit, agarose gel separation	Human monocytic (THP-1) cell line	Treatment for 24 h	50 µM	No differences	Purity, NR; vehicle control, 0.1% DMSO; positive control, staurosporin	Wan et al. (2006)

Table 4.13 End-points (continued)

End-point	Assay or method	Species, strain, cells	Study design, culture time	Dose or concentration	Results[a]	Comments	Reference
Epidermal proliferation	Thymidine incorporation, ODC activity	Mouse, albino hairless (F), (age 4–6 mo); *n* = 4–5	Dorsal skin painted; UV-A exposure 2 h later; skin studied at 4, 24, 48, 72, and 96 h (thymidine) or 4, 24, 48 h (ODC) after treatment	1% in petrolatum (Vaseline)	↑ Thymidine incorporation ↑ ODC	Dose unclear; purity, NR; ventral skin as negative control.	Gange (1981)
No. of dopa-positive melanocytes in epidermis	10% formalin-fixed skin incubated in dopa solution; light microscopy	Mouse, C57BL/6 (age 6–8 wk)	Area of 4 cm^2 shaved 1–2 days before skin painting; incubation of treated skin with dopa 6 days after last application	200 µg × 2/mouse, 2 consecutive days	No differences	Purity, NR; skin area for analysis was unclear; solvent (acetone) control; chemicals that gave positive results were included.	Iwata et al. (1981)
Hyperplasia	Histology	Rat, Fischer 344 (M); 2 tracheas per rat transplanted subcutaneously into post-scapular region, exposed 4 wk later	Pellets containing anthracene were implanted into tracheal explants (6 tracheas/group) for 3 days or 1, 2, 4 or 8 wk	Beeswax pellets containing 1 mg PAH	Mild changes (hyperplasia; similar to the beeswax control, but lasting longer) in 25–50% of explants during 8 wk and moderate changes (transitional epithelium) in 10–20% during 4 wk	PAHs recrystallized; anthracene release from pellets: in vitro/in vivo, 1.2; DMBA and B[a]P: moderate to severe changes in 50–100%.	Topping et al. (1978)

Table 4.13 End-points (continued)

End-point	Assay or method	Species, strain, cells	Study design, culture time	Dose or concentration	Results[a]	Comments	Reference
Liver regeneration	Liver (dry) weight compared with controls	Rats (male), strain not reported	Partially hepatectomized male rats (n = 12) fed anthracene for 10 days	1% in food	No differences	Purity, ≥ 98%; negative control and positive compounds included.	Gershbein (1975)
Intracellular calcium signalling							
Intracellular calcium	Flow cytometry	Primary human mammary epithelial cells (mammoplasty; n = 7)	Incubations, 2 h and 18 h	0.03, 0.3, 3 µM	No differences	Purity, > 95%; PAHs did not interfere with fluorescence; B[a]P and DMBA gave positive results.	Tannheimer et al. (1997)
Intracellular calcium	Flow cytometry	HBP-ALL human T-cell line	Rapid (3 min.); Sustained (4 h);	10 µM	↑, at 3 min No differences at 4 h	All chemicals and reagents were ACS or molecular-biology grade.	Krieger et al. (1994)
Calcium uptake	Filtration method for $^{45}Ca^{2+}$ uptake	Human HBP-ALL T-cell line; 15 000 × g supernatant from cell lysate	In vitro incubation of microsomes with $^{45}Ca^{2+}$, 5 mM ATP and PAH for 5 min; n = 1	0.1, 1, 10 µM	No differences	Purity, NR; DMBA and B[a]P gave dose-dependent statistically significant inhibition.	Krieger et al. (1995)
Ca-ATPase activity	(γ-^{32}P)ATP hydrolysis	Human HBP-ALL T-cell line, 15 000 × g supernatant from cell lysate	Incubation, 30 min at 37 °C; 5 mM ATP; n = 3	10 µM	No differences	Purity, NR; solvent control; B[a]P gave a statistically significant decrease.	
Ca-ATPase activity (SERCA)	(γ-^{32}P)ATP hydrolysis	HPBMC (n = 4); 15 000 × g supernatant from cell lysate		10 µM	No differences	Purity, NR; B[a]P and DMBA gave a dose-dependent positive result, with 99% inhibition at 10 µM.	

Table 4.13 End-points (continued)

End-point	Assay or method	Species, strain, cells	Study design, culture time	Dose or concentration	Results[a]	Comments	Reference
Intracellular calcium	Flow cytometry	HPBMC (n = 10); CD3+ T cells, CD19+ B cells and CD14+ monocytes treated separately	Treatment at 20, 42, or 66 h	10 µM	↑	Purity, > 95%; DMSO at < 0.1% did not differ from non-DMSO control; B[a]P and DMBA gave strong inhibition.	Mounho et al. (1997)
PTK activity	Modification of PTK assay (Pierce Bioproducts, Rockford, Illinois, USA); also, Fyn and ZAP-70 removed by immunoprecipitation	Human HBP-ALL T-cell line (calcium increase dependent on PTK)	Total PTK activity; specific (Fyn and ZAP-70) activity; 5 min exposure; n = 3	10 µM	↑ Transient only for PTK, but not other kinases	Purity, > 95%; DMSO solvent control (DMSO, < 0.1%); DMBA and 3-MC, but not B[a]P, caused statistically significant increases.	Davila et al. (1999)

ACS, American Chemical Society; ATP, adenosine triphosphate; B[a]P, benzo[*a*]pyrene; Ca^{2+}, calcium; dopa, dihydroxyphenylalanine; DMBA, dimethylbenz[*a*]anthracene; DMSO, dimethyl sulfoxide; EDTA, ethylenediaminetetraacetic acid; F, female; FITC, fluorescein isothiocyanate; GJIC, gap junctional intercellular communication; h, hour(s); HPBMC, human peripheral blood mononuclear cell; HUVEC, human umbilical vein endothelial cells; M, male; MAPK, mitogen-activated protein kinases; 3-MC, 3-methylcholanthrene; min, minute; mo, month(s); NR, not reported; ODC, ornithine decarboxylase; PAH, polycyclic aromatic hydrocarbon; PCR, polymerase chain reaction; PTK, protein tyrosine kinase; qPCR, quantitative polymerase chain reaction; SERCA, sarcoplasmic/endoplasmic reticulum calcium ATPases; SL/DT, scrape-loading/dye transfer; TEM, transmission electron microscopy; TER, transepithelial resistance; TPA, 12-*O*-tetra-decanoylphorbol-13-acetate; UV, ultraviolet; VE-cadherin, vascular endothelial cadherin; v/v, volume/volume; wk, week(s); XTT, 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2*H*-tetrazolium-5-carboxanilide, disodium salt; ZO-1, zonula occludens-1.

[a] ↑, increase; ↓, decrease.

shown by transmission electron microscopy. After a 24-hour exposure to anthracene, mRNA expression of vascular endothelial cadherin (VE-cadherin), zona occludens-1 (ZO-1), and occludin was downregulated by 33.2–71.4%, 19.1–21.0%, and 31.9%, respectively. Protein expression of ZO-1 and occludin was downregulated, and VE-cadherin was internalized.

The effects of anthracene were also investigated in rapid (< 1 hour) and sustained (up to 24 hours) inhibition of GJIC in the human bronchial epithelial cell line HBE1 (immortalized by human papillomavirus type 18, HPV18, E6/E7 proteins). Connexin 43 was not inhibited by anthracene (Brózman et al., 2020), whereas p38 MAPK, which is probably involved in GJIC regulation (see Siegrist et al., 2019), was activated (a statistically significant increase in phosphorylation at 1 hour) by anthracene at a concentration of 100 μM.

(ii) Non-human mammalian cells in vitro

The effects of anthracene exposure on GJIC inhibition were evaluated in rat liver epithelial cells (WB F344) (Upham et al., 1994, 1996; Weis et al., 1998; Rummel et al., 1999; Vondrácek et al., 2007), and in murine testicular cells (Kubincová et al., 2019). All the studies used a scrape-loading/dye-transfer assay for GJIC, and none showed statistically significant inhibition of GJIC. [The Working Group noted some inconsistencies in the results among the studies (Upham et al., 1994; Vondrácek et al., 2007; Kubincová et al., 2019). Upham et al. (1994) observed a 60% inhibition of GJIC, when compared with the controls, at all tested doses in rat liver cells treated with anthracene for 90 minutes. In a follow-up study (Upham et al., 1996), however, a shorter treatment time (30 minutes) did not induce GJIC inhibition (no statistics were reported, because the experiment was only carried out twice). In the studies by Weis et al. (1998), Rummel et al. (1999), Vondrácek et al. (2007), and Upham et al. (2008), carried out in rat liver epithelial WB-F344 cells, anthracene did not inhibit GJIC at concentrations up to 350 μM. In the study by Kubincová et al. (2019), anthracene did not inhibit GJIC at concentrations up to 200 μM in mouse testicular Leydig TM3 cells or Sertoli TM4 cells.]

(b) Alters cell proliferation or cell death

(i) Human cell lines

Drwal et al. (2017) studied the effect of anthracene on cell proliferation in human placental choriocarcinoma cell lines BeWo and JEG-3. The doses used were those identified in studies of exposure of the general population: 10 ng/mL (placenta) and 80 ng/mL (maternal blood). Treatment with anthracene for 24 hours or 72 hours did not alter cell proliferation, as measured by the Alamar Blue assay, but significantly increased cell viability in both cell lines, JEG-3 (80 ng/mL) and BeWo (10 ng/mL), at 72 hours. In the same study, Drwal et al. (2017) showed that exposure of JEG-3 cells to anthracene for 72 hours increased cyclin D1 and CDK2 but decreased cyclin A2 at 10 ng/mL and decreased BAX at 10 and 80 ng/mL. On the other hand, identical exposure of BeWo cells resulted in increased BAX at 10 and 80 ng/mL, and also in increased caspase-3 at 10 mg/mL. The study showed different cell type-dependent actions on apoptosis; a pro-apoptotic effect (increased BAX and caspase-3) in BeWo cells and an anti-apoptotic effect (decreased BAX and increased CDK2 and cyclin D1) in JEG-3 cells. In another study, Wan et al. (2006) compared induction of apoptosis in human monocytic THP-1 cells by flow cytometry. Anthracene did not alter the percentage of cells in apoptosis and necrosis, compared with controls.

(ii) Non-human mammals in vivo

Gange (1981) studied epidermal cell proliferation, using ornithine decarboxylase (ODC) and thymidine incorporation, in groups of four or five female albino hairless mice (age, 4–6 months). The dorsal skin was painted with 1% anthracene

in petrolatum and irradiated with UV-A light 2 hours later; the ventral skin of the same animal served as the matched control. Anthracene plus UV-A irradiation caused statistically significant increases in thymidine incorporation (at 48 hours and 96 hours after treatment) and in ODC activity (at 4 hours and 24 hours). Anthracene without irradiation caused a small but statistically significant increase in ODC (at 4 hours).

Iwata et al. (1981) studied the activation of melanocytes (as number of dopa-positive melanocytes in epidermis) by several PAHs in C57BL/6 mice. Anthracene (two consecutive days) and DMBA, the control (1 day only), were painted onto the skin and three or four (width, 2 mm) sections of fixed skin were incubated in dihydroxyphenylalanine solution (0.1%; 24 hours), for 6 days after the last application. Although the area for analysis was unclear, anthracene induced an average of 2.0 active melanocytes, compared with > 100 active melanocytes induced by the positive control (DMBA).

Topping et al. (1978) subcutaneously transplanted tracheas from male Fischer 344 rats into isogenic animals and, 4 weeks later, implanted beeswax pellets containing 1 mg of anthracene (recrystallized before use) into the tracheas. Beeswax pellets without PAH were used as a negative control. Beeswax pellets caused mild changes, but beeswax pellets releasing anthracene induced mild to moderate epithelial changes of 10–20%, as hyperplastic responses, within 4 weeks (Topping et al., 1978). [The Working Group noted that DMBA and B[a]P induced moderate to severe changes, including squamous metaplasia, in 50–100%.]

In another study, Gershbein reported that exposure of partially hepatectomized Holtzman (HLZ) or Charles River male rats to anthracene (at 1% in the feed; daily for 7 days) had no effect on the extent of liver regeneration over a period of 10 days post-operation (Gershbein, 1975).

(iii) Non-human mammalian cells in vitro

Shabad et al. (1972) described epithelial changes in tissue cultures of embryonic kidney (embryo age 19–21 days) from mice (BALBc, C3H/A, or C57BL/CBA F1 hybrids) treated daily with 8 mg of anthracene (purity not reported) during the last week of pregnancy. Anthracene induced diffuse hyperplasia and solid epithelial areas that were not seen in the controls but did not induce nodular proliferation or papillary growth as was observed for the positive control (DMBA).

Nuclear size, as a measure of cell proliferation, was assessed in rat trachea epithelial cells exposed for 3 hours to anthracene, other PAHs, various activation-dependent carcinogens, and direct-acting carcinogens. Anthracene did not induce an increase in nuclear size after cells were further cultured for 24, 72, or 120 hours, compared with other compounds (Fowlie et al., 1991).

Anthracene did not alter cell proliferation, as measured by cell number and percentage S-phase cell count, in hepatic epithelial stem-like rat cell (WB-F344) (Chramostová et al., 2004).

(c) Intracellular calcium

In human primary mammary epithelial cells from mammoplasty (n = 7) cultured for up to 18 hours with various PAH-compounds, anthracene (purity, > 95%), compared with the positive control (B[a]P), did not significantly alter intracellular Ca^{2+} levels at any time point or concentration, or in any cell preparation from different individuals (Tannheimer et al., 1997). In a series of studies, anthracene was reported to induce a small and transient Ca^{2+} mobilization response (Krieger et al., 1994, 1995; Mounho et al., 1997) in a human T-cell line (HPB-ALL) and human peripheral blood mononuclear cells. However, in human peripheral blood mononuclear cells, anthracene did not inhibit the activities of transmembrane sarcoendoplasmic reticulum calcium

ATPases SERCA2b or SERCA3, or plasma membrane Ca^{2+}-ATPase in human erythrocyte ghosts (Krieger et al., 1995). Anthracene at 10 µM significantly increased protein tyrosine kinase (PTK) activity in HPB-ALL human T cells, but did not alter other kinases (i.e. Fyn and ZAP-70) known to play important roles in T-cell activation and that have been observed to be activated by a 10-minute exposure to PAHs (Davila et al., 1999). [The Working Group noted that the effects of anthracene on Ca^{2+} signalling are smaller and often transient when compared with the effects of other PAHs.]

4.3 Evaluation of high-throughput in vitro toxicity screening data

Anthracene was tested in high-throughput toxicity screening assays under the Toxicology in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes of the government of the USA (Thomas et al., 2019). Chemical samples of high purity were procured, prepared in DMSO stock solutions at a concentration of approximately 20 mM, and tested over a period of several years in biochemical and cellular bioassays measuring a wide variety of biological end-points. In addition, chemical analysis of the samples was done in high-throughput fashion at an early and a late stage of the sample testing lifetime, as described in Tice et al. (2013). Testing results data from the concentration–response testing design for all end-points were analysed for significant activity, and an active/inactive "hit call" was made for each response, together with a potency value (Filer et al., 2017). For all active calls, individual concentration–response curves were examined to ensure that biologically meaningful activity was detected. Bioassay end-points were mapped, where possible, to the key characteristics of carcinogens using the "kc-hits" software (the key characteristics of carcinogens – high-throughput screening discovery tool, available from: https://gitlab.com/i1650/kc-hits; Reisfeld et al., 2022) to aid in providing mechanistic insights (Chiu et al., 2018). The detailed results are available in the supplementary material for this volume (Annex 2, Supplementary material for Section 4, Evaluation of high-throughput in vitro toxicity screening data, online only, available from: https://publications.iarc.who.int/631) and are briefly summarized below.

The results for anthracene high-throughput toxicity testing in the CompTox Chemicals Dashboard encompassed 979 assay end-points, of which 280 were mapped to the key characteristics of carcinogens. The cytotoxicity limit for anthracene, on the basis of a panel of cellular cytotoxicity and viability assays, was estimated to be > 1 mM (US EPA, 2022). There were 17 positive hit calls for concentration–response curves mapped to end-points relevant to the key characteristics, but 12 of these had quality control flags indicating low confidence results. The five without flags mapped to the key characteristics "modulates receptor-mediated effects" (four end-points) and "alters cell proliferation, cell death, or nutrient supply" (one end-point). Three of the positive results for "modulates receptor-mediated effects" concerned upregulation of cytochrome P450 gene expression (CYP1A1, CYP1A2, and CYP2B6) in the human liver cell line HepaRG, for which the half-maximal activity concentrations (AC_{50}s) were 10.1, 18.0, and 14.7 µM, respectively. [The Working Group noted that HepaRG cells have xenobiotic metabolic activity.] The fourth positive result was for AR antagonist activity in the 22Rv1 human prostate carcinoma epithelial cell line, for which the AC_{50} was 22.3 µM. An additional AR antagonist assay had a positive hit call but was flagged for "less than 50% efficacy"; anthracene was inactive in two other AR antagonist assays. [The Working Group considered this to be weak evidence of AR modulation activity.] A single positive hit call (without flags) for the key characteristic "alters cell proliferation, cell death, or nutrient supply",

for cell cycle arrest in the human liver HepG2 cell line, had an AC_{50} of 115.8 μM.

The chemical analysis of anthracene included two different stock solutions. For one (Tox21_202226), the expected structure and purity were confirmed on initial testing but "low concentration 5–30% of expected value" was found on later analysis. The second sample (Tox21_300014) gave inconclusive results on initial testing, and an incorrect molecular weight was found on the second analysis (NIH, 2022). Mapping of specific samples to bioactivity testing results was not available in the public data. [The Working Group considered the testing results for anthracene to be of low confidence since it was not possible to link specific samples to bioactivity testing.]

5. Summary of Data Reported

5.1 Exposure characterization

Anthracene is a three-ring polycyclic aromatic hydrocarbon (PAH) mainly produced from coal tar. It is a High Production Volume chemical with a world production of about 20 000 tonnes per year. Anthracene is mainly used as an intermediate in the manufacture of dyes and pigments, pyrotechnics, coatings, wood preservatives, pesticides, and organic chemicals.

Anthracene release or disposal into the environment takes place because of industrial use or unintended formation during industrial processes. Additionally, anthracene is formed together with other PAHs during the incomplete combustion or pyrolysis of organic matter from both natural and anthropogenic sources, with predominance of the latter. Therefore, anthracene is ubiquitous in the environment. Anthracene has been detected in foodstuffs as a result of environmental contamination (via water, soil, and/or air) and/or unintended formation during food processing.

Occupational exposure to anthracene occurs in a variety of industries and activities, including carbon black manufacture, coking, tear-off of old coal-tar roofs, asphalt paving, firefighting, manufacture of creosote or creosote-containing products, production of carbon anodes for aluminium electrolysis, and production of fireproof material. In these diverse settings, exposure to anthracene is mainly by inhalation and dermal contact.

Anthracene exposure of the general population occurs from multiple routes, i.e. via ingestion of food and beverages/water, inhalation of polluted air, and through contact with contaminated soils or consumer products. Contaminated food is the major route of anthracene intake by the non-smoking and non-occupationally exposed population. The most significant sources of exposure of the general population via inhalation are tobacco smoke, biomass burning (indoors or outdoors), and traffic and industry emissions.

Biological monitoring of anthracene exposure in workers and the general population has seldom been performed.

Overall, occupation, smoking habits, living or working in industrial or urban polluted areas, and cooking using biomass as fuel are the main determinants of anthracene exposure.

5.2 Cancer in humans

No data were available to the Working Group.

5.3 Cancer in experimental animals

Treatment with anthracene caused an increase in the incidence of either malignant neoplasms or an appropriate combination of benign and malignant neoplasms in two species (mouse and rat).

Anthracene was administered orally (in feed) in one study that complied with Good Laboratory

Practice (GLP), in male and female Crj:BDF_1 mice. In females, anthracene caused an increase in the incidence of hepatocellular neoplasms, including carcinoma and adenoma or carcinoma (combined) of the liver, and histiocytic sarcoma at multiple tissue sites.

Anthracene was administered orally (in feed) in one study that complied with GLP in male and female F344/DuCrj rats. In males, anthracene caused an increase in the incidence of hepatocellular neoplasms including carcinoma and adenoma or carcinoma (combined) of the liver, and transitional cell papilloma or carcinoma (combined) of the urinary bladder. In females, anthracene caused an increase in the incidence of renal cell adenoma or carcinoma (combined) of the kidney and endometrial stromal sarcoma of the uterus.

Anthracene was tested by oral administration (gavage) in male and female transgenic Hras128 and non-transgenic Sprague-Dawley rats. In male transgenic rats, anthracene caused a significant increase in the incidence of mammary adenoma or adenocarcinoma (combined).

5.4 Mechanistic evidence

The absorption, distribution, and excretion of anthracene in humans is documented by its presence in the urine after experimental cutaneous exposure and as a result of occupational exposures. Anthracene has also been detected in the urine, blood, and several tissues of the general population. A single study reported on 1-hydroxyanthracene in human hair. Anthracene is absorbed through rat skin and from the stomach in vivo, and through natural or excised skin of several mammalian species in vitro. Anthracene is extensively metabolized in rats or rabbits via its 1,2-oxide to 1,2-dihydrodiol (major product) and 1,2-dihydro-2-hydroxy-1-anthryl-mercapturic acid, whereas oxidation at positions 9 and 10 results in the formation of 9,10-dihydrodiol and related more oxidized products including 9,10-anthraquinone. Anthracene metabolism in rats or rat liver microsomes also produces 9-methyl or 9,10-dimethyl derivatives that undergo further oxidation at methyl groups and/or aromatic rings.

Data were available for anthracene for the following key characteristics of carcinogens: "is electrophilic or can be metabolically activated to an electrophile", "is genotoxic", "induces epigenetic alterations", "induces oxidative stress", "induces chronic inflammation", is immunosuppressive", "modulates receptor-mediated effects", "causes immortalization", and "alters cell proliferation, cell death, or nutrient supply".

Overall, the mechanistic evidence for anthracene with regard to the key characteristics of carcinogens "is genotoxic", "induces oxidative stress", and "modulates receptor-mediated effects" is suggestive in experimental systems.

There is suggestive evidence that anthracene is genotoxic in experimental systems. No data were available in humans exposed to anthracene or in human primary cells. DNA damage was shown in several studies performed in human cell lines, mammalian cells in vitro, and in several non-mammalian experimental systems. This was especially true when anthracene photoactivation and/or modification by interaction with nitrogen dioxide (NO_2) occurred. However, DNA damage was not shown in all the studies, leading to unexplained incoherence across studies of different end-points and different systems. Thus, anthracene could be considered a pro-genotoxic compound. High mutagenicity in urine from ICR mice exposed to anthracene in combination with NO_2 was shown by the Ames test. In non-human mammalian in vitro models, three out of eight studies showed positive results for several genotoxicity end-points. In addition, in non-mammalian experimental systems, positive findings for genotoxicity were noted in 10 out of 29 studies without metabolic activation, whereas 14 out of 29 studies gave positive results with metabolic activation.

There is suggestive evidence that anthracene induces oxidative stress. In exposed humans and human primary cells, there was inconsistent data, including oxidative damage to DNA. Only one study, in human peripheral blood lymphocytes, with the limitations on understanding the source of cells, reported a significant association between superoxide anion radicals and anthracene exposure. There is also suggestive evidence that anthracene induces oxidative stress in experimental systems. In the human cell line HaCaT, anthracene combined with ultraviolet (UV) induced oxidative stress, as measured by the production of reactive oxygen species. In other experimental systems including two studies in non-human mammalian cells in vitro and several in non-mammalian models, anthracene increased oxidative stress measured by a range of oxidative stress markers, such as malondialdehyde, reactive oxygen species, protein carbonyls, and altered antioxidant enzyme and glutathione-*S*-transferase activities.

There is suggestive evidence that anthracene modulates receptor-mediated effects. No data were available in humans exposed to anthracene or human primary cells. Evidence from experimental systems suggests that anthracene may activate multiple receptor-signalling pathways known to play critical roles in mediating endocrine disruption, including the aryl hydrocarbon receptor (AhR), estrogen receptor (ER), early growth response protein 1 (EGR-1), and peroxisome proliferator-activated receptor alpha and beta/delta (PPARα and PPARβ/δ). There are four studies in human cancer cells in vitro (MCF7, A549, and HCT-116) showing weak estrogenic activity and a significant increase in EGR-1, PPARα, and PPARβ/δ luciferase activity.

There was a paucity of data or inconsistent evidence for the following key characteristics, "is electrophilic or can be metabolically activated to an electrophile", "induces epigenetic alterations", and "induces chronic inflammation".

No data were available for the other key characteristics.

Data for anthracene from the assay battery of the Toxicity Forecaster (ToxCast) research programme in the USA were considered supportive for the key characteristic "modulates receptor-mediated effects" on the basis of induction of target genes for AhR (CYP1A1 and CYP1A2) and constitutive androstane receptor (CYP2B6) in the human liver cell line HepaRG. Anthracene was active in two androgen receptor (AR) assays, but there is low confidence in the results because additional AR assays were without activity.

6. Evaluation and Rationale

6.1 Cancer in humans

There is *inadequate evidence* in humans regarding the carcinogenicity of anthracene.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of anthracene.

6.3 Mechanistic evidence

There is *limited mechanistic evidence*.

6.4 Overall evaluation

Anthracene is *possibly carcinogenic to humans (Group 2B)*.

6.5 Rationale

The Group 2B evaluation for anthracene is based on *sufficient evidence* for cancer in experimental animals. The *sufficient evidence* for cancer in experimental animals is based on an increase

in the incidence of either malignant neoplasms or an appropriate combination of benign and malignant neoplasms in two species (mouse and rat) in two studies that complied with GLP. The mechanistic evidence was *limited*. There is suggestive evidence that anthracene is genotoxic, induces oxidative stress and modulates receptor-mediated effects in experimental systems. The evidence regarding cancer in humans was *inadequate*, as no studies were available.

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