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BENZENE

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

1. EXPOSURE DATA

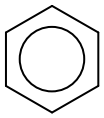
1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 71-43-2
Primary name: benzene
IUPAC systematic name: benzene

1.1.2 Structural and molecular formulae, and relative molecular mass

Structural formula:



From O'Neil (2006) and Lide (2008)

Molecular formula: C_6H_6
Relative molecular mass: 78.1

1.1.3 Chemical and physical properties of the pure substance

From HSDB (2018)

Description: clear, colourless, volatile, highly flammable liquid

Boiling point: 80.1 °C

Melting point: 5.558 °C

Density: 0.8756 g/cm^3

Refractive index: 1.5011 at 20 °C

Solubility: slightly soluble in water (1.8 g/L at 25 °C); miscible with acetic acid, acetone, chloroform, ethyl ether, and ethanol

Viscosity: 0.604 mPa at 25 °C

Vapour pressure: 94.8 mmHg at 25 °C

Stability: benzene is a very stable molecule due to its aromaticity, that is, the delocalization of pi electrons in the benzene molecule creating a resonance; catalysts are often needed to make benzene undergo a chemical reaction; benzene is volatile with a boiling point of 80 °C, and is highly flammable

Flash point: –11.1 °C

Octanol/water partition coefficient: log K_{ow}, 2.13; conversion factor (20 °C, 101 kPa): 1 ppm = 3.19 mg/m^3.

1.1.4 Technical products and impurities

The impurities found in commercial products are toluene, xylene, phenol, thiophene, carbon disulfide, acetylnitrile, and pyridine. Thiophene-free benzene has been specially treated to avoid destroying the catalysts used in reactions with benzene. Refined nitration-grade benzene is free of hydrogen sulfide and sulfur dioxide (HSDB, 2018).

1.2 Production and use

1.2.1 Production

(a) Production process

Benzene was first isolated by Faraday in 1825 from a liquid condensed by compressing oil gas; Mitscherlich first synthesized it in 1833 by distilling benzoic acid with lime. Benzene was first recovered commercially from light oil derived from coal tar in 1849, and from petroleum in 1941 (IARC, 1982).

Benzene can be produced in several ways. One method is by catalytic reforming, which involves the dehydrogenation of cycloparaffins, dehydroisomerization of alkyl cyclopentanes, and the cyclization and subsequent dehydrogenation of paraffins. The feed to the catalytic reformer (platinum-rhenium on an alumina support of high surface area) for benzene is thermally cracked naphtha cut at 71–104 °C. The benzene product is most often recovered from the reformate by solvent extraction techniques (Fruscella, 2002).

Benzene can also be prepared by cracking, a multistep process where crude oil is heated, steam is added, and the gaseous mixture is then briefly passed through a furnace at temperatures of 700–900 °C. The dissolved compounds undergo fractional distillation, which separates out the different components, including benzene (Fruscella, 2002).

Alternatively, benzene can be prepared from toluene by hydrodealkylation. In the presence of a catalyst (chromium, molybdenum, and/or platinum), toluene and hydrogen are compressed to pressures of 20–60 atmospheres and the mixture is heated to temperatures of 500–660 °C. This reaction converts the mixture to benzene and methane, and benzene is separated out by distillation (Fruscella, 2002).

(b) Production volume

Benzene is listed as a high production volume chemical by the Organisation for Economic Co-operation and Development (OECD, 2009). In 2012, global benzene production was approximately 42.9 million tonnes. In the USA, production volumes during 1986–2002 were more than 1 billion pounds [> 450 000 tonnes] (HSDB, 2018). In order of volume produced, the five countries producing the greatest quantities of benzene in 2012 were China, the USA, the Republic of Korea, Japan, and Germany (Merchant Research & Consulting Ltd, 2014). In 2014, the industry reported benzene production and consumption in western Europe (Germany, Belgium, France, Italy, Luxembourg, the Netherlands, Denmark, Ireland, the United Kingdom, Greece, Spain, Portugal, Austria, Finland, and Sweden – the EU-15 – plus Norway and Switzerland) of 6.7 and 7.5 million tonnes, respectively (PetroChemicals Europe, 2015).

The use of benzene for the production of ethylbenzene, cumene, cyclohexane, and nitrobenzene accounts for 90% of annual benzene consumption. In order of volume consumed, China, the USA, and western Europe consume about half of the total benzene produced (IHS Markit, 2017).

The United States Environmental Protection Agency (EPA) report published in February 2017 (Report No. 17-P-0249) reports a total benzene consumption of 57 701 737 237 gallons (equivalent to 1.9×10^8 tonnes; 1 gallon = 3.7858 L, benzene density of 0.879 g/cm^3) for 84 facilities in the USA in 2014 (EPA, 2017).

1.2.2 Uses

Historically, benzene was used as a degreaser of metals, a solvent for organic materials, a starting and intermediate material in the chemical and drug industries (e.g. to manufacture rubbers, lubricants, dyes, detergents, and pesticides), and an additive to unleaded gasoline

(ATSDR, 2007; Williams et al., 2008; NTP, 2016). Benzene use has diminished since its carcinogenic properties became widely publicized (IARC, 1982); however, some countries have continued to use benzene in specific products such as glue (Vermeulen et al., 2004).

Benzene occurs naturally in petroleum products (e.g. crude oil and gasoline), and is also added to unleaded gasoline for its octane-enhancing and anti-knock properties. Typically, the concentration of benzene in these fuels is 1–2% by volume (ATSDR, 2007). Benzene concentration in fuels sold in the European Union must be less than 1.0% by volume (European Commission, 2009).

The percentage of benzene in gasoline has varied with the refinery and time period from which it originated. Until 1931, the benzene content of the gasoline imported into the United Kingdom was 1% v/v (Lewis et al., 1997). In 1971, Parkinson reported that gasoline in the United Kingdom contained 2.8–5.8% benzene v/v (Parkinson, 1971). In Canada in the 1970s and the 1980s, benzene content in fuel was reported as 0.7–3.7% (Armstrong et al., 1996); in Australia, benzene content of 1–5% by weight during 1950–1990 was reported (Glass et al., 2000).

Gasoline can be enriched with benzene by adding benzene-toluene-xylene, which is generated during coke making. Where necessary, sidestream petroleum is added to adjust the octane rating; for example, reformate includes 5–12% benzene (Glass et al., 2000). Before 1950, a small proportion of gasoline enriched with benzene sold in the United Kingdom included up to 36% benzene (Lewis et al., 1997). Gasoline enriched with benzene included up to approximately 10% benzene in Canada during 1914–1938 (Armstrong et al., 1996) and in Australia until around 1970 (Glass et al., 2000).

The primary use of benzene today is in the manufacture of organic chemicals. In Europe, benzene is mainly used to make styrene, phenol, cyclohexane, aniline, maleic anhydride, alkylbenzenes, and chlorobenzenes. It is an intermediate in the production of anthraquinone, hydroquinone, benzene hexachloride, benzene sulfonic acid, and other products used in drugs, dyes, insecticides, and plastics (ICIS, 2010). In the USA, the primary use of benzene is in the production of ethylbenzene, accounting for 52% of the total benzene demand in 2008. Most ethylbenzene is consumed in the manufacture of styrene, which is used in turn in polystyrene and various styrene copolymers, latexes, and resins. The second-largest use of benzene in the USA (accounting for 22% of demand) is in the manufacture of cumene (isopropylbenzene), nearly all of which is consumed in phenol production. Benzene is also used to make chemical intermediates, including cyclohexane, used in making certain nylon monomers (15%); nitrobenzene, an intermediate for aniline and other products (7%); alkylbenzene, used in detergents (2%); chlorobenzenes, used in engineering polymers (1%); and miscellaneous other uses (1%) (Kirschner, 2009).

1.3 Measurement and analysis

1.3.1 Detection and quantification

Common standard methods to assay benzene in air are presented in Table 1.1, along with selected methods for measuring some biomarkers of exposure in urine.

Assays to monitor benzene in air were first developed to measure air concentration in the workplace, including personal exposure of workers, and to assess compliance with occupational limits. Typically, to measure 8-hour exposure, air is pumped through cartridges containing charcoal or other suitable sorbents for the duration of the entire work shift. In the laboratory, benzene is desorbed from sorbent using solvents such as carbon disulfide (NIOSH, 2003, method 1501) or high-temperature thermal desorption (NIOSH, 1996, method 2549), and analysed with either a gas

Table 1.1 Representative methods for the analysis of benzene in air and its main urinary biomarkers

Sample matrix	Analyte	Assay procedure	Limit of detection	Reference
Air	Benzene	Pumping air through solid sorbent tube, solvent desorption, and GC-FID	0.5 µg/sample (sample volume 5–30 L)	NIOSH (2003), method 1501
	Benzene	Pumping air through solid sorbent tube, thermal desorption, and GC-MS	100 ng per tube or less (sample volume 1–6 L)	NIOSH (1996), method 2549
	Benzene	Real-time monitor with FTIR detector	0.32 ppm for a 10 m absorption pathlength	NIOSH(2002), method 3800
	Benzene	Portable GC-PID	0.02 ppm	NIOSH (1994), method 3700
	Benzene	Passive sampling [with solid sorbent device], solvent/thermal desorption, and GC-MS	Variable depending on geometry of sampler and sampling time	EPA (2014)
Urine	*t*,*t*-MA	HPLC-UV analysis	5 µg/L	Lee et al. (2005)
	SPMA	SPE LC-MS/MS analysis	0.2 µg/L	NIOSH (2014), method 8326
	Benzene	HS GC-MS analysis	0.025 µg/L	Fustinoni et al. (1999)

FTIR, Fourier-transform infrared spectroscopy; FID, flame ionization detection; GC, gas chromatography; HPLC-UV, high-pressure liquid chromatography, ultraviolet spectroscopy; HS, head space; LC-MS/MS, liquid chromatography, tandem mass spectrometry; MS, mass spectrometry; PID, photoionization detector; SPE, solid phase extraction; SPMA, *S*-phenylmercapturic acid; *t*,*t*-MA, *trans*,*trans*-muconic acid

chromatograph equipped with a flame ionization detector (NIOSH, 2003, method 1501) or a mass spectrometer (NIOSH, 1996, method 2549). As an alternative, passive samplers do not need a pump and allow benzene sampling via air diffusion through them; see EPA (2014) for a review of different assays using passive samplers for the determination of volatile organic compounds, including benzene. The sensitivity of both active and passive assays depends on sample volume, desorption method, and instrumental analysis; a higher sampling volume, the use of thermal desorption, and detection by mass spectrometer are associated with greater sensitivity (detection by mass spectrometer also offers high specificity). The design determines the sampling rate for passive samplers; radial geometry warrants a high flow rate and therefore larger sampling volume over a specific sampling time (Cocheo et al., 2000).

A real-time monitor can be used to check for benzene leaks and to measure short-term exposure, especially during critical operations, allowing the simultaneous sampling of air and detection of benzene. Benzene can be separated from other chemicals by portable gas chromatography and detected by photoionization detector (NIOSH, 1994, method 3700), or can be measured by extractive Fourier-transform infrared spectrometry (NIOSH, 2002, method 3800).

The alternative method of measuring benzene exposure by biomonitoring dates to the 1980s (Lauwerys, 1983); the first biomarkers, such as phenol, have been progressively abandoned in favour of biomarkers that are less abundant but more specific. The currently recommended biomarkers for assessment of benzene exposure in the workplace include urinary *trans*,*trans*-muconic acid (*t*,*t*-MA), urinary *S*-phenylmercapturic acid (SPMA), and urinary benzene (INRS, 2017).

t,*t*-MA is a urinary metabolite of benzene accounting for about 4% of the absorbed dose. Formed and excreted in urine with rapid kinetics

with a half-life of about 5 hours (Boogaard & van Sittert, 1995), it is useful for assessment of recent exposure. It is measured using high-performance liquid chromatography with an ultraviolet detector (Lee et al., 2005), and standardized assays are present on the market. Its limitation is poor specificity, as *t*,*t*-MA is also produced by the metabolism of the preservative sorbic acid or sorbates contained in food and beverages (Ruppert et al., 1997; Weaver et al., 2000). *t*,*t*-MA is recommended when exposure is higher than 0.2 ppm (Kim et al., 2006a), depending on the amount of sorbic acid preservatives in the diet.

SPMA is a urinary metabolite of benzene accounting for less than 1% of the absorbed dose; it is formed and excreted in urine with rapid kinetics (half-life of ~9 hours; Boogaard & van Sittert, 1995). SPMA in urine is a specific biomarker, and is assayed using solid phase extraction followed by liquid chromatography coupled with tandem mass spectrometry (NIOSH, 2014, method 8326). The limitations of the use of this biomarker are the few standardized assays available and the high cost of the equipment to perform the assay. The variability associated with genetic polymorphism of glutathione *S*-transferase enzymes also affects urinary levels of SPMA (see Section 4.1).

Unmetabolized benzene is excreted in urine in a tiny proportion (< 0.1%) and with rapid kinetics (a half-life of a few hours). It is a specific biomarker, being uniquely indicative of exposure to benzene. It is assayed using online headspace sampling followed by gas chromatography or mass spectrometry (Fustinoni et al., 1999). A limitation in the use of urinary unmetabolized benzene is the lack of standardized assays; in addition, the volatility of benzene in urine may cause the loss of the analyte if no precautions are taken during sampling and in the storage of samples.

Both SPMA and urinary benzene are currently the biomarkers of choice to assess exposure to benzene in studies involving the general population (Fustinoni et al., 2005; Lovreglio et al., 2011; Andreoli et al., 2015).

1.3.2 Assessment of occupational exposure in epidemiological studies

A variety of exposure assessment methods have been used in epidemiological studies of workers potentially exposed to benzene; methods are summarized in the following sections. Additional details on exposure assessment methods used in key epidemiological studies evaluated by the Working Group are provided in Section 1.6.

(a) Occupational cohorts compared with the general population

Many early studies of chemical and petroleum industry workers compared mortality and cancer incidence in the workers and in the general population (e.g. Decouflé et al., 1983; Consonni et al., 1999; Divine et al., 1999; Koh et al., 2014) in terms of either standardized mortality ratios and/or standardized incidence ratios. Benzene was known to be present at such facilities, but benzene exposure estimates were not provided and benzene may not have been specifically mentioned in such studies. Where benzene is mentioned, the metrics are usually expressed as exposed/not exposed, sometimes with the duration or era of the exposed job included. In all cases, there could have been individuals occupationally exposed to benzene in the general population (comparison group).

(b) Expert assessment using interviews, personal questionnaires, or job-specific modules

In occupational studies, some investigators have classified workers with respect to benzene exposure from questionnaires, including those that probe for specific determinants of exposure, such as job-specific modules (e.g. Reid et al., 2011). Benzene exposure may be categorized

semiquantitatively, for example, "no exposure" versus "probable exposure", or "high" versus "medium" versus "low" exposure (e.g. Adegoke et al., 2003; Black et al., 2004; Miligi et al., 2006; Krishnadasan et al., 2007; Seidler et al., 2007). The interpretation of such exposure categories varies from one study to another, depending on the era, country, and industry sectors evaluated, for example.

In population-based studies, exposure must be assessed across a range of occupations and industries by evaluating the type and duration of jobs reported by study participants.

(c) Expert assessment using job characteristics with no individual-level measurements

In some studies, experts classify workers within certain employment start-date periods, industry sectors, and/or job or task categories as exposed or not exposed to benzene (e.g. Koh et al., 2011; Linet et al., 2015). These experts are usually from the specific facility, or at least from the industry sector, and are often occupational hygienists. In most studies the exposure groupings appeared to be performed before case identification, for example in cohort studies, or the assessors were case-blind for case–control studies. This methodology can be used for cohort studies (Infante et al., 1977; Wong, 1987a; Koh et al., 2011), or in case–control studies (e.g. Wong et al., 2006). Duration of exposure is a common metric in these types of studies, and provides a semiquantitative dimension to the exposure assessment. The metrics commonly used in these analyses are exposure category (where provided) and duration of exposed job. Broad exposure groupings were based on employment structure in several studies, for example hourly (potentially higher risk of exposure) versus salaried (potentially lower risk of exposure) workers (e.g. Wen et al., 1983; Wongsrichanalai et al., 1989; Honda et al., 1995). Some similar exposure assessments have a semiquantitative element, for example providing an exposure dimension of high, medium, or low for the work area (McMichael et al., 1975; Rushton & Alderson, 1981).

(d) Exposure assessment using quantitative measurements grouped by job characteristics

The strongest exposure estimates are those where measured benzene exposure data from relevant facilities were attributed by experts to individual job titles or work areas (e.g. Dosemeci et al., 1994). Exposure data may have been collected on an industry- or cohort-wide basis and then applied to specific individual participants, notably in nested case–control studies. This methodology has been applied in China in population-based case–control studies (Bassig et al., 2015), where measured exposure data from many industries has been available since the 1950s (e.g. Wong et al., 2010; Friesen et al., 2012).

There will be some imprecision in the application of a (usually) limited number of data points to other individuals, perhaps employed at other facilities or over different timeframes. Exposure may vary between facilities, between workers, and between days for the same worker, regardless of how average exposure data are assigned. It is important to ensure that the measurement data are representative of usual exposure (normal working circumstances), and include jobs for which lower and higher levels of exposure have been measured. The exposure estimates are quantitative and usually expressed as averaged mean benzene intensity (ppm or mg/m^3) or cumulative exposure (ppm-years or (mg/m^3)-years). The exposure grouping may take into account measured exposure data from multiple sites across a range of industry sectors (e.g. Portengen et al., 2016).

Data on personal exposure to benzene were not usually available before 1970, so extrapolations back in time may be needed. Exposure modifiers, for example, historical changes in work processes, percentage of benzene in petrol, or the presence of ventilation, may have been

used to estimate exposure for jobs and for eras where measured data may not be available or applicable (Armstrong et al., 1996; Lewis et al., 1997; Glass et al., 2000). These exposures were usually estimated with the aid of occupational hygienists from within the industry, and are discussed in more detail in Section 1.6.1. Smith et al. (1993) used such methodology to estimate total hydrocarbon exposure, from which Wong et al. (1999) estimated benzene exposure.

1.3.3 Exposure assessment for molecular epidemiology

Several factors should be considered in the design of epidemiological mechanistic studies. These include the congruency in the time period of effect or disease onset relative to exposure, the magnitude of effects observed, and inter- and intraindividual variability in the response.

For studies on cancer, long-term average exposure is relevant. The latency for leukaemia can be relatively short, for example less than 10 years (Finkelstein, 2000; Richardson, 2008), so exposure during this period should be characterized.

Shorter periods of more recent exposure should be considered for other end-points such as leukopenia (Lan et al., 2004), or chromosomal aberrations (Zhang et al., 1998; Marchetti et al., 2012) including genetic damage (Liu et al., 1996; Zhang et al., 2016). To identify changes in leukocyte numbers, for example, exposure to benzene in the 180 days before blood collection is relevant (Ward et al., 1996).

In a cross-sectional study, it is important to collect both exposure and outcome data for the same individuals to account for inter- and intraindividual variability associated with relevant parameters, for example, diet, smoking, shift work, and time-of-day effects. Data describing these factors should be collected systematically and incorporated within the analyses.

In assessing the exposure, a sufficient number of participants are needed to account for the variability in uptake and human metabolism, particularly where the biomarker of effect is labile (e.g. oxidative stress). In addition, repeated measurements to estimate average exposure are advisable to account for day-to-day variability in exposure.

Investigators should use recognized and validated methods of collection and analysis, ensuring quality by taking into account the most relevant parameters, including the limit of detection.

1.4 Occurrence and exposure

1.4.1 Occupational exposure

Benzene is a ubiquitous pollutant that is present in several industries and occupations, including the production and refining of oil and gas, the distribution, sale, and use of petroleum products, coke production, the manufacture and use of chemical products, automobile repair, shoe production, firefighting, and various operations related to engine exhaust. Due to the high volatility of benzene, occupational exposure to benzene mainly occurs via inhalation. Benzene also penetrates skin, but the degree of dermal absorption of benzene will depend upon the exposure scenario. Dermal absorption will vary according to the tasks being performed (e.g. dipping machinery parts, immersion of hands, or using petroleum-based products as degreasing agents), the benzene content of the product, the composition of the product containing benzene, contact time, and the area of the body on which the chemical resides (Kalnas & Teitelbaum, 2000; Williams et al., 2011; Jakasa et al., 2015). In these scenarios, the exposure will not usually be to pure benzene.

The major industries and occupations in which workers are potentially exposed to benzene are reviewed in the following sections. This

summary is not exhaustive, and the interested reader is referred to several reviews of occupational exposure to benzene across industries that have been published for Europe and North America (Runion & Scott, 1985; Nordlinder & Ramnäs, 1987; van Wijngaarden & Stewart, 2003; Capleton & Levy, 2005; Williams et al., 2008) and Asia (Kang et al., 2005; Liang et al., 2005; Navasumrit et al., 2005; Liu et al., 2009; Park et al., 2015). For some industries or applications, information in the literature is limited. For example, the use of pure benzene as a solvent and reagent in chemical laboratories is well known, but no report on exposure level of benzene was found for laboratory technicians apart from in the petroleum industry.

Although not exhaustive, Table 1.2 gives a summary of reported personal full-shift airborne benzene concentrations, while Table 1.3 summarizes biomonitoring data for the industries.

(a) Production, refining, and distribution of petroleum and petroleum-derived products

The petroleum industry can be divided into upstream and downstream segments. The upstream segment refers to conventional exploration, extraction, and production of crude oil and natural gas, described in the following section, as well as unconventional oil and gas development (UOGD). UOGD involves high-volume hydraulic fracturing, commonly referred to as "fracking", which is coupled to (vertical or horizontal) drilling to extract oil and gas from shale formations (i.e. extraction of materials other than crude oil and natural gas). UOGD includes the process of injecting large volumes of water, proppants (often sand), and potentially hazardous chemicals into wellbores at high pressure, fracturing the rock and enabling the outflow of trapped oil or gas from shale formations (EPA, 2013). The downstream segment consists of refinery operations (production and ancillary operations within the refinery and distribution depots, e.g. tank dipping, pump repairs, filter cleaning), distribution (loading of ships, railcars and road tankers, delivery to service stations), and retail of the petroleum fractions (attendant or self-service filling of customer vehicles).

(i) Upstream petroleum industry (conventional oil and gas extraction)

During drilling, the revolving steel bit must be lubricated and cooled, the well requires pressure support, and the rock cuttings must be transported to the surface. Drilling fluid, a complex oil- or water-based mixture, is used for these purposes. The characteristics of the hydrocarbon base oils in the drilling fluids have changed over time. Diesel as a base oil for drilling was gradually replaced in the early 1980s in the United Kingdom and Norway by petroleum-mineral oils with a reduced aromatic content; non-aromatic mineral oils (aromatic content < 0.01%) were used after 1998 (Gardner, 2003; Steinsvåg et al., 2006, 2007; Bråtveit et al., 2012). The mud-handling areas were originally designed for water-based mud that did not generate vapours, with open flow lines and mud pits. Other than measurements of oil mist and oil vapour, there have been very limited attempts to characterize the exposure regarding its composition. Theoretically, however, hydrocarbon and benzene exposure can occur through contamination of the drilling fluid from the geological formation in which it is drilled, or from hydrocarbons that are added to the drilling fluid to improve drilling properties, as in diesel and drilling fluids containing aromatics in the 1980s (Verma et al., 2000; Steinsvåg et al., 2007). With the exception of eight area measurements made during drilling in Canada showing a full-shift concentration of 0.006 mg/m^3 (with a highest measurement of 0.019 mg/m^3 and one personal measurement of < 0.010 mg/m^3), no information on this exposure scenario was available (Verma et al., 2000).

Table 1.2 Occupational exposure to benzene in air: personal measurements

Reference	Location, collection year	Occupational description, setting	*n*	Sampling time	Exposure concentration (mg/m^3)[a]	Exposure range (mg/m^3)[a]	Comments/additional data[a]
Upstream petroleum industry, unconventional							
Esswein et al. (2014)	USA, 2013	Flowback operations, workers gauging tanks	17	Full shift (typically 12 h)	AM (SD), 0.25 (0.16) ppm [0.8 (0.51)]	0.01–0.37 ppm [0.032–1.18]	Task-based short-term (2.5–30 min)
		Flowback operations, workers not gauging tanks	18	Full shift (typically 12 h)	AM (SD), 0.04 (0.03) ppm [0.13 (0.096)]	0.004–0.05 ppm [0.013–0.16]	
Upstream petroleum industry, conventional							
Bråtveit et al. (2007)	Norway, 2005	Process operators	35	657 min (range, 450–730 min)	AM (SD), 0.042 (0.132) ppm [0.13 (0.42)] GM, 0.005 ppm [0.016]	< 0.001–0.69 ppm [< 0.003–2.2]	Exposure varied according to tasks performed
		Flotation work	6		AM (SD), 0.221 (0.267) ppm [0.71 (0.85)] GM, 0.114 ppm [0.360]	0.030–0.688 ppm [0.095–2.2]	
		Sampling	11		AM (SD), 0.005 (0.005) ppm [0.16 (0.16)] GM, 0.003 ppm [0.096]	< 0.001–0.014 ppm [< 0.003–0.04]	
		Miscellaneous	18		AM (SD), 0.005 (0.01) ppm [0.16 (0.03)] GM, 0.003 ppm [0.096]	< 0.0010.023 ppm [< 0.003–0.07]	
Steinsvåg et al. (2007)	Norway, 1994–2003	Process and drilling operations (12 installations)	367	12 h	AM (SD), 0.037 (0.099) ppm [0.12 (0.32)] GM (GSD), 0.007 (5.7) ppm [0.22 (18.21)]	< LOD–2.6 ppm [< LOD–8.31]	165 measurements < LOD were set to LOD/√2

Table 1.2 (continued)

Reference	Location, collection year	Occupational description, setting	*n*	Sampling time	Exposure concentration (mg/m³)[a]	Exposure range (mg/m³)[a]	Comments/additional data[a]
Steinsvåg et al. (2007) (cont.)		Deck workers	29		AM (SD), 0.17 (0.51) ppm [0.54 (1.63)] GM (GSD), 0.010 (14) ppm [0.03 (44.7)]	< LOD–2.6 ppm [< LOD–8.31]	> LOD = 10
		Process operators	204		AM (SD), 0.036 (0.097) ppm [1.15 (0.31)] GM (GSD), 0.008 (5.3) ppm [0.026 (16.93)]	< LOD–0.97 ppm [< LOD–3.1]	> LOD = 101
		Laboratory	40		AM (SD), 0.012 (0.019) ppm [0.038 (0.06)] GM (GSD), 0.006 (3.7) ppm [0.019 (11.82)]	< LOD–0.11 ppm [< LOD–0.35]	> LOD = 13
		Mechanics	78		AM (SD), 0.006 (0.011) ppm [0.019 (0.035)] GM (GSD), 0.002 (4.5) ppm [0.006 (14.37)]	< LOD–0.08 ppm [< LOD–0.26]	> LOD = 37
		Electricians	16		AM (SD), 0.015 (0.017) ppm [0.048 (0.05)] GM (GSD), 0.007 (5.7) ppm [0.019 (18.85)]	< LOD–0.05 ppm [< LOD–0.16]	> LOD = 4
Kirkeleit et al. (2006b)	Norway, 2004	Crude oil production, vessel	139	592 min (range, 43–931 min)	AM, 0.43 ppm [1.37] GM (GSD), 0.02 (12.42) ppm [0.06 (39.7)]	< 0.001–16.75 ppm [< 0.003–53.5]	LOD, 0.001 ppm [0.003]

Table 1.2 (continued)

Reference	Location, collection year	Occupational description, setting	*n*	Sampling time	Exposure concentration (mg/m³)[a]	Exposure range (mg/m³)[a]	Comments/additional data[a]
Kirkeleit et al. (2006b) (cont.)		Process operators	30	669 min (range, 182–915 min)	AM, 0.39 ppm [1.25] GM (GSD), 0.01 (9.68) ppm [0.03 (30.92)]	< 0.001–7.3 ppm [< 0.003–23.32]	
		Deck workers	47	564 min (range, 43–866 min)	AM, 0.89 ppm [2.84] GM (GSD), 0.02 (19.11) ppm [0.06 (61.04)]	< 0.001–16.75 ppm [< 0.003–53.5]	The high exposure levels represent cleaning and maintenance of crude oil cargo tanks
		Mechanics	31	632 min (range, 257–705 min)	AM, 0.07 ppm [0.22] GM (GSD), 0.007 (12.04) ppm [0.02 (38.4)]	< 0.001–0.51 ppm [< 0.003–1.63]	
		Contractors	31	518 min (range, 190–931 min)	AM, 0.11 ppm [0.35] GM (GSD), 0.05 (4.90) ppm [0.16 (15.65)]	< 0.001–0.42 ppm [< 0.003–1.34]	
Verma et al. (2000)	Canada, 1985–1996	Conventional oil/gas	198	Long-term	AM, 0.206 GM, 0.036	0.003–7.78	For occupational groups see paper
		Conventional gas	838		GM, 0.010	0.006–57.6	
		Pipeline	8		AM, 0.392 GM, 0.350	0.16–1.54	
		Heavy oil processing	236		AM, 0.112 GM, 0.051	< 0.003–1.60	
Oil spill clean-up operations							
Gjesteland et al. (2017)	Norway, 2016	Sampling boats	21	10.8 h (range, 5.2–14.3 h)	AM, 0.43 ppm [1.37] GM (GSD), 0.20 (4.52) ppm [0.64 (14.44)]	0.01–1.52 ppm [0.03–4.86]	Field trial with spill of two fresh oils (22 workers, > 2 d)
		Workers on release ship and oil recovery ship	11	9.8 h (range, 5.2–12.5 h)	AM, 0.05 ppm [0.16] GM (GSD), 0.02 (0.02) ppm [0.064 (0.064)]	0.002–0.10 ppm [0.006–0.32]	
Downstream, petroleum refinery industry							
Almerud et al. (2017)	Sweden, 2009–2011	Process technicians, refinery I	132	Full shift (8 or 12 h)	AM, 0.153	95% CI, 0.01–0.022; maximum, 3.77	
		Maintenance workers, refinery I	67		AM, 0.0059	95% CI, 0.004–0.009; maximum, 1.32	

Table 1.2 (continued)

Reference	Location, collection year	Occupational description, setting	*n*	Sampling time	Exposure concentration (mg/m³)[a]	Exposure range (mg/m³)[a]	Comments/additional data[a]
Almerud et al. (2017) (cont.)		Process technicians outdoor, refinery II	66		AM, 0.0137	95% CI, 0.0083–0.023; maximum, 0.27	
		Laboratory workers, refinery I	25		AM, 0.0046	95% CI, 0.0034–0.0062; maximum, 0.0154	
		Laboratory workers, refinery II	11		AM, 0.0084	95% CI, 0.0034–0.021; maximum, 0.02	
Akerstrom et al. (2016)	Sweden, 2011–2013	Turnarounds, refinery I	43	Full shift (8 or 12 h)	AM, 0.61	95% CI, 0.23–1.60 µg/m³	
		Turnarounds, refinery II	26		AM (SD), 0.96 (1.3) GM (GSD), 0.23 (0.0075)	0.007–4.5	
		Oil harbour workers (jetty workers and dock workers)	34		AM, 0.31	95% CI, 0.08–1.2	
		Sewage tanker drivers	16		AM, 0.36	95% CI, 0.068–1.9	
Widner et al. (2011)	USA, 1977–2005	Refinery and dock workers	406	480–661 min	NR	0.006–15 ppm [0.19–47.9]	GM not calculated because > 50% of measurements < LOD
		Dock connecting crew	179	535–664 min	GM (GSD), 0.023 (11) ppm [0.073 (35.1)]	0.010–15 ppm [0.03–47.9]	
		Contractor–tankerman	38	326–463 min	GM (GSD), 0.25 (8.8) ppm [0.8 (28.1)]	0.010–9.8 ppm [0.03–31.3]	
Kreider et al. (2010)	USA, 1977–2006	Routine operation, all areas and job titles	624	> 180 min	AM, 0.091 ppm [0.29]	Minimum–maximum detected, 0.004–6.0 ppm [0.013–19.2] 75th, 95th percentile, 0.043, 0.31 ppm [0.14–0.99]	GM not calculated because > 50% of measurements < LOD

Table 1.2 (continued)

Reference	Location, collection year	Occupational description, setting	*n*	Sampling time	Exposure concentration (mg/m³)[a]	Exposure range (mg/m³)[a]	Comments/additional data[a]
Kreider et al. (2010) (cont.)		Start up	50		AM, 0.046 ppm [0.15]	Minimum–maximum detected, 0.015–0.29 ppm [0.048–0.93] 75th, 95th percentile, 0.05, 0.17 ppm [0.16, 0.54]	
		Turnaround	471		AM, 0.17 ppm [0.54] GM (GSD), 0.032 (6.7) ppm [0.1 (21.4)]	Minimum–maximum detected, 0.004–9.200 ppm [0.013–29.4] 75th, 95th percentile, 0.12, 0.68 ppm [0.38, 2.17]	
CONCAWE (2002)	Europe, 1999–2001	Offsite refinery operator	6	451–498 min	AM, 0.3 GM, 0.2	10–90th percentiles, 0.1–0.5	
		Laboratory technician blending test gasoline for research	7	215–487 min	AM, 3.7 GM, 1.6	10–90th percentiles, 0.2–8.3	
CONCAWE (2000)	Europe, 1993–1998	Onsite operators (including catalytic reformer, gasoline blending)	97	Full shift	AM, 0.22	0.008–7.88	91% corresponding to full shift (8 or 12 h)

Table 1.2 (continued)

Reference	Location, collection year	Occupational description, setting	*n*	Sampling time	Exposure concentration (mg/m³)[a]	Exposure range (mg/m³)[a]	Comments/additional data[a]
CONCAWE (2000) (cont.)		Refinery offsite operators (tank farm, including dipping, sampling, valve operation, dewatering, loading rail cars)	321		AM, 0.32	0.008–23.3	
		Refinery maintenance workers (pump maintenance, instrument calibration, enclosed equipment)	373		AM, 0.41	0.008–18.1	
		Refinery laboratory technicians (including product analysis, octane rating testing)	628		AM, 0.30	0.0015–5.0	
		Tank cleaners (including sludge cleaning)	49		AM, 2.10	0.008–38.7	
Downstream, distribution							
Lovreglio et al. (2016)	Italy, NR	Fuel tanker drivers	17	8 h	AM (SD), 0.28 (0.248) Median, 0.246	0.0074–1.017	
CONCAWE (2002)	Europe, 1999–2001	Rail car operators, top loading with vapour recovery)	21	64–363 min	AM, 0.5 GM, 0.4	10–90th percentiles, 0.2–0.7	
		Rail car operators, top loading without vapour recovery	16	165–450 min	AM, 4.0 GM, 1.4	10–90th percentiles, 0.3–10	
CONCAWE (2002)	Europe, 1999–2001	Road tanker distribution; drivers, bottom loading with vapour recovery	33	185–555 min	AM, 0.6 GM, 0.4	10–90th percentiles, 0.2–1.2	Pre-2000 specification gasoline

Table 1.2 (continued)

Reference	Location, collection year	Occupational description, setting	*n*	Sampling time	Exposure concentration (mg/m³)[a]	Exposure range (mg/m³)[a]	Comments/additional data[a]
CONCAWE (2000)	Europe, 1993–1998	Marine and rail loading; ship deck crew, open loading	41	Full shift	AM, 0.56	0.08–5.4	91% corresponding to full shift (8 or 12 h)
		Ship deck crew, closed loading	2		AM, 0.56	0.51–0.6	
		Ship deck crew, unloading	32		AM, 0.51	0.023–3.7	
		Jetty staff	46		AM, 0.37	0.023–1.7	
CONCAWE (2000)	Europe, 1993–1998	Road tanker distribution Road tanker drivers, top loading	69	Full shift	AM, 2.07	0.04–48.2	
		Road tanker drivers, bottom loading (without vapour recovery)	223		AM, 0.82	0.008–15	
		Road tanker drivers, bottom loading (with vapour recovery)	137		AM, 0.37	0.03–1.99	
		Drivers, other category or unspecified	56		AM, 1.26	0.07–19.2	
		Road tanker terminal rack operators	126		AM, 0.64	0.003–4.2	
		Road tanker terminal supervisors/ operators	151		AM, 0.36	0.001–3.1	
		Road tanker terminal maintenance	52		AM, 0.52	0.001–7.9	
Foo (1991)	Singapore	Petroleum delivery tanker drivers	14	Full shift	AM, 1.10 ppm [3.51] GM, 0.81 ppm [2.59]	0.08–2.37 ppm [0.26–7.57]	21 gasoline stations Short-term exposure (n = 7): AM, 3.1 ppm [9.9], range 0.07–11.6 ppm [0.22–37.05]

Table 1.2 (continued)

Reference	Location, collection year	Occupational description, setting	*n*	Sampling time	Exposure concentration (mg/m³)[a]	Exposure range (mg/m³)[a]	Comments/additional data[a]
Petrochemical manufacturing							
Sahmel et al. (2013)	USA, 1974–1999	Use of petroleum-based raw materials;	2359	8 h	AM (SD), 0.54 (5.0) ppm [1.72 (15.97)] Median, 0.042 ppm [0.13]	NR	
		Routine employee exposure (all) 1974–1986	1289		AM (SD), 0.885 (6.72) ppm [2.83 (21.47)] Median, 0.12 ppm [0.38]	NR	Median exposure during time periods corresponding to year when OEL changed
		1987–1999	1070		AM (SD), 0.125 (0.676) ppm [0.4 (2.16)] Median, 0.016 ppm [0.051]	NR	
		1974–1983	916		AM (SD), 1.103 (7.739) ppm [3.52 (24.72)] Median, 0.19 ppm [0.61]	NR	Median exposure during time periods stratified according to key process changes
		1984–1991	865		AM (SD), 0.206 (2.024) ppm [0.66 (6.47)] Median, 0.01 ppm [0.03]	NR	
		1992–1999	578		AM (SD), 0.148 (0.578) ppm [0.47 (1.85)] Median, 0.021 ppm [0.067]	NR	
Williams & Paustenbach (2005)	USA, 1976–1987	Petrochemical manufacturing facility (acetic acid); mainly process operators	749	4–10 h	AM (SD), 1.75 (3.8) ppm [5.59 (12.14)]	NR	See paper for mean exposure levels for various production processes/areas
Coke production							
He et al. (2015)	China, NR	Topside, plant A	27	8 h	AM (SD), 0.705 (0.259)	0.268–1.197	Plant A: top charging of coal; no air pollution control
		Topside, plant B	28		AM (SD), 0.290 (0.11)	0.085–0.489	Plant B: stamp charging of coal; bag house for air pollution control

Table 1.2 (continued)

Reference	Location, collection year	Occupational description, setting	*n*	Sampling time	Exposure concentration (mg/m³)[a]	Exposure range (mg/m³)[a]	Comments/additional data[a]
Bieniek & Łusiak (2012)	Poland, 2005–2010	Cokery workers	202	Full shift	0.15	0.01–1.79	
		Coke oven workers	122		Median, 0.16	5–95th percentile, 0.04–0.60	
		Coke by-products	37		Median, 0.37	5–95th percentile, 0.061–1.39	
		Other workers in the coke plant	43		Median, 0.09	5–95th percentile, 0.011–0.292	Electricians and supervising personnel
Kivistö et al. (1997)	Estonia, 1994	Cokery workers	18	Full shift	AM (SD), 1.3 (2.7) ppm [4.15 (8.62)] Median, 0.4 ppm [1.28]	0.09–11.7 ppm [0.29–37.37]	
		Benzene factory workers	20		AM (SD), 1.6 (3.3) ppm [5.11 (10.54)] Median, 0.6 ppm [1.92]	0.06–14.7 ppm [0.19–46.96]	
Drummond et al. (1988)	UK, 1986	Battery workers	NR	Full shift	AM, 0.31 ppm [0.99]	NR	Each worker measured for 3–5 consecutive shifts
		Refining process of benzene	NR		AM, 1.32 ppm [4.22]	Maximum, 4.3 ppm [13.74]	
Petrol stations							
Campo et al. (2016)	Italy, 2008–2009	Petrol station attendants	89	~5 h	Median, 0.059	5–95% CI, 0.005–0.284	
Lovreglio et al. (2016)	Italy, NR	Filling station attendants	13	8 h	AM (SD), 0.02 (0.015) Median, 0.0138	0.0045–0.0534	
Lovreglio et al. (2014)	Italy, NR	Filling station attendants	24	8 h	AM (SD), 0.023 (0.017) Median, 0.02	0.0045–0.0663	
Bahrami et al. (2007)	Islamic Republic of Iran, NR	Petrol station workers	25	2–4 h	AM (SD), 1.40 (0.80) ppm [4.47 (2.56)]	0.2–3.1 ppm [0.64–9.9]	
Navasumrit et al. (2005)	Thailand, NR	Petrol station attendants	50	8 h	AM (SD), 121.67 (14.37) ppb [0.39 (0.046)] GM, 86.4 ppb [0.28]	2.80–439.9 ppb [0.0089–1.42]	
CONCAWE (2002)	Europe, 1993–1998	Service station attendants, without vapour recovery	26	189–465 min	AM, 0.3 GM, 0.3	10–90th percentile, 0.2–0.5	Pre-2000 specification gasoline

Table 1.2 Occupational (continued)

Reference	Location, collection year	Occupational description, setting	*n*	Sampling time	Exposure concentration (mg/m³)[a]	Exposure range (mg/m³)[a]	Comments/additional data[a]
CONCAWE (2002) (cont.)		Service station attendants, with vapour recovery	7	288–437 min	AM, 0.1 GM, 0.1	10–90th percentile, 0.1–0.1	
		Service station cashiers	13	235–490 min	AM, 0.2 GM, 0.2	0.1–0.2	
		Service station workers, miscellaneous	6	237–280 min	AM, 0.2 GM, 0.1	0.1–0.2	
CONCAWE (2000)	Europe, 1993–1998	Service station attendants, without vapour recovery	417	Full shift	AM, 0.25	0.001–1.9	91% corresponding to full shift (8 or 12 h)
		Service station cashiers	268		AM, 0.05	0.001–1.92	
		Petrol pump maintenance workers	2		AM, 0.55	0.16–0.93	
		Service station workers, miscellaneous	5		AM, 0.03	0.01–0.10	
Lagorio et al. (1994)	Italy, 1991–1992	Petrol station attendants	27	8 h	AM (SD), 1.73 (5.53)	NR	Alkylated and lead-free gasoline: 2.86% and 2.65% benzene by volume, respectively
Lagorio et al. (1993)	Italy, 1992	Filling station attendants	111	8 h	AM (SD), 0.55 (2.46) GM (GSD), 0.12 (3.82)	0.001–28.02	111 filling stations
Foo (1991)	Singapore, NR	Gasoline kiosk attendants	54	Full shift	AM, 0.20 ppm [0.64] GM, 0.16 ppm [0.51]	0.028–0.71 ppm [0.89–2.27]	21 gasoline stations Short-term exposure (n = 49): AM, 6.6 ppm [21.08]; GM, 1.0 ppm [3.19]; range, 0.064–179 ppm [0.20–571.78]
Runion & Scott (1985)	USA, 1978–1783	Retail service stations	1478	Full shift	AM (SD), 0.06 (0.02) ppm [0.19 (0.06)] GM (GSD), 0.02 (5.4) ppm [0.06 (17.25)]	< 1.0 to > 10 ppm [< 3.19 to > 31.9] Range, NR	

Table 1.2 (continued)

Reference	Location, collection year	Occupational description, setting	*n*	Sampling time	Exposure concentration (mg/m³)[a]	Exposure range (mg/m³)[a]	Comments/additional data[a]
Automobile repair							
Egeghy et al. (2002)	USA, 1998–1999	Mechanics	197	4 h	AM (SD), 0.118 (0.166) Median, 0.0597	< 0.009–1.14	Self-administered sampling; benzene content of gasoline < 1%
Javelaud et al. (1998)	France, 1996	Mechanics	65	8 h	AM (SD), 0.48 (1.49) GM, 0.06 Median, 0.14	< 0.005–9.31	23 garages
Hotz et al. (1997)	Country NR, 1994–1995	Mechanics	156	8 h	Median, 0.01 ppm [0.032]	5–95th percentile, < LOD–0.14 ppm [< LOD–0.45]	
Foo (1991)	Singapore, NR	Motorcar service mechanics	54	Full shift	AM, 0.17 ppm [0.54] GM, 0.10 ppm [0.32]	0.014–1.7 ppm [0.045–5.43]	21 gasoline stations
Nordlinder & Ramnäs (1987)	Sweden, NR	Mechanics, small garage (summer)	> 100	Full shift	AM, 1.6	NR	
		Mechanics, small garage (winter)			AM, 6.8	NR	
		Mechanics, medium and large garages (summer)			AM, 0.4	NR	
		Electricians, medium and large garages (summer)			AM, 1.0	NR	
		Mechanics, medium and large garages (winter)			AM, 0.8	NR	
		Electricians, medium and large garages (winter)			AM, 1.4	NR	
Exposure from engine exhaust							
Arayasiri et al. (2010)	Thailand, 2006	Traffic police	24	8 h	AM (SD, 0.0382 (0.0027) Median, 0.039	(0.0155–0.069)	
		Office police	24		AM (SE), 0.007 (0.0005) Median, 0.0062	0.0036–0.014	
Manini et al. (2008)	Italy, 2005	Traffic police	19	6 h	AM, 0.0061	0.0003–0.012	

Table 1.2 (continued)

Reference	Location, collection year	Occupational description, setting	*n*	Sampling time	Exposure concentration (mg/m³)[a]	Exposure range (mg/m³)[a]	Comments/additional data[a]
Bahrami et al. (2007)	Islamic Republic of Iran, NR	Taxi drivers	60	2–4 h	AM (SD), 0.31 (0.22) ppm [0.99 (0.7)]	0.07–0.95 ppm [0.22–3.03]	
Manini et al. (2006)	Italy, 2004	Taxi drivers	37	24 h	AM (SD), 0.006 (0.0017)	NR	Non-smokers, ambient concentration in taxi during the 12 h shift, 0.0075 (0.0019)
Crebelli et al. (2001)	Italy, 1998–1999	Traffic police	139	7 h	AM (SD), 0.009 (0.011) GM (GSD), 0.0068 (0.002)	0.0013–0.0767	
		Office police	63		AM (SD), 0.0038 (0.0015) GM (GSD), 0.0035 (0.0015)	0.0011–0.0083	
Fustinoni et al. (1995)	Italy, 1994	Traffic wardens, urban and outdoors	20	5 h	AM (SD), 0.053 (0.03)	0.02–0.108	
		Traffic wardens, indoors (clerks)	19		AM (SD), 0.029 (0.008)	0.017–0.044	
Navasumrit et al. (2005)	Thailand, NR	Cloth vendors	22	8 h	AM (SD), 22.61 (1.32) ppb [0.073 (0.004)] Median, 21.1 ppb [0.067]	13.9–40.7 ppb [0.044–0.13]	
		Grilled-meat vendors	21		AM (SD), 28.19 (2.23) ppb [0.09 (0.007)] Median, 24.61 ppb [0.078]	16.8–52.0 ppb [0.054–0.17]	
Shoemaking							
Azari et al. (2012)	Islamic Republic of Iran, NR	Shoemakers, 12 workshops (October)	48	8 h	Mean (SE), 1.10 (0.11) ppm [3.51 (0.35)]	NR	Three consecutive months (October–December), examined effects of climate change and restriction of air flow due to closure of windows and shutdown of general ventilation systems
		Shoemakers, 12 workshops (November)			Mean (SE), 1.37 (0.14) ppm [4.38 (0.45)]	NR	
		Shoemakers, 12 workshops (December)			Mean (SE), 1.52 (0.18) ppm [4.86 (0.57)]	NR	

Table 1.2 (continued)

Reference	Location, collection year	Occupational description, setting	*n*	Sampling time	Exposure concentration (mg/m³)[a]	Exposure range (mg/m³)[a]	Comments/additional data[a]
Estevan et al. (2012)	Spain, 2002–2007	Shoemakers: 2002–2003	329	NR	AM (SD), 0.05 (0.15)	NR	18–26% of samples were ≥ LOD (0.01)
		Shoemakers: 2004–2005	218		AM (SD), 0.07 (0.14)	NR	
		Shoemakers: 2006–2007	302		AM (SD), 0.05 (0.14)	NR	
Zhang et al. (2011)	China, NR	Shoemakers	44	8 h	AM (SD), 44.81 (33.59) GM (GSD), 27.91 (3.29)	2.57–146.11	
Vermeulen et al. (2004)	China, 2000–2001	Large shoe factory (safety shoes): all workers	2667	8 h	AM, 3.46 ppm [11.05] GM (GSD), 1.28 (3.64) ppm [4.09 (11.63)]	10–90th percentiles, 0.20–7.00 ppm [0.64–22.4]	No glues reported to contain benzene
		Large shoe factory (safety shoes): cutting	427		AM, 0.45 ppm [1.44] GM (GSD), 0.34 (2.05) ppm [1.09 (6.55)]	0.17–0.15 ppm [0.54–3.67]	
		Large shoe factory (safety shoes): modelling	735		AM, 2.74 ppm [8.75] GM (GSD), 1.71 (2.81) ppm [5.46 (8.98)]	0.38–6.04 ppm [1.21–19.29]	
		Large shoe factory (safety shoes): fitting	1096		AM, 2.19 ppm [7] GM (GSD), 1.12 (2.98) ppm [3.58 (9.52)]	0.26–4.68 ppm [0.83–14.95]	
		Large shoe factory (safety shoes): finishing	241		AM, 8.35 ppm [26.67] GM (GSD), 2.91 (3.33) ppm [9.3 (10.64)]	0.65–11.69 ppm [2.08–37.34]	
		Large shoe factory (safety shoes): packing	168		AM, 15.55 ppm [49.67] GM (GSD), 7.60 (3.47) ppm [24.28 (11.08)]	1.43–43.06 ppm [4.57–137.55]	
		Small shoe factory (luxury shoes): all workers	116	8 h	AM, 21.86 ppm [69.83] GM (GSD), 14.4 (2.31) ppm [46 (7.38)]	10–90th percentiles, 5.23–50.63 ppm [16.71–161.73]	6 of 7 glues contained benzene (0.60–34% benzene)

Table 1.2 (continued)

Reference	Location, collection year	Occupational description, setting	*n*	Sampling time	Exposure concentration (mg/m³)[a]	Exposure range (mg/m³)[a]	Comments/additional data[a]
Vermeulen et al. (2004) (cont.)		Small shoe factory (luxury shoes): cutting	41		AM:10.96 ppm [35.01] GM (GSD), 10.24 (1.45) ppm [32.71 (4.63)]	6.53–16.26 ppm [20.86–51.94]	
		Small shoe factory (luxury shoes): modelling	18		AM, 9.04 ppm [28.88] GM (GSD), 7.75 (1.75) ppm [24.76 (5.59)]	4.45–18.69 ppm [14.21–59.7]	
		Small shoe factory (luxury shoes): fitting	47		AM, 29.31 ppm [93.62] GM (GSD), 21.34 (2.34) ppm [68.17 (7.47)]	7.06–65.17 ppm [22.55–208.17]	
		Small shoe factory (luxury shoes): finishing	10		AM, 54.64 ppm [174.54] GM (GSD), 28.03 (3.30) ppm [89.54 (10.54)]	7.62–179.60 ppm [24.34–573.69]	
Printing							
Portengen et al. (2016)	China, 1949 to after 2000	Printing	232	NR	AM, 94.1 GM (GSD), 8.2 (13.0)	NR	40% of measurements < LOD (3.19)
Kang et al. (2005)	Republic of Korea, 1992–2000	Offset printing	4	NR	AM (SD), 0.017 (0.012) ppm [0.0543 (0.038)] GM (GSD), 0.014 ppm [0.0447]	0.008–0.034 ppm [0.0255–0.11]	
Handling of jet fuel							
Smith et al. (2010)	USA, NR	US Air Force personnel					LOD, 0.9 µg/m³ Jet fuel JP-8 (0.004–0.007% benzene)
		All	69	Full shift	GM (GSD), 0.0016 (0.0035)	< LOD–0.0364	
		Group assumed exposed to concentration	25	Full shift	GM (GSD), 0.0029 (0.0034)	< LOD–0.0364	
Egeghy et al. (2003)	USA, NR	US Air Force personnel					Jet fuel JP-8 (0.0002–0.0123 weight% benzene)
		Group exposed to low concentration	140	4 h	Median, 0.0031	< 0.001–0.0613	
		Group exposed to moderate concentration	38	4 h	Median, 0.0074	0.0014–1.85	
		Group exposed to high concentration	114	4 h	Median, 0.252	0.0061–6.63	

Table 1.2 (continued)

Reference	Location, collection year	Occupational description, setting	*n*	Sampling time	Exposure concentration (mg/m³)[a]	Exposure range (mg/m³)[a]	Comments/additional data[a]
Holm et al. (1987)	Sweden, 1983–1984	Swedish National Defence	92	12 h	GM (GSD), 0.06 (4.0)	Maximum, 7.2	Jet fuel MC-77 (equivalent to JP4 (< 1% benzene)
		All samples	46	8 h (TWA)	GM (GSD), 0.06 (4.1)	Maximum, 4.1	
		Jet fuel handling	6		GM (GSD), 0.03 (2.6)	Maximum, 0.1	
		Flight service	28		GM (GSD), 0.08 (3.6)	Maximum, 1.2	
		Workshop service	12		GM (GSD), 0.05 (5.7)	Maximum, 4.1	
		Pure jet fuel exposure	38		GM (GSD), 0.06 (4.2)	Maximum, 4.1	
		Mixed solvents exposure	8		GM (GSD), 0.11 (3.1)	Maximum, 0.5	
Firefighting							
Reinhardt & Ottmar (2004)	USA, 1992–1995	Initial attack (full shift)	45	13.3 h (range, 12–18 h)	GM, 3 ppb [0.096]	Maximum, 24 ppb [0.077]	13 d of initial attack incidents
		Initial attack (at fires)		3.3 h (range, 2–10 h)	GM, 14 ppb [0.045]	Maximum, 43 ppb [0.14]	
		Project wildfires (full shift)	84	13.9 h (range, 4–24 h)	GM, 4 ppb [0.013]	Maximum, 249 ppb [0.8]	17 d at eight separate project wildfires
		Project wildfires (at fires)		10.4 h (range, 2–24 h)	GM, 6 ppb [0.019]	Maximum, 384 ppb [1.23]	
		Prescribed burns (full shift)	200	11.5 h (range, 6–18 h)	GM, 16 ppb [0.051]	Maximum, 58 ppb [0.19]	39 prescribed burns
		Prescribed burns (at fires)		7 h (range, 2–13 h)	GM, 28 ppb [0.089]	Maximum, 88 ppb [0.28]	
Austin et al. (2001)	Canada, NR	Structural fires	9	Short-term	AM (SD), 3.38 (3.45) ppm [10.8 (11.02)]	0.12–10.76 ppm [0.38–34.37]	Area samples (not personal)
Bolstad-Johnson et al. (2000)	USA, 1998	Structural fires	95	Short-term	AM (SD), 0.383 (0.425) ppm [1.22 (1.36)]	0.07–1.99 ppm [0.22– 6.36]	25 fires

AM, arithmetic mean; CI, confidence interval; d, day(s); GM, geometric mean; GSD, geometric standard deviation; h, hour(s); LOD, limit of detection; min, minute(s); *n*, number of measurements; NR, not reported; OEL, occupational exposure limit; ppb, parts per billion; ppm, parts per million; SD, standard deviation; SE, standard error; TWA, time-weighted average

[a] Exposure concentrations and range given in mg/m³, unless indicated otherwise; if published in another unit, the concentration in mg/m³ is given in square brackets

Table 1.3 Summary of selected studies on the biological monitoring of occupational exposure to benzene

Reference	Country, year	Occupational description	No. of participants	Benzene exposure in air (μg/m³)[a, b]	Urinary *t,t*-MA (μg/g creatinine)[a,c]	Urinary SPMA (μg/g creatinine)[a,c]	Urinary benzene (μg/L)[a,d]	Other biomarkers[a]
Campo et al. (2016)	Italy, NR	Filling station attendants	89	Median, 59 (5–284)[e]	Median, 127 (27–522)[e] μg/L	Median, 0.19 (< 0.1–1.28)[e] μg/L	Median, 0.339 (0.090–2.749)[e]	NR
		Unexposed workers	90	4 (1–18)[e]	Median, 117 (< 20–509)[e] μg/L	Median, < 0.1 (< 0.1–0.99)[e] μg/L	Median, 0.157 (0.054–2.554)[e]	NR
Lv et al. (2014)	China, NR	Shoe manufacturing workers	55	GM, 6980	NR	GM, 99[e]	NR	NR
Fustinoni et al. (2011)	Poland, NR	Petrochemical refinery workers	71	Median, 190 (50–2310)[e]	NR	Median, 0.65 (0.12–5.3)[e]	Median, 0.55 (0.117–7.487)[e]	NR
		Petrochemical office workers	97	NR	NR	Median, 0.40 (< 0.10–2.29)[e]	Median, 0.32 (0.083–2.316)[e]	NR
Carrieri et al. (2010)	Italy, 2006	Petrochemical workers	29	0.014 (< 0.001–0.280) ppm [45 (< 3–890)]	101 (< 6.86–746)	2.8 (< 0.06–38.59)	NR	NR
Lovreglio et al. (2010)	Italy, NR	Fuel tanker drivers	18	307 (7.4–1017)	134 (16–400)	2.94 (0.25–12.13)	2.96 (0.16–10.4)	Urinary phenol, 19 (5.0–33.0) mg/L
		Filling station attendants	23	23.5 (4.5–66.3)	86 (11–157)	0.79 (0.05–3.33)	0.62 (0.04–2.87)	Urinary phenol, 17.1 (8.0–29.0) mg/L
		Controls	31	4.6 (< 3.0–11.5)	93 (13–734)	0.65 (0.03–4.48)	1.23 (< 0.02–11.4)	Urinary phenol, 18.6 (3.0–36.0) mg/L
Hoet et al. (2009)	NR	Petrochemical workers	110	< 0.1 ppm [< 320]	50 (< 20–980)	0.97 (0.21–12.78)	0.270 (< 0.10–5.35)	Blood benzene, 0.405 (< 0.10–13.58) μg/L
Bråtveit et al. (2007)	Norway, 2004–2005	Petrochemical workers	12	0.042 (< 0.001–0.69) ppm [130 (< 3–2200)]	NR	NR	3.9 (0.5–34) nmol/L	Post shift; blood benzene, 1.8 (1.0–4.0) nmol/L
		Catering operator and office employees	9	NR	NR	NR	1.6 (0.5–4.0) nmol/L	Blood benzene, 1.8 (1.0–4.0) nmol/L

Table 1.3 (continued)

Reference	Country, year	Occupational description	No. of participants	Benzene exposure in air (μg/m³)[a, b]	Urinary *t,t*-MA (μg/g creatinine)[a,c]	Urinary SPMA (μg/g creatinine)[a,c]	Urinary benzene (μg/L)[a,d]	Other biomarkers[a]
Bahrami et al. (2007)	Islamic Republic of Iran, NR	Taxi drivers	60	0.31 (0.07–0.95) ppm [990 (220–3030)]	310 (90–1270)	NR	NR	NR
		Petrol station workers	9	1.40 (0.2–3.1) ppm [4470 (640–9900)]	2640 (1200–3280)	NR	NR	NR
		Controls	18	ND	170 (10–350)	NR	NR	NR
Manini et al. (2006)	Italy, 2004	Taxi drivers	21 NS	7.5	122	GM, 2.14	GM, 0.44	NR
			16 S	8.1	154	GM, 3.79	GM, 2.58	NR
Kim et al. (2006a)	China, 2000–2001	Shoemaking factory workers	164 women	Median, 1.28 (0.017–88.9) ppm [4090 (54–284 000)]	Median, 13.5 (0.644–426) μmol/L	Median, 262 (1.50–29 400) nmol/L	Median, 283 (6.21–53 900) nmol/L	NR
			86 men	Median, 1.05 (0.122–50.2) ppm [3350 (390–160 350)]	Median, 10.3 (1.50–370) μmol/L	Median, 137 (3.68–33 000) nmol/L	Median, 216 (19.4–42 600) nmol/L	NR
		Clothes manufacturing workers (controls)	87 women	Median, 3.40 (0.146–21.2) ppb [10.86 (0.47–67.72)]	Median, 1.06 (0.152–6.17) μmol/L	Median, 1.94 (0.591–86.4) nmol/L	Median, 1.48 (0.091–7.47) nmol/L	NR
			52 men	Median, 3.71 (0.146–533) ppb [11.85 (0.47–1702.55)]	Median, 1.09 (0.132–5.78) μmol/L	Median, 3.24 (0.591–68.1) nmol/L	Median, 1.59 (0.091–130) nmol/L	NR
Fustinoni et al. (2005)	Italy, 1999–2000	Filling station attendants	78	Median, 61 (11–478)	NS: Median, 49 (< 10–581) μg/L	Median, 5.8 (0.2–10.9) μg/L	Median, 0.342 (0.042–2.836)	NR
					S: Median,144 (15–321) μg/L	Median, 7.5 (0.2–24.8) μg/L	Median, 1.168 (0.055–5.111)	Section 1.01 NR
		Traffic police	77	Median, 22 (9–316)	NS: Median, 82 (< 10–416) μg/L	NS: Median, 5.3 (0.2–13.8) μg/L	NS: Median, 0.151 (0.025–0.943)	NR
					S: Median, 213 (52–909) μg/L	S: Median, 9.1 (2.4–13.8) μg/L	S: Median, 0.753 (0.054–4.246)	NR
		Office workers	58	Median, 6 (< 6–115)	NS: Median, 33 (< 10–1089) μg/L	NS: Median, 4.1 (0.2–12.5) μg/L	NS: Median, 0.133 (< 0.015–0.409)	NR
					S: Median, 71 (< 10–270) μg/L	S: Median, 8.0 (0.2–13.9) μg/L	S: Median, 0.331 (0.064–4.615)	NR

Table 1.3 (continued)

Reference	Country, year	Occupational description	No. of participants	Benzene exposure in air (μg/m³)[a, b]	Urinary *t,t*-MA (μg/g creatinine)[a,c]	Urinary SPMA (μg/g creatinine)[a,c]	Urinary benzene (μg/L)[a,d]	Other biomarkers[a]
Fustinoni et al. (2005) (cont.)		Bus drivers	152	Median, 21 (< 6–92)	NS: Median, 57 (< 10–536) μg/L	NS: Median, 5.6 (0.2–13.3) μg/L	NR	NR
					S: Median, 174 (< 10–695) μg/L	S: Median, 9.3 (0.2–65.9) μg/L	NR	NR
		Researchers	49	Median, 9 (< 6–46)	NS: Median, 51 (< 10–181) μg/L	NS: Median, 9.0 (0.2 – 182.2) μg/L	NR	NR
					S: Median, 195 (< 10–444) μg/L	S: Median, 13.7 (3.0–19.9) μg/L	NR	NR
Chakroun et al. (2002)	Tunisia, NR	Tanker fillers	20	0.16 (0.02–0.42) ppm [510 (63.89–1340)]	350 (80–1110)	NR	NR	NR
		Filling station attendants	10	0.20 (0.09–0.52) ppm [640 (290–1660)]	310 (150–590)	NR	NR	NR
		Controls	20	ND	110 (20–390)	NR	NR	NR
Waidyanatha et al. (2001, 2004)	China, ~1995	Rubber, adhesive, and paint manufacturers	42	14.5 (1.65–30.6) ppm [46 320 (5270–97 740)]	16 200 (1140–77 800) μg/L	712 (050–5890) μg/L	8.42 (0.837–27.9)	NR
				109 (31.5–329) ppm [348 180 (100 620–1 050 920)]	51 300 (7250–133 000) μg/L	9420 (123–27 500) μg/L	50.2 (1.30–284)	NR
		Sewing machine manufacturing workers (controls)	41	0.015 (0.0–0.11) ppm [48 (0.0–350)]	108 (020–338) μg/L	21 (2–79) μg/L	0.145 (0.027–2.06)	NR
Kivistö et al. (1997)	Estonia, 1994	Benzene production (in winter)	25	1.6 (0.06–14.7) ppm [5110 (190–46 960)]	38 (< 0.2–210) μmol/L	99 (< 0.3–1030)	965 (10–6250) nmol/L	Benzene in blood, 174 (8–1160) nmol/L
		Cokery workers (in winter)	27	1.3 (0.09–11.7) ppm [4150 (290–37 370)]	11 (< 0.2–35) μmol/L	73 (< 0.3–1020)	372 (22–1750) nmol/L	Benzene in blood, 160 (18–1690) nmol/L
		Rural controls (in winter)	10	0.009 ppm [28.75]	0.8 (< 0.2–8.1) μmol/L	2.1 (< 0.3–18)	12 (2–45) nmol/L	Benzene in blood, 7 (< 3–22) nmol/L

Table 1.3 (continued)

Reference	Country, year	Occupational description	No. of participants	Benzene exposure in air (µg/m³)[a, b]	Urinary *t,t*-MA (µg/g creatinine)[a,c]	Urinary SPMA (µg/g creatinine)[a,c]	Urinary benzene (µg/L)[a,d]	Other biomarkers[a]
Boogaard & van Sittert (1995, 1996)	Several countries including Belgium, Germany, and the Netherlands, 1992–1994	Natural gas production platforms	24	< 100–19 200	< 10–9920 µmol/mol creatinine	< 0.5–378 µmol/mol creatinine	NR	NR
		Chemical manufacturing	130	< 10–100 000	< 10–31 300 µmol/mol creatinine	< 1–1096 µmol/mol creatinine	NR	NR
		Oil refineries with aromatic plants	16	110–3300	8–1200 µmol/mol creatinine	0.9–46.4 µmol/mol creatinine	NR	NR
		Fuel tanker drivers and gasoline attendants	14	NR	9–830 µmol/mol creatinine	0.5–8. µmol/mol creatinine	NR	NR
		Employees without potential benzene exposure	38 NS	NR	29 µmol/mol creatinine	0. 94 µmol/mol creatinine	NR	NR
			14 S	NR	46 µmol/mol creatinine	1.71 µmol/mol creatinine	NR	NR

GM, geometric mean; ND, not detected; NR, not reported; NS, non-smokers; ppb, parts per billion; ppm, parts per million; S, smokers; SPMA, *S*-phenylmercapturic acid; *t,t*-MA, *trans,trans*-muconic acid

[a] Benzene exposure and biomarker concentrations are reported as mean (minimum–maximum), if not indicated otherwise

[b] Exposure concentration and range given in µg/m³ unless indicated otherwise; if published in another unit, the conversion to µg/m³ is given in square brackets

[c] Exposure concentration and range given in µg/g creatinine unless indicated otherwise; if published in another unit, the conversion to µg/g creatinine is given in square brackets

[d] Exposure concentration and range given in µg/L unless indicated otherwise; if published in another unit, the conversion to µg/L is given in square brackets

[e] 5–95th percentile

The separation and processing of crude oil and natural gas into crude oil, condensate, gas, and produced water before transport to shore via pipelines or tank ships takes place in a closed processing equipment and pipeline system. All four petroleum streams contain benzene, however, and the likelihood of exposure to benzene increases whenever the system is opened. The composition of crude oil and gas condensate varies between oil and gas fields and depends upon several factors, such as geological conditions in the reservoirs and the production age of the oil field, but typically lies within the range of < 0.01 and 3.0% by weight (Verma & des Tombe, 1999; Verma et al., 2000; Kirkeleit et al., 2006a), with benzene content in condensate being higher. The full-shift mean exposure in the production of oil and natural gas is usually well below 1 ppm [3.19 mg/m^3] benzene, the 8-hour permissible exposure limit set by the Occupational Safety and Health Administration (OSHA, 2017), during ordinary activity (Glass et al., 2000; Verma et al., 2000; Kirkeleit et al., 2006a; Bråtveit et al., 2007; Steinsvåg et al., 2007) (Table 1.2). However, some specific tasks, such as cleaning and maintenance of tanks and separators, pipeline pigging operations, and storage tank gauging, may cause short-term exposures in excess of this (Runion, 1988; CONCAWE, 2000; Glass et al., 2000; Verma et al., 2000; Kirkeleit et al., 2006a; Esswein et al., 2014).

With technological advances and more efficient reservoir completion techniques, UOGD has grown in the past decades. The only study available for this segment indicates that the potential for exposure is higher than for conventional oil and gas extraction (Esswein et al., 2014; Table 1.2).

(ii) Downstream petroleum industry: refining

The full-shift exposure to benzene during ordinary activity in the refining petroleum industry tends to be higher than for upstream activities, but still with average values well below 1 ppm [3.19 mg/m^3] (Nordlinder & Ramnäs, 1987; Verma et al., 1992, 2001; CONCAWE, 2000, 2002; Glass et al., 2000; Akerstrom et al., 2016; Almerud et al., 2017) (see Table 1.2). However, the range of exposure indicates potential for exceeding 1 ppm [3.19 mg/m^3]; this is particularly true for refinery maintenance, laboratory technicians, and dock workers. Specific tasks such as sampling, opening of vessels for maintenance and cleaning, and loading of petrol may cause high short-term exposure (Runion, 1988; Hakkola & Saarinen, 1996; Vainiotalo & Ruonakangas, 1999; Davenport et al., 2000; Verma et al., 2001; Kreider et al., 2010; Widner et al., 2011). However, while workers before 2000 were likely to have been exposed to higher concentrations of benzene because of a higher content of benzene in reformate stream (Burns et al., 2017), the range of benzene exposures reported in recent studies is considerably reduced (Campagna et al., 2012; Akerstrom et al., 2016; Almerud et al., 2017; Burns et al., 2017). Some of the reported exposure levels are given in Table 1.2.

(iii) Downstream petroleum industry: distribution

In the petroleum transport chain there is a potential for exposure at each point where the products are stored and transferred, and the reported exposures tend to be higher than for production and refinery workers (Halder et al., 1986; Javelaud et al., 1998; CONCAWE, 2000, 2002; Glass et al., 2000). However, because of a lowered content of benzene in petrol (Verma & des Tombe, 2002; Williams & Mani, 2015), as well as the recent introduction of vapour recovery systems in the petroleum distribution chain in at least developed countries, the exposure to benzene for these groups of workers has declined over the years. Some of the reported exposure levels are given in Table 1.2.

Williams et al. (2005) reviewed the available industrial hygiene data describing exposure during the marine transport of products

containing benzene (1975–2000). Although there were differences in sampling strategies and in the benzene content of the liquids being transported, air monitoring data revealed concentrations of 0.2–2.0 ppm [0.64–6.4 mg/m³] during closed-loading and 2–10 ppm [6.4–31.9 mg/m³] during open-loading operations. These estimates are somewhat higher than average values, but in line with the range of exposures reported in other reviews (CONCAWE, 2000, 2002; Verma et al., 2001).

(iv) Oil spill clean-up operations

The petroleum production and distribution scenario for which there is a lack of knowledge on exposure levels is the clean-up of an oil spill. In an oil spill field trial in the North Sea in 2016, full-shift measurements of benzene for personnel closest to the slick yielded a geometric mean exposure of 0.2 ppm benzene [0.64 mg/m³] (Gjesteland et al., 2017). No exposure to benzene was detected in personal samples collected during the Deepwater Horizon spill of light crude oil (Ahrenholz & Sylvain, 2011). In the Prestige and Nakhodka spills of heavy fuel oil, the measured benzene exposure was low because of the low content of volatile organic compounds (Morita et al., 1999; Pérez-Cadahía et al., 2007).

(v) Retail petrol stations

Averaged full-shift exposures of up to 0.65 mg/m³ (McDermott & Vos, 1979; Runion & Scott, 1985; Foo, 1991; Lagorio et al., 1993; CONCAWE, 2000, 2002; Verma et al., 2001; Chakroun et al., 2002; van Wijngaarden & Stewart, 2003; Fustinoni et al., 2005) and 59 µg/m³ [0.059 mg/m³] (Carrieri et al., 2006; Lovreglio et al., 2010, 2014; Campo et al., 2016) have been measured before and after 2000, respectively. Reported benzene exposure levels (Table 1.2 and Table 1.3) suggest that, in higher-income countries, at least, they have decreased with time. The decline is mainly ascribed to a decrease in benzene content in gasoline, as well as the installation of vapour recovery systems at retail gas stations capturing vapours during vehicle fuelling. The information on exposure for petrol station attendants in low- and middle-income countries is scarce, but available studies indicate somewhat higher concentrations of benzene for these workers compared with those reported from more developed countries (Navasumrit et al., 2005; Bahrami et al., 2007).

(b) Exposure from engine exhaust

Benzene from engine exhaust represents a potential exposure for professional drivers and urban workers, including taxi drivers, police, street workers, and others employed at workplaces with exposure to exhaust gases from motor vehicles (Nordlinder & Ramnäs, 1987). Reported exposure concentrations for these workers differ with region (Table 1.2). Reported median exposures for traffic police in Italy (2005) and Thailand (2006) were 6.1 µg/m³ and 38.2 µg/m³, respectively (Manini et al., 2008; Arayasiri et al., 2010). Cloth vendors and grilled-meat vendors in Thailand have been reported to have experienced mean exposures of 22.61 ppb [73 µg/m³] and 28.19 ppb [90 µg/m³], respectively (Navasumrit et al., 2005). Although the data for urban workers in low- and middle-income countries are scarce, the available information on both workers and outdoor air concentrations (see Section 1.4.2) indicates exposure to higher concentrations for these workers relative to the levels typical of higher-income countries.

(c) Automobile repair

Workers employed in automobile repair shops and recycling are potentially exposed to benzene through contact with gasoline vapour and engine products. Measured mean exposures before 2000 are typically less than 1 ppm (Nordlinder & Ramnäs, 1987; Foo, 1991; Hotz et al., 1997; Javelaud et al., 1998; Egeghy et al., 2002) (Table 1.2).

(d) Coke production

Benzene exposure is a potential hazard in the carbonization of coal to form coke used in the manufacture of steel, produced in the refining of the crude coke fractions and the by-products. China is currently the largest coke producer globally; average benzene exposure concentrations of 0.705 and 0.290 mg/m^3 were measured during a survey of two plants, where charging and pushing activities accounted for almost 70% of the exposure at the topside (He et al., 2015). During the period 2005–2010 in Poland, median exposures of 0.09–0.37 mg/m^3 according to job category were reported (Bieniek & Łusiak, 2012). Median exposure at a cokery in a shale oil petrochemical plant in Estonia was reported as 0.4 ppm [1.28 mg/m^3] one decade earlier (Kivistö et al., 1997). Average exposure for coke oven workers in the USA during 1978–1983 was reported as 8.46 ppm [27.02 mg/m^3] (van Wijngaarden & Stewart, 2003), while reported mean levels in the United Kingdom in 1986 ranged from 0.31 ppm [0.99 mg/m^3] in coke oven workers to 1.32 ppm [4.22 mg/m^3] in by-product workers (refining process of benzene) (Drummond et al., 1988).

(e) Rubber manufacturing

Benzene has historically been used in the manufacture of rubber, including the production of tyres and general rubber goods, and the process of retreading. It has also been used as a component in cement, glue, binding agents, and release agents, but has mainly been replaced by other agents (IARC, 2012). Some of the solvents used today still contain low benzene concentrations, however. From a pooled dataset on rubber manufacture workers in China used in a nested case–cohort study within the National Cancer Institute-Chinese Academy of Preventive Medicine (NCI-CAPM) cohort (n = 585), arithmetic and geometric means of 157.3 mg/m^3 and 45.6 mg/m^3 (geometric standard deviation, GSD, 6.4 mg/m^3) were reported from 1949 until after 2000 (Portengen et al., 2016). Averages of 1.42 ppm [4.54 mg/m^3] (n = 179) and 0.34 ppm [1.09 mg/m^3] (n = 4358) for rubber manufacture and production of tyres and inner tubes, respectively, have been reported from the USA and Canada (Runion & Scott, 1985; van Wijngaarden & Stewart, 2003).

The exposure levels in a cohort of workers producing rubberized food-coating materials have been estimated several times (Rinsky et al., 1981, 1987; Paustenbach et al., 1992; Crump, 1994; Utterback & Rinsky, 1995). In the latest retrospective assessment, the highest exposures (involving the jobs of neutralizer, quencher, knifeman, and spreader) were typically 50–90 ppm during 1939–1946 (lower during 1942–1945) and 10–40 ppm during 1947–1976 at the 50th percentile (Williams & Paustenbach, 2003). These estimated exposure levels were two to four times as great as for other jobs in this same cohort.

Kromhout et al. (1994) performed an exposure assessment of solvents in 10 rubber-manufacturing plants in the Netherlands in 1988. The use of particular solvents varied widely, and those selected for the quantitative assessment of exposure were based on the individual solvents, cements, and release and bonding agents used in the plants included in the study. The final assessment was restricted to paraffins, aromatic compounds, chlorinated hydrocarbons, ketones, alcohols, and esters. Benzene was not included, suggesting that the products used in the European rubber industry did not contain benzene from the late 1980s (Kromhout et al., 1994).

(f) Shoemaking

Shoemaking consists of several steps, including: the cutting of the material (leather, rubber, plastic, etc.), fitting of parts, sewing and gluing the various parts together, and finally the trimming and buffing of the shoes (Wang et al., 2006). Benzene is used as a solvent in glues, adhesives, and paint in the shoe-manufacturing process. Dermal exposure to benzene has

been reported as low, and does not significantly contribute to systemic exposure of benzene (Vermeulen et al., 2004). Although no longer as relevant in Europe and North America as in the past, this source of occupational benzene exposure is still of importance in some countries, notably in Asia.

In a recent Chinese study of shoe factory workers, mean exposures of 21.86 ppm [69.83 mg/m^3] and 3.46 ppm [11.05 mg/m^3] were reported for a small and large factory, respectively (Vermeulen et al., 2004). Benzene and toluene exposures were partly determined by the degree of contact with glues, the benzene and toluene content of each glue, air movement, and ventilation patterns. From a pooled dataset on workers in the shoemaking industry in China used in a nested case–cohort study within the NCI-CAPM cohort (n = 635), arithmetic and geometric means of 69.2 mg/m^3 and 8.1 mg/m^3 (GSD, 10.8 mg/m^3) were reported for the period from 1949 to after 2000 (Portengen et al., 2016).

In a benzene exposure assessment in 12 Iranian shoemaking workshops (semiautomated, year not given) mean exposures (standard error) for three consecutive months were 1.10 (0.11) ppm [3.51 (0.35) mg/m^3], 1.37 (0.14) ppm [4.38 (0.45) mg/m^3], and 1.52 (0.18) ppm [4.86 (0.57) mg/m^3] (Azari et al., 2012).

In the shoemaking industry in Spain, where benzene was unintentionally present in the adhesive as a contamination, the mean benzene exposure concentrations for the periods 2002–2003, 2004–2005, and 2006–2007 were 0.05 mg/m^3, 0.07 mg/m^3, and 0.05 mg/m^3, respectively (Estevan et al., 2012).

(g) Firefighting

Because of the incomplete combustion and pyrolysis of organic and synthetic materials, respectively, firefighters are potentially exposed to benzene during firefighting (municipal and wildfire), overhaul, and training. The heterogeneity of types of fires, time spent at fires, and types of structure or material burning, as well as the limited collection of data due to the extreme conditions, have hampered the characterization of exposure to benzene by firefighters and data are scarce. However, the few reported data suggest that the full-shift exposure is much less than 0.5 ppm, and is higher for the knockdown of wildfires compared with structure fires (Reinhardt & Ottmar, 2004); the potential for short-term exposure much higher than 1 ppm [3.19 mg/m^3] has also been reported (Bolstad-Johnson et al., 2000; Austin et al., 2001).

(h) Occupational use of products containing benzene

Benzene was formerly a common solvent and ingredient in a variety of products, including paint, printing inks, and glues, and is a natural component in products derived from petroleum. However, the benzene content in these products has either been replaced or reduced following regulations and other initiatives in the 1980s and 1990s.

(i) Application of paint

Benzene has been largely replaced as a solvent in paint, but is still used in some countries. Although this was a significant source of benzene exposure historically, data are lacking on benzene exposure during the use of paint that contains benzene as a constituent or contamination. In a review of benzene exposure in industries using paint in China, combining all the years during 1956–2005, relevant median exposures were reported for many activities, including: spray painting, 43.9 mg/m^3 (maximum, 3212 mg/m^3); brush painting, 58.2 mg/m^3 (maximum, 3373.5 mg/m^3); mixing, 53.6 mg/m^3 (maximum, 139.4 mg/m^3); immersion, 27.4 mg/m^3 (maximum, 540.0 mg/m^3); and paint manufacturing, 15.08 mg/m^3 (maximum, 344.0 mg/m^3) (Liu et al., 2009). From a pooled dataset on spray painting in China (n = 3754) used in a nested case–cohort study within the NCI-CAPM

cohort, arithmetic and geometric means of 62.5 mg/m^3 and 9.4 (GSD, 8.9) mg/m^3 averaged over the period from 1949 to after 2000 were reported (Portengen et al., 2016). The corresponding exposure concentrations for painting (n = 1099) were 115.3 mg/m^3 and 17.1 (GSD, 10.2) mg/m^3. In a pilot study, eight painters in small car repair shops in Italy were reported to have experienced an arithmetic mean exposure of 9.8 mg/m^3 (range, 0.4–53 mg/m^3) over a period of 236–323 min (Vitali et al., 2006). The authors ascribed the benzene exposure mainly to fuel vapour and gasoline used for degreasing and paint dilution.

(ii) Printing industry

Benzene was withdrawn from its significant use as a solvent of printing inks in Europe in the 1950s, but was used in the USA in the rotogravure processes from the 1930s until the beginning of the 1960s (IARC, 1996). Reported mean exposures from the printing industry are 0.58 ppm [1.85 mg/m^3] in the USA (van Wijngaarden & Stewart, 2003), and 0.017 ppm [0.0543 mg/m^3] in the Republic of Korea (Kang et al., 2005), but it is still a concern in some low- and middle-income countries. From the pooled dataset from the NCI-CAPM cohort (n = 232), arithmetic and geometric means of 94.1 mg/m^3 and 8.2 (GSD, 13.0) mg/m^3 averaged over the period from 1949 until after 2000 were reported (Portengen et al., 2016).

(iii) Use of petroleum-based products containing benzene in small amounts

Benzene is a residual component (< 0.1%) in petroleum-based products such as mineral spirit, jet fuel, degreasing agents, and other solvents. There are insufficient data to draw any conclusions on air concentrations generated when using these products, but estimations and reported exposure after simulations and controlled testing performed in relation to lawsuits can be found in several publications (Fedoruk et al., 2003; Williams et al., 2008; Hollins et al., 2013). There have been some reports on exposure to benzene during handling of various types of jet fuel; although exposure concentrations vary between the studies, work tasks, and circumstances, the reported values indicate a potential for exceeding exposures of 1 ppm [3.19 mg/m^3] (Holm et al., 1987; Egeghy et al., 2003; Smith et al., 2010).

(i) Biological monitoring of occupational exposure to benzene

Although the measurement of benzene in air is the most common method of investigating exposure in occupational settings, biomonitoring is considered the best technique as the characteristics of the individual and the use of protective equipment are taken into account. Moreover, when dermal exposure is a consideration, biological monitoring is the only system that can integrate both exposure routes.

A summary of selected studies on occupational exposure to benzene using biological monitoring is provided in Table 1.3. Investigated occupational settings include: the petrochemical industry (Boogaard & van Sittert, 1995, 1996; Kirkeleit et al., 2006b; Bråtveit et al., 2007; Hoet et al., 2009; Carrieri et al., 2010; Fustinoni et al., 2011; Hopf et al., 2012); cookery (Kivistö et al., 1997); and manufacturing, including chemical manufacturing (Boogaard & van Sittert, 1995, 1996; Kivistö et al., 1997), shoemaking (Kim et al., 2006a; Lv et al., 2014), adhesive production, and rubber and paint manufacturing (Waidyanatha et al., 2001, 2004). Exposure to gasoline vapours encountered by filling station attendants, tanker fillers, and fuel tanker drivers (Boogaard & van Sittert, 1995, 1996; Chakroun et al., 2002; Fustinoni et al., 2005; Bahrami et al., 2007; Lovreglio et al., 2010; Campo et al., 2016) and traffic exhaust exposure, such as that incurred by traffic police, and taxi and bus drivers (Fustinoni et al., 2005; Manini et al., 2006; Bahrami et al., 2007), were also investigated. A few studies have

investigated exposure to benzene encountered by firefighters (Caux et al., 2002; Fent et al., 2014).

Benzene is present in a complex mixture of chemicals in the large majority of these settings, although this percentage can be small in the case of gasoline vapours and traffic exhaust fumes, for example.

In 1995 and 1996, Boogaard and van Sittert investigated 184 workers exposed to benzene in various occupational settings (natural gas production platforms, chemical manufacturing, oil refineries, fuel tank drivers, and gasoline attendants), measuring personal benzene exposure and two minor urinary metabolites (*t*,*t*-MA and SPMA) in urine samples collected at the end of shifts. Personal exposure ranged from less than 0.01 to 100 mg/m^3. A group of 52 unexposed employees was also investigated as controls. It was estimated that about 4% and 0.1% of the inhaled dose was excreted in urine as *t*,*t*-MA and SPMA, respectively, with half-lives of about 5 hours and 9 hours. The correlation between personal benzene exposure and both biomarkers was very good, demonstrating their utility as biomarkers of exposure. Owing to the presence of background levels of *t*,*t*-MA in the urine of workers not exposed to benzene, this biomarker would be of limited use for assessing low benzene concentrations (Boogaard & van Sittert, 1995, 1996).

In later years, other studies in China investigated manufacturing workers exposed to high benzene concentrations in the rubber, adhesive, and paint production industries (up to 329 ppm [1051 mg/m^3]) (Waidyanatha et al., 2004) and in factories manufacturing glue, shoes, and sporting goods (up to 107 ppm [342 mg/m^3]) (Qu et al., 2003). Several benzene metabolites, such as urinary phenol, catechol, hydroquinone, *t*,*t*-MA, and SPMA, were investigated and all found to be correlated with personal benzene exposure. SPMA and *t*,*t*-MA demonstrated their superior ability as biomarkers of recent exposure, however; they were present in lower background concentrations in workers not exposed to benzene and they revealed a higher sensitivity in correlating with lower concentrations of occupational benzene. Urinary unmetabolized benzene was also measured, and demonstrated a very good correlation with personal benzene exposure and with the other urinary biomarkers (Waidyanatha et al., 2001).

Another study in China in 2000 applied urinary biomarkers to assess exposure in 250 shoemaking workers, using 139 clothes manufacturing workers as controls. Biomarkers were consistently elevated when the median benzene exposure level of the group was at or above 0.2 ppm for *t*,*t*-MA and SPMA, 0.5 ppm for phenol and hydroquinone, and 2 ppm for catechol (Kim et al., 2006a).

Much lower occupational exposures in fuel tanker drivers, filling station attendants, taxi and bus drivers, and traffic police were reported in Italy, with levels of up to 1017 µg/m^3 [1.017 mg/m^3] (Fustinoni et al., 2005; Manini et al., 2006; Lovreglio et al., 2010; Campo et al., 2016). Only the most specific biomarkers were measured in these studies, including urinary *t*,*t*-MA, SPMA, and unmetabolized benzene. These studies reported on the possibility of correlating very low benzene concentrations with both SPMA and urinary benzene, but not with *t*,*t*-MA. Moreover, these studies demonstrated the impact of tobacco smoking on the levels of biomarkers; smokers without occupational exposure to benzene had higher levels of benzene biomarkers than non-smoking filling station attendants (Fustinoni et al., 2005).

[The Working Group noted that, considered together, these studies showed that urinary SPMA and unmetabolized benzene are the most specific and sensitive biomarkers for the investigation of low occupational exposures, such as those found in most work settings. They are short-term biomarkers of exposure, and the best sampling time is at the end of the exposure or shift.]

1.4.2 General population exposure

Benzene is present ubiquitously in the environment, for example as a result of emissions from forest fires and volcanoes. However, the major environmental sources of benzene are anthropogenic. Such sources include industrial emissions, the burning of coal and oil, motor vehicle exhaust, and fuel evaporation. The primary route of environmental exposure to benzene is through inhalation, although exposure from ingestion of water and foods contaminated with benzene can also occur (ATSDR, 2007). Exposure to benzene can occur in microenvironments due to the evaporation of gasoline from parked cars in attached garages, while driving, or while pumping gasoline, or by spending time outdoors in close proximity to heavily trafficked areas or gasoline service stations. Benzene is a component of tobacco smoke; exposure therefore occurs when smoking or inhaling sidestream smoke (environmental tobacco smoke) (IARC, 2004).

(a) Outdoor air levels of benzene

Outdoor air concentrations of benzene vary widely throughout the world (see Table 1.4). In a review of air quality data from 42 European countries in 2014, the European Environment Agency reported no exceedances of the annual limit for benzene (5 μg/m^3) (European Environment Agency, 2016). Earlier, Guerreiro et al. (2014) reported that very few (0.9%) monitoring stations in Europe in 2011 exceeded this annual guideline for benzene. Over the period from mid-2009 to November 2012, mean and median benzene levels in northern Italy (Mestre) averaged 1.8 and 1.1 μg/m^3, respectively (Masiol et al., 2014). For a 5-year period from 2009 to 2013, benzene levels as measured at a single monitoring station in Edmonton, Canada, averaged 0.72 μg/m^3 (Bari & Kindzierski, 2017). In 2013, average benzene levels across 343 monitoring stations in the USA ranged from 0 ppb carbon (equivalent to ppb multiplied by the number of carbon atoms) in Queen Valley, a sparsely populated town in southern Arizona, to 8.27 ppb carbon [~1.38 ppb = 4.41 μg/m^3] in Steubenville, an industrial city in eastern Ohio (ATSDR, 2015). Based on data from seven continuous monitors in Tehran, Islamic Republic of Iran, in 2012 and 2013, annual benzene concentrations of 3.444 μg/m^3 were reported (Miri et al., 2016). The highest reported levels were in China, where benzene levels averaged 6.81 ppb [21.75 μg/m^3] over approximately 20 years, with city-specific averages from 0.73 ppb [2.33 μg/m^3] (Hong Kong Special Administrative Region) to 20.47 ppb [65.39 μg/m^3] (Ji'nan) (Zhang et al., 2017).

There is evidence that benzene outdoor air concentrations have declined significantly over time in Europe (> 70% decline during 2000–2014) (European Environment Agency, 2016) and the USA (66% decline during 1994–2009) (EPA, 2010). In addition to long-term trends, levels may vary seasonally. Jiang et al. (2017) reported average benzene concentrations in outdoor air of 502.5, 116.8, 111.21, and 294.8 parts per trillion [1.61, 0.37, 0.36, and 0.94 μg/m^3] in the spring, summer, autumn, and winter, respectively in Orleans, France. Similarly, outdoor air concentrations of benzene in the United Kingdom were reported to vary over the calendar year, with higher levels in the winter than during the summer (Duarte-Davidson et al., 2001).

Disasters may affect short-term air quality. After the Deepwater Horizon oil spill in the Gulf of Mexico in April 2010, mean benzene concentrations in air over the ensuing 5 months averaged 4.83 μg/m^3 (min., 0.12 μg/m^3; max., 81.89 μg/m^3) and 2.96 μg/m^3 (min., 0.14 μg/m^3; max., 290 μg/m^3) in regional and coastal areas of Louisiana, USA, respectively. These concentrations were higher than those measured from six urban areas in the state over the same period, which averaged 0.86 μg/m^3 (min., 0.51 μg/m^3; max., 2.33 μg/m^3) (Nance et al., 2016).

Table 1.4 Environmental monitoring of benzene

Reference	Country, year	No. of samplings	Sampling matrix	Exposure concentration (mean)[a]	Range[a]	Comments
Bruinen de Bruin et al. (2008)	European Union, from 2003	11 13 8 10 7 9 6 17 11 12 3 8	Personal exposures	5.1 (average overall) 2.0 (Helsinki) 2.3 (Leipzig) 3.2 (Brussels) 3.3 (Arnhem) 3.3 (Budapest) 4.1 (Dublin) 4.2 (Nijmegen) 5.2 (Catania) 7.5 (Athens) 8.0 (Nicosia) 8.5 (Milan) 9.4 (Thessaloniki)	NR	7 d average levels of benzene (μg/m^3) measured in indoor work (12 cities; n = 150; AM, 5.1); indoor home (9 cities; n = 59; AM, 3.2); and outdoor work (12 cities; n = 91; AM, 2.7) environments
Masiol et al. (2014)	Italy, 2000–2013	102 074	Outdoor air	1.8	0–10.2	
Miri et al. (2016)	Islamic Republic of Iran, March 2012–March 2013	NR	Outdoor air	3.444	NR	
Bari & Kindzierski (2017)	Canada, 2009–2013	NR	Outdoor air	0.72	Maximum, 3.31	
Jiang et al. (2017)	France, Oct 2010–Aug 2011	49 30 30 56	Outdoor air	502.50 ppt (spring) [1.61] 116.80 ppt (summer) [0.37] 111.21 ppt (fall) [0.36] 294.80 ppt (winter) [0.94]	16.8–2296 ppt [0.05–7.33] 16.6–674.4 ppt [0.05–2.15] 14.6–431.5 ppt [0.046–1.38] 49.8–1163.3 ppt [0.16–3.72]	2 h samples
McMahon et al. (2017)	USA, 2015–2016	116	Drinking-water wells	NR	< 0.026–0.127 μg/L	Benzene detection frequencies (≥ 0.013 μg/L) were 9.3%, 13.3%, and 2.4% in Eagle Ford (Texas), Fayetteville (Arkansas), and Haynesville (Texas) shale hydrocarbon production areas, respectively

Table 1.4 (continued)

Reference	Country, year	No. of samplings	Sampling matrix	Exposure concentration (mean)[a]	Range[a]	Comments
Zhang et al. (2017)	China, 1990–2014	NR	Outdoor air	4.42 ppb (Beijing) [14.12] 14.16 ppb (Guangzhou) [45.23] 6.95 ppb (Shanghai) [22.2] 3.94 ppb (Jiaxing) [12.59] 3.76 ppb (Nanjing) [12.01] 6.30 ppb (Hangzhou) [20.12] 6.61 ppb (Macau) [21.11] 13.09 ppb (Changchun) [41.81] 20.10 ppb (Changzhou) [64.2] 20.47 ppb (Ji'nan) [65.39] 11.36 ppb (Lianyungang) [36.29] 4.71 ppb (Nanning) [15.05] 6.47 ppb (Zhengzhou) [20.67] 6.45 ppb (Dongguan) [20.6] 0.92 ppb (Tianjin) [2.94] 1.89 ppb (Anshan) [6.04] 1.61 ppb (Shenyang) [5.14] 1.42 ppb (Shaoxing) [4.54] 0.94 ppb (Tai'an) [3.00] 0.73 ppb (Hong Kong SAR) [2.33]	NR	

AM, arithmetic mean; d, day(s); NR, not reported; ppb, parts per billion; ppt, parts per trillion; SAR, Special Administrative Region

[a] Exposure concentration and range given in μg/m^3; if published in another unit, the conversion to μg/m^3 is given in square brackets.

(b) Personal exposures to benzene

A study published in 2008 reported on personal monitoring data for benzene collected in 12 European cities, with the lowest arithmetic mean concentration reported for residents of Helsinki, Finland (2.0 µg/m^3), and the highest for residents of Thessaloniki, Greece (9.4 µg/m^3) (Bruinen de Bruin et al., 2008).

(c) Benzene in drinking-water and food

Benzene exposure can occur due to ingestion of water and food contaminated with benzene (ATSDR, 2007). During 1985–2002, the United States Geological Survey detected benzene in 37 of 1208 (3.1%) domestic water well samples that were collected at sites across the country; all but one sample had concentrations that were less than 1 µg/L (Rowe et al., 2007). In 2015 and 2016, a small proportion of the samples from 116 drinking-water (domestic and public supply) wells in the Eagle Ford (9.3%), Fayetteville (13.3%), and Haynesville (2.4%) shale hydrocarbon production areas in Texas and Arkansas, USA, had detectable levels, and all concentrations were less than 0.15 µg/L (McMahon et al., 2017).

Based on a review of studies published during 1996–2013, relatively low concentrations were reported in carbonated beverages and other foodstuffs (< 1 ppb); the highest levels (18 ppb) were found in organ meats (Salviano Dos Santos et al., 2015). Over a 5-year period (1996–2006), the United States Food and Drug Administration evaluated 70 "table-ready" foods. Benzene was found in all of them except American cheese and vanilla ice cream; levels ranged from 1 ppb (in milk-based infant formula and raw strawberries) to 190 ppb (fully cooked ground beef) (Fleming-Jones & Smith, 2003). Medeiros Vinci et al. (2012) detected benzene in 58% of 455 food samples purchased and analysed from four supermarkets in Belgium in 2010, with the highest mean levels found in smoked (18.90 µg/kg) and canned (7.40 µg/kg) fish, as well as in fatty fish (3.1 µg/kg) and ready-to-eat salads (2.79 µg/kg). Mean levels were much lower in non-fatty (0.52 µg/kg) fish, raw meat (0.31 µg/kg), and eggs (below the limit of detection).

(d) Biomonitoring of benzene exposure

Nationally conducted surveys that include a biomonitoring component have documented benzene exposures in the general population (see Table 1.5). Based on data collected as part of the Canadian Health Measures Survey during 2012–2013 for people aged 12–79 years (n = 2488), geometric mean blood benzene concentrations were 0.036 µg/L (Haines et al., 2017). Based on the United States National Health and Nutrition Examination Survey (NHANES) in 2001–2002, 2003–2004, 2005–2006, and 2007–2008, median benzene blood concentrations for the United States population were 0.03 µg/L (n = 837), 0.027 µg/L (n = 1345), 0.026 µg/L (n = 3091), and less than the limit of detection (n = 2685), respectively (US Department of Health and Human Services, 2018). Using NHANES biomonitoring data, Arnold et al. (2013) reported differences in median blood benzene concentrations between those individuals who had pumped gasoline into a car or motor vehicle during the previous 3 days (0.029 µg/L) and those who had not (0.025 µg/L). Benzene concentrations were also higher for individuals who reported having inhaled diesel exhaust during the previous 3 days (0.039 µg/L) compared with those who had not (0.027 µg/L).

Biomonitoring studies have also documented environmental exposure to benzene by measuring metabolites of benzene in urine. The Korean National Environmental Health Survey, which was conducted among adults aged 19 years and older during 2012–2014 (n = 6376), reported geometric mean levels of urinary *t*,*t*-MA of 58.8 µg/L (Choi et al., 2017). Among 336 adults (age, 35–69 years) living in central Italy who had cotinine levels less than 100 µg/g creatinine (the cut-off value above that was used to define a smoker), reported median

Table 1.5 Summary of selected studies with biological monitoring of environmental exposure to benzene[a]

Reference	Country, year	Population	*n*	Biomarker concentration (μg/L)[a, b]					Comments
				Urinary *t,t*-MA	Urinary SPMA	Urinary benzene	Blood benzene	Breast milk	
Haines et al. (2017)	Canada, 2012–2013	Adults (12–79 yr)	2488	NR	NR	NR	GM, 0.036 (0.020–0.067)[c]	NR	CHMS uses a stratified, multistage household-based sampling strategy; sample size indicated is the number of unweighted participants
US Department of Health and Human Services (2018)	USA, 2001–2002	Adults (≥ 12 yr)	837	NR	NR	NR	Median, 0.030 (0.100–0.190)[d]	NR	NHANES uses a complex multistage probability design; sample size indicated is the number of unweighted participants; 25th percentiles not provided
	2003–2004		1345	NR	NR	NR	Median, 0.027 (0.064–0.170)[d]	NR	
	2005–2006		3091	NR	NR	NR	Median, 0.026 (0.056–0.220)[d]	NR	
	2007–2008		2685	NR	NR	NR	Median, < LOD (0.041–0.198)[d]	NR	
	2011–2012		2466	NR	Median, < LOD (1.07–1.95)[d]	NR	NR	NR	
Choi et al. (2017)	Republic of Korea, 2012–2014	Adults (≥ 19 yr)	6376	GM, 58.8 (30.2–118)[c]	NR	NR	NR	NR	
Schoeters et al. (2017)	Belgium, 2003–2004	Adolescents (14–15 yr)	1586	GM, 99 (92–107)	NR	NR	NR	NR	FLEHS uses a stratified clustered multistage design; geometric mean concentrations are adjusted for age, sex, smoking, and creatinine levels

Table 1.5 (continued)

Reference	Country, year	Population	*n*	Biomarker concentration (µg/L)[a, b]					Comments
				Urinary *t,t*-MA	Urinary SPMA	Urinary benzene	Blood benzene	Breast milk	
Tranfo et al. (2017)	Italy, NR	Adults (35–69 yr) with cotinine < 100 µg/g creatinine	336	85.48 µg/g creatinine	0.23 µg/g creatinine	NR	NR	NR	
Blount et al. (2010)	USA (Baltimore, Maryland)	Women	12	NR	NR	NR	NR	Median, 0.080	Convenience sample via announcements and word of mouth
Protano et al. (2012)	Italy, NR	Children (5–11 yr)	396	127.59 (13.76–972.918) µg/g creatinine	0.62 (0.06–4.35) µg/g creatinine	NR	NR	NR	
Lovreglio et al. (2011)	Italy (Puglia), 2009	Adult men	137	52.0 (< 20 to 734) µg/g creatinine	< 0.03 (< 0.03–5.22) µg/g creatinine	0.08 (< 0.02 to 11.40)	NR	NR	
Fustinoni et al. (2010)	Italy, 2007–2008	Adults (19–75 yr)	108	NR	NR	0.122 (0.083–0.294)[c]	NR	NR	
Fabietti et al. (2004)	Italy (Rome), NR	Women	23	NR	NR	NR	NR	0.06 (0.01–0.18) µg/kg	

CHMS, Canadian Health Measures Survey; FLEHS, Flemish Environment and Health Study; GM, geometric mean; LOD, limit of detection; NHANES, US National Health and Nutrition Examination Survey; NR, not reported; yr, year(s)

[a] Biomarker concentrations are reported as arithmetic mean levels (minimum–maximum) unless indicated otherwise.

[b] Concentrations are given in µg/L (micrograms/L) unless indicated otherwise.

[c] 25–75th percentile

[d] 75–95th percentile

urinary levels of *t,t*-MA and SPMA were 85.48 and 0.23 µg/g creatinine, respectively (Tranfo et al., 2017). Fustinoni et al. (2010) reported a urinary benzene level of 0.122 µg/L (median) in 108 Italian men and women.

A few studies have examined the exposure of adolescents and children to benzene using biomonitoring data. Geometric mean concentrations of urinary *t,t*-MA, adjusted for age, sex, smoking status, and creatinine concentrations in adolescents aged 14 and 15 years, were reported by the Flemish Environment and Health Study of 99 µg/L in 2003–2004 (n = 1586), 94 µg/L in 2007–2008 (n = 206), and 61 µg/L in 2013 (n = 204) (Schoeters et al., 2017). Based on urine samples collected from 396 Italian children (age, 5–11 years), Protano et al. (2012) reported mean levels of 127.59 and 0.62 µg/g creatinine for *t,t*-MA and SPMA, respectively.

In workers who are not exposed to benzene through their occupation, the combined effects of smoking and environmental tobacco smoke contribute, on average, 85% and 23% to total benzene exposure among smokers and non-smokers, respectively (Weisel, 2010). In a 2009–2011 nationally representative study of exposure to volatile organic compounds in Canada, statistically significant differences in indoor residential concentrations of benzene were detected between homes with and without smokers (difference, 1.12 µg/m^3) (Zhu et al., 2013). Geometric mean benzene concentrations in blood were 0.136 and 0.024 µg/L for smokers and non-smokers, respectively, as assessed using biomonitoring data from the 2003–2004 NHANES survey (Kirman et al., 2012). Similarly, Tranfo et al. (2017) reported urinary levels of *t,t*-MA and SPMA of 141.32 and 1.83 µg/g creatinine in smokers, compared with 90.68 and 0.20 µg/g creatinine in non-smokers, respectively.

1.5 Regulations and guidelines

The International Labour Organization Benzene Convention (C136) Article 2(1) states: "Whenever harmless or less harmful substitute products are available, they shall be used instead of benzene or products containing benzene." This convention was passed in 1971 and ratified by 38 countries (ILO, 1971). The European Union classified benzene as a category I carcinogen under Directive 67/548/EEC (European Commission, 1967). Benzene is not allowed to be placed on the market with the exception of fuel, or used as a substance or as a constituent of mixtures in concentration greater than 0.1% by weight (EU-OSHA, 2006). The USA withdrew benzene from consumer products in 1978 (IARC, 1982).

1.5.1 Occupational exposure limits

(a) USA

The 8-hour permissible exposure and short-term limits set by the Occupational Safety and Health Administration are 1 ppm [3.19 mg/m^3] and 5 ppm [15.95 mg/m^3], respectively (CFR 1910.1028) (OSHA, 2017) (Table 1.6).

Occupational exposure limit (OEL) recommendations for benzene have been made by the American Conference of Governmental Industrial Hygienists (ACGIH). ACGIH recommends a threshold limit value (TLV) during an 8-hour work shift of 0.5 ppm [1.6 mg/m^3] and a short-term exposure limit (STEL) of 2.5 ppm [~8 mg/m^3]. ACGIH also recommends a biological exposure index (BEI) for *t,t*-MA in urine of 500 µg/g creatinine and for SPMA in urine of 25 µg/g creatinine (ACGIH, 2012). The United States National Institute for Occupational Safety and Health (NIOSH) recommended exposure level (REL) for the time-weighted average is 0.1 ppm [0.32 mg/m^3] (NIOSH, 2010) and the short-term limit value is 1 ppm [3.2 mg/m^3].

Table 1.6 International occupational exposure limits for benzene

Country	Limit value – 8 h		Limit value – short-term		Remarks
	ppm	mg/m³	ppm	mg/m³	
Australia	1	3.2			
Austria	1	3.2	4	12.8	TRK value (based on technical feasibility)
Belgium	1	3.25			
Canada – Ontario	0.5		2.5		
Canada – Quebec	1	3	5	15.5	
China		6		10 (1)	(1) 15 min average value
Denmark	0.5	1.6	1.0	3.2	
European Union	1	3.25			
Finland	1 (1)	3.25 (1)			(1) Binding limit value
France	1	3.25			
Germany (AGS)	0.6 (1) 0.06 (2)	1.9 (1) 0.2 (2)	4.8 (1)(3)	15.2 (1)(3)	(1) Workplace exposure concentration corresponding to the proposed tolerable cancer risk (2) Workplace exposure concentration corresponding to the proposed preliminary acceptable cancer risk (3) 15 min average value
Hungary				3	
Ireland	1	3			
Israel	0.5	1.6	2.5 (1)	8 (1)	(1) 15 min average value
Italy	1	3.25			skin
Japan	10				
Japan – JSOH	1 (1)(2) 0.1 (1)(3)				(1) Reference value corresponding to an individual excess lifetime risk of cancer (2) Individual excess lifetime risk of cancer 10^{-3} (3) Individual excess lifetime risk of cancer 10^{-4}
Latvia	1	3.25			
New Zealand	1		2.5		
Poland		1.6			
Romania	1	3.25			
Singapore	1	3.18			
Republic of Korea	1	3	5	16	
Spain	1	3.25			Skin
Sweden	0.5	1.5	3 (1)	9 (1)	(1) 15 min average value
Switzerland	0.5	1.6			
The Netherlands		3.25			
Turkey	1	3.25			

Table 1.6 (continued)

Country	Limit value – 8 h		Limit value – short-term		Remarks
	ppm	mg/m³	ppm	mg/m³	
USA – NIOSH	0.1	0.32	1 (1)	3.2	(1) Ceiling limit value (15 min)
USA – OSHA	1		5		
United Kingdom	1				

Current OELs are reported here but are subject to revisions over time

AGS, German Committee on Hazardous Substances; h, hour(s); JSOH, Japan Society for Occupational Health; min, minute(s); NIOSH, National Institute for Occupational Safety and Health; NR, not reported; OEL, occupational exposure limit; OSHA, Occupational Safety and Health Administration; ppm, parts per million; TRK, technical guidance concentration

From GESTIS (2017)

(b) Europe

The European Union and most European countries have an OEL of 1 ppm, as does the Scientific Committee on Occupational Exposure Limits (SCOEL) (from 1991), but a few countries have opted for lower values (Table 1.6). The biological exposure limits set by the committee are 28 µg of benzene per litre of blood and 46 µg SPMA per gram of creatinine (SCOEL, 2014). The OEL set by the European Chemicals Agency (ECHA) is 1 ppm (3.25 mg/m^3) (Annex III of Directive 2004/37/EC, European Commission, 2004).

In Germany, the Committee for Hazardous Substances has proposed a tolerable risk of 4 : 1000 and an acceptable risk of 4 : 10 000 (changing to 4 : 100 000), applicable over a working lifetime of 40 years with continuous exposure every working day. For benzene, the tolerable and acceptable risks correspond to 8-hour concentrations of 1.9 mg/m^3 and 0.2 mg/m^3 (0.02 mg/m^3 by 2018), respectively (Bau, 2013).

1.5.2 Environmental exposure limits

(a) Air

The World Health Organization (WHO) states that there is no safe level of exposure to benzene; for general guidance, the concentrations of airborne benzene associated with excess lifetime risks of leukaemia of 1×10^{-4}, 1×10^{-5}, and 1×10^{-6} are 17, 1.7, and 0.17 µg/m^3, respectively (WHO, 2000). The benzene air concentration limit in Europe since 1 January 2010 is 5 µg/m^3 averaged over 1 year (European Commission, 2008). The maximum limit value for benzene in petrol (gasoline) is 1.0% v/v limit (Directive 2009/30/EC, European Commission, 2009).

The United States EPA has specified cancer risk levels: 1×10^{-4}, 1×10^{-5}, and 1×10^{-6} risk, corresponding to concentrations of 13–45, 1.3–4.5, and 0.13–0.45 µg/m^3, respectively. The EPA reference concentration, the estimated continuous inhalation exposure without risk to health, is 3×10^{-2} mg/m^3 (EPA, 2000).

The United States Agency for Toxic Substances and Disease Registry has derived minimal risk levels for acute duration (≤ 14 days) of 0.009 ppm, intermediate duration (15–364 days) of 0.006 ppm, and chronic duration (≥ 365 days) of 0.003 ppm (ATSDR, 2007).

WHO guidelines for indoor air recommend reducing indoor benzene concentrations to the lowest achievable level by eliminating indoor sources of benzene and adjusting ventilation (WHO, 2010).

(b) Water

WHO guidelines for drinking-water recommend a maximum concentration of benzene of 0.01 mg/L (WHO, 2003, 2008). The European Council Directive 98/83/EC on the quality of water intended for human consumption (adopted in 1998) has set the benzene limit to 0.001 mg/L water (European Commission, 1998).

The United States EPA sets regulatory limits for the amount of benzene contaminants in water provided by public water systems: specified cancer risk levels of 1×10^{-4}, 1×10^{-5}, and 1×10^{-6} correspond to drinking-water concentrations of 100–1000, 10–100, and 1–10 µg/L, respectively. The EPA reference dose is 4×10^{-3} mg/kg per day (EPA, 2000).

1.6 Exposure assessment methods in epidemiological studies of cancer

1.6.1 Industry-based studies of occupational exposure

Selected epidemiological studies of cancer and occupational exposure are summarized in Table 1.7. The most common metrics of benzene exposure in these studies are the presumption

Table 1.7 Exposure assessment method for selected occupational epidemiological studies of exposure to benzene

Exposure assessment method	Description of population and exposure assessment	Exposure metrics reported	Strengths of specific study	Limitations of specific study	Exposure assessment reference	Epidemiology Reference
Expert exposure estimation for individual participants' work histories based on measured benzene exposure data	Distribution workers in Canadian petroleum industry; retrospective estimates account for job, site, and era in participants' work histories; base estimates from exposure measurements	Mean intensity 0.0–6.16 ppm [0.0–19.6 mg/m^3]; cumulative exposure 0.0–219.8 ppm-yr [0.0–702.1 (mg/m^3)-yr]; dermal exposure ranking	Work histories and site information well characterized; exposure estimates based on personal measurements collected from 1970 onwards; some task-based hydrocarbon measurements used to validate estimates	Relatively few data points for some base estimates; extrapolation back to as early as 1910 increases uncertainty; potential for other hydrocarbon exposures	Armstrong et al. (1996)	Schnatter et al. (1996)
	Marketing and distribution workers in UK petroleum industry; retrospective estimates of each job or task in the participants' work histories; base estimates developed from exposure measurements adjusted using modifying factors (e.g. job activity, % benzene in fuel, loading technology)	Mean intensity < 0.02 to ≥ 0.4 ppm [< 0.06 to ≥ 1.28 ppm]; cumulative exposure < 0.45 to ≥ 45 ppm-yr [< 1.44 to ≥ 143 (mg/m^3)-yr] Peaks by frequency: daily, weekly, monthly; intensity: 1–3 ppm [3–10 mg/m^3], > 3 ppm [> 10 mg/m^3]; peaks by duration: 1–15 min, 15–60 min Potential for skin exposure (none, low medium, high)	Based on measured exposure data; background exposure assigned for 40% work histories less likely to need extrapolation	Limited job history information for participants pre-1975; extrapolation back to as early as 1910 increases uncertainty; relatively few data points for some base estimates; potential for other hydrocarbon exposures	Lewis et al. (1997)	Rushton & Romaniuk (1997)

Table 1.7 (continued)

Exposure assessment method	Description of population and exposure assessment	Exposure metrics reported	Strengths of specific study	Limitations of specific study	Exposure assessment reference	Epidemiology Reference
Expert exposure estimation for individual participants' work histories based on measured benzene exposure data (cont.)	Upstream, refinery, and distribution workers in Australian petroleum industry; retrospective estimates account for each job or task in the participants' work histories; base estimates from exposure measurements adjusted with modifying factors (e.g. exposure differences over time or between worksites)	Intensity group range ≤ 0.1 to > 3.2 ppm [≤ 0.32 to > 10.2 mg/m^3]; cumulative exposure mean and range 4.7 (0.01–57.3) ppm-yr [15.0 (0.03–183) (mg/m^3)-yr]; peak as exposure to products with > 70% benzene	Work histories and site information from companies well established; estimates based on measured exposure data; the majority of participants' exposure in 1970s, so less extrapolation needed	Relatively few data points for some estimates; extrapolation back to as early as 1955 increases uncertainty; potential for other hydrocarbon exposures	Glass et al. (2000)	Glass et al. (2003)
	Petroleum industry workers from Canada, UK, and Australia (see Armstrong et al., 1996; Lewis et al., 1997; Glass et al., 2003); exposure assessment by individual study; pooled data compared and adjusted by country	Mean average intensity (SD) 0.22 (0.7) ppm [0.7 (2.24) mg/m^3], mean maximum intensity (SD) 0.41 (1.3) ppm [1.31 (4.2) mg/m^3]; median cumulative exposure (SD) 5.2 (17.0) ppm-yr [16.6 (54.3) (mg/m^3)-yr]; peaks > 3 ppm [10 mg/m^3] for 15–60 min; dermal exposure likelihood; exposure certainty ranking	All studies used measured exposure data; exposure estimation quality scores allowed sensitivity analyses	Relatively few data points for some base estimates; some extrapolation back to pre-1920; different countries, industry sectors, and eras may limit comparability of exposure estimates; potential for other hydrocarbon exposures	Armstrong et al. (1996), Lewis et al. (1997), Glass et al. (2003, 2010, 2017)	Schnatter et al. (2012), Rushton et al. (2014)

Table 1.7 (continued)

Exposure assessment method	Description of population and exposure assessment	Exposure metrics reported	Strengths of specific study	Limitations of specific study	Exposure assessment reference	Epidemiology Reference
Expert exposure assessment for individual participants' work histories based on measured benzene exposure data, taking account of job title, site, and era	Workers in two USA waterproof cloth manufacturing facilities; JEMs based on air sampling data and detailed work histories to provide individual time-specific exposure estimates; Rhomberg et al. (2016) used Monte Carlo techniques to estimate exposures used in tertile, quartiles, and quintiles	Cumulative exposure 0.001 to > 400 ppm-yr [0.003 to > 1280 (mg/m^3)-yr] (Rinsky et al., 1987), 6.64 ppm [21.2 mg/m^3] platform, 10.46 ppm [33.4 mg/m^3] scrap area (Utterback & Rinsky, 1995)	Occupational hygiene measurements for some sites; exposure estimates adjusted to era; compared exposure estimates with contemporary TLVs; no other exposures	Limited occupational hygiene measurements at some sites; some measurements are spot samples and area samples (not personal); accuracy of detector tube and combustible gas indicator measurements unclear	Rinsky et al. (1981), Paustenbach et al. (1992), Crump (1994), Utterback & Rinsky (1995)	Schnatter et al. (1996), Rinsky et al. (2002), Rhomberg et al. (2016)
Expert assessment using exposure measurements grouped by work characteristic (e.g. job title, work area, industry)	Workers in USA chemical plant; job titles of workers in three areas of a chemical plant assigned to four exposure categories based on measured data	Cumulative exposure groups: 0–3.9, 4.0–24.9, and > 25 ppm-yr [0–12, 13–79, and > 80 (mg/m^3)-yr] (Collins et al., 2015)	Measured exposure data available, adjusted for time period, department, and job	Some estimates based on few personal measurements per job (extent of personal data unclear); most exposures before 1980 estimated without personal exposure data (Collins et al., 2003); limited detail on exposure estimation methods; potential exposure to other known or suspected human carcinogens	Bloemen et al. (2004)	Collins et al. (2003), Bloemen et al. (2004), Collins et al. (2015)

Table 1.7 (continued)

Exposure assessment method	Description of population and exposure assessment	Exposure metrics reported	Strengths of specific study	Limitations of specific study	Exposure assessment reference	Epidemiology Reference
Categoric expert assessment of exposure to form industry JEM by era (1970–1979, 1980–1989, 1990–1999, 2000–2009)	Workers in Norwegian offshore petroleum industry; industry experts coded workers' job histories into 27 job categories in five job sections; exposure burden score created for each job by summing task scores (multiplying categoric scores from intensity, duration, and frequency); job-STEL scores created by summing task-STEL scores (adjusting categoric scores for frequency of task and peak/task)	Intensity 0–0.040 ppm [0–0.130 mg/m^3]; cumulative exposure 0–0.948 ppm-yr [0–3.03 (mg/m^3)-yr] (Stenehjem et al., 2015); STEL probability score	Expert job grouping, some personal measurement data; limited range of tasks and exposures all likely low; extrapolation back to 1970 only	Limited benzene exposure data available (most post-2000); personal measurement data did not cover all jobs and time periods; potential exposure to other known and suspected human carcinogens	Steinsvåg et al. (2007, 2008), Bråtveit et al. (2011, 2012)	Stenehjem et al. (2015)
Expert assessment of job title/area use of JEM to derive exposure estimates	Workers in 672 Chinese facilities in range of industries in 12 cities (712 factories in Yin et al., 1994); estimated using ambient exposure measurements, and production and process information for seven calendar periods for each job title; individual work histories linked to measured exposure data	For leukaemia cases intensity 6.5–487 mg/m^3, cumulative exposure 37.7–5438.4 (mg/m^3)-yr (Yin et al., 1989)	Individualized exposure assessments based on participants' work histories; exposure estimates predictive of benzene poisonings in a validation paper (Dosemeci et al., 1997)	Comparatively few measured data points in pre-1975 period; most measurements based on short-term ambient samples, not personal measurements; overall, 22% of estimates have a high confidence rating	Dosemeci et al. (1994, 1997), Yin et al. (1994), Portengen et al. (2016)	Yin et al. (1996b), Hayes et al. (1997), Linet et al. (2015)

Table 1.7 (continued)

Exposure assessment method	Description of population and exposure assessment	Exposure metrics reported	Strengths of specific study	Limitations of specific study	Exposure assessment reference	Epidemiology Reference
Expert assessment of job title and allocation of ppm exposure estimates, then grouped into categories	Chemical workers from seven USA plants; jobs classified as continuous, intermittent, or no exposure; exposure in ppm assigned to tasks in jobs; estimates varied by era	Cumulative exposure presented in three exposure categories: < 180, 180–719, ≥ 720 ppm-mo [< 575, 575–2297, ≥ 2300 (mg/m^3)-mo] (Wong, 1987b)	Exposure based on measured data adjusted for production and process changes for five of the seven plants	Exposure data sparse before 1970, requiring extrapolation to pre-1910; proportion of exposure data obtained via personal versus fixed ambient sampling unclear; limited employment records for two of the seven plants; potential for other unspecified chemical exposures	Wong (1987a,b)	Wong (1987a,b)
Expert assessment from job title based on measured hydrocarbon exposure data and extrapolation for era	Distribution workers in USA petroleum industry; 8-h TWA THC exposure (for each task and summed) and annual frequency of peak exposures estimated for eight job categories in case–control study (four for cohort study) for four eras (pre-1950, 1950–1964, 1965–1974, 1975–1985)	Cumulative exposure in ppm-yr, peak of at least 500 ppm [1600 mg/m^3]; THC averaged over 15–90 min	Individualized exposure assessments based on participant work histories using measured personal and ambient sample data	Based on THC, not benzene; few data for certain jobs; measured data from 1975–1980 extrapolated to earlier periods back to pre-1950	Smith et al. (1993)	Wong et al. (1993, 1999)
Expert assessment of workplace to form JEM, then applied to participants' job histories	Workers in Italian shoe factory; questionnaires used to gather data on determinants of exposure (e.g. amount of glue, % benzene, production rate, work process changes over time); modelled exposure estimates used to form JEM	Intensity 0–92 ppm [0–294 mg/m^3], mean cumulative exposure (SD) 58.4 (93.9), range 0–522.4 ppm-yr [0–1670 (mg/m^3)-yr] (Seniori Costantini et al., 2003) calculated; dichotomization at 40 ppm-yr [128 (mg/m^3)-yr] used (Costantini et al., 2009)	Model validated using measured exposure data; historical changes in benzene concentration in glue and work processes characterized	Complete job history data available only for 16% cohort; no measured personal exposure data; potential for other exposures (i.e. solvents in glues) unspecified	Seniori Costantini et al. (2003)	Costantini et al. (2009)

Table 1.7 (continued)

Exposure assessment method	Description of population and exposure assessment	Exposure metrics reported	Strengths of specific study	Limitations of specific study	Exposure assessment reference	Epidemiology Reference
Expert assessment of job title/area; industry JEM converted to ppm exposure estimates	Gas and electric utility workers in France; TWA estimations (expressed in units of exposure) based on JEM	Cumulative unit-yr (conversion to ppm-yr); range 0 to ≥ 1.98 ppm-yr [0–6.32 (mg/m^3)-yr])	Estimates considered measured occupational data from other studies; exposure estimates accounted for changes in % benzene in petrol	Relative exposures between groups only (e.g. "use of solvents" for cleaning or degreasing and "exposure to gasoline"); no measured data from the population of interest; potential for other exposures (e.g. herbicides, chlorinated solvents, styrene, ionizing radiation)	Guénel et al. (2002)	Guénel et al. (2002)

h, hour(s); JEM, job–exposure matrix; min, minute(s); mo, month(s); ppm, parts per million; SD, standard deviation; STEL, short-term exposure limit; THC, total hydrocarbons; TLV, threshold limit value; TWA, time-weighted average; yr, year(s)

of occupational exposure by duration (years), average exposure intensity (ppm or mg/m^3), or cumulative exposure, which is the intensity of exposure multiplied by the number of years exposed (ppm-years or (mg/m^3)-years). These metrics indicate that inhalation is the major route of entry, although some studies have also considered dermal exposure (e.g. Lewis et al., 1997; Schnatter et al., 2012; Rushton et al., 2014). The likelihood of peak exposure (using various definitions of peak) has also been examined in some studies (e.g. Lewis et al., 1997; Schnatter et al., 2012; Stenehjem et al., 2015).

The main sectors where exposure assessment for benzene has been carried out for epidemiological studies are the petroleum industry (e.g. Wong et al., 1993 ; Armstrong et al., 1996 ; Lewis et al., 1997 ; Glass et al., 2000; Steinsvåg et al., 2007, 2008; Bråtveit et al., 2011), the chemical industry (e.g. Wong, 1987a, b), and industries that use benzene in manufacturing processes (e.g. Rinsky et al., 1981; Yin et al., 1994; Utterback & Rinsky, 1995), including shoemaking (Seniori Costantini et al., 2003).

Exposure to benzene is often assessed by experts who group workers by job or facility (where appropriate) and then assign exposure to each person using a job–exposure matrix, which may have a time dimension. The exposure estimates in the job–exposure matrix may be quantitative, that is, based on personal and/or area benzene sampling (Rinsky et al., 1981), or they may be semiquantitative. Relative measures can later be translated into benzene concentration (e.g. ppm or mg/m^3) (Guénel et al., 2002; Bråtveit et al., 2012). Very large studies where multiple experts examine different facilities can increase variability in assessments, but this can be mitigated by standardization across facilities (e.g. Portengen et al., 2016).

Most cohort studies and their nested case–control studies are retrospective, with some including participants from as early as 1910 (Wong, 1987a, b; Armstrong et al., 1996; Lewis et al., 1997). Because exposure data were sparse before 1970, the validity of exposure estimates extrapolated to earlier time periods may be uncertain (e.g. Rinsky et al., 1981; Utterback & Rinsky, 1995; Collins et al., 2015). Even for recent time periods, measured data may not be available or may be inadequate to describe exposures from all jobs. In some studies, data from one facility may be attributed to workers at a similar facility, for example offshore workers on different platforms (Bråtveit et al., 2012; Stenehjem et al., 2015). These differences in data availability may result in varying exposure assessments and outcomes (see Section 2.1.1).

Personal sampling data became more common from the 1970s onwards. Recent studies are therefore more likely to assess exposure using personal measurement data, from which more robust exposure estimates can be derived. It is preferable to assess a high proportion of the participants' time at risk of exposure with contemporary exposure measurement data (Glass et al., 2000; Vlaanderen et al., 2010). When personal measurement data are available, temporal and between-worker exposure variability should be considered (Kromhout et al., 1993).

Changes in facilities over time have been considered in some studies listed in Table 1.7; for example, Dosemeci et al. (1994) and Wong (1987a) took production rate into account. Portengen et al. (2016) used a modelling process to consider several factors affecting exposure. Some studies incorporated factors to account for changes over time and between sites, for example due to changing technology and variations in products handled (Armstrong et al., 1996; Lewis et al., 1997; Glass et al., 2000).

Uncertainty is also introduced when exposure to benzene is based on modelling from total hydrocarbon exposure, as the proportion of benzene may vary with the source of the hydrocarbons (e.g. Smith et al., 1993).

Studies based mainly on grab or area sampling data (e.g. Rinsky et al., 1981; Dosemeci et al., 1994; Yin et al., 1994) have been used to derive average long-term exposure estimates, which can be less certain than those based on individual-level measurement data collected over longer periods (e.g. full work shifts).

Other exposures may have been incurred by participants in the studies listed in Table 1.7, for example, from other hydrocarbons for petroleum industry workers. Coexposures identified in these studies are listed in the limitations column. Some coexposures, for example styrene, have been associated with an increased risk of leukaemia (e.g. Guénel et al., 2002). Other exposures may not have been described, including low exposure to X-rays for some petroleum industry workers and possibly 1,3-butadiene for some refinery workers (Akerstrom et al., 2016; Almerud et al., 2017).

The application of validation methods can increase confidence in the exposure estimates. Such methods include the use of exposure estimation quality scores (e.g. Schnatter et al., 2012) and the assessment of interrater agreement (e.g. Steinsvåg et al., 2008).

1.6.2 General population studies

(a) Childhood cancer

Epidemiological studies focused on associations between benzene in outdoor air pollution and risks of childhood cancer in Denmark, France, Italy, and the USA. Primary methods to assess exposure to benzene are summarized for selected studies in Table 1.8, which provides a summary of the general approach and metric(s) that were used, along with strengths and limitations. All the studies used a geographical information system (GIS) to manage spatially referenced data from different sources in their benzene exposure assessments.

One investigation (Heck et al., 2014) used routine air monitoring data from 1990 to 2007 (collected every 12 days) from 39 monitors in the state of California (163 696 square miles or 423 970 km^2), USA, and developed exposure estimates by linking maternal residences to the closest outdoor air monitor. However, not all monitors were operating throughout the study period; for example, in 2008 there were only 17 benzene monitors in operation (Cox et al., 2008). In addition, stationary monitors were often sited near heavy industry, busy freeways, or in agriculturally rich areas (Heck et al., 2014).

All other key studies relied on Gaussian dispersion models to predict outdoor benzene concentrations in air, for example: the California Line Source Dispersion model, version 4 (CALINE4) (Vinceti et al., 2012), the Danish Operational Street Pollution Model (Raaschou-Nielsen et al., 2001), or the EPA Assessment System for Population Exposure Nationwide (ASPEN) (Symanski et al., 2016; Janitz et al., 2017). Developed by the Department of Transportation in California, USA, CALINE4 is an air dispersion model for roads (and other linear air pollutant sources) used to estimate outdoor air concentrations of benzene and other contaminants at defined locations in a given area. The National-Scale Air Toxics Assessment (NATA) uses ASPEN, a dispersion model that relies upon a national inventory of emissions data for hazardous air pollutants, as well as other characteristics that affect the fate and transport of pollutants in the environment (e.g. the rate, location, and height of release of pollutants, and wind speed and direction).

The CALINE4 model used in the Italian study by Vinceti et al. (2012) used locally collected traffic flow data for a single year, but relied on vehicular emission factors over a longer period (1990–2007). One drawback in using the ASPEN model is that modelled estimates are only available for selected years (i.e. 1996, 1999, 2002, 2005, and 2011). Symanski et al. (2016) used all available estimates at the time of their study (until 2005) whereas Janitz et al. (2017) relied on data

Table 1.8 Exposure assessment from selected environmental epidemiological studies of benzene exposure

Exposure assessment method	Location	Exposure metrics reported	Strengths[a]	Limitations[a]	Reference
Childhood cancers: routine air monitoring data					
Outdoor air measurements of benzene obtained from stationary (state) regulatory monitors that collected 24-h samples every 12 d; linked to geocoded participant residences (buffer of 2 km for ALL and 6 km for AML)	California, USA	Residential benzene levels (μg/m^3) calculated for each maternal trimester of pregnancy, entire pregnancy period, and child's first year of life	Exposure estimates available for pregnancy and childhood (first year of life) periods	Variable distances between residences and closest monitor; unable to account for residential mobility during pregnancy or the first year of life	Heck et al. (2014)
Childhood cancers: Gaussian dispersion models					
Modelling outdoor air concentrations of benzene from vehicular emissions at geocoded residential addresses using CALINE4 (considers traffic flow, vehicle emissions factors, and meteorological data)	Northern Italy	Quartiles of average annual residential benzene levels < 0.10, ≥ 0.10–0.25, ≥ 0.25–0.50, and ≥ 0.50 μg/m^3; quartiles of maximum hourly residential benzene levels < 2, ≥ 2–4, ≥ 4–6, and ≥ 6 μg/m^3	Validation conducted with air measurements from monitoring stations; considered coexposures to PM_{10}	Uncertainty associated with emissions and traffic data sources, and use of a single calendar year to estimate exposures; limited validation due to small number of air monitoring stations; Pearson's correlation coefficient of 0.43 between modelled and monitored (n = 6 monitors) data; unable to account for residential mobility during childhood (up to 14 yr from birth)	Vinceti et al. (2012)
Modelled annual census tract level estimates of outdoor benzene levels for 1996, 1999, 2002, and 2005 from the US EPA NATA linked to geocoded maternal addresses at birth of infants	Texas, USA	Quartile estimates of outdoor benzene levels (based on the distribution in the controls for each NATA year): low, medium, medium–high, and high	NATA estimates account for point, mobile, and area sources of benzene emissions; considered coexposures to 1,3-butadiene and PAHs	Modelled annual estimates available only at the census tract level for specific year (1996, 1999, 2002, and 2005); unable to account for residential mobility during pregnancy and early childhood (up to 4 yr from birth)	Symanski et al. (2016)
Address at birth linked to the census tract concentration for benzene using the 2005 US EPA NATA database (see Symanski et al., 2016)	Oklahoma, USA	Quartiles of estimated outdoor benzene levels: 0.11 to < 0.39, 0.39 to < 0.67, 0.67 to < 0.91, and 0.91–2.03 μg/m^3	NATA estimates account for point, mobile, and area sources of benzene emissions	Modelled annual estimates of outdoor benzene levels for 1 yr only (2005) to assess exposure at birth; unable to account for residential mobility during pregnancy and childhood (up to 19 yr from birth)	Janitz et al. (2017)

Table 1.8 (continued)

Exposure assessment method	Location	Exposure metrics reported	Strengths[a]	Limitations[a]	Reference
Annual benzene concentrations for grids of area 10 m^2 (Paris), 25 m^2 (inner suburbs), or 50 m^2 (outer suburbs), estimated from a dispersion model linked to air monitoring data; benzene estimates linked to geocoded addresses at the time of diagnosis (cases) or inclusion (controls), and data on proximal roadways using the Navteq database	Paris and surrounding areas, France	Subjects were classified based on whether estimated annual benzene concentration at their residence was < 1.3 μg/m^3 (median exposure for the controls) or ≥ 1.3 μg/m^3; major road length classified as low, medium, and high	Use of an air dispersion model to account for vehicular emissions, meteorology, and information on fate, transport, and transformation of pollutants; inclusion of a term to account for local traffic in the exposure metric	Unable to account for residential mobility before time of diagnosis (up to 14 yr from birth)	Houot et al. (2015)
Modified version of the Operational Street Pollution Model used to estimate average residential exposure to benzene; estimated air concentrations based on measurements made during 1994–1995 at four sites; included other info (e.g. traffic pattern, vehicle emission factors, meteorology); residential history ascertained from the Danish population registry	Denmark	Tertiles of cumulative exposure to benzene (in 1000 ppb-d): < 0.5, 0.5 to < 1.3, and ≥ 1.3	Temporally resolved estimates during pregnancy and during the child's life; accounted for residential mobility; validation conducted with 204 air measurements in urban and rural locations	Did not account for sources of pollution other than traffic; benzene exposure estimated using measurements taken after case diagnosis (1968–1991); validation results indicate poor correlation in rural areas between modelled and monitored results	Raaschou-Nielsen et al. (2001)
Cancer in adults					
Self-reported via completed questionnaires	Rochester, Minnesota, USA	Ever exposed regularly to benzene or derivative (yes/no)	May capture exposure to benzene in work and non-work environments	Little contrast in exposure metric; recall of exposures may not be accurate	Antwi et al. (2015)
Address at baseline was linked to the census tract concentration for benzene using the 2005 US EPA NATA database (see Symanski et al., 2016)	California, USA	Quintile estimates of outdoor benzene levels	NATA estimates account for point, mobile, and area sources of benzene emissions	Use of modelled annual estimates of outdoor benzene levels for 1 yr (2005) to assess exposures at baseline; unable to account for residential mobility during follow-up period; no information about exposure in non-residential environments, exposure to cigarette smoke, and housing characteristics that may influence exposures at home	Garcia et al. (2014)

Table 1.8 (continued)

Exposure assessment method	Location	Exposure metrics reported	Strengths[a]	Limitations[a]	Reference
Reconstructed levels of benzene (from multiple sources of contamination) in the water distribution system using fate and transport models linked to residential histories of navy and marine personnel stationed at the base	US Marine Corps Base, Camp Lejeune, North Carolina	Quartiles of cumulative exposure (μg/L-mo) to benzene: < 2, 2–45, > 45–110, and > 110–601	Rigorous methods used to reconstruct solvent contamination of drinking-water sources	Inaccuracies in residential histories likely; did not account for time spent away from the base for training or deployment	Bove et al. (2014)

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CALINE4, California Line Source Dispersion Model, version 4; d, day(s); h, hour(s); mo, month(s); NATA, National-Scale Air Toxics Assessment; PAHs, polycyclic aromatic hydrocarbons; PM_{10}, particulate matter of diameter < 10 μm; ppb, parts per billion; US EPA, United States Environmental Protection Agency; yr, year(s)

[a] List not exhaustive

for a single year (2005). Because the NATA model inputs change over time, Symanski et al. (2016) conducted a sensitivity analysis by limiting the study population to cases and controls born within 1 year of a NATA release; estimated odds ratios were similar in magnitude, but less precise. Two investigations focused their assessments on exposures due to emissions from vehicular traffic: Raaschou-Nielsen et al. (2001) and Vinceti et al. (2012).

Houot et al. (2015) derived final estimates at geocoded locations using geostatistical methods that combined the dispersion modelled data for a 10 m^2 grid in the city of Paris, a 25 m^2 grid in the inner suburb, and a 50 m^2 grid in the outer suburb with available air monitoring data.

Studies based in the USA (Symanski et al., 2016; Janitz et al., 2017) used NATA estimates that were generated for all census tracts within the continent of North America. Census tract boundaries are drawn based on population size (average population size, 4000 people) and therefore vary by size and shape.

Because the exposure assessments in the reviewed studies relied on a records-based linkage to develop the exposure metrics, there was no response or recall bias in the exposure assessments. The study by Raaschou-Nielsen et al. (2001) offered an advantage over other studies because it addressed residential mobility in estimates of cumulative exposure; residential histories obtained from a national database, from 9 months before birth to the time of diagnosis, were used. All other studies relied on a single residence (either at birth or at the time of diagnosis) upon which to base the exposure assessment. The use of a single residence may have increased uncertainty in the exposure assessments, particularly in studies that included children diagnosed at older ages (e.g. 14–19 years) (Vinceti et al., 2012; Houot et al., 2015; Janitz et al., 2017).

A strength of the studies by Raaschou-Nielsen et al. (2001) and Heck et al. (2014) was their ability to construct temporally resolved estimates of exposure during pregnancy and childhood that allowed for an assessment of exposure at different life stages. However, none of the studies incorporated information on time spent away from the residence for the mother or the child and, by not accounting for exposures in other environments (e.g. maternal exposures at work), uncertainty in the exposure assessments was likely introduced.

Outdoor air includes multiple pollutants from diverse natural and anthropogenic sources; the air pollutant mixture can therefore vary both locally and regionally. Methods for addressing multiple exposures included the application of co-pollutant models (Symanski et al., 2016) and factor analysis (Heck et al., 2014). Information on indoor air sources of benzene (e.g. environmental tobacco smoke) was unavailable in all studies, as was information on housing characteristics (e.g. living in a residence with an attached garage); only one investigation had information about maternal smoking (Symanski et al., 2016).

In most of the studies, the control population (all of the investigations in Table 1.8 used a case–control study design) represented the source population and was therefore unlikely to be affected by exposure-related selection bias. However, some bias may have been introduced in the investigation by Heck et al. (2014) who excluded 2978 cases and 142 188 controls from the parent study because residences were not within defined buffers around a stationary air monitor (2 km for acute lymphoblastic leukaemia and 6 km for acute myeloid leukaemia). Vinceti et al. (2012) also excluded individuals living in mountainous areas (< 10% of the total population in the study area) because the CALINE4 dispersion model was not developed to incorporate rocky terrain in predicting air pollutant concentrations near roadways.

Vinceti et al. (2012) presented results from a validation study and, based on measurements collected at six monitoring stations, reported a

modest correlation (Pearson correlation coefficient, 0.43) between the CALINE4 modelled estimates and outdoor air benzene levels. Raaschou-Nielsen et al. (2001) compared the results from their dispersion model with passive sampler measurements of benzene at various street locations in Copenhagen, Denmark and in rural areas. Pearson correlation coefficients of 0.62–0.68 were reported for urban locations (range in values based on differences in meteorological inputs); correlations were much lower for rural locations (0.15–0.19) where there is little variation in traffic levels. Regarding the NATA data, previous studies reported good agreement between the ASPEN modelled estimates and monitored levels of benzene in ambient air (Symanski et al., 2016).

(b) Cancer in adults

Studies on cancer risks associated with environmental benzene exposure have used a variety of approaches in their exposure assessments (see Table 1.8 for a summary).

In a nested case–control study of 82 cases and 83 controls among lifelong never-smokers of the Shanghai Cohort Study (a prospective cohort of 18 244 Chinese men, aged 45–64 years at enrolment) (Yuan et al., 2014), exposures to benzene were assessed using SPMA based on measured concentrations of stored urine samples collected at baseline. While SPMA is a specific biomarker for benzene exposure, its half-life in the body is relatively short; relying on a single urinary measurement of SPMA is problematic as it is not representative of average exposure.

Two drinking-water systems at the United States Marine Corps Base, Camp Lejeune, North Carolina were contaminated with tetrachloroethylene and other solvents, including benzene, from 1975 until February 1985. Bove et al. (2014) reconstructed monthly contaminant levels in the water distribution system using fate and transport models; these were linked to residential histories of marine and navy personnel living at the base to generate lagged (10-, 15-, and 20-year) and unlagged estimates of cumulative exposure. Exposures may have been misclassified due to errors in the reconstructed levels of benzene in the water distribution system, as well as inaccuracies in identifying units assigned to the base, in determining the location of the barracks or housing for marine/navy personnel with families, or in accounting for time spent away from the base for training or deployment.

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