STYRENE, STYRENE-7,8-OXIDE, AND QUINOLINE

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International Agency for Research on Cancer
World Health Organization

STYRENE AND STYRENE-7,8-OXIDE

1. Exposure Data

1.1 Styrene

1.1.1 Identification of the agent

(a) Nomenclature

Chem. Abstr. Serv. Reg. No.: 100-42-5

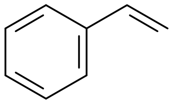
Previously used Chem. Abstr. Serv. Reg. No.: 79637-11-9

Chem. Abstr. Serv. name: Ethenylbenzene

IUPAC systematic name: Styrene

Synonyms: Cinnamene; cinnamenol; cinnamol; phenylethene; phenethylene; phenylethylene; styrol; styrole; styrolene; vinylbenzene; vinylbenzol

(b) Structural and molecular formulae, and relative molecular mass



Styrene

Molecular formula: C_8H_8

Relative molecular mass: 104.15

(c) Chemical and physical properties of the pure substance

Description: Colourless, viscous liquid with a pungent odour (WHO, 1983)

Melting/freezing point: −31 °C (IARC, 2002)

Boiling point: 145 °C at 101.3 kPa (IARC, 2002)

Density: 0.906 g/cm^3 at 25 °C (Merck, 2017a)

Relative density: $d_{20/4}$, 0.9060 (water, 1) (IARC, 2002)

Solubility in organic solvents: Miscible with acetone, benzene, carbon tetrachloride, (diethyl) ether, ethanol, heptane (Chevron Phillips Chemical Co., 2010)

Solubility in water: 0.31 g/L at 25 °C (NTP, 2016a)

Vapour pressure: 867 Pa at 25 °C (IARC, 2002)

Saturated vapour concentration: 8500 ppm at 25 °C (EPA, 1993)

Relative vapour density: 3.6 (air, 1) (IARC, 2002)

Evaporation rate: 1.92 (nBuAc, 1) (Chevron Phillips Chemical Co., 2010)

Odour threshold: Low: 0.20 mg/m^3 (pure) and 0.43 mg/m^3 (stabilized); high: 860 mg/m^3 (Ruth, 1986)

Reactivity: Polymerizes readily at room temperature in the presence of oxygen and oxidizes on exposure to light and air (WHO, 1983). Styrene is stabilized by a small amount of a polymerization inhibitor; if this is not present in adequate concentration, styrene can polymerize and explode its container. Polymerization is also accelerated at temperatures above 66 °C (NIOSH, 1983); recommended storage temperature is 25 °C or less (Shell, 2017). The vapours are heavier than air and spread along the ground; distant ignition is possible (Shell, 2017).

Octanol/water partition coefficient (P): log K_{ow}, 2.95 (IARC, 2002)

Conversion factor: 1 ppm = 4.26 mg/m^3 at normal temperature (25 °C) and pressure (101 kPa) (IARC, 2002)

(d) Technical products and impurities

Styrene monomer is available as a commercial product with different levels of purity (i.e., 99.7% to >99.9%) The impurities present and their concentrations depend upon the manufacturing route, as well as plant performance characteristics. The typical inhibitor content of the standard grade is 10–15 ppm 4-*tert*-butylcatechol (CEFIC, 2007). The trace components in a commercial product of purity 99.93% are listed in Table 1.1 (Chevron Phillips Chemical Co., 2010).

Table 1.1 Trace components present in commercially produced styrene

Trace chemical	Concentration (ppm)
α-methylstyrene	175
Σ *m*- and *p*-xylene	120
o-xylene	125
Cumene	100
Propylbenzene	60
Ethylbenzene	50
Phenylacetylene	50
Σ *m*- and *p*-ethyltoluene	20
Aldehydes (as benzaldehyde)	15
4-*tert*-butylcatechol	12
Vinyltoluene	10
Σ *m*- and *p*-divinylbenzene	< 10
Peroxides (as benzoyl peroxides)	5
o-divinylbenzene	< 5
Polymerized styrene	1
Benzene	< 1
Chlorides (as Cl)	< 1
Sulfur	< 1
Toluene	< 1

ppm, parts per million.
Adapted from Chevron Phillips Chemical Co. (2010).

1.1.2 Production and use of styrene

Worldwide, styrene is one of the most important monomers for polymers and copolymers that are used in a wide range of applications. Globally, it is estimated that more than 15 000 industrial plants in many countries produce or use styrene in the manufacturing of polymeric products (The Styrene Forum, 2017).

(a) Production process

Styrene was first isolated in 1831 by distillation of storax, a natural balsam. Commercial production of styrene via dehydrogenation of ethylbenzene began in Germany in 1925 (Tossavainen, 1978).

There are two commercially viable methods of producing styrene. The most important, which accounts for over 90% of total world styrene production, is catalytic dehydrogenation in the vapour phase of high-purity ethylbenzene. Common catalysts are based on ferric oxide (Fe_2O_3) with chromia (Cr_2O_3) as a stabilizer and potassium oxide as a coke retardant (Behr, 2017). Typically, the crude product of the dehydrogenation process consists of 64% styrene, 32% ethylbenzene, 2% toluene, 1% benzene, and 1% other substances. The isolation of pure styrene from the mixture by distillations is difficult because of the similar boiling points of styrene and ethylbenzene (Behr, 2017).

The second process involves oxidation of ethylbenzene to its hydroperoxide and reaction with propylene to yield propylene oxide. The co-product α-methylphenyl carbinol is then dehydrated to styrene (Behr, 2017). A third process, involving oxidative dehydrogenation of ethylbenzene to styrene with carbon dioxide, has been proposed (Chon, 2003).

(b) Production volume

Styrene is considered to be a high production volume chemical (USDOE, 2012). In 2004, the global styrene demand was reported to be over 24 million metric tonnes (CEFIC, 2007). In 2010, the global production of styrene was 27.5 million United States tons [25 million tonnes], of which approximately 4.4 million United States tons [4 million tonnes] originated in the USA. In 2012, the world production of styrene monomer exceeded 26.4 million metric tonnes (Aghayarzadeh et al., 2014).

China consumes far more styrene than other countries. In 2014, 30% of the world consumption of styrene was estimated to be by China (IHS Markit, 2017). Styrene consumption is expected to remain relatively constant, growing at an average rate of 1.6% per year during 2014–2019. Higher growth in the production of expandable polystyrene (EPS) is predicted, especially in construction where it is being increasingly used as concrete forms and as insulation, driven by demand for higher energy efficiency. Styrene consumption for EPS production is expected to grow at an average rate of 2.3% per year during 2019–2024. Styrene consumption for the production of acrylonitrile–butadiene–styrene (ABS) resins and styrene–butadiene rubber (SBR) is expected to see the highest annual growth rates of 3.6% and 4.1%, respectively (IHS Markit, 2017).

The production of styrene in the USA has risen steadily since 1960. Between 1960 and 2006, estimated production ranged from a low of 1740 million pounds [~7.9 × 10^5 tonnes] in 1960 to a high of 11 897 million pounds [~54 × 10^5 tonnes] in 2000. In 2006, eight United States manufacturers produced an estimated 11 387 million pounds [~51 × 10^5 tonnes] of styrene; the three largest producers accounted for 54% of production. United States consumption of styrene in 2006 was 9600 million pounds [~43 × 10^5 tonnes], more than 99% of which was in the production of polymers and copolymers (NTP, 2016a).

The USA is a producer and net exporter of styrene to the rest of the world. In 2014, the production capacity of styrene in Canada and the USA was 880 thousand tonnes and 4.8 million tonnes, respectively. The amount of styrene imported into the USA recently has been small, and only from Canada. In 2014, the USA exported 1.53 million tonnes of styrene (ICIS, 2014).

In 2016, 1 767 053 metric tons of styrene monomer was produced in Japan (Statista, 2017).

In 2016, China imported 3.5 million tonnes of styrene monomer; 1.23 million tonnes (35%) of this quantity came from the Republic of Korea, making it the largest supplier of styrene monomer to China. Meanwhile, China's total styrene monomer demand has gradually increased from 8.49 million tonnes in 2013 to 9.1 million tonnes in 2016, at an average annual growth rate of 2.38%. According to industry sources, China's annual domestic styrene monomer production was about 8.39 million tonnes in 2017, and was expected to rise by 2.3 million tonnes per year to 10.7 million tonnes by 2019 (Plastemart.com, 2017).

Styrene is presently manufactured in and/or imported into the European Economic Area at a rate of 1–10 million tonnes per year (ECHA, 2017).

(c) Uses

In the 1930s, styrene was used mainly in the production of synthetic rubber; the application of styrene as a solvent and cross-linking agent in the production of fibreglass-reinforced plastics started in the 1950s (Tossavainen, 1978). The resins generally contain between 30% and 50% styrene by weight (Haberlein, 1998). Today, styrene is primarily used as a monomer in the production of polystyrene plastics and resins.

Styrene producers sell styrene monomer to companies that use styrene to make various compounds and resins. Fabricators then process the resins into a wide variety of products (Cohen et al., 2002).

According to The Styrene Forum (2017), there are six major styrene resin families: (i) polystyrene (PS); (ii) SBR; (iii) styrene–butadiene latex (SBL); (iv) ABS; (v) styrene-based unsaturated polyester resins (UPR); and (vi) styrene–acrylonitrile (SAN). Industry estimates of the relative amounts of styrene consumed by these six resin families are as follows: PS, 50%; SBR, 15%; SBL, 12%; ABS, 11%; UPR, 11%; and SAN, 1% (The Styrene Forum, 2017). The uses, according to Chevron Phillips Chemical Co. (2017) are variable across these resin families. PS is primarily used in packaging, disposables, and low-cost consumer products. Improved grades of PS resins are used in higher-performance applications, such as home electronics and appliances. Uses of PS include as EPS beads in food and beverage packaging, building insulation, and cushion packaging. SBR, a thermoplastic synthetic elastomer, is used in the production of tyres. SBL is another thermoplastic synthetic elastomer used in carpet backing, for example. ABS and SAN have many uses in the consumer durables market. Styrene-based UPR are used in gel-coating and laminating operations in the production of fibreglass-reinforced plastic products such as boats, bathtubs, shower stalls, tanks, and drums, that is, items that provide a long service life in both indoor and outdoor applications (The Styrene Forum, 2017).

In addition, recycled polystyrene is used in packaging, construction materials, video cassettes, office supplies, and other products. A company in Oregon, USA, is developing a production plant that can convert scrap polystyrene into a liquid monomer (Association of Oregon Recyclers, 2017).

1.2 Styrene-7,8-oxide

1.2.1 *Identification of the agent*

(a) Nomenclature

Chem. Abstr. Serv. Reg. No.: 96-09-3; (*R*)-(+)-styrene-7,8-oxide: 20780-53-4; (*S*)-(-)-styrene-7,8-oxide: 20780-54-5; (±)-styrene-7,8-oxide: 67253-49-0

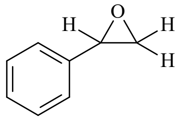
Previously used Chem. Abstr. Serv. Reg. No.: 62497-63-6

Chem. Abstr. Serv. name: 2-Phenyloxirane

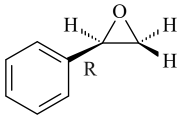
Synonyms: Epoxyethylbenzene; 1,2-(epoxyethyl)benzene; 1,2-epoxy-1-phenylethane; a,β-epoxystyrene; phenethylene oxide; 1-phenyl-1,2-epoxyethane; phenylethylene oxide; phenyloxirane; styrene epoxide; styrene oxide; styryl oxide

(b) Structural and molecular formulae, and relative molecular mass

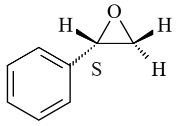
Styrene-7,8-oxide exists as two optical isomers and the commercial product is a racemic mixture.



(±)-styrene-7,8-oxide



(*R*)-(+)-styrene-7,8-oxide



(*S*)-(-)-styrene-7,8-oxide

Molecular formula: C_8H_8O

Relative molecular mass: 120.15

(c) Chemical and physical properties of the pure substance

Description: Clear, colourless to straw-coloured liquid with a sweet pleasant odour (PubChem, 2017)

Melting/freezing point: –37 °C (Merck, 2017b)

Boiling point: 193–195 °C at 101.3 kPa (Merck, 2017b)

Density: 1.05 g/cm^3 at 20 °C (Merck, 2017b)

Relative density: $d_{20/4}$, 1.051–1.054 (water, 1) (Merck, 2017b)

Solubility in organic solvents: Soluble in acetone, benzene, carbon tetrachloride, heptane, and methanol (IARC, 1994)

Solubility in water: 3 g/L at 25 °C (Merck, 2017b)

Vapour pressure: 0.3 mm Hg = 40 Pa at 20 °C (Merck, 2017b)

Relative vapour density: 4.30 (air, 1) (HSDB, 2017b)

Odour threshold: Low: 0.3093 mg/m^3; high: 1.9640 mg/m^3 (Ruth, 1986)

Reactivity: Polymerizes exothermically and reacts violently with water in the presence of catalysts (acids, bases, certain salts). Should be stored at +15 to +25 °C. Decomposition temperature: > 250 °C (Merck, 2017b).

Octanol/water partition coefficient (P): log K_{ow}, 1.61 (IARC, 1994)

Conversion factor: 1 ppm = 4.91 mg/m^3 at normal temperature (25 °C) and pressure (101.3 kPa) (IARC, 1994)

(d) Technical products and impurities

Typical product specification for styrene-7,8-oxide is 99% minimal purity and 0.1–0.2% maximal water content (IARC, 1994).

1.2.2 Production and use of styrene-7,8-oxide

(a) Production process

Styrene-7,8-oxide is produced commercially by the reaction of styrene with chlorine and water to form styrene chlorohydrin, followed by cyclization with aqueous base to produce styrene-7,8-oxide. It is also prepared by epoxidation of styrene with peroxyacetic acid (IARC, 1994). Styrene-7,8-oxide may be synthesized by air oxidation of styrene over cobalt-containing (Co_3O_4) catalysts (Lu et al., 2010).

Styrene monooxygenase produced by recombinant *Escherichia coli* can catalyse the enantiomeric oxidation of styrene to yield (*S*)-(-)-styrene-7,8-oxide (Panke et al., 2002).

(b) Production volume

Information available in 1991 indicated that styrene-7,8-oxide was produced by three companies in Japan and one company in the USA (IARC, 1994). In 2009, there was still only one United States manufacturer of styrene-7,8-oxide that had been identified (HSDB, 2017b).

Styrene-7,8-oxide is registered according to the European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation, and is manufactured in and/or imported into the European Economic Area in quantities of 100–1000 metric tonnes per year (ECHA, 2017).

(c) Uses

Styrene-7,8-oxide is used as a reactive plasticizer or diluent for epoxy resins and in the production of phenethyl alcohol (2-phenylethanol) and styrene glycol, and their derivatives (PubChem, 2017). It is used as a reactive plasticizer, in surface coatings, as a food-grade flavour, in styrene glycol, in cosmetics, and in perfumes (Bajpai & Mukherjee, 2017).

1.3 Measurement and analysis

1.3.1 Detection and quantification

(a) Air

Styrene and styrene-7,8-oxide concentrations in air during the lamination process in the reinforced plastics industry were measured by Pfäffli et al. (1979). The substances were sampled on charcoal tubes and desorbed with dichloromethane immediately after the sampling, and assayed by capillary column gas chromatography. The identification was performed by a mass spectrometer coupled with a gas chromatograph.

According to the National Institute for Occupational Safety and Health (NIOSH) Method 1501 for measurements of styrene in workplace air, the sample is adsorbed on charcoal and desorbed with carbon disulfide, and styrene determined by capillary column gas chromatography (GC) with a flame ionization detector (FID); the estimated limit of detection is 0.4 µg per sample (NIOSH, 1994).

Styrene in workplace air can also be sampled on a solid sorbent and desorbed with ethyl acetate; styrene is then determined by GC-FID (Tornero-Velez et al., 2000).

A thermal desorption GC mass spectrometry (MS) method to determine styrene in air and evaluate styrene levels in the workplace and its surrounding area was developed by Fernández-Villarrenaga Martín et al. (2000).

Styrene has been measured in ambient air and indoor air as part of exposure to volatile organic carbons (VOCs) of children (Adgate et al., 2004) and the general population (Rehwagen et al., 2003). Indoor air and ambient air were sampled by passive sampling followed by extraction with acetone and/or carbon disulfide (2:1 volume/volume) or carbon disulfide followed by GC-MS analysis. The quantitation limit for styrene was 0.6 µg/m^3 in the study on children (Adgate et al., 2004), and the detection limits in the general-population study were 0.01–0.05 µg/m^3 if converted to a sampling interval of 4 weeks (Rehwagen et al., 2003).

Styrene-7,8-oxide can be determined in air samples by GC-MS or GC-FID. The samples were collected on a solid sorbent and desorbed thermally with ethyl acetate or carbon disulfide (Pellizzari et al., 1976; Fjeldstad et al., 1979; Taylor, 1979; Stampfer & Hermes, 1981; Tornero-Velez et al., 2000). A detection limit as low as 2 ng/m^3 was reported (Krost et al., 1982).

(b) Water, soil, sediment, etc.

United States Environmental Protection Agency (EPA) Method 8260B can be used to determine the concentration of various VOCs, including styrene, by GC-MS in a variety of matrices such as groundwater, aqueous sludges, waste solvents, oily wastes, tars, soils, and sediments. Samples may be analysed using direct injection, purge-and-trap (PT), closed-system vacuum distillation, static headspace (solid samples), or desorption from trapping media (air samples) (EPA methods 5021, 5030, 5032, and 5041). The practical quantification limits are 5 µg/L for groundwater samples, 5 µg/kg (wet weight) for low-level soil and sediment samples, 250 µg/L for water-miscible liquid waste samples, 625 µg/kg for high-level soil and sludge samples, and 2500 µg/L for non-water-miscible waste samples (EPA, 1996).

Styrene-7,8-oxide and other electrophiles can be determined in environmental samples by reaction in aqueous solution with 4-nitrothiophenol to form thioethers; these have absorption maxima at about 445 nm and can be separated using high-performance liquid chromatography (HPLC). Styrene-7,8-oxide has two absorption maxima, at 339 nm and 340 nm. The level of detection was less than 1 part per billion (ppb) in water (Cheh & Carlson, 1981).

(c) Blood and urine

A rapid and simple PT-GC technique for the measurement of styrene in urine and blood samples was developed by Prieto et al. (2000, 2002).

Methods of isotope-dilution GC-MS have been described for determination of styrene and styrene-7,8-oxide in blood. Positive ion chemical ionization allowed the detection of styrene at concentrations greater than 2.5 µg/L blood and of styrene-7,8-oxide at concentrations greater than 0.05 µg/L blood (Tornero-Velez et al., 2001).

An alternative method for the measurement of styrene-7,8-oxide is reaction with valine, followed by derivatization with pentafluorophenyl isothiocyanate and analysis via negative ion chemical ionization GC and tandem mass spectrometry (MS/MS) (styrene-7,8-oxide detection limit, 0.025 µg/L blood). The detection limit for styrene-7,8-oxide by these two methods were 10–20-fold lower than those of the GC assays based upon either electron-impact MS or FID (Tornero-Velez et al., 2001).

Levels of unmetabolized styrene in urine can be determined by headspace solid-phase microextraction followed by GC-MS analysis, with a detection limit of 0.2 µg/L (Fustinoni et al., 2008).

Mandelic acid (MA) and phenylglyoxylic acid (PGA), urine metabolites of styrene and styrene-7,8-oxide, can be determined by HPLC (Ghittori et al., 1997; Marhuenda et al., 1997) or by liquid chromatography (LC) with MS/MS using negative ion mode and quantification by selected reaction monitoring (Manini et al., 2002). The detection limit of the HPLC method is 15 mg/L for MA and is 2 mg/L for PGA. The limit of detection for both MA and PGA is 0.1 mg/L using the LC-MS/MS method.

1.3.2 Styrene and styrene-7,8-oxide biomarkers in exposure assessment

Measurement of biological indicators of exposure incorporates the influence of multiple routes of absorption and the use of personal protective equipment within a comprehensive exposure assessment. The relationship between air concentrations and biological measures of exposure to styrene has been studied extensively. About 95% of the absorbed styrene is excreted in urine as MA and PGA. Reliable, sensitive, and specific analytical methods exist for monitoring occupational exposure to styrene and styrene-7,8-oxide. Among the biological monitoring methods available (Section 1.3.1), measurements of MA and PGA in urine are the most commonly used biological indices of exposure to styrene and styrene-7,8-oxide. Styrene itself can be measured in alveolar air, blood, and urine, and styrene-7,8-oxide and the haemoglobin adducts of styrene-7,8-oxide can be measured in blood. Table 1.2 and Table 1.3 provide summary data from occupational studies in which both personal inhalation exposure concentrations and biological indicators of styrene and styrene-7,8-oxide exposures in urine and blood, respectively, have been reported in reinforced plastics manufacturing workers.

(a) Mandelic acid and phenylglyoxylic acid in urine

Reliable, sensitive, and specific analytical methods exist for MA and PGA in urine (Marhuenda et al., 1997; Manini et al., 2002). MA and PGA are produced by sequential metabolism, MA appearing first in the urine (Guillemin & Bauer, 1979). The relationship between the excreted levels of MA and PGA varies according to factors such as the intensity of exposure and the sampling time. The biological half-life of PGA is longer than that of MA; accumulation of PGA can occur during a working week, whereas MA is mostly cleared within 24 hours (Perbellini

Table 1.2 Urine biomarker levels and their correlation coefficients (*r*) with styrene (and styrene-7,8-oxide) inhalation exposure concentrations in reinforced plastics manufacturing workers

Reference Location, collection date	Occupation description	No. of workers and/or samples	Sampling matrix and time	Mandelic acid + phenylglyoxylic acid		Mandelic acid		Phenylglyoxylic acid		Styrene	
				Mean exposure (range and/or SD) (mg/g creatinine)[a]	*r*	Mean exposure (range and/or SD) (mg/g creatinine)[a]	*r*	Mean exposure (range and/or SD) (mg/g creatinine)[a]	*r*	Mean exposure (range and/or SD) (µg/L)[b]	*r*
Guillemin et al. (1982) Switzerland, 10 plants; NR	All workers	88	End of shift	NR	0.747	1003.7 (SD, 1206.8)	0.749	339.1 (SD, 360.2)	0.706		
	Hand lamination, containers of various sizes	4				1341.6 (SD, 756.2)		352.4 (SD, 98.1)			
	Hand and spray lamination of boats 13 m long and small objects	5				976.8 (SD, 485.4)		307.1 (SD, 163.3)			
	Hand, spray, and automatic system lamination of silos and small boats	8				655.1 (SD, 305.8)		240.2 (SD, 124.0)			
	Hand lamination of inside coating of oil tanks	6				1246.6 (SD, 1233.9)		255.8 (SD, 155.7)			
	Hand, spray, and artificial marble production and lamination of boats, showers, tables, sinters, etc.	12				715.6 (SD, 782)		187.6 (SD, 145.5)			

Table 1.2 (continued)

Reference Location, collection date	Occupation description	No. of workers and/or samples	Sampling matrix and time	Mandelic acid + phenylglyoxylic acid		Mandelic acid		Phenylglyoxylic acid		Styrene	
				Mean exposure (range and/or SD) (mg/g creatinine)[a]	*r*	Mean exposure (range and/or SD) (mg/g creatinine)[a]	*r*	Mean exposure (range and/or SD) (mg/g creatinine)[a]	*r*	Mean exposure (range and/or SD) (μg/L)[b]	*r*
Guillemin et al. (1982) (cont.)	Automatic system, pipes and others objects	3				551.7 (SD, 107.1)		230.8 (SD, 39.3)			
	Hand, spray, and vacuum lamination of basins, walls, baths, etc.	14				1179.5 (SD, 663.4)		465.0 (SD, 216.4)			
	Hand, spray, automatic system, UV-hardening, and silica reinforcement of large pipes	19				175.4 (SD, 127.7)		145.3 (SD, 102.4)			
	Hand, spray, and vacuum lamination of cabins, walls, etc.	15				2334.3 (SD, 1891.2)		763.4 (SD, 596.0)			
	Hand lamination of parts of car bodies	2				305.5 (SD, 68.6)		132.5 (SD, 118.1)			
Ikeda et al. (1982) Japan, five boat production plants; NR	Hand lamination	118	End of shift	NR	0.88	NR	0.86	NR	0.82		

Table 1.2 (continued)

Reference Location, collection date	Occupation description	No. of workers and/or samples	Sampling matrix and time	Mandelic acid + phenylglyoxylic acid		Mandelic acid		Phenylglyoxylic acid		Styrene	
				Mean exposure (range and/or SD) (mg/g creatinine)[a]	*r*	Mean exposure (range and/or SD) (mg/g creatinine)[a]	*r*	Mean exposure (range and/or SD) (mg/g creatinine)[a]	*r*	Mean exposure (range and/or SD) (µg/L)[b]	*r*
Imbriani et al. (1986) Italy; NR	Boat manufacturing	121	End of shift							51 (median) (19.7–189.0)	0.89
Triebig et al. (1989) Germany, four plants; NR	Lamination of boats, pipes, or containers	36	End of shift	0.36 (0.02–4.29) g/L	NR	0.21 (median) (0.01–3.64) g/L	0.676	0.19 (median) (0.01–0.87) g/L	0.845		
Truchon et al. (1992) Canada (Quebec), three plants; NR	Chopper gun use	7	End of shift			0.73 (0.08–1.75) mmol/mmol cr					
	Painting (gel coat)	9				0.58 (0.11–0.94) mmol/mmol cr					
	Laminating (rollers)	18				1.25 (0.28–1.90) mmol/mmol cr					
	Foreman	8				0.28 (0.03–1.10) mmol/mmol cr					

Table 1.2 (continued)

Reference Location, collection date	Occupation description	No. of workers and/or samples	Sampling matrix and time	Mandelic acid + phenylglyoxylic acid		Mandelic acid		Phenylglyoxylic acid		Styrene	
				Mean exposure (range and/or SD) (mg/g creatinine)[a]	*r*	Mean exposure (range and/or SD) (mg/g creatinine)[a]	*r*	Mean exposure (range and/or SD) (mg/g creatinine)[a]	*r*	Mean exposure (range and/or SD) (μg/L)[b]	*r*
Truchon et al. (1992) (cont.)	Cutter	11				0.24 (0.05–0.96) mmol/mmol cr					
	Warehouse work	19				0.05 (0.00–0.21) mmol/mmol cr					
	Finishing	31				0.08 (0.00–0.39) mmol/mmol cr					
	Mould repair	8				0.02 (0.00–0.08) mmol/mmol cr					
Gobba et al. (1993) Italy, 10 plants; NR	Hand lamination	65	End of shift	13.03 (0.31–53.22; SD, 12.76) mol/L	0.81	9.73 (0.24–40.23; SD, 9.94) mol/L	0.82	3.30 (0.07–12.99; SD, 2.82) mol/L	0.78	605.38 (38.40–2169.60; SD, 515.33) nmol/L	0.86
	Hand lamination	198		NR		NR		NR		556.13 (18.24–2015.04; SD, 461.76) nmol/L	0.88
Galassi et al. (1993) Italy, 87 plants; 1978–1990	Hand lamination	2386	End of shift			682 (GM, 450) (GSD, 2.75)					
	Spraying laminating	250				404 (GM, 211) (GSD, 3.3)					
	Rolling	63				327 (GM, 182) (GSD, 3.08)					
	Semi-automatic process	121				243 (GM, 154) (GSD, 2.59)					
	Non-process work	762				186 (GM, 94) (GSD, 3.27)					

Table 1.2 (continued)

Reference Location, collection date	Occupation description	No. of workers and/or samples	Sampling matrix and time	Mandelic acid + phenylglyoxylic acid		Mandelic acid		Phenylglyoxylic acid		Styrene	
				Mean exposure (range and/ or SD) (mg/g creatinine)[a]	*r*	Mean exposure (range and/ or SD) (mg/g creatinine)[a]	*r*	Mean exposure (range and/ or SD) (mg/g creatinine)[a]	*r*	Mean exposure (range and/or SD) (µg/L)[b]	*r*
Ghittori et al. (1997) Italy; NR	Fibreglass-reinforced plastics	22	End of shift			580.0 (GM, 472.0) (GSD, 2.0)	0.86	174.0 (GM, 156.6) (GSD, 1.64)	0.82	25.6 (GM, 18.8) (GSD, 2.39)	0.83
Haufroid et al. (2001) Belgium; NR	Fibreglass-reinforced plastics	30	End of shift	434.9 (20.3–1757.8)	0.92	314.6 (15.5–1410.2)	0.90	120.3 (4.8–347.7)	0.93	18.2 ppm (0.9–68.9 ppm) [77.5 (3.8–293.5)]	
Prieto et al. (2002) Spain; NR	Boat construction	34	End of shift	GM 128	0.862	104.5 (GM, 91.1) (15–230; SD, 53.1)	0.834	42.6 (GM, 37.0) (10–83; 21.1)	0.841	5.7 (5.1 GM) (1.7–15.3; SD, 2.9)	0.788[c]
Teixeira et al. (2007) Portugal; NR	Fibreglass-reinforced plastics	72	Next morning	443 (23–1770; SD, 44)	0.85						
Fustinoni et al. (2008) Italy; NR	Fibreglass-reinforced plastics	8	End of shift; repeated (3–4×)	226.30 (51.73–779.61)	0.974 (0.787)[d]	148.13 (30.64–515.12)	0.975 (0.766)[d]	77.97 (20.89–248.99)	0.931 (0.818)[d]	7.5 (2.1–29.7)	0.810 (0.451)[d]
	Varnish workers	13		69.52 (16.11–178.31)		40.01 (7.95–130.71)		24.02 (8.13–56.71)		4.3 (1.8–53.6)	
Tranfo et al. (2012) Italy, two plants	Hand lay-up open-moulding process	7	End of shift	103 (76.7–132.3; SD, 21)	0.74						
	Compression closed moulding	12		85.9 (2.52–218.4; SD, 75.6)							

Table 1.2 (continued)

Reference Location, collection date	Occupation description	No. of workers and/or samples	Sampling matrix and time	Mandelic acid + phenylglyoxylic acid		Mandelic acid		Phenylglyoxylic acid		Styrene	
				Mean exposure (range and/ or SD) (mg/g creatinine)[a]	*r*	Mean exposure (range and/ or SD) (mg/g creatinine)[a]	*r*	Mean exposure (range and/ or SD) (mg/g creatinine)[a]	*r*	Mean exposure (range and/or SD) (µg/L)[b]	*r*
Bonanni et al. (2015) Italy, four plants; 2011–2013	Plant A: motorcycle helmets	20	End of shift	7.3 (median) (2.7–30.1) (25–75th percentile)	0.729						
	Plant B: fibreglass-reinforced plastic containers and pieces	12		76.7 (median) (20.9–117.1) (25–75th percentile)							
	Plant C: compression closed moulding	14		33.8 (median) (12.5–126.9) (25–75th percentile)							
	Plant D: fibreglass-reinforced plastic containers and pieces	12		331.1 (median) (214.1–400.1) (25–75th percentile)							
Carbonari et al. (2015) Italy, two plants	Fibreglass-reinforced plastics workers	30	End of shift	47.14 (SD, 427.26) (95th percentile)	0.895	NR	0.948	NR	0.821	43.92 (SD, 123.64 mg/g creatinine)	0.419

cr, creatinine; GM, geometric mean; GSD, geometric standard deviation; NR, not reported; SD, standard deviation.

[a] Concentrations given in mg/g creatinine unless indicated otherwise.

[b] Concentrations given in µg/L unless indicated otherwise.

[c] A high correlation was also reported between styrene in blood and styrene in urine: *r* = 0.732.

[d] Correlation coefficient for exposure to styrene-7,8-oxide (in brackets).

Table 1.3 Blood biomarker levels and their correlation coefficients (*r*) with styrene and styrene-7,8-oxide inhalation exposure levels in reinforced plastics manufacturing workers

Reference	Location; collection date	Occupation description	No. of workers and/or samples	Sampling matrix and time	Styrene			Styrene-7,8-oxide			Comments/ additional data
					Mean exposure (µg/L)^{a}	Range and/ or SD (µg/L)^{a}	*r*	Mean exposure (µg/L) ^{a}	Range and/or SD (µg/L)^{a}	*r*	
Cherry et al. (1980)	United Kingdom, one plant; 1979	Boat industry	27	End of shift	6.9 µmol/L	2.0–20.9 µmol/L	0.44				
Triebig et al. (1989)	Germany, four plants; NR	Lamination of boats, pipes, or containers	36	End of shift	390	50–4820	0.823				
Gobba et al. (1993)	Italy, 10 plants; NR	Hand lamination	100	End of morning shift	5.3 µmol/L	0.16–20.80 µmol/L	0.86				Urine styrene and blood styrene *r* = 0.89
			36		5.65 µmol/L	0.48–17.93; 5.24 µmol/L	0.88				
Korn et al. (1994)	Germany, one plant; NR	Reinforced polyester resin production	13	Next morning	NR	78–836	0.87	NR	0.9–4.1	0.88	Blood styrene-styrene-7,8-oxide correlation *r* = 0.82
Somorovská et al. (1999)	Slovakia; NR	All workers	36	End of shift	601.2	1104.5					
		Hand laminators	9		2098.2	1330.8					
		Medium-exposed sprayers	12		81.3	80.3					
		Maintenance workers	15		84.5	81.9					
Prieto et al. (2002)	Spain; NR	Boat construction	34	End of shift	53.9	9.9–186.7	0.698				
Serdar et al. (2006)	USA, 17 plants; 1996–1999	All workers	295; 212	End of shift	83	< 1–2050	0.85	0.069	< 0.050–0.393	0.34	Blood styrene/ styrene-7,8-oxide correlation *r* = 0.49

NR, not reported; SD, standard deviation.

[a] Concentrations are given in µg/L unless indicated otherwise.

et al., 1988). The kinetics of MA and PGA formation and elimination can be influenced by exposure to other solvents, including ethylbenzene, phenylglycol, some pharmaceuticals, and alcoholic beverages, thus limiting the specificity of metabolite analyses as markers of styrene and styrene-7,8-oxide exposure. Prieto et al. (2002) observed that co-exposure to acetone reduced the concentrations of MA and PGA in urine. The sum of the two excreted metabolites (MA+PGA) is less affected by these confounding factors, and is therefore better suited for monitoring exposure to styrene and styrene-7,8-oxide (Ong et al., 1994). The reported correlation coefficients between personal inhalation exposures to styrene and styrene-7,8-oxide and creatinine-adjusted MA+PGA concentrations in urine are generally higher than those for the unadjusted values. Holz et al. (1995) observed urine MA+PGA concentrations of less than 10 mg/g creatinine in 25 control subjects who were not exposed to styrene, indicating that non-occupational exposure to styrene may occur but at a magnitude that will not likely influence biological monitoring results.

A strong correlation between measured styrene inhalation concentrations and MA+PGA concentrations in urine has been observed in multiple studies (see Table 1.2). These studies indicate a strong correlation (average, 0.84; range, 0.73–0.974) between the post-shift MA+PGA urine concentration and occupational inhalation exposure to styrene. Haufroid et al. (2001) measured a mean airborne styrene concentration of 18.2 ppm (range, 0.9–68.9 ppm) [77.5 (3.8–293.5) mg/m^3] in 30 workers in a fibreglass-reinforced plastics factory. The relationships observed between airborne styrene concentration and the concentrations of MA+PGA in post-shift urine samples were not different when considering MA+PGA (correlation coefficient (r) = 0.92, $P < 0.0001$) and MA ($r = 0.90$, $P < 0.0001$) or PGA ($r = 0.93$, $P < 0.0001$) alone. Urine concentrations of MA+PGA, MA, and PGA corresponding to inhalation exposure to 20 ppm [85 mg/m^3] of styrene were 420, 307, and 113 mg/g creatinine, respectively. Prieto et al. (2002) reported a mean air concentration of styrene of 70.5 mg/m^3 after 4 hours of exposure in 34 fibreglass boat construction workers. The geometric mean MA+PGA concentration in urine at the end of the 4-hour exposure was 128 mg/g creatinine with a correlation coefficient of 0.862 with the inhalation exposure. Using the regression equation provided by Prieto et al. (2002), inhalation exposure to 20 ppm [85 mg/m^3] of styrene is associated with a PGA+MA concentration of 170 mg/g creatinine in urine. Teixeira et al. (2007) reported a mean MA+PGA concentration of 443 mg/g creatinine in urine samples collected before the work shift in the morning, following personal inhalation exposure measurements of an 8-hour time-weighted average (TWA) air concentration of styrene of 30.4 ppm [129.5 mg/m^3] ($r = 0.85$), in 75 fibreglass-reinforced plastics workers.

(b) Styrene in urine

Reliable, sensitive, and specific analytical methods exist for styrene in urine (Imbriani et al., 1986; Ghittori et al., 1997; Fustinoni et al., 2008). Strong correlations between measured inhalation exposure to styrene and styrene concentrations in urine have been reported in six studies (Imbriani et al., 1986; Gobba et al., 1993; Ghittori et al., 1997; Prieto et al., 2002; Fustinoni et al., 2008; Carbonari et al., 2015) (see Table 1.2). Imbriani et al. (1986) reported a median breathing-zone air concentration of 109 mg/m^3 and a corresponding median concentration of 51 µg/L styrene in urine ($r = 0.89$) at the end of the 4-hour work shift in 121 workers in a plastic boat factory. A mean urine concentration of 43 µg/L was estimated to be associated with an inhalation exposure concentration of 20 ppm [85 mg/m^3] styrene. Gobba et al. (1993) reported a geometric mean breathing-zone air concentration of 87.9 mg/m^3 styrene and a mean styrene concentration of 556.13 nmol/L [57.9 µg/L] in urine ($r = 0.88$) at the end of the 8-hour work shift in 198 fibreglass-reinforced plastics manufacturing workers. The authors calculated a urine styrene concentration of 38 µg/L to correspond to a styrene inhalation exposure of 20 ppm [85 mg/m^3]. Ghittori et al. (1997) reported a mean breathing-zone air concentration of 112 mg/m^3 styrene and a mean styrene concentration in urine of 25.6 µg/L at the end of an 8-hour work shift (r = 0.83) in 22 fibreglass-reinforced plastics workers. The urine concentration of styrene associated with an air concentration of 20 ppm [85 mg/m^3] was 18 µg/L. Prieto et al. (2002) reported a mean styrene concentration of 5.7 µg/L in urine after 34 workers were exposed to a 4-hour mean styrene breathing-zone air concentration of 70.5 mg/m^3 (r = 0.788) in a fibreglass boat manufacturing plant. The urine concentration of styrene associated with an inhalation exposure of 20 ppm of styrene was 6.6 µg/L. Fustinoni et al. (2008) reported mean styrene inhalation exposure concentrations of 3.4 mg/m^3 for 13 varnish workers and 18.2 mg/m^3 for 8 reinforced plastics workers exposed to styrene. The measured mean urine concentrations of styrene were 4.3 µg/L for varnish workers and 7.5 µg/L for plastics workers at the end of the 8-hour work shift, with a correlation of 0.810 between the air and urine styrene levels.

These studies indicate that styrene in urine can be used as a biomarker for styrene exposure. Styrene in urine does not appear to be affected by co-exposure to other solvents or alcohol (Prieto et al., 2002). However, monitoring styrene in urine can be limited by the fact that less than 1% of absorbed styrene is eliminated unchanged in urine (NTP, 2008). Precautions are necessary to avoid contamination of the sample from airborne styrene concentrations, because the monitored biomarker is the parent compound. In addition, the timing of sample collection is critical; because of the fast elimination kinetics, the sample should be obtained immediately after the cessation of exposure.

(c) Styrene and styrene-7,8-oxide in blood

The measurement of styrene and styrene-7,8-oxide in blood has only been published in a few studies to date (Somorovská et al., 1999; Serdar et al., 2006) (see Table 1.3). Somorovská et al. (1999) investigated styrene exposure and styrene levels in blood as well as other end-points including DNA strand breaks, chromosomal aberrations, immune parameters, and genotyping of polymorphic genes (see Section 4.2.1) in 44 workers exposed to styrene in a hand lamination plant in Europe. The mean breathing-zone air styrene concentration was 101 mg/m^3 and the mean blood concentration of styrene was 601.2 µg/L. The mean air and blood styrene concentrations were 199 mg/m^3 and 2098.2 µg/L for hand laminators (group exposed to high concentrations), 55 mg/m^3 and 81.3 µg/L for sprayers (group exposed to medium concentrations), and 27 mg/m^3 and 84.5 µg/L for maintenance workers (group exposed to low concentrations), respectively.

Serdar et al. (2006) measured styrene and styrene-7,8-oxide in personal breathing-zone air and blood samples collected repeatedly from 295 reinforced plastics workers in the USA. The median breathing-zone air styrene concentration was 9.14 ppm [85.19 mg/m^3] and the median blood concentration of styrene was 0.083 mg/L (r = 0.85). The median breathing-zone air styrene-7,8-oxide concentration was 17.10 ppb [84.03 µg/L] and the median blood concentration of styrene-7,8-oxide was 0.069 µg/L (r = 0.34). Styrene inhalation exposure was 535-fold higher than exposure to styrene-7,8-oxide, and the blood concentrations of styrene were 1200-fold higher than those of styrene-7,8-oxide.

(d) Other styrene and styrene-7,8-oxide biomarkers

Styrene-7,8-oxide albumin and haemoglobin adducts are specific biomarkers for styrene and styrene-7,8-oxide exposure, and correlate well with inhalation exposures to these compounds. However, the biomarker measurements have some disadvantages, including low concentrations and short half-life and/or lifespan in blood, and the analytical methods are time-consuming and not sufficiently sensitive for haemoglobin adducts (Teixeira et al., 2007; Fustinoni et al., 2008).

1.4 Occurrence and exposure

1.4.1 *Environmental occurrence*

Because of the extensive commercial use of styrene, people come into contact with styrene in air, food, water, consumer products, and the built environment. Styrene can be emitted to the air from industrial production and use of styrene and styrene-based polymers, motor-vehicle emissions and other combustion processes, off-gassing of building materials and consumer products, and cigarette smoking (IARC, 1994; ATSDR, 2010). Styrene has been measured in outdoor air (generally less than 1 ppb [4.3 μg/m^3]), but higher levels are generally found in indoor air, drinking-water, groundwater, surface water, soil, and food (Cohen et al., 2002; IARC, 2002). The presence of styrene in packaged foods is reported to be primarily due to monomer migrating from polystyrene containers (WHO, 1983). For the general population, daily styrene intake is expected to be orders of magnitude lower than daily intakes for workers in occupations with exposure to high concentrations of styrene (Cohen et al., 2002). Nevertheless, most of the general population has detectable levels of styrene in their biological fluids (e.g. blood and breast milk) (IARC, 2002; Blount et al., 2010; CDC, 2018). Although styrene exposure is common, arising from multiple sources, styrene is not a persistent chemical; it does not persist in air, water, or soil (Health Canada, 1993).

Styrene is not known to bioaccumulate in humans for extended periods of time (Bond & Bolt, 1989; Pekari et al., 1993; IARC, 2002; ATSDR, 2010).

The general public is indirectly exposed to styrene-7,8-oxide via metabolism of styrene. Styrene-7,8-oxide adducts of albumin and haemoglobin were detected in people who were not occupationally exposed to styrene or styrene-7,8-oxide (Yeowell-O’Connell et al., 1996).

(a) Ambient air

Styrene has been detected in the atmosphere in many locations. Its presence in air is principally due to emissions from industrial processes involving styrene and its polymers and copolymers. Other sources of styrene in the environment include vehicle exhaust, cigarette smoke, and other emissions from the combustion and incineration of styrene polymers (WHO, 1983).

In the USA, there was an overall decrease in styrene emissions from 2005 to 2015 driven mainly by decreases in styrene air releases from the plastics and rubber and transportation equipment industries. These reductions were substantial enough to effect a 46% decrease in the total air release of 180 United States Occupational Safety and Health Administration carcinogens reported to the Toxics Release Inventory (EPA, 2015).

Ambient air monitoring data from the USA include databases compiled and maintained by the California Air Resources Board. The 20 test stations are located in urban areas, representing the greatest proportion of the California population. Styrene is measured from a 24-hour sample collected once each month. Based on the measurements from each test station for each month from 1989 to 1995, the average reading for styrene was approximately 0.2 ppb [0.9 μg/m^3] over 6 years. The detection level for styrene was 0.1 ppb [0.4 μg/m^3] and the highest measurement was 2.9 ppb [12.4 μg/m^3] (Styrene Information & Research Center, 2001).

Styrene levels of 1.1–6.6 μg/m^3 were measured in air samples from the Pennsylvania Turnpike

Allegheny Mountain Tunnel in 1979. The mean concentration in the tunnel intake air was less than 0.1 µg/m³ (Hampton et al., 1983). Air concentrations of styrene in the vicinity of five rural hazardous waste sites in New Jersey, USA of up to 15.5 ppb [66.0 µg/m³] were measured (LaRegina et al., 1986).

As part of the Minnesota Children's Pesticide Exposure Study (MNCPES) survey of VOCs in households with children, styrene was quantified in 39% of outdoor samples (n = 100) with a mean of 0.5 µg/m³ (limit of quantitation, 0.6 µg/m³) in 1997 (Adgate et al., 2004).

In Canada, styrene levels in ambient air were determined in a survey of 18 sites (mostly urban) in 1988–1990. The mean concentrations in 586 24-hour samples ranged from 0.09 µg/m³ to 2.35 µg/m³ (Newhook & Caldwell, 1993). In a survey of VOCs in outdoor environments proximal to apartment dwellings in Leipzig, Germany in 2000–2001, Rehwagen et al. (2003) determined a mean styrene concentration of 0.09 µg/m³ (n = 222, 4-week samples). Median ambient styrene concentrations collected once a month at six sites in the Hyogo Prefecture, Japan during 2005–2009 were 0.25–0.73 µg/m³ (n = 60) (Okada et al., 2012).

Thermal degradation of styrene-containing polymers also releases styrene into ambient air (Hoff et al., 1982; Lai & Locke, 1983; Rutkowski & Levin, 1986). Styrene levels ranged from 0.003 ppm to 2.01 ppm [0.013–8.56 mg/m³] and, along with benzene, toluene, naphthalene, and 1,3-butadiene, accounted for 31% of the total concentration of VOCs found in smoke from municipal structural fires (Austin et al., 2001).

Although styrene-7,8-oxide was identified in air samples collected in the Los Angeles Basin and in other unidentified areas in the USA, measurements were not reported (IARC, 1985).

(b) Indoor air

For residential exposure, median concentrations obtained by personal air sampling are generally in the range of 1–4 µg/m³ (Wallace et al., 1985; Wallace, 1986). Off-gassing of styrene from some styrene-containing household products may contribute to indoor air levels (Knöppel & Schauenburg, 1989; Hodgson, 1999; Willem & Singer, 2010). Indoor air studies conducted in residential settings in Canada, Finland, France, Germany, and the USA have generally been consistent with the earlier findings of Wallace et al. (1985), and Wallace (1986). The MNCPES study determined an average indoor styrene air concentration of 1.4 µg/m³ (n = 101; 82% of samples above the limit of quantitation of 0.6 µg/m³) and average personal air concentrations of 1.2 µg/m³ (n = 73; 90% of samples above the limit of quantitation of 0.6 µg/m³) (Adgate et al., 2004). In a national survey of styrene levels in indoor air in 757 single-family dwellings and apartments, representative of the homes of the general population of Canada in 1991, the mean 24-hour concentration was 0.28 µg/m³, with values ranging from none detected (limit of detection, 0.48 µg/m³) up to 129 µg/m³ (Newhook & Caldwell, 1993). A national survey of indoor air VOCs was repeated in Canada during 2009–2011 for 3857 residences (Zhu et al., 2013). Although arithmetic means of VOCs declined 2–5-fold for 11 volatiles common to both Canadian studies, the exception was an increase in styrene from 0.30 µg/m³ in the 1992 study (n = 757) to 1.13 µg/m³ [geometric mean (GM), 0.72 µg/m³] in the 2009–2011 survey. The following indoor residential styrene concentrations were measured: 0.84 µg/m³ (GM, n = 201) for a 1996–1998 study conducted in Helsinki, Finland (Edwards et al., 2001); 1.47 µg/m³ (arithmetic mean, n = 1499) for a 1994–2001 study conducted in apartments in Leipzig, Germany (Rehwagen et al., 2003); and 1.0 µg/m³ (GM, n = 490) for a 2003–2005 study conducted in France (Billionnet et al., 2011).

(c) Tobacco

Styrene is one of the hundreds of individual components that may be quantified in tobacco smoke (IARC, 1986; Darrall et al., 1998; Health Canada, 1999; IARC, 2004). The styrene content of cigarette smoke has been reported to be 18–48 µg per cigarette (WHO, 1983) and, by a more recent assessment, 0.5–10.0 µg per cigarette (CDC, 2010). Exposure to styrene is approximately 6 times higher for smokers than for non-smokers, and tobacco smoke is the major source of styrene exposure for smokers (Wallace et al., 1987, 1989). Measurements in homes with and without smokers revealed that average styrene concentrations in the homes of smokers were approximately 0.5 µg/m^3 higher than those in the homes of non-smokers. The 2009–2011 indoor air study of Zhu et al. (2013) obtained a significantly higher estimate of styrene concentration in the houses of smokers relative to those of non-smokers by 0.44 µg/m^3 ($P = 0.001$), and in the apartments of smokers relative to those of non-smokers by 0.70 µg/m^3 ($P = 0.001$). Hodgson et al. (1996) also found that environmental tobacco smoke can contribute significantly to indoor airborne styrene concentrations. Environmental tobacco smoke was estimated to contribute 8% of the total styrene inhalation exposure of all non-smoking Californians (Miller et al., 1998). Chambers et al. (2011) assessed the impact of cigarette smoking on concentrations of VOCs in blood using 2003–2004 United States National Health and Nutrition Examination Survey (NHANES) data. The authors estimated a weighted median and 95th percentile styrene blood concentration of 0.072 ng/mL and 0.180 ng/mL, respectively, for daily smokers ($n = 290$). For less than daily smokers, the weighted median and 95th percentile were less than 0.03 ng/mL and 0.068 ng/mL, respectively ($n = 864$). Chambers et al. (2011) estimated a 0.010 ng/mL increase in blood styrene per cigarette per day.

(d) Water

Although styrene has been detected occasionally in estuaries, inland waters, and drinking-water, its presence is usually traceable to an industrial source or to improper disposal (WHO, 1983). In surveys of Canadian drinking-water supplies, the frequency of detection of styrene was low; when detected, it was generally at a concentration of less than 1 µg/L (Newhook & Caldwell, 1993). After accidental drinking-water contamination with styrene in Spain, transient levels of up to 900 µg/L were reported (Arnedo-Pena et al., 2003). Emissions of VOCs were studied from three heavily polluted rivers (Huijiang, Nancun, and Zengbian) in fast-developing Guangzhou, south China (Chen et al., 2013). Concentrations of styrene in water samples ($n = 16$) ranged from 14 300 µg/L to 36 500 µg/L (Chen et al., 2013).

Styrene-7,8-oxide released to the environment is not expected to persist in water. Hydrolytic half-lives of 0.17, 28, and 40.9 hours have been reported for styrene-7,8-oxide at pH values of 3, 7, and 9, respectively (Schmidt-Bleek et al., 1982). Although styrene-7,8-oxide may enter the environment through industrial discharges or spills in wastewater, it has rarely been detected in source drinking-water (IARC, 1994). In a survey of 4000 samples of wastewater taken from both industrial and publicly owned treatment centres in the USA, styrene-7,8-oxide was found at one site (IARC, 1994).

(e) Food and food packaging

Styrene has been detected in a wide range of foods and beverages (IARC, 1994). In a follow-up analysis of the United States Food and Drug Administration (FDA) Total Diet Study that focused on VOCs in 70 foods sampled between 1996 and 2000, the highest styrene concentrations were observed in strawberries (range, 12–350 µg/kg) and avocados (range, 3–550 µg/kg) [mean levels were not reported] (Fleming-Jones & Smith, 2003).

Analysis of styrene in 133 plastic food containers from retail food outlets in the United Kingdom showed concentrations ranging from 16 mg/kg to 1300 mg/kg; 73% of containers had styrene concentrations of 100–500 mg/kg, and only five containers had levels exceeding 1000 mg/kg. The food in the containers had levels of monomer ranging from less than 1 µg/kg to 200 µg/kg, although 77% of the foods had levels of less than 10 µg/kg and 26% had levels of less than 1 µg/kg (Gilbert & Startin, 1983). A more recent analysis conducted by the FDA, specific to polystyrene packaging, showed that styrene concentrations in foods had not significantly changed since the 1980s, ranging from 2.6 µg/kg to 163 µg/kg (Genualdi et al. 2014).

1.4.2 Occupational exposure

Workers can be exposed to both styrene and styrene-7,8-oxide in the industries and operations where they are produced and used, for example: in the production of styrene-containing polymer resins, plastics, and rubber products; in the fabrication of reinforced-polyester plastics composites; and in the use of products containing styrene, such as paints, adhesives, metal cleaners, and varnishes (US NLM, 2018). The most significant exposures to both styrene and styrene-7,8-oxide, measured in air and in biological media, occur in the manufacture of fibreglass-reinforced polyester products; exposures are generally lower in the production of styrene, polystyrene, and styrene-based plastics and rubbers. During lamination and curing, about 10% of the styrene may evaporate into the workplace air (NIOSH, 1983; Crandall & Hartle, 1985). Occupational exposure to styrene-7,8-oxide occurs in industries manufacturing or using styrene and styrene polyester resins due to its formation from styrene as an oxidation product. Styrene-7,8-oxide has been detected in association with styrene, but at much lower levels, in industries where unsaturated polyester resins are used (Pfäffli et al., 1979; Pfäffli & Säämänen, 1993; Rappaport et al., 1996; Nylander-French et al., 1999; Serdar et al., 2006). The ratio of styrene to styrene-7,8-oxide in the air in reinforced plastic manufacturing is approximately 1000:1 (see Section 1.4.2(a) and Table 1.4, last column).

(a) Production and processing of reinforced plastics

In terms of the numbers of workers exposed and exposure concentrations, occupational exposure to styrene is greatest in the fabrication of objects from fibreglass-reinforced polyester composite plastics, such as boats, tanks, wall panels, bath and shower units, and automotive parts. Exposure to styrene in this industry has been summarized in several publications (see Table 1.5). Styrene serves as a solvent and a reactant for the unsaturated polyester resin, in which it constitutes about 40% by weight. In the open-mould process, a releasing agent is usually applied to the mould, a first coat containing pigments (gel coat) is applied, then successive layers of chopped and/or woven fibreglass are deposited manually or with a chopper gun at the same time as the resin is sprayed or brushed on, and then the surface is rolled. During lamination and curing, about 10% of the styrene may evaporate into the workplace air (NIOSH, 1983; Crandall & Hartle, 1985).

Exposure to styrene-7,8-oxide has only been documented in a few reports (Table 1.4). In Finnish factories producing boats, car parts, and building materials from polyester-based reinforced plastics, both styrene and styrene-7,8-oxide were measured. The average styrene levels in personal breathing-zone samples were 132.9 ± 109.6 ppm [567 ± 467 mg/m^3] for hand lay-up and 130.2 ± 68.8 ppm [554 ± 293 mg/m^3] for spray application, and the average styrene-7,8-oxide concentration was 0.04 ± 0.02 ppm [0.20 ± 0.10 mg/m^3] for hand lay-up and 0.12 ± 0.07 ppm [0.59 ± 0.34 mg/m^3] for spray application (Pfäffli et al., 1979). In a Norwegian

Table 1.4 Personal styrene and styrene-7,8-oxide inhalation exposure levels in reinforced plastics manufacturing workers

Reference	Location; collection date	Occupation description	No. workers and/or samples	Sampling duration	Styrene		Styrene-7,8-oxide		Styrene-7,8-oxide concentration as a percentage of styrene concentration (%)
					Mean exposure (mg/m^3)[a]	Range or SD (mg/m^3)[a]	Mean exposure (µg/)[b]	Range or SD (µg/m^3)[b]	
Fjeldstad et al. (1979)	Norway, one plant; NR	Mudguards	5	2 h	54 ppm (median) [230.02]	28–170 ppm [119.27–724.15]	38 ppb (median) [186.74]	28–86 ppb [137.6–422.61]	0.05–0.1 (median, 0.07)
		Car bodies	6		108 ppm [460.05]	65–278 ppm [276.88–1184.2]	48 ppb	12–71 ppb [58.97–348.9]	0.018–0.025 (median, 0.44)
		Other car parts	2		NR	31–51 ppm [132.05–217.25]	NR	29–64 ppb [142.51–314.5]	0.094–0.125
		Fibre machines	2		NR	17–46 ppm [72.42–195.95]	NR	< 3–4 ppb [< 14.74–19.66]	0.009–0.018
		Antenna elements	2		NR	89–102 ppm [379.11–434.49]	NR	41–65 ppb [201.48–319.42]	0.046–0.064
		Biological toilets	4		147 ppm [626.18]	83–289 ppm [353.56–1231.06]	19 ppb [93.37]	16–28 ppb [78.63–137.6]	0.008–0.034 (median, 0.011)
Pfäffli et al. (1979)	Finland, two plants; NR	Hand-lay-up application	29	20–60 min	132.9 ppm [566.12]	109.6 ppm [466.86]	0.04 ppm [196.4]	0.02 ppm [98.2]	0.03
		Spray application	8		130.2 ppm [554.61]	68.8 ppm [293.07]	0.12 ppm [589.2]	0.07 ppm [343.7]	0.09
Rappaport et al. (1996)	USA, one plant; 1987–1988	Laminators	16 (11)[c]	Full-shift; repeated (7×)	130	NR	182	NR	0.14
		Service	6 (2)[c]		27.9	NR	77.6	NR	0.28
		Mould repair	3		117	NR	198	NR	0.17
		Patcher	8 (2)[c]		13.6	NR	96	NR	0.71
		Painter	6 (1)[c]		27.7	NR	158	NR	0.57
		Spray operator	1 (1)[c]		141	NR	74.4	NR	0.05
Nylander-French et al. (1999)	Finland, 30 plants; 1988–1990	All workers	237	84	122	107	183	184	0.15
		Hand lamination of large objects	108		156	105	199	189	0.13
		Hand lamination of small objects	49		150	125	213	191	0.14

Table 1.4 (continued)

Reference	Location; collection date	Occupation description	No. workers and/or samples	Sampling duration	Styrene		Styrene-7,8-oxide		Styrene-7,8-oxide concentration as a percentage of styrene concentration (%)
					Mean exposure (mg/m^3)^a	Range or SD (mg/m^3)^a	Mean exposure (µg/)^b	Range or SD (µg/m^3)^b	
Nylander-French et al. (1999) (cont.)		Spraying and gel-coating	11		130	53.7	382	276	0.29
		Automated lamination	23		55.8	32.3	95.3	64.2	0.17
		Assembly and mould preparation	28		49.7	40.3	140	139	0.28
		Foremen	18		42.6	92.5	71.2	77.7	0.17
		Boats	137		132	96.4	225	199	0.17
		Small and form parts	34		134	98.7	160	169	0.12
		Sheets/elements and car	39		90.3	127	126	130	0.14
		Containers and tubes	28		106	127	86	126	0.08
Serdar et al. (2006)	USA, 17 plants; 1996–1999	All workers	328	Full-shift; repeated (2–3×)	9.14 ppm (median) [38.93]	< 1–117 [< 4.26–498.39]	17.1 ppb [84.03]	< 1–138 ppb [< 4.91–678.15]	0.19
		Boat building	138		4.41 ppm [18.79]	< 1–68.6 ppm [< 4.26–292.22]	9.47 ppb [46.54]	< 1–51.1 ppb [< 4.91–251.11]	0.21
		Hot tub manufacture	13		6.85 ppm [29.18]	< 1–62.9 ppm [< 4.26–267.94]	16 ppb [78.63]	< 1–48.8 ppb [< 4.91–239.81]	0.23
		Pipe and tank	50		16 ppm [68.16]	1.67–79.0 ppm [7.11–336.52]	17.8 ppb [87.47]	2.02–138 ppb [9.93–678.15]	0.11
		Recreational vehicles	48		45.1 ppm [192.11]	6.74–117 ppm [28.71–498.39]	44 ppb [216.22]	10.4–109 ppb [51.11–535.64]	0.10
		Truck	76		4.22 ppm [17.98]	< 1–46.3 ppm [< 4.26–197.22]	22.2 ppb [109.09]	3.75–64.8 ppb [18.43–318.43]	0.53
		Laminators in boat building	70		14.4 ppm [61.34]	< 1–68.6 ppm [< 4.26–292.22]	13.3 ppb [65.36]	< 1–51.1 ppb [< 4.91–251.11]	0.09
		Laminators of hot tubs	7		9.84 ppm [41.92]	< 1–62.9 ppm [< 4.26–267.94]	36.4 ppb [178.87]	< 1–48.8 ppb [< 4.91–239.81]	0.37

Table 1.4 (continued)

Reference	Location; collection date	Occupation description	No. workers and/or samples	Sampling duration	Styrene		Styrene-7,8-oxide		Styrene-7,8-oxide concentration as a percentage of styrene concentration (%)
					Mean exposure (mg/m^3)[a]	Range or SD (mg/m^3)[a]	Mean exposure (µg/)[b]	Range or SD (µg/m^3)[b]	
Serdar et al. (2006) (cont.)		Laminators of pipes and tanks	42		18.1 ppm [77.1]	2.57–79.0 ppm [10.95–336.52]	21.2 ppb [104.18]	2.56–138 ppb [12.58–678.15]	0.12
		Laminators of recreational vehicles	30		60.5 ppm [257.71]	14.4–117 ppm [61.34–498.39]	59 ppb [289.93]	10.4–109 ppb [51.11–535.64]	0.10
		Laminators of trucks	30		21.6 ppm [92.01]	3.84–46.3 ppm [16.36–197.22]	27.7 ppb [136.12]	15.9–64.8 ppb [78.13–318.43]	0.13
Fustinoni et al. (2008)	Italy; NR	Fibreglass-reinforced plastics workers	8	Full-shift; repeated (3–4×)	18.2 (median)	2.3–93.4	133.5 (median)	39.5–281.5	0.73
		Varnish workers	13		3.4	0.55–16.0	12.2	6.7–32.0	0. 36

h, hour(s); min, minute(s); NR, not reported; ppb, parts per billion; ppm, parts per million; SD, standard deviation.

[a] Concentrations are given in mg/m^3 unless indicated otherwise.

[b] Concentrations are given in µg/m^3 unless indicated otherwise.

[c] Number of workers with styrene-7,8-oxide measurements.

Table 1.5 Personal styrene inhalation exposure levels in reinforced plastics manufacturing workers

Reference	Location; collection date	Occupation description	No. workers and/or samples	Sampling duration	Mean exposure (mg/m³)[a]	Exposure range (GSD) (mg/m³)[a]
Guillemin et al. (1982)	Switzerland, 10 plants; NR	All workers	90	Full shift	47.2 ppm [201.06]	2–199 ppm (SD, 44.1) [201.06–847.68 (187.85)]
		Hand lamination, containers of various sizes	4		50.9 ppm [216.82]	27–64 ppm (SD, 16.3) [115.01–272.62 (69.43)]
		Hand and spray lamination; boats 13 m long, small objects	5		75.8 ppm [322.89]	41.12 ppm (SD, 29.30) [175.16 (124.81)]
		Hand, spray, automatic system lamination, silos and small boats	8		35.1 ppm [149.52]	17–50 ppm (SD, 11.6) [72.42–212.99 (49.41)]
		Hand lamination, inside coating of oil tanks	6		50.0 ppm [212.99]	11–109 ppm (SD, 33.6) [46.86–464.31 (143.13)]
		Hand, spray, and other	13		29.4 ppm [125.24]	3–94 ppm (SD, 33.4) [12.78–400.41 (142.27)]
		Automatic system, pipes and others objects	3		27.0 ppm [115.01]	17–39 ppm (SD, 11.1) [72.42–166.13 (47.28)]
		Hand, spray, and vacuum lamination, basins, walls, baths, etc.	15		52.7 ppm [224.49]	9–101 ppm (SD, 24.1) [224.49–430.23 (102.66)]
		Hand, spray, automatic system, UV-hardening, large pipes	19		11.3 ppm [48.13]	2–21 ppm (SD, 7.2) [8.52–89.45 (30.67)]
		Hand, spray, and vacuum lamination, cabins, walls, etc.	15		101.5 ppm [432.36]	9–199 ppm (SD, 64.6) [38.34–847.68 (275.18)]
		Hand lamination, parts of car bodies	2		23.0 ppm [97.97]	13–33 ppm (SD, 14.1) [55.38–140.57 (60.06)]
Ikeda et al. (1982)	Japan, five plants; NR	Hand lamination over boat shell mould	25	4 h	GM, 119 ppm [506.91]	34–256 ppm (1.6) [144.83–1090.49 (6.82)]
		Installation of ribs; laminators	3		GM, 17 ppm [72.42]	10–28 ppm (1.7) [42.6–119.27 (7.24)]
		Installation of ribs; laminator helpers	5		GM, < 1 ppm [< 4.26]	< 1–2 ppm (5.6) [< 4.26–8.52 (23.85)]
		Installation of division plates; laminators	5		GM, 22 ppm [93.71]	6–44 ppm (2.1) [25.56–187.43 (8.95)]

Table 1.5 (continued)

Reference	Location; collection date	Occupation description	No. workers and/or samples	Sampling duration	Mean exposure (mg/m³)[a]	Exposure range (GSD) (mg/m³)[a]
Ikeda et al. (1982) (cont.)		Installation of division plates; laminator helpers	5		GM, < 1 ppm [< 4.26]	ND
		Auxiliary lamination on deck	5		GM, 13 ppm [55.38]	2–43 ppm (4.0) [8.52–183.17 (183.17)]
		Lamination on hold walls	4		GM, 128 ppm [545.24]	104–211 ppm (1.4) [443.01–898.80 (5.96)]
		Equipment	8		GM, 2 ppm [8.52]	1–17 ppm (2.8) [4.26–72.42 (11.93)]
Crandall & Hartle (1985)	USA, seven plants; NR	Hull lamination	168	Full shift	77.7 ppm [330.98]	1.6–183 ppm (SD, 41.5) [6.82–779.53 (176.78)]
		Deck lamination	114		73.4 ppm [312.66]	12.3–160 ppm (SD, 38.1) [52.39–681.55 (162.3)]
		Small parts lamination	70		45.4 ppm [193.39]	9.3–130 ppm (SD, 22.0) [39.62–553.76 (93.71)]
		Gel coating	45		47.5 ppm [202.34]	5–103 ppm (SD, 27.3) [21.3–438.75 (116.29)]
Imbriani et al. (1986)	Italy; NR	Boat manufacturing	121	4 h	109 (median)	11.3–536.0 (2.332)
Sullivan & Sullivan (1986)	Canada, 10 plants; 1981	Boat lamination	59	Full shift	GM, 108 ppm [460.05]	327 ppm max (2.18) [1392.93 (9.29)]
		Non-boat lamination	23		GM, 93 ppm [396.15]	316 ppm max (1.72) [1346.07 (7.33)]
		Chopper gun use	8		GM, 115 ppm [489.87]	316 ppm max (2.35) [1346.07 (10.01)]
		Gel-coat spraying	6		GM, 58 ppm [247.06]	135 ppm max (2.93) [575.06 (12.48)]
		Filament winding	3	5–25 min	GM, 125 ppm [532.46]	181 ppm max (1.41) [771.01 (6.01)]
Triebig et al. (1989)	Germany, four plants; NR	Laminating boats, pipes, or containers	36	Full shift	18 ppm (median) [76.67]	3–251 ppm [12.78–1069.19]
		Plant A	12		136 ppm [579.32]	48–251 ppm [204.47–1069.19]
		Plant B	10		14 ppm [59.64]	10–40 ppm [42.60–170.39]
		Plant C	9		13 ppm [55.38]	3–32 ppm [12.78–136.31]
		Plant D	5		17 ppm [72.42]	14–29 ppm [59.64–123.53]

Table 1.5 (continued)

Reference	Location; collection date	Occupation description	No. workers and/or samples	Sampling duration	Mean exposure (mg/m^3)^a	Exposure range (GSD) (mg/m^3)^a
Jensen et al. (1990)	Denmark, 30 plants; 1955–1988	Fibreglass-reinforced plastics workers (1955–1970)	227	1–60 min	714	10–4700
		Fibreglass-reinforced plastics workers (1971–1980)	1117		274	4–1905
		Fibreglass-reinforced plastics workers (1981–1988)	1184		172	1–4020
		Hand lay-up (1955–1970)	94		542	24–2400
		Hand lay-up (1971–1980)	851		279	7–1905
		Hand lay-up (1981–1988)	84		142	1–961
		Spray-up (1955–1970)	77		1031	50–4700
		Spray-up (1971–1980)	125		288	21–1600
		Spray-up (1981–1988)	60		234	12–4018
Geuskens et al. (1992)	Netherlands, four plants; NR	Filament winding	18	Full shift	[GM, 314]	134–716
		Spraying	62		[GM, 227]	48–602
		Hand laminating	180		[GM, 148]	18–538
Truchon et al. (1992)	Canada, three plants; NR	Chopper gun use	7	Full-shift	564	307–938
		Painting (gel coat)	9		517	280–843
		Laminating (rollers)	18		502	292–865
		Foreman	8		97	18–279
		Cutter	11		75	16–234
		Warehouse work	19		35	9–187
		Finishing	31		34	8–110
		Mould repair	8		28	8–147
Galassi et al. (1993)	Italy, 87 plants; 1978–1990	Hand laminating	1028	NR	227 (GM, 165)	GSD, 2.48
		Spraying laminating	166		134 (GM, 82)	GSD, 3.18
		Rolling	40		163 (GM, 104)	GSD, 3.39
		Semi-automatic process	71		85 (GM, 48)	GSD, 3.03
		Non-process work	159		71 (GM, 38)	GSD, 3.8
Gobba et al. (1993)	Italy, 10 plants; NR	Hand lamination	64	Full shift	GM, 1090.4 µmol/m^3 (113.6 mg/m^3)	76.8–7396.8 µmol/m^3 [8–770.4]
		Hand lamination	211		GM, 843.84 µmol/m^3 [87.9]	23–7396.8 µmol/m^3 [2.4–770.4]

Table 1.5 (continued)

Reference	Location; collection date	Occupation description	No. workers and/or samples	Sampling duration	Mean exposure (mg/m^3)[a]	Exposure range (GSD) (mg/m^3)[a]
Ghittori et al. (1997)	Italy; NR	Fibreglass-reinforced plastics workers	22	Full shift	112.7; GM, 98.6	44–228 (1.72)
Lenvik et al. (1999)	Norway, 234 plants; 1972–1996	Different lamination processes (1972–1996)	7011	Variable (min to h)	49.4 ppm (median, 33.0 ppm) [210.43 (140.57)]	
		Different lamination processes (1972–1976)	7011		62 ppm [264.1] (median)	
		Different lamination processes (1992–1996)	7011		7.1 ppm [30.24] (median)	
Somorovská et al. (1999)	Slovakia; NR	All workers	44	Full shift	101.2	SD, 102.4
		Hand laminators	17		199.1	SD, 101.6
		Medium-exposed sprayers	12		55	SD, 22.9
		Maintenance workers	15		27.3	SD, 25.1
Haufroid et al. (2001)	Belgium; NR	Fibreglass-reinforced plastics workers	30	Full shift	18.2 ppm [77.53]	0.9–68.9 ppm [3.83–297.75]
Prieto et al. (2002)	Spain; NR	Boat construction	34	Full shift	70.5	15–157
Teixeira et al. (2007)	Portugal; NR	Fibreglass-reinforced plastics workers	75	Full shift	30.4 ppm [129.5]	0.5–114 (SD, 3.7) ppm [2.13–485.61 (15.76)]
Tranfo et al. (2012)	Italy, two plants; NR	Hand lay-up open-mould process	7	Full shift	41.58	20.34–72.31 (SD, 18.73)
		Compression closed moulding	12		30.33	2.53–104.17 (SD, 26.34)
Bonanni et al. (2015)	Italy, four plants; 2011–2013	Plant A: motorcycle helmets	20	Full shift	43 (median)	5.0–157.5 [25–75 percentile]
		Plant B: fibreglass-reinforced plastic containers and pieces	12		31.5 (median)	4.9–47.4 [25–75 percentile]
		Plant C: compression closed moulding	14		24.1 (median)	7.2–28.3 [25–75 percentile]
		Plant D: fibreglass-reinforced plastic containers and pieces	12		94.0 (median)	27.9–129.3 [25–75 percentile]
		Plant A: moulders	7		139.7 (median)	58.6–178.3 [25–75 percentile]
		Plant D: moulders	9		114.9 (median)	89.3–143.3 [25–75 percentile]
Carbonari et al. (2015)	Italy, two plants; NR	Fibreglass-reinforced plastics workers	30	Full shift	28.75 (median)	142.37 [95th percentile]

GM, geometric mean; GSD, geometric standard deviation; h, hour(s); min, minute(s); ND, not determined; NR, not reported; ppm, parts per million; SD, standard deviation.

[a] Concentrations are given in mg/m^3 unless indicated otherwise.

factory where similar processes were used, styrene levels ranged from 17 ppm to 289 ppm [72–1230 mg/m^3] and styrene-7,8-oxide levels ranged from less than 0.003 ppm to 0.08 ppm [< 0.015–0.39 mg/m^3] (Fjeldstad et al., 1979). Similarly, the measured mean styrene-7,8-oxide concentration was 0.16 mg/m^3 for the 19 workers most heavily exposed to styrene in a boat manufacturing company in the USA (Rappaport et al., 1996). Säämänen et al. (1993) calculated a ratio of styrene-7,8-oxide to styrene of 1:1000 from measurements obtained in 32 Finnish plants. This ratio is fairly consistent across all the available studies in which both styrene and styrene-7,8-oxide were measured simultaneously (Table 1.4). Nylander-French et al. (1999) measured a mean 8-hour TWA concentration of 122 mg/m^3 (range, 3.2–608 mg/m^3; median, 103 mg/m^3) for styrene and 183 µg/m^3 (range, 0–883 µg/m^3; median, 110 µg/m^3) for styrene-7,8-oxide in 126 workers employed in 30 different reinforced plastics facilities (70% of which were boat manufacturing) in Finland. Exposure to styrene-7,8-oxide was positively correlated with exposure to styrene in selected job groups, and was greatest for hand lamination followed by assembly and mould preparation (Nylander-French et al., 1999). Serdar et al. (2006) reported on styrene and styrene-7,8-oxide exposure in 328 workers in the reinforced plastics industry in the USA. The median breathing-zone concentrations were 9.14 ppm (< 1–117 ppm) [39 (< 4.26–498 mg/m^3)] for styrene and 17.1 ppb (< 1–138 ppb) [84 (< 4.91–678 µg/m^3)] for styrene-7,8-oxide. The highest exposure levels were measured in the manufacture of recreational vehicles (median, 45.1 ppm [192.1 mg/m^3] for styrene and 44 ppb [216 µg/m^3] for styrene-7,8-oxide) in all workers. For laminators in different product groups, styrene and styrene-7,8-oxide exposure levels ranged from 9.84 ppm to 60.5 ppm [42–258 mg/m^3] and 13.3 ppb to 59 ppb [65–290 µg/m^3], respectively. Styrene exposure levels were typically 535-fold higher than for styrene-7,8-oxide. In general, the exposure levels were lower than those observed in previous studies (Fjeldstad et al., 1979; Pfäffli et al., 1979; Rappaport et al., 1996; Nylander-French et al., 1999).

Several factors influence the concentrations of styrene and styrene-7,8-oxide in workplace air. The manufacture of objects with a large surface area, such as boats, truck parts, baths, and showers, by the open-mould process results in the highest exposure. Tranfo et al. (2012) measured styrene exposure levels in two different production sites, one using an open moulding process and the other a closed compression moulding process. The median values for styrene exposure were 31.1 mg/m^3 for open moulding ($n = 10$) and 24.4 mg/m^3 for closed compression moulding ($n = 14$) (Tranfo et al., 2012). In a detailed survey of 12 plants making fibreglass in Washington State, USA, 40% of 8-hour samples contained styrene at concentrations of more than 100 ppm [430 mg/m^3] (Schumacher et al., 1981); of these, chopper-gun operators were exposed to the highest concentrations, followed by laminators and gel-coat applicators. However, boat-building workers were exposed to the highest concentrations of all sectors. For 11 plants, a relationship was seen between level of exposure and the quantity of resin consumed per month per exposed employee (Schumacher et al., 1981). Similar results were reported by Sullivan and Sullivan in their survey of 10 plants in Ontario, Canada, who also noted that although dilution ventilation and often auxiliary fans were used in almost all plants, there was little use of local exhaust ventilation (Sullivan & Sullivan, 1986). Gel coaters are generally exposed to lower concentrations because they work in ventilated booths (Crandall & Hartle, 1985). The presence of flexible-exhaust ventilation hoses was reported to reduce styrene concentrations by a factor of 2 at a boat construction company in Japan (Ikeda et al., 1982). So-called low styrene emission (LSE) resins are thought to reduce styrene exposure (Säämänen et al., 1991b; Säämänen, 1998). However, Nylander-French et al. (1999) did not observe a significant difference in styrene exposure between standard or LSE resin, and the use of LSE resins resulted in exposure to significantly greater concentrations of styrene-7,8-oxide ($P < 0.001$) than in the use of standard resins.

Jensen et al. (1990) analysed historical styrene air concentration measurement data from the archives of the Danish National Institute of Occupational Health in the selection of industrial cohorts for inclusion in epidemiological studies in Denmark. A mean styrene concentration of 265 mg/m^3 was measured in a total of 2528 air samples collected from 256 workplaces during 1955–1988. The concentration of styrene decreased from 714 mg/m^3 in the early period (1955–1970) to 172 mg/m^3 in the later period (1981–1988). Spraying and unspecified lay-up and production of boats, carriages, and stationary containers were associated with the highest concentrations (Jensen et al., 1990).

Wearing a respirator appropriate for organic vapours reduces, but does not eliminate, styrene exposure (Brooks et al., 1980; Ikeda et al., 1982; Bowman et al., 1990; Truchon et al., 1992; Gobba et al., 2000). Truchon et al. (1992) reported that respirators were worn most often by gel-coat and chopper-gun operators but not by laminators, who consider that they hinder their work. Other investigators reported that single-use dust respirators, which provide no protection against styrene vapours, were often the only type of protection worn (Schumacher et al., 1981; Sullivan & Sullivan, 1986).

Despite early reports that percutaneous absorption of styrene was an important route of exposure, measurement of biological indicators of the exposure of workers who did and did not wear gloves and other forms of protective clothing indicated that absorption through the skin contributes negligibly to overall exposure in the manufacture of fibreglass-reinforced polyester products (Brooks et al., 1980; Bowman et al., 1990; Truchon et al., 1992). Limasset et al. (1999) compared the patterns of urinary excretion of styrene metabolites in four groups of workers who performed the same task at the same time in the same workshop, but wearing different protective equipment (total protection with an insulating suit and mask, respiratory equipment only, skin protection only, or no protection). The urinary excretion level of the group with total protection did not differ significantly from that of the group with respiratory protection only.

Other substances may be found in the workplace air during the production of unsaturated polyester-reinforced plastics, although at levels usually considerably lower than that of styrene. These compounds include: solvents mainly used to clean tools and equipment, such as ketones (e.g. acetone); chlorinated hydrocarbons (e.g. dichloromethane), aliphatic alcohols and esters, aromatic hydrocarbons, and organic peroxides used as initiators (e.g. methyl ethyl ketone peroxide and benzoyl peroxide); hydroquinone and analogues used as inhibitors (e.g. hydroquinone, quinone, and catechol); dusts and fibres originating mainly from filler and reinforcement materials (e.g. glass fibres, silica, and asbestos); foaming agents such as isocyanates; and cobalt salts and amines used as accelerators (Pfäffli et al., 1979; Högstedt et al., 1983; NIOSH, 1983; Coggon et al., 1987; Jensen et al., 1990; Bellander et al., 1994).

(b) Production of styrene-butadiene rubber

Workers are also exposed to styrene during the production of styrene-butadiene rubber (SBR) (Table 1.6). In two adjacent SBR production plants in the USA, the measured TWA concentrations of styrene were 0.94 ppm and 1.99 ppm [4.00 mg/m^3 and 8.50 mg/m^3], with an overall range of 0.03–12.30 ppm [0.13–52.40 mg/m^3] (Meinhardt et al., 1982). The mean concentrations in 159 personal air samples collected in various departments at another SBR production plant in the USA were usually below 1 ppm

Table 1.6 Personal styrene inhalation exposure levels in styrene–butadiene rubber manufacturing workers

Reference	Location; collection date	Occupation description	No. workers and/or samples	Sampling duration	Styrene (ppm [mg/m³])		Butadiene (ppm [mg/m³])		Benzene (ppm [mg/m³])	
					Mean exposure	Exposure range (GSD)	Mean exposure	Exposure range (GSD)	Mean exposure	Exposure range (GSD)
Checkoway & Williams (1982)	USA, one plant; 1979	Tank farm	8	Full shift	13.67 [58.23]	0.51–65.16 [2.17–277.56]	20.03 [44.31]	0.14–53.37 [0.31–118.07]	0.03 [0.096]	0–0.08 [0–0.26]
		Reactor and recovery	28		0.93 [3.96]	0–2.32 [0–9.88]	0.77 [1.70]	0–3.11 [0–6.88]	0.02 [0.064]	0–0.11 [0–0.35]
		Solution	12		0.99 [4.22]	0.27–1.68 [1.15–7.16]	0.59 [1.31]	0–2.18 [0–4.82]	0.10 [0.32]	0–0.24 [0–0.77]
		Shipping and receiving	2		0.13 [0.55]	0.08–0.18 [0.34–5.03]	0.08 [0.18]	0.03–0.12 [0.07–0.27]	0 [0]	
		Storeroom	1		0.48 [2.04]		0.08 [0.18]		0.10 [0.32]	
		Factory service	56		1.69 [7.20]	0–17.48 [0–74.46]	0.37 [0.82]	0–1.46 [0–3.23]	0.04 [0.13]	0–0.93 [0–2.97]
		Maintenance	52		0.57 [2.43]	0–2.35 [0–10.01]	0.97 [2.15]	0–20.70 [0–45.79]	0.07 [0.22]	0–0.24 [0–0.77]
Meinhardt et al. (1982)	USA, two plants; 1943–1976	Plant A	55 [area samples]	TWA	0.94 [4.0]	0.03–6.46 (SD, 1.23) [0.13–27.52 (5.24)]	1.24 [2.74] (*n* = 41)	0.11–4.17 (SD, 1.2) [0.24–9.23 (2.65)]	0.10 [0.32] (*n* = 3)	0.08–0.14 (SD, 0.04) [0.26–0.45 (0.11)]
		Plant B	35 [area samples]		1.99 [8.48]	0.05–12.30 (SD, 3.0) [0.21–52.39 (12.78)]	13.5 [29.87] (*n* = 47)	0.34–174.0 (SD, 29.9) [0.75–384.93 (66.15)]		

GSD, geometric standard deviation; SD, standard deviation; TWA, time-weighted average.

[4.3 mg/m^3], except for factory service and tank farm workers who were exposed to mean concentrations of 1.69 ppm and 13.7 ppm [7.20 mg/m^3 and 58.4 mg/m^3], respectively (Checkoway & Williams, 1982). An average styrene concentration of 3.53 ppm [15.0 mg/m^3], with a standard deviation of 14.3 ppm [60.9 mg/m^3], was measured in 3649 samples collected in five SBR plants in the USA during 1978–1983 (Matanoski et al., 1993). Macaluso et al. (1996) used industrial hygiene data obtained from the same facilities as Matanoski et al. (1993) and, together with a series of air dispersion models, estimated how TWA styrene exposure levels in the SBR industry may have changed since the 1940s (Macaluso et al., 1996). Their calculations suggest that TWA exposures declined from an average of 1.8 ppm [7.7 mg/m^3] during the 1940s to 0.1 ppm [0.4 mg/m^3] in the 1990s.

No data were available for measurements of styrene-7,8-oxide exposures in the production of SBR and other styrene-based polymers.

(c) Production of styrene monomer and polymers

Average exposure to styrene in styrene production and polymerization factories has been reported as rarely exceeding 85 mg/m^3 and is usually a result of occasional bursts and leakages of reactors, tubing, and other equipment (Tossavainen, 1978; Pfäffli et al., 1979; Samimi & Falbo, 1982; Pfäffli & Säämänen, 1993; Rappaport et al., 1996; Nylander-French et al., 1999). Surveys conducted in plants in the USA developing or manufacturing styrene-based products during 1962–1976 showed that the average exposure of employees in all jobs was less than 10 ppm [42.6 mg/m^3] (NIOSH, 1983). Peak concentrations of up to 50 ppm [213 mg/m^3] were measured during the drumming of styrene (Ott et al., 1980). Wolff et al. (1978) measured the highest levels of styrene in polymerization, manufacturing, and purification areas (mean, 8–35 ppm [34–149 mg/m^3]), whereas levels of less than 5 ppm [21 mg/m^3] were measured in maintenance, laboratory, and packaging operations. In a German styrene production, polymerization, and processing plant, samples acquired during 1975–1976 in various areas of the plant contained up to 6.8 ppm [29.0 mg/m^3] of styrene; most values were less than 1 ppm [4.3 mg/m^3] (Thiess & Friedheim, 1978). Air samples in a polystyrene manufacturing area contained up to 47 ppm [200 mg/m^3] of styrene; most values were less than 1 ppm [4.3 mg/m^3] (Thiess & Friedheim, 1978).

In an acrylic ester–styrene copolymer [incorrectly called polystyrene by Samimi & Falbo (1982)] production plant in the USA, breathing-zone concentrations ranged from none detected (< 1 ppb [4.3 μg/m^3]) to 19.8 ppm [84.3 mg/m^3] (n = 50), with an average of about 0.6 ppm [2.5 mg/m^3]; the highest concentrations occurred during styrene unloading operations (Samimi & Falbo, 1982).

Styrene was measured as a thermal degradation product in the air of a Finnish factory during the processing of polystyrene, impact polystyrene, and ABS resins (Hoff et al., 1982); the 6-hour mean concentrations were 0.4, 0.1, and 0.06 mg/m^3, respectively. Styrene levels measured in personal 8-hour samples collected during polystyrene and ABS moulding in three different companies in the USA during 1978–1980 varied considerably: 8–67 ppm [34–285 mg/m^3] (Burroughs, 1979); 1.4–3.8 mg/m^3 (Belanger & Elesh, 1980); and less than 0.01 mg/m^3 [below the limit of detection] (Ruhe & Jannerfeldt, 1980).

Styrene-7,8-oxide exposure was reported in only one study conducted in the styrene and polystyrene production industry. Korn et al. (1994) measured styrene and styrene-7,8-oxide concentrations of 78–836 μg/L and 0.9–4.1 μg/L, respectively, in the blood of 13 workers exposed to styrene concentrations of 10–73 ppm in the production of reinforced polyester resins. Styrene inhalation exposure was strongly correlated with styrene blood levels (r = 0.87). A strong linear relationship was also observed between styrene-7,8-oxide in blood and styrene in ambient air ($r = 0.88$), between styrene-7,8-oxide in blood and styrene in blood($r = 0.82$), and a steady-state level of styrene-7,8-oxide of about 1 µg/L blood at a styrene inhalation exposure of 20 ppm [85.19 mg/m^3] was calculated.

(d) Miscellaneous operations

In a study of the styrene concentrations that firefighters are exposed to, air samples taken during the knockdown phase of a fire contained styrene at a mean concentration of 1.3 ppm [5.5 mg/m^3]; none was detected during the overhaul phase (Jankovic et al., 1991). During working operations at a hazardous waste site in the USA in 1983, a mean styrene concentration of 235 µg/m^3 (maximum, 678 µg/m^3) was measured in air for a group of workers nearest the areas where chemically contaminated materials were handled (Costello, 1983). During the manufacture of polyester paints, lacquers, and putties in Finland, occasional exposure to high concentrations of styrene was recorded, with 5% of measurements above 20 ppm [85 mg/m^3]; use of the same products resulted in exposure of less than 1 ppm [4.3 mg/m^3] (Säämänen et al., 1991a). Application of polyester putty during cable splicing operations for a telephone company in the USA resulted in short-term levels (3–16 minutes) ranging over 2–16 ppm [8.5–68 mg/m^3] in four samples (Kingsley, 1976).

In four 100-minute area air samples taken in 1982 at a college in the USA during a sculpture class in which polyester resins were used, styrene concentrations of 0.8–1.2 ppm [3.4–5.1 mg/m^3] were measured; two personal breathing-zone air samples contained styrene at 2.8 ppm and 3.0 ppm [11.9 mg/m^3 and 12.8 mg/m^3] (Reed, 1983). Taxidermists who used polyester resins during specimen preparation were shown to be exposed for short periods (2–34 minutes) to concentrations of styrene ranging from 5 ppm to less than 50 ppm [21 mg/m^3 to < 213 mg/m^3] (Kronoveter & Boiano, 1984a).

Styrene exposure has also been reported in photocopy operations. Stefaniak et al. (2000) reported that the personal exposure of photocopier operators to styrene varied from 0.1 ppb to 0.7 ppb [0.43–2.98 µg/m^3] in three photocopy centres. Stefaniak et al. (2017) also investigated the emissions of airborne VOCs, including styrene, during desktop fused deposition modelling 3-dimensional and laser printing. The average of styrene emissions varied from 100.5 ± 11.7 µg/m^3 (black colour) to 252.1 ± 128.7 µg/m^3 (natural colour) for fused deposition modelling 3-dimensional printing and from 4.4 µg/m^3 to 8.1 µg/m^3 for 80 pages of laser printing.

No data were available for the measurement of styrene-7,8-oxide exposures in these miscellaneous operations.

1.4.3 Exposure of the general population

(a) Biomonitoring data

The United States Centers for Disease Control and Prevention *National Report on Human Exposure to Environmental Chemicals* provides an ongoing assessment of the exposure of the United States population to styrene and other environmental chemicals by biomonitoring, conducted on random samples of NHANES participants. The median blood styrene concentration declined in the United States population from 0.041 ng/mL in 1988–1994 to less than 0.030 ng/mL in 2001–2008, and the 95th percentile declined from 0.177 ng/mL in 1988–1994 to 0.130 ng/mL in 2007–2008 (Su et al., 2011; CDC, 2018; Table 1.7).

Styrene exposures vary by region and season. Children enrolled in the School Health Initiative: Environment, Learning, Disease study in Minneapolis, Minnesota displayed seasonal variation in blood styrene with a range of median concentrations of 0.07–0.11 ng/mL, exceeding the national median (Sexton et al., 2005). The

Table 1.7 Concentrations of styrene in blood of United States and Italian general populations

Population	Age (years)	Sample size	Blood styrene percentiles (ng/mL)				Survey years	Source
			50th	75th	90th	95th		
GuLF Study, USA (smokers)	< 30 (17.6%), 30–45 (35.1%), > 45 (47.2%), NR (0.1%)	234	NR	NR	NR	1.110	2011–2013	Doherty et al. (2017)
GuLF Study, USA (non-smokers)	< 30 (17.6%), 30–45 (35.1%), > 45 (47.2%), NR (0.1%)	141	NR	NR	NR	0.882	2011–2013	Doherty et al. (2017)
USA	12–60+	2719	< 0.03	0.045	0.096	0.130	2007–2008	NHANES IV (CDC, 2018)
USA	12–60+	2808	< 0.03	0.047	0.099	0.135	2005–2006	NHANES IV (CDC, 2018)
USA	20–59	1245	< 0.03	0.050	0.089	0.120	2003–2004	NHANES IV (CDC, 2018)
USA	20–59	950	< 0.03	0.080	0.130	0.200	2001–2002	NHANES IV (CDC, 2018)
Louisiana, USA[a]	15–60+	297	0.021	0.036	0.049	0.056	2002	Uddin et al. (2014)
Minnesota, USA[b]	6–10	103	0.07	0.18	0.74	0.85	2000 (Feb)	Sexton et al. (2005)
Minnesota, USA[b]	6–10	108	0.09	0.18	0.54	0.68	2000 (May)	Sexton et al. (2005)
Minnesota, USA[b]	6–10	54	0.09	0.10	0.11	0.11	2001(Feb)	Sexton et al. (2005)
Minnesota, USA[b]	6–10	88	0.11	0.12	0.17	0.21	2001 (May)	Sexton et al. (2005)
USA	20–59	2476	0.021	NR	0.110	0.158	1999–2004	NHANES 1999–2004; Su et al. (2011)
USA	20–59	624	0.041	NR	0.129	0.177	1988–1994	NHANES III: 1988–1994; Su et al. (2011)
Italy	20–59	81	0.17	NR	NR	0.51	Prior to 1993	Brugnone et al. (1993)

GuLF, Gulf Long-term Follow-up; NHANES, United States National Health and Nutrition Examination Survey; NR, not reported.

[a] Population of Calcasieu and Lafayette parishes, Louisiana.

[b] Children enrolled in School Health Initiative: Environment, Learning, Disease study, Minneapolis.

Compiled by the Working Group.

95th percentile concentration of styrene in blood of participants ranged from 0.11 ng/mL to 0.85 ng/mL (Sexton et al., 2005), comparable to that of an Italian population of 0.51 ng/mL, assessed before 1993 (Brugnone et al., 1993). Sexton et al. (2005) noted that high concentrations of styrene in blood among children are unlikely to be explained by tobacco use, and suggest an unknown source of styrene.

After the 2010 *Deepwater Horizon* incident, the Gulf Long-term Follow-up study evaluated benzene, toluene, ethylbenzene, xylenes, and styrene concentrations in blood of study participants approximately 3 years after the spill (Doherty et al., 2017; Kwok et al., 2017; Table 1.7). Most participants (95%) lived in a county adjacent to the Gulf coast, and most (89%) had worked on the oil spill. For non-smokers (*n* = 141), the GM exposure was 0.052 ng/mL [consistent with the range of 50th percentile values reported in Table 1.7 of < 0.03–0.17] and the 95th percentile exposure was 0.882 ng/mL (Doherty et al., 2017). For smokers (*n* = 234), the GM exposure was 0.098 ng/mL and the 95th percentile exposure was 1.110 ng/mL (Doherty et al., 2017). [According to Chambers et al. (2011), a cigarette smoking habit at a rate of 1 pack per day is estimated to increase blood styrene concentration by 0.2 ng/mL (assuming 20 cigarettes per pack), which may partially account for the 0.228 ng/mL difference in the 95th percentiles between non-smokers and smokers observed by Doherty et al. (2017).]

Styrene was detected in manually expressed human breast milk from a convenience sample of 12 healthy women from the Baltimore, Maryland metropolitan area who were breastfeeding, at least 30 days postpartum. The average styrene concentration in the breast milk was 0.219 ng/mL, with a range of 0.055–0.710 ng/mL and median of 0.129 ng/mL (Blount et al., 2010).

Pierce & Tozer (1992) reported a styrene concentration of 1.12 ± 1.06 ppm (mean ± standard deviation) in the adipose tissue samples of non-occupationally exposed individuals; samples were obtained from three elective surgery patients and eight postmortem donors (styrene detected in 7 samples).

(b) Total intake estimates

Total intake of styrene is estimated on the basis of two studies; although in general agreement with each other, the studies differ in the estimated contribution of styrene from food and inhaled air.

Tang et al. (2000) estimated that styrene exposure for the general population is in the range of 18.2–55.2 μg per person per day (0.3–0.8 μg/kg body weight (bw)), mainly from inhaled styrene (> 90% of the total intake), as well as form food intake. For smokers, intake of styrene due to 20 cigarettes was estimated to exceed the total daily intake from food and air in a single day.

For the Canadian general population, daily total styrene intake was estimated to range from <0.19 μg/kg bw to > 0.85 μg/kg bw. Intakes from ambient air ranged from 0.004 μg/kg bw per day up to 0.17 μg/kg bw per day, and those from indoor air from 0.07 μg/kg bw per day up to 0.10 μg/kg bw per day. Intake from food was calculated to range from less than 0.11 μg/kg bw per day to more than 0.58 μg/kg bw per day. The estimated intakes from drinking-water and soil were negligible. Potential exposure from cigarette smoke was estimated to be 2.86 μg/kg bw per day for adults. The Canadian study estimated that styrene in food may represent a major exposure source for the general population (Health Canada, 1993; Newhook & Caldwell, 1993).

(c) Food intake estimates

The general-population exposure to styrene from food ingestion has been estimated in several studies, most often using predictive models that consider styrene migration from food-contact materials (FCMs) and dietary consumption factors. Using this methodology, Lickly et al. (1995) estimated dietary styrene exposure at 9 μg per day from the use of polystyrene in FCMs in the USA. A prior study of residents of the United Kingdom in 1983 estimated a styrene intake of 1–4 μg per day (MAFF, 1989). Holmes et al. (2005) employed a probabilistic modelling approach, considering the variation in consumption among individuals in the United Kingdom, and estimated a median daily intake of styrene from food contaminated with FCMs to be 0.039 μg/kg bw per day for adults (2.3 μg per day per 60 kg bw), 0.048 μg/kg bw per day for youths, and 0.035 μg/kg bw per day for seniors.

Studies with dairy products have consistently shown the importance of fat content in the solvation and mass transfer of styrene from polystyrene and styrene–acrylonitrile copolymer food packaging (Ehret-Henry et al., 1994; López et al., 2008; Tawfik & BaAbdullah, 2014). Vitrac & Leblanc (2007) estimated a styrene intake of 1–35 μg per day (5th and 95th percentiles) from consumption of yogurt packaged in polystyrene cups based on migration modelling and yearly purchase data from 5400 households in France. El-Ziney & Tawfik (2016) assessed styrene monomer migration levels in dairy products packaged in polystyrene containers, and found that styrene levels increased with dairy fat content and storage temperature. Styrene intakes for nine packaged dairy products were calculated as 1.1–10.2 µg per day per person, assuming a modest 100 g intake of dairy product. Consumption of all tested dairy products (900 g) amounted to 50.6 µg per day per person (El-Ziney & Tawfik, 2016).

Philo et al. (1997) measured styrene-7,8-oxide in polystyrene FCMs under the premise that it may form from oxidation of residual styrene monomer. Styrene-7,8-oxide was detected in 11 of 16 food packaging articles at concentrations of up to 2.9 mg/kg. Investigating the potential for food contamination, the same pattern of migration as that for styrene monomer was assumed. The concentration of styrene-7,8-oxide in food was estimated to be 0.002–0.150 µg/kg based on a packaging content of 0.5–3.0 mg/kg.

1.5 Regulations and guidelines

1.5.1 *Exposure limits and guidelines*

Occupational exposure limits and guidelines for styrene are presented in Table 1.8. Deutsche Forschungsgemeinschaft has classified styrene as Category 5, “Substances that cause cancer in humans or animals or that are considered to be carcinogenic for humans and for which a MAK value [maximum permissible concentration at the workplace] can be derived” (DFG, 2017a). No regulations or guidelines have been established for occupational exposure to styrene-7,8-oxide.

A tolerable daily intake of 7.7 µg/kg bw for styrene has been established by the World Health Organization, with a guideline value of 20 µg/L in drinking-water (WHO, 2004). The EPA has set a maximum contaminant level for styrene in public water systems in the USA at 0.1 mg/L (EPA, 2001).

The FDA has established regulations for the use of polymers and copolymers of styrene in products in contact with food in the USA (FDA, 2017). For styrene and methyl methacrylate copolymers as components of paper and paperboard in contact with fatty foods, the monomer content in the copolymer is limited to 0.5%. For styrene–acrylic copolymers, the level of residual styrene monomer in the polymer should not exceed 0.1% by weight. In the European Union, Commission Regulation No. 10/2011 on plastic materials and articles intended to come into contact with food was published on 14 January 2011 (EU, 2011).

1.5.2 *Reference values for biological monitoring of exposure*

Biological monitoring reference values for exposure to styrene, based on styrene metabolite levels in urine, are given in Table 1.9. No regulations or guidelines have been established for occupational exposure to styrene-7,8-oxide.

1.6 Exposure assessment of epidemiological studies

The exposure assessments in key epidemiological studies investigating lymphohaematopoietic cancers discussed in Section 2 are summarized and evaluated in this section (see also Table 1.10 and Table 1.11). The studies are divided in the same way here as they are presented in Section 2. Cohort studies have been conducted in three broad categories: the reinforced plastics industry, the synthetic rubber industry, and the styrene monomer and polymers industries. There are also relevant epidemiological case–control studies conducted in samples of the general population. Methods for assessing the two fundamental dimensions of exposure – duration and intensity – will be described, followed by a description of the exposure metrics used in epidemiological models. An evaluation of the quality of the exposure assessments follows these summaries (Section 1.6.3).

Table 1.8 Occupational exposure limits and guidelines for styrene

Country or region	8-hour limit (ppm)	8-hour limit (mg/m³)	Short-term limit (ppm)[a]	Short-term limit (mg/m³)[a]
Australia	50	213	100	426
Austria	20	85	80	340
Belgium	50	216	100	432
Canada, Ontario	35		100	
Canada, Quebec	50	213	100	426
China		50		100
Czechia		200		1000
Denmark	25	105	25[b]	105[b]
Finland	20	86	100	430
France	23.3[c]	100[c]	46.6[c]	200[c]
Germany (DFG)[d]	20	86	40[e]	172[e]
Hungary[f]		50		
Ireland	20	85	40	170
Israel	20	85	40	170
Italy	50	100	215	430
Japan (JSOH)[g]	20	85		
Latvia		10		30
Mexico	50	215	100	425
Netherlands	25	106	50	213
New Zealand	50	215	100	425
Norway	25	106	37.5	160
Philippines	100	425		
Poland[g]	24	50	72	200
Republic of Korea	20	85	40	170
Singapore	50	213	100	426
Spain	20	86	40	172
Sweden	10	43	20	86
Switzerland	20	85	40	170
Thailand	100	426	200	852
Turkey	100	426		
United Kingdom[h]	100	430	250[i]	1065[i]
USA (ACGIH)[j]	20	85	40	170
USA (NIOSH)	50	215	100	425
USA (OSHA)	100	420	200	852

ACGIH, American Conference of Governmental Industrial Hygienists; DFG, Deutsche Forschungsgemeinschaft; JSOH, Japan Society for Occupational Health; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Safety and Health Administration; ppm, parts per million.

[a] 15-minute average value.

[b] Ceiling value.

[c] Indicative statutory limit value.

[d] Category 5, “Substances that cause cancer in humans or animals or that are considered to be carcinogenic for humans and for which a MAK [maximum concentration at the workplace] value can be derived”.

[e] 30-minute average value.

[f] Suspected of having carcinogenic potential.

[g] Absorption through the skin may be a significant source of exposure.

[h] Maximum exposure limit, obligation to reduce as much as possible.

[i] 10-minute average value.

[j] A4, not classifiable as a human carcinogen.

Sources: HSE (2011); ILO (2011); Finnish Ministry of Social Affairs and Health (2016); ACGIH (2017); DFG (2017b); IFA (2017); OSHA (2018).

Table 1.9 Reference values for biological monitoring of exposure to styrene

Determinant	Sampling time	Biological exposure index[a]	BAT[b]	Finland[c]
Mandelic acid plus phenylglyoxylic acid in urine	End of shift	400 mg/g creatinine[d]	600 mg/g creatinine	1.2 mmol/L[e]
Styrene in urine	End of shift	40 µg/L	NA	NA

BAT, Biologischer Arbeitsstoff-Toleranzwert (biological tolerance value); NA, not applicable.

[a] American Conference of Governmental Industrial Hygienists (ACGIH, 2017).

[b] Deutsche Forschungsgemeinschaft (Schaller & Triebig, 2012).

[c] Finnish Ministry of Social Affairs and Health (2016).

[d] Non-specific, as it is also observed after exposure to other chemicals such as ethylbenzene.

[e] Next morning sample.

Compiled by the Working Group.

1.6.1 Occupational cohort studies

(a) Reinforced plastics industry

Analyses of the risk of cancer have been conducted for several cohorts of workers exposed to styrene in the reinforced plastics industry: a European industry-wide study (Kogevinas et al., 1994; Loomis et al., 2019); a Danish industry-wide study (Christensen et al., 2018); a United Kingdom industry-wide study (Coggon et al., 2015); a United States industry-wide study (Collins et al., 2013); and a small study of two boatbuilding facilities in Washington State, USA (Bertke et al., 2018). There were significant overlaps between some of these cohorts; these are discussed in more detail in Section 2.2.

(i) European industry-wide study

Approximately 41 000 workers in plants in six European countries were studied by Kogevinas and colleagues (Kogevinas et al., 1994; Loomis et al., 2019). These workers were employed in 287 plants where the main product was reinforced plastic, and more than 50% of these workers were estimated to have been exposed to styrene. Employment records were used to determine duration of exposure and to assign workers to common-exposure job groups. Intensity of exposure to styrene was estimated using 16 500 personal air samples covering the period 1955–1990, although data on exposures before 1970 were only available from Denmark. Production records and detailed job-task information were used to estimate styrene intensities specific to country, time period, and job. Workers were assigned an exposure intensity based on the job held for the longest time. Summary measures of exposure included time since first exposure, average exposure, and cumulative exposure.

(ii) Danish industry-wide study

Workers in 443 small- to medium-sized factories making reinforced plastics during 1964–2007 were identified and followed through national registers, including the cancer registry, to identify incident cases as opposed to mortality (mortality was recorded by all the other cohort studies) (Christensen et al., 2017, 2018). There were 72 292 such workers (1.7 million person-years), making this by far the largest published study. Data were available on dates of hiring and leaving employment, but not job titles or tasks. The investigators took advantage of the variability in working conditions among the large number of small shops with a few employees in each to estimate exposure intensity and probability for each cohort member over their working life, using information about the company's products and work practices, in an analysis conducted for cancers of the lymphoid and haematopoietic system (Christensen et al., 2018).

Styrene exposure intensity was estimated by building a statistical model of the determinants of 1122 personal measurements of styrene airborne

Table 1.10 Comparison of exposures and exposure metrics: key epidemiological (occupational cohort) studies of styrene

Principal reference	Exposure assessment reference	Study location	Exposure period	Mean exposed years	Mean intensity (ppm)	Mean cumulative exposure (ppm-years)	Important co-exposures	Exposure intensity estimation	Exposure metrics	Exposure assessment limitations
Reinforced plastics										
Collins et al. (2013)	Wong (1990)	USA	1948–1977	4.3[a]	28[a]	120[b]	NA	IH surveys	Duration of exposure, cumulative and average exposure, cumulative number of peak exposure periods	27% of cohort missing exposure information for recent years
Coggon et al. (2015)	Coggon et al. (1987)	United Kingdom	1947–1984	3.5[c]	50[d]	175[b]	NA	Expert judgment	High-exposure job for at least 1 year	10% of cohort missing exposure information for recent years
Bertke et al. (2018)	Crandall & Hartle (1985), Ruder et al. (2016)	USA	1959–1978	0.4 (median)[e]	23[f]	9[b]	NA	IH surveys	High versus low exposure, duration	33% of cohort missing exposure data for recent years
Christensen et al. (2018)	Kolstad et al. (2005)	Denmark	1964–2007	3.5[g]	23[h]	81[b]	NA	Predictive model	Cumulative exposure, average intensity, average probability, duration	Exposure information missing for early and recent years
Loomis et al. (2019)	Kogevinas et al. (1994)	6 European countries	1945–1991	2.2[i]	63[i]	158[i]	NA	IH surveys	Cumulative exposure, average intensity, duration	Exposure data missing for early years
Synthetic rubber										
Sathiakumar et al. (2015)	Macaluso et al. (2004), Macaluso et al (1996)	USA and Canada	1943–1991	11[j]	1.5[k]	17[l]	Butadiene	Expert judgment	Cumulative exposure	21% of cohort missing exposure information for recent years
Production of styrene monomer and polymers										
Hodgson & Jones (1985)		United Kingdom	1945–1974	7[m]	50[n]	350[b]	Benzene, butadiene	None	Exposed or unexposed	Exposure defined by employment

Table 1.10 (continued)

Principal reference	Exposure assessment reference	Study location	Exposure period	Mean exposed years	Mean intensity (ppm)	Mean cumulative exposure (ppm-years)	Important co-exposures	Exposure intensity estimation	Exposure metrics	Exposure assessment limitations
Bond et al. (1992)	Ott et al. (1980)	USA	1937–1977	7[o]	5[p]	35[b]	Benzene, butadiene	IH surveys	Intensity or duration categories	No individual quantitative exposure estimates

IH, industrial hygiene; ppm, parts per million; TWA, time-weighted average.

Notes on calculating mean exposure duration, intensity and cumulative exposure:

[a] From Collins et al. (2013), p. 196.

[b] Product of mean duration and mean intensity.

[c] From Coggon et al. (1987), Table 2: weighted average “length of potential exposure to styrene”.

[d] From Coggon et al. (1987), Table 2: weighted average “grade”: high = 70 ppm, moderate = 25, low = 5, based on p. 95, statement that “...high exposure category corresponds to ... 40–100 ppm”.

[e] From Bertke et al. (2018), Table I.

[f] From Ruder et al. (2016), p. 98: mean high exposure in plant A = 42.5 ppm/day; plant B = 71.7 ppm/day; low exposure at plants A and B = 5 ppm/day; weighted mean using population data from table 1.

[g] From Christensen et al. (2018), Table 2: person-years weighted mean duration of employment.

[h] From Kolstad et al. (2005), p. 159: geometric mean of long-term samples 98.5 mg/m^3 = 23 ppm.

[i] From Loomis et al. (2019), Table 1.

[j] From Macaluso et al. (2004), Table III: all employees mean cumulative exposure = 17 ppm-years, divided by mean intensity.

[k] From Macaluso et al. (2004), Fig. 2.

[l] From Macaluso et al. (2004), Table 3: all employees mean cumulative exposure = 17 ppm-years.

[m] From Hodgson & Jones (1985), Table 6, footnote a: mean years exposed for referents = 6.6.

[n] From Hodgson & Jones (1985), p. 350: “It is believed that the exposures of the exposed workers would in general have been well below the hygienic standard of 100 ppm (420 mg/m^3) with isolated excursions to higher levels associated with certain faults and some maintenance work”.

[o] From Ott et al. (1980), Table 11: weighted mean exposure duration for groups exposed to styrene.

[p] From Ott et al. (1980), pp. 448–450: mean TWAs were well below 10 ppm in all processes, generally less than 5 ppm.

Table 1.11 Comparison of exposures and exposure metrics: key epidemiological (case–control) studies of styrene in the general population

Principal reference	Exposure period	Percentage of study controls ever exposed	Mean exposed years	Mean intensity (ppm)	Mean cumulative exposure (ppm-years)	Exposure intensity method	Exposure metrics	Exposure assessment limitations
Gérin et al. (1998)	Pre-1950–1980s	1.78[a]	NA	NA	NA	Expert judgment	Categorical based on estimated duration, concentration, and frequency of exposure	Exposure metrics only semiquantitative
Scélo et al. (2004)	Pre-1950s–2002	1.51	< 1[b]	< 1[c]	< 1[b]	Expert judgment	Cumulative exposure, duration	Exposure metrics only semiquantitative
Miligi et al. (2006)	Pre-1940s–1990s	2.25	NA	NA	NA	Expert judgment	Categorical probability and exposure intensity	Exposure metrics only semiquantitative
Seidler et al. (2007)	1940s–2000	23.8	NA	NA	~5[d]	Expert judgment	Categorical intensity	Exposure metrics only semiquantitative
Cocco et al. (2010)	1940s–2000	2.36	NA	1.5[e]	NA	Expert judgment	Cumulative exposure categories (based on duration, intensity, and probability scores), duration	Exposure metrics only semiquantitative
Karami et al. (2011)	1940s–2000s	1.18	NA	NA	NA	Expert judgment	Probability, cumulative exposure, average exposure, and duration	Exposure metrics only semiquantitative

NA, not available; ppm, parts per million.

[a] Lymphomas as end-point.

[b] Calculated using data from Scélo et al. (2004), Table 5.

[c] Calculated using data from Scélo et al. (2004), Table 2.

[d] Calculated using data from Seidler et al. (2007), Table 2.

[e] Calculated using data from Cocco et al. (2010), Supplementary Table F.

Compiled by the Working Group.

concentrations gathered in 133 companies between 1970 and 2011. The production process, products manufactured, and the decade in which this took place were important predictors, allowing the investigators to produce estimates of styrene concentrations in all participating factories using these determinants (Christensen et al., 2018).

Exposure probability was also estimated for each company and assigned to each worker. A mailed survey in 2013 (11 493 responses, 76% response rate) asked a stratified random sample of workers about the work practices and products in their plant (Christensen et al., 2017, 2018). From these data, a model was built to predict the probability of an individual worker being exposed to styrene. Important determinants were calendar year, production process (lamination or other processes), products (boats, wind turbine wings, or other products), sex, occupation, and company size (Christensen et al., 2018).

Summary measures of exposure included: duration of exposure, mean exposure probability, and (for the analyses of cancers of the lymphoid and haematopoietic system; Christensen et al., 2018) mean exposure intensity and cumulative exposure score (the product of exposure intensity and probability, summed over all exposed years). The cumulative exposure score was analysed in tertiles based on the person-year exposure distribution. Time windows of exposure were also investigated with a priori division of time before onset into three windows: less than 15 years, 15–29 years, and 30 years or more.

(iii) United Kingdom industry-wide study

Eight of the United Kingdom factories in the European-wide cohort study (Kogevinas et al., 1994) were also studied separately with follow-up extended through 2012 (Coggon et al., 2015). The cohort included 7970 workers who began work in reinforced plastics factories between the 1940s and 1970s (start dates varied by plant). Cohort entry ended in the early 1980s (again, varying by plant). Work records were used to identify start and end dates of exposed jobs. No air monitoring data were available, and an expert industrial hygiene survey was not performed. Managers and staff assisted in classifying jobs into four categories of potential styrene exposure: high (hand laminators); moderate (frequently near styrene operations); low (occasionally near styrene operations); and background (all other). Summary measures of exposure were assessed by the highest category of exposure held by each participant: high for 1 year or longer, high for less than 1 year, low and/or moderate, and background.

(iv) United States industry-wide study

Potential exposure to styrene during 1948–1977 of a cohort of approximately 16 000 workers from 30 plants in the USA producing reinforced plastics was first studied by Wong (1990) and then by Collins et al. (2013). Work records were used to estimate duration of styrene exposure and to assign workers to work areas and jobs. An industrial hygiene survey was conducted at each plant, including detailed analyses of plant records and air monitoring data [whether these were personal breathing-zone or area samples was not indicated]. Airborne styrene exposure intensity was estimated for each job and work area over the period 1948–1977. Summary measures of exposure used by Collins et al. in the 2013 updated mortality analyses were duration of exposure, average exposure, cumulative exposure, and the cumulative number of peak exposure periods, defined as 15-minute periods with mean exposure of more than 100 ppm (considered the threshold for acute irritation). A total of 27% of the cohort members worked past 1977, the end of the period for which exposures were estimated, and therefore had truncated individual exposure estimates. [Although this unmeasured exposure was likely to have been low (average exposure intensities in the industry fell substantially during the follow-up period), this missing information for more than one quarter of the cohort may still have introduced important exposure misclassification for some of the long-term workers.]

(v) Boatbuilding facilities in Washington State, USA

NIOSH studied two boatbuilding facilities in Washington State that used styrene in the construction of fibreglass-reinforced plastic boats (Crandall & Hartle, 1985; Ruder et al., 2016; Bertke et al., 2018). All 1678 employees who worked at one of the two facilities for at least 1 year between 1959 and 1978 were followed until 2011. Work records were used to determine start and end dates of employment, but job title information was incomplete and not used to estimate the exposure to styrene of workers. Industrial hygiene surveys collecting both personal and area styrene air concentrations were conducted in 1978 and used to classify work areas as exposed to either high or low concentrations. In company A, mean styrene exposure in the areas of high concentration was 42.5 ppm (range, 12–85 ppm), and in company B the mean styrene exposure in the areas of high concentration was 71.7 ppm (range, 10–183 ppm). There was considerable heterogeneity of personal breathing-zone exposure concentrations within the areas of high concentration, but all workers were assigned a mean exposure because of the lack of individual job or task information. For the 555 workers still employed in 1978, there was no information on exposure subsequent to that date. Both plants ceased production in about 1990, meaning that all exposure estimates in later years were incomplete for one third of the cohort. The summary measure of exposure was "high" versus "low" styrene exposure.

(b) Synthetic rubber industry

A large and long-running study of workers at six North American factories producing SBR developed quantitative exposure estimates and used these data to quantify risk of mortality from cancer (Macaluso et al., 1996, 2004; Graff et al., 2005; Sathiakumar et al., 2015). Duration of exposure was determined from work histories, which were available for 97% of the cohort. Combinations of department and job title (*n* = 8281) were grouped by occupational hygienists into 308 homogeneous exposure groups based on similar products, processes, and environmental conditions. The intensities of exposures to styrene, 1,3-butadiene, and benzene were estimated for each homogeneous exposure group in different time periods covering the study period 1943–1991. The process for estimating these styrene and other chemical intensities used technical specifications for jobs, tasks, materials, and work areas supplemented by interviews with managers and workers, quantitative models based on assumptions about ventilation and other determinants of exposure, as well as expert judgment. Job-exposure matrices were then constructed for each combination of work area, job group, and year. When combined with individual work histories, this yielded individual exposure intensity estimates for each worker in each year. The primary summary measure of exposure was cumulative exposure, used in several ways in statistical models including as a continuous variable, in deciles, and with varying time lags. Exposure intensity estimates and work history records ended in 1991; for the 21% of workers still employed after that date, no exposure estimates were available for that period.

(c) Styrene monomer and polymers industry

Studies of workers in petrochemical plants where styrene was manufactured were conducted in the 1990s and earlier. These used very limited exposure classification methods, usually simply comparing the mortality of employees in a factory with that of the general population. Hodgson & Jones (1985) studied mortality in a cohort of styrene production workers in the United Kingdom. Exposed versus non-exposed workers were distinguished based on the production process area in which they worked, and their mortality was studied separately. No other exposure assessment was conducted to inform the epidemiological analyses. A styrene-based production cohort of chemical employees in the USA was studied first by Ott et al. (1980) and then by Bond et al. (1992). Work records were available to calculate the period of employment; this was used to estimate duration of exposure to a wide range of different chemicals, including styrene. An exposure assessment was conducted using industrial hygiene surveys (with both area and personal monitoring data), historical data on production and plant layout, work records, and other relevant data. The investigators estimated exposure intensities for job and area combinations and then used these to assign exposures to individual cohort members. There were other carcinogenic exposures, including benzene and butadiene. Analyses of mortality were presented for categories of duration of exposure and for groupings of different chemical exposures, including styrene and other potentially important co-exposures. No quantitative exposure–response modelling for styrene and cancer mortality was presented.

1.6.2 General-population studies

From the 1990s onwards, at least six case–control studies of cancer investigating occupational chemical exposures including styrene used variations of a common approach, starting from a self-reported job history collected on each subject (Gérin et al., 1998; Scélo et al., 2004; Miligi et al., 2006; Seidler et al., 2007; Cocco et al., 2010; Karami et al., 2011). Experts then evaluated job information and assigned exposure scores to each job, combining these to yield individual exposure estimates. Exposure assignments based on job, industry, and tasks were often supplemented with detailed follow-up questions when a reported job was likely to have incurred exposure to chemicals of interest. For example, there might be specific questions for painters, pesticide applicators, and machinists.

The highest-quality exposure assessment methods were observed in the studies by Scélo et al. (2004), Seidler et al. (2007), and Cocco et al. (2010), which used similar exposure assessment methods. Face-to-face interviews with cases and controls were used to gather information on all jobs held for at least 1 year. Specialized questionnaires were used for jobs judged a priori to involve exposure to chemicals of interest (18 supplementary questionnaires in the study by Scélo et al., 2004; 14 supplementary questions in each of the studies by Seidler et al., 2007 and Cocco et al., 2010). Experts evaluated each job for exposure to a list of chemicals of interest, including styrene. Because jobs were evaluated and not individuals, the raters were necessarily blind to case or control status. In the study by Scélo et al. (2004) this work was performed by experts in industrial hygiene; these individuals were selected in each of the 15 centres from which cases and controls were obtained, and attended training workshops during which the exposure assessment protocol was developed and validation exercises were regularly conducted. A single industrial physician evaluated the jobs in the study by Seidler et al. (2007), and trained industrial hygienists from each of the participating centres across the six European countries performed the evaluations in the study by Cocco et al. (2010).

The three studies used essentially the same scoring system. Each job was scored for exposure to each chemical on three dimensions: intensity, the relative exposure level (reported as an approximate air concentration) of the chemical for workers engaged in that job; frequency, the typical proportion of work time involving contact with the chemical; and confidence, the experts' degree of certainty that a worker in the job was truly exposed to the chemical. Each of these three dimensions was scored on a semiquantitative three- or four-point scale (scales varied slightly among the three studies). The duration of exposure was also calculated for each worker in Scélo et al. (2004) and Cocco et al. (2010) from the self-reported start and stop dates of each job held.

Scélo et al. (2004) and Seidler et al. (2007) trained their experts to estimate styrene exposure intensity on a three-point scale using the following air concentration ranges: low intensity, 0.5–5.0 ppm; medium intensity, more than 5 ppm to 50 ppm; and high intensity, more than 50 ppm. Using the midpoints of these three categories (2.5, 25, and 100 ppm), cumulative exposures could be calculated for each participant.

The other three key case–control studies (Gérin et al., 1998; Miligi et al., 2006; Karami et al., 2011) used similar methods to those described above with slight variations; however, they did not attempt to relate their semiquantitative exposure intensity estimates to air concentrations. In other ways, they were quite similar in terms of strengths and weaknesses to the studies of Scélo et al. (2004), Seidler et al. (2007), and Cocco et al. (2010).

1.6.3 Evaluation of exposure assessment quality of epidemiological studies

The exposure assessments of the key epidemiological studies cited in this *Monograph* are evaluated according to five principal considerations: exposure opportunity, carcinogenic co-exposures, completeness of exposure history data, accuracy of exposure intensity measurement, and appropriateness of exposure metrics used in the epidemiological models of risk of cancer.

(a) Exposure opportunity

An ideal epidemiological study for investigating the carcinogenicity of styrene would evaluate a population exposed to a high concentration over a long period of time. The Working Group evaluated each study against this ideal under the heading of exposure opportunity. Ideally, this cohort would not have other carcinogenic exposures, or at least these other exposures would not be correlated with styrene exposures. This first consideration of quality is not strictly about the exposure assessment, but concerns the exposure to the chemical of interest and its distribution across the population and over time. A rough indicator of exposure opportunity can be calculated as the product of the mean intensity of styrene exposure (ppm) over the entire cohort and the mean exposure duration (years). This product is the mean cumulative exposure (ppm-years) for the entire cohort; it was calculated for both cohort and case–control studies (Table 1.10 and Table 1.11), with several assumptions made due to different amounts and quality of information provided in the publications.

Not surprisingly, the occupational cohort studies report much higher mean cumulative exposures than the general-population case–control studies. Within the cohort studies, there was also a fairly wide range depending on the average air concentration and the duration of employment (including turnover) of the exposed cohort. Three of the cohorts – Bond et al. (1992), Sathiakumar et al. (2015), and Bertke et al. (2018) – experienced relatively low mean cumulative exposures, indicating lower exposure opportunity. In the studies by Bond et al. (1992) and Bertke et al. (2018), the average duration of exposure (mean exposed years) was short (~7 years and < 1 year, respectively), and in the study by Sathiakumar et al. (2015) the average intensity of styrene exposure was reportedly low, with mean exposure of about 1.5 ppm-years. The other five studies (Hodgson & Jones, 1985; Collins et al., 2013; Coggon et al., 2015; Christensen et al., 2018; Loomis et al., 2019) reported relatively high exposure opportunity as estimated by the mean cumulative exposure.

Where this type of evaluation was possible with the data available, the key case–control studies had much lower mean cumulative exposures, as expected. The statistical power of a study to detect an elevated risk of cancer is a function of both the exposure opportunity and the sample size, particularly the number of cases. A study with low mean cumulative exposure may still have sufficient power to detect an effect if the effect is very large. The statistical power of the case–control studies is discussed further in Section 2.3.

(b) Carcinogenic co-exposures

There were important co-exposures to chemicals established as human carcinogens by the International Agency for Research on Cancer (IARC) in three of the cohort studies – Hodgson & Jones (1985) (benzene, butadiene), Bond et al. (1992) (benzene and butadiene), and Sathiakumar et al. (2015) (butadiene) – limiting the value of these studies in evaluating the carcinogenicity of styrene. Sufficient evidence exists for the carcinogenicity of benzene in humans for the end-point of acute non-lymphocytic leukaemia, including acute myeloid leukaemia. Limited evidence exists in humans for cancer of the lung, non-Hodgkin lymphoma, chronic lymphoid leukaemia, multiple myeloma, and chronic myeloid leukaemia, and for acute myeloid leukaemia in children (IARC, 2018). Sufficient evidence also exists for the carcinogenicity of 1,3-butadiene in humans for the end-points of leukaemia and/or lymphoma (IARC, 2012b). The issue of co-exposure with other human carcinogens is considered again in Section 2.3 as a problem of potential confounding. Here we note that in these cohort studies the exposure assessments did not convincingly provide independent estimates of styrene intensity or duration that would confidently allow the effects of styrene to be separated from those of the other potential carcinogens using conventional statistical methods. The absence of co-exposures of other known carcinogens is a strength of the epidemiological studies in the reinforced plastics industry (see Section 2.2.1).

(c) Completeness of exposure histories

All of the cohort studies used work records to document exposure duration, time since first exposure, and other temporal variables. Many also estimated intensities of exposure (see the following section) and then used the work histories to assign time-varying exposure intensities to cohort members. In four of the cohort studies (Collins et al., 2013; Coggon et al., 2015; Sathiakumar et al., 2015; Bertke et al., 2018), the periods for which exposure information were available ended before the end of follow-up, meaning that a fraction of cohort members had truncated exposure histories. These truncations were common in Collins et al. (2013), Sathiakumar et al. (2015), and Bertke et al. (2018) (occurring for 27%, 21%, and 33% of the cohort members, respectively), and could have had a significant impact on the accuracy of the exposure assessments and therefore the fit of the exposure–risk models. Completeness of exposure histories was not an important concern in any of the case–control studies.

(d) Accuracy of exposure intensity measurement

The principal route of styrene exposure for the epidemiological studies discussed here is via inhalation, and the breathing-zone air concentration in ppm or mg/m^3 (1 ppm = 4.26 mg/m^3) is the primary measure of exposure intensity. A wide variety of methods were used to measure exposure intensity in the eight key cohort studies (Table 1.10); the case–control studies of higher quality all used similar semiquantitative methods based on expert judgement (Table 1.11).

Hodgson & Jones (1985) and Coggon et al. (1987, 2015) used only the judgement of investigators, informed by input from company records or plant personnel. Based on limited measurements in some plants in later years, Coggon et al. (1987, 2015) estimated that the high-concentration exposure category corresponded to an average intensity of 40–100 ppm.

The SBR cohort study by Sathiakumar et al. (2015) used an extensive industrial hygiene analysis to develop time- and job-specific estimates of styrene and butadiene exposure intensities for individual cohort members (Macaluso et al., 2004). The exposure assessors based estimates of exposure intensity on mathematical models predicting exposure levels from production process and environmental conditions, and not on air measurements. However, NIOSH conducted styrene air monitoring in two facilities that employed cohort members during 1976–1977, and the NIOSH data were used as a comparison or partial validation of the exposure estimates of the teams.

The remaining cohort studies – Bond et al. (1992), Collins et al. (2013), Bertke et al. (2018), Christensen et al. (2018), and Loomis et al. (2019) – all used styrene air concentration measurements in some way to estimate the styrene exposure intensities of cohort members, but there were important differences in methods used and the likely accuracy of assignments. In the epidemiological analyses of the styrene-based production cohort in the USA (Bond et al., 1992), the primary epidemiological analyses used simple qualitative measures, such as work area and exposure grouping; however, this did not permit separate quantitative estimates of styrene and other potential carcinogens, notably butadiene. Similarly, the NIOSH cohort of boat builders did not assign individual exposure intensity estimates to each worker; rather, each worker was assigned to either potentially high or low concentrations of exposure (Bertke et al., 2018).

The United States industry-wide reinforced plastics cohort study (Collins et al., 2013) relied on an extensive industrial hygiene survey to estimate styrene concentrations in air for particular areas and/or job titles. These estimates were then used as inputs to individual exposure histories with annual intensity estimates for each cohort member. There were parallel estimates of the number of peak exposures for each work area and/or job title. Peaks were defined as 15-minute intervals when exposure exceeded 100 ppm. Despite these strengths, there are important gaps in the documentation of the methods used by Collins et al. (2013), described in earlier papers by Wong (1990) and Wong et al. (1994), that limit confidence in their exposure estimates. For example, the industrial hygiene survey data are not available, even in summary form.

The European industry-wide study was informed by an extensive industrial hygiene survey and assigned exposure intensities according to job title based on air monitoring data and, in the case of incomplete data, modelling (Loomis et al., 2019).

Finally, the Danish reinforced plastics industry study (Christensen et al., 2018) used a detailed exposure assessment method, as summarized in Section 1.6.1(a)(ii), to estimate both intensity and probability of styrene exposure for each cohort member over their working lifetime.

The better-quality case–control exposure assessments – that is, the studies of Scélo et al. (2004), Seidler et al. (2007), and Cocco et al. (2010) – were semiquantitative, using expert judgements of exposure intensity that were dependent upon explicit air concentration ranges. However, these were probably not as accurate as the exposure intensity estimates in the cohort studies of Bond et al. (1992), Collins et al. (2013), Sathiakumar et al. (2015), Bertke et al. (2018), Christensen et al. (2018), or Loomis et al. (2019). In addition to the lower exposure opportunity, the case–control studies probably had a greater degree of non-differential exposure misclassification than the more informative cohort studies.

In summary, the estimation of styrene exposure intensity appears to have been most reliably estimated by Christensen et al. (2018) and Loomis et al. (2019).

(e) Appropriateness of exposure metrics

Identifying the so-called ideal exposure metric (or summary measure of exposure) for carcinogenicity studies of styrene requires knowledge, or a strong assumption, of the pathophysiological mechanism (Kriebel et al., 2007). The best metric might even differ from one cancer site to another because of internal dose dynamics. Despite this uncertainty about the ideal form, occupational cancer epidemiology has often used cumulative exposure and its components (average exposure intensity and duration) as exposure metrics. There is good empirical evidence that these are often proportional to risk of cancer when applied to the data for known carcinogens such as asbestos and silica (IARC, 2012a). It is important to stress that no one standard summary measure of exposure can be said a priori to be closer to the so-called ideal metric for a particular chemical and target organ; it is therefore reasonable to fit models with several of these metrics.

Another well-recognized consideration in evaluating summary measures of exposure is that cancers typically develop after long periods of latency; it is therefore important to evaluate associations between exposures and their effect by evaluating exposures occurring at different time periods before the onset of disease. The only key epidemiological study to investigate multiple quantitative summary measures of exposure (cumulative exposure, average intensity, average probability, and duration) in time windows of exposure was that of Christensen et al. (2018). Several others (Collins et al., 2013; Sathiakumar et al., 2015; Loomis et al., 2019) used a simpler approach, such as setting a minimum latency that each exposed worker had to achieve before at-risk follow-up time began accruing, or the use of exposure lagging.

1.6.4 Overall summary of exposure assessment in key epidemiological studies

Analyses of the exposure assessments for the key epidemiological studies indicate that two of the cohort studies (Christensen et al., 2018; Loomis et al., 2019) are likely to be more informative than others for two reasons: the substantial exposure experience of cohort members (duration and intensity of exposure to styrene) and the use of high-quality, well-documented exposure assessment methods. Other good-quality exposure data are found in Collins et al. (2013) and Coggon et al. (2015). Several case–control studies (Scélo et al., 2004; Seidler et al., 2007; Cocco et al., 2010) were of relatively high quality in terms of assessment methods; however, the prevalence of styrene exposure and estimated average levels of exposure were considerably lower in these general-population studies than for the cohort studies, limiting their informativeness.

2. Cancer in Humans

2.1 Introduction

Styrene is an important industrial chemical and a major intermediate in the manufacture of both synthetic rubber and certain plastics. Epidemiological studies covering the working populations in all major industries using styrene have been conducted. Industry-based cohorts have evaluated the exposure to styrene of workers in the reinforced plastics, synthetic rubber, and styrene monomer and polymers industries. General-population studies include case–control studies in adults and children.

Early research in occupational cohorts focused mainly on the potential associations between exposure to styrene and leukaemia and lymphomas, whereas more recent analyses have also evaluated several other outcomes,