STYRENE

This substance was considered by a previous Working Group, in February 1978 (IARC, 1979). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

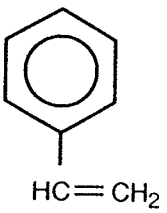
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 100-42-5
Replaced CAS Reg. No.: 79637-11-9
Chem. Abstr. Name: Ethenylbenzene
IUPAC Systematic Name: Styrene
Synonyms: Cinnamene; phenethylene; phenylethene; phenylethylene; styrol; styrole; styrolene; vinylbenzene; vinylbenzol

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_8H_8 Relative molecular mass: 104.15

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless, viscous liquid with a pungent odour (WHO, 1983)
(*b*) *Boiling-point*: 145.2 °C (Lide, 1991)
(*c*) *Melting-point*: –30.6 °C (Lide, 1991)
(*d*) *Density*: 0.9060 at 20 °C/4 °C (Lide, 1991)
(*e*) *Spectroscopy data*: Infrared [81 (grating)], ultraviolet [94], nuclear magnetic resonance and mass spectral data have been reported (Sadtler Research Laboratories, 1991; US National Library of Medicine, 1993a).
(*f*) *Solubility*: Slightly soluble in water (30 mg/100 ml at 20 °C); soluble in acetone, carbon tetrachloride, diethyl ether, ethanol and *n*-heptane; very soluble in benzene and petroleum ether (WHO, 1983)

(*g*) *Volatility*: Vapour pressure, 867 Pa at 25 °C; relative vapour density (air = 1), 3.6 (WHO, 1983)

(*h*) *Stability*: Lower explosive limit, 1.1% by volume in air (WHO, 1983; Dow Chemical Co., 1989)

(*i*) *Reactivity*: Polymerizes easily at room temperature in the presence of oxygen and oxidizes on exposure to light and air (WHO, 1983)

(*j*) *Octanol–water partition coefficient (P)*: log P, 3.05 (Sangster, 1989)

(*k*) *Conversion factor*: $mg/m^3 = 4.26 \times ppm$[a]

1.1.4 *Technical products and impurities*

Styrene is available as a commercial product with the following specifications: purity, 99.6–99.9% min.; ethylbenzene, 85 ppm max.; polymer content, 10 ppm max.; *para-tert*-butylcatechol (inhibitor), 10–15 ppm or 45–55 ppm; aldehydes (as benzaldehyde), 200 ppm max.; peroxides (as H_2O_2), 0.0015 wt% or 100 ppm max.; benzene, 1 ppm max.; sulfur, 25 ppm max.; chlorides (as chlorine), 50 ppm max. (Dow Chemical Co., 1991; Chevron Chemical Co., 1992; Amoco Chemical Co., 1993)

1.1.5 *Analysis*

(*a*) *Environmental monitoring*

Styrene in workplace air can be determined by packed capillary column gas chromatography with a flame ionization detector. The sample is adsorbed on charcoal and desorbed with carbon disulfide. This method (NIOSH Method 1501) has an estimated limit of detection of 0.001–0.01 mg per sample (Eller, 1984).

US EPA Method 8240 can be used to determine the concentration of various volatile organic compounds, including styrene, by gas chromatography–mass spectrometry, in a variety of matrices, including groundwater, aqueous sludges, waste solvents, oily wastes, tars, soils, sediments and others. Samples may be analysed using direct injection or the purge-and-trap method (US EPA Method 5030); the practical quantification limits are 5 µg/L for groundwater samples, 5 µg/kg for low-level soil and sediment samples, 250 µg/L for water-miscible liquid waste samples, 625 µg/L for high-level soil and sludge samples and 2500 µg/L for non-water-miscible waste samples (US Environmental Protection Agency, 1986).

(*b*) *Biological monitoring*

Biological methods for monitoring exposure to styrene have been reviewed (Guillemin & Berode, 1988; American Conference of Governmental Industrial Hygienists, 1991; Lauwerys & Hoet, 1993; Pekari *et al.*, 1993). Generally accepted biological indicators of exposure are mandelic acid (2-hydroxy-2-phenylacetic acid) and phenylglyoxylic acid, the main metabolites of styrene, in urine and styrene in blood. Gas chromatographic procedures

---

[a]Calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming normal temperature (25 °C) and pressure (101.3 kPa)

have been described for the quantitative determination of urinary phenylglyoxylic and mandelic acids which involve solvent extraction of the acids and their subsequent determination as derivatives by flame ionization detection on packed or capillary columns (Guillemin & Bauer, 1976; Flek & Šedivec, 1980; Bartolucci *et al.*, 1986; Dills *et al.*, 1991). High-pressure liquid chromatography is widely used for the determination of these metabolites. The acids may or may not be solvent extracted, are separated on reverse-phase columns and quantified with an ultraviolet detector (Ogata & Sugihara, 1978; Ogata & Taguchi, 1987, 1988; Chua *et al.*, 1993). Styrene has been determined in blood by gas chromatography with flame ionization or mass selective detection either after solvent extraction (Karbowski & Braun, 1978) or by head-space techniques (Pezzagno *et al.*, 1985; Bartolucci *et al.*, 1986; Brugnone *et al.*, 1993).

Measurement of adducts of styrene-7,8-oxide (see monograph, p. 328) to N-terminal valine in haemoglobin has been proposed for monitoring occupational exposure. After enrichment of adducted globin chains by ion-exchange chromatography, the samples are analysed by gas chromatography–mass spectrometry after Edman degradation (Christakopoulos *et al.*, 1993).

1.2 Production and use

1.2.1 *Production*

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; Lewis *et al.*, 1983; US National Institute for Occupational Safety and Health, 1983).

Styrene is produced mainly by catalytic dehydrogenation of high-purity ethylbenzene in the vapour phase. Typical catalysts are based on ferric oxide with the additives chromia (stabilizer) and potassium oxide (coke retardant) (Lewis *et al.*, 1983). Fractionation of the product results in separation of high-purity styrene, unconverted ethylbenzene and minor reaction by-products such as toluene and benzene (WHO, 1983).

A smaller amount of styrene is produced as a co-product from a propylene oxide process. In this route, ethylbenzene is oxidized to its hydroperoxide and reacted with propylene to yield propylene oxide. The co-product methyl phenyl carbinol is then dehydrated to styrene (Mannsville Chemical Products Corp., 1987; Collins & Richey, 1992). Limited data on production of styrene in Japan, Taiwan and the USA are presented in Table 1. Production levels in western Europe are similar to those in the USA, although specific data are not available. Global production of styrene in 1992 was 14 282 thousand tonnes (European Chemical Industry Council, 1994). Global production in the early 1980s was estimated at 10 000 thousand tonnes per year (WHO, 1983).

Information available in 1991 indicated that styrene was produced by nine companies in Japan, six each in China and the USA, five in France, four in Brazil, three each in Canada, Germany and the Republic of Korea, two each in Argentina, Bulgaria and the United Kingdom and one each in Australia, the former Czechoslovakia, Italy, Mexico, Poland, Saudi Arabia, Spain, the former USSR, Venezuela and the former Yugoslavia (Chemical Information Services Ltd, 1991).

Table 1. Production of styrene in selected regions (thousand tonnes)

Country or region	Year					
	1982	1984	1986	1988	1990	1992
Japan	1086	1421	1402	1733	2161	2182
Taiwan	NR	NR	243	331	355	338
USA	2695	3497	3578	4075	3636	4056[a]

From Anon. (1985, 1989a, 1993); Japan Petrochemical Industry Association (1993)
NR, not reported
[a]Preliminary

1.2.2 *Use*

Styrene is one of the most important monomers worldwide, and its polymers and copolymers are used in an increasingly wide range of applications. The major uses for styrene are in plastics, latex paints and coatings, synthetic rubbers, polyesters and styrene-alkyd coatings (Collins & Richey, 1992). The broad spectrum of uses includes construction, packaging, automotive and household goods (Mannsville Chemical Products Corp., 1987).

Packaging is the single largest use in which styrene-containing resins, particularly foams, are used as fillers and cushioning. Construction applications include pipes, fittings, tanks, lighting fixtures and corrosion-resistant products. Household goods include synthetic marble, flooring, disposable tableware and moulded furnishings. Transport applications range from tyres to reinforced plastics and automobile body putty (Mannsville Chemical Products Corp., 1987).

Most styrene is converted to polystyrene resins, which are readily moulded and are compatible with a range of colourants, modifiers and fillers. They are used extensively in the fabrication of plastic packaging, disposable beverage tumblers, toys and other moulded goods. Expandable polystyrene beads are used for disposable cups, containers and packaging as well as for insulation. Copolymers and adducts are the second largest family of styrene derivatives. Acrylonitrile–butadiene–styrene (ABS) and styrene–acrylonitrile resins have a variety of applications, including in appliance, automotive, construction, pipes and electronics mouldings (Mannsville Chemical Products Corp., 1987).

A variety of special resins have the styrene functionality. Styrene–butadiene rubber, used for tyres and other elastomer applications, is the largest volume synthetic rubber produced in the USA. Styrene–butadiene latex is used for carpet backing and paper processing. Styrene is the essential co-reactant and solvent in unsaturated polyesters used in reinforced plastic fabrications, including boats, corrosion-resistant tanks and pipes and automobile body parts (Mannsville Chemical Products Corp., 1987). Typical use patterns for styrene in the USA for several years are presented in Table 2. In Japan, the use patterns in 1993 were: polystyrene, 64%; acrylonitrile–butadiene–styrene resins, 10%; styrene–butadiene rubber, 7%; unsaturated polyesters, 5%; styrene–acrylonitrile, 4%; and other applications, 10% (Japan Petrochemical Industry Association, 1993).

Table 2. Use patterns (%) for styrene in the USA

Use	1983	1986	1989	1992
Polystyrene	52	55	55	54
Expandable polystyrene	–	–	–	12
Acrylonitrile–butadiene–styrene resins	9	9	10	10
Styrene–butadiene rubber	7	7	5	7
Styrene–butadiene latexes	6	6	5	6
Unsaturated polyester resins	6	6	5	–
Exports	15	13	13	–
Miscellaneous[a]	5	4	7	11[b]

From Anon. (1983, 1986, 1989b, 1992)

[a]Includes other copolymers and styrene–acrylonitrile

[b]Including unsaturated polyester resins, styrenated alkyds and acrylic ester–styrene copolymers

1.3 Occurrence

1.3.1 *Natural occurrence*

Styrene has been identified in trace amounts in the gummy exudate (storax balsam) from the damaged trunks of certain trees, probably from the natural degradation of the cinnamic acid derivatives that occur in large quantities in these exudates (Furia & Bellanca, 1971; Tossavainen, 1978; Duke, 1985).

1.3.2 *Occupational exposure*

The National Occupational Exposure Survey conducted by the National Institute for Occupational Safety and Health between 1981 and 1983 indicated that 1 112 000 US employees were potentially exposed to styrene at work (US National Institute for Occupational Safety and Health, 1993). The estimate is based on a survey of US companies and did not involve actual measurements of exposure.

Workers may be exposed in a number of industries and operations, including styrene production, production of polystyrene and other styrene-containing polymer resins, plastics and rubber products fabrication, fabrication of reinforced-polyester plastics composites and use of products containing styrene, such as floor waxes and polishes, paints, adhesives, putty, metal cleaners, autobody fillers and varnishes (US National Institute for Occupational Safety and Health, 1983).

(*a*) *Production of styrene and polystyrene*

Average exposure to styrene in styrene production and polymerization factories has been reported rarely to exceed 20 ppm [85 mg/m^3] and is usually due to occasional bursts and leakages of reactors, tubing and other equipment (Tossavainen, 1978). Surveys conducted in US plants engaged in the development or manufacture of styrene-based products between 1962 and 1976 showed that the average exposure of employees in all jobs was below 10 ppm

[43 mg/m^3]. Peak concentrations of up to 50 ppm [213 mg/m^3] were measured during the drumming of styrene. Batch polymerization of styrene in 1942 produced concentrations up to 88 ppm [375 mg/m^3] during filling operations; subsequent continuous polymerization processes generally resulted in exposure levels of 1 ppm [4.26 mg/m^3] or below (Ott *et al.*, 1980). In a US plant where styrene was produced and polymerized, the highest levels of styrene were found in polymerization, manufacturing and purification areas (mean, 8–35 ppm [34–149 mg/m^3]), while levels of less than 5 ppm [21 mg/m^3] occurred in maintenance, laboratory and packaging operations. Urinary mandelic acid and blood styrene were undetectable in most samples taken from these workers at the end of a shift: < 10 mg/g creatinine for mandelic acid (5 ng/ml) and < 2 ng/ml for styrene in blood. The maximal concentrations were 140 mg/g creatinine for mandelic acid and 90 ng/ml blood for styrene (Wolff *et al.*, 1978). In a German styrene production, polymerization and processing plant, samples taken in 1975–76 in various areas of the plant contained none (< 0.01 ppm [0.04 mg/m^3]) to 6.8 ppm [29 mg/m^3], most values being below 1 ppm [4.3 mg/m^3]. In a part of the plant where polystyrene was manufactured, area samples in 1975 contained from none (< 0.01 ppm [0.04 mg/m^3]) to 47 ppm [200 mg/m^3], most values being below 1 ppm. Of 67 employees engaged in either area of the plant, six had urinary concentrations of mandelic acid above 50 mg/L (Thiess & Friedheim, 1978).

Other substances that may be found in workplace air during the manufacture of styrene and polystyrene include benzene, toluene, ethylbenzene, other alkylbenzene compounds and ethylene (Ott *et al.*, 1980; Lewis *et al.*, 1983; US National Institute for Occupational Safety and Health, 1983). Exposure to benzene was previously a primary concern in these processes. In the US plant described above, the time-weighted average concentration of benzene in styrene monomer manufacture was 0.3–14.7 ppm [1–47 mg/m^3] between 1953 and 1972. Samples taken in 1942 during a washing operation in the polymerization plant contained up to 63 ppm [202 mg/m^3] (Ott *et al.*, 1980).

(*b*) *Production of styrene–butadiene rubber and other styrene-based polymers*

Concentrations of styrene in area samples and breathing-zone air measured in 1965 in various plants of a US styrene–butadiene latex manufacturing company (see above) were 4–22 ppm [17–94 mg/m^3]. The initial stages of the process, including loading, operating and cleaning of polymerization reactors, involved the most exposure, and operators in these job categories were found to be exposed to concentrations ranging from 3.6 to 7.3 ppm [15.3–31 mg/m^3] in 1973 (Ott *et al.*, 1980).

In two adjacent US plants where styrene–butadiene rubber was produced, the time-weighted average concentrations of styrene were 0.94 and 1.99 ppm [4 and 8.5 mg/m^3], with an overall range of 0.03–12.3 ppm [0.13–52.4 mg/m^3] (Meinhardt *et al.*, 1982). The mean concentration in 159 personal air samples taken in 1979 in various departments in another US styrene–butadiene rubber production plant were usually below 1 ppm [4.3 mg/m^3], except for factory service and tank farm workers, for whom the means were 1.69 and 13.67 ppm [7.2 and 58.2 mg/m^3], respectively (Checkoway & Williams, 1982). Company data provided by five out of eight US styrene–butadiene rubber plants for the period 1978–83 gave an average styrene level in 3649 samples from all plants of 3.53 ppm [15 mg/m^3], with a standard deviation of 14.3 ppm [61 mg/m^3] (Matanoski *et al.*, 1993).

In a US plant where acrylic ester–styrene copolymers [wrongly called polystyrene by the authors] were produced, concentrations in the breathing zone in 50 samples ranged from less than 1 ppb [4.3 μg/m^3] to 19.8 ppm [84 mg/m^3] with an average of [about 600 ppb; 2.5 mg/m^3]; the highest concentrations occurred during styrene unloading operations (Samimi & Falbo, 1982).

The numerous other substances to which workers may be exposed in these processes include 1,3-butadiene, acrylonitrile, acrylates, acrylic acid, α-methylstyrene (*meta*-vinyltoluene, see monograph, p. 373), 4-vinylcyclohexene (see monograph, p. 347), toluene, benzene, ammonia, formaldehyde, colourants and a variety of solvents (Ott *et al.*, 1980; Samimi & Falbo, 1982; US National Institute for Occupational Safety and Health, 1983).

(*c*) *Processing of styrene-based polymers*

Styrene was measured as a thermal degradation product in the air of a Finnish factory during the processing of polystyrene, impact polystyrene and acrylonitrile–butadiene–styrene resins. The mean concentrations (6 h) were 0.4, 0.1 and 0.06 mg/m^3, respectively (Pfäffli, 1982). Personal 8-h samples taken in 1978, 1979 and 1980 in US companies where acrylonitrile–butadiene–styrene moulding occurred contained < 0.01–[5.9] mg/m^3 (Burroughs, 1979; Belanger & Elesh, 1980; Ruhe & Jannerfeldt, 1980).

Styrene is one of the volatile organic compounds produced during extrusion and vulcanization of styrene–butadiene rubber. Rappaport and Fraser (1977) reported styrene at concentrations of 61–146 ppb [0.3–0.6 mg/m^3] in the curing area of the press room of a passenger car tyre manufacturing company. Area samples taken in the vulcanization and extrusion areas of shoe-sole, tyre retreading and electrical cable insulation plants contained styrene at concentrations of 2–500 μg/m^3 (vulcanization) and 0–20 μg/m^3 (extrusion) (Cocheo *et al.*, 1983). A more complete description of the work environment encountered in the rubber products manufacturing industry may be found in a previous monograph (IARC, 1982).

(*d*) *Manufacture of glass fibre-reinforced polyester products*

Occupational exposure to styrene is most extensive, with respect to number of workers and levels of exposure, in the fabrication of objects from glass fibre-reinforced polyester composite plastics, such as boats, tanks, wall panels, bath and shower units and automotive parts (US National Institute for Occupational Safety and Health, 1983). 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 fibre glass 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 (US National Institute for Occupational Safety and Health, 1983; Crandall & Hartle, 1985). Exposure to styrene in this industry has been extensively documented and summarized in several reports (US National Institute for Occupational Safety and Health, 1983; WHO, 1983; Pfäffli & Säämänen, 1993). Table 3 lists levels of occupational exposure to styrene (personal breathing zone samples)

reported in various countries in the larger studies. Table 4 gives the concentrations of the classical biological indicators of exposure from various studies.

Several factors influence the level of styrene in air. The manufacture of objects with large surface areas, such as boats, truck parts, baths and showers, by the open-mould process results in the highest exposure. Data from 28 plants producing reinforced plastics products in the USA showed that the average exposure to styrene in open-mould processes was two to three times higher than that in press-mould processes: 24–82 ppm [102–350 mg/m^3] *versus* 11–26 ppm [47–111 mg/m^3] (Lemasters *et al.*, 1985a). In a detailed survey of 12 plants making fibreglass in Washington State, USA, 40% of 8-h samples contained more than 100 ppm [426 mg/m^3]. Chopper gun operators had the highest exposure, followed by laminators and gel-coat applicators; boat-building involved higher exposures than any other sector. A relationship was seen between level of exposure and the quantity of resin used by an employee (Schumacher *et al.*, 1981). Essentially similar results were reported by Sullivan and Sullivan (1986) in their survey of 10 plants in Ontario, Canada. They also found that dilution ventilation and often auxiliary fans were used in almost all plants, but there was little use of local exhaust ventilation. This was also the case for boat construction in the USA. Gel coaters have lower exposure because they generally work in ventilated booths (Crandall & Hartle, 1985). The presence of flexible exhaust ventilation hoses was reported to reduce styrene concentrations by a factor of two in a boat construction company in Japan (Ikeda *et al.*, 1982). So-called 'low-styrene emission resins' are in theory promising for reducing exposure, but their potential to do so in the workplace has not been sufficiently validated and they are not widely used (A.D. Little, Inc., 1981; Sullivan & Sullivan, 1986; Säämänen *et al.*, 1993).

Measurement of biological indicators of exposure complements the picture based on air levels because biological levels incorporate the influence of other routes of absorption and of the use of personal protective equipment. Despite early reports that percutaneous absorption of styrene was an important source 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 makes a negligible contribution to overall exposure in the manufacture of glass fibre-reinforced polyester products (Brooks *et al.*, 1980; Bowman *et al.*, 1990; Truchon *et al.*, 1992). Wearing a respirator appropriate for organic vapours reduces exposure markedly, but not entirely (Brooks *et al.*, 1980; Ikeda *et al.*, 1982; Bowman *et al.*, 1990; Truchon *et al.*, 1992). Respirators are worn most often by gel-coat and chopper gun operators but not by laminators, who consider that they hinder their work (Truchon *et al.*, 1992). Single-use dust respirators, which provide unsatisfactory protection, were often the only type of protection worn (Schumacher *et al.*, 1981; Sullivan & Sullivan, 1986).

Other substances may be found in workplace air in plants for the production of unsaturated polyester reinforced plastics, although at levels usually considerably lower than that of styrene. These include: solvents, mainly used to clean tools and equipment, such as ketones (e.g. acetone), chlorinated hydrocarbons (e.g. dichloromethane), aliphatic alcohols and esters and aromatic hydrocarbons; organic peroxides used as initiators (e.g. methylethyl ketone peroxide, benzoyl peroxide); styrene oxide and other oxidation products resulting from the reaction of peroxides with styrene; hydroquinone and analogues used as inhibitors (e.g. hydroquinone, quinone, catechol); dusts and fibres originating mainly from filler and

Table 3. Occupational exposure to styrene in the fibre glass-reinforced plastics industry in various countries

Country and year of survey	No. of plants	Job/task	Duration of sampling	No. of samples	Air concentration in personal breathing zone (mg/m^3)		Reference
					Mean	Range	
Canada (Ontario)	10	All jobs	25 min	126	[< 4.3–716][a]	[< 4.3–1393]	Sullivan & Sullivan (1986)
1981		Boat laminating		59	[430] GM	[8.1] GSD	
		Non-boat laminating		23	[123] GM	[29.4] GSD	
		Chopper gun use		8	[554] GM	[7.7] GSD	
		Gel-coat spraying		6	[298] GM	[7.7] GSD	
		Filament winding		3	[533] GM	[6.0] GSD	
Canada (Quebec)	3	Chopper gun use	8-h	7	564	307–938	Truchon *et al.* (1992)
NR		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	
Denmark							Jensen *et al.* (1990)
1955–70	30	NR	1–60 min	227	714	10–4700	
1971–80	97	NR		1117	274	4–1905	
1981–88	129	NR		1184	172	1–4020	
Italy	87	Hand laminating	Variable	1028	227		Galassi *et al.* (1993)
1978–90		Spray laminating		166	134		
		Rolling		40	163		
		Semi-automatic process operators		71	85		
		Non-process work		159	71 (38 GM)	3.8 GSD	
Italy	10	NR	8 h	64 subjects	113.6 GM	8–770.4	Gobba *et al.* (1993)
NR							

Table 3 (contd)

Country and year of survey	No. of plants	Job/task	Duration of sampling	No. of samples	Air concentration in personal breathing zone (mg/m^3)		Reference
					Mean	Range	
Japan	5	Boat fabrication	4 h				Ikeda *et al.* (1982)
NR		Hull lamination		25	[507] GM	[145–1091]	
		Hull lamination with local exhaust ventilation		9	[277] GM	[196–383]	
		Lamination of hold walls		25	[537] GM	[371–916]	
Switzerland	10	NA	Full shift	90	[201]	[8–848]	Guillemin *et al.* (1982)
NR							
Netherlands	4	Filament winding	4 h	18	NR	134–716	Geuskens *et al.* (1992)
NR		Spraying		62	NR	48–602	
		Hand laminating		180	NR	18–538	
USA	7	Boat fabrication	Full shift				Crandall & Hartle (1985)
NR		Hull lamination		168	[331]	[7–780]	
		Deck lamination		114	[313]	[52–682]	
		Small parts lamination		70	[193]	[34–554]	
		Gel coating		45	[202]	[23–439]	
Europe (5 countries)[f]		Lamination	Variable				Bellander *et al.* (1994)
< 1980		Boat fabrication		1703	[332]		
≥ 1980				2993	[234]		
< 1980		Containers		437	[247]		
≥ 1980				1098	[187]		
< 1980		Panels and construction		401	[213]		
≥ 1980				846	[145]		
< 1980		Small pieces		486	[251]		
≥ 1980				629	[158]		
≥ 1980		Hand lamination		3205	[281]		
≥ 1980		Spray lamination		414	[132]		
≥ 1980		Non-manual lamination		231	[68]		
1955–90							

Table 3 (contd)

Country and year of survey	No. of plants	Job/task	Duration of sampling	No. of samples	Air concentration in personal breathing zone (mg/m^3)		Reference
					Mean	Range	
USA 1967–78	30	Spray-up/lay-up Gel-coating Winding Sheet-moulding compound production Foaming Mixing Casting Cut, press and weigh Other jobs[d]	8 h TWA	NR	[256][c] [192] [170] [170] [128] [107] [85] [64] [≤ 43]	[21–511] [43–256] [64–362] [43–341] [64–213] [9–341] [21–192] [21–341] [0–213]	A.D. Little, Inc. (1981)

GM, geometric mean; GSD, geometric standard deviation; NR, not reported

[a]Range of arithmetic means for different plants

[b]Italian plants reported by Galassi *et al.* (1993) and Finland, Norway, Sweden and the United Kingdom

[c]Typical level

[d]Includes general and non-production, finish and assembly, store and ship, office and other, injection moulding, field service, preform production and pultrusion

Table 4. Occupational exposure to styrene in the fibre glass-reinforced plastics industry

Country and year of survey	No. of plants	Job/task	No. of samples	Concentrations at end of shift						Reference
				Mandelic acid in urine (mg/g creatinine)		Phenylglyoxylic acid in urine (mg/g creatinine)		Styrene in blood (mg/L)		
				Mean	SD	Mean	SD	Mean	SD	
Canada (Québec) NR	3	Chopper gun operation	7	[980]	[980]					Truchon *et al.* (1992)
		Painting (gel coat)	9	[750]	[310]					
		Laminating (rolling)	18	[1690]	[605]					
		Foreman	8	[350]	[470]					
		Cutting	11	[320]	[380]					
		Warehouse worker	19	[70]	[70]					
		Finishing	31	[110]	[120]					
		Mould repair	8	[30]	[50]					
Germany 1980, 1983	1	Boat industry	11	816–1660[a]		200–342[a]		0.70–0.92[a]		Triebig *et al.* (1989)
Italy NR	4	Refrigerating containers	6	493	434	121	96	0.32	0.42	Bartolucci *et al.* (1986)
		Flooring tiles	6	428	248	72	22	0.42	0.16	
		Fibre-glass canoes	5	270	54	62	24	0.52	0.32	
		Fibre-glass tanks	3	323	129	132	41	NR		
Italy 1978–90	118	Hand lamination	2386	450 GM	2.75 GSD					Galassi *et al.* (1993)
		Spray lamination	250	211 GM	3.3 GSD					
		Rolling	63	182 GM	3.08 GSD					
		Semiautomatic process operation	121	154 GM	2.59 GSD					
		Non-process work	762	94 GM	3.27 GSD					
Switzerland NR	10	NR	88	1004	1207	339	360			Guillemin *et al.* (1982)
United Kingdom 1979	1	Boat industry	27	[780]	555			[0.72]	[0.43]	Cherry *et al.* (1980)

NR, not reported; GM, geometric mean; GSD, geometric standard deviation
[a]Range of means for different days

reinforcement materials (e.g. glass fibres, silica, asbestos); foaming agents such as isocyanates; and cobalt salts and amines used as accelerators (Pfäffli *et al.*, 1979; A.D. Little, Inc., 1981; Makhlouf, 1982; Högstedt *et al.*, 1983; US National Institute for Occupational Safety and Health, 1983; Coggon *et al.*, 1987; Jensen *et al.*, 1990; Bellander *et al.*, 1994). Table 5 gives the concentrations of such substances measured in studies covering several plants in various countries.

Acetone, used extensively as a cleaning solvent, is the major concurrent exposure with styrene. In the study of A.D. Little, Inc. (1981), involving industrial hygiene surveys in 30 US plants, maximal levels of various typical concomitant exposures were reported for five of the plants (Table 5). The following substances were not detected or were reported as zero concentration: benzene, hydrogen fluoride, arsine, phosphine, stibine, formaldehyde, acetaldehyde, acetic acid, hydrochloric acid, free silica and cresol. The concomitant exposures generally occurred at concentrations orders of magnitude lower than those permitted by the US Occupational Safety and Health Administration. Benzene was not reported in any of 2528 air samples containing styrene in the Danish work environment (Jensen *et al.*, 1990).

(*e*) *Miscellaneous operations*

In a study of exposures of firefighters, samples taken during the 'knockdown' phase of a fire contained styrene at a 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 US hazardous waste site in 1983, a mean styrene concentration of 235 μg/m^3 was associated with heavy exposure; 100 μg/m^3 were measured near use of heavy equipment, but none was detected in 45 other samples (maximum, 678 μg/m^3) (Costello, 1983). During the manufacture of polyester paints, lacquers and putties in Finland, occasional high exposure to styrene was recorded, with 5% of measurements above 20 ppm [85 mg/m^3]; use of the same products resulted in exposures below 1 ppm [4.3 mg/m^3] (Säämänen *et al.*, 1991). Application of polyester putty during cable splicing operations for a US telephone company resulted in short-term levels (3–16 min) ranging from 2 to 16 ppm [8.5–68 mg/m^3] in four samples (Kingsley, 1976). In a Japanese plant where plastic buttons were manufactured from polyester resins, the 8-h time-weighted average concentration of styrene for 34 workers was 7.1 ppm [30 mg/m^3], with a maximum of 28 ppm [119 mg/m^3] (Kawai *et al.*, 1992).

Four 100-min air samples taken in 1982 at a US college during a sculpture class in which polyester resins were used contained concentrations ranging from 0.8 to 1.2 ppm [3.4–5.1 mg/m^3]; two personal samples contained 2.8 and 3.0 ppm [11.9 and 12.8 mg/m^3]. The concentration of methyl ethyl ketone peroxide was below the detection limit (< 0.02 ppm) (Reed, 1983).

Taxidermists who used polyester resins during specimen preparation were shown to be exposed for short periods (2–15 min) to concentrations of styrene ranging from 21 to 300 mg/m^3 (11 samples) (Kronoveter & Boiano, 1984a,b).

In two US cooking ware manufacturing companies where styrene-based resins were used, the 8-h time-weighted concentrations of styrene ranged from 0.2 to 81 ppm [0.9–

Table 5. Concentrations of substances other than styrene in workplace air in the reinforced plastics industry

Country	No. of plants	Substance	Concentration	Reference
Denmark	256 (2528 samples)	Acetone	Mean, 131 mg/m^3 (in 90% of samples)	Jensen *et al.* (1990)
		Dichloromethane	Mean, 51 mg/m^3 (in 8% of samples)	
		Xylene	Mean, 49 mg/m^3 (in 6% of samples)	
		Toluene	Mean, 113 mg/m^3 (in 5% of samples)	
		Tetrachloroethylene	Mean, 7 mg/m^3 (in 2% of samples)	
		Trichloroethylene	Mean, 5 mg/m^3 (in 1% of samples)	
		Isododecane	Mean, 4 mg/m^3 (in 2% of samples)	
Switzerland	10	Acetone	10–300 ppm [24–720 mg/m^3]	Guillemin *et al.* (1982)
		Peroxides	'Background'	
		Dust	0.5–2.5 mg/m^3 (peak, 12 mg/m^3)	
		Glass fibres	0.05 fibres/ml (peak, 1 fibre/ml)	
USA	5	Acetone	ND–59 ppm [ND–142 mg/m^3] max (5 plants)	A.D. Little, Inc. (1981)
		Dichloromethane	ND–15 ppm [ND–52 mg/m^3] max (2 plants)	
		Toluene	1.5–35 ppm [5.7–132 mg/m^3] max (2 plants)	
		Vinyl toluene	< 0.02–70 ppm [< 0.1–338 mg/m^3] max (2 plants)	
		Carbon monoxide	0–< 5 ppm [0–< 5.7 mg/m^3] max (2 plants)	
		Xylene	2 ppm [8.7 mg/m^3] max (1 plant)	
		Mineral spirits	30 ppm max (1 plant)	
		Hexane	10 ppm [32 mg/m^3] max (1 plant)	
		Benzyl chloride	0.7 ppm [3.6 mg/m^3] max (1 plant)	
		Cyclohexanone	5 ppm [20 mg/m^3] max (1 plant)	
		Quinone	0.03 ppm [0.13 mg/m^3] max (1 plant)	
		Epichlorohydrin	Trace (1 plant)	
		Toluene diisocyanate	0.007 ppm [0.05 mg/m^3] max (1 plant)	
		Methylene diisocyanate	0.0009 ppm [0.004 mg/m^3] max (1 plant)	
		Nuisance dust	4.5–< 6 mg/m^3 max (2 plants)	
		Chromium	0.01 mg/m^3 max (1 plant)	
		Cobalt	0.001 mg/m^3 max (1 plant)	
Finland	10	Acetone	78 ppm (3–565 ppm) [187 (7.2–1356 mg/m^3)]	Pfäffli *et al.* (1992)
		Peroxides	0.05 ppm	
		Dimethylphthalate	0.1 mg/m^3	
		Total dust	< 5 mg/m^3	
Finland	2	Acetophenone	0.47 ppm [2.3 mg/m^3]	Pfäffli *et al.* (1979)
		Benzaldehyde	0.48 ppm [2.1 mg/m^3]	
		Styrene oxide	< 1 mg/m^3	See monograph, p. 323

ND, not detected

345 mg/m^3]; two short-duration samples (24 min) contained 142 and 186 ppm (605 and 792 mg/m^3] (Fleeger & Almaguer, 1988; Barsan *et al.*, 1991).

1.3.3 *Air*

Styrene has been detected in the atmosphere in many locations. Its presence in air is due principally 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 forms of combustion and incineration of styrene polymers (WHO, 1983).

Styrene emissions reported to the European Union by member countries (Bouscaren *et al.*, 1987) are shown in Table 6. Air emissions in the USA, reported to the US Environmental Protection Agency by industrial facilities, declined from 15 580 tonnes in 1989 to 12 900 tonnes in 1991 (US National Library of Medicine, 1993b). Ambient air levels of styrene sampled in the vicinity of seven reinforced plastic processors in three US states ranged from 0.29 to 2934 μg/m^3, and those in communities near the processors from not detected (< 0.15 μg/m^3) to 23.8 μg/m^3 (McKay *et al.*, 1982). 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 < 0.1 μg/m^3 (Hampton *et al.*, 1983).

Table 6. Estimated emissions of styrene in member countries of the European Union (thousand tonnes/year)

Country	Source	
	Road (gasoline)	Chemical industry
Belgium	0.5	0.75
Denmark	0.28	NR
France	2.9	3.4
Germany	2.9	3.4
Greece	0.5	N
Ireland	0.19	NR
Italy	3.0	3.5
Luxembourg	0.02	0.03 (other sources)
Netherlands	0.7	1.45
Portugal	0.5	0.3
Spain	2.0	1.2
United Kingdom	3.0	3.7
Total	16.0	18.0

From Bouscaren *et al.* (1987); NR, not reported

Except in highly polluted areas, styrene concentrations in outdoor air are generally < 1 μg/m^3. In indoor air, e.g. mobile homes, the mean concentrations are frequently somewhat higher (< 1–6 μg/m^3), smoking making a significant contribution (Connor *et al.*,

1985; Wallace *et al.*, 1987a,b; Shah & Singh, 1988; Weschler *et al.*, 1992). The styrene content of cigarette smoke has been reported to be 18–48 μg/cigarette (WHO, 1983). Off-gassing of styrene from some styrene-containing household products may also contribute to indoor air levels (Knöppel & Schauenburg, 1989).

Styrene levels in ambient air were determined in a survey of 18 sites (mostly urban) in Canada in 1988–90. The mean concentrations in 586 24-h samples ranged from 0.09 to 2.35 μg/m^3. 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-h concentration was < 0.48 μg/m^3 (limit of detection); individual values ranged up to 129 μg/m^3 (average, 0.28 μg/m^3) (Newhook & Caldwell, 1993).

Thermal degradation of styrene-containing polymers also releases styrene into ambient air (Hoff *et al.*, 1982; Lai & Locke, 1983; Rutkowski & Levin, 1986). Gurman *et al.* (1987) reported that styrene monomer is the main volatile product of the thermal decomposition of polystyrene, comprising up to 100% of the volatiles.

In order to illustrate the relative significance of various sources of exposure to styrene, Fishbein (1992) approximated exposure levels in several environments and compared nominal daily intakes from those sources (Table 7).

Table 7. Estimated daily intake of styrene from different sources of exposure

Source	Estimated concentration	Nominal daily intake[a]
Reinforced plastics industry	200 000 μg/m^3	2 g
Styrene polymerization	10 000 μg/m^3	100 mg
Within 1 km of a production unit	30 μg/m^3	600 μg
Polluted urban atmosphere	20 μg/m^3	400 μg
Urban atmosphere	0.3 μg/m^3	6 μg
Indoor air	0.3–50 μg/m^3	6–1000 μg
Polluted drinking-water (2 L/day)	1 μg/L	2 μg
Cigarette smoke (20 cigarettes/day)	20–48 μg/cigarette	400–960 μg

From Fishbein (1992)

[a]Calculated on the assumption of a daily respiratory intake of 10 m^3 at work and 20 m^3 at home or in an urban atmosphere

1.3.4 *Water*

Although styrene has been detected occasionally in estuaries and inland waters and in drinking-water, its presence is usually traceable to an industrial source or to improper disposal (WHO, 1983; Law *et al.*, 1991). In surveys of Canadian drinking-water supplies, the frequency of detection of styrene was low; when detected, it was generally at a concentration of < 1 μg/L (Newhook & Caldwell, 1993).

1.3.5 *Food*

Polystyrene and its copolymers have been used widely as food packaging materials, and residual styrene monomer can migrate into food from the packaging (WHO, 1983). Analysis

of styrene in 133 plastic food containers from retail food outlets in the United Kingdom showed concentrations ranging from 16 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 < 1 to 200 μg/kg, although 77% of the foods had levels below 10 μg/kg and 26% had levels below 1 μg/kg (Gilbert & Startin, 1983).

Styrene has been detected as a natural constituent of a wide range of foods and beverages, the highest measured levels occurring in cinnamon (Maarse, 1992a,b; Steele, 1992). Enzymatic degradation of cinnamic acid derivatives was proposed as a possible source (Oliviero, 1906; Ducruet, 1984).

1.4 Regulations and guidelines

1.4.1 *Occupational exposure limits*

Occupational exposure limits and guidelines for styrene are presented in Table 8. A tolerable daily intake of 7.7 μg/kg bw for styrene has been established by WHO (1993), with a guideline value of 20 μg/L in drinking-water. The US Environmental Protection Agency (1993) has set the drinking-water standard for styrene at 0.1 ppm (100 μg/L).

Table 8. Occupational exposure limits and guidelines for styrene

Country or region	Year	Concentration (mg/m^3)	Interpretation
Argentina	1991	215	TWA
		425	STEL (15 min)
Australia	1983	215	TWA
		425	STEL
Austria	1982	420	TWA
Belgium	1984	215	TWA; skin
		425	
Brazil	1978	328	TWA
Bulgaria	1984	5	TWA
Canada	1986	215	TWA; skin
		425	STEL
Chile	1983	172	TWA
China	1981	40	TWA
Czechoslovakia	1985	200	TWA
		1000	STEL
Denmark	1988	105	TWA
Finland	1993	85	TWA
		420	STEL
France	1990	215	TWA
Germany	1993	85	TWA; substance with systemic effects (onset < 2 h)[a]
Hungary	1978	50	TWA; suspected of having carcinogenic potential; irritant
		100	Ceiling
India	1983	420	TWA
		525	STEL

Table 8 (contd)

Country or region	Year	Concentration (mg/m^3)	Interpretation
Indonesia	1978	420	Ceiling
Italy	1978	300	TWA
Japan	1983	210	TWA
Mexico	1984	215	TWA
		425	STEL
Netherlands	1986	420	TWA
Poland	1982	100	TWA
Romania	1975	250	Average
		350	Maximum
Sweden	1991	90	TWA; skin
		200	STEL (15 min)
Switzerland	1987	215	TWA; provisional[a]
Taiwan	1981	420	TWA
United Kingdom	1992	420	TWA; maximum exposure limit
		1050	STEL (10 min)
USA			
ACGIH (TLV)	1994	213	TWA; skin
		426	STEL
OSHA (PEL)	1992	426	TWA
		852	Ceiling
		2556	AMP
NIOSH (REL)	1992	215	TWA
		425	Ceiling
Venezuela	1978	420	TWA
		525	Ceiling

From Cook (1987); Arbejdstilsynet (1988); ILO (1991); US Occupational Safety and Health Administration (OSHA) (1992); US National Institute for Occupational Safety and Health (NIOSH) (1992); American Conference of Governmental Industrial Hygienists (ACGIH) (1993); Deutsche Forschungsgemeinschaft (1993); Työministeriö (1993); UNEP (1993)

TWA, time-weighted average; STEL, short-term exposure limit; TLV, threshold limit value; AMP, acceptable maximum peak above the acceptable ceiling concentration for an 8-h shift for 5 min in any 3 h; PEL, permissible exposure level; REL, recommended exposure level; skin, absorption through the skin may be a significant source of exposure

[a]There is no reason to fear a risk of damage to the developing embryo or fetus when exposure limits are adhered to (Group C).

The US Food and Drug Administration (1993) has established regulations for the use of polymers and copolymers of styrene in products in contact with food. 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%.

1.4.2 *Reference values for biological monitoring of exposure*

The relationship between external (air concentrations) and biological measures of exposure has been studied more extensively for styrene than for most other organic compounds in the occupational environment. Correlations between the concentration of

styrene in air and in venous blood and with mandelic acid and phenylglyoxylic acid in urine have been described by a number of investigators and reviewed by Guillemin and Berode (1988), the American Conference of Governmental Industrial Hygienists (1993), Lauwerys and Hoet (1993) and Pekari *et al.* (1993).

For example, the concentration of mandelic acid in urine that corresponds to inhalation of 50 ppm styrene (213 mg/m^3) for 8 h would be 800–900 mg/g creatinine at the end of a shift and 300–400 mg/g creatine the following morning (Droz & Guillemin, 1983; Guillemin & Berode, 1988; Pekari *et al.*, 1993). The phenylglyoxylic acid concentration in urine that corresponds to an 8-h exposure to 50 ppm styrene would be expected to be 200–300 mg/g creatinine at the end of a shift and about 100 mg/g creatinine the following morning (American Conference of Governmental Industrial Hygienists, 1991; Pekari *et al.*, 1993). The styrene concentration in blood that corresponds to an 8-h exposure at 50 ppm styrene would be expected to be 0.5–1 mg/L at the end of a shift and about 0.02 mg/L in blood the following morning (Guillemin & Berode, 1988; American Conference of Governmental Industrial Hygienists, 1991).

Each year, the American Conference of Governmental Industrial Hygienists (1993) and the Deutsche Forschungsgemeinschaft (1993) publish biological reference values for use in interpreting the results of biological monitoring for styrene in the workplace. The results must be interpreted in relation to the different definitions of those reference values. Biological exposure indices are reference values intended for use as guidelines for evaluating potential health hazards in the practice of industrial hygiene. The indices represent the levels of the determinants that are most likely to be observed in specimens collected from healthy workers exposed by inhalation to air concentrations at the level of the threshold limit value (American Conference of Governmental Industrial Hygienists, 1993). The biological tolerance value for a working material is defined as the maximal permissible quantity of a chemical compound or its metabolites, or any deviation from the norm of biological parameters induced by those substances in exposed humans. According to current knowledge, these conditions generally do not impair the health of an employee, even if exposure is repeated and of long duration. Biologische arbeitsstofftoleranzwerte (BAT) values are defined as ceiling values for healthy individuals (Deutsche Forschungsgemeinschaft, 1993). Biological monitoring reference values for exposure to styrene, based on styrene metabolite levels in urine or styrene in blood, are given in Table 9.

2. Studies of Cancer in Humans

2.1 Case reports

Cases of leukaemia and lymphoma were identified among workers engaged in the production of styrene–butadiene rubber (Lemen & Young, 1976), in the manufacture of styrene–butadiene (Block, 1976) and in the manufacture of styrene and polystyrene (Nicholson *et al.*, 1978). A total of 19 cases of leukaemia and eight of lymphoma were reported in these studies. Exposure to benzene, butadiene, ethyl benzene and other chemicals could also have occurred in these operations.

Table 9. Reference values for biological monitoring of exposure to styrene

Determinant	Sampling time	Biological exposure index[a]	BAT[b]
Mandelic acid in urine	End of shift	800 mg/g creatinine[c]	2000 mg/L
	Prior to next shift	300 mg/g creatinine[c]	Does not apply
Phenylglyoxylic acid in urine	End of shift	240 mg/g creatinine[c]	Does not apply
	Prior to next shift	100 mg/g creatinine[c]	Does not apply
Mandelic acid plus phenylglyoxylic acid in urine	End of shift	Does not apply	2500 mg/L
Styrene in venous blood	End of shift	0.55 mg/L[d]	
	Prior to next shift	0.02 mg/L[d]	Does not apply

[a]American Conference of Governmental Industrial Hygienists (1993)
[b]Biologische arbeitsstofftoleranzwerte; Deutsche Forschungsgemeinschaft (1993)
[c]Nonspecific, as it is also observed after exposure to other chemicals such as ethylbenzene
[d]Semiquantitative, because of short half-life of styrene in blood

2.2 Cohort studies

2.2.1 *Styrene–butadiene rubber manufacture*

The mortality of workers engaged in the rubber industry in the USA, where there is potential exposure to styrene, among other chemicals, has been investigated in a number of studies (Andjelkovic *et al.*, 1976; McMichael *et al.*, 1976; Monson & Nakano, 1976; Andjelkovic *et al.*, 1977; Matanoski *et al.*, 1990). Several showed elevated standardized mortality ratios (SMRs) for cancers at various sites. All of these studies are described in detail in previous *IARC Monographs* (IARC, 1979, 1982, 1986, 1987a, 1992). In the only study (McMichael *et al.*, 1976) in which exposure to styrene–butadiene was specified, an association (relative risk [RR], 6.2; 99.9% confidence interval [CI], 4.1–13) between lymphatic and haematopoietic malignancies and work in the styrene–butadiene rubber manufacture department of a rubber plant was suggested.

A retrospective cohort study (Meinhardt *et al.*, 1982) was conducted in two plants where styrene–butadiene rubber was produced (plants A and B) in eastern Texas, USA, which included 1662 (plant A) and 1094 (plant B) white men who had been employed for at least six months (total, 53 929 person-years at risk). Follow-up was from 1943 to 1976 (plant A) and from 1950 to 1976 (plant B). The study was conducted after the initial finding of two cases of lymphatic and haematopoietic cancer at one of the plants. Environmental samples were taken only at the time of the study: mean exposures to styrene were 0.94 ppm at plant A (4 mg/m^3) and 1.99 ppm (8.5 mg/m^3) at plant B; those for 1,3-butadiene were 1.24 ppm (2.74 mg/m^3) and 13.5 ppm (30 mg/m^3), respectively. Traces of benzene were also detected in plant A. The SMR for all causes of death was 80 [95% CI, 70–90] for workers in plant A, and nine deaths from cancers of the lymphatic and haematopoietic tissues occurred between January 1943 and March 1976 (5.79 expected), giving an SMR of 155 [95% CI, 71–295]. Further analysis showed that these nine men had been employed between January 1943 and December 1945 during operation of a batch process, for which period the expected number

was 4.3, giving an SMR of 212 [95% CI, 97–402]. The SMR for leukemias was 278 [95% CI, 90–648]. In plant B no significant excess mortality from any cancer was found: 11 cancer deaths were observed and 21 expected; there were two deaths from neoplasms of lymphatic and haematopoietic tissues (2.6 expected).

Matanoski *et al.* (1990) studied a cohort of 12 110 male workers in the USA and Canada who had worked for a minimum of one year in any of eight plants where styrene–butadiene rubber was manufactured. Limited information on exposure was available: the average exposure to styrene in five of the eight plants ranged between 0.29 and 6.66 ppm [1.23–28.4 mg/m^3] (mean, 3.53 ppm [15 mg/m^3]) for the period 1978–83 (Matanoski *et al.*, 1993). The subcohorts at each plant were followed from various times between 1943 and 1982, for a total of 251 431 person-years of follow-up. Vital status was known for 96.6% of the workers, and by the end of the study 20% of the cohort had died. SMRs were calculated from country- and race-specific mortality rates. The SMR for all cancers was 0.85 (95% CI, 0.78–0.93), and no significant excess for cancer at any site was observed for the total cohort. An examination of specific causes of death in the subset of workers involved in production (adjusted for age, ethnicity and calendar year) showed an excess of all lymphatic and haematopoietic neoplasms in the subgroup of 371 black production workers (SMR, 5.1; 6 observed; 95% CI, 1.9–11). Three of the maligancies were leukaemias (SMR, 6.6; 95% CI, 1.4–19). These results were questioned (Cole *et al.*, 1993), because in one plant no records were available for active workers and in another plant ethnicity was not designated on all records (Matanoski *et al.*, 1993). When those two plans were omitted, the SMR for leukaemia in black production workers was 8.3 (Matanoski *et al.*, 1993).

A case–control study of 59 cases of lymphohaematopoietic cancer (Santos-Burgoa *et al.*, 1992) was conducted within the US cohort studied by Matanoski *et al.* (1990). A total of 193 controls were matched to cases by plant, age, year of employment, duration of employment and survival of the case. Each job was assigned an estimated exposure to styrene and 1,3-butadiene by a panel of experts in the rubber industry, who ranked jobs from low to high. Analysis showed an association between leukaemia and exposure to 1,3-butadiene (odds ratio, 9.4; 95% CI, 2.1–23) and a nonsignificant association with exposure to styrene (odds ratio, 3.1; 95% CI, 0.84–11). When exposures to both styrene and 1,3-butadiene were included in a conditional logistic regression model, the odds ratio for 1,3-butadiene remained elevated (7.4; 95% CI, 1.3–41), but the estimated association of leukaemia with styrene was decreased (odds ratio, 1.1; 95% CI, 0.23–5.0). Because of criticism about the use of controls matched for duration of work, a new set of three controls per case was selected and matched on all previously matched variables except duration of work (Matanoski *et al.*, 1993). Exposure to styrene was not significantly associated with lymphatic and haematopoietic cancers, whereas the association with exposure to 1,3-butadiene remained significant.

2.2.2 *Styrene manufacture and polymerization*

A study by Frentzel-Beyme *et al.* (1978) of 1960 German workers engaged in the manufacture of styrene and polystyrene between 1931 and 1976 for a minimum of one month showed no significant excess mortality from cancer. The cohort had accumulated only 20 138 person-years. Follow-up was 93% of the German workers but only 29% of non-German

workers. There were 74 deaths (96.5 expected) available for analysis. One death from lymphatic and haematopoietic cancer was observed, with less than one expected. In 1975, concentrations of styrene in the plant were generally below 1 ppm [4.3 mg/m^3], but higher concentrations were occasionally recorded (Thiess & Friedheim, 1978). [The Working Group noted that insufficient information was provided to assess the risk for cause-specific deaths by exposure period or duration of exposure.]

Ott *et al.* (1980) studied a cohort assembled from four US plants where styrene-based products were developed and produced. Exposure to styrene varied by process. During batch polymerization in 1942, the styrene concentrations were 5–88 ppm [21–375 mg/m^3]; in continuous polymerization and extrusion units, the concentrations were below 10 ppm [43 mg/m^3] and generally below 1 ppm in 1975 and 1976. Cohorts from each plant had been exposed between 1937 and 1960 and were followed from 1940 to 1975. Other potential exposures included benzene, acrylonitrile, 1,3-butadiene, ethylbenzene, dyes and pigments. Age- and race-specific US mortality rates were used to calculate the expected numbers of deaths. A total of 2904 workers with a minimum of one year of employment were followed, of whom 303 had died (425.0 expected). A total of 58 cancer deaths were observed, whereas 76.5 were expected. Seven were from lymphatic and haematopoietic cancers, except leukaemia (SMR, 132 [95% CI, 58–272]), and six were from leukaemia (SMR, 176 [95% CI, 64–383]). Bond *et al.* (1992) updated the study, adding a further 11 years of observations. A total of 687 deaths were reviewed; again, mortality from all causes and all neoplasms was lower that expected (overall SMR, 76 [95% CI, 70–82]; cancer SMR, 81; 95% CI, 69–95), and 28 of the deaths were due to lymphatic and haematopoietic malignancies (SMR, 144; 95% CI, 95–208). There were five cases of lymphatic and haematopoietic cancer (3.9 expected) among workers in the styrene monomer and finishing areas and five multiple myelomas (1.7 expected), six leukaemias (3.6 expected) and four non-Hodgkin's lymphomas (2.9 expected) in the polymerization, colouring and extrusion department.

Hodgson and Jones (1985) reported on 622 men who had worked for at least one year in the production, polymerization and processing of styrene at a plant in the United Kingdom between 1945 and 1978. Of these, 131 men were potentially exposed to styrene in laboratories and 491 in production of styrene monomer, polymerization of styrene or manufacture of finished products. No measurements of exposure were provided, but many other chemicals were present in the working environment. Expected numbers of deaths were calculated on the basis of national rates. There were 34 deaths (43.1 expected) among the 622 exposed workers. A significant excess of deaths from lymphoma (3 observed, 0.56 expected) was observed. An analysis of cancer registrations for this population revealed an additional case of lymphatic leukaemia, giving a total of four incident cases of lymphatic and haematopoietic cancer, whereas 1.6 would have been expected from local cancer registration rates [standardized incidence ratio (SIR), 250; 67–640]. Additionally, three incident cases of laryngeal cancer were found (0.5 expected).

2.2.3 *Use in reinforced plastics*

Okun *et al.* (1985) studied 5021 workers who had been employed in two reinforced-plastic boat-building facilities in the USA for at least one day between 1959 and 1978. On the basis of industrial hygiene surveys, 2060 individuals were classified as having had high

exposure to styrene, with means in the two facilities of 42.5 ppm and 71.7 ppm [181 and 305 mg/m^3]. Of these, 48% had worked for one month to one year and only 7% for more than five years. There were 47 deaths in the high-exposure group (41.5 expected); no case of lymphatic or haematopoietic cancer was observed (approximately one expected).

Coggon *et al.* (1987) studied a cohort of 7949 men and women who had been employed during 1947–84 at eight British facilities where glass-reinforced plastics were manufactured. Of these, 5434 had worked in jobs entailing exposure to styrene, but only 2458 had done so for at least one year. Hand laminators (the most highly exposed) were estimated to have had 8-h time-weighted exposures to styrene of 40–100 ppm [170–426 mg/m^3]. The main analysis was restricted to seven facilities where a satisfactory proportion of the cohort had been traced (average, 96.7%). A total of 100 deaths from cancer were observed (SMR, 93 [95% CI, 76–113]), including one from Hodgkin's disease (SMR, 78), one from myeloma (SMR, 89), one from leukaemia (SMR, 33) and 51 from cancers of the lung, pleura and mediastinum (SMR, 126 [94–166]). No information was available on smoking habits. No death was recorded from non-Hodgkin's lymphoma in exposed subjects. The excess of lung cancer was concentrated particularly among workers who had had one to nine years of exposure to styrene, but risk did not increase with time since first exposure. Follow-up of this cohort was later extended to 1990 as part of an international collaborative study (Kogevinas *et al.*, 1994a) (see below). By the time of that analysis, the previous deficit of lymphatic and haematopoietic cancer had largely disappeared (13 deaths; SMR, 88; 95% CI, 47–151) and the excess of lung cancer was less marked (77 deaths; SMR, 106; 95% CI, 84–132).

Wong (1990) and Wong *et al.* (1994) reported on a cohort of 15 826 male and female employees who had worked at one of 30 reinforced-plastics plants in the USA for at least six months between 1948 and 1977. Workers were followed until 1989; vital status was determined using Social Security Administration files, the National Death Index and the records of credit agencies. A total of 307 932 person-years at risk were accumulated. Expected numbers of deaths were based on national age-, gender-, cause- and year-specific death rates for whites, as no information was available on race. Exposure to styrene was calculated in a job–exposure matrix that included work history and current and past time-weighted average exposures. A total of 1628 (10.3%) members of the cohort were found to have died, and death certificates were obtained for 97.4% of them. The overall mortality rate was 108 (95% CI, 103–113), and the mortality rate from all cancers was 116 (95% CI, 105–127). Mortality from cancers at a number of sites was increased significantly: oesophagus: 198, 14 observed, 95% CI, 105–322; bronchus, trachea and lung: 141, 162 observed, 95% CI, 120–164; cervix uteri: 284, 10 observed, 95% CI, 136–521; and other female genital organs: 202, 13 observed, 95% CI, 107–345. No excess was observed for lymphohaematopoietic cancers (82; 31 observed; 95% CI, 56–117). For workers involved in open-mould processing with high exposure to styrene, the SMR for lymphatic and haematopoietic cancers was 141 (four observed cases). For the highest cumulative exposure ($>$ 100 ppm$\times$years) and $>$ 20 years of latency, the SMR was 134 (5–373). The data were analysed by Cox regression with age, gender, length of exposure and cumulative exposure included in the model. Neither cumulative exposure nor length of exposure was significant in the model for lymphatic and haematopoietic cancer. No positive dose–response relationship was found for any other cancer that occurred in excess. [The Working Group noted that the

possibility that the two exposure variables included in the regression model were correlated may have reduced the likelihood of accurate assessment.]

Kogevinas *et al.* (1994a,b) described a historical cohort mortality study of 40 688 workers employed in 660 plants of the reinforced plastics industry and enrolled in eight subcohorts in Denmark, Finland, Italy (two), Norway, Sweden and the United Kingdom (two). Exposure to styrene was reconstructed from job and production records, environmental measurements and, in Italy, biological monitoring. An exposure database was constructed on the basis of about 16 500 personal air samples and 18 695 measurements of styrene metabolites in urine. Styrene exposure levels decreased considerably during the study period. The data from Denmark were considered to be representative of all six countries: They showed exposures of about 200 ppm [852 mg/m^3] in the 1950s, about 100 ppm [426 mg/m^3] in the late 1960s and about 20 ppm [85 mg/m^3] in the late 1980s. The 40 688 workers accumulated 539 479 person-years at risk and were followed for an average of 13 years. Workers lost to follow-up and those who emigrated constituted 3.0% of the total cohort, and in no individual cohort did the proportion exceed 8.0%; 60% of the cohort had less than two years' exposure and 9% had more than 10 years' exposure. The WHO mortality data bank was used to compute national mortality reference rates by sex, age (in five-year groups) and calendar year. No excess was observed for mortality from all causes [2196 deaths; SMR, 96; 95% CI, 92–100] or from all neoplasms (550 deaths; SMR, 91; 83–98). The mortality rate in exposed workers for neoplasms of the lymphatic and haematopoietic tissues was not elevated (50 deaths; SMR, 96; 95% CI, 71–127) and was not associated with length of exposure. Evaluation of risk by job type also showed no significant pattern. In an analysis by country, one of the cohorts in the United Kingdom and that from Denmark had moderate increases in mortality from lymphatic and haematopoietic cancer (Table 10). An increased risk for those cancers was observed in Poisson regression models for years since first exposure ($p = 0.012$) and for average exposure ($p = 0.019$) but not for cumulative exposure (see Table 11). Within the models there was an increasing trend in risk for lymphatic and haematopoietic cancer with average intensity of exposure, culminating in an RR of 3.6 (95% CI, 1.0–13) for the highest category, > 200 ppm; for more than 20 years since first employment, the RR was 4.0 (95% CI, 1.3–12). Although there were no increased risks for cancers of the pancreas, kidney or oesophagus, nonsignificant increases in risks at these sites were seen with time since first exposure or cumulative exposure to styrene.

Kolstad *et al.* (1994) evaluated the incidence of malignancies in lymphohaematopoietic tissues among male Danish workers, some 12 800 of whom were included in the mortality study of Kogevinas *et al.* (1994a,b). Using national pension fund records from 1964 onwards, they identified 36 525 'exposed' male workers who had been employed in 386 industries that were identified by industry experts as ever having produced reinforced plastics; however, the 36 525 workers may not all have been exposed to styrene. The mean annual levels of styrene calculated for 128 of these companies reflect the exposures measured in the industry, which range from 180 ppm [767 mg/m^3] in 1964–70 to 43 ppm [183 mg/m^3] in 1976–88. Duration of employment was calculated from pension fund payments made beginning in 1964–89. SIRs were calculated on the basis of national rates standardized for sex, age and year of diagnosis, and 95% CIs were calculated on the basis of the Poisson distribution. Within the cohort,

Table 10. Mortality from lymphatic and haemotopoietic malignancies in the international study on European workers exposed to styrene, by subcohort

Subcohort	No. of deaths among exposed workers	SMR	95% CI
Denmark[a]	24	122	78–181
Finland[b]	3	106	22–310
Italy 1	1	99	3–552
Italy 2	2	65	8–234
Norway	1	34	1–187
Sweden	3	58	12–168
United Kingdom 1[c]	13	88	47–151
United Kingdom 2	3	121	25–355

From Kogevinas *et al.* (1994a). SMR, standardized mortality ratio; CI, confidence interval

[a]Also included by Kolstad *et al.* (1994)

[b]Extended follow-up of part of a previous study (Härkönen *et al.*, 1984a)

[c]Extended follow-up of Coggon *et al.* (1987)

there were 112 malignancies of the lymphatic and haematopoietic system, with 93.7 expected (SIR, 1.2; 95% CI, 0.98–1.4). In workers with > 10 years since first employment, the SIR for leukaemia was 157 (107–222). The excess was due to cases in workers who had had less than one year of employment. For those employed in 1964–70, the SIR was 1.3 (1.0–1.7). The SIR for leukaemia more than 10 years after first short-term employment (2.3; 1.4–3.6) was the only significant increase; for workers with more than one year of employment, the corresponding SIR was 1.0 (0.52–1.7). For workers with less than 10 years since first employment, the only significant increase was for lymphomas (21 observed; 1.7; 1.0–2.5), with similar increases for short- and long-term employees. For all lymphatic and haematopoietic cancers, a similar risk differential was seen with duration of exposure.

Table 12 summarizes the characteristics of cohort and nested case–control studies on mortality from neoplasms of the lymphatic and haematopoietic tissues among workers exposed to styrene.

2.3 Case–control studies

Flodin *et al.* (1986) conducted a matched case–control study of 59 cases of acute myeloid leukaemia and 354 controls in Sweden to assess potential risk factors, which included radiation, medications and various occupational exposures. Cases were aged 20–70 years and were identified at hospitals in Sweden between 1977 and 1982. Two series of controls were drawn from a population register: one was matched to cases for sex, age (within five years) and location, and the other was a random population sample. Information on exposure was obtained through a questionnaire mailed to subjects. Reported exposure to styrene was

Table 11. Mortality from neoplasms of the lymphatic and haematopoietic tissues (ICD8 200–208) by cumulative exposure (ppm × years), time since first exposure and average exposure (ppm) to styrene

	No. of cases observed	RR	95% CI
Cumulative exposure (years)			
< 75	20	1	
75–99	8	0.98	0.43–2.3
200–499	10	1.2	0.57–2.7
≥ 500	9	0.84	0.35–2.0
Test for linear trend (*p* value)		0.65	
Time since first exposure (years)			
< 10	13	1	1
10–19	25	2.9	1.3–6.5
> 20	9	4.0	1.3–12
Test for linear trend (*p* value)		0.012	
Average exposure (years)[a]			
< 60	7	1	
60–99	9	1.7	0.59–4.8
100–119	10	3.1	1.1–9.1
120–199	13	3.1	1.0–9.1
≥ 200	8	3.6	0.98–13
Test for linear trend (*p* value)		0.019	

From Kogevinas *et al.* (1994a). Calculated on the basis of exposure model A, no lag; Poisson regression analysis. Models for cumulative and average exposure are adjusted by age, sex, country, calendar period and time since first exposure. RR, relative risk; CI, confidence interval

[a]For malignant lymphomas, the RR and 95% CI are for data from five countries, excluding Finland, because the model comprising the full data set did not converge

found to be a risk factor (standardized rate ratio, 19; 95% CI, 1.9–357), but the number of exposed subjects (3/59 cases and 1/354 controls) was small.

A population-based case–control study of cancer comprised 3730 histologically confirmed male cases of cancer at 11 major sites (including non-Hodgkin's lymphoma) newly diagnosed between 1979 and 1986 among residents of Montréal, Canada, aged 35–70 and ascertained in 19 major hospitals (Siemiatycki, 1991). The exposure of each subject to 293 occupational agents was evaluated by a group of chemists on the basis of jobs held, and cases of cancer at each site were compared with those in the rest of the study population, after adjustment for age, ethnic group, alcohol drinking and tobacco smoking. One percent of subjects were classified as ever having been exposed to styrene. The only significant increase in risk was seen for cancer of the rectum (odds ratio, 1.7; 90% CI, 0.8–3.8; six cases). A higher risk (odds ratio, 4.1; 90% CI, 1.4–11.8, five cases) was seen for subjects with 'substantial' exposure to styrene (subjects with exposure to styrene at medium or high concentration and frequency and with at least five years accumulated duration of exposure, up to five years before onset of disease).

Table 12. Characteristics of cohort and nested case–control studies of mortality from neoplasms of the lymphatic and haematopoietic tissues (L&H) among workers exposed to styrene

Reference (country)	Type of plant; study period; number of subjects; minimal period employed; follow-up	No. of deaths/ cancer deaths	Results[a]				Comments
			N	SMR	95% CI	Site	
Frentzel-Beyme et al. (1978) (Germany)	Styrene and polystyrene manufacture (one facility); 1931–76; 1960 subjects; 1 month; 93% German, 29% non-German	74/11	1	–	–	Lymphoma	Malignant neoplasm of the spleen; less than one death expected from neoplasms of the L&H
Ott *et al.* (1980) (USA)	Dow Chemical workers in development or production of styrene-based products; 1940–75; 2904 men; 1 year; 97.0%	303/58	13 21	149 161	80–256 100–246	L&H, mortality L&H, incidence	Excess incidence of lymphatic leukaemia (SIR, 427; 95% CI, 172–879; 7 cases); highest risks in workers exposed to styrene, ethylbenzene and other fumes, solvents and colourants
Bond *et al.* (1992) (USA)	Dow Chemical workers in development or production of styrene-based products (updating of Ott *et al.*, 1980); 1940–86; 2904 men; 1 year; 96.7%	687/162	28	144	95–208	L&H, mortality	Elevated incidences of multiple myeloma and Hodgkin's disease
Okun *et al.* (1985) (USA)	Reinforced plastics boat building (two facilities); 1959–78; 5201 subjects; 1 day; 98.1%	176/36	0	–	–	–	Less than one death expected from neoplasms of the L&H
Hodgson & Jones (1985) (United Kingdom)	Production, polymerization and processing of styrene; 1945–78; 622 men; 1 year; 99.7% exposed, 99.4% referents	34/10	3 0 4	[536 – [250	110–1566] – 68–640]	Lymphomas, mortality Leukaemias, mortality L&H, incidence	
Coggon *et al.* (1987) (United Kingdom)	Production of glass-reinforced plastics (8 facilities)[b]; 1947–84; 7949 subjects; no minimal employment; variable, 99.7–61.9%	693/181	6	[40	15–88]	L&H, mortality	Only one of six deaths among subjects with high exposure to styrene; extended follow-up of this cohort included by Kogevinas *et al.* (1994a,b)
Wong *et al.* (1994) (USA)	Reinforced plastics manufacturing plants (30 facilities); 1948–89; 15 826 subjects; 6 months; 83.9%	1628/425	425 31 11	116 82 74	105–127 56–117 37–133	All neoplasms L&H Leukaemia	Higher risk of L&H among workers with cumulative exposure > 100 ppm-years at > 20 years since first exposure (SMR, 134; 5 deaths), and among workers in open-mould processing (SMR, 141; 4 deaths)

Table 12 (contd)

Reference (Country)	Type of plant; study period; number of subjects; minimal period employed; follow-up	No. of deaths/ cancer deaths	Results[a]				Comments
			N	SMR	95% CI	Site	
Kolstad *et al.* (1994) (Denmark)	Production of glass-reinforced plastics and other plastics (552 facilities); 1970–89; 53 720 subjects (36 525 exposed to styrene); no minimal employment; 98.2%	NR/1915[d]	112 42	120 122	98–144 88–165	L&H, incidence Leukaemia, incidence	Significantly higher incidence of leukaemia (SIR, 157) at ≥ 10 years since first exposure; incidence of leukaemia higher among short-term workers with estimated higher exposure to styrene; part of this cohort included by Kogevinas *et al.* (1994a,b)
Kogevinas *et al.* (1994a,b) (six European countries)	Production of glass-reinforced plastics (660 facilities); 1945–91; varies between cohorts; 40 688 workers; 97%	2714/686	550 50 12 7 23	91 96 77 111 104	83–98 71–127 40–134 45–229 66–157	All neoplasms L&H Non-Hodgkin's lymphoma Hodgkin's disease Leukaemia	Mortality shown for exposed workers only; risk for L&H increased with latency (p for linear trend = 0.012) and with average exposure (p for linear trend = 0.019); risk did not increase with duration of exposure or cumulative exposure; excess risk observed for cancer of the pancreas
Meinhardt *et al.* (1982) (USA)	Styrene-butadiene rubber plants (2 facilities); 1943–76; 2756 men; 6 months, 96.8%	332/56	11	[132	66–236]	L&H	Highest risk (SMR, 212, 9 deaths) among workers in plant A first employed during operation of batch process
McMichael *et al.* (1976) (USA)	Rubber workers in styrene–butadiene synthetic plant (one facility); 1964–73; 6678 men; no minimal employment; NR	NR	NR	6.2 3.9	4.1–12.5 2.6–8.0	L&H Lymphatic leukaemia	Nested case–control study; odds ratios are for workers in styrene–butadiene plant *versus* other workers; 99.9% CI
Santos-Burgoa *et al.* (1992) (USA)	Styrene–butadiene rubber manufacture (8 facilities); 1943–82; 12 110 men; one year; 96.6%	NR	26 18	1.1 0.9	0.2–5.0 0.2–5.5	Leukaemia Multiple myeloma and other lymphoma (ICD 202–203)	Nested case–control study of 59 cases of L&H cancer and 193 controls; odds ratios for exposure to styrene adjusted for concomitant exposure to 1,3-butadiene; unadjusted RR for leukaemia was 2.9 (0.8–10.3)

NR, not reported

[a]N, number of deaths/cases; SMR, standardized mortality ratio; CI, confidence interval

[b]Includes one company in which only a low proportion of subjects could be traced.

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 *Mouse*

Groups of 50 male and 50 female B6C3F1 mice, six weeks old, received daily administrations of 150 or 300 mg/kg bw styrene (purity, 99.7%) in corn oil by gastric intubation on five days per week for 78 weeks. Control groups of 20 male and 20 female mice received corn oil alone. The study was terminated at 91 weeks. Body weights of treated females were slightly reduced, and survival was slightly reduced in high-dose males (20/20, 46/50, 39/50) and females (18/20, 40/50, 38/50). The combined incidences of adenoma and carcinoma of the lung in male mice were: 0/20 (control), 6/44 (low-dose) and 9/43 (high-dose) ($p = 0.02$; Cochran-Armitage test for trend). The mean incidence among untreated controls at the laboratory was 12%, the highest incidence being 20% in two control groups. There was a significant ($p = 0.034$; Cochran-Armitage) increasing trend in the incidence of hepatocellular adenoma in female mice (control, 0/20; low-dose, 1/44; high-dose, 5/43) (US National Cancer Institute, 1979a).

Groups of 50 male and 50 female B6C3F1 mice, six weeks old, received daily administrations of 203 or 406 mg/kg bw styrene in a mixture (solution of 70% styrene and 30% β-nitrostyrene) in corn oil by gastric intubation on three days per week for 78 weeks. Control groups of 20 male and 20 female mice received corn oil only. The study was terminated at 92 weeks. Body weights of high-dose female mice were slightly reduced. Survival among males was 18/20 (control), 43/50 (low-dose) and 33/50 (high-dose), and that among females was 17/20, 47/50 and 38/50, respectively. The combined incidences of adenoma and carcinoma of the lung in males were 0/20 (control), 11/44 (low-dose; $p = 0.016$, Fisher's exact test) and 2/43 (high-dose) (US National Cancer Institute, 1979b). [The Working Group noted the high β-nitrostyrene content of the mixture.]

3.1.2 *Rat*

Groups of 50 male and 50 female Fischer 344/N rats, six weeks old, received daily administrations of 1000 or 2000 mg/kg bw styrene (purity, 99.7%) in corn oil by gastric intubation on five days a week for 78 weeks. Control groups of 20 male and 20 female rats received corn oil only. Because of high mortality in the high-dose groups by week 23, additional groups of 50 male and 50 female rats administered 500 mg/kg styrene in corn oil by gastric intubation on five days per week for 103 weeks were included in the study, and additional groups of 20 male and 20 female rats receiving only corn oil were included as vehicle controls for these animals. All surviving rats were killed at 104–105 weeks. Body weights of the mid- and high-dose male rats were slightly reduced. Survival was poor in both high-dose males (17/20, 18/20, 44/50, 47/50, 6/50) and females (15/20, 18/20, 46/50, 46/50, 7/50) in comparison with controls ($p < 0.001$, Cox's test). There was no treatment-related increase in the incidence of any type of tumour in male or female rats (US National Cancer Institute, 1979a).

Groups of 40 male and 40 female Sprague-Dawley rats, 13 weeks old, were administered 0 (control), 50 or 250 mg/kg bw styrene (purity, > 99%) in olive oil by gastric intubation daily on four to five days a week for 52 weeks. The study was terminated [duration unspecified] when the last animal died. There was no treatment-related effect on body weight; survival of female rats receiving the high dose was reduced [data not provided]. No treatment-related increase in the incidence of tumours was reported (Conti *et al.*, 1988). [The Working Group noted the incomplete reporting and the short duration of treatment.]

Groups of 50 male and 70 female Sprague-Dawley rats, seven weeks old, were administered 125 or 250 ppm [mg/L] styrene (purity, 98.9%) daily in the drinking-water for 104 weeks. Control groups of 76 male and 104 female rats received drinking-water without styrene. At 52 weeks, 10 rats per sex and group were removed from the study for a scheduled interim kill. There was a significant reduction in water consumption among treated male and female rats and a significant reduction in body weight among high-dose females ($p < 0.05$, Student's *t* test). There was no treatment-related effect on survival and no evidence of chronic toxicity or carcinogenicity (Beliles *et al.*, 1985). [The Working Group noted the low level of exposure.]

Groups of 50 male and 50 female Fischer 344/N rats, six weeks old, received daily administrations of 350 and 700 mg/kg bw (males) or 175 and 350 mg/kg bw (females) styrene in a mixture (solution of 70% styrene and 30% β-nitrostyrene) in corn oil by gastric intubation on three days a week for 79 weeks. Control groups of 20 male and 20 female rats received corn oil only. The study was terminated at 108 weeks. The body weights of male rats were slightly reduced. There was no effect on survival in male (16/20, 34/50, 31/50) or female (12/20, 33/50, 31/50) rats, and there was no treatment-related increase in the incidence of any type of tumour (US National Cancer Institute, 1979b). [The Working Group noted the high β-nitrostyrene content of the mixture.]

3.2 Prenatal exposure followed by postnatal oral administration

3.2.1 *Mouse*

A group of 29 pregnant O20 mice received a single administration of 1350 mg/kg bw styrene (purity, 99%) in olive oil by gastric intubation on day 17 of gestation. A control group of nine pregnant mice received olive oil alone. Preweaning mortality was 43% among offspring of dams receiving styrene and 22% among offspring of controls. Groups of 45 male and 39 female progeny from the dams that received styrene were administered 1350 mg/kg bw styrene in olive oil by gastric intubation once a week from weaning until 16 weeks of age. Control groups of 20 male and 22 female mice with no prenatal exposure received olive oil alone. Administration of styrene was stopped at 16 weeks because of high mortality related to treatment (64% survival at 20 weeks). Centrilobular necrosis of the liver was frequent in mice that died within the first 20 weeks. The experiment was terminated at 120 weeks. At the time of observation of the first tumour, 19 control males and 23 treated males and 21 female mice and 32 treated females were still alive. In the progeny that received weekly administrations of styrene, the combined incidence of lung adenomas and carcinomas was significantly ($p < 0.01$) increased over that in vehicle controls: males, 8/19 *versus* 20/23, and females, 14/21 *versus* 32/32. There was no treatment-related difference in the incidences of

tumours at other sites in the progeny and no treatment-related difference in tumour incidences between control and styrene-treated dams (Ponomarkov & Tomatis, 1978). [The Working Group noted the high mortality in treated mice early in the study.]

A group of 15 pregnant C57Bl mice received a single administration of 300 mg/kg bw styrene (purity, 99%) in olive oil by gastric intubation on day 17 of gestation. A control group of five pregnant mice received olive oil only. There was no treatment-related effect on neonatal mortality. Groups of 27 male and 27 female progeny of dams that received styrene were administered 300 mg/kg bw styrene in olive oil by gastric intubation once a week from weaning up to 120 weeks. Control groups of 12 male and 13 female mice received olive oil alone. The experiment was terminated at 120 weeks. There was no treatment-related effect on body weight or survival. At the time of observation of the first tumour, 12 male controls and 24 treated male progeny, 13 female controls and 24 treated progeny, and 10 control and 5 treated dams were still alive. There was no treatment-related difference in the incidences of tumours at any site in dams or progeny (Ponomarkov & Tomatis, 1978). [The Working Group noted the small numbers of animals.]

3.2.2 *Rat*

A group of 21 pregnant BDIV rats received a single administration of 1350 mg/kg bw styrene (purity, 99%) in olive oil by gastric intubation on day 17 of gestation. A control group of 10 pregnant rats received olive oil alone. There was a slight treatment-related increase in neonatal mortality. Groups of 73 male and 71 female progeny of dams that received styrene were administered 500 mg/kg bw styrene in olive oil by gastric intubation weekly from weaning up to 120 weeks. Control groups of 36 male and 39 female rats received olive oil alone. The experiment was terminated at 120 weeks. There was no treatment-related effect on body weight or survival. At the time of observation of the first tumour, 32 control and 54 treated male progeny and 35 control and 68 treated female progeny were still alive. Stomach tumours occurred in three female rats (adenoma, fibrosarcoma, carcinosarcoma) administered styrene and in one female rat (fibrosarcoma) in the control group. Non-neoplastic stomach lesions [morphology and incidence unspecified] were reported in rats administered styrene. There was no significant treatment-related increase in tumour incidence at any site (Ponomarkov & Tomatis, 1978).

3.3 Inhalation

Rat: Groups of 30 male and 30 female Sprague-Dawley rats, 13 weeks old, were exposed by inhalation in chambers to 25, 50, 100, 200 or 300 ppm styrene [105, 210, 420, 840, 1260 mg/m^3] (purity, > 99%) for 4 h per day on five days a week for 52 weeks. The control groups comprised 60 male and 60 female rats. The study was terminated when the last animal died [duration unspecified] . No treatment-related effect on body weight or survival was reported [data not provided]. The combined incidence of benign and malignant mammary tumours was greater in treated female rats than in controls: 34/60 controls, 24/30 at 25 ppm, 21/30 at 50 ppm, 23/30 at 100 ppm, 24/30 at 200 ppm and 25/30 at 300 ppm [$p = 0.01$; Fisher's exact test; highest-dose animals compared with controls]. The incidence of malignant mammary tumours was significantly increased in treated females: 6/60 controls, 6/30 at 25 ppm, 4/30 at

50 ppm, 9/30 at 100 ppm, 12/30 at 200 ppm and 9/30 at 300 ppm [$p < 0.01$, Cochran-Armitage trend test]) (Maltoni *et al.*, 1982; Conti *et al.*, 1988). [The Working Group noted the incomplete reporting of the data and the high incidence of spontaneous mammary tumours in animals of this strain.]

3.4 Intraperitoneal administration

3.4.1 *Mouse*

In a screening assay based on increased multiplicity and incidence of lung tumours in a strain of mice highly susceptible to development of this neoplasm, a group of 25 female A/J mice, six to eight weeks old, received intraperitoneal injections of 20 μmol styrene (purity, > 99%) in olive oil three times a week for a total of 20 injections. A vehicle control group of 25 mice received olive oil alone. The study was terminated 20 weeks after the last injection, and gross and microscopic examination was performed on all mice administered styrene; only lung tissue was examined from controls. There was no treatment-related increase in the incidence of lung tumours (3/25 *versus* 1/25 in controls). All 25 animals in a positive control group treated with 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) developed lung tumours (Brunnemann *et al.*, 1992).

3.4.2 *Rat*

Groups of 40 male and 40 female Sprague-Dawley rats, 13 weeks old, received four intraperitoneal injections of 50 mg/animal styrene (purity, > 99%) in olive oil at two-month intervals. Control groups received injections of olive oil alone. The study was terminated when the last animal died [duration unspecified]. No treatment-related effect on body weight or survival was reported [data not provided]. There was no treatment-related increase in the incidence of benign and/or malignant tumours (Conti *et al.*, 1988). [The Working Group noted the incomplete reporting of data, the short duration of treatment and the low total dose.]

3.5 Subcutaneous administration

Rat: Groups of 40 male and 40 female Sprague-Dawley rats, 13 weeks old, received a single subcutaneous injection of 50 mg/animal styrene (purity, > 99%) in olive oil. Control groups of 40 male and 40 female rats received a subcutaneous injection of olive oil alone. The study was terminated when the last animal died [duration unspecified]. No treatment-related effect on body weight or survival was reported [data not provided]. The authors reported that there was no treatment-related increase in the incidence of benign and/or malignant tumours (Conti *et al.*, 1988). [The Working Group noted the incomplete reporting of data and the single low-dose treatment.]

4. Other Data Relevant for an Evaluation of Carcinogenicity and Its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

The pharmacokinetics and metabolism of styrene have been reviewed (WHO, 1983; Henschler, 1987; WHO, 1987; Guillemin & Berode, 1988; Bond, 1989; Beratergrenium für Umweltrelevante Altstoffe, 1993).

4.1.1 *Humans*

(a) Absorption

In several studies, the pulmonary retention of styrene was 60–70% of the inhaled dose. In these studies, volunteers or workers were exposed to styrene for: over 1 h to 51.4, 216.1, 376 ppm [223, 936, 1629 mg/m^3] and 2 h to 117 ppm [507 mg/m^3] (Stewart *et al.*, 1968), 2 h to 70 ppm [303 mg/m^3] (Wigaeus *et al.*, 1983, 1984; Löf *et al.*, 1986a), 2 h to 210 mg/m^3 [48 ppm] at different workloads (Åstrand, 1986), 2 h and 5 h to 24 ppm [104 mg/m^3] (Fiserova-Bergerova & Teisinger, 1965), 6 h to 80 ppm [347 mg/m^3] (Ramsey *et al.*, 1980), 8 h to 22, 129, 235 ppm [95, 559, 1018 mg/m^3] (Bardoděj & Bardodějová, 1970), 8 h to 32–85 mg/m^3 [7.4–20 ppm] (Engström *et al.*, 1978a) and 8 h to 20, 40, 100, 200 mg/m^3 [4.6, 9.2, 23.0, 46 ppm] (Wieczorek & Piotrowski, 1985).

Styrene in ambient air is absorbed through the skin at 2–5% of the dose absorbed in the respiratory tract (Riihimäki & Pfäffli, 1978; Wieczorek, 1985). Liquid styrene was found to penetrate the skin at a rate of 1 μg/(cm^2×min). Contact of one hand (500 cm^2) for 30 min with liquid styrene was estimated to be equivalent, in terms of absorption, to 4% of the dose retained in the body during exposure to 50 ppm [213 mg/m^3] for 8 h (Berode *et al.*, 1985).

(b) Distribution

As the partition coefficients between air and different body tissues are 4100 for fat, 84–154 for other organs and 59 for blood, styrene was concluded to accumulate exclusively in fat tissue (Droz & Guillemin, 1983). Analysis of styrene in subcutaneous fat suggested accumulation and slow release (Wolff *et al.*, 1977; Engström *et al.*, 1978a,b). Its half-life was estimated from determinations in subcutaneous fat of six subjects exposed to 50 ppm (2 h), 15 and 20 ppm (8 h each) to be between two and five days (Engström *et al.*, 1978a,b). This finding led to the proposal that styrene levels in the body increase during a working week, and arguments for and against the hypothesis have been presented (see Bond, 1989). According to the physiologically based pharmacokinetic model of Perbellini *et al.* (1988) (described below), the styrene concentration in fat tissue increases during a working week because of high enrichment. In a study of workers exposed to 37 ppm [160 mg/m^3] styrene, no evidence was found that it accumulates during a working week (Pekari *et al.*, 1993).

(c) Elimination in exhaled air and in urine

Only 0.7–4.4% of the amount of styrene absorbed was found to be exhaled unchanged (Stewart *et al.*, 1968; Fernández & Caperos, 1977; Caperos *et al.*, 1979; Guillemin & Bauer,

1979; Ramsey *et al.*, 1980). At the end of a 2-h exposure to 300 mg/m^3 [69 ppm], the quotients arterial blood:alveolar air and arterial blood:inhaled air at steady state were found to be 62 and 7.5 (Wigaeus *et al.*, 1983). The large difference between the two values is due to rapid metabolic elimination of styrene. The higher value represents determination of the partition coefficient blood:air of styrene *in vivo* and is similar to the thermodynamic partition coefficient human blood:air determined *in vitro* at 37 °C, which was 61 (Wigaeus *et al.*, 1983), 59 (Droz & Guillemin, 1983) and 48 (Csanády *et al.*, 1994).

Unchanged styrene was also excreted in urine of workers exposed to a mean time-weighted styrene concentration of 87.9 mg/m^3 [20.3 ppm]. The concentration in urine was about one-tenth that in blood (Gobba *et al.*, 1993).

(*d*) *Metabolic elimination*

In several studies, disappearence of styrene was measured in blood of workers and volunteers after exposure for 2–6 h to concentrations of 70 ppm [303 mg/m^3] and 80 ppm [347 mg/m^3] styrene for 1.5 h (Teramoto & Horiguchi, 1978), 4 h (Wigaeus *et al.*, 1983) and 41 h (Ramsey *et al.*, 1980) after exposure. For periods between 1.5 and 2 h, a fast elimination phase was observed, with half-lives of 0.58 h (Ramsey *et al.*, 1980), 0.67 h (Teramoto & Horiguchi, 1978) and 0.68 h (Wigaeus *et al.*, 1983). In the study of Ramsey *et al.* (1980), a second phase was distinguished, with a half-life of 13 h. A total blood clearance of 1.5–1.6 L/(kg×h) was calculated from the fast phase (Ramsey *et al.*, 1980; Wigaeus *et al.*, 1983). This value was almost identical to that for total blood flow through the liver, indicating that a high-affinity perfusion-limited pathway exists. Contributions from extrahepatic metabolism, uptake by adipose tissues and exhalation were considered to be small (Wigaeus *et al.*, 1983).

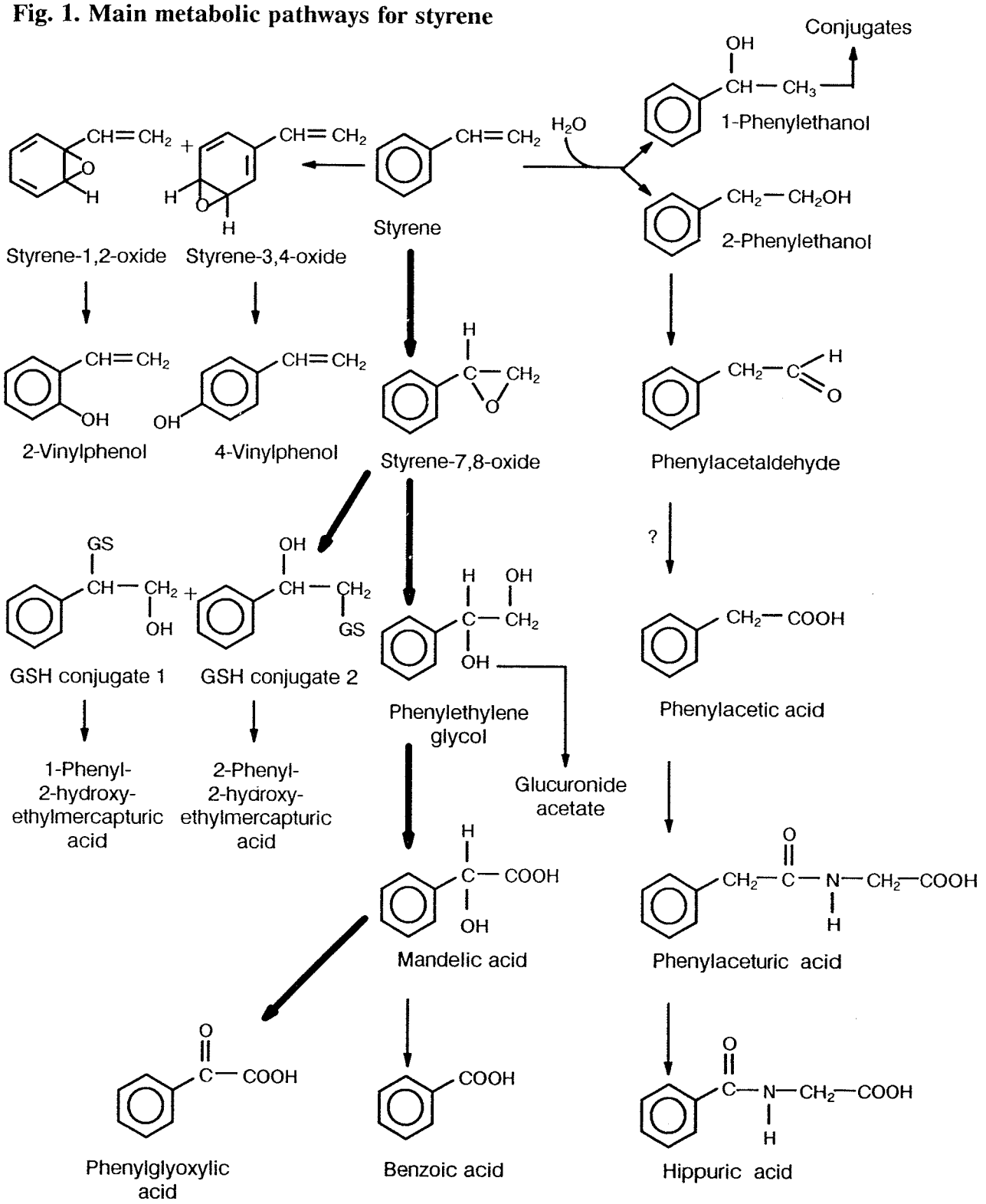
Experimental 2-h exposure to styrene at 296 mg/m^3 [68 ppm] led to a significantly lower styrene level in the blood of occupationally pre-exposed subjects (14.7 μmol/L) than of those not previously exposed (21.2 μmol/L). The mean values for total clearance were 1.5 L/(kg×h) in the reference group and 2.0 L/(kg×h) in the pre-exposed group (Löf *et al.*, 1986a).

In workers, a linear correlation was found between atmospheric styrene concentrations up to about 150 ppm [650 mg/m^3] and concentrations in venous blood (Bartolucci *et al.*, 1986; Brugnone *et al.*, 1993; Gobba *et al.*, 1993; Korn *et al.*, 1994). No linear correlation was found, however, between atmospheric and arterial blood concentrations of styrene in two volunteers exposed for 2 h to 26, 77, 201 and 386 ppm styrene [110, 328, 856 and 1672 mg/m^3]. The relatively higher blood concentrations at the two higher doses seem to indicate saturability of styrene metabolism (Löf & Johanson, 1993).

(*e*) *Metabolites*

The metabolic pathways of styrene are shown in Figure 1. Styrene is oxidized to styrene-7,8-oxide by the cytochrome P450-mediated monooxygenase system. The responsible isozyme, first identified in human liver, was considered to be the ethanol-inducible CYP2E1 (Guengerich *et al.*, 1991); however, more recent evidence suggests that CYP2B6 is the main catalyst, followed by CYP2E1 and CYP1A2, and additional isozymes with lower activity for styrene may be involved (Nakajima *et al.*, 1993). Styrene has a high affinity for both CYP2B6

Fig. 1. Main metabolic pathways for styrene



Adapted from Ohtsuji & Ikeda (1971), Leibman (1975), Bardodej (1978), Vainio *et al.* (1984) and Watabe *et al.* (1978). Main pathways are indicated by thick arrows. GS, glutathione; GSH, reduced glutathione

and CYP2E1 isozymes (Michaelis-Menten constant [K_m] about 0.1 mmol/L), and other isozymes may be responsible for low-affinity catalysis.

In volunteers exposed for 2 h to about 300 mg/m^3 [70 ppm] styrene, styrene-7,8-oxide was found in venous blood at a mean concentration of 0.05 μmol/L [6 μg/L] (Wigaeus *et al.*, 1983). Similar styrene-7,8-oxide concentrations, up to 0.04 μmol/L [4.8 μg/L] and 4.1 μg/L, were present in venous blood of workers exposed to styrene at concentrations up to 371 mg/m^3 [86 ppm] (mean, 99 mg/mg^3 [23 ppm]) (Löf *et al.*, 1986b) and up to 73 ppm [311 mg/m^3] (Korn *et al.*, 1994). Exposure to 20 ppm [87 mg/m^3] styrene gave rise to a mean styrene-7,8-oxide concentration of 1 μg/L (Korn *et al.*, 1994). These concentrations are 5–20 times lower than the corresponding concentrations in the blood of styrene-exposed rodents (see below). Enzymatic hydrolysis of styrene-7,8-oxide yields phenylethylene glycol, which reached a blood concentration of 15–20% of the styrene concentration in blood of workers exposed for 2 h to 300 mg/m^3 [69 ppm] styrene (Wigaeus *et al.*, 1983; Löf *et al.*, 1986a). Phenylethylene glycol (S enantiomer:R enantiomer, about 3) and 2-phenylethanol have been found in urine of styrene-exposed workers (Korn *et al.*, 1985, 1987). Phenylethylene glycol is further oxidized to mandelic and phenylglyoxylic acids, which are the main metabolites found in urine of people exposed to styrene, with 57–85% and 10–33% of an absorbed dose of styrene excreted as mandelic and phenylglyoxylic acids (Bardoděj & Bardodějová, 1970; Guillemin & Bauer, 1979). Mandelic acid was excreted in styrene-exposed workers as a racemic mixture with a 1.2-fold excess of the R enantiomer (Drummond *et al.*, 1989). In other studies, a 1.5-fold excess of the S enantiomer was found (Korn *et al.*, 1985, 1987).

Urinary excretion of mandelic acid and phenylglyoxylic acid is biphasic. After an 8-h exposure of workers to styrene at concentrations of 26–130 mg/m^3 [6.1–30.5 ppm], both metabolites had a half-life of about 2.5 h for the first and 30 h for the second phase (Wieczorek & Piotrowski, 1988). These compounds are used in assessing occupational exposure to styrene. According to several studies, an exposure to 20 ppm [80 mg/m^3] styrene corresponds, the following morning, to a combined mandelic acid and phenylglyoxylic acid level of about 2.9 mmol/L (Pekari *et al.*, 1993).

Alcohol inhibits urinary excretion of mandelic and phenylglyoxylic acids (Berode *et al.*, 1986; Černý *et al.*, 1990).

Conjugation of styrene-7,8-oxide with glutathione is of minor importance in humans, since urinary excretion of thioethers or of the mercapturic acid, *N*-acetyl-*S*-(2-phenyl-2-hydroxyethyl)cysteine, after exposure to styrene for 2 h at about 210 mg/m^3 [48 ppm] amounted to only about 1% or less of the absorbed styrene (Aringer *et al.*, 1991; Norström *et al.*, 1992).

Small amounts of 4-vinylphenol (0.3% of mandelic acid) were found in urine of workers exposed to styrene at 130 ppm [563 mg/m^3], indicating that ring oxidation of styrene leading to the formation of styrene-3,4-oxide is a minor metabolic pathway (Pfäffli *et al.*, 1981).

Several physiologically based pharmacokinetic models have been developed which are useful in predicting the behaviour of styrene in humans. The models of Droz and Guillemin (1983) and Perbellini *et al.* (1988), validated for experimental exposures to styrene at up to 100 ppm [433 mg/m^3], simulate styrene concentrations in blood and alveolar air and urinary

excretion of mandelic acid and phenylglyoxylic acid during a working week. The models of Ramsey and Andersen (1984) and Löf and Johanson (1993) were validated with data on styrene in exhaled air and in arterial blood during and after experimental exposures to styrene at up to 376 and 386 ppm, respectively. Both models predict partially saturated metabolism at the highest exposure. Values for the K_m (0.36 mg/L in blood and 0.01 mmol/L [1 mg/L] in liver) and for the maximal rate of metabolism (V_{max}) (184 mg/h) were obtained in the first model by scaling from data obtained in rats. The V_{max} (2.9 mmol/h [300 mg/h]) was obtained in the second model by fitting to experimental data.

Csanády *et al.* (1994) developed a model that simulates the behaviour of both styrene and styrene-7,8-oxide. It was validated with data on styrene in exhaled air and venous blood after exposure to up to 376 ppm [1600 mg/m^3] and with data on concentrations of styrene-7,8-oxide in blood of workers exposed to styrene at up to 72 ppm [305 mg/m^3]. Interactions between inhaled styrene (20 and 50 ppm [85 and 213 mg/m^3]) and 1,3-butadiene (5 and 15 ppm [11 and 33 mg/m^3]) were predicted in a physiologically based pharmacokinetic model by extrapolation from data obtained in rats. No influence of 1,3-butadiene on styrene metabolism was seen, but styrene at 20 and 50 ppm reduced the metabolism of 1,3-butadiene at 15 ppm to 81 and 63%, respectively (Filser *et al.*, 1993a).

(f) Haemoglobin adducts

In a study of US fibreglass-reinforced plastics workers, passive personal measurements indicated individual exposures to styrene in air of 1–44 ppm [4.26–187.4 mg/m^3] (arithmetic mean, 17.2 ppm [73.3 mg/m^3]); extrapolation from urinary mandelic acid values gave an average air concentration of 15.2 ppm [64.8 mg/m^3]. As measured by gas chromatography–mass spectrometry, the concentration of adducts of styrene-7,8-oxide to the N-terminal valine, *N*-(1-hydroxy-2-phenylethyl)valine, in haemoglobin was higher among the workers than among a control group of library workers; however, 43% of the exposed and none of the controls were smokers, and an eight-fold variation in the level of styrene-7,8-oxide–haemoglobin adducts was seen among the exposed workers. Furthermore, one exposed laminator showed an adduct level 5000-fold higher than others. Similar variation was seen among the controls. When trichotomized exposure categories were used on the basis of individuals' usual job assignment during the preceding four months, a dose–response relationship was seen, with a mean of 8.1 ± 0.8 pmol/g (including the highly deviant individual, 34.5 ± 11.6 pmol/g) for the high-exposure category, 4.7 ± 0.7 for the medium-low-exposure category and 2.2 ± 6.8 for the control group (Brenner *et al.*, 1991).

In a study of workers in Sweden using unsaturated polyester resin, styrene-induced adducts to the N-terminal valine of haemoglobin were measured by enrichment of adducted globin chains with ion-exchange chromatography and gas chromatography–mass spectrometry. Increased levels were seen in seven of 17 reinforced plastic workers (mean, 28 pmol/g globin) in relation to three out of 11 controls (mean, ≤ 13 pmol/g globin). A linear correlation was seen in a regression analysis between individual adduct levels and free styrene-7,8-oxide (r = 0.7) and styrene glycol (r = 0.9) in blood and with mandelic acid in urine (r = 0.9). Extrapolation from the concentrations of the metabolite in urine provides an estimate of about 75 ppm [319.5 mg/m^3] styrene in workplace air (Christakopoulos *et al.*, 1993).

No carboxylic acid esters were detected in six workers exposed to styrene (Sepai *et al.*, 1993).

4.1.2 *Experimental systems*

(*a*) *Styrene*

The uptake and elimination of styrene were investigated in male Wistar rats during and after a 5-h steady-state exposure to styrene vapours at concentrations varying from 50 to 2000 ppm [217–8666 mg/m^3] (Withey & Collins, 1979) and following intravenous administration of styrene at doses of 1.34, 4.01, 6.70 and 9.36 mg/kg bw (Withey & Collins, 1977). Styrene concentration–time courses were analysed in a two-compartment model. The rate coefficient for elimination from the central compartment was affected by dose, indicating saturation of metabolic elimination. The administered dose did not affect the apparent volume of distribution, which was about 10 times larger than the blood volume, indicating extensive distribution of styrene to the tissues. The concentration of styrene in perirenal fat was 10 times higher than that in any organ, indicating a great affinity of styrene for lipid depots.

Teramoto and Horiguchi (1978) investigated the absorption and distribution of styrene in rats [strain unspecified] after a 4-h exposure to styrene vapours at 500 and 1000 ppm [2166 and 4333 mg/m^3]. A significant enrichment of styrene in adipose tissues was reported. In another experiment, the authors found no accumulation of styrene in the body after exposure to styrene at about 700 ppm [3033 mg/m^3] for 4 h a day for five days.

The pharmacokinetics and distribution of styrene were investigated in male Sprague-Dawley rats after a 6-h exposure to styrene at concentrations of 80, 200, 600 and 1200 ppm [347, 867, 2600 and 5200 mg/m^3] (Ramsey & Young, 1978). At each exposure level, the styrene concentration in blood increased rapidly during exposure and approached a maximal value at the end of exposure. The relationship between exposure concentration and blood concentration measured at the end of exposure was nonlinear, since a 15-fold increase in the exposure concentration resulted in a 63-fold increase in blood levels, indicating that metabolism of styrene became saturated. The measured styrene concentrations in blood and adipose tissue were used to develop a physiologically based pharmacokinetic model (Ramsey & Andersen, 1984).

The effects of the cytochrome P450 inhibitor, pyrazole, and of the inducer, phenobarbital, on the results of repeated exposures to styrene were investigated in male Fischer 344 rats (Andersen *et al.*, 1984) by evaluating measured blood styrene concentration–time courses in a physiologically based pharmacokinetic model. The metabolism of styrene was lower in rats pretreated with pyrazole (300 mg/kg 0.5 h before exposure) than in controls. After pretreatment with phenobarbital (80 mg/kg per day for four days before exposure), the V_{max} was increased about six fold. Repeated exposures to styrene at 1000 ppm [4333 mg/m^3] for 6 h/day for four days before exposure resulted in a two-fold increase in the value of V_{max}.

Administration of single oral doses of 500 mg/kg bw styrene to untreated male Fischer 344 rats and to another group of rats 16 h after exposure by inhalation to 1000 ppm styrene for 6 h a day for four days did not significantly alter the area under the blood concentration–time curve (Mendrala *et al.*, 1993).

The uptake, distribution and elimination of styrene have been investigated in Sprague-Dawley rats and B6C3F1 mice in closed chambers after inhalation and after intraperitoneal and oral administration (Filser *et al.*, 1993a,b). In both species, the rate of metabolism of inhaled styrene was dependent on concentration. Deviations from linearity due to saturation of metabolic activation of styrene became apparent at concentrations above 200–300 ppm [867–1300 mg/m^3] in both species (Ramsey & Andersen, 1984; Filser *et al.*, 1993b). Saturation of metabolism was reached at atmospheric concentrations of about 700 ppm [3033 mg/m^3] in rats and 800 ppm [3466 mg/m^3] in mice. In rats, pretreatment with diethyldithiocarbamate (200 mg/kg) reduced metabolism of styrene at an average body concentration of 0.34 μmol/kg to only 2% of that in control animals; pretreatment was somewhat less effective in mice. The ability of styrene to influence its own metabolism during chronic exposure was investigated by exposing rats and mice for 6 h a day for five days to atmospheric concentrations of 150 and 500 ppm [650 and 2166 mg/m^3]; no significant effect on the rate of metabolism of inhaled styrene was found. The experimental data were then used in a two-compartment model in order to calculate pharmacokinetic parameters. Clearance due to uptake, reflecting the transfer rate of styrene due to inhalation, was 63 ml/min for a 250-g rat and 12 ml/min for a 25-g mouse. These values represent 54% (rat) and 47% (mouse) of the alveolar ventilation (Arms & Travis, 1988). At steady state, the clearances of styrene uptake and of metabolism in relation to atmospheric concentrations below 300 ppm [1300 mg/m^3] were almost equal. Consequently, less than 5% of the styrene reaching the body was exhaled unchanged in mice and rats exposed to styrene vapours at concentrations below that level. Maximal accumulation, determined as the thermodynamic partition coefficient whole body:air (ppm_{body}/ppm_{air}), was almost identical in the two species (about 420). These values were corroborated by estimates calculated on the basis of the oil:air and water:air partition coefficients. The bioaccumulation factor body:air was lower than the thermodynamic partition coefficient due to metabolic elimination. The lowest value for the bioaccumulation factor in rats, 2.7, was reached at a steady-state exposure concentration below 10 ppm [43 mg/m^3]; in mice, it was 5.9, reached at below 20 ppm [87 mg/m^3]. The V_{max} was estimated to be 224 μmol/h per kg in rats and 625 μmol/h per kg bw in mice (Table 13).

Dermal uptake was estimated to be 9.4% of total uptake (skin plus inhalation) in male Fischer 344 rats whose fur was closely clipped (McDougal *et al.*, 1990).

The tissue distribution of styrene and its metabolites was investigated in NMRI mice after intraperitoneal injection of 343 mg/kg bw [7-^{14}C]-styrene (Löf *et al.*, 1983). Radioactivity was distributed rapidly in the tissues, but the results are difficult to evaluate in relation to pharmacokinetics.

The distribution and elimination of styrene was investigated in male CD2F1 mice after intraperitoneal injection of 200 mg/kg bw styrene (Pantarotto *et al.*, 1980). Absorption and elimination processes were described by first-order kinetics. Styrene was rapidly distributed among the tissues, and marked enrichment occurred in perirenal fat.

Pharmacokinetic interactions between styrene and 1,3-butadiene in Sprague-Dawley rats were investigated in a two-compartment model (Laib *et al.*, 1992) and in a physiological pharmacokinetic model (Filser *et al.*, 1993a). 1,3-Butadiene did not influence the metabolism of styrene, whereas styrene inhibited the metabolism of 1,3-butadiene. The

inhibition could be described by assuming a competitive mechanism at atmospheric styrene concentrations up to 100 ppm [433 mg/m^3].

Table 13. Maximal rate of styrene metabolism in mice and rats

Species	Strain	V_{max} (μmol/h per kg)	Reference
Mouse	B6C3F1	625	Filser *et al.* (1993b)
	Unspecified	253	Ramsey & Anderson (1984)
	B6C3F1	600	Csanády *et al.* (1994)
Rat	Sprague-Dawley	224	Filser *et al.* (1993b)
	Sprague-Dawley	115	Ramsey & Anderson (1984)[a]
	Sprague-Dawley	224	Csanády *et al.* (1994)[b]
	Fischer 344	96	Andersen *et al.* (1984)

[a]Data set of Ramsey and Young (1978) reanalysed in a physiological pharmacokinetic model
[b]Data set of Filser *et al.* (1993b) reanalysed in a physiological pharmacokinetic model

Physiological pharmacokinetic models were developed to describe the disposition and metabolism of styrene in rat and man (Andersen *et al.*, 1984; Ramsey & Andersen, 1984; Paterson & Mackay, 1986) and in rat, mouse and man (Csanády *et al.*, 1994). In the last model, the metabolism of styrene was linked to styrene-7,8-oxide. The influence of alveolar ventilation and the blood:air partition coefficient for styrene on the pharmacokinetics of styrene and styrene-7,8-oxide were discussed.

(*c*) *Metabolites*

Monooxygenase-dependent epoxidation of styrene to styrene-7,8-oxide is the earliest step in the metabolism of styrene, as demonstrated *in vitro* in isolated perfused rat liver (Beije & Jenssen, 1982; Belvedere *et al.*, 1984), rat liver microsomes (Watabe *et al.*, 1978; Foureman *et al.*, 1989) and purified cytochrome P450 enzymes from rat liver (Foureman *et al.*, 1989). In all species examined (male and female Sprague-Dawley rats, CD1 mice, New Zealand rabbits and Dunkin Hartley guinea-pigs), monooxygenase-dependent formation and epoxide hydrolase-dependent hydration of styrene-7,8-oxide were more active in liver than in lungs, kidneys, spleen or heart (Cantoni *et al.*, 1978). Styrene monooxygenase and epoxide hydrolase activities have been detected in rabbit liver before birth (Romano *et al.*, 1985).

Intermittent exposure (6 h per day, five days per week, 11 weeks) of male Wistar rats to 300 ppm [1300 mg/m^3] styrene enhanced the activities of drug hydroxylating (ethoxycoumarin *O*-deethylase, cytochrome P450) and conjugating (epoxide hydrolase) enzymes in liver and kidneys by up to two fold (Vainio *et al.*, 1979). A 24-h exposure of male Han/Wistar rats to 500 ppm [2166 mg/m^3] styrene led to a 2.4-fold increase in styrene metabolism in liver microsomes, which was reported to be related to induction of cytochrome P450IIE1 (Elovaara *et al.*, 1991).

Styrene can also be oxidized in the presence of human erythrocytes *in vitro* by oxyhaemoglobin (Tursi *et al.*, 1983). Non-enzymatic epoxidation of styrene by haemoglobin and

myoglobin requires the presence of either molecular oxygen or hydrogen peroxide (Ortiz de Montellano & Catalano, 1985; Rao *et al.*, 1993). Styrene-7,8-oxide can also be formed experimentally in a number of co-oxidation reactions by peroxidase and other oxidants (Belvedere *et al.*, 1983; Ortiz de Montellano & Grab, 1986; Mickiewicz & Rzeczycki, 1988).

Species-specific kinetics of the styrene and styrene-7,8-oxide metabolizing systems have been investigated under the same experimental conditions in hepatic microsomes obtained from male Fischer rats, male Sprague-Dawley rats, male B6C3F1 mice and humans (Mendrala *et al.*, 1993). When extrapolated to conditions *in vivo*, the K_m values for human, rat and mouse cytochrome P450-dependent monooxygenases were essentially similar, ranging from 9 μg/g liver in humans to 4.3 μg/g liver in mice not pretreated with styrene; the V_{max} values were relatively similar in rats and mice (41–62 mg/h/kg bw) but were much lower in the five human samples (3.2 mg/h per kg bw). The K_m values for epoxide hydrolase were low in humans (1.2 μg/g liver), intermediate in rats (16–27 μg/g liver) and high in mice (89 μg/g liver); the V_{max} values ranged from 27 mg/h per kg bw in humans to 98 mg/h per kg bw in mice. Glutathione *S*-transferase activity towards styrene-7,8-oxide was apparently lower for humans (168 mg/h per kg bw) than for rodents (1280–2490 mg/h per kg bw).

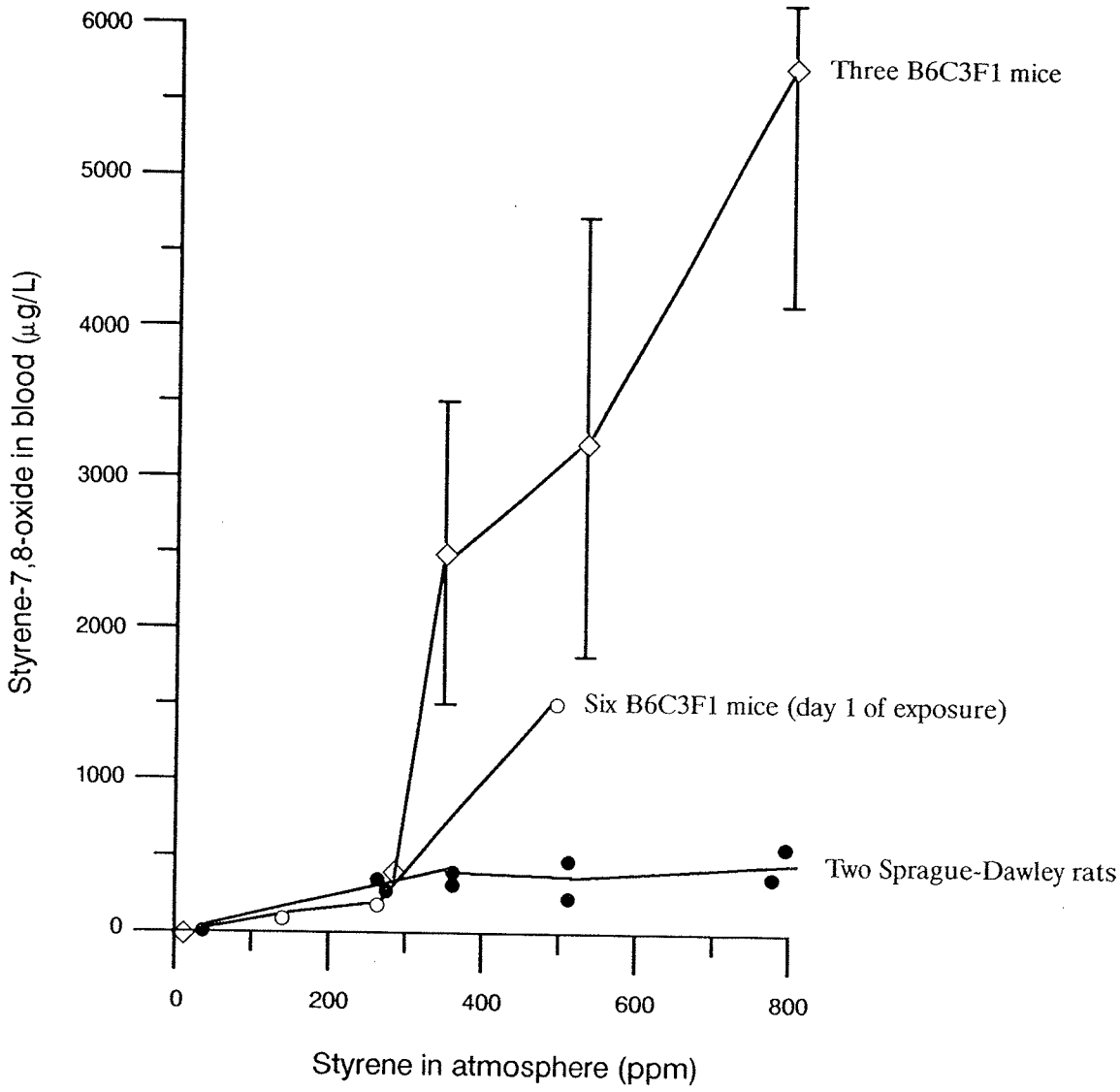
In a study reported in an abstract (Bogan *et al.*, 1993), kinetic parameters of oxidative styrene metabolism were investigated in hepatocytes of male Sprague-Dawley rats and male B6C3F1 mice. The apparent K_m values for the suspensions were (mean ± SD): 25.5 ± 7.8 μmol/L for rats and 11.7 ± 0.3 μmol/L for mice. The V_{max} values were: 3.1 ± 0.3 nmol/min per (5×10^6 viable cells) in rat hepatocytes and 11.4 ± 0.7 nmol/min per (5×10^6 viable cells) in those of mice. These values were used to calculate maximal metabolic elimination rates *in vivo* on the basis of the amount of cells in the incubations, the cell densities in the livers of rats (143×10^6 per g) and mice (103×10^6 per g) and liver weights of 10 g for rats weighing 250 g and 1.4 g for mice weighing 25 g. The scaled values for one rat and one mouse *in vivo* were 53.2 ± 5.2 μmol/h and 19.4 ± 1.2 μmol/h.

Styrene-7,8-oxide has been shown to be formed as a metabolite of styrene *in vivo* in male Fischer rats, male Sprague-Dawley rats, male NMRI mice, male and female B6C3F1 mice, male DBA/2 mice and male Swiss mice (Löf *et al.*, 1984; Kessler *et al.*, 1992; Mendrala *et al.*, 1993; Morgan *et al.*, 1993a). Styrene-7,8-oxide was determined in blood, liver, lungs, kidneys and subcutaneous fat of male NMRI mice 2 h after intraperitoneal administration of [7-^{14}C]-styrene (1.1–5.1 mmol/kg bw). The concentration in subcutaneous fat (up to about 100 nmol/g) was several times higher than that in other tissues (up to 5–20 nmol/g) (Löf *et al.*, 1984).

In Sprague-Dawley rats, the styrene-7,8-oxide concentration in blood reached a maximum of about 0.3 mg/L at atmospheric styrene concentrations above 360 ppm [1560 mg/m^3] (Kessler *et al.*, 1992). In the mouse strains investigated (DBA2, Swiss and B6C3F1), the styrene-7,8-oxide concentrations in blood increased greatly at styrene concentrations above 250 ppm [1083 mg/m^3] (Kessler *et al.*, 1992; Morgan *et al.*, 1993a,b), reaching a value of about 6 mg/L at 800 ppm [3466 mg/m^3], which was suggested to be due to glutathione depletion (Kessler *et al.*, 1992). This conjecture was confirmed in mice exposed for 6 h/day for three days to constant concentrations of styrene vapours in excess of 260 ppm [1127 mg/m^3] (Morgan *et al.*, 1993a,b). Physiologically based pharmacokinetic modelling of this effect suggests that glutathione transferase-mediated detoxification of styrene-7,8-oxide is

decreased (Csanády *et al.*, 1994). The amount of styrene-7,8-oxide in blood of humans exposed to styrene at concentrations below 100 ppm [433 mg/m^3] (Wigaeus *et al.*, 1983; Löf *et al.*, 1986b; Korn *et al.*, 1994) was 5–20 times lower than the corresponding values in rodents (Fig. 2).

Fig. 2. Concentrations of styrene-7,8-oxide in blood of male rodents in relation to concentrations of styrene in air



From Kesslet *et al.* (1992) and Morgan *et al.* (1993b)

A proportion of styrene-7,8-oxide is further metabolized by microsomal epoxide hydrolase to styrene glycol (Oesch *et al.*, 1971; Watabe *et al.*, 1978). A coupled mono-oxygenase–hydrolase multi-enzyme complex with direct substrate transfer was assumed by Oesch (1973) which would result in a first-pass effect for styrene-7,8-oxide formed from styrene within the endoplasmic reticulum.

After intraperitoneal administration of [7-^{14}C]-styrene (1.1–5.1 mmol/kg bw) to male NMRI mice, styrene glycol was detected in all tissues examined (blood, liver, lungs, kidneys, brain, pancreas, subcutaneous fat), with the highest concentration in kidney. The concentrations increased linearly with dose and were proportional to the respective styrene-7,8-oxide concentrations (see above) in the tissues (Löf *et al.*, 1984). Further metabolism of styrene glycol yields mandelic acid, phenylglyoxylic acid and hippuric acid, which are the main metabolites excreted in the urine of Wistar rats after intraperitoneal treatment with styrene (Ohtsuji & Ikeda, 1971).

Rat microsomal monooxygenase is stereoselective, preferring the S to the R form (Foureman *et al.*, 1989), and the metabolism of styrene glycol is stereoselective in rats *in vivo* (Drummond *et al.*, 1990). Racemic styrene glycol is excreted only as *R*-mandelic acid; *S*-styrene glycol is excreted principally as that enantiomer. In another study, the ratio of *R*-:*S*-mandelic acid was between 2 and 4, depending on the pretreatment of rats (Elovaara *et al.*, 1991).

A proportion of styrene-7,8-oxide is conjugated with glutathione, although direct conjugation of styrene without prior epoxide formation may also occur (Stock *et al.*, 1986). The glutathione conjugates with styrene-7,8-oxide are transformed into the mercapturic acids *N*-acetyl-*S*-(1-phenyl-2-hydroxyethyl)cysteine, *N*-acetyl-*S*-(2-phenyl-2-hydroxyethyl)-cysteine and *N*-acetyl-*S*-(phenylacetyl)cysteine and excreted in urine. About 10% of a single intraperitoneal dose of 250 mg/kg bw to female Wistar rats was excreted as mercapturic acids (Seutter-Berlage *et al.*, 1978). After 6-h exposures of male Sprague-Dawley rats to 25–200 ppm styrene [108–867 mg/m^3], the amount of the two major mercapturic acids excreted during 24 h was about 74% of the excreted amount of mandelic acid and phenylglyoxylic acid at the highest exposure concentration (Truchon *et al.*, 1990).

Other putative metabolites identified in urine of styrene-exposed rats were 1-phenylethanol, 2-phenylethanol (Bakke & Scheline, 1970) and phenaceturic acid (Delbressine *et al.*, 1980). The occurrence of small amounts of 4-vinylphenol (0.1% of styrene dose) in the urine of rats treated orally with 100 mg/kg bw styrene (Bakke & Scheline, 1970) suggested formation of the ring epoxide, styrene-3,4-oxide, as an intermediary metabolite of styrene (Pantarotto *et al.*, 1978).

Since glutathione conjugates are formed, the effect of styrene on glutathione levels was studied. Glutathione levels in the livers of male Wistar rats were significantly depleted, to 75% and 44%, following exposures (6 h per day, four days) to styrene at 200 and 400 ppm [867 and 1733 mg/m^3], respectively. After exposure to 300 ppm styrene [1300 mg/m^3] for 6 h per day, five days per week for 2–11 weeks, glutathione levels reached a minimum of 72% of the control level in lungs and 41% in liver after two weeks but returned to 110% in lungs and 80% in liver after six weeks (Vainio *et al.*, 1979). A 24-h exposure of male Han/Wistar rats to 500 ppm styrene [2166 mg/m^3] resulted in glutathione levels of 84% of the control level in liver and 34% in lung; the concentration in kidneys was unaffected (Elovaara *et al.*, 1991). The hepatic glutathione content was reduced to about 50% of control levels for about 5 h following intraperitoneal injection of 300 mg/kg bw styrene to male Wistar rats (Katoh *et al.*, 1989).

(c) *Protein adducts*

Exposure to styrene results in binding to several amino acids in proteins *in vivo*. In rats administered 0.5, 1, 2 and 3 mmol styrene/kg bw by intraperitoneal injection, concentrations of the cysteine adduct of styrene-7,8-oxide in globin were measured after carbon–sulfur bond cleavage by the Raney nickel procedure (Ting *et al.*, 1990). A linear increase was seen in the amount of adduct produced with dose. Treatment with 1 mmol/kg styrene yielded 2.3 nmol/g globin. Alkylation was also determined following intraperitoneal administration of styrene to rats at 0, 0.5, 1 and 3 mmol/kg bw and of styrene-7,8-oxide at 0, 0.1, 0.3 and 1 mmol/kg bw (Rappaport *et al.*, 1993). The dose–response curves for alkylation of haemoglobin and albumin cysteine were linear and indicated that about 2% of the styrene dose was available as styrene-7,8-oxide in blood.

Byfält Nordqvist *et al.* (1985) administered [7-^{14}C]-styrene intraperitoneally to mice at doses of 0.12–4.9 mmol/kg bw. The valine adduct in haemoglobin, determined by a modified Edman procedure, constituted about 3% of total alkylation. Latriano *et al.* (1991) exposed rats for 6 h per day for five days to 1000 ppm styrene and found a 25-fold increase in valine adducts over that in controls.

4.2 Toxic effects

4.2.1 *Humans*

The odour threshold for styrene is 70 μg/m^3 [16 ppb] (WHO, 1987). It causes irritation of eyes, throat and respiratory tract at 84 mg/m^3 [19 ppm] (Lorimer *et al.*, 1976, 1978). Subjective health complaints were usually not seen in the glass-reinforced plastics industry with concentrations of styrene below 105 mg/m^3 [24 ppm] (Geuskens *et al.*, 1992).

Central and peripheral nervous system effects have been observed in styrene-exposed workers. Nerve conduction velocities were decreased (Lilis *et al.*, 1978; Rosén *et al.*, 1978; Cherry & Gautrin, 1990; Murata *et al.*, 1991), and electroencephalographic (Seppäläinen & Härkönen, 1976), dopaminergic (Mutti *et al.*, 1984a; Arfini *et al.*, 1987; Checkoway *et al.*, 1992), functional (Lindström *et al.*, 1976; Cherry *et al.*, 1980; Baker *et al.*, 1985; Gregersen, 1988) and psychiatric impairments (Flodin *et al.*, 1989) have been noted. Most effects have been seen at concentrations of about 100 ppm [433 mg/m^3] styrene, although memory and neurobehavioural disturbances were seen at 10–30 ppm [43–130 mg/m^3] and above (Flodin *et al.*, 1989; Letz *et al.*, 1990). Other studies have shown no evidence of neurotoxicity (Triebig *et al.*, 1989). The hearing threshold was unchanged in workers exposed to less than 150 mg/m^3 [35 ppm] (Muijser *et al.*, 1988; Möller *et al.*, 1990). In a mortality study of styrene-exposed workers, an increased number of deaths attributed to 'symptoms, senility and ill-defined conditions' was ascribed to a high local registration of these conditions in comparison with national statistics (Bond *et al.*, 1992).

The effects of styrene on the respiratory tract of workers exposed to concentrations above 100 mg/m^3 [433 ppm] include chronic bronchitis (Härkönen, 1977) and obstructive pulmonary changes (Chmielewski & Renke, 1976). Cases of styrene-induced asthma (Moscato *et al.*, 1987; Hayes *et al.*, 1991) and one of contact dermatitis (Sjöborg *et al.*, 1984) have also been reported.

Several studies reported signs of liver damage, as measured by liver enzyme activities in serum, but it was concluded in a review that no clear-cut trend towards altered liver function could be demonstrated (WHO, 1983). Elevated serum bile acid concentrations were observed in one study (Edling & Tagesson, 1984) but not in another (Härkönen *et al.*, 1984a). In one study, altered kidney function was indicated by increased urinary excretion of albumin in styrene-exposed workers (Askergren *et al.*, 1981).

Early studies on the effects of styrene on the haematopoietic and immune system did not consistently reveal changes (WHO, 1983). In a group of reinforced plastics workers exposed to 60 mg/m^3 [14 ppm] styrene, an increased number of peripheral blood monocytes was noted (Hagmar *et al.*, 1989); in another group of workers, changes in lymphocyte subpopulations were observed (Mutti *et al.*, 1992).

4.2.2 *Experimental systems*

Acute exposure of animals to styrene causes irritation of the skin and respiratory tract and central nervous system effects. Liquid styrene is a skin irritant which, on direct contact, causes erythema. Long-term contact with styrene results in blistering of the skin and development of dermatitis, which is thought to result from defatting of the skin. Single exposures of rats and guinea-pigs to 1300 ppm [5633 mg/m^3] styrene resulted in central nervous system effects, including weakness and unsteadiness. After exposure to 2500 ppm [10.8 g/m^3] styrene for 10 h, both rats and guinea-pigs lost consciousness; exposure to 5000–10 000 ppm [21.7–43.3 g/m^3] resulted in unconsciousness and death. The principal pathological findings in these animals were severe pulmonary irritation, congestion, oedema, haemorrhage and leukocytic infiltration (Bond, 1989).

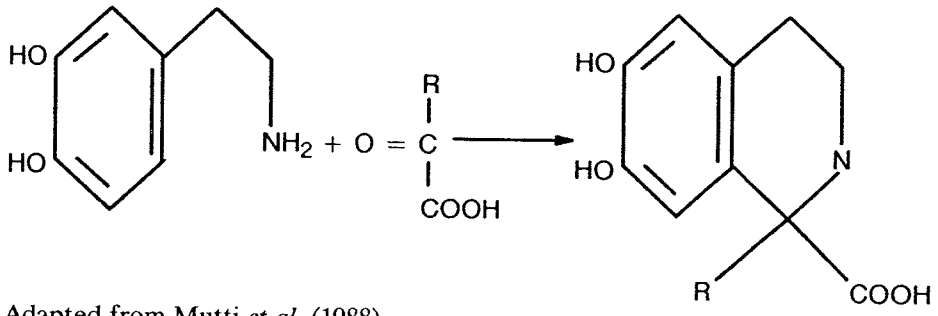
Ohashi *et al.* (1985) investigated the respiratory toxicity of styrene in rats. Epithelial changes occurred in the nose and trachea of animals exposed to 800 ppm [3466 mg/m^3] styrene for 4 h per day for eight weeks. The changes included vacuolation of epithelial cells, nuclear pyknosis and exfoliation of epithelial cells. Changes in the nasal mucosa occurred at exposure levels of 30 ppm [130 mg/m^3]. Morphological damage was more severe in the upper than in the lower respiratory tract.

Early studies on the neurotoxicity of styrene gave equivocal results (WHO, 1983), but a decrease in the activity of monoamine oxidase was seen in male rats after repeated oral doses of styrene (Zaprianov & Bainova, 1979). In subsequent studies in male rabbits, exposure to styrene caused a dose-dependent decrease in striatal and tuberoinfundibular dopamine content and an increase in homovanillic acid content, consistent with disturbance of the dopaminergic functions of the brain (Mutti *et al.*, 1984b). The levels of norepinephrine were unchanged, suggesting that the metabolites of styrene, phenyl glyoxylic acid and mandelic acid, condense with dopamine and deplete it through a direct chemical reaction of the α-keto acids (Fig. 3; Mutti *et al.*, 1988).

An increase in the prevalence of glial marker proteins was noted in Sprague-Dawley rats exposed to 320 ppm [1386 mg/m^3] styrene for three months (Rosengren & Haglid, 1989), and was taken to be an indication of brain damage. Mild neurobehavioural disturbances were seen in rats exposed to 1400 ppm [6066 mg/m^3] styrene for 18 weeks (Kulig, 1989) and in mice exposed to 425 ppm [1841 mg/m^3] for two weeks (Teramoto *et al.*, 1988). Disturbances

of the auditory system were observed only with combined exposure to trichloroethylene (Rebert *et al.*, 1993).

Fig. 3. Possible molecular basis for dopamine condensation: 1,2,3,4-tetrahydroisoquinolines are formed non-enzymatically in the Pictet-Spengler reaction of the carbonylic group of an α-keto acid with the aminic group of dopamine.



Adapted from Mutti *et al.* (1988)

Exposure of B6C3F1 mice to 259 ppm [1122 mg/m^3] styrene for 6 h a day for 14 days induced hepatic necrosis (Morgan *et al.*, 1993c). Hepatotoxicity in rats occurs concomitantly with depletion of glutathione and may be either a direct effect of styrene or mediated by lipid peroxidation (Srivastava *et al.*, 1983; Décarie & Chakrabarti, 1989; Katoh *et al.*, 1989).

Morphological changes have been observed in rat kidney (Chakrabarti *et al.*, 1987) and respiratory mucosa (Ohashi *et al.*, 1986) after exposure to styrene. Srivastava *et al.* (1989) showed that exposure of adult male Wistar rats to 400 mg/kg bw (but not 200 mg/kg bw) styrene daily by gavage for 60 days damaged seminiferous tubules, with reduced sperm count in the epididymis and changes in testicular enzymes, but had no effect on body or testicular weight. The same authors showed that young rats are more sensitive than older animals, with similar changes in sperm count and testicular enzymes when exposed to 200 mg/kg bw (but not 100 mg/kg bw) daily by gavage for the first 60 days of life (Srivastava *et al.*, 1992a). Only slight, transient effects were observed in male offspring of lactating dams exposed during lactation to 400 mg/kg bw styrene daily (Srivastava *et al.*, 1992b).

Effects in kidney and lung are associated with depletion of glutathione (Chakrabarti & Tuchweber, 1987; Elovaara *et al.*, 1990) and possibly with direct toxicity of glutathione conjugates on the kidney (Chakrabarti & Malick, 1991). At 210 mg/m^3, styrene inhibited δ-aminolaevulinate dehydratase activity in rat erythrocytes and bone marrow (Fujita *et al.*, 1987).

Styrene suppressed the activity of mouse splenic T lymphocyte killer cells *in vitro* (Grayson & Gill, 1986). Male Swiss mice dosed orally with 20–50 mg/kg bw styrene daily for five days showed impairment of humoral and cell-mediated immunity (Dogra *et al.*, 1989); a similar dose regimen given for four weeks decreased the resistance of mice to viral, malarial and hookworm infections (Dogra *et al.*, 1992).

4.3 Reproductive and prenatal effects

4.3.1 *Humans*

The frequency of spontaneous abortions among women with definite or assumed exposure to styrene has been investigated in a number of studies. The majority do not indicate an increased risk in association with occupational exposure to styrene (Hemminki *et al.*, 1980; Härkönen & Holmberg, 1982; Lindbohm *et al.*, 1985; Ahlborg *et al.*, 1987; Taskinen *et al.*, 1989; Lindbohm *et al.*, 1990). A study in Canada (McDonald *et al.*, 1988) found an increased risk for spontaneous abortions (18 observed; SMR, 158; 90% CI, 102–235) among women employed in polystyrene manufacture. The expected figures were derived from the experience of 47 316 pregnant women who had worked for 30 h or more per week at the start of pregnancy. No styrene concentrations were given, and most of these women had had mixed exposures. Two studies in Finland found no increase in the frequency of spontaneous abortion or congenital malformation among the wives of men exposed occupationally to styrene (Taskinen *et al.*, 1989; Lindbohm *et al.*, 1991).

Exposure to styrene has been mentioned in some case reports of central nervous system defects in children born to mothers who were exposed to organic solvents during pregnancy (Holmberg, 1977, 1979). A cohort study showed no increased risk for congenital malformations among children of styrene-exposed women or of women married to styrene-exposed men (Härkönen *et al.*, 1984b).

A study on menstrual dysfunction among 174 styrene-exposed and 449 unexposed women from 36 US reinforced plastics companies showed no increase in risk associated with exposure to styrene (Lemasters *et al.*, 1985b). Children born to the 50 women with the highest exposure to styrene (mean, 82 ppm) had a 4% reduction in birth weight ($p = 0.08$); the women were also exposed to other, unidentified solvents (Lemasters *et al.*, 1989).

4.3.2 *Experimental systems*

Styrene has been shown to cross the placenta of rats. Sprague-Dawley rats exposed for 5 h on day 17 of gestation to 1000 (six rats) or 2000 (five rats) ppm styrene [4330 or 8660 mg/m^3] had blood levels, respectively, of about 35 μg/g and 88 μg/g and fetal levels of 17 μg/g and 48 μg/g tissue (Withey & Karpinski, 1985). Transfer was also shown to occur on the 16th day of pregnancy in CD1,crj mice injected intravenously with 5 μCi (5 μl) [8-^{14}C]styrene. By 6 h, the levels in the fetus were similar to those in maternal brain (Kishi *et al.*, 1989).

The reproductive toxicity of styrene has been reviewed by Jakobsen (1990) and very extensively by Brown (1991), who critically reviewed work published in 1960–90, including the extensive Russian and eastern European literature. The overall conclusion was that there is little indication that styrene exerts any specific developmental or reproductive toxicity.

Murray *et al.* (1978) carried out a standard teratological investigation in rats and rabbits using production-grade styrene (> 99.5% pure). Groups of 23–29 pregnant Sprague-Dawley rats were exposed (whole body) for 7 h per day to 0, 300 or 600 ppm styrene [0, 1299 or 2598 mg/m^3] (with one control group for each exposure level) from days 6 to 15 of gestation, and the fetuses removed for examination on day 21. Groups of 24–32 rats were dosed by

gavage with 90 or 150 mg/kg bw styrene twice daily (total doses, 180 and 300 mg/kg bw per day) from days 6 to 15 of gestation and the fetuses examined on day 21. All treatments reduced weight gain in the dams during days 6–9, but there was no overall adverse effect on number or size of litters, resorptions, fetal weight or crown–rump length. The incidences of external, visceral or skeletal malformations were not increased, and variations were within historical control limits. Groups of 16–19 pregnant New Zealand white rabbits were exposed (whole body) for 7 h per day to 0, 300 or 600 ppm styrene (with one control group for each exposure level) from days 6 to 18 of gestation and the fetuses removed for examination on day 29. No toxicity and no effect on the body weight of the dams were observed, and no effects were seen on litter number or size, resorptions, fetal weight or crown–rump length. No malformed fetuses were found in any group and, other than a slightly increased incidence of unossified fifth sternebrae (within historical control range), no other variation was observed.

A three-generation reproduction study was carried out in rats by Beliles *et al.* (1985). Groups of Sprague-Dawley rats were exposed constantly to styrene in the drinking-water at concentrations of 0, 125 or 250 ppm [541 or 1082 mg/L] (averages measured, 112 and 221 ppm [485 and 957 mg/L]) for two years. After 90 days' treatment, groups of 10 males and 20 females and 15 and 30 controls were mated to produce an F1 generation. These pups were kept on the respective treatments and subsequently mated to produce two further generations (F2 and F3) of one litter each, all of which continued to be exposed to styrene in the drinking-water. No treatment-related change in fertility, litter size, pup viability, survival, sex ratio, body weight or bone-marrow cytogenetics was observed.

In a study of a variety of chemicals which are not known to be developmental toxins, given to Sprague-Dawley rats at lethal or near lethal doses in order to study the effects of severe maternal toxicity on fetal development, styrene (99% pure) was administered by gavage at a dose of 1147 mg/kg bw per day from days 6 to 15 of gestation. It produced a very marked reduction in maternal weight gain during the entire pregnancy, but in 13 animals that survived to day 20 there was no adverse effect on litter size, resorptions, fetal weight, malformations or variations, except for an inceased proportion of fetuses with an enlarged renal pelvis (Chernoff *et al.*, 1990).

On the basis of the suggestion that toxic doses of chemicals that induce hepatic metallothionein in pregnant rats (and thus sequester zinc in their livers) can lead to developmental toxicity by inducing zinc deficiency in the embryos, Sprague-Dawley rats were dosed on day 11 of gestation with 300 mg/kg bw styrene orally. They showed no specific induction of metallothionein, no changes were seen in zinc levels in the fetuses and no developmental toxicity was seen in the eight litters examined (Daston *et al.*, 1991).

Zaidi *et al.* (1985) showed that exposure of albino rats [strain unspecified] to 200 mg/kg bw styrene by gavage during lactation increase the number of striatal dopamine receptors in pups at two and three weeks of age, resulting in some behavioural effects. No effects were seen if the rats were exposed only during gestation.

Groups of 12 Wistar rats were fed throughout gestation and lactation on a diet containing either a high (20% casein) or a low (8% casein) protein level. From day 6 of gestation onwards, half of the animals were given orally 100 mg/kg bw styrene daily. The low-protein diet slightly impaired postnatal growth and development of the pups, but those given styrene

as well were markedly affected, with effects on brain enzymes and receptor activity. Styrene had no adverse effect in the animals fed the high protein diet (Khanna *et al.*, 1991).

When Wistar rats were exposed to 50 or 300 ppm styrene [217 or 1299 mg/m^3] by inhalation for 6 h per day (analysed levels, 60 and 293 ppm [260 and 1269 mg/m^3]) on days 7–21 of gestation, no adverse effect was observed in the dams, but pup body weight on the day of delivery was depressed at both dose levels. Pup brain weight and protein content were not affected, but the levels of cerebral serotonin and 5-hydroxyindoleacetic acid were significantly reduced in the one-day-old pups exposed to the high-dose level (Kishi *et al.*, 1992).

Exposure of male (C3H/He×C57Bl/6J)F1 mice to styrene by inhalation (whole body) at 150 or 300 ppm [650 or 1299 mg/m^3] for 6 h daily for five days, or to 175, 350 or 700 mg/kg bw intraperitoneally daily for five days did not increase the frequency of abnormal sperm heads at examination three and five weeks after the start of treatment (Salomaa *et al.*, 1985).

4.4 Genetic and related effects

4.4.1 *Humans*

Several reviews on the genetic toxicology of styrene include data on human genetic biomonitoring (Barale, 1991; European Centre for Ecotoxicology and Toxicology of Chemicals, 1992; Norppa & Sorsa, 1993; Scott, 1993). Most data published since the re-evaluation of styrene (IARC, 1987b) relate to attempts to find adducts, DNA breakage or cytogenetic damage in association with occupational exposure to styrene.

(*a*) *DNA adducts*

Liu *et al.* (1988) measured adducts in one styrene-exposed worker by the ^{32}P-postlabelling technique; they reported a modification level of 8.6×10^{-7} nucleotides.

The numbers of DNA adducts were compared in lamination workers exposed to styrene at 200–400 mg/m^3 in two plants and in agricultural workers, by a ^{32}P-postlabelling method (Vodička & Hemminki, 1993; Vodička *et al.*, 1993). O^6-Guanine adducts were measured specifically using authentic standards. More than five times higher levels of O^6-(2-hydroxy-1-phenylethyl)-2′-deoxyguanosine-3′-monophosphate were detected among the exposed workers than in controls. The level of adducts in one exposed group was 4.7 (SD ± 1.9) adducts per 10^8 nucleotides, whereas it was 0.3 (SD ± 0.3) adducts per 10^8 nucleotides in the controls. The mean adduct level was 7.3 (SD ± 4.9) in workers in the second plant and 1.1 (SD ± 1.3) in the control group.

(*b*) *Alkali-labile sites/DNA single-strand breakage*

Using the alkaline elution technique, Walles *et al.* (1993) demonstrated single-strand DNA breaks in the leukocytes of 17 men occupationally exposed to low concentrations of styrene in a plastics factory. [The Working Group noted that this method does not distinguish between alkali-labile sites and single-strand breaks in DNA.] The time-weighted average concentration of styrene in the breathing zone during an 8-h shift was 7.0 ppm [29.4 mg/m^3] (range, 0.04–20 ppm [0.17–85.2 mg/m^3]), and the arithmetic mean urinary mandelic acid concentration was 70 mg/g creatinine at the end of the shift. An exposure-dependent

increase in the frequency of single-strand breaks was observed at the end of the shift, but not before a shift or the following morning, suggesting repair of the damage. There was no effect of age, years of employment or use of wet snuff. Smoking influenced the frequency of single-strand breaks during a shift, but the increase due to working was significant in both smokers and nonsmokers. Linear regression analysis indicated that an 8-h exposure to 18 ppm [76 mg/m^3] styrene, or the resulting urinary mandelic acid concentration of 240 mg/g creatinine, would result in a doubling of the normalized area above the DNA elution curve from the value for no styrene.

In a previous study by the same group, single-strand breakage at the end of a shift was increased in reinforced plastics industry workers manufacturing large plastic containers and exposed to much higher levels (estimated average, 300 mg/m^3 on the basis of an average post-shift urinary mandelic acid concentration of 9.4 ± 6.4 mmol/L and a blood styrene glycol concentration of 2.5 ± 1.5 μmol/L) than in the later study. The method used was the alkaline DNA unwinding technique. Pre-shift analyses were not done (Mäki-Paakkanen *et al.*, 1991).

(*c*) *Cytogenetic damage in lymphocytes*

Since the first published report of an association between exposure to styrene in the reinforced plastics industry and chromosomal damage in the lymphocytes of workers (Meretoja *et al.*, 1978a), studies have appeared reporting both the presence and absence of three cytogenetic end-points: chromosomal aberrations, sister chromatid exchange and micronuclei (Table 14). The conflicting nature of the results reported may be due to a number of factors. The early studies involved small numbers of individuals exposed to high levels, the highest exposures being those of workers in the reinforced plastics industry. In later studies, improved cytogenetic techniques were used, and two important confounding factors, age and smoking, were identified.

In the only study performed in the polystyrene manufacturing industry (Fleig & Thiess, 1978; Thiess & Fleig, 1978), the frequency of chromosomal aberrations in 12 employees with 2–39 years of exposure was not increased over that in controls matched for sex and age. The styrene concentrations in air were generally below 1 ppm [4.3 mg/m^3], and the mandelic acid concentrations in urine were generally less than 50 mg/L. In the study of Fleig and Thiess (1978), an additional five workers in styrene monomer manufacture were included who had been employed for 14–25 years and had mandelic acid concentrations of less than 40 mg/L urine. No difference was seen in chromosomal aberration frequency as compared with that in matched controls. In contrast, the aberration frequency in 14 workers processing unsaturated polyester resins was greater than that in 20 controls. These workers had been exposed for 2–24 years (mean, 7.9 years) and had urinary mandelic acid concentrations of 102–> 1500 mg/L, indicating a much higher exposure than in the styrene monomer and polystyrene manufacturing industry.

Thiess *et al.* (1980) also found no significant increase in the frequency of chromosomal aberrations in 24 employees after 4–27 years of exposure to an average styrene monomer concentration of 6 ppm (1–11.5 ppm [25 (4.3–50) mg/m^3]) in a laboratory or 58.1 ppm (0.7–178 ppm [250 (3–760) mg/m^3]) in a pilot plant, when compared with a matched control group.

Table 14. Cytogenetic observations in lymphocytes from people occupationally exposed to styrene

No. exposed	No. of referents	Length of exposure (years)		Styrene in air (ppm)		Urinary mandelic acid (μg/g creatinine)		Cytogenetic observation			Reference
		Range	Mean	Range	Mean	Range	Mean	CA	MN	SCE	
10	3	1–15	3.2	≤ 300		53–1646	570	+			Meretoja *et al.* (1978a)
16	6	1–15	6.3	≤ 300		23–3257	239	+		–	Meretoja *et al.* (1978a)
5	20	14–25		≤ 10		19–40 mg/L	30	–			Fleig & Thiess (1978)
12	20	3–39		0–47	2	< 5–100 mg/L	32	–			
14	20	2–24		50–300		102–> 1500 mg/L	593	(+)			
12	12	3–34		0–9		10–109 mg/L		–			Thiess & Fleig (1978)
6	6	0.5–10		14–192	39	225–2100	490	+			Högstedt *et al.* (1979)
24	24	4–27		0.7–170	58.1	0–320 mg/L		–			Thiess *et al.* (1980)
36	37	0.3–12		1–382	138			+			Andersson *et al.* (1980)
20	21	0.3–12		1–382	138					(+)	
16	13	0.6–9.3		1–211	70	90–4300 mg/L		–		–	Watanabe *et al.* (1981)
18	6	0.2–30		40–50		0–1041 mg/L	332	–		–	Watanabe *et al.* (1983)
38	20	1–23		1–36	13	9–316	65		+		Högstedt *et al.* (1983)
25 (22)[a]	22 (20)	1–22	9.4	7–> 96		45–1108 mg/L	458	+		(+)	Camurri *et al.* (1983)
43 (35)[a]	33 (28)	1–22		7–> 96		45–1440 mg/L	479	+			Camurri *et al.* (1984)
18	9			2–44	13.2			–		–	Hansteen *et al.* (1984)
15	13	1–26			24	< 152–304		–			Nordenson & Beckman (1984)
12	12	1–26			24	< 152–304			+		Nordenson & Beckman (1984)
36	19	1–11		1–236	36	35–972 μg/L	–			P	Pohlová & Srám (1985)
22	22	1–11		9–132		40–3000 μg/L	–				
21	21	1–25		8–63	24	0–1103 mg/L	243	–	–	–	Mäki-Paakkanen (1987)
32	32		18.8	27–55				+			Forni *et al.* (1988)
8	8		4.5	9–44				–			
11	11		10	28–140	61			–			Jablonická *et al.* (1988)
11	15	0.1–25.4	8.1	1–39	13	< 6–317[b]	128[b]	–			Hagmar *et al.* (1989)
20	22	0.1–25.4	8.1	1–39	13	< 6–317[b]	128[b]		–		

Table 14 (contd)

No. exposed	No. of referents	Length of exposure (years)		Styrene in air (ppm)		Urinary mandelic acid (μg/g creatinine)		Cytogenetic observation			Reference
		Range	Mean	Range	Mean	Range	Mean	CA	MN	SCE	
7	8 (smokers)		8.6	1.7–131	50		275			–	Kelsey *et al.* (1990)
13	12 (nonsmokers)		7.2	5.8–130	55		323			–	
11	11 (smokers)		6.4			< 152–3271 mg/L	1674	–	–	–	Mäki-Paakkanen *et al.* (1991)
6	6 (nonsmokers)		7.2			< 152–2526 mg/L	989	?	–	–	
17	17 (all)		6.7		70	< 152–3271 mg/L	1430	–	–	–	
10	9		2.7	1–44	11.2	96–2496	243		+	–	Brenner *et al.* (1991)
15	–				≤ 1.5						Yager *et al.* (1990, 1993)
16	–			0.2–55.3[c]	2–25				–	+	
17	–				> 25						
50	54			5–182	43			–	–	–	Sorsa *et al.* (1991)
25	54			1–133	11			–	–	–	
7	7	1–18		5–24	12[d]	46–345	186	–	–		Tomanin *et al.* (1992)
11	11	1.5–15		27–104	45[d]	423–1325	725	+	–		

CA, chromosomal aberrations; MN, micronuclei; SCE, sister chromatid exchange; +, positive; (+), weakly positive; –, negative; ?, inconclusive; blank, not tested

[a]Numbers in parentheses, samples for which data on both CA and SCE were available

[b]Mandelic acid + phenylglyoxylic acid (mmol/mmol creatinine)

[c]Linear regression analysis

[d]Assuming exposure to 50 ppm = 800 mg mandelic acid per g creatinine (American Conference of Governmental Hygienists, 1984)

Camurri *et al.* (1983) studied 25 workers at six sites (2–7 workers per site) in the reinforced plastics industry who were exposed to styrene at increasing concentrations ranging from 30 to > 400 mg/m^3 (7–> 96 ppm) and 22 matched controls. They found a significant increase in the frequency of chromosomal aberrations (mainly of the chromatid type) in relation to exposure level. A significant linear regression was also reported for individual aberration frequencies in relation to the concentration of urinary mandelic acid plus phenylglyoxylic acid, which are indicators of recent exposure to styrene. The authors noted that other chemicals in the work environments may play a role in the process of chromosomal damage but concluded that styrene was probably the cause of the observed damage. [The Working Group noted that the frequencies of chromosomal aberrations in both exposed and control subjects were unusually high.] An increase in the frequency of sister chromatid exchange was also reported in workers exposed to the three highest styrene concentrations, but there was no dose–response relationship.

Andersson *et al.* (1980) measured chromosomal aberration and sister chromatid exchange frequencies in a group of Swedish boat builders who had worked with fibreglass reinforced plastics in 1973–78. The workers were divided into a low-dose group (137 mg/m^3 ×years; 22 workers for chromosomal aberrations, 14 for sister chromatid exchange) and a high-dose group (1204 mg/m^3×years; 16 workers for chromosomal aberrations, six for sister chromatid exchange) on the basis of cumulated exposure to styrene. There were 37 controls for the studies of chromosomal aberrations and 21 for studies of sister chromatid exchange. Both groups had small but significantly increased frequencies of chromosomal aberrations, so that there was no difference in aberration frequency between the groups. Although a correlation between frequency and accumulated exposure was reported for the low-dose group for 6–283 mg/m^3×years, the relationship was not substantiated in the high-dose group (710–1589 mg/m^3×years). A slight increase in the frequency of sister chromatid exchange was reported in the high-dose group only. [The Working Group did not consider that increase to be of biological significance.]

In a study by Forni *et al.* (1988), chromosomal aberrations were measured in 40 controls and 40 workers from two factories with high (factory A) and low (factory B) cumulative exposure-years, based on measurements of styrene in air; however, current exposures were higher in factory B than in factory A, as also documented by measurement of mandelic acid. In 32 workers in factory A, the frequency of chromosomal type aberrations was highly significantly increased over that in 32 matched controls (1.2 *versus* 0.3%). In workers in factory B, an increased frequency of chromatid aberrations (2.25 *versus* 1.0%) but not of the chromosomal type was recorded.

Mäki-Paakkanen *et al.* (1991) reported a correlation between total years of exposure to styrene and the percentage of cells with chromosomal aberrations in a group of 17 workers and 17 controls at a reinforced plastics plant where large plastic containers were made. Only nonsmokers had a small but significant increase, however, and only when gaps were included. [The Working Group did not consider the finding significant.] They found no increase in the frequencies of micronuclei or of sister chromatid exchange in workers exposed to styrene.

In a longitudinal study of 48 workers at reinforced plastic boat manufacturing facilities (Yager *et al.*, 1990, 1993), a clear relationship was established between the level of styrene exposure and the induction of sister chromatid exchange in smokers and nonsmokers

involved in the production of reinforced plastics. The concentrations of styrene in air exhaled by exposed individuals, measured seven times during one year, were plotted against the mean sister chromatid exchange frequencies, which were measured twice in the same year. A linear regression analysis showed a highly significant correlation between these two parameters. The authors reported that the relative contribution of each variable to regression of sister chromatid exchange frequency showed that smoking contributed about 62% and styrene exposure about 25% of the total variation. No increase in the frequency of micronuclei was observed in four samples taken during the year.

Tomanin *et al.* (1992) studied chromosomal aberration and micronucleus induction in workers in two factories where polyester resin was used. Seven workers were engaged at small fibreglass manufacturing plants and were exposed to styrene at 21–100 mg/m^3 [5–24 ppm]; 10 workers in boat manufacturing plants had exposures of 112–435 mg/m^3 [27–104 ppm]. The mean chromosomal aberration frequency in the latter group was significantly greater than that in matched controls, but that of the former group was not. [The Working Group noted that this result might indicate a relationship between styrene exposure and aberration frequency.] For individuals within the more heavily exposed group, however, there was no clear correlation between urinary mandelic acid and chromosomal aberration frequency. The authors stated that there was no correlation between aberration frequency and length of exposure. [The Working Group noted that other factors may be involved in the process of chromosomal damage besides exposure to styrene.] Micronucleus frequency was not significantly increased in exposed workers.

In three studies, induction of micronuclei was reported in lymphocytes of workers in the reinforced plastics industry. In only one of the studies (Brenner *et al.*, 1991) did the staining method used allow differentiation between subsequent cell divisions. The differences in the frequencies of micronuclei between the groups were highly significant. [The Working Group noted that there were some deficiencies in the matching of controls in this study.]

In a preliminary study of glycophorin A variants, an increased frequency was found in styrene-exposed workers, but the results were confounded by differences in smoking habits and in age between the high and low exposure groups (Compton-Quintana *et al.*, 1993).

[The Working Group noted the following points: Exposure assessment is a general problem in studies of genotoxic effects. Measurements of styrene in the air or of styrene metabolites in urine or blood of individuals provide estimates of exposure that occurred on the day of sample collection or on the previous day.

Although the lifetime of lesions leading to cytogenetic changes is unknown, such changes may reflect recent exposure or exposure over many years. The situation is further complicated by the fact that no two occupational situations or workplaces are alike, and individual differences and seasonal variation are found in work load and intensity. Methodological differences in measurements of exposure in the various studies also make comparisons difficult. Time-weighted average concentrations of styrene in air do not take into account occasional high peak exposures, which may be important. The roles of individual genetic susceptibility to styrene and differences in its metabolism are also poorly understood. Consequently, it is difficult to establish a definitive relationship between styrene

exposure and chromosomal damage, although the methodological problems would tend to reduce the difference between exposed and unexposed workers.

Styrene is the most abundant compound in the air of plants in which reinforced plastics are used and would seem to be the likely cause of the observed chromosomal damage in workers; however, other factors may be involved. Styrene oxide, for example, may be present in the air of some work sites because of oxidation of styrene by various peroxides in lamination resins (Pfäffli & Säämänen, 1993). The possible role of the many other chemicals used in this branch of industry (see section 1) in inducing chromosomal damage in workers in the reinforced plastics industry has not been well characterized. Available data suggest that chromosomal aberrations occur more frequently in the lymphocytes of reinforced plastics laminators than do sister chromatid exchanges or micronuclei. Data obtained in animals exposed to styrene *in vivo*, however, suggest that DNA damage resulting from human exposure to styrene would produce primarily sister chromatid exchange rather than chromosomal aberrations.]

4.4.2 *Experimental systems*

(*a*) *DNA adducts*

A comprehensive review of DNA and protein binding by styrene and styrene oxide is available (Phillips & Farmer, 1994).

Byfält Nordqvist *et al.* (1985) reported that binding of ^{14}C-styrene to DNA in liver occurred in mice after intraperitoneal injection, and the adduct radiolabel co-chromatographed with 7-(hydroxyphenylethyl)guanine. In a subsequent study, ^{3}H-styrene was administered by inhalation to mice and rats for up to 9 h in a closed inhalation chamber, and DNA was isolated from liver and lungs (rats only) and purified to constant specific radioactivity. Radioactivity counts in the adduct fractions of nucleotides corresponded to very low binding levels: the covalent binding indices—(μmol adduct/mol DNA nucleotide)/(mmol chemical/kg bw)—in mouse liver were 0.05–0.18, and no binding was seen at the limit of detection of < 0.1 in rat liver. The index was 0.07 in the lungs of two of four female rats (Cantoreggi & Lutz, 1993).

(*b*) *Mutation and allied effects* (see also Table 15)

The SOS Chromotest in *Escherichia coli* strain PQ37 indicated negative results for DNA repair in one study and a positive result but no dose–response relationship in another.

Most studies have not demonstrated bacterial mutagenicity of styrene. This was a consistent finding in the absence of exogenous metabolic activation, but a few positive responses were reported in strains TA1535 and TA100 of *Salmonella typhimurium* in the presence of exogenous metabolic activation.

In a single study with *Saccharomyces cerevisiae*, styrene induced gene conversion, recombination and reverse mutation. Forward mutation was not induced in two studies with *Schizosaccharomyces pombe*.

Chromosomal aberrations were induced in one study in the plant *Allium cepa*. In a single study with *Drosophila melanogaster*, styrene induced sex-linked recessive lethal mutations but not aneuploidy.

Styrene induced DNA strand breaks in primary cultures of rat hepatocytes in one study. An exogenous metabolic activation system was required for mutation induction at the *hprt* locus of Chinese hamster V79 cells. Induction of sister chromatid exchange in Chinese hamster ovary cells required either exogenous metabolic activation or red blood cells, in separate studies. Sister chromatid exchange was induced in rat lymphocytes in a single study, and weak induction of chromosomal aberrations was seen in two studies with cultured Chinese hamster lung fibroblasts, one in the absence and one in the presence of exogenous metabolic activation.

Styrene did not induce transformation of C3H10T½ mouse cells *in vitro*, either alone or in a two-stage transformation assay with 3-methylcholanthrene.

Styrene induced sister chromatid exchange and micronuclei in human lymphocytes in whole blood cultures. Styrene at 2.0 mmol/L induced a 4.9-fold increase in sister chromatid exchange frequency in whole blood cultures but only a weak, 1.3-fold increase in isolated human lymphocytes (Norppa & Järventaus, 1992). Styrene also induced chromosomal aberrations in a dose-dependent manner in human whole blood cultures, but the response was weaker in isolated lymphocytes.

In mice *in vivo*, DNA strand breaks were induced in a single study and sister chromatid exchange in several; chromosomal aberrations were induced in only one of seven studies and micronuclei in two of six.

A positive dose–response relationship was seen for sister chromatid exchange frequency in peripheral blood and spleen lymphocytes and lung cells of B6C3F1 female mice exposed to concentrations of 125, 250 or 500 ppm [532.5, 1065 or 2130 mg/m^3] styrene by inhalation for 6 h a day for 14 days. Analysis of chromosomal breakage in splenocytes and lung cells and of micronuclei in blood erythrocytes and splenocytes showed no exposure-related response (Kligerman *et al.*, 1992).

In a comparative study of Porton rats and LACA Swiss mice, sister chromatid exchanges in splenocytes and micronuclei in bone-marrow cells were analysed following single intraperitoneal injections of 150–3000 mg/kg bw styrene, and sperm morphology was studied after five daily injections of 50–2000 mg/kg. Styrene produced weak but significant responses at all of three end-points in mice and in sperm morphology and sister chromatid exchange in rats (Simula & Priestly, 1992).

Preston and Abernathy (1993) exposed male rats to styrene at concentrations up to 1000 ppm [4260 mg/m^3] for 6 h per day for four weeks and found no increase in the frequencies of either chromosomal aberrations or sister chromatid exchange in peripheral lymphocytes. In a positive control group exposed to ethylene oxide at 150 ppm [270 mg/m^3], however, the frequency of sister chromatid exchange was increased but that of chromosomal aberrations was not.

Kligerman *et al.* (1993) exposed mice and rats to styrene by inhalation at concentrations of up to 500 ppm [2130 mg/m^3] for 6 h/day for 14 consecutive days. Small but significant concentration-related increases in the frequencies of sister chromatid exchange were noted in both mice and rats. There was no significant increase in DNA strand breakage in rats or in the frequencies of chromosomal aberrations or micronuclei in either rats or mice.

Table 15. Genetic and related effects of styrene

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
ECB, *Escherichia coli*, SOS repair	?	0	100.0000	Głośnicka & Dziadziuszko (1986)
ECB, *Escherichia coli*, SOS repair	–	0	10000.0000	Brams *et al.* (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	(+)	52.0000	Vainio *et al.* (1976)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	0.0000	de Meester *et al.* (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500.0000	Stoltz & Withey (1977)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	–	250.0000	Watabe *et al.* (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	104.0000	Busk (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	250.0000	De Flora (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	312.0000	Florin *et al.* (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	1000.0000[c]	de Meester *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	500.0000	Brams *et al.* (1987)
SA3, *Salmonella typhimurium* TA1530, reverse mutation	+	+	0.0200[c]	de Meester *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+	0.5000	Vainio *et al.* (1976)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+	52.0000	de Meester *et al.* (1977)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	500.0000	Stoltz & Withey (1977)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	0	–	250.0000	Watabe *et al.* (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	104.0000	Busk (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	250.0000	De Flora (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	312.0000	Florin *et al.* (1980)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	0	+	521.0000	Poncelet *et al.* (1980)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+	1 000.0000[c]	de Meester *et al.* (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	52.0000	Vainio *et al.* (1976)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	0.0000	de Meester *et al.* (1977)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500.0000	Stoltz & Withey (1977)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	0	–	250.0000	Watabe *et al.* (1978)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	104.0000	Busk (1979)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	312.0000	Florin *et al.* (1980)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1 000.0000[c]	de Meester *et al.* (1981)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	52.0000	Vainio *et al.* (1976)

Table 15 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	0.0000	de Meester *et al.* (1977)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	500.0000	Stoltz & Withey (1977)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	0	–	250.0000	Watabe *et al.* (1978)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	104.0000	Busk (1979)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	250.0000	De Flora (1979)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	1 000.0000[c]	de Meester *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500.0000	Brams *et al.* (1987)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	52.0000	Vainio *et al.* (1976)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	0.0000	de Meester *et al.* (1977)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500.0000	Stoltz & Withey (1977)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	–	250.0000	Watabe *et al.* (1978)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	104.0000	Busk (1979)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	250.0000	De Flora (1979)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	312.0000	Florin *et al.* (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1 000.0000[c]	de Meester *et al.* (1981)
SCG, *Saccharomyces cerevisiae*, gene conversion	+	0	104.0000	Del Carratore *et al.* (1983)
SCH, *Saccharomyces cerevisiae*, homozygosis	+	0	104.0000	Del Carratore *et al.* (1983)
SCR, *Saccharomyces cerevisiae*, reverse mutation	+	0	104.0000	Del Carratore *et al.* (1983)
SZF, *Schizosaccharomyces pombe*, forward mutation	–	–	10 400.0000	Loprieno *et al.* (1976)
SZF, *Schizosaccharomyces pombe*, forward mutation	0	–	2 080.0000	Bauer *et al.* (1980)
ACC, *Allium cepa*, chromosomal aberrations	+	0	90.0000	Linnainmaa *et al.* (1978a,b)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+	0	182.0000	Donner *et al.* (1979)
DMN, *Drosophila melanogaster*, aneuploidy	–	0	500.0000	Penttilä *et al.* (1980)
DIA, DNA strand breaks, rat primary hepatocytes *in vitro*	+	0	312.0000	Sina *et al.* (1983)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus	–	0	1 771.0000	Loprieno *et al.* (1976)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus	–	+	6 250.0000	Beije & Jenssen (1982)
SIC, Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	–	+	455.0000	de Raat (1978)
SIC, Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	–	+[d]	830.0000	Norppa *et al.* (1985)
SIR, Sister chromatid exchange, rat lymphocytes *in vitro*	+	0	50.0000	Norppa *et al.* (1985)
CIC, Chromosomal aberrations, Chinese hamster lung cells *in vitro*	–	(+)	250.0000	Matsuoka *et al.* (1979)

Table 15 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
CIC, Chromosomal aberrations, Chinese hamster lung cells *in vitro*	(+)	0	100.0000	Ishidate & Yoshikawa (1980)
TCM, Cell transformation, C3H10T1/2 mouse cells	-	0	10.0000	Male *et al.* (1985)
SHL, Sister chromatid exchange, human whole blood lymphocytes *in vitro*	+	0	104.0000	Norppa *et al.* (1980a)
SHL, Sister chromatid exchange, human whole blood lymphocytes *in vitro*	+	0	104.0000	Norppa & Vainio (1983)
SHL, Sister chromatid exchange, human whole blood lymphocytes *in vitro*	+[e]	0	50.0000	Norppa *et al.* (1983)
SHL, Sister chromatid exchange, human whole blood lymphocytes *in vitro*	+	0	1.0000	Chakrabarti *et al.* (1993)
MIH, Micronucleus formation, human whole blood lymphocytes *in vitro*	+	0	270.0000	Linnainmaa *et al.* (1978a)
CHL, Chromosomal aberrations, human whole blood lymphocytes *in vitro*	+	0	270.0000	Linnainmaa *et al.* (1978a)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	0	50.0000	Pohlova *et al.* (1985)
CHL, Chromosomal aberrations, human whole blood lymphocytes *in vitro*	+	0	208.0000	Jantunen *et al.* (1986)
HMM, Host-mediated assay, *Saccharomyces cerevisiae* gene conversion in mouse	+		1000.0000	Loprieno *et al.* (1976)
DVA, DNA strand breaks, mouse, various organs *in vivo*	+		170.0000×1 ip	Walles & Orsén (1983)
DVA, Single-strand DNA breakage, rat peripheral lymphocytes *in vivo*	-		450.0000 inhal. 6 h/d×14	Kligerman *et al.* (1993)
SVA, Sister chromatid exchange, mouse bone-marrow and liver cells *in vivo*	+		850.0000 inhal. 6 h/d×4	Conner *et al.* (1979)
SVA, Sister chromatid exchange, mouse bone-marrow, liver and alveolar macrophages *in vivo*	+		580.0000 inhal. 6 h/d×4	Conner *et al.* (1980)
SVA, Sister chromatid exchange, mouse bone-marrow cells *in vivo*	+		500.0000×1 ip	Sharief *et al.* (1986)
SVA, Sister chromatid exchange, mouse lymphocytes *in vivo*	+		450.0000 inhal. 6 h/d×14	Kligerman *et al.* (1992)
SVA, Sister chromatid exchange, mouse lung cells *in vivo*	+		450.0000 inhal. 6 h/d×14	Kligerman *et al.* (1992)
SVA, Sister chromatid exchange, mouse splenocytes *in vivo*	(+)		450.0000×1 ip	Simula & Priestly (1992)
SVA, Sister chromatid exchange, rat splenocytes *in vivo*	+		750.0000×1 ip	Simula & Priestly (1992)
SVA, Sister chromatid exchange, rat peripheral lymphocytes *in vivo*	+		225.0000 inhal. 6 h/d×14	Kligerman *et al.* (1993)
MVM, Micronucleus formation, mouse bone-marrow cells *in vivo*	+		250.0000×1 ip	Norppa (1981)
MVM, Micronucleus formation, mouse splenocytes *in vivo*	-		900.0000 inhal. 6 h/d×14	Kligerman *et al.* (1992)
MVM, Micronucleus formation, mouse erythrocytes *in vivo*	-		900.0000 inhal. 6 h/d×14	Kligerman *et al.* (1992)
MVM, Micronucleus formation, mouse bone-marrow cells *in vivo*	(+)		600.0000×1 ip	Simula & Priestly (1992)
MVR, Micronucleus formation, rat bone-marrow cells *in vivo*	-		3000.0000×1 ip	Simula & Priestly (1992)
MVR, Micronucleus formation, rat peripheral lymphocytes *in vivo*	-		450.0000 inhal. 6 h/d×14	Kligerman *et al.* (1993)

Table 15 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
MVC, Micronucleus formation, Chinese hamster bone-marrow cells *in vivo*	–		1000.0000×1 ip	Penttilä *et al.* (1980)
CBA, Chromosomal aberrations, rat bone-marrow cells *in vivo*	+		270.0000 inhal. 6 h/d; 5 d/wk; 9 wk	Meretoja *et al.* (1978b)
CBA, Chromosomal aberrations, Chinese hamster bone-marrow cells *in vivo*	–		225.0000 inhal. 6 h/d; 5 d/wk; 3 wk	Norppa *et al.* (1980b)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	–		500.0000×4 po	Sbrana *et al.* (1983)
CBA, Chromosomal aberrations, rat bone-marrow cells *in vivo*	–		900.0000 inh. 6 h/d; 5 d/wk; 1 yr	Sinha *et al.* (1983)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	–		750.0000×1 ip	Sharief *et al.* (1986)
CVA, Chromosomal aberrations, mouse splenocytes *in vivo*	–		900.0000 inhal. 6 h/d×14	Kligerman *et al.* (1992)
CVA, Chromosomal aberrations, mouse lung cells *in vivo*	–		900.0000 inhal. 6 h/d×14	Kligerman *et al.* (1992)
CVA, Chromosomal aberrations, rats peripheral lymphocytes *in vivo*	–		450.0000 inhal. 6 h/d×14	Kligerman *et al.* (1993)
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	–		0.0000	Meretoja *et al.* (1978a)
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	(+)		80.0000	Andersson *et al.* (1980)
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	–		40.0000	Watanabe *et al.* (1981)
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	(+)		35.0000	Camurri *et al.* (1983)
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	–		29.0000	Watanabe *et al.* (1983)
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	–		7.5000	Hansteen *et al.* (1984)
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	–		14.0000	Mäki-Paakanen (1987)
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	–		31.0000	Kelsey *et al.* (1990)
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	+		9.0000	Yager *et al.* (1990)
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	–		6.0000	Brenner *et al.* (1991)
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	–		41.0000[f]	Mäki-Paakanen *et al.* (1991)
MVH, Micronucleus formation, human lymphocytes *in vivo*	+		2.5000	Sorsa *et al.* (1991)
MVH, Micronucleus formation, human lymphocytes *in vivo*	+		7.3000	Högstedt *et al.* (1983)
MVH, Micronucleus formation, human lymphocytes *in vivo*	–		14.0000	Nordenson & Beckman (1984)
MVH, Micronucleus formation, human lymphocytes *in vivo*	–		14.0000	Mäki-Paakanen (1987)
MVH, Micronucleus formation, human lymphocytes *in vivo*	+		7.5000	Hagmar *et al.* (1989)
MVH, Micronucleus formation, human lymphocytes *in vivo*	–		6.0000	Brenner *et al.* (1991)
			41.0000[f]	Mäki-Paakanen *et al.* (1991)

Table 15 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
MVH, Micronucleus formation, human lymphocytes *in vivo*	-		25.0000	Sorsa *et al.* (1991)
MVH, Micronucleus formation, human lymphocytes *in vivo*	-		26.0000[f]	Tomanin *et al.* (1992)
MVH, Micronucleus formation, human lymphocytes *in vivo*	-		9.0000	Yager *et al.* (1993)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	-		0.0000	Fleig & Thiess (1978)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	+		0.0000	Meretoja *et al.* (1978a)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	-		0.5500	Theiss & Fleig (1978)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	+		22.0000	Högstedt *et al.* (1979)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	+		19.0000	Andersson *et al.* (1980)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	-		33.0000	Thiess *et al.* (1980)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	-		40.0000	Watanabe *et al.* (1981)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	+		7.0000	Camurri *et al.* (1983)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	-		29.0000	Watanabe *et al.* (1983)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	-		7.5000	Hansteen *et al.* (1984)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	-		14.0000	Nordenson & Beckman (1984)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	-		22.0000	Pohlova & Srám (1985)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	-		14.0000	Mäki-Paakanen (1987)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	+		0.0000	Forni *et al.* (1988)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	-		36.0000	Jablonická *et al.* (1988)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	-		7.5000	Hagmar *et al.* (1989)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	-		41.0000[f]	Mäki-Paakanen *et al.* (1991)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	-		25.0000	Sorsa *et al.* (1991)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	+		26.0000[f]	Tomanin *et al.* (1992)
DVH, DNA single-strand breaks, human lymphocytes *in vivo*	+		6.0000	Brenner *et al.* (1991)
DVH, DNA single-strand breaks, human lymphocytes *in vivo*	+		41.0000[f]	Mäki-Paakanen *et al.* (1991)
DVH, DNA single-strand breaks, human lymphocytes *in vivo*	+		10.0000	Walles *et al.* (1993)
BVD, Binding (covalent) to DNA, mouse liver *in vivo*	+		114.0000×1 ip	Byfält Nordqvist *et al.* (1985)
BVD, Binding (covalent) to DNA, mouse liver *in vivo*	(+)		110.0000 inhal. 9 h	Cantoreggi & Lutz (1993)
BVD, Binding (covalent) to DNA, rat liver and lung *in vivo*	?		39.0000 inhal. 6 h	Cantoreggi & Lutz (1993)
SPM, Sperm morphology, mouse *in vivo*	(+)		200.0000×5 ip	Simula & Priestly (1992)
SPR, Sperm morphology, rat *in vivo*	(+)		1000.0000×5 ip	Simula & Priestly (1992)

Table 15 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Protein binding				
BVP, Binding (covalent) to haemoglobin, mouse *in vivo*	+		114.0000×1 ip	Byfält Nordqvist *et al.* (1985)
BHP, Binding (covalent) to haemoglobin, humans *in vivo*	(+)		6.0000 inhal.	Brenner *et al.* (1991)
BHP, Binding (covalent) to haemoglobin, humans *in vivo*	(+)		45000.0000[f] inhal.	Christakopoulos *et al.* (1993)

[a] +, positive; (+), weakly positive; –, negative; 0, not tested; ?, inconclusive (variable response within several experiments within an adequate study)
[b] In-vitro tests, μg/ml; in-vivo tests, mg/kg bw
[c] Atmospheric concentration (μg/ml)
[d] Activation by erythrocytes
[e] Purified lymphocytes showed weaker response: LED, 208 μg/ml
[f] Based on urinary mandelic acid concentration

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Styrene has been produced since the 1920s by catalytic dehydrogenation of ethylbenzene. It is one of the most important monomers, worldwide, and finds major use in the production of polystyrene, acrylonitrile–butadiene–styrene resins, styrene–butadiene rubbers and latexes, and unsaturated polystyrene resins. Occupational exposure levels, measured both by air measurements and biological monitoring, have been highest in the manufacture of fibre glass-reinforced polyester products and lower in the production of styrene, polystyrene and styrene-based plastics and rubbers.

5.2 Human carcinogenicity data

Epidemiological studies of styrene have been done in three types of industry: production of glass-reinforced plastic products, production of styrene monomer and styrene polymerization and production of styrene–butadiene rubber. The malignancies observed in excess most frequently are of the lymphatic and haematopoietic system.

In a European multinational study of over 40 000 workers in the glass-reinforced plastics industry, no overall excess of deaths from lymphatic and haematopoietic cancers was observed in comparison with national controls. Within the cohort, the risks for these cancers were significantly related to average intensity of exposure and to years since first exposure but were not related to cumulative exposure.

A study of cancer incidence in the reinforced plastics industry in Denmark involved 12 800 male workers who had been included within the European multinational mortality study and a further 24 000 workers with lower probability of exposure to styrene. A nonsignificant overall increase in risk was seen for lymphatic and haematopoietic cancer. The increase was concentrated mainly in those workers not previously included in the international cohort, in short-term workers with at least 10 years since first employment and in those employed before 1970.

In a large study of the reinforced plastics industry in the USA, no overall increase in risk for lymphatic and haematopoietic cancer was seen, although a nonsignificant increase was found among workers with the highest exposure.

A study of chemical workers in the production of styrene and styrene derivatives in the USA found a nonsignificant association between exposure to styrene and lymphatic and haematopoietic cancers. A smaller study from the United Kingdom also found a nonsignificant association with cancers at this site but lacked detailed information on exposure.

A large cohort study of the styrene–butadiene rubber industry showed increased risks for lymphatic and haematopoietic malignancies, but a nested case–control analysis that evaluated exposure to both styrene and butadiene found no relationship with exposure to styrene. Two additional studies showed increased risks for lymphatic and haematopoietic cancers but provided little information on exposure to styrene.

Exposures to styrene are highest in the reinforced plastics industry, where less opportunity for confounding occurs than in the other industries studied. The two largest, most

informative, but partly overlapping, studies of reinforced plastics manufacturers have certain features that are suggestive of a cancer hazard insofar as, in one, risk increased with average intensity of exposure and time since first exposure, and in the other risk was greatest in men employed at times when the highest exposures occurred. More importantly, however, they do not indicate an increase in risk with increasing cumulative exposure to styrene (as the excesses occurred mainly in short-term employees), and there is no overall increase in risk for lymphatic and haematopoietic cancer in studies of the reinforced plastics industry.

5.3 Animal carcinogenicity data

Styrene was tested for carcinogenicity in mice and rats by oral administration and in rats by inhalation exposure. Administration of styrene by gastric intubation resulted in a small increase in the incidence of pulmonary tumours in male mice and of hepatocellular adenomas in females and no increase in tumour incidence in rats. Prenatal exposure followed by postnatal gastric intubation of styrene resulted in a significant increase in the occurrence of pulmonary tumours in male and female mice of one strain and no increase in tumour incidence in rats. Exposure of rats to styrene by inhalation in one study was associated with an increase in the incidence of mammary tumours in females; however, because of limitations in the reporting of the data, the results of the study were considered to be inconclusive. Two studies by gastric intubation of a styrene/β-nitrostyrene mixture in mice and rats were of limited value for the evaluation.

5.4 Other relevant data

Styrene is absorbed by inhalation and dermal transfer in both man and rat. In man, 60–70% of inhaled styrene is absorbed. It is rapidly distributed throughout the body in treated rats. A large percentage of absorbed styrene is excreted as urinary mandelic and phenylglyoxylic acids, glutathione conjugates forming a minor fraction of the metabolites. Saturation of metabolic activation of styrene becomes apparent at concentrations above 200–300 ppm (850–1280 mg/m^3) in rats and mice, and above 100–200 (430–850 mg/m^3) ppm in humans. The dominant first metabolite is styrene-7,8-oxide, the formation of which appears to be catalysed in man principally by the cytochrome P450 isoenzyme CYP2B6 but also by CYP2E1 and CYP1A2. Isolated erythrocytes are also capable of nonenzymatic conversion of styrene to styrene-7,8-oxide. The amounts of styrene-7,8-oxide present in the blood of rats and mice exposed to styrene at concentrations below 100 ppm (430 mg/m^3) were about 5–20 fold greater than those in similarly exposed humans.

Exposure to styrene leads to the formation of both protein and DNA adducts in man, rat and mouse. The levels of the N-terminal valine adduct of haemoglobin, *N*-(1-hydroxy-2-phenylethyl)valine, have been found to be four times higher in styrene-exposed workers than in controls, and the levels of the DNA adduct, O^6-(2-hydroxy-1-phenylethyl)-2′-deoxyguanosine-3′-monophosphate, have been found to be about five times higher than in controls.

Central and peripheral neurotoxicity have been described in workers, rats and rabbits exposed to styrene, but the mechanism has not been established.

No clear association was seen in a number of studies between occupational exposure of either mothers or fathers to styrene and the frequency of spontaneous abortions or congenital malformations. In rats and rabbits exposed to styrene at doses up to those that induce maternal toxicity, no adverse reproductive effect has been observed. Damage to seminiferous tubules and decreased sperm counts have been observed in male rats.

Some 25 studies on chromosomal aberrations, micronuclei and sister chromatid exchange have been performed in workers exposed to styrene in various countries and different industries. These have provided variable results with regard to the association between exposure to styrene and chromosomal damage. While clear dose–response relationships were not observed, those studies that showed effects were conducted in the reinforced plastics industry, where exposure to styrene is high; only one study was available on the styrene monomer and polystyrene manufacturing industries. Chromosomal aberrations were observed in 9 of 22, sister chromatid exchange in 3 of 12 and micronuclei in 3 of 11 studies.

The frequency of single-strand DNA breakage/alkali-labile sites was increased in workers exposed to styrene at less than 20 ppm (85 mg/m^3).

Chromosomal aberrations have not been seen in most studies in rodents, while several studies indicate weak induction of sister chromatid exchange in various tissues of rats and mice. Contradictory results have been obtained with regard to the induction of micronuclei in mice.

Significant increases have been observed consistently in the frequency of sister chromatid exchange and chromosomal aberrations in human lymphocytes *in vitro*. Most studies did not show mutation in bacteria, although mutation was seen in some studies in the presence of an exogenous metabolic activation system.

5.5. Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of styrene.

There is *limited evidence* in experimental animals for the carcinogenicity of styrene.

In making the overall evaluation, the Working Group took into consideration the following supporting evidence: Styrene is metabolized to styrene-7,8-oxide, which binds covalently to DNA and shows activity in various in-vitro and in-vivo assays for genetic effects. The genetic and related effects of styrene are therefore associated with its oxidation, which also occurs, e.g. in human whole blood cultures, where styrene induces dose-related responses of chromosomal damage at low concentrations. Styrene-7,8-oxide is detected in blood of workers exposed to styrene. Adducts in haemoglobin and DNA, DNA single-strand breaks/alkali-labile sites, as well as significant increases in the frequency of chromosomal damage have been found in workers exposed to styrene in the reinforced plastics industry. Positive results are associated with higher overall styrene levels and negative results with decreasing exposures to styrene. Although in human studies the role of other contaminants

[1]For definition of the italicized terms, see Preamble, pp. 27–30.

cannot be excluded, their occurrence is variable and their concentrations are very low in comparison with that of styrene.

Overall evaluation

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

6. References

A.D. Little, Inc. (1981) *Industrial Hygiene Evaluation of Retrospective Mortality Study Plants*, Boston

Ahlborg, G., Jr, Bjerkedal, T. & Egenaes, J. (1987) Delivery outcome among women employed in the plastics industry in Sweden and Norway. *Am. J. ind. Med.*, **12**, 507–517

American Conference of Governmental Industrial Hygienists (1984) *TLVs® Threshold Limit Values for Chemical Substances in the Work Environment Adopted by ACGIH for 1984–85*, Cincinnati, OH, p. 62

American Conference of Governmental Industrial Hygienists (1991) *Documentation of Threshold Limit Values and Biological Exposure Indices*, 6th Ed., Cincinnati, OH

American Conference of Governmental Industrial Hygienists (1993) *1993–1994 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices*, Cincinnati, OH, pp. 32, 60

Amoco Chemical Co. (1993) *Sales Specification Bulletin: Styrene Monomer* (Bulletin SM-1j), Chicago, IL

Andersen, M.E., Gargas, M.L. & Ramsey, J.C. (1984) Inhalation pharmacokinetics: evaluating systemic extraction, total in vivo metabolism, and the time course of enzyme induction for inhaled styrene in rats based on arterial blood:inhaled air concentration ratios. *Toxicol. appl. Pharmacol.*, **73**, 176–187

Andersson, H.C., Tranberg, E.A., Uggla, A.H. & Zetterberg, G. (1980) Chromosomal aberrations and sister-chromatid exchanges in lymphocytes of men occupationally exposed to styrene in a plastic-boat factory. *Mutat. Res.*, **73**, 387–401

Andjelkovic, D., Taulbee, J. & Symons, M. (1976) Mortality experience of a cohort of rubber workers, 1964–1973. *J. occup. Med.*, **18**, 387–394

Andjelkovic, D., Taulbee, J., Symons, M. & Williams, T. (1977) Mortality of rubber workers with reference to work experience. *J. occup. Med.*, **19**, 397–405

Anon. (1983) Chemical profile: styrene. *Chem. Mark. Rep.*, **224**, 54

Anon. (1985) Facts & figures for the chemical industry. *Chem. Eng. News*, **63**, 22–86

Anon. (1986) Chemical profile: styrene. *Chem. Mark. Rep.*, **230**, 49–50

Anon. (1989a) Facts & figures for the chemical industry. *Chem. Eng. News*, **67**, 36–90

Anon. (1989b) Chemical profile: styrene. *Chem. Mark. Rep.*, **236**, 40, 46

Anon. (1992) Chemical profile: styrene. *Chem. Mark. Rep.*, **242**, 16, 45

Anon. (1993) Facts & figures for the chemical industry. *Chem. Eng. News*, **71**, 38–83

Arbejdstilsynet [Labour Inspection] (1988) *Graensevaerdier for Stoffer og Materialer* [Limit Values for Compounds and Materials] (No. 3.1.0.2), Copenhagen, p. 29

Arfini, G., Mutti, A., Vescovi, P., Ferroni, C., Ferrarri, M., Giaroli, C., Passeri, M. & Franchini, I. (1987) Impaired dopaminergic modulation of pituitary secretion in workers occupationally exposed to styrene: further evidence for PRL response to TRH stimulation. *J. occup. Med.*, **29**, 826–830

Aringer, L., Löf, A. & Elinder, C.-G. (1991) The applicability of the measurement of urinary thioethers. A study of humans exposed to styrene during diet standardization. *Int. Arch. occup. environ. Health*, **63**, 341–346

Arms, A.D. & Travis, C.C. (1988) *Reference Physiological Parameters in Pharmacokinetic Modeling* (EPA/600/6-88/004), Washington DC, US Environmental Protection Agency

Askergren, A., Allgén, L.-G., Karlsson, C., Lundberg, I. & Nyberg, E. (1981) Studies on kidney function in subjects exposed to organic solvents. I. Excretion of albumin and β-2-microglobulin in the urine. *Acta med. scand.*, **209**, 479–483

Åstrand, I. (1986) Approached to toxicological studies in man. In: Hodel, C.M., ed., *FEST-Toxicology in Europe*, Cambridge, Elsevier, pp. 6–9

Baker, E.L., Jr, Smith, T.J. & Landrigan, P.J. (1985) The neurotoxicity of industrial solvents: a review of the literature. *Am. J. ind. Med.*, **8**, 207–217

Bakke, O.M. & Scheline, R.R. (1970) Hydroxylation of aromatic hydrocarbons in the rat. *Toxicol. appl. Pharmacol.*, **16**, 691–700

Barale, R. (1991) The genetic toxicology of styrene and styrene oxide. *Mutat. Res.*, **257**, 107–126

Bardoděj, Z. (1978) Styrene, its metabolism and the evaluation of hazards in industry. *Scand. J. Work Environ. Health*, **Suppl. 7**, 95–103

Bardoděj, Z. & Bardodějová, E. (1970) Biotransformation of ethylbenzene, styrene and alpha-methylstyrene in man. *Am. ind. Hyg. Assoc. J.*, **31**, 206–209

Barsan, M.E., Kinnes, G.M. & Blade, L. (1991) *Health Hazard Evaluation Report, Rubbermaid, Inc., Reynolds, IN* (Report No. 90-261-2124), Cincinnati, OH, National Institute for Occupational Safety and Health

Bartolucci, G.B., De Rosa, E., Gori, G.P., Chiesura Corona, P., Perbellini, L. & Brugnone, F. (1986) Biomonitoring of occupational exposure to styrene. *Appl. ind. Hyg.*, **1**, 125–131

Bauer, C., Leporini, C., Bronzetti, G., Corsi, C., Nieri, R., Del Carratore, R. & Tonarelli, S. (1980) The problem of negative results for sytene in the in vitro mutagenesis test with metabolic activation (microsomal assay): explanation by gas chromatographic analysis. *Boll. Soc. Ital. Biol. sper.*, **56**, 203–207

Beije, B. & Jenssen, D. (1982) Investigation of styrene in the liver perfusion/cell culture system. No indication of styrene-7,8-oxide as the principal mutagenic metabolite produced by the intact rat liver. *Chem.-biol. Interactions*, **39**, 57–76

Belanger, P.L. & Elesh, E. (1980) *Health Hazard Evaluation Determination, Bell Helmets, Inc., Norwalk, CA* (Report No. 79-36-656). Cincinnati, OH, National Institute for Occupational Safety and Health

Beliles, R.P., Butala, J.H., Stack, C.R. & Makris, S. (1985) Chronic toxicity and three-generation reproduction study of styrene monomer in the drinking water of rats. *Fundam. appl. Toxicol.*, **5**, 855–868

Bellander, T., Kogevinas, M., Pannett, B., Bjerk, J.E., Breum, N.O., Ferro, S., Fontana, V., Galassi, C., Jensen, A.A. & Pfäffli, P. (1994) Part II: Historical exposure to styrene in the manufacture of glass-reinforced polyester products in six European countries. In: Kogevinas, M., Ferro, G., Saracci, R., Andersen, A., Bellander, T., Biocca, M., Bjerk, J.E., Breum, N.O., Coggon, D., Fontana, V., Ferro, S., Galassi, C., Gennaro, V., Hutchings, S., Jensen, A.A., Kolstad, H., Lundberg, I., Lynge, E., Pannett, B., Partanen, T. & Pfäffli, P., *IARC Historical Multicentric Cohort Study of Workers Exposed to Styrene. Report of the Epidemiological Study and the Industrial Hygiene Investigation* (IARC intern. tech. Rep. 94/002), Lyon, IARC, pp. 63–127

Belvedere, G., Tursi, F., Elovaara, E. & Vainio, H. (1983) Styrene oxidation to styrene oxide coupled with arachidonic acid oxidation by soybean lipoxygenase. *Toxicol. Lett.*, **18**, 39–44

Belvedere, G., Elovaara, E. & Vainio, H. (1984) Activation of styrene to styrene oxide in hepatocytes and subcellular fractions of rat liver. *Toxicol. Lett.*, **23**, 157–162

Beratergrenium für Umweltrelevante Altstoffe [Advisory Committee on Existing Chemicals of Environmental Relevance] (1993) *Styrene (Ethylbenzene)* (Report 48, Gesellschaft Deutscher Chemiker [Society of German Chemists]), Weinheim, VCH Verlagsgesellschaft

Berode, M., Droz, P.-O. & Guillemin, M. (1985) Human exposure to styrene. VI. Percutaneous absorption in human volunteers. *Int. Arch. occup. environ. Health*, **55**, 331–336

Berode, M., Droz, P.O., Boillat, M.A. & Guillemin, M. (1986) Effect of alcohol on the kinetics of styrene and its metabolites in volunteers and in workers. *Appl. ind. Hyg.*, **1**, 25–28

Block, J.B. (1976) A Kentucky study: 1950–1975. In: Ede, L., ed., *Proceedings of NIOSH Styrene–Butadiene Rubber Briefing, Covington, Kentucky, April 30, 1976* (HEW Publ. No. (NIOSH) 77-129), Cincinnati, OH, National Institute for Occupational Safety and Health, pp. 28–32

Bogan, R., Csanády, G.A. & Filser, J.G. (1993) Michaelis–Menten parameters of styrene metabolism in hepatocytes of rat and mouse—comparison with *in vivo* data (Abstract No. 22). *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **Suppl. 347**, R6

Bond, J.A. (1989) Review of the toxicology of styrene. *C.R.C. crit. Rev. Toxicol.*, **19**, 227–249

Bond, G.G., Bodner, K.M., Olsen, G.W. & Cook, R.R. (1992) Mortality among workers engaged in the development or manufacture of styrene-based products—an update. *Scand. J. Work Environ. Health*, **18**, 145–154

Bouscaren, R., Frank, R. & Veldt, C. (1987) *Hydrocarbons. Identification of Air Quality Problems in Member States of the European Communities* (Report No. EUR-10646-EN; US NTIS PB88-187992), Luxembourg, European Commission

Bowman, J.D., Held, J.L. & Factor, D.R. (1990) A field evaluation of mandelic acid in urine as a compliance monitor for styrene exposure. *Appl. occup. environ. Hyg.*, **5**, 526–535

Brams, A., Buchet, J.P., Crutzen-Fayt, M.C., de Meester, C., Lauwerys, R. & Léonard, A. (1987) A comparative study, with 40 chemicals, of the efficiency of the *Salmonella* assay and the SOS chromotest (kit procedure). *Toxicol. Lett.*, **38**, 123–133

Brenner, D.D., Jeffrey, A.M., Latriano, L., Wazneh, L., Warburton, D., Toor, M., Pero, R.W., Andrews, L.R., Walles, S. & Perera, F.P. (1991) Biomarkers in styrene-exposed boatbuilders. *Mutat. Res.*, **261**, 225–236

Brooks, S.M., Anderson, L., Emmett, E., Carson, A., Tsay, J.-Y., Elia, V., Buncher, R. & Karbowsky, R. (1980) The effects of protective equipment on styrene exposure in workers in the reinforced plastics industry. *Arch. environ. Health*, **35**, 287–294

Brown, N.A. (1991) Reproductive and developmental toxicity of styrene. *Reprod. Toxicol.*, **5**, 3–29

Brugnone, F., Perbellini, L., Wang, G.Z., Maranelli, G., Raineri, E., De Rosa, E., Saletti, C., Soave, C. & Romeo, L. (1993) Blood styrene concentrations in a 'normal' population and in exposed workers 16 hours after the end of the workshift. *Int. Arch. occup. environ. Health*, **65**, 125–130

Brunnemann, K.D., Rivenson, A., Cheng, S.C., Saa, V. & Hoffmann, D. (1992) A study of tobacco carcinogenesis. XLVII. Bioassays of vinylpyridines for genotoxicity and for tumorigenicity in A/J mice. *Cancer Lett.*, **65**, 107–113

Burroughs, G.E. (1979) *Health Hazard Evaluation Determination. Piper Aircraft Corporation, Vero Beach, FL* (Report No. 78-110-585), Cincinnati, OH, National Institute for Occupational Safety and Health

Busk, L. (1979) Mutagenic effects of styrene and styrene oxide. *Mutat. Res.*, **67**, 201–208

Byfält Nordqvist, M., Löf, A., Osterman-Golkar, S. & Walles, S.A.S. (1985) Covalent binding of styrene and styrene-7,8-oxide to plasma proteins, haemoglobin and DNA in the mouse. *Chem.-biol. Interactions*, **55**, 63–73

Camurri, L., Codeluppi, S., Pedroni, C. & Scarduelli, L. (1983) Chromosomal aberrations and sister-chromatid exchanges in workers exposed to styrene. *Mutat. Res.*, **119**, 361–369

Camurri, L., Codeluppi, S., Scarduelli, L. & Candela, S. (1984) Sister chromatid exchanges in workers exposed to low doses of styrene. *Basic Life Sci*, **29B**, 957–963

Cantoni, L., Salmona, M., Facchinetti, T., Pantarotto, C. & Belvedere, G. (1978) Hepatic and extrahepatic formation and hydration of styrene oxide *in vitro* in animals of different species and sex. *Toxicol. Lett.*, **2**, 179–186

Cantoreggi, S. & Lutz W.K. (1993) Covalent binding of styrene to DNA in rat and mouse. *Carcinogenesis*, **14**, 355–360

Caperos, J.R., Humbert, B. & Droz, P.O. (1979) Styrene exposure. II. Studies of absorption, excretion and metabolism in human subjects. *Int. Arch. occup. environ. Health*, **42**, 223–230 (in French)

Černý, S., Mráz, J., Flek, J. & Tichy, M. (1990) Effect of ethanol on the urinary excretion of mandelic and phenylglyoxylic acids after human exposure to styrene. *Int. Arch. occup. environ. Health*, **62**, 243–247

Chakrabarti, S. & Malick, M.A. (1991) In vivo nephrotoxic action of an isomeric mixture of *S*-(1-phenyl-2-hydroxyethyl)glutathione and *S*-(2-phenyl-2-hydroxyethyl)glutathione in Fischer-344 rats. *Toxicology*, **67**, 15–27

Chakrabarti, S.K. & Tuchweber, B. (1987) Effect of various pretreatments on the acute nephrotoxic potential of styrene in Fischer-344 rats. *Toxicology*, **46**, 343–356

Chakrabarti, S.K., Labelle, L. & Tuchweber, B. (1987) Studies on the subchronic nephrotoxic potential of styrene in Sprague-Dawley rats. *Toxicology*, **44**, 355–365

Chakrabarti, S.K., Duhr, M.-A., Senécal-Quevillon, M. & Richer, C.-L. (1993) Dose-dependent genotoxic effects of styrene on human blood lymphocytes and the relationship to its oxidative and metabolic effects. *Environ. mol. Mutag.*, **22**, 85–92

Checkoway, H. & Williams, T.M. (1982) A hematology survey of workers at a styrene–butadiene synthetic rubber manufacturing plant. *Am. ind. Hyg. Assoc. J.*, **43**, 164–169

Checkoway, H., Costa, L.G., Camp, J., Coccini, T., Daniell, W.E. & Dills, R.L. (1992) Peripheral markers of neurochemical function among workers exposed to styrene. *Br. J. ind. Med.*, **49**, 560–565

Chemical Information Services Ltd (1991) *Directory of World Chemical Producers 1992/93 Edition*, Dallas, TX, p. 535

Chernoff, N., Woodrow Setzer, R., Miller, D.B., Rosen, M.B. & Rogers, J.M. (1990) Effects of chemically induced maternal toxicity on prenatal development in the rat. *Teratology*, **42**, 651–658

Cherry, N. & Gautrin, D. (1990) Neurotoxic effects of styrene: further evidence. *Br. J. ind. Med.*, **47**, 29–37

Cherry, N., Waldron, H.A., Wells, G.G., Wilkinson, R.T., Wilson, H.K. & Jones, S. (1980) An investigation of the acute behavioural effect of styrene on factory workers. *Br. J. ind. Med.*, **37**, 234–240

Chevron Chemical Co. (1992) *Technical Data Sheet: Chevron Styrene Monomer*, Houston, TX

Chmielewski, J. & Renke, W. (1976) Clinical and experimental research into the pathogenesis of toxic effects of styrene. III. Morphology, coagulation and fibronolysis systems of the blood in persons exposed to the action of styrene during their work. *Bull. Inst. mar. trop. Med. Gdynia*, **27**, 63–68

Christakopoulos, A., Bergmark, E., Zorcec, V., Norppa, H., Mäki-Paakanen, J. & Osterman-Golkar, S. (1993) Monitoring occupational exposure to styrene from hemoglobin adducts and metabolites in blood. *Scand. J. Work Environ. Health*, **19**, 255–263

Chua, S.C., Lee, B.L., Liau, L.S. & Ong, C.N. (1993) Determination of mandelic acid and phenylglyoxylic acid in the urine and its use in monitoring of styrene exposure. *J. anal. Toxicol.*, **17**, 129–132

Cocheo, V., Bellomo, M.L. & Bombi, G.G. (1983) Rubber manufacture: sampling and identification of volatile pollutants. *Am. ind. Hyg. Assoc. J.*, **44**, 521–527

Coggon, D., Osmond, C., Pannett, B., Simmonds, S., Winter, P.D. & Acheson, E.D. (1987) Mortality of workers exposed to styrene in the manufacture of glass-reinforced plastics. *Scand. J. Work Environ. Health*, **13**, 94–99

Cole, P., Delzell, E. & Acquavella, J. (1993) Exposure to butadiene and lymphatic and hematopoietic cancer. *Epidemiology*, **4**, 96–103

Collins, D.E. & Richey, F.A., Jr (1992) Synthetic organic chemicals. In: Kent, J.A., ed., *Riegel's Handbook of Industrial Chemistry*, 9th Ed., New York, Van Nostrand Reinhold, pp. 800–862

Compton-Quintana, P.J.E., Jensen, R.H., Bigbee, W.L., Grant, S.G., Langlois, R.G., Smith, M.T. & Rappaport, S.M. (1993) Use of the glycophorin A human mutation assay to study workers exposed to styrene. *Environ. Health Perspectives*, **99**, 297–301

Conner, M.K., Alarie, Y. & Dombroske, R.L. (1979) Sister chromatid exchange in regenerating liver and bone marrow cells of mice exposed to styrene. *Toxicol. appl. Pharmacol.*, **50**, 365–367

Conner, M.K., Alarie, Y. & Dombroske, R.L. (1980) Sister chromatid exchange in murine alveolar macrophages, bone marrow, and regenerating liver cells induced by styrene inhalation. *Toxicol. appl. Pharmacol.*, **55**, 37–42

Connor, T.H., Theiss, J.C., Hanna, H.A., Monteith, D.K. & Matney, T.S. (1985) Genotoxicity of organic chemicals frequently found in the air of mobile homes. *Toxicol. Lett.*, **25**, 33–40

Conti, B., Maltoni, C., Perino, G. & Ciliberti, A. (1988) Long-term carcinogenicity bioassays on styrene administered by inhalation, ingestion and injection and styrene oxide administered by ingestion in Sprague-Dawley rats, and *para*-methylstyrene administered by ingestion in Sprague-Dawley rats and Swiss mice. *Ann. N.Y. Acad. Sci.*, **534**, 203–234

Cook, W.A., ed. (1987) *Occupational Exposure Limits—Worldwide*, Akron, OH, American Industrial Hygiene Association, pp. 125, 153, 215

Costello, R.J. (1983) *Health Hazard Evaluation Determination, Chem-Dyne Hazardous Waste Site, Hamilton, OH* (Report No. 83-307-1561), Cincinnati, OH, National Institute for Occupational Safety and Health

Crandall, M.S. & Hartle, R.W. (1985) An analysis of exposure to styrene in the reinforced plastic boat-making industry. *Am. J. ind. Med.*, **8**, 183–192

Csanády, G.A., Mendrala, A.L., Nolan, R.J. & Filser, J.G. (1994) A physiologic pharmacokinetic model for styrene and styrene-7,8-oxide in mouse, rat and man. *Arch. Toxicol.* (in press)

Daston, G.P., Overmann, G.J., Taubeneck, M.W., Lehman-McKeeman, L.D., Rogers, J.M. & Keen, C.L. (1991) The role of metallothionein induction and altered zinc status in maternally mediated developmental toxicity: comparison of the effects of urethane and styrene in rats. *Toxicol. appl. Pharmacol.*, **110**, 450–463

Décarie, S. & Chakrabarti, S. (1989) Metabolism and hepatorenal toxicity due to repeated exposure to styrene in spontaneously hypertensive rats (SHR). *J. Toxicol. environ. Health*, **27**, 455–465

De Flora, S. (1979) Metabolic activation and deactivation of mutagens and carcinogens. *Ital. J. Biochem.*, **28**, 81–103

Delbressine, L.P.C., Ketelaars, H.C.J., Seutter-Berlage, F. & Smeets, F.L.M. (1980) Phenaceturic acid, a new urinary metabolite of styrene in the rat. *Xenobiotica*, **10**, 337–342

Del Carratore, R., Bronzetti, G., Bauer, C., Corsi, C., Nieri, R., Paolini, M. & Giagoni, P. (1983) Cytochrome P-450 factors determining synthesis in strain D7 *Saccharomyces cerevisiae*. An alternative system to microsomal assay. *Mutat. Res.*, **121**, 117–123

Deutsche Forschungsgemeinschaft (1993) *MAK and BAT Values 1993* (Report No. 29), Weinheim, VCH Verlagsgesellschaft, pp. 71, 129

Dills, R.L., Wu, R.L., Checkoway, H. & Kalman, D.A. (1991) Capillary gas chromatographic method for mandelic and phenylglyoxylic acids in urine. *Int. Arch. occup. environ. Health*, **62**, 603–606

Dogra, R.K.S., Khanna, S., Srivastava, S.N., Shukla, L.J. & Shanker, R. (1989) Styrene-induced immunomodulation in mice. *Int. J. Immunopharmacol.*, **11**, 577–586

Dogra, R.K.S., Chandra, K., Chandra, S., Gupta, S., Khanna, S., Srivastava, S.N., Shukla, L.J., Katiyar, J.C. & Shanker, R. (1992) Host resistance assays as predictive models in styrene immunomodulation. *Int. J. Immunopharmacol.*, **14**, 1003–1009

Donner, M., Sorsa, M. & Vainio, H. (1979) Recessive lethals induced by styrene and styrene oxide in *Drosophila melanogaster*. *Mutat. Res.*, **67**, 373–376

Dow Chemical Co. (1989) *The Dow Family of Styrenic Monomers*, Midland, MI

Dow Chemical Co. (1991) *Sales Specification: Styrene Monomer (Product No. 81352)*, Midland, MI

Droz, P.O. & Guillemin, M.P. (1983) Human styrene exposure. V. Development of a model for biological monitoring. *Int. Arch. occup. environ. Health*, **53**, 19–36

Drummond, L., Caldwell, J. & Wilson, H.K. (1989) The metabolism of ethylbenzene and styrene to mandelic acid: stereochemical considerations. *Xenobiotica*, **19**, 199–207

Drummond, L., Caldwell, J. & Wilson, H.K. (1990) The stereoselectivity of 1,2-phenylethanediol and mandelic acid metabolism and disposition in the rat. *Xenobiotica*, **20**, 159–168

Ducruet, V. (1984) Comparison of the headspace volatiles of carbonic maceration and traditional wine. *Lebensmittel. Wissenschaft. Technol.*, **17**, 217–221

Duke, J.A. (1985) *CRC Handbook of Medical Herbs*, Boca Raton, FL, CRC Press, p. 323

Edling, C. & Tagesson, C. (1984) Raised serum bile acid concentrations after occupational exposure to styrene: a possible sign of hepatoxicity? *Br. J. ind. Med.*, **41**, 257–259

Eller, P.M., ed. (1984) *NIOSH Manual of Analytical Methods*, 3rd Ed., Vol. 1 (DHHS (NIOSH) Publ. No. 84-100), Washington DC, US Government Printing Office, pp. 1501-1–1501-7

Elovaara, E., Vainio, H. & Aitio, A. (1990) Pulmonary toxicity of inhaled styrene in acetone-, phenobarbital- and 3-methylcholanthrene-treated rats. *Arch. Toxicol.*, **64**, 365–369

Elovaara, E., Engström, K., Nakajima, T., Park, S.S., Gelboin, H.V. & Vainio, H. (1991) Metabolism of inhaled styrene in acetone-, phenobarbital- and 3-methylcholanthrene-pretreated rats: stimulation and stereochemical effects by induction of cytochromes P450IIE1, P450IIB and P450IA. *Xenobiotica*, **21**, 651–661

Engström, J., Åstrand, I. & Wigaeus, E. (1978a) Exposure to styrene in a polymerization plant. Uptake in the organism and concentration in subcutaneous adipose tissue. *Scand. J. Work Environ. Health*, **4**, 324–329

Engström, J., Bjurström, R., Åstrand, I. & Övrum, P. (1978b) Uptake, distribution and elimination of styrene in man. Concentration in subcutaneous adipose tissue. *Scand. J. Work Environ. Health*, **4**, 315–323

European Centre for Ecotoxicology and Toxicology of Chemicals (1992) *Styrene Toxicology. Investigations on the Potential for Carcinogenicity* (Technical Report No. 52), Brussels

European Chemical Industry Council (1994) *EC Criteria Document*, Brussels

Fernández, J.G. & Caperos, J.R. (1977) Exposure to styrene. I. Experimental study of pulmonary absorption and excretion in humans. *Int. Arch. occup. environ. Health*, **40**, 1–12 (in French)

Filser, J.G., Johanson, G., Kessler, W., Kreuzer, P.E., Stei, P., Baur, C. & Csanády, G.A. (1993a) A pharmacokinetic model to describe toxicokinetic interactions between 1,3-butadiene and styrene in rats: predictions for human exposure. In: Sorsa, M., Peltonen, K., Vainio, H. & Hemminki, K., eds, *Butadiene and Styrene: Assessment of Health Hazards* (IARC Scientific Publications No. 127), Lyon, IARC, pp. 65–78

Filser, J.G., Schwegler, U., Csanády, G.A., Greim, H., Kreuzer, P.E. & Kessler, W. (1993b) Species-specific pharmacokinetics of styrene in rat and mouse. *Arch. Toxicol.*, **67**, 517–530

Fiserova-Bergerova, V. & Teisinger, J. (1965) Pulmonary styrene vapor retention. *Ind. Med. Surg.*, **34**, 620–622

Fishbein, L. (1992) Exposure from occupational versus other sources. *Scand. J. Work Environ. Health*, **18** (Suppl. 1), 5–16

Fleeger, A.K. & Almaguer, D. (1988) *Health Hazard Evaluation Report, Polymer Engineering, Inc., Reynolds, IN* (Report No. 87-384-1895), Cincinnati, OH, National Institute for Occupational Safety and Health

Fleig, I. & Thiess, A.M. (1978) Mutagenicity study of workers employed in the styrene and polystyrene processing and manufacturing industry. *Scand. J. Work Environ. Health*, **4** (Suppl. 2), 254–258

Flek, J. & Šedivec, V. (1980) Simultaneous gas chromatographic determination of urinary mandelic and phenylglyoxylic acids using diazomethane derivatization. *Int. Arch. occup. environ. Health*, **45**, 181–188

Flodin, U., Fredriksson, M., Axelson, A., Persson, B. & Hardell, L. (1986) Background radiation, electrical work, and some other exposures associated with acute myeloid leukemia in a case–referent study. *Arch. environ. Health*, **41**, 77–84

Flodin, U., Ekberg, K. & Andersson, L. (1989) Neuropsychiatric effects of low exposure to styrene. *Br. J. ind. Med.*, **46**, 805–808

Florin, I., Rutberg, L., Curvall, M. & Enzell, C.R. (1980) Screening of tobacco smoke constituents for mutagenicity using the Ames' test. *Toxicology*, **15**, 219–232

Forni, A., Goggi, E., Ortisi, E., Cecchetti, R., Cortona, G., Sesana, G. & Alessio, L. (1988) Cytogenetic findings in styrene workers in relation to exposure. In: Seemayer, N.H. & Hadnagy, W., eds, *Environmental Hygiene*, Berlin, Springer, pp. 159–162

Foureman, G.L., Harris, C., Guengerich, F.P. & Bend, J.R. (1989) Stereoselectivity of styrene oxidation in microsomes and in purified cytochrome P-450 enzymes from rat liver. *J. Pharmacol. exp. Ther.*, **248**, 492–497

Frentzel-Beyme, R., Theiss, A.M. & Wieland, R. (1978) Survey of mortality among employees engaged in the manufacture of styrene and polystyrene at the BASF Ludwigshafen works. *Scand. J. Work Environ. Health*, **4** (Suppl. 2), 231–239

Fujita, H., Koizumi, A., Furusawa, T. & Ikeda, M. (1987) Decreased erythrocyte δ-aminolevulinate dehydratase activity after styrene exposure. *Biochem. Pharmacol.*, **36**, 711–716

Furia, T.E. & Bellanca, N., eds (1971) *Fenaroli's Handbook of Flavor Ingredients*, Cleveland, OH, Chemical Rubber Co.

Galassi, C., Kogevinas, M., Ferro, G. & Biocca, M. (1993) Biological monitoring of styrene in the reinforced plastics industry in Emilia Romagna, Italy. *Int. Arch. occup. environ. Health*, **65**, 89–95

Geuskens, R.B.M., van der Klaauw, M.M., van der Tuin, J. & van Hemmen, J.J. (1992) Exposure to styrene and health complaints in the Dutch glass-reinforced plastics industry. *Ann. occup. Hyg.*, **36**, 47–57

Gilbert, J. & Startin, J.R. (1983) A survey of styrene monomer levels in foods and plastic packaging by coupled mass spectrometry–automatic headspace gas chromatography. *J. Sci. Food Agric.*, **34**, 647–652

Głośnicka, R. & Dziadziuszko, H. (1986) Mutagenic action of styrene and its metabolites. II. Genotoxic activity of styrene, styrene oxide, styrene glycol and benzoic acid tested with the SOS chromotest. *Bull. Inst. mar. trop. Med. Gdynia*, **37**, 295–302

Gobba, F., Galassi, C., Ghittori, S., Imbriani, M., Pugliese, F. & Cavalleri, A. (1993) Urinary styrene in the biological monitoring of styrene exposure. *Scand. J. Work Environ. Health*, **19**, 175–182

Grayson, M.H. & Gill, S.S. (1986) Effect of in vitro exposure to styrene, styrene oxide, and other structurally related compounds on murine cell-mediated immunity. *Immunopharmacology*, **11**, 165–173

Gregersen, P. (1988) Neurotoxic effects of organic solvents in exposed workers: two controlled follow-up studies after 5.5 and 10.6 years. *Am. J. ind. Med.*, **14**, 681–701

Guengerich, F.P., Kim, D.-H. & Iwasaki, M. (1991) Role of human cytochrome P-450 IIE1 in the oxidation of many low molecular weight cancer suspects. *Chem. Res. Toxicol.*, **4**, 168–179

Guillemin, M.P. & Bauer, D. (1976) Human exposure to styrene. II. Quantitative and specific gas chromatographic analysis of urinary mandelic and phenylglyoxylic acids as an index of styrene exposure. *Int. Arch. Occup. Environ. Health*, **37**, 57–64

Guillemin, M.P. & Bauer, D. (1979) Human exposure to styrene. III. Elimination kinetics of urinary mandelic and phenylglyoxylic acids after single experimental exposure. *Int. Arch. occup. environ. Health*, **44**, 249–263

Guillemin, M.P. & Berode, M. (1988) Biological monitoring of styrene: a review. *Am. Ind. Hyg. Assoc. J.*, **49**, 497–505

Guillemin, M.P., Bauer, D., Martin, B. & Marazzi, A. (1982) Human exposure to styrene. IV. Industrial hygiene investigations and biological monitoring in the polyester industry. *Int. Arch. occup. environ. Health*, **51**, 139–150

Gurman, J.L., Baier, L. & Levin, B.C. (1987) Polystyrenes: a review of the literature on the products of thermal decomposition and toxicity. *Fire Mater.*, **11**, 109–130

Hagmar, L., Högstedt, B., Welinder, H., Karlsson, A. & Rassner, F. (1989) Cytogenetic and hematological effects in plastics workers exposed to styrene. *Scand. J. Work Environ. Health*, **15**, 136–141

Hampton, C.V., Pierson, W.R., Schuetzle, D. & Harvey, T.M. (1983) Hydrocarbon gases emitted from vehicles on the road. 2. Determination of emission rates from diesel and spark-ignition vehicles. *Environ. Sci. Technol.*, **17**, 699–708

Hansteen, I.-L., Jelmert, Ø., Torgrimsen, T. & Førsund, B. (1984) Low human exposure to styrene in relation to chromosome breaks, gaps and sister chromatid exchanges. *Hereditas*, **100**, 87–91

Härkönen, H. (1977) Relationship of symptoms to occupational styrene exposure and to the findings of electroencephalographic and psychological examination. *Int. Arch. occup. environ. Health*, **40**, 231–239

Härkönen, H. & Holmberg, P.C. (1982) Obstetric histories of women occupationally exposed to styrene. *Scand. J. Work Environ. Health*, **8**, 74–77

Härkönen, H., Lehtniemi, A. & Aitio, A. (1984a) Styrene exposure and the liver. *Scand. J. Work Environ. Health*, 10, 59–61

Härkönen, H., Tola, S., Korkala, M.L. & Hernberg, S. (1984b) Congenital malformations, mortality and styrene exposure. *Ann. Acad. Med.*, **13**, 404–407

Hayes, J.P., Lambourn, L., Hopkirk, J.A.C., Durham, S.R. & Newman Taylor, A.J. (1991) Occupational asthma due to styrene. *Thorax*, **46**, 396–397

Hemminki, K., Franssila, E. & Vainio, H. (1980) Spontaneous abortions among female chemical workers in Finland. *Int. Arch. occup. environ. Health*, **45**, 123–126

Henschler, D., ed. (1987) Styrol [Styrene]. In: *Deutsche Forschungsgemeinschaft Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten* [German Research Association Toxicological and Occupational MAK Limits], 13th Ed., Vol. 15, Weinheim, VCH Verlagsgesellschaft, pp. 1–26 (in German)

Hodgson, J.T. & Jones, R.D. (1985) Mortality of styrene production, polymerization and processing workers at a site in Northwest England. *Scand. J. Work Environ. Health*, **11**, 347–352

Hoff, A., Jacobsson, S., Pfäffli, P., Zitting, A. & Frostling, H. (1982) Degradation products of plastics. Polyethylene and styrene-containing thermoplastics—analytical, occupational, and toxicologic aspects. *Scand. J. Work Environ. Health*, **8** (Suppl. 2), 3–60

Högstedt, B., Hedner, K., Mark-Vendel, E., Mitelman, F., Schütz, A. & Skerfving, S. (1979) Increased frequency of chromosome aberrations in workers exposed to styrene. *Scand. J. Work Environ. Health*, **5**, 333–335

Högstedt, B., Åkesson, B., Axell, K., Gullberg, B., Mitelman, F., Pero, R.W., Skerfving, S. & Welinder, H. (1983) Increased frequency of lymphocyte micronuclei in workers producing reinforced polyester resin with low exposure to styrene. *Scand. J. Work Environ. Health*, **9**, 241–246

Holmberg, P.C. (1977) Central nervous defects in two children of mothers exposed to chemicals in the reinforced plastics industry. Chance or a causal relation? *Scand. J. Work Environ. Health*, **3**, 212–214

Holmberg, P.C. (1979) Central-nervous-system defects in children born to mothers exposed to organic solvents during pregnancy. *Lancet*, **ii**, 177–179

IARC (1979) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 19, *Some Monomers, Plastics and Synthetic Elastomers, and Acrolein*, Lyon, pp. 231–274

IARC (1982) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 28, *The Rubber Industry*, Lyon

IARC (1986) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 39, *Some Chemicals Used in Plastics and Elastomers*, Lyon, pp. 155–179

IARC (1987a) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, pp. 136–137, 332–334, 345–347

IARC (1987b) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 6, *Genetic and Related Effects: An Updating of Selected IARC Monographs from Volumes 1 to 42*, Lyon, pp. 498–501

IARC (1992) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 54, *Occupational Exposures to Mists and Vapours from Strong Inorganic Acids; and Other Industrial Chemicals*, Lyon, pp. 237–285

Ikeda, M., Koizumi, A., Miyasaka, M. & Watanabe, T. (1982) Styrene exposure and biologic monitoring in FRP boat production plants. *Int. Arch. occup. environ. Health*, **49**, 325–339

ILO (1991) *Occupational Exposure Limits for Airborne Toxic Substances: Values of Selected Countries* (Occupational Safety and Health Series No. 37), 3rd Ed., Geneva, pp. 368–369 (Substance No. 1835)

Ishidate, M., Jr & Yoshikawa, K. (1980) Chromosome aberration tests with Chinese hamster cells *in vitro* with and with metabolic activation—a comparative study on mutagens and carcinogens. *Arch. Toxicol.*, **Suppl. 4**, 41–44

Jablonická, A., Karelová, J., Poláková, H. & Vargová, M. (1988) Analysis of chromosomes in peripheral blood lymphocytes of styrene-exposed workers. *Mutat. Res.*, **206**, 167–169

Jakobsen, B.M. (1990) *Effects on Reproduction of Styrene, Toluene and Xylene.* Part I. *Styrene. Summary and Evaluation of Effects on Reproduction* (KEMI Report Series 2/90), Solna, Nordic Council of Ministers, pp. 11–35

Jankovic, J., Jones, W., Burkhart, J. & Noonan, G. (1991) Environmental study of firefighters. *Ind. occup. Hyg.*, **35**, 581–602

Jantunen, K., Mäki-Paakkanen, J. & Norppa, H. (1986) Induction of chromosome aberrations by styrene and vinylacetate in cultured human lymphocytes: dependence on erythrocytes. *Mutat. Res.*, **159**, 109–116

Japan Petrochemical Industry Association (1993) *Petrochemical Industry of Japan*, Tokyo, pp. 21–22

Jensen, A.A., Breum, N.O., Bacher, J. & Lynge, E. (1990) Occupational exposures to styrene in Denmark 1955–88. *Am. J. ind. Med.*, **17**, 593–606

Karbowski, R.J. & Braun, W.H. (1978) Quantitative determination of styrene in biological samples and expired air by gas chromatography–mass spectrometry (selected ion monitoring). *J. Chromatogr.*, **160**, 141–145

Katoh, T., Higashi, K. & Inoue, N. (1989) Sub-chronic effects of styrene and styrene oxide on lipid peroxidation and the metabolism of glutathione in rat liver and brain. *J. toxicol. Sci.*, **14**, 1–9

Kawai, K., Yasugi, T., Mizunuma, K., Horiguchi, S., Morioka, I., Miyashita, K., Uchida, Y. & Ikeda, M. (1992) Monitoring of workers exposed to a mixture of toluene, styrene and methanol vapours by means of diffusive air sampling, blood analysis and urine analysis. *Int. Arch. occup. environ. Health*, **63**, 429–435

Kelsey, K.T., Smith, T.J., Hammond, S.K., Letz, R. & Little, J.B. (1990) Sister-chromatid exchanges in lymphocytes from styrene-exposed boat builders. *Mutat. Res.*, **241**, 215–221

Kessler, W., Jiang, X. & Filser, J.G. (1992) Pharmacokinetics of styrene-7,8-oxide in the mouse and the rat. In: Kreutz, R. & Piekarski, C., eds, *32nd Annual Meeting of the German Society of Occupational Medicine, Köln, 1992*, Stuttgart, Gentner Verlag, pp. 622–626

Khanna, V.K., Husain, R., Hanig, J.P. & Seth, P.K. (1991) Increased neurobehavioral toxicity of styrene in protein-malnourished rats. *Neurotoxicol. Teratol.*, **13**, 153–159

Kingsley, I. (1976) *Health Hazard Evaluation Determination, New York Telephone and Telegraph Company, NY* (Report No. 75-178-295), Cincinnati, OH, National Institute for Occupational Safety and Health

Kishi, R., Katakura, Y., Okui, T., Ogawa, H., Ikeda, Y. & Miyake, H. (1989) Placental transfer and tissue distribution of ^{14}C-styrene: an audioradiographic study in mice. *Br. J. ind. Med.*, **46**, 376–383

Kishi, R., Katakura, Y., Ikeda, T., Chen, B.Q. & Miyake, H. (1992) Neurochemical effects in rats following gestational exposure to styrene. *Toxicol. Lett.*, **63**, 141–146

Kligerman, A.D., Allen, J.W., Bryant, M.F., Campbell, J.A., Collins, B.W., Doerr, C.L., Erexson, G.L., Kwanyuen, P. & Morgan, D.L. (1992) Cytogenetic studies of mice exposed to styrene by inhalation. *Mutat. Res.*, **280**, 35–43

Kligerman, A.D., Allen, J.W., Erexson, G.L. & Morgan, D.L. (1993) Cytogenetic studies of rodents exposed to styrene by inhalation. In: Sorsa, M., Peltonen, K., Vainio, H. & Hemminki, K., eds, *Butadiene and Styrene: Assessment of Health Hazards* (IARC Scientific Publications No. 127), Lyon, IARC, pp. 217–224

Knöppel, H & Schauenburg, H. (1989) Screening of household products for the emission of volatile organic compounds. *Environ. int.*, **15**, 413–418

Kogevinas, M., Ferro, G., Andersen, A., Bellander, T., Biocca, M., Coggon, D., Gennaro, V., Hutchings, S., Kolstad, H., Lundberg, I., Lynge, E., Partanen, T. & Saracci, R. (1994a) Cancer mortality in a historical cohort study of workers exposed to styrene. *Scand. J. Work Environ. Health*, **20**, 249–259

Kogevinas, M., Ferro, G., Saracci, R., Andersen, A., Bellander, T., Biocca, M., Bjerk, J.E., Breum, N.O., Coggon, D., Fontana, V., Ferro, S., Galassi, C., Gennaro, V., Hutchings, S., Jensen, A.A., Kolstad, H., Lundberg, I., Lynge, E., Pannett, B., Partanen, T. & Pfäffli, P. (1994b) *IARC Historical Multicentric Cohort Study of Workers Exposed to Styrene. Report of the Epidemiological Study and the Industrial Hygiene Investigation* (IARC intern. tech. Rep. 94/002), Lyon, IARC

Kolstad, H.A., Lynge, E., Olsen, J. & Breum, N. (1994) Do styrene exposed workers have an increased risk of lymphohaematopoietic malignancies? *Scand. J. Work Environ. Health* (in press)

Korn, M., Wodarz, R., Drysch, K., Schoknecht, W. & Schmahl, F.W. (1985) Stereometabolism of styrene in man: gas chromatographic determination of phenylethyleneglycol enantiomers and phenylethanol isomers in the urine of occupationally-exposed persons. *Arch. Toxicol.*, **58**, 110–114

Korn, M., Wodarz, R., Drysch, K. & Schmahl, F.W. (1987) Stereometabolism of styrene in man. Urinary excretion of chiral styrene metabolites. *Arch. Toxicol.*, **60**, 86–88

Korn, M., Gfrörer, W., Filser, J.G. & Kessler, W. (1994) Styrene-7,8-oxide in blood of workers exposed to styrene. *Arch. Toxicol.* (in press)

Kronoveter, K.J. & Boiano, J.M. (1984a) *Health Hazard Evaluation Report, Charlie's Taxidermy and Gifts, Fleetwood, PA* (Report No. 83-276-1499), Cincinnati, OH, National Institute for Occupational Safety and Health

Kronoveter, K.J. & Boiano, J.M. (1984b) *Health Hazard Evaluation Report, Pennsylvania Institute of Taxidermy, Ebensburg, PA* (Report No. 84-322-1502), Cincinnati, OH, National Institute of Occupational Safety and Health

Kulig, B.M. (1989) The neurobehavioral effects of chronic styrene exposure in the rat. *Neurotoxicol. Teratol.*, **10**, 511–517

Lai, S.-T. & Locke, D.C. (1983) Stepwise pyrolysis–liquid chromatography and pyrolysis–gas chromatography of polystyrene. *J. Chromatogr.*, **255**, 511–527

Laib, R.J., Tucholski, M., Filser, J.G. & Csanády, G.A. (1992) Pharmacokinetic interaction between 1,3-butadiene and styrene in Sprague–Dawley rats. *Arch. Toxicol.*, **66**, 310–314

Latriano, L., Wazneh, L., Dong, Z., Lu, S.-J., Snyder, C. & Jeffrey, A.M. (1991) Exposure to styrene: comparison of DNA and haemoglobin adducts as biomarkers. In: Garner, R.C., Farmer, P.B., Steel, G.T. & Wright, A.S., eds, *Human Carcinogen Exposure Biomonitoring and Risk Assessment*, Oxford, Oxford University Press, pp. 305–314

Lauwerys, R.R. & Hoet, P. (1993) *Industrial Chemical Exposure: Guidelines for Biological Monitoring*, 2nd Ed., Boca Raton, FL, Lewis Publishers, pp. 143–159

Law, R.J., Fileman, T.W. & Matthiessen, P. (1991) Phthalate esters and other industrial organic chemicals in the North and Irish seas. *Water Sci. Technol.*, **24**, 127–134

Leibman, K.C. (1975) Metabolism and toxicity of styrene. *Environ. Health Perspectives*, **11**, 115–119

Lemasters, G.K., Carson, A. & Samuels, S.J. (1985a) Occupational styrene exposure for twelve product categories in the reinforced plastics industry. *Am. ind. Hyg. Assoc. J.*, **46**, 434–441

Lemasters, G.K., Hagen, D. & Samuels, S.J. (1985b) Reproductive outcomes in women exposed to solvents in 36 reinforced plastics companies. I. Menstrual dysfunction. *J. occup. Med.*, **27**, 490–494

Lemasters, G.K., Samuels, S.J., Morrison, J.A. & Brooks, S.M. (1989) Reproductive outcomes of pregnant workers employed at 36 reinforced plastics companies. II. Lowered birth weight. *J. occup. Med.*, **31**, 115–120

Lemen, R.A. & Young, R. (1976) Investigation of health hazards in styrene–butadiene rubber facilities. In: Ede, L., ed., *Proceedings of NIOSH Styrene–Butadiene Rubber Briefing, Covington, Kentucky, April 30, 1976* (HEW Publ. No. (NIOSH) 77-129), Cincinnati, OH, National Institute for Occupational Safety and Health, pp. 3–8

Letz, R., Mahoney, F.C., Hershman, D.L., Woskie, S. & Smith, T.J. (1990) Neurobehavioral effects of acute styrene exposure in fiberglass boatbuilders. *Neurotoxicol. Teratol.*, **12**, 665–668

Lewis, P.J., Hagopian, C. & Koch, P. (1983) Styrene. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, M., eds, *Kirk–Othmer Encyclopedia of Chemical Technology*, Vol. 21, 3rd Ed., New York, John Wiley & Sons, pp. 770–801

Lide, D.R., ed. (1991) *CRC Handbook of Chemistry and Physics*, 72nd Ed., Boca Raton, FL, CRC Press, pp. 3–468, 6–76

Lilis, R., Lorimer, W.V., Diamond, S. & Selikoff, I.J. (1978) Neurotoxicity of styrene in production and polymerization workers. *Environ. Res.*, **15**, 133–138

Lindbohm, M.-L., Hemminki, K. & Kyyrönen, P. (1985) Spontaneous abortions among women employed in the plastics industry. *Am. J. ind. Med.*, **8**, 579–586

Lindbohm, M.-L., Taskinen, H., Sallmén, M. & Hemminki, K. (1990) Spontaneous abortions among women exposed to organic solvents. *Am. J. ind. Med.*, **17**, 449–463

Lindbohm, M.-L., Hemminki, K., Bonhomme, M.G., Anttila, A., Rantala, K., Heikkilä, P. & Rosenberg, M.J. (1991) Effects of paternal occupational exposure on spontaneous abortions. *Am. J. public Health*, **81**, 1029–1033

Lindström, K., Härkönen, H. & Hernberg, S. (1976) Disturbances in psychological functions of workers occupationally exposed to styrene. *Scand. J. Work Environ. Health*, **3**, 129–139

Linnainmaa, K., Meretoja, T., Sorsa, M. & Vainio, H. (1978a) Cytogenetic effects of styrene and styrene oxide on human lymphocytes and *Allium cepa*. *Scand. J. Work Environ. Health*, **4** (Suppl. 2), 156–162

Linnainmaa, K., Meretoja, T., Sorsa, M. & Vainio, H. (1978b) Cytogenetic effects of styrene and styrene oxide. *Mutat. Res.*, **58**, 277–286

Liu, S.F., Rappaport, S.M., Pongracz, K. & Bodell, W.J. (1988) Detection of styrene oxide–DNA adducts in lymphocytes of a worker exposed to styrene. In: Bartsch, H., Hemminki, K. & O'Neill, I.K., eds, *Methods for Detecting DNA Damaging Agents in Humans: Applications in Cancer Epidemiology and Prevention* (IARC Scientific Publications No. 89), Lyon, IARC, pp. 217–222

Löf, A. & Johanson, G. (1993) Dose-dependent kinetics of inhaled styrene in man. In: Sorsa, M., Peltonen, K., Vainio, H. & Hemminki, K., eds, *Butadiene and Styrene: Assessment of Health Hazards* (IARC Scientific Publications No. 127), Lyon, IARC, pp. 89–99

Löf, A., Gullstrand, E. & Byfält Nordqvist, M. (1983) Tissue distribution of styrene, styrene glycol and more polar styrene metabolites in the mouse. *Scand. J. Work Environ. Health*, **9**, 419–430

Löf, A., Gullstrand, E., Lundgren, E. & Byfält Nordqvist, M. (1984) Occurrence of styrene-7,8-oxide and styrene glycol in mouse after the administration of styrene. *Scand. J. Work Environ. Health*, **10**, 179–187

Löf, A., Lundgren, E. & Byfält Nordqvist, M. (1986a) Kinetics of styrene in workers from a plastics industry after controlled exposure: a comparison with subjects not previously exposed. *Br. J. ind. Med.*, **43**, 537–543

Löf, A., Lundgren, E., Nydahl, E.-M. & Byfält Nordqvist, M. (1986b) Biological monitoring of styrene metabolites in blood. *Scand. J. Work Environ. Health*, **12**, 70–74

Loprieno, N., Abbondandolo, A., Barale, R., Baroncelli, S., Bonatti, S., Bronzetti, G., Cammellini, A., Corsi, C., Corti, G., Frezza, D., Leporini, C., Mazzaccaro, A., Nieri, R., Rosellini, D. & Rossi, A.M. (1976) Mutagenicity of industrial compounds: styrene and its possible metabolite styrene oxide. *Mutat. Res.*, **40**, 317–324

Lorimer, W.B., Lilis, R., Nicholson, W.J., Anderson, H., Fischbein, A., Daum, S., Rom, W., Rice, C. & Selikoff, I.J. (1976) Clinical studies of styrene workers: initial findings. *Environ. Health Perspectives*, **17**, 171–181

Lorimer, W., Lilis, R., Fischbein, A., Daum, S., Anderson, H., Wolff, M.S. & Selikoff, I.J. (1978) Health status of styrene–polystyrene polymerization workers. *Scand. J. Work Environ. Health*, **4** (Suppl. 2), 220–226

Maarse, H. (1992a) *Natural Occurrence and Routes of Formation of Styrene in Food* (TNO Report No. B92.084), Zeist, TNO Nutrition and Food Research

Maarse, H. (1992b) *Quantities of Styrene in 6 Selected Food Products* (TNO Report No. B92.553), Zeist, TNO Nutrition and Food Research

Makhlouf, J. (1982) Polyesters, unsaturated. In: Mark, H.F., Othmer, D.F., Overberger, C.G. & Seaborg, G.T., eds, *Kirk–Othmer Encyclopedia of Chemical Technology*, 3rd Ed., Vol. 18, New York, John Wiley & Sons, pp. 575–594

Mäki-Paakkanen, J. (1987) Chromosomal aberrations, micronuclei and sister-chromatid exchanges in blood lymphocytes after occupational exposure to low levels of styrene. *Mutat. Res.*, **189**, 399–406

Mäki-Paakkanen, J., Walles, S., Osterman-Golkar, S. & Norppa, H. (1991) Single-strand breaks, chromosome aberrations, sister chromatid exchanges, and micronuclei in blood lymphocytes of workers exposed to styrene during the production of reinforced plastics. *Environ. mol. Mutag.*, **17**, 27–31

Male, J., Lillehaug, J.R., Djurhuus, R. & Pryme, I.F. (1985) In vitro transformation and tumor promotion studies of styrene and styrene oxide. *Carcinogenesis*, **6**, 1367–1370

Maltoni, C., Ciliberti, A. & Carretti, P. (1982) Experimental contributions in identifying brain potential carcinogens in the petrochemical industry. *Ann. N.Y. Acad. Sci.*, **381**, 216–249

Mannsville Chemical Products Corp. (1987) *Chemical Products Synopsis: Styrene*, Cortland, NY

Matanoski, G.M., Santos-Burgoa, C. & Schwartz, L. (1990) Mortality of a cohort of workers in the styrene–butadiene polymer manufacturing industry (1943–1982). *Environ. Health Perspectives*, **86**, 107–117

Matanoski, G., Francis, M., Correa-Villaseñor, A., Elliott, X., Santos-Burgoa, C. & Schwarz, L. (1993) Cancer epidemiology among styrene–butadiene rubber workers. In: Sorsa, M., Peltonen, K., Vainio, H. & Hemminki, K., eds, *Butadiene and Styrene: Assessment of Health Hazards* (IARC Scientific Publications No. 127) Lyon, IARC, pp. 363–374

Matsuoka, A., Hayashi, M. & Ishidate, M., Jr (1979) Chromosomal aberration tests on 29 chemicals combined with S9 mix *in vitro*. *Mutat. Res.*, **66**, 277–290

McDonald, A.D., Lavoie, J., Côté, R. & McDonald, J.C. (1988) Spontaneous abortion in women employed in plastics manufacture. *Am. J. ind. Med.*, **14**, 9–14

McDougal, J.N., Jepson, G.W., Clewell, H.J., III, Gargas, M.L. & Andersen, M.E. (1990) Dermal absorption of organic chemical vapors in rats and humans. *Fundam. appl. Toxicol.*, **14**, 299–308

McKay, R.T., Lemasters, G.K. & Elia, V.J. (1982) Ambient air styrene levels in communities near reinforced plastic processors. *Environ. Pollut.* (Series B), **4**, 135–141

McMichael, A.J., Spirtas, R., Gamble, J.F. & Tousey, P.M. (1976) Mortality among rubber workers: relationship to specific jobs. *J. occup. Med.*, **18**, 178–185

de Meester, C., Poncelet, F., Roberfroid, M., Rondelet, J. & Mercier, M. (1977) Mutagenicity of styrene and styrene oxide. *Mutat. Res.*, **56**, 147–152

de Meester, C., Duverger-van Bogaert, M., Lambotte-Vandepaer, M., Mercier, M. & Poncelet, F. (1981) Mutagenicity of styrene in the *Salmonella typhimurium* test system. *Mutat. Res.*, **90**, 443–450

Meinhardt, T.J., Lemen, R.A., Crandall, M.S. & Young, R.J. (1982) Environmental epidemiologic investigation of the styrene–butadiene rubber industry. Mortality patterns with discussion of the hematopoietic and lymphatic malignancies. *Scand. J. Work Environ. Health*, **8**, 250–259

Mendrala, A.L., Langvardt, P.W., Nitschke, K.D., Quas, J.F. & Nolan, R.J. (1993) In vitro kinetics of styrene and styrene oxide metabolism in rat, mouse, and human. *Arch. Toxicol.*, **67**, 18–27

Meretoja, T., Järventaus, H., Sorsa, M. & Vainio, H. (1978a) Chromosome aberrations in lymphocytes of workers exposed to styrene. *Scand. J. Work Environ. Health*, **4** (Suppl. 2), 259–264

Meretoja, T., Vainio H. & Jarventaus, H. (1978b) Clastogenetic effects of styrene exposure on bone marrow cells of rats. *Toxicol. Lett.*, **1**, 315–318

Mickiewicz, W. & Rzeczycki, W. (1988) Effect of styrene and other alkyl benzene derivatives on oxidation of FAD- and NAD-linked substrates in rat liver mitochondria. *Biochem. Pharmacol.*, **37**, 4439–4444

Möller, C., Ödkvist, L., Larsby, B., Tham, R., Ledin, T. & Bergholtz, L. (1990) Otoneurological findings in workers exposed to styrene. *Scand. J. Work Environ. Health*, **16**, 189–194

Monson, R.R. & Nakano, K.K. (1976) Mortality among rubber workers. I. White male union employees in Akron, Ohio. *Am. J. Epidemiol.*, **103**, 284–296

Morgan, D.L., Mahler, J.F., Dill, J.A., Price, H.C., Jr, O'Connor, R.W. & Adkins, B., Jr (1993a) Styrene inhalation toxicity studies in mice. III. Strain differences in susceptibility. *Fundam. appl. Toxicol.*, **21**, 326–333

Morgan, D.L., Mahler, J.F., Dill, J.A., Price, H.C., Jr, O'Connor, R.W. & Adkins, B., Jr (1993b) Styrene inhalation toxicity studies in mice. II. Sex differences in susceptibility of B6C3F1 mice. *Fundam. appl. Toxicol.*, **21**, 317–325

Morgan, D.L., Mahler, J.F., O'Connor, R.W., Price, H.C., Jr & Adkins, B., Jr (1993c) Styrene inhalation toxicity studies in mice. I. Hepatotoxicity in B6C3F1 mice. *Fundam. appl. Toxicol.*, **20**, 325–335

Moscato, G., Biscaldi, G., Cottica, D., Pugliese, F., Candura, S. & Candura, F. (1987) Occupational asthma due to styrene: two case reports. *J. occup. Med.*, **29**, 957–960

Muijser, H., Hoogendijk, E.M.G. & Hooisma, J. (1988) The effects of occupational exposure to styrene on high-frequency hearing thresholds. *Toxicology*, **49**, 331–340

Murata, K., Araki, S. & Yokoyama, K. (1991) Assessment of the peripheral, central, and autonomic nervous system function in styrene workers. *Am. J. ind. Med.*, **20**, 775–784

Murray, F.J., John, J.A., Balmer, M.F. & Schwetz, B.A. (1978) Teratologic evaluation of styrene given to rats and rabbits by inhalation or by gavage. *Toxicology*, **11**, 335–343

Mutti, A., Vescovi, P.P., Falzoi, M., Arfini, G., Valenti, G. & Franchini, I. (1984a) Neuroendocrine effects of styrene on occupationally exposed workers. *Scand. J. Work Environ. Health*, **10**, 225–228

Mutti, A., Falzoi, M., Romanelli, A. & Franchini, I. (1984b) Regional alterations of brain catecholamines by styrene exposure in rabbits. *Arch. Toxicol.*, **55**, 173–177

Mutti, A., Falzoi, M., Romanelli, A., Bocchi, M.C., Ferroni, C. & Franchini, I. (1988) Brain dopamine as a target for solvent toxicity: effects of some monocyclic aromatic hydrocarbons. *Toxicology*, **49**, 77–82

Mutti, A., Buzio, C., Perazolli, F., Bergamaschi, E., Bocchi, M.C., Selis, L., Mineo, F. & Franchini, I. (1992) Lymphocyte subsets in workers occupationally exposed to styrene. *Med. Lav.*, **83**, 167–177 (in Italian)

Nakajima, T., Elovaara, E., Gonzalez, F.J., Gelboin, H.V., Vainio, H. & Aoyama, T. (1993) Characterization of the human cytochrome P450 isozymes responsible for styrene metabolism. In: Sorsa, M., Peltonen, K., Vainio, H. & Hemminki, K., eds, *Butadiene and Styrene: Assessment of Health Hazards* (IARC Scientific Publications No. 127), Lyon, IARC, pp. 101–108

Newhook, R. & Caldwell, I. (1993) Exposure to styrene in the general Canadian population. In: Sorsa, M., Peltonen, K., Vainio, H. & Hemminki, K., eds, *Butadiene and Styrene: Assessment of Health Hazards* (IARC Scientific Publications No. 127), Lyon, IARC, pp. 27–33

Nicholson, W.J., Selikoff, I.J. & Seidman, H. (1978) Mortality experience of styrene–polystyrene polymerization workers. Initial findings. *Scand. J. Work Environ. Health*, **4** (Suppl. 2), 247–252

Nordenson, I. & Beckman, L. (1984) Chromosomal aberrations in lymphocytes of workers exposed to low levels of styrene. *Hum. Hered.*, **34**, 178–182

Norppa, H. (1981) Styrene and vinyltoluene induce micronuclei in mouse bone marrow. *Toxicol. Lett.*, **8**, 247–251

Norppa, H. & Järventaus, H. (1992) Induction of sister-chromatid exchanges by 2-aminofluorene in cultured human lymphocytes with and without erythrocytes. *Mutat. Res.*, **282**, 135–138

Norppa, H. & Sorsa, M. (1993) Genetic toxicity of 1,3-butadiene and styrene. In: Sorsa, M., Peltonen, K., Vainio, H. & Hemminki, K., eds, *Butadiene and Styrene: Assessment of Health Hazards* (IARC Scientific Publications No. 127), Lyon, IARC, pp. 185–193

Norppa, H. & Vainio, H. (1983) Induction of sister-chromatid exchanges by styrene analogues in cultured human lymphocytes. *Mutat. Res.*, **116**, 379–387

Norppa, H., Sorsa, M., Pfäffli, P. & Vainio, H. (1980a) Styrene and styrene oxide induce SCEs and are metabolized in human lymphocyte cultures. *Carcinogenesis*, **1**, 357–361

Norppa, H., Sorsa, M. & Vainio, H. (1980b) Chromosomal aberrations in bone marrow of Chinese hamsters exposed to styrene and ethanol. *Toxicol. Lett.*, **5**, 241–244

Norppa, H., Vainio, H. & Sorsa, M. (1983) Metabolic activation of styrene by erythrocytes detected as increased sister chromatid exchanges in cultured human lymphocytes. *Cancer Res.*, **43**, 3579–3582

Norppa, H., Tursi, F. & Einistö, P. (1985) Erythrocytes as a metabolic activation system in mutagenicity tests. In: Janiaud, P., Averbeck, D. & Moustacchi, E., eds, *Mutagenesis and Genetic Toxicology. Theoretical and Practical Results* (INSERM Vol. 119), Paris, Editions INSERM, pp. 35–50

Norström, Å., Löf, A., Aringer, L., Samuelsson, R., Andersson, B., Levin, J.-O. & Näslund, P. (1992) Determination of *N*-acetyl-*S*-(2-phenyl-2-hydroxyethyl)cysteine in human urine after experimental exposure to styrene. *Chemosphere*, **24**, 1553–1561

Oesch, F. (1973) Mammalian epoxide hydrases: inducible enzymes catalysing the inactivation of carcinogenic and cytotoxic metabolites derived from aromatic and olefinic compounds. *Xenobiotica*, **3**, 305–340

Oesch, F., Jerina, D.M. & Daly, J. (1971) A radiometric assay for hepatic epoxide hydrase activity with [7-^{3}H] styrene oxide. *Biochim. biophys. Acta.*, **227**, 685–691

Ogata, M. & Sugihara, R. (1978) High performance liquid chromatographic procedure for quantitative determination of urinary phenylglyoxylic, mandelic and hippuric acids as indices of styrene exposure. *Int. Arch. occup. environ. Health*, **42**, 11–19

Ogata, M. & Taguchi, T. (1987) Quantitation of urinary metabolites of toluene, xylene, styrene, ethylbenzene, benzene and phenol by automated high performance liquid chromatography. *Int. Arch. occup. environ. Health*, **59**, 263–272

Ogata, M. & Taguchi, T. (1988) Simultaneous determination of urinary creatinine and metabolites of toluene, xylene, styrene, ethylbenzene and phenol by automated high performance liquid chromatography. *Int. Arch. occup. environ. Health*, **61**, 131–140

Ohashi, Y., Nakai, Y., Ikeoka, H., Koshimo, H., Esaki, Y., Horiguchi, S. & Teramoto, K. (1985) Electron microscopic study of the respiratory toxicity of styrene. *Osaka City med. J.*, **31**, 11–21

Ohashi, Y., Nakai, Y., Ikeoka, H., Koshimo, H., Nakata, J., Esaki, Y., Horiguchi, S. & Teramoto, K. (1986) Degeneration and regeneration of respiratory mucosa of rats after exposure to styrene. *J. appl. Toxicol.*, **6**, 405–412

Ohtsuji, H. & Ikeda, M. (1971) The metabolism of styrene in the rat and the stimulatory effect of phenobarbital. *Toxicol. appl. Pharmacol.*, **18**, 321–328

Okun, A.H., Beaumont, J.J., Meinhardt, T.J. & Crandall, M.S. (1985) Mortality patterns among styrene-exposed boatbuilders. *Am. J. ind. Med.*, **8**, 193–205

Oliviero, M. (1906) Reduction of cinnamic acid to cinnamene by moulds. *J. Pharmacol. chim.*, **24**, 62–64 (in French)

Ortiz de Montellano, P.R. & Catalano, C.E. (1985) Epoxidation of styrene by hemoglobin and myoglobin. *J. biol. Chem.*, **260**, 9265–9271

Ortiz de Montellano, P.R. & Grab, L.A. (1986) Cooxidation of styrene by horseradish peroxidase and glutathione. *Mol. Pharmacol.*, **30**, 666–669

Ott, M.G., Kolesar, R.C., Scharnweber, H.C., Schneider, E.J. & Venable, J.R. (1980) A mortality survey of employees in the development or manufacture of styrene-based products. *J. occup. Med.*, **22**, 445–460

Pantarotto, C., Fanelli, R., Bidoli, F., Morazzoni, P., Salmona, M. & Szczawinska, K. (1978) Arene oxides in styrene metabolism, a new perspective in styrene toxicity? *Scand. J. Work Environ. Health*, **4** (Suppl. 2), 67–77

Pantarotto, C., Fanelli, R., Belletti, I. & Bidoli, F. (1980) Determination of styrene in biological specimens by gas chromatography–selected ion monitoring: distribution in mice. *Anal. Biochem.*, **105**, 340–347

Paterson, S. & Mackay, D. (1986) A pharmacokinetic model of styrene inhalation with the fugacity approach. *Toxicol. appl. Pharmacol.*, **82**, 444–453

Pekari, K., Nylander-French, L., Pfäffli, P., Sorsa, M. & Aitio, A. (1993) Biological monitoring of exposure to styrene—assessment of different approaches. *J. occup. Med. Toxicol.*, **2**, 115–126

Penttilä, M., Sorsa, M. & Vainio, H. (1980) Inability of styrene to induce nondisjunction in *Drosophila* or a positive micronucleus test in the Chinese hamster. *Toxicol. Lett.*, **6**, 119–123

Perbellini, L., Mozzo, P., Turri, P.V., Zedde, A. & Brugnone, F. (1988) Biological exposure index of styrene suggested by a physiologico-mathematical model. *Int. Arch. occup. environ. Health*, **60**, 187–193

Pezzagno, G., Ghittori, S., Imbriani, M. & Capodaglio, E. (1985) Urinary elimination of styrene in experimental and occupational exposure. *Scand. J. Work Environ. Health*, **11**, 371–379

Pfäffli, P. (1982) Degradation products of plastics. III. Industrial hygiene measurements. *Scand. J. Work Environ. Health*, **8** (Suppl. 2), 27–43

Pfäffli, P. & Säämänen, A. (1993) The occupational scene of styrene In: Sorsa, M., Peltonen, K., Vainio, H. & Hemminki, K., eds, *Butadiene and Styrene: Assessment of Health Hazards* (IARC Scientific Publications No. 127), Lyon, IARC, pp. 15–26

Pfäffli, P., Vainio, H. & Hesso, A. (1979) Styrene and styrene oxide concentrations in the air during the lamination process in the reinforced plastics industry. *Scand. J. Work Environ. Health*, **5**, 158–161

Pfäffli, P., Hesso, A., Vainio, H. & Hyvönen, M. (1981) 4-Vinylphenol excretion suggestive of arene oxide formation in workers occupationally exposed to styrene. *Toxicol. appl. Pharmacol.*, **60**, 85–90

Pfäffli, P., Nylander, L., Säämanen, A., Niemelä, R. & Kalliokoski, P. (1992) Exposure to chemicals in the reinforced plastics industry. *Työ ja ihminen*, **6**, 111–126 (in Finnish)

Phillips, D.H. & Farmer, P.B. (1994) Evidence for DNA and protein binding by styrene and styrene oxide. *C.R.C. crit. Rev. Toxicol.* (in press)

Pohlová, H. & Srám, R.J. (1985) Cytogenetic analysis of peripheral blood lymphocytes of workers occupationally exposed to styrene. *J. Hyg. Epidemiol. Microbiol. Immunol.*, **28**, 155–161

Pohlová, H., Rössner, P. & Srám, R.J. (1985) Cytogenetic analysis of human peripheral blood lymphocytes in culture exposed *in vitro* to styrene and styrene oxide. *J. Hyg. Epidemiol. Microbiol. Immunol.*, **29**, 269–274

Poncelet, F., de Meester, C., Duverger-van Bogaert, M., Lambotte-Vandepaer, M., Roberfroid, M. & Mercier, M. (1980) Influence of experimental factors on the mutagenicity of vinylic monomers. *Arch. Toxicol.*, **Suppl. 4**, 63–66

Ponomarkov, V. & Tomatis, L. (1978) Effects of long-term oral administration of styrene to mice and rats. *Scand. J. Work Environ. Health*, **4** (Suppl. 2), 127–135

Preston, R.J. & Abernethy, D.J. (1993) Studies of the induction of chromosomal aberration and sister chromatid exchange in rats exposed to styrene by inhalation. In: Sorsa, M., Peltonen, K., Vainio, H. & Hemminki, K., eds, *Butadiene and Styrene: Assessment of Health Hazards* (IARC Scientific Publications No. 127), Lyon, IARC, pp. 225–233

de Raat, W.K. (1978) Induction of sister chromatid exchanges by styrene and its presumed metabolite styrene oxide in the presence of rat liver homogenate. *Chem.-biol. Interactions*, **20**, 163–170

Ramsey, J.C. & Andersen, M.E. (1984) A physiologically based description of the inhalation pharmacokinetics of styrene in rats and humans. *Toxicol. appl. Pharmacol.*, **73**, 159–175

Ramsey, J.C. & Young, J.D. (1978) Pharmacokinetics of inhaled styrene in rats and humans. *Scand. J. Work Environ. Health*, **4** (Suppl. 2), 84–91

Ramsey, J.C., Young, J.D., Karbowski, R.J., Chenoweth, M.B., MacCarty, L.P. & Braun, W.H. (1980) Pharmacokinetics of inhaled styrene in human volunteers. *Toxicol. appl. Pharmacol.*, **53**, 54–63

Rao, S.I., Wilks, A. & Ortiz de Montellano, P.R. (1993) The roles of His-64, Tyr-103, Tyr-146, and Tyr-151 in the epoxidation of styrene and β-methylstyrene by recombinant sperm whale myoglobin. *J. biol. Chem.*, **268**, 803–809

Rappaport, S.M. & Fraser, D.A. (1977) Air sampling and analysis in a rubber vulcanization area. *Am. ind. Hyg. Assoc. J.*, **38**, 205–210

Rappaport, S.M., Ting, D., Jin, Z., Yeowell-O'Connel, K., Waidyanatha, S. & McDonald, T. (1993) Application of Raney nickel to measure adducts of styrene oxide with hemoglobin and albumin. *Chem. Res. Toxicol.*, **6**, 238–244

Rebert, C.S., Boyes, W.K., Pryor, G.T., Svensgaard, D.J., Kassay, K.M., Gordon, G.R. & Shinsky, N. (1993) Combined effects of solvents on the rat's auditory system: styrene and trichloroethylene. *Int. J. Psychophysiol.*, **14**, 49–49

Reed, L.D. (1983) *Health Hazard Evaluation Determination, Columbia College, Columbia, MO* (Report No. 81-326-1247), Cincinnati, OH, National Institute for Occupational Safety and Health

Riihimäki, V. & Pfäffli, P. (1978) Percutaneous absorption of solvent vapors in man. *Scand. J. Work Environ. Health*, **4**, 73–85

Romano, M., Garattini, E. & Salmona, M. (1985) Perinatal development of cytochrome P-450, cytochrome C reductase, aryl hydrocarbon hydroxylase, styrene monooxygenase and styrene epoxide hydrolase in rabbit liver microsomes and nuclei. *Dev. Pharmacol. Ther.*, **8**, 232–242

Rosén, I., Haeger-Aronsen, B., Rehnström, S. & Welinder, H. (1978) Neurophysiological observations after chronic styrene exposure. *Scand. J. Work Environ. Health*, **4**, Suppl. 2, 184–194

Rosengren, L.E. & Haglid, K.G. (1989) Long term neurotoxicity of styrene. A quantitative study of glial fibrillary acidic protein (GFA) and S-100. *Br. J. ind. Med.*, **46**, 316–320

Ruhe, R.L. & Jannerfeldt, E.R. (1980) *Health Hazard Evaluation Report, Metamora Products Corporation, Elkland, PA* (Report No. HE-80-188-797), Cincinnati, OH, National Institute for Occupational Safety and Health

Rutkowski, J.V. & Levin, B.C. (1986) Acrylonitrile–butadiene–styrene copolymers (ABS): pyrolysis and combustion products and their toxicity—a review of the literature. *Fire Mater.*, **10**, 93–105

Säämanen, A., Antilla, A. & Pfäffli, P. (1991) *Styreeni* [Styrene] (Altisteet Työssä 9), Helsinki, Työterveyslaitos Työsuojelurahasto [Work Environment Fund] (in Finnish)

Säämanen, A., Pfäffli, P. & Niemelä, R. (1993) *Altistumishuippujen Vähentäminen Polyesterilujitemuovityössä* [Reduction of Peak Exposures in the Reinforced Plastics Industry] (Työsuojelurahaston hanke No. 90201), Helsinki, Työsuojelurahasto Työterveyslaitos [Work Environment Fund]

Sadtler Research Laboratories (1991) *Sadtler Standard Spectra. 1981–1991 Supplementary Index*, Philadelphia, PA

Salomaa, S., Donner, M. & Norppa, H. (1985) Inactivity of styrene in the mouse sperm morphology test. *Toxicol. Lett.*, **24**, 151–155

Samimi, B. & Falbo, L. (1982) Monitoring of workers exposure to low levels of airborne monomers in an acrylic ester–styrene copolymer production plant. *Am. ind. Hyg. Assoc. J.*, **43**, 858–862

Sangster, J. (1989) Octanol–water partition coefficients of simple organic compounds. *J. phys. chem. Ref. Data*, **18**, 1111–1143

Santos-Burgoa, C., Matanoski, G.M., Zeger, S. & Schwartz, L. (1992) Lymphohematopoietic cancer in styrene–butadiene polymerization workers. *Am. J. Epidemiol.*, **136**, 843–854

Sbrana, I., Lascialfari, D., Rossi, A.M., Loprieno, N., Bianchi, M., Tortoreto, M. & Pantarotto, C. (1983) Bone marrow cell chromosomal aberrations and styrene biotransformation in mice given styrene on a repeated oral schedule. *Chem.-biol. Interactions*, **45**, 349–357

Schumacher, R.L., Breysse, P.A., Carlyon, W.R., Hibbard, R.P. & Kleinman, G.D. (1981) Styrene exposure in the fiberglass fabrication industry in Washington State. *Am. ind. Hyg. Assoc. J.*, **42**, 143–149

Scott, D. (1993) Cytogenetic studies of workers exposed to styrene: a review. In: Sorsa, M., Peltonen, K., Vainio, H. & Hemminki, K., eds, *Butadiene and Styrene: Assessment of Health Hazards* (IARC Scientific Publications No. 127), Lyon, IARC, pp. 275–286

Sepai, O., Anderson, D., Street, B., Bird, I., Farmer, P.B. & Bailey, E. (1993) Monitoring of exposure to styrene oxide by GC–MS analysis of phenylhydroxyethyl esters in hemoglobin. *Arch. Toxicol.*, **67**, 28–33

Seppäläinen, A.M. & Härkönen, H. (1976) Neurophysiological findings among workers occupationally exposed to styrene. *Scand. J. Work Environ. Health*, **3**, 140–146

Seutter-Berlage, F., Delbressine, L.P.C., Smeets, F.L.M. & Ketelaars, H.C.J. (1978) Identification of three sulphur-containing urinary metabolites of styrene in the rat. *Xenobiotica*, **8**, 413–418

Shah, J.J. & Singh, H.B. (1988) Distribution of volatile organic chemicals in outdoor and indoor air. A national VOCs (volatile organic chemicals) data base. *Environ. Sci. Technol.*, **22**, 1381–1388

Sharief, Y., Brown, A.M., Backer, L.C., Campbell, J.A., Wesbrook-Collins, B, Stead, A.G. & Allen, J.W. (1986) Sister chromatid exchange and chromosome aberration analyses in mice after in vivo exposure to acrylonitrile, styrene, or butadiene monoxide. *Environ. Mutag.*, **8**, 439–448

Siemiatycki, J., ed. (1991) *Risk Factors for Cancer in the Workplace*, Boca Raton, FL, CRC Press

Simula, A.P. & Priestly, B.G. (1992) Species differences in the genotoxicity of cyclophosphamide and styrene in three in vivo assays. *Mutat. Res.*, **271**, 49–58

Sina, J.F., Bean, C.L., Dysart, G.R., Taylor, V.I. & Bradley, M.O. (1983) Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. *Mutat. Res.*, **113**, 357–391

Sinha, A.K., Jersey, G.C., Linscombe, V.A., Adams, R.L., Mueller, A.M. & McClintock, M.L. (1983) Cytogenetic evaluation of bone marrow cells from rats exposed to styrene vapor for one year. *Fundam. appl. Toxicol.*, **3**, 95–98

Sjöborg, S., Fregert, S. & Trulsson, L. (1984) Contact allergy to styrene and related chemicals. *Contact Derm.*, **10**, 94–96

Sorsa, M., Anttila, A., Järventaus, H., Kubiak, R., Norppa, H., Nylander, L., Pekari, K., Pfäffli, P. & Vainio, H. (1991) Styrene revisited—exposure assessment and risk estimation in reinforced plastics industry. In: Gledhill, B.L. & Mauro, F., eds, *New Horizons in Biological Dosimetry*, New York, Wiley-Liss, pp. 187–195

Srivastava, S.P., Das, M. & Seth, P.K. (1983) Enhancement of lipid peroxidation of rat liver on acute exposure to styrene and acrylamide a consequence of glutathione depletion. *Chem.-biol. Interactions*, **45**, 373–380

Srivastava, S., Seth, P.K. & Srivastava, S.P. (1989) Effect of styrene administration on rat testis. *Arch. Toxicol.*, **63**, 43–46

Srivastava, S., Seth, P.K. & Srivastava, S.P. (1992a) Effect of styrene on testicular enzymes of growing rat. *Indian J. exp. Biol.*, **30**, 399–401

Srivastava, S., Seth, P.K. & Srivastava, S.P. (1992b) Biochemical and morphological studies in testes of rat offspring of mothers exposed to styrene during lactation. *Pharmacol. Toxicol.*, **70**, 314–316

Steele, D.H. (1992) *The Determination of Styrene and Benzene in Selected Foods* (MRI Project No. 6450), Kansas City, MO, Midwest Research Institute

Stewart, R.D., Dodd, H.C., Baretta, E.D. & Schaffer, A.W. (1968) Human exposure to styrene vapor. *Arch. environ. Health*, **16**, 656–662

Stock, B.H., Schreiber, J., Guenat, C., Mason, R.P., Bend, J.R. & Eling, T.E. (1986) Evidence for a free radical mechanism of styrene-glutathione conjugate formation catalyzed by prostaglandin H synthase and horseradish peroxidase. *J. biol. Chem.*, **261**, 15915–15922

Stoltz, D.R. & Withey, R.J. (1977) Mutagenicity testing of styrene and styrene epoxide in *Salmonella typhimurium*. *Bull. environ. Contam. Toxicol.*, **17**, 739–742

Sullivan, E.A. & Sullivan, J.L. (1986) Styrene exposure in the reinforced plastics industry in Ontario. *Occup. Health Ontario*, **7**, 38–55

Taskinen, H., Anttila, A., Lindbohm, M.-L., Sallmén, M. & Hemminki, K. (1989) Spontaneous abortions and congenital malformations among the wives of men occupationally exposed to organic solvents. *Scand. J. Work Environ. Health*, **15**, 345–352

Teramoto, K. & Horiguchi, S. (1978) Absorption, distribution and elimination of styrene in man and experimental animals. *Arh. hig. rada. toksikol.*, **30** (Suppl.), 431–437

Teramoto, K., Horiguchi, S., Wakitani, F., Tojyo, F., Tokimoto, T. & Kuribara, H. (1988) Effects of styrene on wheel-running and ambulatory activities in mice. *J. toxicol. Sci.*, **13**, 133–139

Thiess, A.M. & Fleig, I. (1978) Chromosome investigations on workers exposed to styrene/polystyrene. *J. occup. Med.*, **20**, 747–749

Thiess, A.M. & Friedheim, M. (1978) Morbidity among persons employed in styrene production, polymerisation and processing plants. *Scand. J. Work Environ. Health*, **4** (Suppl. 2), 203–214

Thiess, A.M., Schwegler, H. & Fleig, I. (1980) Chromosome investigations in lymphocytes of workers employed in areas in which styrene-containing unsaturated polyester resins are manufactured. *Am. J. ind. Med.*, **1**, 205–210

Ting, D., Smith, M.T., Doane-Setzer, P. & Rappaport, S.M. (1990) Analysis of styrene oxide–globin adducts upon reaction with Raney nickel. *Carcinogenesis*, **11**, 755–760

Tomanin, R., Ballarin, C., Bartolucci, G.B., De Rosa, E., Sessa, G., Iannini, G., Cupiraggi, A.R. & Sarto, F. (1992) Chromosome aberrations and micronuclei in lymphocytes of workers exposed to low and medium levels of styrene. *Int. Arch. occup. environ. Health*, **64**, 209–215

Tossavainen, A. (1978) Styrene use and occupational exposure in the plastics industry. *Scand. J. Work Environ. Health*, **4** (Suppl. 2), 7–13

Triebig, G., Lehrl, S., Wetle, D., Schaller, K.H. & Valentin, H. (1989) Clinical and neurobehavioural study of the acute and chronic neurotoxicity of styrene. *Br. J. ind. Med.*, **46**, 799–804

Truchon, G., Gérin, M. & Brodeur, J. (1990) Urinary excretion of mandelic, phenylglyoxylic, and specific mercapturic acids in rats exposed repeatedly by inhalation to various concentrations of styrene vapors. *Can. J. Physiol. Pharmacol.*, **68**, 556–561

Truchon, G., Ostiguy, C., Drolet, D., Mergler, D., Campagna, D., Bélanger, S., Larribe, F. & Huel, G. (1992) Neurotoxic effects among styrene-exposed workers. I. Environmental and biological monitoring of exposure. *Trav. Santé*, **8**, S11–S14 (in French)

Tursi, F., Samaia, M., Salmona, M. & Belvedere, G. (1983) Styrene oxidation to styrene oxide in human erythrocytes is catalyzed by oxyhemoglobin. *Experientia*, **39**, 593–594

Työministeriö [Ministry of Labour] (1993) *Limit Values 1993*, Helsinki, p. 17

UNEP (1993) *IRPTC Data Profiles on Styrene*, Geneva

US Environmental Protection Agency (1986) Method 8240. Gas chromatography/ mass spectrometry for volatile organics. In: *Test Methods for Evaluating Solid Waste—Physical/Chemical Methods*, 3rd ed., Vol. 2 (US EPA No. SW-846), Washington DC, Office of Solid Waste and Emergency Response, pp. 8240-1–8240-43

US Environmental Protection Agency (1993) National primary drinking water regulations. *US Code fed. Regul.*, **40**, Subpart D, 141.32, p. 673

US Food and Drug Administration (1993) Food and drugs. *US Code fed. Regul.*, **Title 21**, Parts 172.515, 172.615, 173.20, 173.25, 173.70, 175.105, 175.125, 175.300, 175.320, 176.170, 176.180, 177.1010, 177.1030, 177.1200, 177.1210, 177.1640, 177.1810, 177.1820, 177.1830, 177.2260, 177.2420, 177.2600, 177.2710, 177.2800, 178.2010, 178.3790, 181.30, pp. 48–55, 57–59, 105–108, 110–111, 147–167, 129–144, 208–215, 219–226, 275–276, 280–284, 294–297, 299–301, 309–315, 325–339, 380–381, 405

US National Cancer Institute (1979a) *Bioassay of Styrene for Possible Carcinogenicity (CAS No. 100-42-5)* (Tech. Rep. Ser. No. 185; DHEW Publ. No. (NIH 79-1741), Washington DC, US Government Printing Office

US National Cancer Institute (1979b) *Bioassay of a Solution of β-Nitrostyrene and Styrene for Possible Carcinogenicity (CAS No. 102-96-5, CAS No. 100-42-5)* (Tech. Rep. Ser. No. 170; DHEW Publ. No. (NIH 79-1726)), Washington DC, US Government Printing Office

US National Institute for Occupational Safety and Health (1983) *Criteria for a Recommended Standard. Occupational Exposure to Styrene* (NIOSH Publication No. 83-119), Cincinnati, OH

US National Institute for Occupational Safety and Health (1992) *NIOSH Recommendations for Occupational Safety and Health. Compendium of Policy Documents and Statements* (DHHS (NIOSH) Publ. No. 92-100), Cincinnati, OH, Division of Standards Development and Technology Transfer, p. 121

US National Institute for Occupational Safety and Health (1993) *National Occupational Exposure Survey (1981–1983)*, Cincinnati, OH

US National Library of Medicine (1993a) *Hazardous Substances Data Bank (HSDB)*, Bethesda, MD

US National Library of Medicine (1993b) *Toxic Chemical Release Inventory (TRI) Data Banks* [TRI87, TRI88, TRI89, TRI90, TRI91], Bethesda, MD

US Occupational Safety and Health Administration (1992) Air contaminants. *US Code fed. Regul.*, **Title 29**, Part 1910.1000, pp. 6–34

Vainio, H., Pääkkönen, R., Rönnholm, K., Raunio, V. & Pelkonen, O. (1976) A study of the mutagenic activity of styrene and styrene oxide. *Scand. J. Work Environ. Health*, **3**, 147–151

Vainio, H., Järvisalo, J. & Taskinen, E. (1979) Adaptive changes caused by intermittent styrene inhalation on xenobiotic biotransformation. *Toxicol. appl. Pharmacol.*, **49**, 7–14

Vainio, H., Hietanen, E. & Belvedere, G. (1984) Pharmacokinetics and metabolism of styrene. In: Bridges, J.W. & Chasseaud, L.F., eds, *Progress in Drug Metabolism*, Vol. 8, London, Taylor & Francis, pp. 203–239

Vodička, P. & Hemminki, K. (1993) ^{32}P-Postlabelling of DNA adducts in styrene oxide-modified DNA and in workers exposed to styrene. In: Sorsa, M., Peltonen, K., Vainio, H. & Hemminki, K., eds, *Butadiene and Styrene: Assessment of Health Hazards* (IARC Scientific Publications No. 127) Lyon, IARC, pp. 109–118

Vodička, P., Vodičkova, L. & Hemminki, K. (1993) ^{32}P-Postlabelling of DNA adducts of styrene-exposed lamination workers. *Carcinogenesis*, **14**, 2059–2061

Wallace, L.A., Pellizzari, E.D., Hartwell, T.D., Sparacino, C., Whitmore, R., Sheldon, L., Zelon, H. & Perritt, R. (1987a) The TEAM [total exposure assessment methodology] study: personal exposures to toxic substances in air, drinking water, and breath of 400 residents of New Jersey, North Carolina, and North Dakota. *Environ. Res.*, **43**, 290–307

Wallace, L.A., Pellizzari, E.D., Hartwell, T.D., Perritt, R. & Ziegenfus, R. (1987b) Exposures to benzene and other volatile compounds from active and passive smoking. *Arch. environ. Health*, **42**, 272–279

Walles, S.A.S. & Orsén, I. (1983) Single-strand breaks in DNA of various organs of mice induced by styrene and styrene oxide. *Cancer Lett.*, **21**, 9–15

Walles, S.A.S., Edling, C., Anundi, H. & Johanson, G. (1993) Exposure dependent increase in DNA single strand breaks in leukocytes from workers exposed to low concentrations of styrene. *Br. J. ind. Med.*, **50**, 570–574

Watabe, T., Isobe, M., Sawahata, Y., Yoshikawa, K., Yamada, S. & Takabatake, E. (1978) Metabolism and mutagenicity of styrene. *Scand. J. Work Environ. Health*, **4** (Suppl. 2), 142–155

Watanabe, T., Endo, A., Sato, K., Ohtsuki, T., Miyasaka, M., Koizumi, A. & Ikeda, M. (1981) Mutagenic potential of styrene in man. *Ind. Health*, **19**, 37–46

Watanabe, T., Endo, A., Kumai, M. & Ikeda, M. (1983) Chromosome aberrations and sister chromatid exchanges in styrene-exposed workers with reference to their smoking habits. *Environ. Mutag.*, **5**, 299–309

Weschler, C.J., Hodgson, A.T. & Wooley, J.D. (1992) Indoor chemistry: ozone, volatile organic compounds, and carpets. *Environ. Sci. Technol.*, **26**, 2371–2377

WHO (1983) *Styrene* (Environmental Health Criteria 26), Geneva

WHO (1987) *Air Quality Guidelines for Europe* (WHO Regional Publications, European Series No. 23), Copenhagen, pp. 118–126

WHO (1993) *Guidelines for Drinking-water Quality*, 2nd Ed., Vol. 1, Geneva, p. 67

Wieczorek, H. (1985) Evaluation of low exposure to styrene. II. Dermal absorption of styrene vapours in humans under experimental conditions. *Int. Arch. occup. environ. Health*, **57**, 71–75

Wieczorek, H. & Piotrowski, J.K. (1985) Evaluation of low exposure to styrene. I. Absorption of styrene vapours by inhalation under experimental conditions. *Int. Arch. occup. environ. Health*, **57**, 57–69

Wieczorek, H. & Piotrowski, J.K. (1988) Kinetic interpretation of the exposure test for styrene. *Int. Arch. occup. environ. Health*, **61**, 107–113

Wigaeus, E., Löf, A., Bjurström, R. & Byfält Nordqvist, M. (1983) Exposure to styrene. Uptake, distribution, metabolism and elimination in man. *Scand. J. Work Environ. Health*, **9**, 479–488

Wigaeus, E., Löf, A. & Byfält Nordqvist, M. (1984) Uptake, distribution, metabolism, and elimination of styrene in man. A comparison between single exposure and co-exposure with acetone. *Br. J. ind. Med.*, **41**, 539–546

Withey, J.R. & Collins, P.G. (1977) Pharmacokinetics and distribution of styrene monomer in rats after intravenous administration. *J. Toxicol. environ. Health*, **3**, 1011–1020

Withey, H. & Collins, P.G. (1979) The distribution and pharmacokinetics of styrene monomer in rats by the pulmonary route. *J. environ. Pathol. Toxicol.*, **2**, 1329–1342

Withey, J.R. & Karpinski, K. (1985) Fetal distribution of styrene in rats after vapor phase exposures. *Biol. Res. Pregnancy*, **6**, 59–64

Wolff, M.S., Daum, S.M., Lorimer, W.V. & Selikoff, I.J. (1977) Styrene and related hydrocarbons in subcutaneous fat from polymerization workers. *J. Toxicol. environ. Health*, **2**, 997–1005

Wolff, M.S., Lilis, R., Lorimer, W.V. & Selikoff, I.J. (1978) Biological indicators of exposure in styrene polymerisation workers. Styrene in blood and adipose tissue and mandelic and phenyglyoxylic acids in urine. *Scand. J. Work Environ. Health*, **4** (Suppl. 2), 114–118

Wong, O. (1990) A cohort mortality study and a case–control study of workers potentially exposed to styrene in the reinforced plastics and composites industry. *Br. J. ind. Med.*, **47**, 753–762

Wong, O., Trent, L.S. & Whorton, M.D. (1994) An updated cohort mortality study of workers exposed to styrene in the reinforced plastics and composites industry. *Occup. environ. Med.*, **51**, 386–396

Yager, J.W., Paradisin, W.M., Symanski, E. & Rappaport, S.M. (1990) Sister chromatid exchanges induced in peripheral lymphocytes of workers exposed to low concentrations of styrene. *Prog. clin. biol. Res.*, **340C**, 347–356

Yager, J.W., Paradisin, W.M. & Rappaport, S.M. (1993) Sister-chromatid exchanges in lymphocytes are increased in relation to longitudinally measured occupational exposure to low concentrations of styrene. *Mutat. Res.*, **319**, 155–165

Zaidi, N.F., Agrawal, A.K., Srivastava, S.P. & Seth, P.K. (1985) Effect of gestational and neonatal styrene exposure on dopamine receptors. *Neurobehav. Toxicol. Teratol.*, **7**, 23–28

Zaprianov, Z. & Bainova, A. (1979) Changes in monoamine oxidase activity (MAO) after styrene and ethanol combined treatment of rats. *Activ. nerv. Sup. (Praha)*, **21**, 262–264