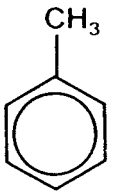
TOLUENE

1. Chemical and Physical Data

1.1 Synonyms

Chem. Abstr. Services Reg. No.: 108-88-3
Chem. Abstr. Name: Methylbenzene
IUPAC Systematic Name: Toluene
Synonyms: Methylbenzol; NCI-CO7272; phenylmethane; toluol

1.2 Structural and molecular formulae and molecular weight



C_7H_8 Mol. wt: 92.15

1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Clear, colourless, inflammable liquid with benzene-like odour (Sandmeyer, 1981; Windholz, 1983)

(*b*) *Boiling-point*: 110.6°C (Weast, 1985)

(*c*) *Melting-point*: -95°C (Weast, 1985)

(*d*) *Density*: 0.8669 (20°/4°C) (Weast, 1985)

(*e*) *Spectroscopy data*: Infrared, ultraviolet and nuclear magnetic resonance spectral data have been reported (Sadtler Research Laboratories, 1980; Pouchert, 1981, 1983, 1985).

(*f*) *Solubility*: Soluble in ethanol, benzene, diethyl ether, acetone, chloroform, glacial acetic acid and carbon disulfide; insoluble in water (Hawley, 1981; Sandmeyer, 1981; Windholz, 1983; Weast, 1985)

(*g*) *Volatility*: Vapour pressure: 28.4 mm Hg at 25°C (Eller, 1984)

(*h*) *Flash-point*: 4.4°C (Sandmeyer, 1981)

(*i*) *Reactivity*: Quite stable in air (Clement Associates, 1977). Reacts photochemically with nitrogen oxides or halogens to form nitrotoluene, nitrobenzene and nitro-

phenol and halogenated products, respectively (Merian & Zander, 1982; US Environmental Protection Agency, 1983)

(*j*) *Octanol/water partition coefficient*: log P = 2.11–2.80 (Hansch & Leo, 1979)

(*k*) *Conversion factor*: $mg/m^3 = 3.77 \times ppm$[1]

1.4 Technical products and impurities

Trade Names: Antisal 1a; CP 25; Methacide

Toluene is marketed principally as nitration and industrial grades, its purity being dependent on the specific gravity and boiling range of the product (Hoff, 1983). Reagent-grade toluene is available with a purity of greater than 99% (Aldrich Chemical Co., 1988). Technical grades (90–120 °C boiling range) are less pure and may contain up to 25% benzene as well as other hydrocarbons (Clement Associates, 1977; Fishbein, 1985).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Toluene is produced during petroleum refining operations, directly as a by-product of styrene manufacture and indirectly as a by-product of coke-oven operations.

It is produced from petroleum as an aromatic mixture with benzene and xylene primarily by catalytic reforming and pyrolytic cracking. Catalytic reforming processes account for about 87% of the total amount of toluene produced in the USA. This process involves dehydrogenation of selected petroleum fractions containing abundant naphthenic hydrocarbons to yield a mixture of aromatics and paraffins. Reforming processes are used to produce a benzene–toluene–xylene reformate from which the individual aromatics are recovered by distillation, washing with nitric acid and redistillation. Only a small fraction of the reformate is used for isolation of the toluene; the bulk of the unseparated toluene in the reformate is used for gasoline blending.

The second largest source of toluene is from pyrolysis gasoline, formed as a by-product during pyrolytic cracking (steam cracking) of heavier hydrocarbons for the manufacture of olefins. Toluene is isolated from pyrolysis gasoline by distillation, removal of olefins and diolefins and redistillation.

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[1] Calculated from: mg/m^3 = (molecular weight/24.45) x ppm, assuming standard temperature (25 °C) and pressure (760 mm Hg)

Toluene is also obtained as a by-product during styrene manufacture when ethylbenzene is dehydrogenated. The toluene isolated from the by-product is used for gasoline blending or as feed for benzene manufacture by the hydrodealkylation process. The production of toluene from coke-oven operations is minimal (Hoff, 1983).

The amounts of isolated toluene (and of total toluene) produced in these different ways in the USA in 1978 were as follows: from catalytic reformate, 3.6 (29.5) million tonnes; from pyrolysis gasoline, 376.8 (708) thousand tonnes; as a styrene by-product, 99.8 (145) thousand tonnes; and derived from coal, 65.8 (79.5) thousand tonnes. These quantities represent a total of 4.2 (30) million tonnes (Fishbein, 1985).

Western Europe and Japan are also major producers of this compound. In 1980, over 85% of the toluene produced in the world was accounted for by the USA, western Europe and Japan. In Japan and western Europe, toluene is produced mainly from pyrolysis gasoline. In all three areas, coke-oven light oil provided less than 10% of the toluene supply in 1980 (Fishbein, 1985).

Data on the production of toluene in the major producing countries are presented in Table 1. World production of toluene in 1980 was estimated at more than 5 million tonnes - approximately one-third of the amount of benzene produced. However, an additional 30 million tonnes of toluene are consumed annually as a constituent of motor fuel (Merian & Zander, 1982).

Table 1. Annual production data for toluene[a] (thousands of tonnes)

Country	1983	1984	1985	1986	1987
Canada	411	395	472	393	396
France	41	39	40	38	33
Germany, Federal Republic of	314	371	391	478	402
Italy	299	313	348	233	178
Japan	831	784	803	805	882
Mexico	223	216	220	238	313
USA	2560[b]	2390[b]	2300[b]	2640	3050

[a]From US International Trade Commission (1984, 1985, 1986); Anon. (1987a, 1988)
[b]Petroleum-derived, not including tar distillation and coke-oven derived toluene

(b) Use

The largest single use of isolated toluene is in the production of benzene *via* the hydrodemethylation process, in which toluene and hydrogen (a reformate by-product) are reacted under high temperature and pressure to yield benzene and methane (Hoff, 1983). This process has been used to balance the supply and demand for benzene (Mannsville Chemical Products Corp., 1981).

The second largest use of toluene is in solvent applications, especially in the paint and coating industry. Significant amounts are also used in inks, adhesives, the leather industry (IARC, 1981), pharmaceuticals and other formulated products. Solvents accounted for 40%

or more of the nonfuel use of toluene in Japan and western Europe in 1980. In the USA in 1981, the use of toluene as a solvent was second only to its use in benzene production *via* hydrodemethylation and accounted for about 26% of nonfuel consumption (Fishbein, 1985).

Isolated toluene is also used directly in several consumer products, such as sanitizing agents, household aerosols, paints and varnishes, paint thinners and antirust preservatives (Fishbein, 1985).

Most of the toluene in the benzene–toluene–xylene mixtures, which is never isolated and remains in various refinery streams, is used in gasoline blending. Toluene has several advantages as a blending agent in gasoline: a high octane number and low volatility, and it blends easily with other inexpensive materials such as *n*–butane, which is highly volatile (Hoff, 1983). It is anticipated that the use of toluene in unleaded gasoline will continue to increase. In 1985, 73–75% of the gasoline used in the USA was unleaded. By 1990, this percentage is expected to rise to 95–100% (Mannsville Chemical Products Corp., 1981). The toluene concentrations in US gasolines are estimated to range from 5 to 22% (wt%; IARC, 1989).

Toluene is used as an intermediate in the production of toluene diisocyanate for use in polyurethane production, and of benzoic acid for use in the manufacture of benzoate and benzyl esters and salts for food preservatives and cosmetic articles such as soaps, perfumes, flavours, creams and lotions. Catalytic disproportionation of toluene has been used to produce benzene and *para*–xylene, with little or no ethylbenzene or *ortho*– or *meta*–xylene. Vinyl toluene, which is produced by alkylation of toluene with ethylene followed by dehydrogenation of ethyltoluene, is used as a modifier in unsaturated polyester resins. Other important chemical products made from toluene include trinitrotoluene and related explosives, benzaldehyde (an important chemical intermediate) and saccharin (Hoff, 1983; US Environmental Protection Agency, 1983; Fishbein, 1985). Small amounts of toluene are used for the manufacture of *para*–cresol, which is used primarily for the manufacture of butylated hydroxytoluene (US Environmental Protection Agency, 1983).

In western Europe, phenol (see monograph, p. 263) is the most important derivative of toluene, followed by toluene diisocyanate and caprolactam. In Japan, toluene is used primarily for benzene and *para*–cresol production (Fishbein, 1985).

Of the estimated 3.3 million tonnes of toluene produced in the USA in 1980, 44% was used to make benzene, 34% to make gasoline, 10% in solvents, 6% to make toluene diisocyanate, and 6% for miscellaneous use (Mannsville Chemical Corp., 1981).

(*c*) *Regulatory status and guidelines*

Occupational exposure limits for toluene in 34 countries or regions are presented in Table 2.

2.2 Occurrence

(*a*) *Natural occurrence*

Toluene occurs in nature in crude oil (US Environmental Protection Agency, 1983), natural gas deposits and the volatile emissions from volcanoes and forest fires (National Research Council, 1976).

Table 2. Occupational exposure limits for toluene[a]

Country or region	Year	Concentration[b] (mg/m³)	Interpretation[c]
Australia	1984	380	TWA
Austria	1985	750	TWA
Belgium	1985	375	TWA
Brazil	1985	S 290	TWA
Bulgaria	1984	50	TWA
Commission of the European Communities	1986	375	TWA
		1875	Maximum
Chile	1985	S 300	TWA
China	1985	100	TWA
Czechoslovakia	1985	200	Average
		1000	Maximum
Denmark	1988	S 190	TWA
Egypt	1985	375 (100 ppm given)	TWA
Finland	1987	S 375	TWA
		S 565	STEL (15 min)
France	1986	375	TWA
		550	STEL (15 min)
German Democratic Republic	1985	200	TWA
		600	STEL
Germany, Federal Republic of	1988	380	TWA
Hungary	1985	100	TWA
		500	STEL
India	1985	S 375	TWA
		S 560	STEL
Indonesia	1985	375	TWA
Italy	1985	S 300	TWA
Japan	1988	375	TWA
Korea, Republic of	1985	375	TWA
		560	STEL
Mexico	1985	S 750	TWA
Netherlands	1986	S 375	TWA
Norway	1981	280	TWA
Poland	1985	100	TWA
Romania	1985	300	Average
		400	Maximum
Sweden	1987	200	TWA
		400	STEL
Switzerland	1985	S 380	TWA
Taiwan	1985	S 375	TWA
UK	1987	S 375	TWA
		S 560	STEL (10 min)

Table 2 (contd)

Country or region	Year	Concentration[b] (mg/m³)	Interpretation[c]
USA[d]			
OSHA	1988	430	TWA
NIOSH	1986	375	TWA
		750	Ceiling
ACGIH	1988	375	TWA
		560	STEL (15 min)
USSR	1986	50	Ceiling
Venezuela	1985	S 375	TWA
		S 560	Ceiling
Yugoslavia	1985	200	TWA

[a]From Direktoratet for Arbeidstilsynet (1981); International Labour Office (1984); Arbeidsinspectie (1986); Commission of the European Communities (1986); Institut National de Recherche et de Sécurité (1986); National Institute for Occupational Safety and Health (1986); Cook (1987); Health and Safety Executive (1987); National Swedish Board of Occupational Safety and Health (1987); Työsuojeluhallitus (1987); American Conference of Governmental Industrial Hygienists (1988); Arbejdstilsynet (1988); Deutsche Forschungsgemeinschaft (1988)

[b]S, skin notation

[c]TWA, 8-h time-weighted average; STEL, short-term exposure limit

[d]OSHA, Occupational Safety and Health Administration; NIOSH, National Institute for Occupational Safety and Health; ACGIH, American Conference of Governmental Industrial Hygienists

(b) Occupational exposure

On the basis of a US National Occupational Exposure Survey, the National Institute for Occupational Safety and Health (1983) estimated that 1 278 000 workers were potentially exposed to toluene in the USA in 1981–83.

Levels of toluene measured in the air in work environments are summarized in Table 3. In the majority of these environments, concurrent exposure to other solvents is likely to have taken place.

Biological monitoring measurements have also been made. Exposures in the manufacture of trapezoid belts resulted in urinary hippuric acid concentrations of 2.1 g/l in workers in the belt department and 9 g/l in those in the weighing room (Capellini & Alessio, 1971). Exposures to toluene on automatic spray finishing machines in a leather finishing operation resulted in urinary hippuric acid levels ranging from 1.5 to 3.66 g/l, with an average of 2.38 g/l. All nine samples were taken at the end of the work shift. Exposures in the washing and topping department in the same plant resulted in urinary hippuric acid levels of 2.16–5.85 g/l, with an average of 4.48 g/l. Concentrations of toluene in a rubber coating plant resulted in post-shift urinary hippuric acid levels of 2.75–6.8 g/l (average, 3.66; Pagnotto & Lieberman, 1967). Post-shift results of biological monitoring of 35 toluene-exposed printing workers ranged from 0.09 to 3.13 mg/l toluene in blood (average, 1.55 mg/l), 0.33 to 11.6 g/l hippuric

Table 3 . Occupational exposures to toluene

Environment	Sampling[a]	Concentration in air	Reference
Printing plants			
Rotogravure plant (Finland)	8-h TWA personal	7-112 ppm (26.4-422 mg/m³)	Mäki-Paakkanen *et al.* (1980)
Printing plant (Japan)	8-h TWA personal	27.1-53.7 ppm (102-203 mg/m³)	Tokunaga *et al.* (1974)
Printing plant (Italy)	7-h TWA personal	37-229 mg/m³	De Rosa *et al.* (1985)
Heliorotogravure printers (Belgium)	Personal		Veulemans *et al.* (1979)
1st printer		102-667 mg/m³	
2nd printer		120-706 mg/m³	
Helper		81-680 mg/m³	
Printing plant (FRG)	Area	13-49 ppm (48.9-185 mg/m³)	Angerer (1979a)
Printing plant (FRG)	Area	36-269 ppm (136-1014 mg/m³)	Angerer (1985)
Photogravure printing factories (Japan)	Area	4-240 ppm (15-905 mg/m³, average)	Ikeda & Ohtsuji (1969)
Manufacture of trapezoid belts (Italy)			Capellini & Alessio (1971)
Belt department	Air, personal	125 ppm (471 mg/m³, average)	
Weighing room	Air	250 ppm (942 mg/m³, average)	
Waste incinerator (USA)	8-h TWA personal		Decker *et al.* (1983)
Incinerator workers		0.19 ppm (0.7 mg/m³)	
Laboratory technicians		0.09 ppm (0.3 mg/m³)	
Waste receivers		0.02 ppm (0.1 mg/m³)	
Unloading tank trucks		0.2 ppm (0.8 mg/m³)	
Tank entry (outside)		15 ppm (57 mg/m³)	
Tank entry (inside)		104 ppm (392 mg/m³)	
Plastic processing factories (FRG)	8-h TWA personal	191-309 ppm (720-1165 mg/m³, mean)	Konietzko *et al.* (1980)

Table 3 (contd)

Environment	Sampling[a]	Concentration in air	Reference
Rubber tyre vulcanization (USA)	Area	0.75–1.5 ppm (2.83–5.66 mg/m³)	Rappaport & Fraser (1977)
Leather finishing (USA)	Short-term area		Pagnotto & Lieberman (1967)
Automatic spray finishing		19–85 ppm (71–320 mg/m³)	
Washing and topping		29–195 ppm (109–735 mg/m³)	
Laboratories (USA)			
Histology	Short-term area	8.9–12.6 ppm (33.6–47.5 mg/m³)	Kilburn *et al.* (1985)
Histopathology	8-h TWA personal	2.0–4.2 ppm (7.5–15.8 mg/m³)	Roper (1980)
Cytopathology	8-h TWA personal	0.17–3.15 ppm (0.6–11.8 mg/m³)	Roper (1980)
Lithography (Poland)			
1968		ND–420 mg/m³	Moszczyński & Lisiewicz (1985)
1969		ND–580 mg/m³	
1972		ND–30 mg/m³	
1976		ND–81 mg/m³	
1978		ND–93 mg/m³	
Manufacture of photographic albums (USA)	TWA personal	0.9–20.0 mg/m³	Baker & Fannick (1983)
Manufacture of tarpaulins (Finland)	8-h TWA personal	20–200 ppm (75–750 mg/m³)	Tähti *et al.* (1981)
Fibrous glasswool plant (USA)	8-h TWA personal	22–66 mg/m³	Dement *et al.* (1973)
Golf club and baseball bat manufacturing plant (USA)	8-h TWA personal	3–8 ppm (11–30 mg/m³)	Rivera & Rostand (1975)
Laminating kitchen counter and bathroom tops (USA)	8-h TWA personal	36–253 mg/m³	Apol (1980)
Rubber coating plant (USA)	Short-term area	34–120 ppm (128–452 mg/m³)	Pagnotto & Lieberman (1967)

Table 3 (contd)

Environment	Sampling[a]	Concentration in air	Reference
Rubber sheet manufacture (UK)	TWA personal	3–280 ppm (11–1050 mg/m³) mean, 57 ppm (215 mg/m³)	Campbell *et al.* (1987)
Parquet floorers (FRG)	8-h TWA personal	mean, 86.7 mg/m³ (max, 750 mg/m³)	Denkhaus *et al.* (1986)
Shoemakers (Japan)		15–200 ppm (57–754 mg/m³, average)	Matsushita *et al.* (1975)

[a]TWA, time-weighted average
[b]ND, not detected

acid in urine (average, 5.03 g/l), < 0.1 to 10.6 mg/l *ortho*-cresol in urine (average, 3.11 mg/l) and 0.1 to 27.1 mg/l phenol in urine (average, 5.29 mg/l; Angerer, 1985). In workers in a factory in the UK that manufactured rubber sheets used in the printing industry, blood toluene levels were 10–18 μmol (0.9–1.6 mg)/l; pre- and post-shift levels of exhaled toluene ranged from 320 to 542 nmol (30–500 μg)/l and urinary hippuric acid levels were 0.72–1.01 mmol (66–93 mg)/mmol creatinine over four years (Campbell *et al.*, 1987). The average concentration of toluene in the blood of parquet floorers was 99 μg/l (max, 2550 μg/l) (Denkhaus *et al.*, 1986).

Occupational exposure of painters and paint manufacturing workers to toluene is described in the monograph on occupational exposures in paint manufacture and painting (see p. 329). Occupational exposures to toluene in petroleum refining and in the production and use of petroleum fuels are described in Volume 45 of the *Monographs* (IARC, 1989).

(*c*) *Air*

Toluene is released into the environment during its production, processing (*via* distillation vents), loading and handling and in transportation and storage operations.

Merian (1982) estimated worldwide atmospheric emissions of toluene to be 6.2 million tonnes. Contributions included losses from refineries (40%), automobile exhausts (32%), solvents (16%), petroleum losses to the sea (8%), losses from the chemical industry (2%) and gasoline evaporation (0.8%).

In the USA, total annual emissions of toluene were estimated to be about 450 thousand tonnes, 99.3% of which was released into the atmosphere and 0.7% into waste waterways (Clement Associates, 1977). The US Environmental Protection Agency (1983) estimated that atmospheric emissions of toluene in the USA during its production in 1979 were 3.0 tonnes/year from catalytic reforming, 0.5 tonnes/year from pyrolytic cracking, 0.1 tonnes/year as a styrene by-product and and 0.2 tonnes/year as a coke oven by-product. In 1979, US emissions were estimated to be about 1 million tonnes, 90% of the loss being due to evaporation of gasoline and automobile exhaust emissions (Fishbein, 1985). In Japan, 250 and 600 thousand tonnes of toluene were lost to the environment in 1976 and 1974, respectively, through its use as a solvent in paint and printing ink industries (Merian & Zander, 1982).

Toluene is transported rapidly from water (where it has low solubility) into the atmosphere. Its half-life in water (1 m deep) is about 5 h; that in the atmosphere is 13 h. It is removed from the atmosphere primarily by reactions with atomic oxygen, aryl- or alkyl-peroxy or hydroxyl radicals, and ozone. Because of its rapid oxidation, toluene would not remain long enough in the atmosphere to be influenced by air-to-surface transfer mechanisms (International Programme on Chemical Safety, 1985).

The tropospheric lifetime of toluene is four days, and average worldwide distribution is approximately 0.00075 mg/m^3 air. Average atmospheric concentrations of 0.0005–1.31 mg/m^3 have been measured, with the highest level being 5.5 mg/m^3, in studies from Europe, Canada and the USA, between 1971 and 1980. In the vicinity of an automobile painting plant, levels of 0.06–0.6 mg/m^3 were reported 16.5–1.6 km downwind from the painting facility, compared with 0.006 mg/m^3 upwind (International Programme for Chemical Safety, 1985). Concentrations of 42 mg/m^3 were recorded in the air in the vicinity of a chemical

reclamation plant after residents had complained of odour and illnesses (US Environmental Protection Agency, 1983).

Mean atmospheric concentrations of toluene in urban areas around the world in 1971–80 include (in mg/m^3): 0.04 in Canada, 0.002–0.2 in the Federal Republic of Germany, 0.03 in Finland, 0.02 in Japan, 0.02–0.07 in the Netherlands, 0.03–0.05 in South Africa, 0.005 in Sweden, 0.04–0.06 in Switzerland and 0.02–0.06 in the UK (Merian & Zander, 1982; US Environmental Protection Agency, 1983). De Bortoli *et al.* (1984) reported 0.007–0.156 mg/m^3 toluene in 15 samples collected in outdoor air in northern Italy. In the USA, measurements were recorded between 1967 and 1978 for atmospheric concentrations in both urban and rural sites in five major regions of the country. The highest mean concentration was reported in the eastern region (0.15 mg/m^3 in New York and New Jersey), followed by 0.14 mg/m^3 in Los Angeles and urban Alabama. Values reported for other regions were much lower (0.001 and 0.002 mg/m^3 in urban Oklahoma and rural Alabama, respectively), and none was detected in several midwestern states (US Environmental Protection Agency, 1983). Toluene was also detected in the expired air of individuals from a US urban population (mean, 0.0084 mg/m^3; Krotoszynski *et al.*, 1979) and in the interior of cars before (0.5 mg/m^3) and after driving (1.0 mg/m^3; Merian & Zander, 1982). A range of 0.02–0.412 mg/m^3 was found in 48 samples collected at German traffic intersections (Seifert & Abraham, 1982). Levels of 0.004 mg/m^3 toluene were measured in two rural areas in the USA between 1971 and 1978; < 0.001 mg/m^3 was measured in six others (Holzer *et al.*, 1977; Merian & Zander, 1982; US Environmental Protection Agency, 1983). Levels of 97–891 mg/m^3 were measured in the smoke of forest fires (Merian & Zander, 1982).

De Bortoli *et al.* (1984) measured 0.017–0.378 mg/m^3 toluene in 14 homes and in one office building in northern Italy. Levels of 0.15–0.9 mg/m^3 toluene were found in US homes polluted with tobacco smoke (US Environmental Protection Agency, 1983). Toluene has been detected in tobacco smoke (IARC, 1986). Seifert and Abraham (1982) found an average concentration of 0.061 mg/m^3 (range, 0.017–0.116 mg/m^3) in kitchens and other rooms of 15 homes in West Berlin; just outside the walls of these dwellings, the measured concentrations averaged 0.035 mg/m^3 (range, 0.016–0.06 mg/m^3). Mølhave (1979) reported a peak level of 0.61 mg/m^3, based on measurements in 14 rooms in homes in Denmark; and Mølhave and Møller (1979) reported an average concentration in 39 homes of 0.09 mg/m^3.

(*d*) *Water*

Drinking-water in Prague, Czechoslovakia, in 1973 contained < 0.1 μg/l toluene (Merian & Zander, 1982), whereas in Toronto, Canada, in 1980 drinking-water contained an average of 2 μg/l (compared to < 1 μg/l before treatment; Otson *et al.*, 1982). Levels of 42–100 μg/l were reported in well water in the vicinity of landfill sites in the USA (US Environmental Protection Agency, 1983). The concentration of toluene in rain water in the Federal Republic of Germany has been reported to be 0.13–0.70 μg/l (US Environmental Protection Agency, 1983; International Programme on Chemical Safety, 1985).

Toluene has been found at concentrations of 1–5 μg/l in water samples from a number of rivers in eastern and midwestern USA, with concentrations ranging up to 12 μg/l in the Mississippi River near New Orleans. Concentrations of 0.8 μg/l have been reported in the

Rhine River in the Federal Republic of Germany and of 1.9 μg/l in Switzerland (Merian & Zander, 1982).

Concentrations of 0.005–0.376 μg/l (mean, 0.061 μg/l) were reported at several coastal sites along the Gulf of Mexico (US Environmental Protection Agency, 1983).

(*e*) *Soil*

Toluene exists in an adsorbed state in soil. In assiciation with clay minerals, its adsorption is inversely proportional to the pH of the soil. Approximately 40–70% of toluene applied to the surface of sandy soils is volatilized. The biodegradation of toluene by microorganisms in the soil ranged from 63–86% after 20 days (Wilson *et al.*, 1981; US Environmental Protection Agency, 1983; Wilson *et al.*, 1983).

(*f*) *Food*

The US Environmental Protection Agency (1983) reported toluene concentrations of < 1 mg/kg in 56 of 59 samples of fish tested; one fish had a level of 35 mg/kg toluene. [It was not clear to the Working Group whether these concentrations were found in whole fish or only in the edible part.]

Toluene was also detected at low concentrations (0.08–0.11 mg/kg) in a few samples of maple syrup packaged in plastic containers (Hollifield *et al.*, 1980).

2.3 Analysis

Methods for the analysis of toluene and its metabolites have recently been reviewed and compiled (Fishbein & O'Neill, 1988) and are summarized in Table 4. Colorimetric detection systems have been developed for toluene in air (ENMET Corp., undated; Matheson Gas Products, undated; Roxan, Inc., undated; The Foxboro Co., 1983; Sensidyne, 1985; National Draeger, Inc., 1987; SKC Inc., 1988).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals[1]

(*a*) *Oral administration*

Rat: Groups of 40 male and 40 female Sprague–Dawley rats, seven weeks old, were administered 500 mg/kg bw toluene (purity, 98.34%) in olive oil by stomach tube on four to five days per week for 104 weeks. Groups of 50 males and 50 females received olive oil alone and served as controls. All rats were maintained until death, and the study was terminated at

[1]The Working Group was aware of a study in progress by inhalation in mice and rats (IARC, 1988).

Table 4. Analytical methods for determining toluene and its metabolites in various matrices[a]

Sample matrix	Sample collection	Sample preparation	Assay procedure	Detection limits	Reference
Air	Passive sampler with charcoal	Desorb (carbon disulfide); inject aliquot using glass capillary column	GC	0.3 mg/m^3 x h	Seifert & Abraham (1983)
	Charcoal tube or passive sampler	Desorb (carbon disulfide); inject aliquot; analyse on packed column	GC–FID	0.01 mg/sample	Eller (1984, 1987)
	Passive sampler with charcoal	Desorb (carbon disulfide); inject aliquot; analyse on packed column	GC–FID	0.2 ppm [0.8 mg/m^3]	Otson *et al.* (1983)
Water		Extract with hexane; inject aliquot	GC–FID	5 µg/l	Otson & Williams (1981)
		Heat in water bath at 25°C for 1 h; inject headspace aliquots	GC–MS	1 µg/l	Otson *et al.* (1982)
Food (maple syrup)	Bulk	Sparge 10 ml with nitrogen; incubate 2 h at 90°C; inject 2 ml of headspace vapours	Headspace GC; GC/MS (confirm)	10–275 µg/l	Fazio & Sherma (1987)
Soil		Wash with distilled water; acidify, steam distill with hexane; remove hexane layer; dry and reduce to 1 ml (nitrogen)	GC–FT–IR	Not given	Gurka & Betowski (1982)
Automobile exhaust gas	Tenax GC polymer adsorbant	Desorb thermally into liquid nitrogen–cooled capillary trap	GC–MS	Not given	Hampton *et al.* (1982)
Alveolar air	Charcoal	Desorb thermally; inject into glass column	GC–MS	Not given	Apostoli *et al.* (1982)
Blood	Heparinize	Add redistilled ethyl benzene dissolved in methanol and water; equilibrate at 60°C for 45 min; remove aliquot headspace and inject	GC–FID	0.05 µg/g	Oliver (1982)
	Heparinize	Purge (nitrogen) at room temperature; trap (Tenax TA); desorb thermally; analyse volatiles on column	GC–MS	< 1 µg/l	Cramer *et al.* (1988)

Table 4 (contd)

Sample matrix	Sample collection	Sample preparation	Assay procedure	Detection limits	Reference
Urine (hippuric acid)		Acidify and extract hippuric acid with chloroform; separate on TLC (*para*-dimethylaminobenzaldehyde for colour development); extract azalactones with ethanol; determine UV absorbancy	TLC–UV	6 μg	Bieniek *et al.* (1982)
Tissue (muscle, liver)	Mince	Add sodium hydroxide and olive oil with internal standard (ethylbenzene); incubate at 35°C for 2.5 h; inject aliquot of headspace vapour	GC–FID	2 μg/g	Miyaura & Isono (1985)

[a]Abbreviations: GC, gas chromatography; FID, flame ionization detection; MS, mass spectrometry; FT–IR, Fourier transform/infrared spectrometry; TLC, thin-layer chromatography; UV, ultraviolet spectrometry

week 141. At week 141, thymomas were reported in 1/37 treated males and 2/40 treated females compared to 0/45 and 0/49 controls. Other haemolymphoreticular tumours were reported in 2/37 treated males and 5/40 treated females compared to 3/45 and 1/49 controls (denominators are numbers of rats alive in each group at 58 weeks, when the first haemolymphoreticular tumour was observed). The authors reported an increase in the total numbers of animals with malignant tumours [types unspecified] at 141 weeks: 18/40 treated males and 21/40 treated females compared to 11/45 and 10/49 controls (denominators are numbers of rats alive in each group at 33 weeks, when the first malignant tumour was observed; Maltoni *et al.*, 1983, 1985). [The Working Group noted the incomplete reporting of tumour pathology in this study and that combining different types of tumours is not usually the most appropriate method for evaluating carcinogenicity (IARC, 1980; Montesano *et al.*, 1986).]

(*b*) *Inhalation*

Rat: Groups of 120 male and 120 female Fischer 344 rats, about seven weeks of age, were exposed by inhalation to 0, 30, 100 or 300 ppm (0, 113, 377 or 1131 mg/m^3) toluene (purity, >99.98%) for 6 h per day on five days per week for up to 24 months. Interim kills were made in all groups at six months (five rats), 12 months (five rats) and 18 months (20 rats). All surviving rats were killed at 24 months; these comprised 71 male and 70 female controls, 73 males and 75 females given the low dose, 68 males and 76 females given the mid-dose, and 67 males and 75 females given the high dose. No increase in the incidence of tumours was reported in the treated groups (Gibson & Hardisty, 1983). [The Working Group noted the incomplete reporting of data on pathology and that the level of exposure was low.]

(c) *Skin application*

Mouse: Toluene was tested as a vehicle control or in combination with various carcinogens in a number of skin painting studies in mice. No skin tumour attributable to toluene alone was observed (Poel, 1962; Frei & Kingsley, 1968; Lijinsky & Garcia, 1972; Doak *et al.*, 1976; Weiss *et al.*, 1986). [The Working Group noted either the small number of animals used in these experiments and the short duration or incomplete reporting of the studies.]

A group of 50 male C3H/HeJ mice, six to ten weeks of age, received applications of 25 µl [21.7 mg] toluene [purity unspecified] on clipped interscapular skin three times a week until death. Mean survival time was 83 weeks. No skin tumour was reported at termination of the study [unspecified], and complete histological examination revealed no treatment-related tumour at other sites (McKee & Lewis, 1987). In a similar study with 50 C3H/HeJ mice (mean survival time, 77 weeks), one skin papilloma was found (McKee *et al.*, 1986).

Seven groups of vehicle controls used for different experiments, each consisting of 50 male C3H/HeJ mice, six to eight weeks old, received applications of 50 mg toluene on the interscapular skin twice a week for 73–120 weeks. Skin tumours [by gross observation] occurred in 3/350 mice (Blackburn *et al.*, 1986).

3.2 Other relevant data

The toxicology of toluene has been reviewed (National Institute for Occupational Safety and Health, 1973; Cohr & Stokholm, 1979; Benignus, 1981a,b; World Health Organization, 1981; International Programme on Chemical Safety, 1985; Anon., 1987b; Low *et al.*, 1988).

(a) *Experimental systems*

(i) *Absorption, distribution, excretion and metabolism*

When dogs were exposed to 0.4–0.6 µg/ml toluene vapour, 91–94% was taken up in the lungs (Egle & Gochberg, 1976). Absorption was complete when toluene was given orally to dogs (Knoop & Gehrke, 1925); the blood level in rats increased more slowly after oral administration than after inhalation (Pyykkö *et al.*, 1977). Absorption through the skin of mice *in vivo* was 4.59 µg/cm^2 per hour (Tsuruta *et al.*, 1987). Toluene penetrated rat skin excised three days after clipping and depilation with cream at a rate one-tenth that of benzene and ten times that of *ortho*-xylene (Tsuruta, 1982).

When ^{3}H-toluene was given to rats either orally or by inhalation, radioactivity 2 h after administration was highest in the adipose tissue, followed by the liver, kidneys and brain (Pyykkö *et al.*, 1977). Similar results were obtained after intramuscular injection of [ring-labelled ^{14}C]toluene to mice (Ogata *et al.*, 1974) and after intraperitoneal injection of [methyl-^{14}C]toluene to mice (Koga, 1978). Levels in the cerebrum, cerebellum and spinal cord were comparable to those in blood of rats after intraperitoneal injection (Savolainen, 1978). Toluene levels in brain and blood were linearly related to toluene levels in inhaled air after rats were exposed to 50, 100, 500 or 1000 ppm (189, 377, 1885 or 3770 mg/m^3) toluene for 3 h (Benignus *et al.*, 1984). The toluene concentration was higher in brain than in blood immediately after exposure. The decrease after termination of exposure was almost parallel in the two tissues but slightly faster in brain than in blood (Benignus *et al.*, 1981). Less than 2%

radioactivity was excreted in bile within 24 h after intraperitoneal injection of 50 mg/kg bw [^{14}C]toluene to rats (Abou-El-Makarem *et al.*, 1967).

When rabbits were given a single oral dose of 350 mg/kg bw toluene, 19% was exhaled unchanged within 12 h (Smith *et al.*, 1954). In rats given ^{3}H-toluene orally or by inhalation, only 1% or less of the initial radioactivity was found in various tissues 24 h after dosing, except for white adipose tissue which contained 3.5–5% (Pyykkö *et al.*, 1977). Similar results were obtained in mice (Koga, 1978).

Toluene is excreted into the urine primarily as hippuric acid (after side-chain oxidation followed by glycine conjugation) and, to a minute extent, as conjugated cresols (after aromatic hydroxylation and sulfation/glucuronidation; International Programme on Chemical Safety, 1985). Of an orally administered dose of 0.3 g/kg bw given to rabbits, 74% was excreted in urine as hippuric acid within 24 h (El Masry *et al.*, 1956). In rats, 0.04–0.11% and 0.4–1.0% of an oral dose of 100 mg/kg bw toluene were excreted in urine as *ortho*-cresol and *para*-cresol, respectively (Bakke & Scheline, 1970); the ratio of *ortho*- and *para*-cresol:hippuric acid varied depending on exposure intensity and strain of rats (Inoue *et al.*, 1984).

Intraperitoneal injection of 370 mg/kg bw toluene to rats resulted in decreased hepatic glutathione levels and increased urinary thioether excretion, suggesting the formation of mercapturic acid(s) as a minor metabolite(s) (van Doorn *et al.*, 1980). Activation of toluene to covalently binding metabolites has been reported. When [methyl^{14}C]-toluene was incubated with rat liver microsomes in the presence of an NADPH-generating system, part of the radioactivity remained in microsomal components after extensive extraction with various solvents and trichloroacetic acid. Treatment with ribonuclease and protease indicated that the radioactivity bound preferentially to proteins (Pathiratne *et al.*, 1986).

Pregnant C57Bl mice were exposed by inhalation to ^{14}C-toluene [theoretical concentration, 2000 ppm (7540 mg/m^3)] for 10 min on days 11, 14 or 17 of gestation, and distribution of the label was determined 0, 0.5, 1, 4 and 24 h after exposure. The label quickly entered the embryo, but uptake was low relative to that in maternal tissues. All fetal activity was extractable, indicating that no firmly bound metabolite was present (Ghantous & Danielson, 1986).

(ii) *Toxic effects*

The oral LD_{50} of toluene in rats has been reported to be about 5 g/kg bw (range, 2.6–7 g/kg bw) depending on age and strain (Wolf *et al.*, 1956; Kimura *et al.*, 1971; Withey & Hall, 1975). The intraperitoneal LD_{50} was reported to be about 1.6 g/kg bw in different strains of rats (Ikeda & Ohtsuji, 1971; Lundberg *et al.*, 1986) and about 1.2 g/kg bw in mice (Schumacher & Grandjean, 1960). The LC_{50} in rats exposed for 6 h was 50 000 mg/m^3 (Cameron *et al.*, 1938), and that in mice exposed for 7 h was 19 950 mg/m^3 (Svirbely *et al.*, 1943). The estimated dermal LD_{50} in rabbits was about 12 mg/kg bw (Smyth *et al.*, 1969). Toluene is only slightly to moderately irritating for skin and eyes of rabbits (Wolf *et al.*, 1956; International Programme on Chemical Safety, 1985).

Minor weight loss was noted in rats exposed to 500 ppm (1900 mg/m^3) toluene for 7 h per day on five days per week for five weeks and in mice exposed to 4000 ppm (15 000 mg/m^3) toluene for 3 h per day for ten weeks (Benignus, 1981a).

Acute inhalation of high concentrations of toluene resulted, depending on species, age and concentration, in more or less pronounced central nervous system depression (Carpenter *et al.*, 1976). Inhalation of concentrations of 2600 ppm (9800 mg/m^3) for several hours led to signs of narcotic effects. Inhalation of 12 000 ppm (45 200 mg/m^3) for 5 min produced marked central nervous system depression in mice and rats (Bruckner & Peterson, 1981a,b).

In rats, subchronic inhalation of toluene (1000 ppm [3770 mg/m^3], 12 h per day for 16 weeks) resulted in reversible reduction of mixed nerve conduction velocity (Takeuchi *et al.*, 1981). Disturbance of circardian rhythm was seen with 4000 ppm [15 000 mg/m^3] 4 h per day for four weeks (Hisanaga & Takeuchi, 1983), and behavioural effects were seen with 4000 ppm [15 000 mg/m^3], 2 h per day for 60 days (Ikeda & Miyake, 1978). Behavioural effects have been reported at exposures as low as 150 ppm (560 mg/m^3) for 30 min in rats (Geller *et al.*, 1979; Wood *et al.*, 1983) and 4 mg/m^3 for ten days in mice (Horiguchi & Inoue, 1977). Neurological signs have been recorded in cats exposed to 25 500 mg/m^3 for 10 min per day for 40 days (Contreras *et al.*, 1979). Exposure disturbed the turnover of neurotransmitters (dopamine, norepinephrine and 5-hydroxytryptamine) in the central nervous system of rats after exposure to 300–375 mg/m^3 for one or a few days (Fuxe *et al.*, 1982; Rea *et al.*, 1984).

No significant toxicity (as determined by blood parameters, urinary parameters, organ weights and histopathological examinations of major organs) was seen after oral administration of up to 590 mg/kg bw toluene to female rats for periods of up to six months (Wolf *et al.*, 1956) or daily 6–8-h inhalation exposures to concentrations below 400 ppm [1500 mg/m^3] for up to 24 months in rats (Jenkins *et al.*, 1970; Gibson & Hardisty, 1983) or for up to 127 days in dogs (Jenkins *et al.*, 1970; Carpenter *et al.*, 1976) or monkeys (Jenkins *et al.*, 1970).

In rats exposed to 8000 mg/m^3 toluene for 8 h per day on six days per week for seven weeks, lung irritation but no systematic haematological change was noted. Signs of central nervous system intoxication, incoordination and paralysis of the hind legs, and congestive changes in lung, liver, kidney, heart and spleen were seen in two dogs exposed to toluene concentrations of 7500 mg/m^3 then 10 000 mg/m^3 for 8 h per day on six days per week for six months; both animals died after 180 days (Fabre *et al.*, 1955).

An increase in the number of kidney casts was noted in rats exposed by inhalation to 750 mg/m^3 toluene for 7 h per day on five days per week for five weeks (International Programme on Chemical Safety, 1985). Hyperaemic glomeruli and albuminuria were reported in two dogs exposed to 7500 mg/m^3 then 10 000 mg/m^3 for 8 h per day on six days per week for six months (Fabre *et al.*, 1955).

Changes in the activity of drug-metabolizing enzymes in the liver were reported in rats exposed to 500 ppm (1875 mg/m^3) for 6 h per day for three days (Toftgård *et al.*, 1982) and following oral administration of 0.7 ml/kg bw for two days (Mungikar & Pawar, 1976; Pyykkö, 1980). Reduction in body weight gain and increases in liver weight and in cytochrome P450 and cytochrome b_5 concentrations, but no toxicity-related specific ultrastructural change in the liver, were observed in male rats exposed to toluene at 6000 mg/m^3 for 8 h per day for four weeks and in male and female rats exposed to up to 3500 mg/m^3 for 8 h per day for six months (Ungváry *et al.*, 1980).

(iii) *Effects on reproduction and prenatal toxicity*

Toluene (5–100 μmol [0.5–9.2 mg]/egg) was injected into the air sac of white Leghorn SK 12 chick embryos on day 2 or 6 of incubation; control eggs received an injection of the vehicle (olive oil). The LD_{50} was reported to be in excess of 100 μmol/egg, although this dose caused 100% mortality when given on day 6 (Elovaara *et al.*, 1979).

Toluene was injected into the yolk sac of fresh fertile chicken eggs prior to incubation. Hatchability of the eggs was 85%, 25% and 0 with exposures of 4.3, 8.7 and 17.4 mg/egg, respectively (McLaughlin *et al.*, 1964).

As reported in an abstract, CD–1 mice were exposed by gavage to 0.3 (0.27), 0.5 (0.45) or 1.0 ml (0.9 mg)/kg bw toluene in cottonseed oil on days 6–15 of gestation or to 1.0 ml/kg on days 12–15. No maternal effect was observed in the groups exposed on days 6–15, but significant embryo lethality was seen at all dose levels, and fetal weight was reduced at 0.5 and 1.0 ml/kg bw. Cleft palates were seen at the highest exposure level. In the groups exposed on days 12–15, only maternal toxicity was seen (Nawrot & Staples, 1979).

In a teratology screening assay, two groups of 30 ICR/SIM mice received 0 or 1800 mg/kg bw per day toluene by oral intubation on days 8–12 of gestation. Dams were allowed to deliver, and the offspring were evaluated for growth and viability in the early neonatal period. No effect was observed in either the dams or the offspring (Seidenberg *et al.*, 1986; Seidenberg & Becker, 1987). Using the same basic protocol, CD–1 mice received 0 or 2350 mg/kg bw per day (50 mice per group) or 0 and 3000 mg/kg bw per day (groups of 46 and 49 mice, respectively) toluene by oral intubation on days 6–13 of gestation. In the first experiment, exposure to toluene was lethal to one dam; no control died, and there was no other effect on dams or offspring. In the second experiment, 3/49 treated dams died; there was no death in the control group, and no other sign of toxicity was observed in dams or their offspring (Hardin *et al.*, 1987).

In four studies, mice were exposed by inhalation to up to 3770 mg/m^3 during various periods of gestation. Exposure to 1500 mg/m^3 resulted in maternal mortality after continuous (24 h/day) but not after intermittent (7 h/day) exposure. Fetal viability was not affected in any study. Fetal growth retardation was noted in one study at 500 mg/m^3 (24 h/day on days 6–13), but not in another at 1500 mg/m^3 (7 h/day on days 6–16). An increased incidence of extra ribs was seen at 3770 mg/m^3 (6 h/day on days 1–17) but a lower incidence was reported at 1500 mg/m^3 (7 h/day on days 6–16). No treatment-related malformation was seen in any study. In the two studies in which offspring were followed postnatally after exposure at 3770 mg/m^3 for 6 h per day on days 1–17, and 1500 mg/m^3 for 7 h per day on days 6–16, no effect on postnatal growth or viability was observed (Hudák & Ungváry, 1978; Shigeta *et al.*, 1982; Ungváry & Tátrai, 1985; Courtney *et al.*, 1986). [The Working Group noted that, on the basis of a non-dose-related increase in the frequency of enlarged renal pelvis and a decreased variability in rib profile, Courtenay *et al.* (1986) concluded that toluene was teratogenic to mice.]

CFY rats were exposed by inhalation to 1500 mg/m^3 toluene (analytical purity) for 24 h per day on days 9–14 of gestation (19 rats), to 1500 mg/m^3 on days 1–8 of gestation (nine rats) or to 1000 mg/m^3 for 8 h per day on days 1–21 of gestation (ten rats). There were 26 control females for exposure on days 9–14 and ten control females for the exposures starting on day 1

of gestation. Exposure to 1500 mg/m^3 caused mortality in 2/19 and 5/9 dams in the groups exposed on days 9–14 and 1–8, respectively; no other maternal effect was reported. Absence of the tail was reported in 2/213 fetuses exposed on days 9–14 as compared to 0/348 fetuses in the control group. On skeletal examination of the group exposed on days 9–14, 7/102 treated fetuses had fused sternebrae and 22/102 had extra ribs; the incidences in the control group were 2/169 and 0/169, respectively. High exposure levels early in development were accompanied by lower fetal body weights at term but no abnormality; the only effect noted following exposure to low levels throughout gestation (days 1–21) was an increased incidence of signs of skeletal retardation (poorly ossified sternebrae, bipartite vertebra centra and shortened 13th rib). No effect on fetal viability was noted with any exposure regimen (Hudák & Ungváry, 1978).

In a subsequent study, groups of 22 or 20 CFY rats were exposed by inhalation to air or to 1000 mg/m^3 toluene for 24 h per day on days 7–14 of gestation. Animals were killed on day 21 of pregnancy and the fetuses were examined by routine teratological techniques. No maternal toxicity was observed in the treated group; an increased incidence of supernumerary ribs was the only effect reported ($p < 0.10$) in the fetuses (Tátrai *et al.*, 1980). [The Working Group noted that it is not clear how the latter data were analysed; it appears that the individual fetus was used as the unit of comparison.] In a further study, exposure by inhalation to 0 or 3600 mg/m^3 toluene (analytical purity) for 24 h per day on days 10–13 of gestation did not appear to affect fetal development adversely although it did potentiate the maternal and embryonic toxic effects of acetylsalicylic acid (Ungváry *et al.*, 1983).

Groups of 12 female Nya:NYLAR mice were given 0, 16, 80 or 400 mg/l toluene in the drinking-water from mating throughout gestation and lactation, and the offspring continued to receive toluene in the drinking-water from weaning until the end of testing. Offspring were observed for viability, surface righting ability at seven days of age, eye and ear opening and startle response at 13–14 days of age, open field activity at 35 days of age and rotorod performance at 45–55 days of age. No treatment-related effect was observed for fluid consumption, growth, viability or appearance of developmental landmarks. Mice exposed to 400 mg/l displayed decreased habituation in the open field apparatus; a non-dose-related impairment of rotorod performance was also observed (Kostas & Hotchin, 1981).

Rats of an inbred strain (Tokai high avoiders) were exposed to 0, 100 or 500 ppm (0, 377 or 1885 mg/m^3) toluene for 7 h per day from day 13 of gestation to postnatal day 48. Developmental endpoints examined included age at pinna detachment, the presence of downy fur, incisor eruption, eye opening, body weight, a righting reflex and responses in a rotorod test. A learning test (Sidman avoidance) was conducted daily for ten days beginning on day 49, 100 or 150. There was no significant difference between the treated groups with respect to acquisition of developmental landmarks, but body growth was greater in the group exposed to 100 ppm. Treated male offspring in both exposure groups were deficient in acquisition of the learning task at initial, but not later, ages; no consistent effect was noted in the learning behaviour of treated female offspring (Shigeta *et al.*, 1986).

Groups of New Zealand white rabbits were exposed to 0 (60 animals), 500 (ten rabbits) or 1000 (eight rabbits) mg/m^3 toluene for 24 h per day on days 7–20 of gestation. Fetuses were examined by routine teratological techniques on day 30 of gestation. Females that received

the high dose either died, aborted or had no live fetuses at term. One female in the low-dose group aborted, but no significant fetal effect was noted (Ungváry & Tátrai, 1985). [The Working Group noted that this paper is a compendium of data on rats, mice and rabbits from one laboratory and presents little detail on experimental results.]

(iv) *Genetic and related effects*

The genetic and related effects of toluene have been reviewed (Dean, 1978, 1985; Fishbein, 1985).

Toluene induced a permanent loss of initiation of DNA replication in *Bacillus subtilis* cells (Winston & Matsushita, 1975). It did not produce differential killing in DNA repair-proficient compared to repair-deficient strains of *B. subtilis rec*$^{+/-}$ (McCarroll *et al.*, 1981a) or *Escherichia coli* (McCarroll *et al.*, 1981b). Toluene did not induce SOS activity in *Salmonella typhimurium* TA1535/pSK1002 (Nakamura *et al.*, 1987) and was not mutagenic to *S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100, UTH8413 or UTH8414 either in the presence or absence of an exogenous metabolic system from uninduced or Aroclor-induced rat and Syrian hamster livers (Lebowitz *et al.*, 1979 (abstract); Nestmann *et al.*, 1980; Bos *et al.*, 1981; Spanggord *et al.*, 1982; Haworth *et al.*, 1983; Connor *et al.*, 1985).

As reported in an abstract, toluene induced chromosomal anaphase alterations in *Vicia faba* (Gomez-Arroyo & Villalobos-Pietrini, 1981).

Toluene induced mitotic arrest (C-mitosis) in embryos of the grasshopper, *Melanoplus sanguinipes* (Liang *et al.*, 1983). It did not induce sex-linked recessive lethal mutations or translocations, but did induce sex-chromosome loss and nondisjunction in male *Drosophila melanogaster* at a dose of 1–1.5% toluene administered in food (Rodriguez Arnaiz & Villalobos-Pietrini, 1985a,b). As reported in an abstract, toluene did not induce recessive lethal mutations in *D. melanogaster* exposed to 500 and 1000 mg/kg for 24 h by feeding (Donner *et al.*, 1981).

Toluene induced DNA single-strand breaks (as measured by alkaline elution) in primary cultures of rat hepatocytes (Sina *et al.*, 1983), but did not cause DNA damage or repair, as measured by the 'nick-translation' assay, in cultured human fibroblasts (Snyder & Matheson, 1985). As reported in an abstract, toluene did not induce mutations in mouse lymphoma L5178Y TK$^{+/-}$ cells *in vitro* or chromosomal aberrations in rat bone marrow *in vivo* (Lebowitz *et al.*, 1979). It did not induce sister chromatid exchange or chromosomal aberrations in cultured human lymphocytes *in vitro* (Gerner-Smidt & Friedrich, 1978). [The Working Group noted that the human lymphocytes were tested without an exogenous metabolic system.]

Toluene was reported to induce chromosomal aberrations in the bone-marrow cells of male albino rats after chronic inhalation exposure to 5.4 or 50.7 mg/m^3 on 4 h per day, five days a week for four months (Aristov *et al.*, 1981) or after subcutaneous injection of 0.8 g/kg bw (Dobrokhotov, 1972). Chromosomal aberrations in bone-marrow cells were reported following subcutaneous injection of 1 g/kg bw daily for 12 days to male albino rats (Lyapkalo, 1973). Neither micronuclei nor chromosomal aberrations were observed in male and female CD-1 mice administered two doses of 1720 mg/kg bw toluene (99% pure) at a 24-h interval by oral gavage (Gad-El-Karim *et al.*, 1984). Increases in the frequency of micronuclei and of

chromosomal aberrations in rat bone-marrow cells were reported after two intraperitoneal injections of 217 mg/kg bw and 435 mg/kg bw (Roh *et al.*, 1987).

Toluene induced micronuclei in bone-marrow polychromatic erythrocytes of male NMRI and B6C3F1 mice after two intraperitoneal doses of 0.12–0.5 ml/kg bw (0.1–0.44 mg/kg) at a 24-h interval (Mohtashamipur *et al.*, 1985). Pretreatment of male NMRI mice with inducers (phenobarbital, Aroclor 1254, 3-methylcholanthrene) or inhibitors (metyrapone, α-naphthoflavone) of cytochrome P450 enhanced the frequency of micronuclei induced by toluene, while simultaneous injections of toluene and inhibitors decreased the observed clastogenic activities (Mohtashamipur *et al.*, 1987).

Toluene and benzene administered concurrently were reported to have an additive effect on induction of chromosomal aberrations (Dobrokhotov, 1972; Dobrokhotov & Enikeev, 1977). Toluene reduced the number of sister chromatid exchanges induced by benzene when both compounds were administered intraperitoneally to DBA/2 mice (Tice *et al.*, 1982) and reduced the clastogenic activity of benzene when the two compounds were simultaneously administered orally to CD-1 mice (Gad-El-Karim *et al.*, 1984), intraperitoneally to Sprague-Dawley rats (Roh *et al.*, 1987) or subcutaneously to NMRI mice (Tunek *et al.*, 1982).

As reported in an abstract, exposure of male rats by inhalation to 300 ppm (1130 mg/m^3) toluene for 6 h per day on five days per week for 15 weeks did not induce chromosomal aberrations in bone-marrow cells (Donner *et al.*, 1981). As reported in an abstract, oral administration of toluene did not induce chromosomal aberrations in bone-marrow cells or dominant lethal mutations in random-bred male SHR mice (Feldt *et al.*, 1985).

As reported in an abstract, toluene did not inhibit intracellular communication (as measured by metabolic cooperation) in Chinese hamster V79 cells (Awogi *et al.*, 1986).

Toluene did not enhance morphological transformation of Syrian hamster embryo cells by the SA7 adenovirus (Casto, 1981).

It did not induce sperm-head abnormalities in mice (Topham, 1980).

(*b*) *Humans*

(i) *Absorption, distribution, excretion and metabolism*

Inhalation is a major route of human exposure to toluene, although skin absorption may occur in occupational settings. An average lung uptake of 53.3% was obtained during exposure of volunteers to 271–1177 mg/m^3 toluene for 5 h (Srbová & Teisinger, 1952). Similar results were obtained in later studies: e.g., 57–72% (Piotrowski, 1967), 53% (Nomiyama & Nomiyama, 1974) and 30–50% (Carlsson, 1982) lung uptake. When volunteers immersed their hands in liquid toluene, skin penetration took place at a rate of 14–23 mg/cm^2 per hour (Dutkiewicz & Tyras, 1968). [The Working Group noted that the absorbed amount of toluene was calculated as the difference between the applied and the remaining amount of toluene, and therefore, the absorption rate may be overestimated.] Immersion of one hand in liquid toluene for 30 min resulted in a blood level (taken from the unexposed arm) of toluene twice as high as that after inhalation of 100 ppm (377 mg/m^3) for 4 h (Sato & Nakajima, 1978), indicating that both respiratory and percutaneous absorption are important. Toluene was

detected in exhaled air after whole-body skin exposure (with no inhalation) to 600 ppm (2260 mg/m^3) toluene for 3.5 h (Riihimäki & Pfäffli, 1978).

After exposure of volunteers to 100 ppm (377 mg/m^3) toluene for 2 h, the fall in the concentration of toluene in blood paralleled that in exhaled air. The decay curve consisted of three components with half-times of 1.7, 30 and 180 min [calculated by the Working Group] for the initial 5 min, 5–120 min and 180–300 min, respectively (Sato & Fujiwara, 1972). The biological half-time for the excretion of urinary metabolites among toluene workers was about 7.5 h (Tokunaga *et al.*, 1974). A shorter half-time was observed after exposure of volunteers (Baelum *et al.*, 1987). The half-time of toluene in adipose tissue of exposed workers was 0.5–2.7 days (Carlsson & Ljungquist, 1982). Toluene was present in the blood of printers several days after the end of exposure (Nise & Ørbaek, 1988).

Most [e.g., 68% (Ogata *et al.*, 1970)] of the toluene absorbed undergoes side-chain oxidation followed by glycine conjugation and is excreted in the urine as hippuric acid. *ortho*-, *meta*- and *para*-Cresols were also identified as minor metabolites of toluene (Angerer, 1979; Woiwode *et al.*, 1979; Woiwode & Drysch, 1981). *ortho*-Cresol levels are about 1/1000 of hippuric acid levels in the urine of workers exposed to toluene (Hasegawa *et al.*, 1983; Inoue *et al.*, 1986). The toluene level in blood is closely related to the level in alveolar air; the concentration of metabolites in urine is correlated with both, but less closely (Brugnone *et al.*, 1976).

Levels of hippuric acid, and to a lesser extent *ortho*-cresol, in urine have been studied intensively as indicators of exposure to (De Rosa *et al.*, 1987), and their validity has been established (Pagnotto & Lieberman, 1967; Ikeda & Ohtsuji, 1969; Capellini & Alessio, 1971; Pfäffli *et al.*, 1979; Bergert *et al.*, 1980; Alessio *et al.*, 1981; Hasegawa *et al.*, 1983; De Rosa *et al.*, 1985, 1987). Metabolite levels in urine samples collected near the end of a working day shift (Alessio *et al.*, 1981; Hasegawa *et al.*, 1983; De Rosa *et al.*, 1985) correlated best with the time-weighted average exposure to toluene; toluene accumulates in the body towards the end of a working week (Konietzko *et al.*, 1980) as a reflection of its biological half-time (Tokunaga *et al.*, 1974). Levels of toluene in the blood have also been used since these are low among nonexposed subjects (Szadkowski *et al.*, 1973). The biological monitoring of exposure to toluene has been reviewed (Lauwerys, 1983).

No significant change in toluene metabolism is induced by exposure to toluene under usual occupational conditions (Wallén, 1986). Simultaneous exposure to other solvents, such as benzene, is known to suppress toluene metabolism (Inoue *et al.*, 1988). Toluene metabolism may differ among populations (Inoue *et al.*, 1986).

When a large dose of ethanol was taken in combination with exposure to toluene, toluene metabolism was inhibited due to metabolic competition between the two chemicals. Blood toluene levels were lower in workers who drank regularly, indicating induction of toluene metabolism by continued ethanol intake-induced metabolism (Waldron *et al.*, 1983). A more rapid apparent clearance of toluene from the blood was seen in smokers compared to nonsmokers occupationally exposed to toluene (Wallén, 1986).

(ii) *Toxic effects*

Subjects who intentionally abuse toluene and workers exposed occupationally (mainly printers and painters) are generally also exposed to other organic solvents (International Programme on Chemical Safety, 1985). Metabolic and toxic interactions between toluene and other solvents may enhance or reduce any adverse effect (Swedish Criteria Group for Occupational Standards, 1985).

Slight hyposmia has been noted in printers (Baelum *et al.*, 1982). Moderate and transient effects on the eye (conjunctival irritation and corneal damage) occurred in workers splashed with liquid toluene (Grant, 1962). Eye and upper airway irritation occurred after a 6.5–h exposure to an air level of 100 ppm (377 mg/m^3) toluene (Baelum *et al.*, 1985), and lachrymation was seen at 1500 mg/m^3 (International Programme on Chemical Safety, 1985). An obstructive ventilatory pattern has been recorded in inhalation abusers of spray paint containing toluene (Reyes de la Rocha *et al.*, 1987). Prolonged exposure of the skin to toluene may cause contact dermatitis (Matsushita *et al.*, 1975).

Volunteers exposed to 100 ppm (377 mg/m^3) toluene for 6 h per day for four days suffered from subjective complaints of headache, dizziness and a sensation of intoxication (Andersen *et al.*, 1983). In subjects exposed to 750 mg/m^3 for 8 h, fatigue, muscular weakness, confusion, impaired coordination, enlarged pupils and accommodation disturbances were experienced; at about 3000 mg/m^3, severe fatigue, pronounced nausea, mental confusion, considerable incoordination with staggering gait and strongly affected pupillary light reflexes were observed. After exposure at the high level, muscular fatigue, nervousness and insomnia lasted for several days (International Programme for Chemical Safety, 1985). Heavy accidental exposure leads to coma (Longley *et al.*, 1967; Griffiths *et al.*, 1972; Bakinson & Jones, 1985).

Similar effects have been observed in cross-sectional studies of workers, including painters (see also the monograph on occupational exposures in paint manufacture and painting) exposed to corresponding or lower levels of toluene (Wilson, 1943; Matsushita *et al.*, 1975; Elofsson *et al.*, 1980; Husman, 1980; Baelum *et al.*, 1982; Winchester & Madjar, 1986). [The Working Group noted that there is probably confounding by other agents.]

Initial signs and symptoms of central nervous system effects with an excitatory stage, followed by central nervous system depression, ataxia, depressed consciousness and coma have also been observed in glue sniffers, who may be exposed to very high levels of toluene (Streicher *et al.*, 1981). Generally, these signs and symptoms are reversible (Benignus, 1981a); however, prolonged glue sniffing (two years or more) may result in permanent encephalopathy (Malm & Lying-Tunell, 1980; King *et al.*, 1981; Schikler *et al.*, 1982; Fornazzari *et al.*, 1983). In particular, cerebellar signs have been reported (Fornazzari *et al.*, 1983). Effects on the peripheral nervous system have also been observed in 'sniffers' (Korobkin *et al.*, 1975). [The Working Group noted that the relationship with toluene is severely confounded by concomitant exposure to other solvents (including alcohol) and drugs with known neurotoxicity (e.g., sedatives and neuroleptics).]

In volunteers exposed to 300 ppm (1130 mg/m^3) toluene for a few hours, impairment of simple reaction times was observed (Gamberale & Hultengren, 1972; Winneke, 1982), whereas 300–375 mg/m^3 caused no such effect (Andersen *et al.*, 1983; Dick *et al.*, 1984;

Anshelm Olson *et al.*, 1985; Iregren, 1986). Disturbances of psychomotor performance have been noted in cross-sectional studies of car and industrial painters exposed to a mixture of solvents including toluene (Hänninen *et al.*, 1976; Elofsson *et al.*, 1980; Biscaldi *et al.*, 1981; Winchester & Madjar, 1986; see also the monograph on occupational exposures in paint manufacture and painting). Changes in short-term memory, in other intellectual functions and in mood have also been reported in painters exposed to a mixture of solvents containing toluene (Hänninen *et al.*, 1976; Elofsson *et al.*, 1980; Winchester & Madjar, 1986). However, the data are not consistent: in one study of toluene-exposed factory workers, there was no such effect (Cherry *et al.*, 1985). Neurobehavioural effects have also been found in subjects mostly exposed to toluene, such as in the printing industry (Iregren, 1986; Hänninen *et al.*, 1987), at levels of 300 mg/m^3 (Iregren, 1986). However, in one study of printers, no such effect was observed (Struwe & Wennberg, 1983). [The Working Group noted that tests have usually been performed within 24 h after the last exposure, so it cannot be determined if the effects are of short duration or may be prolonged].

After three days of intense exposure (in some cases to the point of unconsciousness) to a mixture containing toluene, workers in a factory suffered memory disturbances that continued for months (Stollery & Flindt, 1988). In one study, there were indications of dyschromatopsia in printers exposed to a mixture of solvents, including toluene (Mergler *et al.*, 1988).

Further indications of effects on the central and peripheral nervous systems, have been reported in car and industrial painters (Seppäläinen *et al.*, 1978; Elofsson *et al.*, 1980; Husman & Karli, 1980) and other workers (Triebig *et al.*, 1983) exposed to mixtures of solvents, including toluene (see also the monograph on occupational exposures in paint manufacture and painting). In a study of toluene workers (Cherry *et al.*, 1985) and in printers exposed almost exclusively to toluene (Struwe & Wennberg, 1983; Antti-Poika *et al.*, 1985), no effect on the peripheral nervous system was observed.

'Sniffers' (Bennett & Forman, 1980; Kroeger *et al.*, 1980; Moss *et al.*, 1980; Voigts & Kaufman, 1983; Batlle *et al.*, 1988) and workers exposed accidentally to toluene (Reisin *et al.*, 1975) have been reported to develop both renal tubular damage (e.g., acidosis) and signs of glomerular damage, with haematuria, pyuria and proteinuria (Voigts & Kaufman, 1983). However, severe toluene poisoning has been reported without kidney disease (Brugnone & Perbellini, 1985), and, in a study of industrial spray painters exposed to a mixture of solvents containing toluene, there was no indication of kidney disease (Greenburg *et al.*, 1942). Later reports of workers (mostly painters but also a series of reports that included photogravure workers) exposed to toluene have indicated slight adverse effects on the kidney (Askergren, 1981; Askergren *et al.*, 1981a,b,c; Franchini *et al.*, 1983), although another study showed no effect (Lauwerys *et al.*, 1985; see also the monographs on some petroleum solvents and on occupational exposures in paint manufacture and painting).

Transient effects on the liver have been reported in a few 'sniffers' (Fornazzari *et al.*, 1983; Suzuki *et al.*, 1983); however, no discernable effect was observed in two subjects in coma following acute toluene intoxication (Brugnone & Perbellini, 1985). Slight effects on the liver have been noted in toluene-exposed workers (Greenburg *et al.*, 1942), including printing workers (Szadkowski *et al.*, 1976) and workers using toluene-based glues (Shiojima

et al., 1983), but not among other printers and painters exposed to toluene (Kurppa & Husman, 1982; Waldron *et al.*, 1982; Lundberg & Håkansson, 1985; Boewer *et al.*, 1988).

In one proportionate mortality study (Paganini-Hill *et al.*, 1980) and in one cohort study (Lloyd *et al.*, 1977) of printers, who may be exposed to toluene, there was an excess of liver cirrhosis. [The Working Group noted that the effect cannnot be ascribed with certainty to toluene, since exposure to many other agents had occurred.]

Some early studies (Wilson, 1943; Gattner & May, 1963; Klavis & Wille, 1967) related major myelotoxic effects (leukopenia, anaemia, thrombocytopenia and bone-marrow changes) to exposure to toluene, which were generally associated with benzene contamination of the toluene. Other cross-sectional studies (Bänfer, 1961; Tähti *et al.*, 1981) have displayed no such effect. Some recent studies have shown slightly increased haemoglobin levels (Elofsson *et al.*, 1980) and thrombocytopenia (Beving *et al.*, 1983, 1984) in car painters and workers in paint manufacture exposed to toluene, among other chemicals. Minor changes in white blood cells have also been reported following exposure to toluene (Friborská, 1973; Matsushita *et al.*, 1975).

In human volunteers exposed to 200 ppm (750 mg/m^3) toluene for 6 h per day for two days, the heart rate was increased significantly (Suzuki, 1973).

(iii) *Effects on fertility and on pregnancy outcome*

In the study of Holmberg (1979), described in the monograph on some petroleum solvents, three mothers of children with central nervous system defects, but no control mother, reported having worked with toluene during the first trimester of pregnancy. Two of the mothers of cases had also been exposed to other solvents. In the study of Holmberg *et al.* (1982), described in the monograph on some petroleum solvents, three mothers of children with oral clefts but no control mother reported having worked with toluene during the first trimester of pregnancy. All three had also been exposed to other solvents.

Ericson *et al.* (1984) linked records of female laboratory workers from the 1975 Swedish census to maternity records for 1976. Among the 1161 birth records identified in the laboratory workers, 44 (3.5%) of the children were either born dead or had a significant malformation. Among the 98 354 deliveries in Sweden during the same year, 2504 (2.6%) had a similar outcome. A case–control study of 26 of the children who had died within seven days or who had severe malformations and of 50 controls chosen from among children of laboratory workers was then performed. Exposure to toluene was similar in mothers of cases (8%) and of controls (8%); they had also been exposed to many solvents and other substances.

Axelsson *et al.* (1984) studied the outcome of pregnancy for 745 women born in 1935 and later, who had been engaged in laboratory work at the University of Gothenberg, Sweden, between 1968 and 1979. Data on outcome of pregnancy was obtained by postal survey and from the Medical Birth Register and the Register of Congenital Malformations in Sweden; data on exposure to specific substances were obtained by questionnaire. Toluene exposure during the first trimester of pregnancy was reported by 140 women, 17 of whom (10.2%) had had a spontaneous abortion. This compares with spontaneous abortion rates of 11.5% among women who had not worked in a laboratory during the first trimester and 9.0% among

women who had worked in a laboratory but not with solvents during the first trimester. Cases and controls had been exposed to many solvents and other substances.

Taskinen *et al.* (1986) studied the history of spontaneous abortions in women employed in eight Finnish pharmaceutical factories in 1973–80. The identity numbers of the women were linked to the nationwide hospital discharge data for 1973–81; 1795 pregnancies were thus identified, 142 of which were spontaneous abortions. A case–control study was carried out on women with spontaneous abortions who had been employed during the first trimester and three age-matched controls. Toluene exposure during the first trimester was reported by factory physicians for seven of 38 (18%) cases, compared with 14 of 119 (12%) controls. The corresponding overall relative risk (RR) was 1.6 (95% confidence interval [CI], 0.6–4.5); for those exposed less than once a week, the RR was 1.2 (0.2–6.9), and for those exposed more than once a week, the RR was 1.9 (0.6–6.4). Cases and controls had had exposure to many solvents and other substances.

McDonald *et al.* (1987) compared the chemical exposures of 301 women who had given birth to a child with a severe malformation to that of 301 controls, matched by hospital, gravidity, educational level, maternal age and date of delivery. Cases and controls were restricted to women who had given birth in Montréal in 1982–84 and who had worked for at least 30 h per week during the first 12 weeks of pregnancy. Chemical exposure was assessed by visiting the workplace or by telephone interview with the employer. Overall chemical exposure was assessed to have been more frequent in cases (21%) than in controls (16%). When the solvents were divided into nine chemical categories and the malformation into six anatomical sites, the strongest association was between aromatic solvents and urinary tract abnormalities (nine exposed cases, six of which were hypospadias, *versus* no exposed control). Six of the nine cases were assessed to have been exposed to toluene.

(iv) *Genetic and related effects*

No significant difference in the frequency of chromosomal changes was observed in peripheral blood lymphocytes of 24 workers (aged 29–60) at a rotogravure plant in Italy who were exposed to toluene (mean value, around 200 ppm [750 mg/m^3]) for three to 15 years compared with 24 controls matched for age and sex (Forni *et al.*, 1971). [The Working Group noted that smoking habits were not considered.]

An excess of chromosomal aberrations (chromatid and isochromatid breaks) was reported in the lymphocytes of 14 Swedish workers (aged 23–54) exposed only to toluene for 1.5–26 years (average level, 100–200 ppm [377–750 mg/m^3]) in a rotogravure printing factory in comparison with 49 unexposed workers (Funes-Cravioto *et al.*, 1977). [The Working Group noted that smoking habits were not considered, and details of controls were not given.]

No increase in the frequency of chromosomal aberrations or sister chromatid exchange was found in the peripheral blood lymphocytes of 32 rotogravure workers in Finland (aged 21–50) exposed to toluene (7–112 ppm) for three to 35 years compared to 15 unexposed subjects (Mäki-Paakkanen *et al.*, 1980). No increase in the frequency of sister chromatid exchanges was observed in seven workers in the Swedish paint industry exposed to various solvents, including more than 100 mg/m^3 toluene (Haglund *et al.*, 1980; see also the monograph

on occupational exposures in paint manufacture and painting). [The Working Group noted the small number of workers studied.]

Increases in the frequency of sister chromatid exchange, chromatid breaks, chromatid exchanges and gaps were reported in the peripheral lymphocytes of 20 workers (aged 32–60) at a rotogravure plant in the Federal Republic of Germany who had been exposed to toluene (200–300 ppm [750–1130 mg/m^3]) for more than 16 years, compared to 24 matched controls (Bauchinger *et al.*, 1982). In an abstract, a synergistic effect of smoking and exposure to toluene on the frequency of sister chromatid exchange was also reported (Bauchinger *et al.*, 1983). In the same plant, a higher incidence of chromatid-type aberrations than in controls was observed up to two years after cessation of exposure to toluene; longer after exposure, the aberration yields reached background level (Schmid *et al.*, 1985).

The frequency of chromosomal aberrations in 20 employees at a rotogravure plant exposed mainly to toluene in various printing inks was no different from that in 23 control workers; an increased frequency was observed in smokers in both groups (Pelclová *et al.*, 1987).

3.3 Epidemiological studies of carcinogenicity in humans

In each of the studies described below, exposures were mixed and overlapping, and these studies are cited in several monographs.

Olsson and Brandt (1980) performed a study on solvent exposure among 25 cases of Hodgkin's disease and 50 controls in Sweden (see the monograph on some petroleum solvents). Exposure to toluene was mentioned by six cases and three controls. All exposed cases and controls were exposed to other solvents.

Austin and Schnatter (1983) performed a case–control study on 21 deceased brain tumour patients and two control groups (80 employees in each) from a cohort of employees at a US petrochemical plant, investigating 37 chemicals. Exposure to 12 of these chemicals was more frequent among cases than controls, but toluene was not among these.

Wilcosky *et al.* (1984) performed a case–control study of rubber workers in the USA, described in detail in the monograph on some petroleum solvents. Exposure to toluene was associated with an increased risk for prostatic cancer (relative risk (RR), 2.6; three cases) and lymphatic leukaemia (3.0; two cases). Exposure to 'solvent A' (a proprietary mixture containing mostly toluene) was associated with increased RRs for stomach cancer (1.4; 15 cases), lymphosarcoma (2.6; six cases) and lymphatic leukaemia (2.8; seven cases). [The Working Group noted that the number of cases in each category is small, multiple exposures were evaluated independently of other exposures, and none of the associations is significant.]

Carpenter *et al.* (1988) evaluated the possible association with exposure to 26 chemicals or chemical groups in 89 cases of primary cancers of the central nervous system and 356 matched controls in cohorts of workers at two US nuclear facilities. Toluene, xylene (see monograph, p. 125) and methyl ethyl ketone were evaluated as one chemical group; the matched RR was 2.0 (28 cases; 95% CI, 0.7–5.5) in comparison with nonexposed workers. Almost all cases had had low exposure according to the classification used. The authors reported that the RRs were adjusted for internal and external exposure to radiation. [The

Working Group noted that no separate analysis was reported for the three solvents, nor were exposure levels quantified, and that there were many concurrent exposures.]

4. Summary of Data Reported and Evaluation

4.1 Exposures

Toluene is a major industrial chemical derived mainly from petroleum refining. Major uses of toluene are in the production of benzene and as a solvent in paints, inks and adhesives. Toluene-containing petroleum distillates are extensively and increasingly used in gasoline blending. Toluene is ubiquitous in the environment and is present at high levels in many occupational settings.

4.2 Experimental carcinogenicity data

Toluene was tested for carcinogenicity in one strain of rats by gastric intubation at one dose level and in one strain of rats by inhalation. These studies were inadequate for evaluation. Toluene was used as a vehicle control in a number of skin painting studies. Some of these studies were inadequate for evaluation; in others, repeated application of toluene to the skin of mice did not result in an increased incidence of skin tumours.

4.3 Human carcinogenicity data

Toluene was mentioned as an exposure in four case-control studies involving several anatomical sites of cancer. The results could not be evaluated with regard to toluene itself.

4.4 Other relevant data

In humans, prolonged skin contact with toluene may cause nonallergic contact dermatitis. Exposure to toluene also causes nervous system symptoms and signs. Excessive exposure to toluene may cause adverse effects on the kidney and liver.

Adverse effects on the nervous system have been observed in experimental animals.

In the available studies on spontaneous abortion, perinatal mortality and congenital malformations in humans, the numbers of cases were small and the mothers had also been exposed to other substances.

Embryotoxicity has been seen in some studies in mice and rats but not in rabbits. Embryotoxic effects generally occurred concurrently with maternal toxicity.

Increased frequencies of sister chromatid exchange and chromosomal aberrations in peripheral lymphocytes were observed in one study of workers exposed to toluene but not in two studies of chromosomal aberrations, one of sister chromatid exchange and one in which both effects were investigated. These studies are inconclusive with regard to exposure to toluene.

Toluene induced chromosomal aberrations in rats and micronuclei in mice and rats. Sister chromatid exchange and chromosomal aberrations were not induced in cultured human lymphocytes, in the absence of an exogenous metabolic system. Toluene did not induce morphological transformation in cultured animal cells. Toluene induced DNA damage in cultured animal cells. It did not induce mutation or chromosomal aberrations but induced aneuploidy in *Drosophila*. It did not induce DNA damage or mutation in bacteria. (See Appendix 1.)

4.5 Evaluation[1]

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

There is *inadequate evidence* for the carcinogenicity of toluene in experimental animals.

Overall evaluation

Toluene *is not classifiable as to its carcinogenicity to humans (Group 3).*

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

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