TOLUENE

Data were last evaluated in IARC (1989a).

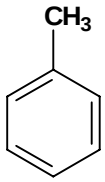
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 108-88-3
Chem. Abstr. Name: Methylbenzene
IUPAC Systematic Name: Toluene
Synonyms: Methylbenzol; phenylmethane

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_7H_8 Relative molecular mass: 92.14

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless liquid with characteristic aromatic hydrocarbon odour (Budavari, 1996)
(*b*) *Boiling-point*: 110.6°C (Lide, 1995)
(*c*) *Melting-point*: –94.9°C (Lide, 1995)
(*d*) *Solubility*: Very slightly soluble in water (515 mg/L at 20°C); soluble in acetone; and miscible with carbon disulfide, chloroform, diethyl ether, ethanol and glacial acetic acid (Budavari, 1996; Verschueren, 1996; Lide, 1997)
(*e*) *Vapour pressure*: 1.3 kPa at 6.4°C; relative vapour density (air = 1), 3.14 (Verschueren, 1996)
(*f*) *Flash point*: 4.4°C, closed cup (Budavari, 1996)
(*g*) *Explosive limits*: Upper, 7.0%; lower, 1.27% by volume in air (American Conference of Governmental Industrial Hygienists, 1992)
(*h*) *Conversion factor*: $mg/m^3 = 3.77 \times ppm$

1.2 Production and use

Production capacities for toluene in western Europe in 1994 were reported as (thousand tonnes): Austria, 4; Belgium, 73; France, 65; Germany, 1185; Italy, 495; the Netherlands, 255; Portugal, 140; Spain, 280 and United Kingdom, 555 (Fabri *et al*., 1996). Production in the United States in 1993 was reported to be 2277 thousand tonnes (United States International Trade Commission, 1994). Information available in 1995 indicated that toluene was produced in 35 countries (Chemical Information Services, 1995).

Toluene is used as a high-octane blending stock in gasoline; as a solvent for paints and coatings, gums, resins, oils, rubber and adhesives; and as an intermediate in the preparation of many chemicals, dyes, pharmaceuticals, detergents and explosives (Lewis, 1993).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES, 1997), as many as 2 million workers in the United States were potentially exposed to toluene (see General Remarks). Occupational exposures to toluene may occur in painting, varnishing, various cleaning operations, laboratories, car repair shops and many other workplaces where toluene is produced or used as solvent or intermediate to prepare other chemicals. Extensive occupational exposure data are presented in a previous monograph (IARC, 1989a).

1.3.2 *Environmental occurrence*

Toluene is released into the atmosphere principally from the volatilization of petroleum fuels and toluene-based solvents and thinners and in motor vehicle exhaust. It is also present in emissions from volcanoes, forest fires and crude oil. It has been detected at low levels in surface water, groundwater, drinking-water and soil samples (United States National Library of Medicine, 1997).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 188 mg/m^3 as the 8-h time-weighted average threshold limit value, with a skin notation, for occupational exposures to toluene in workplace air. Values of 100–380 mg/m^3 are used as standards or guidelines in other countries (International Labour Office, 1991).

The World Health Organization has established a provisional international drinking-water guideline for toluene of 700 µg/L (WHO, 1993).

2. Studies of Cancer in Humans

The epidemiological studies are summarized in Table 1.

Table 1. Summary of epidemiological studies on toluene

Author, country	Study type	Comparison	Size	Results[a]	
Svensson *et al.* (1990), Sweden	Cohort of rotogravure printers. Mortality and cancer incidence	Local region rates	1020	Stomach	SMR, 2.7 (1.1–5.6) SIR, 2.3 (0.9–4.8)
				Colorectal	SMR, 2.2 (0.9–4.5) SIR, 1.5 (0.7–2.8)
				Respiratory	SMR, 1.4 (0.7–2.5) SIR, 1.8 (1.0–2.9)
				Leukaemia/lymphoma	SMR, 1.0 (0.2–2.8)
				Leukaemia	SIR, 1.7 (0.3–4.9)
Walker *et al.* (1993), United States	Cohort of shoe manufacture workers. Mortality	National rates	7814	Men	
				Buccal cavity and pharynx	SMR, 0.9 (0.2–2.2)
				Digestive	SMR, 0.9 (0.6–1.3)
				Colon	SMR, 1.3 (0.8–2.1)
				Lung	SMR, 1.6 (1.2–2.0)
				Kidney	SMR, 1.7 (0.6–3.7)
				Lymphoma and haematopoietic	SMR, 0.9 (0.5–1.6)
				Women	
				Colon	SMR, 1.2 (0.8–1.8)
				Lung	SMR, 1.3 (0.9–1.9)
Blair *et al.* (1998), United States	Cohort of aircraft maintenance workers. Mortality. Internal analysis on multiple myeloma, non-Hodgkin lymphoma and breast cancer	Unexposed within cohort	< 14 457 exposed unexposed	Multiple myeloma	
				Men	RR, 0.9 (0.2–4.8)
				Women	RR, 5.0 (1.1–23.1)
				Non-Hodgkin lymphoma	
				Men	RR, 1.0 (0.2–4.2)
				Women	RR, 2.2 (0.4–13.2)
				Breast (women)	RR, 2.0 (0.9–4.2)
				(Other substances also had excess risks.)	

Table 1 (contd)

Author, country	Study type	Comparison	Size	Results[a]	
Austin & Schnatter (1983), United States	Nested case–control study of brain cancer in petrochemical industry	Other deceased workers	21 cases 2 × 80 controls	Brain	OR < 1.0
Wilcosky *et al.* (1984), United States	Nested case–control study of five types of cancer among rubber workers	20% sample of cohort	4–101 per case series, approx. 1300 controls	'Solvent A' Stomach Respiratory Prostate Lymphosarcoma Lympholeukaemia	 OR, 1.4 (NS) [OR, 1.0] OR, 1.0 OR, 2.6 (NS) OR, 2.8 (NS)
Carpenter *et al.* (1988), United States	Nested case–control study of central nervous system in nuclear workers	Living at time of case occurrence	89 cases 356 controls	Central nervous system	OR, 2.0 (NS)
Olsson & Brandt (1980), Sweden	Case–control study of Hodgkin's lymphoma	Neighbourhood controls	25 cases 50 controls	Hodgkin's lymphoma	[Crude OR, 4.0]

Table 1 (contd)

Author, country	Study type	Comparison	Size	Results[a]	
Gérin *et al.* (1998), Canada	Case-control study, many sites	Population controls and cancer controls	99–857 per case series, 1066 controls	Oesophagus	OR, 1.9 (0.9–4.2)
				Stomach	OR, 1.7 (0.6–4.8)
				Colon	OR, 1.8 (0.7–4.4)
				Rectum	OR, 3.2 (1.3–8.0)
				Pancreas	OR, 0.6 (0.2–2.2)
				Lung	OR, 1.1 (0.5–2.7)
				Prostate	OR, 0.4 (0.1–1.4)
				Melanoma	OR, 0.4 (0.1–0.9)
				Non-Hodgkin lymphoma	OR, 0.9 (0.4–1.9)

SMR, standardized mortality ratio; SIR, standardized incidence ratio; RR, relative risk; OR, odds ratio; NS, not significant
Most of the study groups were exposed to many substances in addition to toluene.
[a] Unless otherwise stated, results pertain to males.

2.1 Industry-based studies

Austin and Schnatter (1983) performed a nested case–control study of brain cancer within a cohort of employees at a petrochemical plant in Texas (United States). Twenty-one deceased brain tumour patients and two control groups (80 deceased ex-employees in each) were selected. Job history records were assessed by industrial hygienists for the purpose of assigning potential for exposure to each of 42 substances, one of which was toluene. Results were expressed as percentages of cases and controls exposed. Cases had lower exposure prevalence than controls (36% versus 45–53%) [leading to an apparent approximate odds ratio of 0.6, 95% CI, 0.2–2.2]. [The Working Group had some difficulty understanding the constitution of the control groups.]

In a nested case–control study among rubber workers in the United States (Wilcosky *et al*., 1984), described in more detail in the monograph on dichloromethane (see this volume), one of the substances evaluated was toluene and another was 'solvent A' (a proprietary mixture containing mostly toluene). For toluene itself, the numbers of exposed cases were very low (less than three for each case series). For lung cancer, the odds ratio was 0.6 based on three exposed cases. For lymphatic leukaemia, there were two cases exposed to toluene (odds ratio, 3.0; $p > 05$).There were somewhat higher numbers exposed to 'solvent A', with increased relative risks for stomach cancer (odds ratio, 1.4; $n = 15$), lymphosarcoma (odds ratio, 2.6; $n = 6$) and lymphatic leukaemia (odds ratio, 2.8; $n = 7$). [The Working Group noted that the numbers of cases exposed to pure toluene was small and the odds ratio estimates imprecise. Workers were typically exposed to multiple exposures and positive associations were found for many of the other substances analysed in this study, indicating a lack of specificity in the toluene or 'solvent A' associations].

Carpenter *et al*. (1988) carried out a nested case–control study of cancer of the central nervous system among workers at two nuclear facilities located in Tennessee (United States). They identified 89 cases (72 males and 17 females) who had died between 1943 and 1979. Four controls, living at the time the case was diagnosed, were matched to each case. Job history records were scrutinized by an industrial hygienist to assess potential exposure to each of 26 chemicals or chemical groups. Toluene, xylene (see this volume) and 2-butanone (methyl ethyl ketone) were evaluated as one chemical group; the matched relative risk was 2.0 (95% confidence interval (CI), 0.7–5.5; $n = 28$) in comparison with unexposed workers. Almost all cases had had low exposure, according to the classification used and there was no dose–response trend. The authors stated that the relative risks were adjusted for internal and external exposure to radiation.

Svensson *et al*. (1990) studied a cohort of 1020 Swedish rotogravure printers exposed primarily to toluene and employed for a minimum period of three months in eight plants during 1925–85. Data were available on air levels of toluene since 1943 in one plant and since 1969 in most. Based on these measurements and on present concentrations of toluene in blood and subcutaneous fat, the yearly average air levels in each plant were estimated. They reached a maximum of about 450 ppm [1700 mg/m^3] in the 1940s and 1950s but were only 30 ppm [113 mg/m^3] by the mid-1980s. Exposure to benzene had occurred up to the beginning of the 1960s, but not since then. Records of

employment were combined with these retrospectively estimated plant-specific exposure levels to derive cumulative exposure estimates. The mortality experience of the cohort, during the follow-up period of 1952–86, was compared with that of the geographical region in which the plants were located, and cancer incidence, during the follow-up period of 1958–85, was analogously compared with regional incidence rates. The 'all causes' standardized mortality ratio (SMR) was 1.0 (129 observed deaths). There was no increase in mortality from non-malignant respiratory diseases (SMR, 0.8; 95% CI, 0.3–1.9; *n* = 5). For all cancers combined, there was some overall excess of mortality (SMR, 1.4; 95% CI, 1.0–1.9; *n* = 41) and morbidity (standardized incidence ratio (SIR), 1.3; 95% CI, 1.0–1.6). Among specific cancers, there were no excess risks for urinary cancers or leukaemias, lymphomas and myelomas. There were indications of excess risk for respiratory tract cancer (SMR, 1.4; 95% CI, 0.7–2.5; *n* = 11; SIR, 1.8; 95% CI, 1.0–2.9; *n* = 16) , for stomach cancer (SMR, 2.7; 95% CI, 1.1–5.6; *n* = 7; SIR, 2.3; 95% CI, 0.9–4.8; *n* = 7) and colo-rectal cancer (SMR, 2.2; 95% CI, 0.9–4.5; *n* = 7; SIR, 1.5; 95% CI, 0.7–2.8; *n* = 9) . Restricting analysis to those with at least five years of exposure did not lead to higher relative risk estimates. Further, there was no dose–response relationship with cumulative toluene dose (ppm years). [The Working Group noted that this study population had the 'purest' exposure to toluene of the groups evaluated in this monograph. This study had the best exposure assessment. Although the absence of an excess risk of nonmalignant respiratory disease is reassuring, it was based on very small numbers and thus does not prove that this cohort had 'normal' smoking habits].

Blair *et al.* (1998) updated a cohort mortality study reported by Spirtas *et al*. (1991) on 14 457 workers who had been employed as civilians for at least one year during the interval 1952 to 1956 in an aircraft maintenance facility located in Utah (United States). The study methods are described in the monograph on dichloromethane (see this volume). About 13% of the cohort were deemed to be exposed to toluene (Stewart *et al*., 1991). Using Poisson regression analysis, rate ratios were estimated for each of three types of cancer, multiple myeloma, non-Hodgkin lymphoma and breast cancer. Among toluene-exposed workers, there was an indication of an excess of multiple myeloma among women (RR, 5.0; 95% CI, 1.1–23.1; *n* = 4) but not among men (RR, 0.9; 95% CI, 0.2–4.8; *n* = 2). There was no meaningful excess risk of non-Hodgkin lymphoma among men (RR, 1.0; 95% CI, 0.1–4.2; *n* = 3) or among women (RR, 2.2; 95% CI, 0.4–13.1; *n* = 2). There was a slight excess of breast cancer (RR, 2.0; 95% CI, 0.9–4.2; *n* = 10). [The Working Group noted that the numbers on which these associations were based were very small and that workers typically had multiple exposures.]

Walker *et al*. (1993) conducted a cohort mortality study among 7814 shoe-manufacturing workers (2529 males and 5285 females) from two plants in Ohio (United States) that have been in operation since the 1930s. The workers, men and women, were potentially exposed to solvents and solvent-based adhesives. It was thought that toluene may have been a predominant exposure, but a hygiene survey in 1977–79 showed that, in addition to toluene (10 measurements ranged from 10 ppm to 72 ppm [38–270 mg/m^3]), there were also 2-butanone (methyl ethyl ketone), acetone, hexane and

several other solvents in concentrations as high as or higher than that of toluene. It is not clear whether these substances were present in earlier years. Benzene (IARC, 1987) may have been present as an impurity of toluene. Mortality follow-up was from 1940 to 1982. Relative risk estimates (SMRs) for white workers were derived by comparison with the general population of the United States. Among men, the SMR for all causes of death combined was close to 1.0, as was the SMR for all cancers combined. This cohort had no excess of lymphatic and haematopoietic cancer as a whole (SMR; 0.9; 95% CI, 0.6–1.3; $n = 29$) nor for any subtype. There were excess risks of lung cancer among men (SMR, 1.6; 95% CI, 1.2–2.0; $n = 68$) and among women (SMR, 1.3; 95% CI, 0.9–1.9; $n = 31$). Relative risk of lung cancer did not increase with increasing duration of employment. Mortality from chronic non-malignant respiratory disease was significantly elevated among men (SMR, 1.6; 95% CI, 1.1–2.2) but was less than expected among women (SMR, 0.8; 95% CI, 0.4–1.3), a finding suggesting a possible contribution of smoking to the male mortality from respiratory cancer. Adjustment for the potential effects of smoking by Axelson's (1978) method reduced the relative risk estimate for lung cancer to 1.4 (95% CI, 1.1–1.8). There were slight excess risks for colon cancer among men (SMR, 1.3; 95% CI, 0.8–2.1; $n = 18$) and among women (SMR, 1.2; 95% CI, 0.8–1.8; $n = 28$). Other cancers showed no excess risk. [The Working Group noted that there was sparse information on what substances were historically present in this workplace. The procedure for adjustment of smoking is imperfect and could leave a confounded estimate.]

2.2 Community-based studies

Olsson and Brandt (1980) carried out a hospital-based case–control study of Hodgkin's disease and chemical exposures in Lund, Sweden. Twenty-five consecutive male cases aged 20–65 years were included. Two neighbourhood-matched controls were selected for each case from the Swedish population register. Interviews with study subjects focused on a detailed job history, and in particular on exposure to solvents. Interview data were supplemented with enquiries to employers in some cases. Using a criterion of at least one year of exposure more than 10 years before diagnosis, 12 of the 25 patients with Hodgkin's disease had been exposed occupationally to organic solvents and six of the 50 controls, giving an odds ratio of 6.6 (95% CI, 1.8–23.8). Six of the cases and three of the controls had been exposed to toluene [crude odds ratio, 4.0]. All toluene-exposed cases and controls were also exposed to other solvents. [The Working Group noted the opportunity for information bias, since the interviewer was not blind to disease status or to the study objectives.]

Using data collected in the population-based case–control study of cancer among male residents of Montreal, Canada, described in the monograph on dichloromethane (see this volume), Gérin *et al*. (1998) carried out an analysis focusing on cancer risks in relation to benzene, toluene, xylene (see this volume) and styrene exposure. For these analyses, the control group for each case series consisted of a combination of the 533 population controls with 533 cancer controls selected at random from the pool of eligible cancer controls. Fifteen per cent of the entire study population had been exposed to toluene at

some time (i.e., lifetime exposure prevalence). Among the main occupations in which toluene exposure was deemed in this study to have occurred were painters (except construction), vehicle mechanics and repairers, shoemakers and carpenters. Cumulative exposure indices were created on the basis of duration, concentration, frequency and the degree of certainty in the exposure assessment, and subjects were subdivided into subgroups with low, medium and high cumulative exposure. Logistic regression analyses were carried out, with adjustment for age, ethnic group, income level and smoking status, as well as asbestos and chromium compounds in the analysis of lung cancer. For the following cancer sites, there was little indication of excess risk in relation to exposure to toluene (results are shown for high exposure or for medium/high combined when numbers were too small): pancreas (odds ratio, 0.6; 95% CI, 0.2–2.2; *n* = 3), lung (odds ratio, 1.1; 95% CI, 0.5–2.7; *n* = 12), prostate (odds ratio, 0.4; 95% CI, 0.1–1.4; *n* = 3), urinary bladder (odds ratio, 1.0; 95% CI, 0.4–2.5; *n* = 7), kidney (odds ratio, 1.0; 95% CI, 0.5–2.1; *n* = 8), melanoma (odds ratio, 0.4; 95% CI, 0.1–0.9; *n* = 5) and non-Hodgkin lymphoma (odds ratio, 0.9; 95% CI, 0.4–1.9; *n* = 8). For the following sites, the odds ratios were above 1.5: oesophagus (odds ratio, 1.9; 95% CI, 0.9–4.2; *n* = 9), stomach (odds ratio, 1.7; 95% CI, 0.6–4.8; *n* = 5), colon (odds ratio, 1.8 ; 95% CI, 0.7–4.4; *n* = 9) and rectum (odds ratio, 3.2; 95% CI, 1.3–8.0; *n* = 8). Most workers exposed to toluene were also exposed to benzene, xylene and perhaps other substances. Further analyses of colon cancer and rectal cancer showed that the apparent excesses related to toluene were not attributable to benzene exposure, but the relative contributions of toluene and xylene could not confidently be disentangled.

3. Studies of Cancer in Experimental Animals

Toluene was tested for carcinogenicity in one strain of rats by gavage 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 (IARC, 1989a).

3.1 Inhalation exposure

3.1.1 *Mouse*

Groups of 60 male and 60 female B6C3F_1 mice, 9–10 weeks of age, were administered toluene (purity, > 99%) by whole-body inhalation at concentrations of 0 (controls), 120, 600 or 1200 ppm [0, 450, 2260 or 4520 mg/m^3] for 6.5 h per day on five days per week for 104 weeks. Exposure concentrations were based on the results from 13-week studies in which deaths were observed at concentrations of 2500 ppm [9400 mg/m^3] and higher. Ten females per group were killed after 15 months. Survival was 17/60, 22/60, 16/60 and 19/60 control, low-, mid- and high-dose males and 30/50,

33/50, 24/50 and 32/50 control, low-, mid- and high-dose females, respectively. All animals were necropsied and all major tissues examined histopathologically. No increase in the incidence of any non-neoplastic or neoplastic lesion was observed (United States National Toxicology Program, 1990).

3.1.2 *Rat*

Groups of 60 male and 60 female Fischer 344 rats, six to seven weeks of age, were administered toluene (purity, > 99%) by whole-body inhalation at concentrations of 0 (controls), 600 or 1200 ppm [0, 2260 or 4520 mg/m^3] for 6.5 h per day on five days per week for 103 weeks. Exposure concentrations were based on the results from 15-week studies in which deaths were observed at concentrations of 3000 ppm [11 300 mg/m^3] and significantly decreased body weights occurred at 2500 ppm [9400 mg/m^3]. Ten females per group were killed after 15 months. Mean body weight was generally similar among groups. Survival was 30/50, 28/50 and 22/50 control, low- and high-dose males and 33/50, 35/50 and 30/50 control, low- and high-dose females, respectively. All animals were necropsied and all major tissues examined histopathologically. No increase in tumours was found in either sex (United States National Toxicology Program, 1990).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

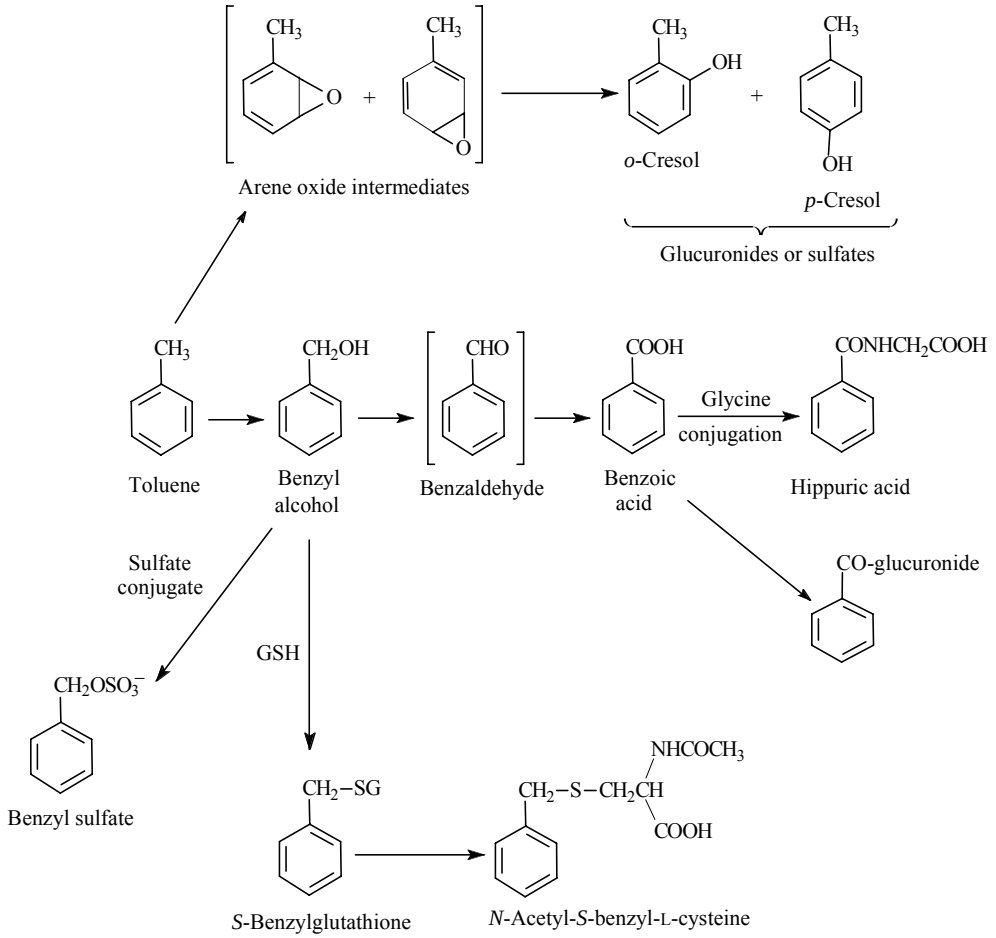
The major metabolic pathway of toluene is to benzyl alcohol, which is oxidized to benzaldehyde and subsequently to benzoic acid (Figure 1). Most of the benzoic acid is converted to hippuric acid, but some is conjugated with UDP-glucuronate to form the acyl-glucuronide. A much smaller fraction of a dose of toluene is converted to *ortho*- and *para*-cresol, which are excreted in urine as the sulfate or glucuronide conjugates.

4.1.1 *Humans*

During inhalation exposure of human volunteers to low levels of toluene (200–300 mg/m^3), approximately 50% of the inhaled toluene was absorbed (Löf *et al*., 1993). Such studies at low toluene exposure are complicated by the presence of toluene from other sources, in blood or in urine (Pierce *et al*., 1996). If the deuterated [$^2H_8$]toluene is used for exposure, this problem is avoided [but an isotope effect may reduce the rate of the metabolism of deuterated toluene compared to normal toluene, possibly by 30–50%]. When toluene is administered orally, it is virtually completely absorbed from the gastrointestinal tract (Baelum *et al*., 1993).

During exposure at 100 ppm [380 mg/m^3], women had a higher toluene concentration in exhaled air than men, both at rest and under a work load of 100 W: a 5 ppm [19 mg/m^3] difference was observed in exhaled levels of approximately 10–20 ppm

Figure 1. Metabolic pathways for toluene



[38–76 mg/m^3]. In both sexes, work tended to increase the toluene concentration in exhaled air by up to 5 ppm; however there was very wide interindividual variation (Baelum, 1990). There was a linear correlation between toluene concentration in ambient air (8-h time-weighted average) of workers exposed to 10–300 ppm [38–1180 mg/m^3] and the post-shift toluene levels in finger-prick blood or the toluene concentration in end-of-shift expired breath (Foo *et al.*, 1988, 1991). A similar correlation was observed between the time-weighted average toluene exposure level during a five-day working week (10–420 mg/m^3) and the toluene concentration in subcutaneous adipose tissue (Nise *et al.*, 1989); the elimination kinetics of toluene in blood showed a three-phase behaviour, with a very rapid phase ($t_{½}$ approximately 10 min), a slower phase ($t_{½}$ approximately 2 h) and a very slow phase ($t_{½}$ 45–180 h). The latter long half-life may be related to slow release from adipose tissue, which accumulates toluene. A semi-empirical

physiological toxicokinetic model of toluene has been developed by Pierce *et al*. (1996). This model takes into account person-specific characteristics like adipose tissue fraction, blood–air partition coefficient, age, ventilation rate and body weight. The hepatic toluene metabolism parameters were taken from the literature, but 'extrahepatic metabolism', as well as the fraction of cardiac output that perfuses adipose tissue were fitted individually to best describe the data. The data show that systemic toluene clearance is well in excess of hepatic blood flow, indicating extensive extrahepatic metabolism. A high adipose fraction is associated with low blood concentrations of toluene, and simulations show that, 98 h after exposure, the adipose tissue contained more than 97% of the toluene present in the body. In human blood, toluene is distributed between red blood cells and plasma at a ratio of approximately 40:60 (Lam *et al*., 1990).

Another physiological toxicokinetic model (Tardif *et al*., 1993b, 1997) has been used to predict potential interactions between, e.g., toluene, ethylbenzene and *meta*-xylene; the model and experimental data from exposed volunteers indicate that no biologically significant changes in their toxicokinetics will occur if these three solvents are present in the air as a mixture within the permissible concentrations for mixtures (Tardif *et al*., 1997). A model approach also predicted that interactions between dichloromethane and toluene at their current threshold limit values are not relevant for humans (Pelekis & Krishnan, 1997).

The analgesic drugs paracetamol and acetylsalicylic acid at normal clinical doses had no acute effect on toxicokinetics of toluene inhaled at 300 mg/m^3 (Löf *et al*., 1990b); similarly, neither carbohydrate diets nor the consumption of 47 g ethanol as wine on the evening before exposure to 200 mg/m^3 toluene for 2 h had any effect on toluene kinetics (Hjelm *et al*., 1994).

Several authors have pointed out that the urinary excretion of hippurate is a poor indicator of exposure to toluene at 200 ppm [760 mg/m^3] or lower (Jonai & Sato, 1988; Foo *et al*., 1991; Pierce *et al*., 1996). Therefore, data on ethnic differences in hippurate or cresol excretion in urine at these low exposure levels (e.g., Inoue *et al*., 1988) are of doubtful significance. Toluene level in expired air may be a more reliable parameter (Foo *et al*., 1991). Although at the level of the individual, data on urinary hippurate cannot be reliably used to estimate low toluene exposures, they can be used at the group level to establish whether at a certain location the toluene exposure remained below a particular threshold (Lauwerys, 1983).

The first step in toluene metabolism is catalysed by several cytochrome P450 species: human liver microsomes convert toluene mainly to benzyl alcohol (over 90%) as well as to *ortho*- and *para*-cresol (3 and 5%, respectively) (Tassaneeyakul *et al*., 1996; Nakajima *et al*., 1997). The major CYP isoenzyme responsible for oxidation to benzyl alcohol is CYP2E1; diethyldithiocarbamate, a selective and potent CYP2E1 inhibitor, decreased benzyl alcohol formation by more than 75%. Also CYP2B6, CYP2C6, CYP1A2 and CYP1A1 (in decreasing order) are active. *para*-Cresol is formed by CYP2B2 and CYP2E1, while CYP1A2 forms both *ortho*-and *para*-cresol (Nakajima *et al*., 1997). Among 35 surgical human liver samples (23 men and 12 women with either

primary liver tumours or hepatic metastases), there was only a four-fold difference in the rate of oxidation by microsomes. No difference was observed between microsomes from smokers and from non-smokers in formation of benzyl alcohol or *para*-cresol, but the formation of *ortho*-cresol was somewhat increased; alcohol consumption had no measurable effect (Nakajima *et al*., 1997).

Human polymorphisms in several enzymes involved in toluene metabolism are known. In Mongoloid populations, deficiency in the low K_m form of aldehyde dehydrogenase H2 (ALDH2) is common: approximately half of the Japanese population lacks this enzyme. In ALDH2-deficient exposed workers, an increased level of benzyl alcohol was found, but benzaldehyde was not detectable; urinary excretion of hippurate was decreased in the deficient individuals. The CYP1A1 polymorphism, alcohol consumption and smoking were all associated with decreased hippurate excretion, but the interdependence was too complex to allow detailed conclusions on the mechanisms to be drawn (Kawamoto *et al*., 1995).

The toxicokinetics of inhaled toluene have been studied in two groups of healthy volunteers. Löf *et al*. (1990a) exposed six women (26–40 years of age) for 4 h while in a sedentary position to toluene at the Swedish hygienic threshold limit of 3.25 mmol/m^3 (or 300 mg/m^3). Three of the women were rapid hydroxylators and three were slow hydroxylators. Of the inhaled toluene, 51% (range, 48–56) was absorbed, leading to a steady-state blood concentration of 5.0 μM (range, 2.9–9.0) after 90 min. The second, rapid half-life time of elimination ($t_{½β}$) was 40 min (range, 25–71 min). Hippurate synthesis was the almost exclusive metabolic pathway, as reflected by its urinary excretion, with *ortho*-cresol excretion 1000-fold lower, in both the rapid and slow hydroxylators. When [$^2H_8$]toluene was used in a similar experiment (Löf *et al*., 1993), three elimination phases with $t_{½}$ of 3 min, 40 min and 740 min were observed. At 4 h after exposure, 65% of the total uptake had been excreted as hippurate; this reached 78% after 20 h. However, in the same period, a more than four-fold higher amount of non-deuterated hippurate was excreted, indicating that at low toluene exposure levels, hippurate cannot be used as an indicator for occupational monitoring (see above). *ortho*-Cresol is not expected to be more reliable for the same reason. This could explain the wide scattering of points when the *ortho*-cresol content in urine was correlated to a presumed toxic effect, urinary excretion of retinol-binding protein, in workers who had been exposed to less than 100 ppm [380 mg/m^3] toluene (Ng *et al*., 1990).

The acute interaction with ethanol was studied by oral administration of toluene as a 2 mg/min infusion for 3 h through a feeding tube into the stomach (Baelum *et al*., 1993). The infusion was chosen such that the exposure level was similar to inhalation of approximately 200 mg/m^3 in combination with light exercise (50 W). Toluene was measured in exhaled air to monitor the toluene concentration in alveolar arterial blood. When ethanol was co-administered orally at a dose of 0.32 g/kg bw, a pronounced increase in the alveolar toluene concentration occurred, from 0.07 (range, 0.00–0.12) without ethanol to 74 (range, 60–93) mg/m^3 with ethanol. The rate of urinary excretion of the hippurate was reduced by ethanol, but otherwise little affected. Excretion of *ortho*-cresol

increased from a total per person of 1.7 (range, 0.6–3.5) μmol without ethanol to 2.9 (range, 2.3–3.7) μmol with ethanol. A very high hepatic extraction ratio of virtually 100% was calculated, but this is probably an overestimate. The results indicate that a single alcoholic drink has a very strong, acute inhibitory effect on the hepatic elimination of toluene. The site of this inhibition has not been identified, but the formation of benzylic alcohol seems to be most affected.

4.1.2 *Experimental systems*

In guinea-pigs, the presence of surfactants (e.g., Triton X-45 or X-100) decreased the skin absorption of toluene (Boman *et al*., 1989). Intermittent skin exposure (for 1 min, every 30 min, repeated eight times) resulted in a blood toluene area-under-the-curve (AUC) of 16% compared to that seen with continuous toluene exposure (Boman *et al*., 1995), with little change in the extent of absorption at each repeated exposure, indicating that the skin did not become more permeable with repeated exposure.

Sullivan and Conolly (1988) compared toluene levels in the blood of Sprague-Dawley rats after inhalation with those seen after subcutaneous or oral administration. They concluded that, at low exposure levels, subcutaneously administered toluene better mimics steady-state levels observed after inhalation exposure, while at high exposures, oral dosage gives satisfactory results. However, orally administered toluene was more rapidly eliminated, presumably because of first-pass oral metabolism.

Tardif *et al*. (1992, 1993a, 1997) have developed a physiologically based toxicokinetic model for toluene in rats (and humans—see Section 4.1.1). They determined the conditions under which interaction between toluene and xylene(s) occurred during inhalation exposure, leading to increased blood concentrations of these solvents, and decreased levels of the hippurates in urine. Similar metabolic interactions have been observed for toluene and benzene in rats (Purcell *et al*., 1990): toluene inhibited benzene metabolism more effectively than the reverse. Tardif *et al*. (1997) also studied the exposure of rats (and humans) to mixtures of toluene, *meta*-xylene and ethylbenzene, using their physiologically based pharmacokinetic model; the mutual inhibition constants for their metabolism were used for simulation of the human situation.

Studies with rat liver microsomes using CYP isoenzyme-specific monoclonal antibodies showed that CYP2E1 and CYP2C11/6 contribute to the oxidation of toluene to benzyl alcohol and *para*-cresol; the 2E1 activity was increased by a one-day fast as well as by ethanol treatment. Phenobarbital and 3-methylcholanthrene treatment reduced the activities of both isoenzymes. CYP2B1/2B contribute to formation of benzyl alcohol, *ortho*- and *para*-cresol, while CYP1A1/1A2 convert toluene to *ortho*-cresol exclusively. Mouse liver microsomes form more *ortho*- and *para*-cresol than those from rats. Effects on the various toluene-metabolizing CYP isoenzymes of sex, age and pregnancy in rat liver have been studied in relation to toluene oxidation. Adult males had higher activities than females, whereas at three weeks of age there was no difference (Nakajima *et al*., 1991, 1992, 1993). Exposure of rats to toluene in air for 6 h (500–4000 ppm [1900–15 200 mg/m^3]) induced the hepatic CYP2E1, CYP2B1/2 and CYP3A1/2, but reduced CYP2C11/6, and had no effect on

CYP1A1/1A2 (Wang *et al*., 1993; see Nakajima & Wang, 1994 for review). Cytochrome activities in the lung of rats, on the other hand, were reduced within 1 h by intraperitoneal toluene exposure (1 g toluene/kg bw) (Furman *et al*., 1991).

Some [*methyl*-^{14}C]toluene becomes covalently bound during incubation with rat liver microsomes (Gut *et al*., 1996).The oxidative metabolism of toluene is induced by phenobarbital (CYP2B1) and benzene (CYP2E1) exposure (Gut *et al*., 1996); phenobarbital also increases covalent binding of toluene, but the nature of this binding has not been determined. At oral and intraperitoneal doses of 100–370 mg/kg toluene, urinary thioether excretion was increased, suggesting that a mercapturate may have been present, but this has not been characterized (van Doorn *et al*., 1980). [Other authors have never mentioned mercapturates as toluene metabolites, although benzyl mercapturic acid has been identified as a metabolite of benzyl alcohol derived from benzyl acetate.]

In isolated rat hepatocytes obtained from acetone- or phenobarbital-treated rats, the metabolism of toluene at low (below 100 μM) or high (100–500 μM) concentration was increased, in particular after phenobarbital treatment. Ethanol (7 and 60 mM) inhibited the overall metabolism of toluene (sum of benzyl alcohol, benzaldehyde, benzoic acid and hippuric acid), leading to accumulation of benzyl alcohol (Smith-Kielland & Ripel, 1993).

When rats were treated with ethanol (2 g ethanol/80 mL liquid diet) or phenobarbital (4 days at 80 mg/kg intraperitoneally) before inhalation exposure to toluene (50–4000 ppm [1900–15 200 mg/m^3]), the urinary excretion of all metabolites (hippurate, acyl glucuronide, benzoate, *ortho*- and *para*-cresol) was increased, in particular after phenobarbital treatment and toluene exposures of about 2000 ppm [7600 mg/m^3] (Wang & Nakajima 1992). In the phenobarbital-treated group, the 4000-ppm exposure became quite toxic, leading to death of several rats. In rats treated only with toluene, the hippurate was by far the major metabolite (over 90%), with the acyl glucuronide appearing at higher toluene concentrations. The contribution of the cresol conjugates was minor.

4.1.3 *Comparison of human and rodent data*

In a general sense, the kinetics and metabolism of toluene in humans, rats and mice are very similar: the hippurate is in all cases by far the major metabolite, while in all species the *ortho*- and *para*-cresols are minor metabolites. To what extent formation of a potentially reactive sulfate conjugate of benzyl alcohol occurs (van Doorn *et al*., 1980; Chidgley *et al*., 1986) is uncertain, mainly because mercapturates formed from toluene have not been characterized. Similarly, whether the covalent binding observed in rat liver microsomes has any toxicological relevance is uncertain.

Although in rats and mice toluene may induce several CYP isoenzymes, exposure in humans is normally too low to be likely to cause such induction; however, toluene sniffers may expose themselves repeatedly to such high concentrations that induction could occur (Nakajima & Wang, 1994).

4.2 Toxic effects

Prolonged contact between toluene and human skin may cause nonallergic contact dermatitis. Human exposure to toluene also causes nervous system symptoms and signs and excessive exposure may cause adverse effects on the kidney and liver. Adverse effects on the nervous system have been observed in experimental animals. In studies of 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 that generally occurs concurrently with maternal toxicity has been seen in some studies in mice and rats but not rabbits (IARC, 1989a).

4.2.1 *Humans*

Increased frequency of subjective symptoms, but no indication of hepatic or renal damage, was observed among 452 toluene-exposed workers, when the actual toluene exposure was 24.7 ± 4.43 ppm [93 ± 17 mg/m^3] (geometric mean ± standard deviation) and toluene represented more than 90% of the airborne solvent vapours (Ukai *et al*., 1993). Similarly, no clinical chemical indication of hepatic damage was observed among 153 workers with exposure to toluene of 1–60 ppm [3.8–230 mg/m^3] during workdays for two to five years (Wang *et al*., 1996).

Several cases of severe metabolic acidosis after recreational toluene sniffing have been described; renal tubule damage has been proposed as the pathogenetic mechanism (Batlle *et al*., 1988; Goodwin, 1988; Pearson *et al*., 1994; Hong *et al*., 1996).

4.2.2 *Experimental systems*

Intraperitoneal injection of male Charles-Foster rats with 0.2 mL of a 5 mmol/L toluene solution on alternate days for 30 days resulted in slight increases of serum aspartate- and alanine aminotransferases, alkaline phosphatase and bilirubin (Rana & Kumar, 1993).

Inhalation exposure to toluene (1000 ppm [3800 mg/m^3], 6 h per day, five days per week for three months) of male Wistar rats had a very slight effect on the hepatic ultrastructure; limited proliferation of smooth endoplasmic reticulum and an increase of lysosomes were observed. Similar findings were observed after six months' exposure to 100 ppm [380 mg/m^3] toluene. The proliferation of smooth endoplasmic reticulum was more prominent after simultaneous exposure to 500 ppm toluene and 500 ppm *meta*-xylene (Rydzyński *et al*., 1992).

Administration of toluene (1 g/kg intraperitoneally) to male CD rats increased the formation of the fluorescent 2′,7′-dichlorofluorescein from the non-fluorescent 2′,7′-dichlorofluorescin by isolated cortical synaptosomes and microsomes, indicating generation of reactive oxygen species, but did not increase the amount of conjugated dienes (Mattia *et al*., 1991).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

In a case–control study (Lindbohm *et al*., 1990), spontaneous abortions were investigated in a cohort of women who had at some time been biologically monitored for exposure to solvents. Data on pregnancies, congenital malformations and spontaneous abortions were collected from national registries and polyclinic archives. Exposure to toluene during pregnancy of cases (women with spontaneous abortion) and controls (normal birth) was assessed by an industrial hygienist based on an extensive questionnaire. The odds ratio for exposure to toluene was slightly elevated; it was higher for 'low' exposure (1.8; 95% CI, 0.7–4.7) than for 'high' exposure (odds ratio, 1.4; 95% CI, 0.4–4.9), and the risk was limited to 'shoe work' (odds ratio, 9.3; 95% CI, 1.0–84.7; 5 cases). 'High/frequent' paternal exposure was also related to spontaneous abortions (odds ratio, 2.3; 95% CI, 1.1–4.7; 28 cases) (Taskinen *et al*., 1989). No relationship between paternal or maternal exposure and congenital malformations was observed. In a similar case–control study on solvent exposure and pregnancy outcome among laboratory assistants (Taskinen *et al*., 1994), the odds ratio for spontaneous abortion was increased among women who were exposed to toluene on at least three days a week during the first trimester of the pregnancy (odds ratio, 4.7; 95% CI, 1.4–15.9; 10 cases). No elevated odds ratio for congenital malformations was observed for any solvent, but the power of the study was limited.

In a study of spontaneous abortions (Ng *et al*., 1992), reproductive and occupational exposure history was obtained from 55 women exposed to toluene (actual mean, 88 ppm [332 mg/m^3]; range, 50–150 ppm [188–565 mg/m^3]) and two control groups (one of which consisted of a 0–25-ppm [0–94 mg/m^3] toluene exposure group). Spontaneous abortion rate was 12.4% among the 50–150-ppm exposed group, 2.9% in the 0–25-ppm exposure group and 4.5% in the control group. [The Working Group noted the low frequency of spontaneous abortions among the controls and the bias-prone method for ascertainment of cases.] Among 20 toluene-exposed rotogravure printers (median actual air toluene concentration, 36 ppm [136 mg/m^3]), plasma follicle stimulating and luteinizing hormone levels were lower than those in 44 unexposed referents (Svensson *et al*., 1992).

Several case series have demonstrated that high exposure to toluene through sniffing during pregnancy induces a syndrome that closely resembles the fetal alcohol syndrome, with pre- and postnatal growth deficiency, microcephaly and developmental delay, typical craniofacial features including micrognathia, small palpebral fissures and ear anomalies (Goodwin, 1988; Hersch, 1989; Arnold *et al*., 1994; Pearson *et al*., 1994).

4.3.2 *Experimental systems*

When pregnant Sprague-Dawley rats were exposed to toluene (6 h per day on days 7 through 17 of gestation), weight suppression of the dams and of the offspring, as well as high fetal mortality and retardation of embryonic growth, but no external, internal or skeletal anomalies, or deterioration of pre- or postweaning behavioural test scores were

observed at an exposure level of 2000 ppm [7540 mg/m^3]. No adverse effects were observed at an exposure level of 600 ppm [2260 mg/m^3] (Ono *et al*., 1995).

Toluene (1.2 g/kg bw per day) given by subcutaneous injection on days 14 through 20 to pregnant Wistar rats caused decreased body weight gain in the pups that persisted into adulthood. No such effect was observed when the same dose was administered on days 8 through 15. No malformations, variations in skeletal development or long-lasting behavioural changes were observed (da Silva *et al*., 1990). Similar reduction in the gain of body and organ weight was observed after administration of 520 mg/kg bw of toluene by gavage to Sprague-Dawley rats on days 6 through 19 of gestation. No effect on the number of implantations, stillbirths or malformations was observed (Gospe *et al*., 1994).

Sprague-Dawley rats exposed to toluene (982 ± 52 ppm [3700 ± 196 mg/m^3], 18 h per day, on seven days per week for 61 days) showed no evidence of histological damage to the testes two weeks or 10 months after cessation of the exposure (Nylén *et al*., 1989). Toluene (the concentration of which decreased during the incubations) did not induce malformations in explanted rat embryos at the highest concentrations tested (0.23–0.09 mg/L), but retarded the growth of the embryos at the lowest concentration tested (0.05–0.02 mg/L) (Brown-Woodman *et al*., 1991).

4.4 Genetic and related effects

4.4.1 *Humans*

Richer *et al*. (1993) exposed five male volunteers to 50 ppm [188.5 mg/m^3] toluene in a controlled exposure chamber for 7 h per day for three days on three occasions at two-week intervals. Blood samples were taken before and after each three-day exposure. No effects upon sister chromatid exchange frequencies were observed.

The frequencies of chromosomal aberrations were measured in peripheral blood lymphocytes of 24 men in Italy (aged 29–60 years) who had been employed for 3–15 years in a rotogravure room in which the annual mean toluene concentrations were 56–277 ppm [210–1040 mg/m^3]. They were compared with data for 24 male, age-matched controls from the general population. No significant difference was observed (Forni *et al.*, 1971). [The Working Group noted that smoking and alcohol drinking 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 [sex unspecified]) exposed to toluene for 1.5–26 years (average level, 100–200 ppm [377–750 mg/m^3]) with occasional excursions to 500–700 ppm [1900–2640 mg/m^3] in a rotogravure printing factory in comparison with 42 healthy, but unmatched unexposed male and female adult controls (Funes-Cravioto *et al.*, 1977). [The Working Group noted that smoking and alcohol drinking habits were not considered, and that the appropriateness of the controls cannot be judged.]

No differences were found in the frequencies of chromosomal aberrations or sister chromatid exchanges in the peripheral blood lymphocytes of 32 men (aged 21–50 years) employed in a rotogravure factory in Finland and exposed to toluene (7–112 ppm

[26–420 mg/m^3]) for 3–35 years in comparison with 15 men (aged 27–62 years) from a research institute. Benzene contamination of the toluene had been checked since 1962 and was always below 0.05%, averaging 0.006% (Mäki-Paakkanen *et al.*, 1980). No increase in the frequency of sister chromatid exchanges was observed in seven workers in the Swedish paint industry who were exposed to various solvents, including more than 100 mg/m^3 toluene, each compared with a control matched by age, sex, place of residence and smoking habits (Haglund *et al.*, 1980; see also IARC, 1989b). [The Working Group noted the small number of workers studied.]

Bauchinger *et al.* (1982) reported increases in the frequencies of sister chromatid exchanges, chromatid breaks, chromatid exchanges and gaps in the peripheral lymphocytes of 20 workers (aged 32–60 years) 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 with 24 matched controls from the same factory. For breaks, exchanges and sister chromatid exchanges per cell ± SE, respectively, the frequencies were: controls, 0.0019 ± 0.0005, 0.004 ± 0.0002, 8.18 ± 0.25; toluene-exposed, 0.0036 ± 0.0002, 0.0015 ± 0.0005, 9.62 ± 0.37. Much of the increase in breaks was due to a single individual and the difference in sister chromatid exchanges was partially due to those who smoked tobacco. For sister chromatid exchanges, grouped according to smoking habits, the results were: (*a*) nonsmokers; controls, 7.75 ± 0.25 (n = 15); toluene-exposed, 8.55 ± 0.27 (n = 8); (*b*) smokers; controls, 8.89 ± 0.41 (n = 9); toluene-exposed, 10.33 ± 0.49 (n = 12). A significant increase in gaps was also found, although this was small: controls, 0.019 ± 0.003; toluene-exposed, 0.0248 ± 0.0024. In an abstract, a synergistic effect of smoking and exposure to toluene on the frequency of sister chromatid exchanges was also reported (Bauchinger *et al.*, 1983). Schmid *et al.* (1985) examined lymphocytes from 27 workers in the same plant who, at the time of blood sampling, had not been exposed to toluene for from four months to five years. In comparison with 26 controls, those who had been exposed within the last two years (n = 13) showed higher numbers of chromatid breaks per 100 cells, whereas those not exposed for more than two years (n = 14) had the same chromatid break frequency as the controls: 0.20 ± 0.05; not exposed to toluene > 2 years, 0.20 ± 0.06; not exposed to toluene < 2 years, 0.39 ± 0.07.

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

In 1990, Pelclová *et al.* extended their analysis of chromosome aberrations in rotogravure printers, carrying out chromosome analysis in peripheral lymphocytes of three groups of workers. There were 42 rotogravure printers (37 smokers, 5 nonsmokers; mean age, 39 years) exposed to rotogravure printing dyes and highly purified toluene at working air concentrations of 104–1170 ppm [390–4380 mg/m^3] for 12 years on average, 28 office and technical employees of the same plant (17 smokers, 11 nonsmokers; mean age, 44 years), more than half of whom worked for 2 h daily in the rotogravure workshop and a control population consisting of 32 employees (17 smokers, 15 nonsmokers; mean

age, 37 years) from a nearby brewery and dairy. Air pollution was stated to be 'high' in this area of the town. Measurements of blood toluene and urinary hippuric acid were made at the end of a work shift. The values (± standard deviation) for the controls, office/technical workers and printers, respectively, were: blood toluene – not measured, 10.3 ± 3.1 and 124.0 ± 63.1 μmol/L; urinary hippuric acid – 6.31 ± 3.41, 12.89 ± 4.64 and 38.28 ± 17.53 mmol/L. Increased incidences of chromatid breaks were observed in the printer and the office/technical groups, while gaps per cell and chromosomal exchanges were increased only in the office/technical group. Chromatid breaks per cell, the most prominent chromosomal damage, in the three groups were: 0.0153 ± 0.0119, 0.0211 ± 0.0143 ($p < 0.01$) and 0.0250 ± 0.0195 ($p < 0.01$), while the frequencies of chromosomal exchanges and gaps were significantly increased only in the office/technical workers: chromosomal exchanges per cell were 0.0013 ± 0.0042, 0.0029 ± 0.0045 ($p < 0.05$) and 0.0007 ± 0.0026; gaps per cell were 0.0288 ± 0.0209, 0.0443 ± 0.0278 ($p < 0.05$) and 0.0371 ± 0.0202. The high incidence of aberrations could be explained by the exposure to toluene, but an influence of rotogravure printing dyes cannot be excluded. Smoking and high air pollution in the urban area were contributing factors in all three groups.

Nise *et al*. (1991) compared the frequencies of chromosomal aberrations and nuclei in lymphocytes of 21 men (aged 30–63 years; 10 smokers, 11 nonsmokers) exposed to toluene for 0.5–37 years during their employment as rotogravure printers and 21 controls (aged 30–63 years [sex not stated]; 13 smokers, 8 nonsmokers). The median time-weighted air level of toluene over a one-week period in 1986 was 150 mg/m^3 for the printers and the median blood concentrations on the day of lymphocyte sampling were: controls ≤ 0.01 μmol/L; toluene-exposed, 1.6 μmol/L (range, 1.0–6.6). Earlier toluene exposures were estimated to be about 800 mg/m^3 in the 1970s and about 1500 mg/m^3 in the 1950s and 1960s (when contaminating benzene exposures would have been about 150 mg/m^3). Lymphocytes were treated with either phytohaemagglutinin (PHA), which stimulates T cells, or pokeweed mitogen (PWM), which stimulates B cells. There was a significant increase in the frequency of micronuclei in PWM-stimulated peripheral blood lymphocytes in the printers, as compared to the controls (2.8‰ versus 1.5‰, $p = 0.03$; all p adjusted for age and smoking). The frequency of small micronuclei (size ratio micronuclei/main nucleus ≤ 0.03) in PWM-stimulated lymphocytes was associated with the exposure (1‰ versus 0.3‰; $p = 0.05$). Furthermore, among the exposed subjects there was an association between blood toluene and small micronuclei (0.17‰ per mmol/L; $p = 0.0005$). Small micronuclei in PHA-treated cultures showed no association with any exposure parameter. However, in the printers, an estimated cumulative exposure index was weakly correlated with the frequency of total micronuclei in PHA-stimulated cells (0.00003‰ per mg/m^3 × year; $p = 0.07$). Among the printers, chromosomal breaks in PHA-stimulated cells were associated with the duration of earlier benzene-contaminated toluene exposure (0.03% per year; $p = 0.01$); benzene contamination was about 10% up to 30 years previously, around 0.5% more recently and falling to < 0.01% at the time of the study.

Popp *et al.* (1992) analysed the frequencies of sister chromatid exchanges and of DNA strand breakage/cross-linking (alkaline elution assay) in a group of 20 women (45 smokers, 16 nonsmokers) working in a shoemaking plant who were exposed to benzene (mean, 4.16 mg/m^3) and toluene (mean, 70.06 mg/m^3) for at least eight years; the results were compared with those from a group of 20 non-exposed women (4 smokers, 16 non-smokers) from the general population. Sister chromatid exchange frequencies were significantly higher, but only marginally so, among the solvent-exposed women compared with all controls: controls, 6.05 ± 1.01; toluene-exposed, 6.55 ± 0.70 ($p < 0.05$, Wilcoxon test); and among the smokers in the control group compared with nonsmokers in the same group. No comment was made upon the higher average sister chromatid exchange frequency in the smoking controls compared with the smoking toluene-exposed group: controls, 7.19 ± 1.43; toluene-exposed, 6.54 ± 0.32. The relative DNA elution rate through polycarbonate filters was significantly increased ($p < 0.001$). The elution rate through polyvinylidene fluoride (HVLP) filters also showed a tendency to increase ($p = 0.052$). The sister chromatid exchange rates of the female workers were significantly correlated ($p < 0.01$) with the relative DNA elution rate through HVLP filters. There was no correlation with the actual benzene and toluene uptake measured by personal air monitoring. Four months after cessation of work, DNA strand breakage decreased significantly ($p < 0.05$) in blood samples of six reinvestigated exposed women.

4.4.2 *Experimental systems* (see Table 2 for references)

The genetic and related effects of toluene have been reviewed (Dean, 1978, 1985; Fishbein, 1988; IARC, 1989a; McGregor, 1994).

When tested in bacteria, toluene did not induce prophage, differential killing or gene mutation. In single studies with *Saccharomyces cerevisiae*, toluene did not induce either gene conversion or gene mutation (WHO, 1985, secondary description).

Toluene did not induce sex-linked recessive lethal mutations or translocations, but did induce sex-chromosome loss and nondisjunction in male *Drosophila melanogaster* and induced mitotic arrest (C-mitosis) in embryos of the grasshopper, *Melanoplus sanguinipes.*

Toluene did not enhance morphological transformation of Syrian hamster embryo cells by the SA7 adenovirus or, as reported in an abstract, disruption of gap-junctional intercellular communication in Chinese hamster V79 cells (Awogi *et al*., 1986).

Toluene induced DNA single-strand breaks (as measured by alkaline elution) in primary cultures of rat hepatocytes but did not cause DNA damage or repair, as measured by the 'nick-translation' assay, in cultured human fibroblasts. Toluene induced *tk* locus mutations in mouse lymphoma L5178Y cells in one study but not in another which was reported as an abstract (Lebowitz *et al*., 1979). It did not induce sister chromatid exchanges or chromosomal aberrations in either Chinese hamster ovary cells (WHO, 1985, secondary description) or human lymphocytes *in vitro*. [The Working Group noted that the tests with human lymphocytes were conducted only without an exogenous metabolic system.]

In a single study, toluene induced kinetochore- and centromere-negative micronuclei in human MCL-5 cells that stably express cDNAs encoding human CYP1A2, CYP2A6,

Table 2. Genetic and related effects of toluene

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, Prophage induction, SOS repair test, DNA strand breaks, cross-links	–	–	100	Nakamura *et al*. (1987)
PRB, Prophage induction, *Escherichia coli* WP2s (λ)	–	–	NG	Rossman *et al*. (1991)
ECL, *Escherichia coli pol*A, differential toxicity (liquid suspension test)	–	–	400000	McCarroll *et al*. (1981b)
ERD, *Escherichia coli rec* strains, differential toxicity	–	–	400000	McCarroll *et al*. (1981b)
BSD, *Bacillus subtilis rec* strains, differential toxicity	–	–	127000	McCarroll *et al*. (1981a)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2150	Nestmann *et al*. (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1000	Bos *et al*. (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	2500	Spanggord *et al*. (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	167	Haworth *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1000	Connor *et al*. (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	2150	Nestmann *et al*. (1980)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1000	Bos *et al*. (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	2500	Spanggord *et al*. (1982)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	167	Haworth *et al*. (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	2150	Nestmann *et al*. (1980)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1000	Bos *et al*. (1981)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	2500	Spanggord *et al*. (1982)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	167	Haworth *et al*. (1983)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	2150	Nestmann *et al*. (1980)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	1000	Bos *et al*. (1981)

Table 2 (contd)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	2500	Spanggord *et al*. (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	2150	Nestmann *et al*. (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1000	Bos *et al*. (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	2500	Spanggord *et al*. (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	167	Haworth *et al*. (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1000	Connor *et al*. (1985)
SAS, *Salmonella typhimurium* UTH8413, reverse mutation	–	–	1000	Connor *et al*. (1985)
SAS, *Salmonella typhimurium* UTH8414, reverse mutation	–	–	1000	Connor *et al.* (1985)
Melanoplus sanguinipes embryo, C-mitosis	+		40 000 ppm inh	Liang *et al*. (1983)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	–		13 000 ppm feed	Rodriguez Arnaiz & Villalobos-Pietrini (1985b)
DMH, *Drosophila melanogaster*, heritable translocations	–		13 000 ppm feed	Rodriguez Arnaiz & Villalobos-Pietrini (1985b)
DMN, *Drosophila melanogaster*, aneuploidy	+		8700 ppm feed	Rodriguez Arnaiz & Villalobos-Pietrini (1985a)
DIA, DNA strand breaks, rat hepatocytes *in vitro*	+	NT	3	Sina *et al*. (1983)
G5T, Gene mutation, mouse lymphoma L5187Y cells, *tk* locus *in vitro*	+	+	200	McGregor *et al*. (1988)
T7S, Cell transformation, SA7/Syrian hamster embryo cells *in vitro*	–	NT	1000	Casto (1981)
DIH, DNA damage, human diploid fibroblasts *in vitro*	–	NT	276	Snyder & Matheson (1985)

Table 2 (contd)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
RIH, DNA repair (nick translation), human diploid fibroblasts *in vitro*	–	NT	276	Snyder & Matheson (1985)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	–	NT	1500	Gerner-Smidt & Friedrich (1978)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	–	NT	92	Richer *et al*. (1993)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	–	NT	1500	Gerner-Smidt & Friedrich (1978)
AIH, Aneuploidy, AHH-1 cells, kinetochore staining *in vitro*	(+)	NT	460	Doherty *et al*. (1996)
AIH, Aneuploidy, MCL-5 cells, kinetochore staining *in vitro*	(+)	NT	460	Doherty *et al*. (1996)
AIH, Aneuploidy, h2E1 cells, kinetochore staining *in vitro*	+	NT	184	Doherty *et al*. (1996)
MIH, Micronucleus test, AHH-1 cells *in vitro*	(+)[c]	NT	460	Doherty *et al*. (1996)
MIH, Micronucleus test, MCL-5 cells *in vitro*	+[c]	NT	9.2	Doherty *et al*. (1996)
MIH, Micronucleus test, h2E1 cells *in vitro*	+[c]	NT	9.2	Doherty *et al*. (1996)
DVA, DNA strand breaks, female BDF_1 mouse blood, bone marrow and liver *in vivo* (comet assay)	–		500 ppm inh 6 h/d 5 d/wk 8 wk	Plappert *et al*. (1994)
MVM, Micronucleus test, CD-1 mouse bone marrow *in vivo*	–		1720 po × 2	Gad-el-Karim *et al*. (1984)
MVM, Micronucleus test, male NMRI mouse bone marrow *in vivo*	+		217 po × 2	Mohtashamipur *et al*. (1985)
MVM, Micronucleus test, CD-1 mouse bone marrow *in vivo*	–		860 po × 1	Gad-el-Karim *et al*. (1986)
MVM, Micronucleus test, male $B6C3F_1$ mouse bone marrow *in vivo*	+		104 ip × 2	Mohtashamipur *et al*. (1987)
MVR, Micronucleus test, male Sprague-Dawley rat bone marrow *in vivo*	(+)		217 ip × 2	Roh *et al*. (1987)

Table 2 (contd)

Test system	Result[a]		Dose (LED or HID)[b]	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
CBA, Chromosomal aberrations, rat bone marrow *in vivo*	+		800 sc × 12	Dobrokhotov (1972)
CBA, Chromosomal aberrations, rat bone marrow *in vivo*	+		1000 sc × 12	Lyapkalo (1973)
CBA, Chromosomal aberrations, male albino rat bone marrow *in vivo*	+		162 ppm inh 4 h/d 5 d/wk 16 wk	Dobrokhotov & Enikeev (1977)
CBA, Chromosomal aberrations, rat bone marrow *in vivo*	–		1.5 ppm inh 4 h/d 5 d/wk 16 wk	Aristov *et al*. (1981)
CBA, Chromosomal aberrations, CD-1 mouse bone marrow *in vivo*	–		1720 po × 2	Gad-el-Karim *et al*. (1984)
CBA, Chromosomal aberrations, male Sprague-Dawley rat bone marrow *in vivo*	+		435 ip × 2	Roh *et al*. (1987)
SPM, Sperm morphology, (CBA × BALB/c) mice *in vivo*	–		900	Topham (1980)

[a] +, positive; (+), weak positive; –, negative; NT, not tested
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; NG, not given; ip, intraperitoneal; sc, subcutaneous; inh, inhalation
[c] Primarily kinetochore-negative micronuclei (greater percentage stain kinetochore-positive at 2–5 mM doses in MCL-5 and h2E1 cells)

CYP3A4, CYP2E1 and epoxide hydrolase and in h2E1 cells which contain a cDNA for CYP2E1; kinetochore-positive micronuclei were induced only at the highest dose. AHH-1 cells constitutively expressing CYP1A1 showed a small increase in micronucleus frequency.

In the single cell gel electrophoresis assay, no DNA breakage/alkali-labile sites were detected in blood, bone marrow or liver of mice exposed to 500 ppm [1900 mg/m^3] toluene for 6 h per day on five days per week for eight weeks. Toluene was reported to induce chromosomal aberrations in the bone-marrow cells of rats following exposure by inhalation and subcutaneous or intraperitoneal injection but not in that of orally dosed mice or in other single rat studies with exposure by inhalation (Donner *et al*., 1981, abstract only), oral gavage (Feldt *et al*., 1985) or intraperitoneal injection (WHO, 1985, secondary description). The frequency of micronucleated bone-marrow cells of rats given intraperitoneal injections was slightly increased, while micronuclei were more frequent in toluene-treated mice after intraperitoneal injection, but not after oral dosing in a different laboratory or after intraperitoneal injection with doses of up to 1000 mg/kg bw (WHO, 1985, secondary description). It was noted that pretreatment of male NMRI mice with inducers (phenobarbital, Aroclor 1254, 3-methylcholanthrene) of cytochrome P450 enhanced the frequency of micronuclei induced by toluene, while simultaneous injections of toluene with inhibitors (metyrapone, α-naphthoflavone) decreased the observed clastogenic activities (Mohtashamipur *et al.*, 1987).

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 greatly reduced the frequency of micronuclei induced by 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, oral administration of toluene did not induce dominant lethal effects in random-bred male SHR mice (Feldt *et al.*, 1985).

Toluene did not induce sperm-head abnormalities in mice.

Toluene can activate cyclin-dependent kinase 2 in rat liver epithelial (RLE) and HL60 cells *in vitro* and it also causes hyperphosphorylation of p53 and pRB105 in these cells. These activities are shared with benzene but, unlike benzene, toluene did not increase the p53–DNA site-specific binding in RLE cells (Dees & Travis, 1994; Dees *et al*., 1996).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Toluene is an industrial chemical produced in high volume, that is used in blending gasoline and as a solvent. Occupational exposure to toluene is extensive and occurs in its production and during the manufacture and use of toluene-containing paints, thinners, cleaning agents, coatings and adhesives. It is commonly detected in ambient air and at low levels in water.

5.2 Human carcinogenicity data

Toluene was mentioned as an exposure in eight studies. Two were community-based case–control studies, one of which involved brain cancer and one involved several types of cancer. Of the six industry-based studies, three were analysed as cohort studies and three were configured as nested case–control studies of one or a few types of cancer. In two of the studies, that of shoe-manufacturing workers in the United States and particularly that of Swedish rotogravure printers, it was believed that toluene was the predominant exposure; in the other studies, there were probably concomitant exposures. Cancers of most sites were not significantly associated with toluene exposure in any study. Stomach cancer mortality was significantly elevated in the Swedish rotogravure printers study, it was slightly, though not significantly, elevated in two other studies, and it was not associated at all in a fourth. Rates of lung cancer were significantly elevated in the cohort of shoe manufacturers and in the Swedish cohort of rotogravure printers, but was not associated at all in two other studies. Colorectal cancer was significantly elevated in the Swedish rotogravure printers study and in the Canadian case–control study, and colon cancer was nonsignificantly elevated in the shoe manufacturers cohort. While results on leukaemias and lymphomas generally showed no association, these were based on small numbers. Considering the multiple exposure circumstances in most studies and the weak consistency of findings, these results are not strong enough to conclude that there is an association.

5.3 Animal carcinogenicity data

Toluene was tested for carcinogenicity by inhalation exposure in one study in mice and in one study in rats. No significant increase in the incidence of tumours was observed. Repeated application of toluene to the skin of mice did not result in an increased incidence of skin tumours.

5.4 Other relevant data

Toluene is mainly converted to benzyl alcohol and excreted as hippurate. Its toxicokinetics in humans have been extensively studied.

Toluene toxicity is most prominent in the central nervous system after acute and chronic exposure. Reproductive toxicity has been observed in exposed humans and rats.

In the more recent cytogenetic studies in occupationally exposed populations, increases in chromosomal aberrations (two studies), micronuclei (one study) and of DNA strand breaks (one study) have been described. These effects have also been observed in rats and mice in some studies and in cultured mammalian cells. DNA adducts have not been detected.

5.5 Evaluation

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

There is *evidence suggesting lack of carcinogenicity* of toluene in experimental animals.

Overall evaluation

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

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