Canadian Environmental Protection Act

PRIORITY SUBSTANCES LIST

SUPPORTING DOCUMENT

TOLUENE

(UNEDITED VERSION)

NHW/DOE January 1993

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1 IDENTITY OF SUBSTANCE

Toluene is a clear, colourless liquid with a sweet, pungent odour (NIOSH, 1973), molecular formula $C_6H_5CH_3$, and structural formula as shown in Figure 1. Synonyms for toluene (CAS Registry No. 108-88-3) include methylbenzene, toluol, and phenylmethane. Trade names include Antisal 1a and Methacide.

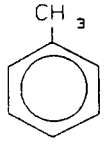

Figure 1. Molecular Structure of Toluene

Technical products in which toluene is the principal ingredient are commonly produced from petroleum by catalytic dehydrogenation of fractions containing methylcyclohexane. The purity and nature of contaminants present in toluene vary widely owing to differences in the methods used for toluene production. Highly purified reagent grade toluene is 99.99% pure, but the industrial grade is only 98% pure, being contaminated with xylenes and traces of benzene (DOE, 1984). In the past, commercial grade toluene may have contained 2% to 15% benzene and up to 10% xylenes (Low *et al.*, 1988).

2 PHYSICAL AND CHEMICAL PROPERTIES

Some physical and chemical properties of toluene under standard conditions are presented in Table 2.1. Toluene is a volatile liquid which is flammable and explosive, with a relatively high vapour pressure (3.8 kPa at 25°C). The solubility of toluene in fresh water is approximately 515 mg/L at 25°C and it is miscible with most organic solvents; its density is 0.867 $g \cdot cm^{-3}$. The log octanol/water partition coefficient of toluene is moderately low (log K_{ow} = 2.69), reflecting its relatively high water solubility. The Henry's constant for toluene is 680 $Pa \cdot m^3 \cdot mol^{-1}$, reflecting its high vapour pressure. Toluene does not absorb ultraviolet light of wavelengths reaching ground level (NRC, 1980), nor infrared radiation at wavelengths of 7 to 13 μm (Sadtler Research Laboratories, 1982).

3 PRODUCTION, USE AND RELEASE TO THE ENVIRONMENT (SOURCES)

3.1 Production and Use

The production capacities, supply, and demand for isolated (purified) toluene in Canada are presented in Table 3.1; toluene present as a natural component in gasoline is not included in the table (see below). The production capacities for toluene totalled 630 kilotonnes in 1989, with forecast production of 438 kilotonnes and imports of 45 kilotonnes, for a total supply of 483 kilotonnes (Corpus Information Services, 1989; Chem-Intell, 1989). Exports for 1989 were projected to be 220 kilotonnes, resulting in a total domestic consumption of 263 kilotonnes of isolated toluene. Toluene is produced at four plants in the Sarnia/Corunna region and at two plants in Montreal (Corpus Information Services, 1989). Toluene production has averaged 65% of production capacity in the 1980s.

The dominant end-use for refined toluene in Canada is the production of benzene by the hydrodealkylation process (Table 3.1). Toluene is also being sought world-wide as a replacement for lead as an octane enhancer in gasoline. As this use increases, the importance of the use of toluene in the hydrodealkylation process is expected to decline, due to the increasing cost of toluene compared to benzene.

Use of toluene as a solvent has steadily increased over the past decade, with about 58 kilotonnes being used in 1989 (Corpus Information Services, 1989). Toluene is used as a solvent in paints, lacquers, inks, adhesives, cleaning agents, and for chemical extractions. As of November 1991, 24 pesticides registered under the *Pest Control Products Act* contained toluene as a solvent (Davis, 1991). These included 20 herbicide or insecticide formulations and four pesticidal paints. Based on data from the Survey of Pesticide Registrants for 1990 (Brien, 1991), it can be estimated that about 5 tonnes of toluene were used as part of field-applied pesticide formulations in 1990 (Chénier, 1992); this accounts for about 0.01% of total solvent uses. Other uses for toluene include the chemical synthesis of other organic chemicals, dyes, and pharmaceuticals (Levelton and Associates Ltd., 1990).

Canada's domestic consumption of toluene is expected to grow only modestly in the near future. Exports to the U.S.A. are expected to continue expanding as toluene use in gasoline blending increases. The 1993 forecast for capacity, production and imports are 595, 500, and 40 kilotonnes, respectively. The total domestic demand and exports are forecasted to be 290 and 250 kilotonnes, respectively (Corpus Information Services, 1989). Canadian toluene production capacity represented only 10% of total North American capacity in 1985 (Corpus Information Services, 1988).

In addition to the above uses for isolated toluene, toluene is a normal component of petroleum along with benzene and xylenes (the aromatic "BTX" components of petroleum) (Kirk

et al., 1983). All toluene present in gasoline in Canada occurs as a result of the normal petroleum refining process; no isolated toluene is added when blending. An estimated 34,000 megalitres of gasoline are sold annually in Canada (Oilweek, 1988); most of this toluene is burned during normal engine operation. Based on a survey of Canadian gasolines carried out in 1989, the toluene content of gasolines averages 8.3% by weight, ranging from 2 to 16% (Madé, 1991). Thus, an estimated 2,000 kilotonnes of toluene is present in the gasoline sold annually in Canada. Therefore, the Canadian total yearly supply of toluene, including both isolated toluene and toluene as a component of gasoline, is 2,483 kilotonnes, and the total yearly domestic consumption is 2,263 kilotonnes.

3.2 Release to the Environment

Toluene is a natural component of coal and petroleum (Kirk *et al.*, 1983). It may thus be introduced into the environment through petroleum seepage and weathering of exposed coal-containing strata; however, the magnitude of the contribution of such releases to toluene concentrations in the environment is unknown (USEPA, 1987a). Toluene is also produced by incomplete combustion of natural fuel materials, making it a component of forest fires (MRI, 1989). Toluene is present in volcanic gases (Isidorov *et al.*, 1990) and is released from vegetation (NRC, 1980). It has been estimated that the amount of toluene released from natural sources is negligible compared to the emissions from anthropogenic sources (Syracuse Research Corporation, 1983).

In addition to the toluene initially present in gasoline, more toluene is formed during combustion in gasoline engines by cracking, disproportionation, and oxidation of other volatile aromatics present in the gasoline (Fishbein, 1985). Given its presence in crude and refined petroleum, toluene can be released to the environment whenever petroleum is released (Syracuse Research Corporation, 1983).

Major sources of emissions of toluene to the atmosphere in Canada are presented in Table 3.2. The principal source of airborne emissions of toluene is solvent uses, accounting for an estimated 51.0% (54.0 kilotonnes/year) of total emissions (106 kilotonnes/year) (see list of references in Table 3.2). Light duty automobiles produce an estimated 32.1% (34.0 kilotonnes/year) of total emissions; total vehicle sources, including light and heavy duty vehicles, marine/air/rail transport and off-road vehicles, account for 37.6% (39.8 kilotonnes/year) of total emissions. Evaporative losses from gasoline marketing account for 3.1% (3.3 kilotonnes/year) of total emissions. Coke oven emissions contribute 1.0% (1.1 kilotonnes/year) of total emissions. Other industrial processes such as production of toluene, benzene and benzoic acid contribute a much smaller proportion of estimated atmospheric emissions (0.2%).

Total emissions of toluene to the atmosphere are expected to decline in the future, primarily due to the planned reduction of volatile organic compounds (VOCs) from light duty

vehicle emissions and the efforts to reduce releases of VOCs from a variety of other sources for purposes of ground-level ozone control (CCME, 1990). For example, by 2005, total VOC emissions from light duty vehicles and solvents are expected to decrease by 53% and 14%, respectively, from their 1985 levels if all control measures identified in Phase I of the NOx-VOC Management Plan are implemented (CCME, 1990). Equivalent reductions for toluene releases from these two sources would result in releases of 16 and 46 kilotonnes per year for light-duty vehicles and solvents, respectively, by 2005.

Toluene is also released to the atmosphere from landfills. The average toluene emissions in landfill gas (predominantly methane) measured at two municipal sites in the state of Washington in the U.S.A. has been reported to be about 4 tonnes of toluene per 20 kilotonnes of methane (Wineman *et al.*, 1985). The estimated total annual atmospheric release of toluene from municipal landfills in Canada is 400 tonnes/year (Wineman *et al.*, 1985; Wood and Porter 1986).

Toluene is emitted to the air in cigarette smoke. It has been estimated that there are 160 μg of toluene per cigarette in mainstream smoke (USDHHS, 1986). In Canada, approximately 56 billion cigarettes were consumed in 1989 (Kaiserman and Allen, 1990). It can be estimated, therefore, that approximately 9 tonnes of toluene are released to the atmosphere each year from this source.

Toluene can be released to the soil through spills of petroleum and other products containing toluene and from leaking underground storage tanks, but the magnitude of such entry is not known (Bobra, 1991). Toluene is released into the soil at waste disposal sites (Barker, 1987; Johnson *et al.*, 1989; Lesage *et al.*, 1990). Toluene can also be released to the soil through pesticide application. The 20 registered herbicide and insecticide formulations containing toluene as a solvent are applied directly to the soil; it can be expected that much of the 5 tonnes/year of toluene in these formulations reaches the soil surface. Based on the application rates recommended for these products, it can be estimated that not more than 5 g/ha of toluene would be applied at any one time (Chénier, 1992).

Toluene can be released into water through petroleum spills (Gilbert *et al.*, 1983) and in industrial and municipal effluents (MOE, 1989a; NAQUADAT, 1991). Total environmental loadings from such sources in Canada are not available. Estimates for the U.S.A. indicate that gasoline and oil spills account for about 90% of all toluene releases into water (Gilbert *et al.*, 1983).

Gilbert *et al.* (1983) estimated that in the U.S.A. in 1978, 99.8% of all toluene releases were directly to the atmosphere, 0.1% to water, and 0.1% to land. Assuming similar proportions for Canada, estimates for releases to water and to land would be 0.1 kilotonnes to

soil and 0.1 kilotonnes to water, based on Canadian atmospheric releases of about 100 kilotonnes per year.

4 ENVIRONMENTAL TRANSPORT, TRANSFORMATION, AND CONCENTRATIONS

4.1 Distribution and Transport

4.1.1 Distribution

Based on toluene's relatively high vapour pressure, moderate water solubility, and low octanol/water partition coefficient, it can be predicted that toluene will be present in the environment primarily in air; it should not accumulate to a significant extent in water, soil, sediment, or biota. Modelling based on toluene's physical/chemical properties tends to confirm these expectations, whether degradation rates are considered or not in the modelling. Mackay *et al.* (1992) presented Levels I, II, and III Fugacity modelling for toluene. Levels I and II modelling indicated that more than 99% of toluene should be distributed into the atmosphere. Based on the assumption that most toluene is released to the atmosphere (section 3.2 above), the level III Fugacity modelling indicates that over 99% of toluene released will be found in the atmosphere; in cases where toluene would be released constantly to the water or soil, modelling indicates a greater proportion of toluene in those compartments. Slooff and Blokzijl (1988) predicted that less than 0.1% of toluene in the environment would be present in sediments, 0.8% in the water (dissolved), 0.6% in the soil, and 98.6% in the atmosphere. Modelling estimates of the distribution of toluene in the environment based on United Kingdom compartment sizes and releases indicated that more than 99% of released toluene should be present in the atmosphere (Nielsen and Howe, 1991). These model calculations assume steady-state or equilibrium distributions. Environmental compartmentalization in the vicinity of the points of release of toluene may vary from the predictions.

Volatilization is the most important transport process in determining the distribution of toluene in the environment. Because of its physical properties, toluene should be rapidly lost from the water column (Syracuse Research Corporation, 1983). The rate is dependent on the water depth, but for a 1 metre depth, the half-life in still water has been estimated at 5.2 hours; it would be shorter for turbulent water (Mackay and Leinonen, 1975). SRI (1980) calculated volatilization rates of 8 days from lakes and 1 to 2 days from rivers. Estimates for the volatilization half-lives from rivers and streams range from 36 minutes to 47 days (USEPA, 1987a). Studies of oil spills in seawater have shown that virtually all toluene in the oil should be lost to the atmosphere within a few days (McAuliffe, 1977).

Half-lives for volatilization from moist surface soils varied from less than 1 day to less than 1 month, depending on the depth of soil considered (SRI, 1980). At depths greater than 10 cm, biodegradation replaces volatilization as the major cause of toluene removal.

4.1.2 Air Transport

Toluene's vapour pressure, water solubility, and lack of strong sorption to soils result in its volatilization to the atmosphere. There is little evidence to indicate that toluene is adsorbed to air particles in the atmosphere. Its movement is subject to removal processes such as wash-out with rain and photodegradation. While washout is considered an insignificant removal process for toluene from air (NRC, 1980; SRI, 1980), photodegradation (see Section 6.2.1) makes long range transportation unlikely.

4.1.3 Water Transport

It has been estimated that 5% of the toluene present in a pond would be adsorbed to suspended sediments, assuming a concentration of suspended sediments of 300 mg/L and an organic carbon content of the sediment of 5% (SRI, 1980). Most adsorbed toluene in water is associated with particles with diameters of less than 10 μm (Wakeham *et al.*, 1985), which are readily transported with the water mass. It has been assumed that water-borne export and volatilization are the predominant processes for removal of toluene from rivers and lakes, respectively (Syracuse Research Corporation, 1983).

4.1.4 Soil Transport and Ground-Water Movement

Gilbert *et al.* (1983) calculated a half-life for volatilization of toluene from the soil surface of 9 seconds.

When water containing toluene was added to 140 cm soil columns at high rates (14 cm of water per day for 45 days), an average of 52% of applied toluene was volatilized from sandy soils with low organic content (0.087% organic carbon) (Wilson *et al.*, 1981); 7.5% of applied toluene eluted through the column and 40.5% was lost, presumably by biodegradation. Volatilization may be lower from soils with high organic contents due to their sorption properties (Syracuse Research Corporation, 1983; Gilbert *et al.*, 1983). Coefficients of adsorption (K_{ads}) for toluene indicate that adsorption increases with increasing soil organic matter (Seip *et al.*, 1986):

forest soil	0.2% organic carbon	$K_{ads} = 0.11$
agricultural soil	2.2% organic carbon	$K_{ads} = 2.08$
forest soil	3.7% organic carbon	$K_{ads} = 4.95$

Based on diffusion coefficients for toluene, volatilization half-lives were calculated for dry soil and wet (25% water content by volume) soil (SRI, 1980). For the top centimetre of soil, the half-lives were less than one hour for dry soil and less than one day for wet soil. For the top 10 centimetres of soil, half-lives were less than three days for dry soil and less than one

month for wet soil. Because the rate of diffusion of toluene is much slower in water than in air, the rates of volatilization are much slower when the soil is saturated with water.

Clay retards downward movement of toluene. Concentration of toluene in pore water of a natural clay deposit below a 5-year old waste disposal site in southern Ontario declined from 1-6 mg/L present in the waste at the surface of the clay deposit, to undetectable levels at a depth of 15 cm (Johnson *et al.*, 1989).

4.2 Environmental Transformation

4.2.1 Atmospheric Degradation

The fate of toluene in the atmosphere has been the subject of several comprehensive reviews (NRC, 1980; Syracuse Research Corporation, 1983; Dumdei and O'Brien, 1984; Finlayson-Pitts and Pitts, 1986; Dumdei *et al.*, 1988; Atkinson, 1990; and others). Toluene is rapidly removed from the atmosphere by photo-oxidation, principally by hydroxyl radicals, the concentration of which is dependent upon solar intensity, temperature, and local trace gas composition of the atmosphere. Principal products of the photo-oxidation of toluene are o-cresol and benzaldehyde. Minor products include m-nitrotoluene, benzyl nitrate, m- and p-cresol and oxidized ring fragmented compounds.

The minimum tropospheric lifetime for toluene has been calculated as 4.5 hours (Finlayson-Pitts and Pitts, 1986). Based on the data and equations given by Güsten *et al.* (1984) for the calculation of a "safe upper limit for the persistence of an organic compound in the troposphere", the predicted half-life for toluene is 3.1 days. The mean atmospheric half-life of toluene in the troposphere has been estimated to be about 4 days (43 daylight hours) but could be as little as 0.8 days in hot weather or as long as 10 days in northern latitudes in winter (NRC, 1980; Syracuse Research Corporation, 1983). The IPCS (1985) reported estimated atmospheric life times at high altitudes in the winter to be in the order of months; summer values for these regions were approximately 4 days. Toluene is not considered to be a significant contributor to stratospheric processes involved in the ozone layer or in global climate change (NRC, 1980).

4.2.2 Aquatic Degradation

In lakes and ponds, it has been estimated that biodegradation of toluene takes place at rates with half-lives from less than 1 week to several weeks, depending on the extent of acclimatization of organisms (SRI, 1980). Biodegradation may predominate over volatilization in the removal of toluene from surface waters in warm weather (Wakeham *et al.*, 1985). In controlled ecosystems using ^{14}C- and ^{3}H-labelled toluene as tracers, the estimated half-life of toluene in coastal water in the U.S.A. in winter (2-10°C) was 6 days, with the loss due mainly

to volatilization. In summer (18-19 °C), the half-life was only 1 day, due to rapid biodegradation; 80% of toluene was converted to CO_2 within 1 week (Wakeham *et al.*, 1985). In surface waters, the estimated biodegradation half-lives ranged from 6.9 hours in water with 10^6 bacterial cells/mL to 7.9 years in water with 10^2 bacterial cells/mL (USEPA, 1987a). Canadian surface waters not subject to direct discharges are expected to have 10^4 to 10^6 bacterial cells/mL; biodegradation half-lives would thus be expected to be between 1 month and 7 hours (Strachan, 1991). Biodegradation is likely to be a significant factor in Canadian situations with high bacterial counts.

Toluene in water can be biodegraded anaerobically as well as aerobically. However, Slooff and Blokzijl (1988) reported that oxygenated conditions are required for rapid degradation. In the U.S.A., toluene in ground water was degraded by only a few percent per week (Wilson *et al.*, 1983). In ground waters, the estimated biodegradation half-lives ranged from 29 days in water with 10^4 bacterial cells/mL to 79 years in water with 10 bacterial cells/mL (USEPA, 1987a). No data are available regarding the fate of toluene under anaerobic conditions beneath the ice cover in winter.

4.2.3 Soil Degradation

Toluene probably biodegrades fairly rapidly in most soils; however, available data are insufficient for prediction of rates (USEPA, 1987a). Half-life times of 83-92 days were reported for the biodegradation of toluene in various soil systems under different experimental conditions (Slooff and Blokzijl, 1988). In sandy soils, an average of 40% of the applied toluene was degraded, with most of the remainder being lost through volatilization (Wilson *et al.*, 1981).

In experimental laboratory studies using soils from above and below the water table from a shallow aquifer, Wilson *et al.* (1983) observed slow degradation of toluene (about 2.5% per week). Swindoll *et al.* (1988) studied the degradation of toluene and other organic compounds by microorganisms in aquifer solids samples. At toluene concentrations of up to 622 μg/g of solids slurry, microbial respiration and uptake into biomass increased with increasing toluene concentrations. At a concentration of 0.5 μg/g solids slurry, the turnover time for toluene was calculated as 3.8 years.

Toluene may act as the sole carbon source for some bacteria in soil; the aromatic ring is hydroxylated by these microbes to produce a mixture of cresols and catechols (Callahan *et al.*, 1979). Subsequent degradation products are similar to those for air photo-oxidation, and degradation rates are expected to be faster than for the initial hydroxylation.

4.3 Bioconcentration

Estimated bioconcentration factors (BCFs) for toluene in aquatic organisms based on its octanol/water partition coefficient and aqueous solubility are 65 and 18, respectively (USEPA, 1987a). Other estimates based on partition coefficients for toluene gave estimates for BCFs of 30 (SRI, 1980) and 15 to 70 (Veith *et al.*, 1980). BCFs lower than 100 generally indicate that a compound is unlikely to undergo significant bioconcentration or biomagnification (USEPA, 1987a).

Experimental studies confirm that toluene is not bioconcentrated to a significant extent in a variety of aquatic organisms. Uptake studies were done with several organisms, including Manila clams (*Tapes semidecussata*) (BCF = 1.25) (Nunes and Benville, 1979), blue mussels (*Mytilus edulis*) (BCF = 4.2) (Hansen *et al.*, 1978, in IPCS, 1985), and bluegill sunfish (*Lepomis macrochirus*) and crayfish (*Orconectes rusticus*) (maximum BCFs of 140 in the hepatopancreas of the crayfish and 45 in the fish spleen) (Berry, 1980). BCF values in eel tissues ranged from less than 1 to 13.2 (Syracuse Research Corporation, 1983). BCFs for the golden ide (orfe) (*Leuciscus idus melanotus*) were 90 on a wet weight basis after a 3-day exposure to 0.05 mg/L toluene (Freitag *et al.*, 1985). Whipple *et al.* (1981) reported accumulation factors ranging from 1.5 to 395 for toluene. The steady-state accumulation factor of 395 was recorded in gonadal eggs of juvenile starry flounder (*Platichthys stellatus*) after exposure for 500 hours to toluene concentrations of 0.088 mg/L (Whipple *et al.*, 1981). Toluene was reported to concentrate in filets of rainbow trout by factors ranging from 57 to 7200 when trout were exposed under similar conditions for 48 hours to industrial effluent containing a variety of organic chemicals (MOE, 1977); however, insufficient data were included in the report to validate results or indicate the likely reason for the wide range in BCFs.

A study in Lake Pontchartrain (part of the Mississippi River estuary near New Orleans, Louisiana, U.S.A.) examined sediment and selected biota for toluene levels (Ferrario *et al.*, 1985). Surface sediment contained little toluene (only 0.7 μg/kg wet weight in one of three samples, from the Inner Harbour Navigation Channel) while oysters (*Crassostrea virginica*) and clams (*Rangia cuneata*) had average levels of 3.4 μg/kg and 14.5 μg/kg, respectively. These levels do not indicate extensive accumulation.

In contrast, algae, with fewer detoxifying mechanisms than higher organisms, have been reported to accumulate toluene. Casserly *et al.* (1983) reported that the BCF for toluene (including all toluene in the alga or sorbed to its external surface) in *Selenastrum capricornutum* was 3016 after a 24-hour exposure to 10 mg/L toluene and 10,030 after 24-hour exposure to 2.0 mg/L toluene in combination with other organic chemicals (total concentration 13.5 mg/L). Toluene BCFs of 380 (dry weight) were recorded in *Chlorella fusca* after exposure to toluene at 0.05 mg/L for 24 hours (Geyer *et al.*, 1984). BCFs for algae higher than those for aquatic

animals were also reported for other volatile aromatic compounds (Lu and Metcalf, 1975), and may reflect both the algae's deficiency of microsomal oxidases as well as surface adsorption.

Miller *et al.* (1976) found no evidence that toluene would bioaccumulate in higher plants; grapes and avocados were shown to metabolize toluene.

4.4 Concentrations in the Environment

4.4.1 Air

4.4.1.1 Urban and Rural Ambient Air

Concentrations of toluene in ambient air in six urban areas and at two rural sites in Canada are presented in Table 4.1 (Dann *et al.*, 1989). In the period from 1983 to 1989, 24-hour mean airborne toluene concentrations at urban locations ranged from 5.2 to 44.2 $\mu g/m^3$ with maxima for individual samples in the range of 9.0 to 145.0 $\mu g/m^3$. The 24-hour mean toluene concentrations at the rural Walpole Island, Ontario, site (1988/1989) were 3.5 and 5.0 $\mu g/m^3$. The highest reported values were for 3-hour samples from Toronto (mean of 53.4 $\mu g/m^3$, maximum of 415.0 $\mu g/m^3$), while the lowest values were for 1-hour samples from the rural Dorset/Egbert area of Ontario (mean of 1.1 $\mu g/m^3$, maximum of 4.6 $\mu g/m^3$, minimum of 0.2 $\mu g/m^3$) (Dann *et al.*, 1989). Mean concentrations of toluene in ambient air at remote (0.18 $\mu g/m^3$), rural (1.31 $\mu g/m^3$), suburban (0.73 $\mu g/m^3$) and urban (10.8 $\mu g/m^3$) sites in the U.S.A. are similar to those in Canada (Shah and Singh, 1988). Values from Europe for suburban and rural areas are also comparable (Nielsen and Howe, 1991).

Evidence indicates that toluene concentrations in ambient air have been reduced since the early 1970s, primarily due to a reduction in emissions of volatile organic compounds (VOC) (including toluene) from light duty vehicles. The mean concentration of toluene in air in downtown Toronto in August 1971 was reported to be 113 $\mu g/m^3$ (Pilar and Graydon, 1973), whereas the mean concentration of toluene at two Toronto sites in the period of November 1988 to February 1989 was 15.6 $\mu g/m^3$ (Dann *et al.*, 1989), based on measurement by comparable methods of analysis. While this variation may be attributable in part to seasonal factors and sites, evidence elsewhere supports the conclusion that there has been a real decline in toluene concentrations. In Los Angeles, mean toluene concentrations also decreased between the 1960s and the 1980s, from 221 $\mu g/m^3$ to 44 $\mu g/m^3$ (Syracuse Research Corporation, 1983), based on unspecified methods of analysis. Mean toluene levels in the Lincoln Tunnel in New Jersey declined by more than four times between 1970 and 1982 (from 691 $\mu g/m^3$ to 162 $\mu g/m^3$), and in this case analytical methods and ventilation rates were similar (Lonneman *et al.*, 1986).

4.4.1.2 Toluene Levels in Air Related to Gasoline Marketing

Toluene concentrations in samples of air in the vicinity of gasoline stations in five Canadian cities (Halifax, Montreal, Toronto, Calgary and Vancouver) between June and August 1985, and January and March 1986, were determined (PACE, 1987; 1989). Mean concentrations of toluene in the immediate vicinity of self-serve gasoline marketing pumps were 1,900 $\mu g/m^3$ in the winter (range from 70 to 10,000 $\mu g/m^3$) and 2,600 $\mu g/m^3$ in the summer (range from 20 to 20,200 $\mu g/m^3$), based on 10-15 minutes personal samples at the pumps; the overall average concentrations at the stations were 535 $\mu g/m^3$ in the winter (range from 0 to 6,450 $\mu g/m^3$) and 202 $\mu g/m^3$ in the summer (range from 0 to 14,500 $\mu g/m^3$) (PACE, 1987; 1989).

4.4.1.3 Air at Contaminated Sites

Mean toluene concentrations were determined for the air columns of seven test drill holes drilled in 1985 at an abandoned landfill site at Ville Lasalle, Quebec. This location had received both municipal and hazardous industrial wastes from 1940 to 1959; observed levels ranged from "not detected" (limit of detection = 2 $\mu g/m^3$) in three drill holes to 31,000 $\mu g/m^3$. The highest concentrations were found in two drill holes in the areas that had received hazardous wastes (Dann and Gonthier, 1986).

4.4.1.4 Indoor Air

Owing to the release of toluene from several indoor sources, concentrations of toluene in indoor air are often higher than those in ambient outside air (Montgomery and Kalman, 1989). Sources in residential indoor air include attached garages (Hawthorne *et al.*, 1986), smoking (USDHHS, 1986), and the use of toluene/solvent-based products such as paints, adhesives, coatings and finishes, paint removers and thinners, upholstery and carpet cleaners and protectors and contact cement (Otson *et al.*, 1983). Other sources of toluene in indoor air are solvent related and include carburetor cleaners, spot and rust removers, bathroom deodorizers, arts and crafts supplies, and nail lacquers. Though quantitative data were not identified, exposure of the public through the use of toluene solvent-based products is in general presumed to be infrequent and low (Bayer *et al.*, 1988; Syracuse Research Corporation, 1983), but may be significant during prolonged home repairs or in other special circumstances.

The mean concentration of toluene in the air in ten Canadian homes was 52 $\mu g/m^3$ as determined by passive sampling (Otson and Benoit, 1985). In a study of 12 homes in the Toronto area (Chan *et al.*, 1990), samples of indoor air were collected in November or December 1986 and again in six of these homes in February or March 1987. The mean concentrations of toluene were 53.6 $\mu g/m^3$ for the earlier samples and 39.9 $\mu g/m^3$ for the later samples; there was no indication in this study of possible sources of toluene in the homes.

Samples of the indoor air of 18 homes near an abandoned waste disposal site in Montreal had a mean concentration of toluene of 37 $\mu g/m^3$, which was not statistically significantly different than that in control homes, located elsewhere (Dann and Gonthier, 1986; Gonthier, 1986). All of the above concentrations are comparable to levels determined in indoor air in the U.S.A., where mean values ranged between 8 and 82 $\mu g/m^3$ (Montgomery and Kalman, 1989; Shah and Heyerdahl, 1988).

4.4.2 Water

From a total of more than 800 water samples taken across Canada from 1985 to 1988, 20 contained quantifiable levels of toluene (detection limit ranged from 0.1 to 1.0 $\mu g/L$, usually 0.5 $\mu g/L$) (NAQUADAT, 1991). Samples with concentrations greater that 0.5 $\mu g/L$ included:

Peace River, Alberta, sewage treatment plant effluent grab (effluent):
32 $\mu g/L$ [10 May 1988]
31 $\mu g/L$ [22 August 1988]

Charlottetown, P.E.I., Brackley well #12 (ground water):
3.9 $\mu g/L$ [20 May 1987]

Harbour Grace, Newfoundland, water supply, Bannerman Lake at outlet to treatment plant (surface water):
0.9 $\mu g/L$ [05 October 1985]

Petit Rocher, New Brunswick, drinking water, sampled from distribution system (drinking water):
0.6 $\mu g/L$ [24 October 1986]

Charlottetown, P.E.I., water supply, Brackley well #9 (ground water):
0.6 $\mu g/L$ [20 May 1986]

These data are not indicative of widespread contamination of water by toluene.

4.4.2.1 Surface Waters

In the NAQUADAT (1991) data base, the only measurement for surface water above 0.5 $\mu g/L$ is that from Harbour Grace, Newfoundland (0.9 $\mu g/L$ in October 1985); in June of 1985, only traces of toluene had been detected at the same site (detection limit of 0.1 $\mu g/L$).

In a survey of water supplies at nine municipalities along the Great Lakes between 1982 to 1983, the mean concentrations of toluene (detection limit of 0.1 μg/L) in raw water were 0.3 μg/L in the summer, 0.1 μg/L in the winter, and 0.5 μg/L in the spring (Otson, 1987).

Subsequent to the discovery of "black tarry" substances at the bottom of the St. Clair River near Sarnia, Ontario, water samples were taken in November, 1985, along a 6 km industrialized section of the river where several petrochemical industries were located (Comba and Kaiser, 1987). Concentrations of toluene ranged from below the detection limit (detection limit of 0.1 μg/L) to 2.2 μg/L. Toluene levels were below the detection limit upstream from the industrialized section and returned to near or below detection levels about 1 km downstream of the industrialized section. A mean toluene concentration of 0.4 μg/L was calculated for the sampling stations along the industrialized section of the river.

The chemical content of effluents from industrial and municipal sources are being monitored in Ontario. Process effluent from petroleum refineries was shown to contain an average toluene concentration of 0.59 μg/L (MOE, 1989a). The refinery with the greatest discharge of toluene had an average daily concentration of 2.08 μg/L (maximum of 17.1 μg/L) and an average daily loading of 0.05 kg/day in the process effluent.

A spill of 1,000 kg of a mixture of toluene, benzene, and xylenes resulted in toluene concentrations in the St. Clair River as high as 22 μg/L (MOE, 1992).

4.4.2.2 Ground Water

Since toluene occurs naturally in petroleum deposits, it can be difficult to distinguish between anthropogenic toluene and that occurring naturally in ground water (Lesage and Lapcevic, 1990; Barker *et al.*, 1988). In a study using eight test wells near Belleville, Ontario, Slaine and Barker (1990) reported a maximum toluene concentration of 295 μg/L. Although the study site was 1.3 km from a landfill, evidence indicated that the presence of toluene in the test wells and adjacent water supply wells was not due to leaching and migration from the landfill; toluene likely originated as natural contamination from the shaly limestone bedrock. Given its relatively high water solubility, contamination of ground water by toluene may thus be prevalent in areas where petroliferous or bituminous shales are the aquifer resource.

In areas near landfill sites, concentrations of toluene in ground water may be considerably higher than those observed in surface waters. Levels observed directly beneath six landfill sites in Ontario (Hamilton, Bayview, New Borden, Borden, Woolwich and North Bay) ranged from less than 0.2 μg/L to 730 μg/L (Barker, 1987). The highest toluene concentrations measured in ground water was in Elmira, Ontario. Samples taken in a contaminated shallow aquifer at a depth of 6 meters beside an existing industrial chemical waste disposal lagoon had toluene concentrations above 3.9 mg/L (Lesage *et al.*, 1990). In Ville Mercier, Quebec, levels as high

as 2.8 mg/L were recorded in ground water around a liquid waste disposal site (Pakdel *et al.*, 1992).

4.4.2.3 Drinking Water

In treated drinking water of 29 Canadian municipalities sampled during August-September and November-December, 1979, the mean concentrations of toluene averaged 2 μg/L and ranged up to 27 μg/L (Otson *et al.*, 1982). Toluene concentrations in treated supplies in this survey were often greater than those in the raw water sources. It was concluded that the levels of toluene increased upon water treatment, although the total organic carbon levels decreased or remained the same. The mechanism of the toluene formation is unknown.

In another survey of water supplies at nine municipalities along the Great Lakes between 1982 to 1983 (Otson, 1987), the mean concentrations of toluene (detection limit = 0.1 μg/L) in raw water were 0.3 μg/L in the summer, 0.1 μg/L in the winter and 0.5 μg/L in the spring. In treated water, the mean toluene concentrations were <0.1, 0.3 and 0.7 μg/L, in the summer, winter and spring, respectively.

In a survey of 44 water supply systems conducted across Ontario in 1987 (detection limit = 0.05 μg/L) toluene was detected at six locations, with values ranging from 0.5 to 1.6 μg/L (MOE, 1989b). Mean concentrations were not reported.

In the Federal-Provincial Drinking Water Sources Toxic Chemical Survey conducted in the Atlantic Region between 1985-1988 (DOE, 1989a-d), toluene was detected at 23/40 sites in New Brunswick, 22/40 sites in Nova Scotia, 33/40 sites in Newfoundland and 20/30 sites in Prince Edward Island (detection limits were 0.5 μg/L in 1985-1987 and 0.2 μg/L in 1988). Concentrations ranged from trace amounts (0.1 to 0.2 μg/L) in raw water to a maximum of 0.6 μg/L in treated water in New Brunswick; from trace amounts in raw water to 0.5 μg/L in treated water in Nova Scotia; from trace amounts to 0.9 μg/L in raw water to 0.4 μg/L in treated water in Newfoundland, and from trace amounts to 3.9 μg/L in raw water to only trace amounts in treated water in Prince Edward Island.

4.4.3 Soils and Sediments

Data on concentrations of toluene in soils have not been identified. Based on pesticidal uses and rates described above, it can be calculated that if all of the toluene applied with a herbicide application was evenly incorporated into the top 10 cm of soil, it would result in a toluene concentration of about 4 μg/kg dry soil. However, based on the volatilization half-lives of 9 seconds from the soil surface and 1 hour to one day for volatilization from the top 1 cm of soil, actual soil concentrations following pesticide applications are probably considerably lower.

Data on concentrations of toluene in sediments in Canada have not been identified. The USEPA (1987a) reported that sediment concentrations exceeded 500 μg/kg in an industrialized area in San Francisco. Ferrario *et al.* (1985) reported surface sediment with 0.7 μg/kg wet weight of toluene from a navigation channel in Louisiana.

4.4.4 Food

Few data on concentrations of toluene in food are available. Toluene has been identified but not quantified by gas chromatography or gas chromatography-mass spectrometry in various food items. It has been detected in roasted filberts, peanuts, and macadamia nuts (Syracuse Research Corporation, 1983), in cheese (Meinhart and Schreier, 1986), in tomatoes and its products (Chung *et al.*, 1983), in baked potatoes (Coleman *et al.*, 1981), in dry red beans (Buttery *et al.*, 1975), in winged beans and soybeans (del Rosario *et al.*, 1984), and in eggs (MacLeod and Cave, 1976). The mean concentration of toluene in the tissues of 59 samples of fish from six states in the U.S.A. including Washington and Alaska was 1 μg/g wet weight; the maximum concentration detected in one fish was 35 μg/g (Syracuse Research Corporation, 1983). However, levels in 95% of the samples were lower than the mean value (Syracuse Research Corporation, 1983). Levels in Canadian foodstuffs were not identified.

4.4.5 Human Tissues and Fluids

In a U.S.A. national survey of toluene in human adipose tissue, the concentrations ranged from not detected (detection limit = 0.0002 μg/g) to 0.250 μg/g and there was a slight trend toward higher concentrations with age. There was about a fivefold variation in concentration by geographic region (Stanley, 1986).

Determination of toluene in mothers' milk for populations in the vicinity of chemical manufacturing plants and/or industrial user facilities in the United States was reported, though not quantified, by Pellizzari *et al.* (1982). Levels were determined by the purge and trap method, followed by thermal desorption and capillary GC-MS analysis. Toluene was detected in 8 of the total of 12 samples collected. The detection limit for these analyses was not specified by the authors.

5 POPULATION EXPOSURES

Estimates of the average daily intake (on a body weight basis) of toluene from various sources for different age groups in the Canadian population and the assumptions on which they are based are presented in Table 5.1. Based on these estimates, the sources of exposure to toluene for Canadians listed in order of their importance are as follows: ambient air, consumer products, gasoline, food and water. For the general population, the most significant route of exposure is inhalation from air, with estimated intakes ranging from 1.0 to 20.4 μg/kg b.w./d. Estimated intake from fish and drinking water is considerably less, ranging from 0.04 to 0.2 μg/kg b.w./d and 0.03 to 0.1 μg/kg b.w./d, respectively. It should be noted, however, that particularly for food, available data are extremely limited.

Estimated intake of toluene at self-serve gasoline stations is less than that from ambient air, ranging from 0.4 to 0.9 μg/kg b.w./d assuming that the average driver spends 10 minutes per week at the gas station. Estimated intake of toluene in consumer products is similar to that from self-serve gasoline stations, ranging from 0 to 1.2 μg/kg b.w./d, assuming that the products contain 5% toluene (Gilbert *et al.*, 1983) and that exposure to these products lasts for 5 to 30 minutes per week. Cigarette smoke is by far the greatest source of exposure to toluene for smokers. Estimated intakes from main-stream smoke range from 45.2 to 57.1 μg/kg b.w./d for individuals 12 years or older.

The total average daily intake of toluene for different age groups can be calculated from Table 5.1. It is estimated that the average daily intake for the 0 to 0.5, 0.5 to 4, 5 to 11, 12 to 19 and 20 to 70 years age groups are 1.8 to 15.5, 2.1 to 18.0, 2.6 to 21.6, 2.3 to 19.6 and 1.6 to 14.2 μg/kg b.w./d, respectively. For smokers, the total daily intake will be much higher, up to 71.3 μg/kg b.w./d for adults.

6 KINETICS AND METABOLISM

6.1 Absorption

Owing to its volatility, the principal route of exposure of humans to toluene is inhalation from air. Absorption of toluene from the lungs is rapid and fairly complete ranging from about 50% to 80% (Low *et al.*, 1988). In humans exposed to 115 ppm (430 mg/m^3) toluene, 57% was absorbed after 1 hour; this decreased to 37% of the inspired dose, which remained stable after 2 to 4 hours of exposure (Nomiyama and Nomiyama, 1974, cited in IPCS, 1985).

Toluene is absorbed more slowly from the gastrointestinal tract than from the lungs; in rats, toluene levels in blood peaked 2 hours after gastric intubation with 100 μL toluene in 400 μL peanut oil (Pyykko *et al.*, 1977). Dermal absorption of toluene vapour is considerably slower than absorption following inhalation of a similar concentration. It was estimated that dermal absorption in clothed volunteers exposed to airborne concentrations of 600 ppm (2,250 mg/m^3) for 3 hours was approximately 1% of the total absorbed dose as determined by the concentrations of toluene in the blood and exhaled air and the metabolite methylhippuric acid in the urine. Inhalation was the source of the remaining 99% of the total absorbed dose (Riihimaki and Pfaffli, 1978). The average skin permeability of the human body to toluene was calculated to be 14-23 mg/cm^2/h based on the surface area of the hands, following the application of pure toluene to the forearm of volunteers (Dutkiewicz and Tyras, 1968, cited in USEPA, 1985).

6.2 Distribution

The amount of toluene taken up initially by various tissues depends on factors such as blood flow to the organs, lipid solubility or partition coefficient between tissue and blood, rate of metabolism and duration of exposure. In one study (Sato, 1988), the partition coefficients of toluene for body fluids and tissues of rabbits ranged from 1 to 3 for most tissues other than adipose tissue and bone marrow for which values were 113.2 and 35.4, respectively. Therefore, toluene accumulates in adipose tissue after prolonged exposure but is distributed initially to highly vascularized, lipid-rich tissues such as the kidney, liver and brain. The half-life for toluene in the adipose tissue of male humans exposed to 300 ppm (1,125 mg/m^3) for 2 hours ranged from 0.5 to 2.7 days (Carlsson and Ljungquist, 1982).

Toluene absorbed from the skin or gastrointestinal tract is distributed to the liver, the major site of toluene metabolism, before reaching the general circulation. In one fatal case following ingestion of toluene (Ameno *et al.*, 1989), concentrations were highest in the liver (except for the stomach contents), followed by the pancreas and brain, with toluene levels in the fat being about half those in the blood.

6.3 Metabolism

In humans, toluene is metabolized primarily by side chain hydroxylation to form benzyl alcohol in a cytochrome P-450 mixed function oxidase - mediated reaction; benzyl alcohol is subsequently oxidized to benzaldehyde and benzoic acid (Ogata *et al.*, 1970). Benzoic acid is then activated by liver enzymes to form a coenzyme A derivative, which then reacts with glycine to form hippuric acid, the major urinary metabolite.

Based on the identification of small amounts (0.04-1.0% of administered doses) of free and conjugated o- and p-cresol in the urine of rats following ingestion of toluene, it has been hypothesized that toluene is metabolized by an additional minor pathway, in which it undergoes ring hydroxylation to form reactive arene oxide intermediates and subsequently o- and p-cresol which are excreted in the urine as sulphate or glucuronide conjugates (Low *et al.*, 1988). In humans exposed to toluene, hippuric acid, o-cresol, p-cresol and phenol have been detected in the urine (Andersen *et al.*, 1983; Angerer, 1979 in IPCS; Baelum *et al.*, 1987).

6.4 Elimination

Following ingestion or inhalation in both humans and animals (rats and rabbits), toluene is excreted initially primarily as the unchanged compound by expiration and later (within 12 hours after exposure) mainly as the metabolite, hippuric acid, in the urine. Availability of glycine for conjugation with toluene to form hippuric acid may be a limiting factor in the rate of toluene excretion (Astrand *et al.*, 1972).

There are sex-dependent variations in the rate of excretion of toluene in humans, based on studies of occupationally-exposed populations. The exhalation of toluene in expired air for male and female subjects was 17.6 and 9.4%, respectively, of the absorbed dose. The slower elimination rate in females probably results from greater accumulation in the higher percentage of fatty tissue (Sato, 1988). Further, the amount of body fat may affect the extent of toluene expiration. Obese subjects accumulate more toluene and eliminate it more slowly (Veulemans and Masschelein, 1978, cited in USEPA, 1985).

6.5 Interactions

The initial and rate-limiting step in toluene metabolism, the cytochrome P-450-mediated oxidation to benzyl alcohol, can be affected by substances known to induce or inhibit mixed-function oxidases (Dossing *et al.*, 1983; USEPA 1985). Treatment with common drugs known to inhibit microsomal oxidation, namely cimetidine and propranolol, had no effect on toluene metabolism (Dossing *et al.*, 1984), but concomitant exposure to the tranquillizer diazepam enhanced CNS impairment caused by toluene.

Ethanol induces cytochrome P450-dependent enzymes in rats, amongst which are enzymes that both inhibit and stimulate the metabolism of volatile hydrocarbons. At high doses (*e.g.*, 2.82 g/kg b.w.), ethanol preferentially acts initially as an inhibitor; 16 - 18 h after ingestion of ethanol, the metabolism-enhancing effect predominates (Sato, 1988).

Concomitant exposure to xylene or benzene may competitively inhibit the metabolism of toluene since all of these compounds are metabolized by a similar hepatic microsomal cytochrome P-450-dependent enzyme system (Sato, 1988). Toluene inhibits the metabolism of benzene in rodents and thus reduced the haematotoxic and clastogenic effects of this compound at unspecified "high" concentrations, but not at lower levels [100 ppm (75 mg/m^3) in humans and 25 ppm (94 mg/m^3) in rats] (Dean 1985). Formation of phenol and hydroquinone, metabolic products of benzene, was reduced in workers exposed concomitantly to toluene (Inoue *et al.*, 1988). In addition, levels of o-cresol and hippuric acid, metabolites of toluene, were also reduced. It is possible, therefore, that concomitant exposure to toluene may have a protective effect against the toxic effects of benzene.

7 MAMMALIAN TOXICOLOGY

7.1 Acute (Single Exposure) Toxicity

Although it is difficult to compare the results of available studies of acute toxicity owing to variations in experimental protocols and strains, there is some indication that sensitivity differs considerably among species decreasing in the following order: rabbit, guinea pig, mouse and rat. Acute (6 to 7 h) inhalation LC_{50} values of from 20,000 to 26,000 mg/m^3 and 45,000 mg/m^3 in mice and rats, respectively, have been reported. Acute toxicity by the oral route is low with LD_{50}s in rats ranging between 2.6 and 7.5 g/kg b.w., depending on the strain, age and sex. Acute dermal toxicity appears to be quite low (24-h covered contact LD_{50} of 14.1 mL/kg b.w. or approximately 12.2 g/kg b.w. in rabbits). In all species studied, the effects found with increasing dose were irritation of the mucous membranes, signs of effects on the central nervous system such as incoordination, mydriasis, narcosis, tremors, prostration, and anaesthesia and death (IPCS, 1985).

There is a biphasic response of the central nervous system to acute toluene exposure with initial excitability, followed by a depression in response which is dose-related. This response is typical of narcotic drugs (IPCS, 1985). In anaesthetized mongrel dogs exposed via inhalation to 2 mL of toluene delivered into a bag full of air for 5 to 6 hours (Ikeda *et al.*, 1990), there was a biphasic narcotic response in 21 out of 25 dogs. Four of the 25 dogs developed transient arrhythmia with fluctuation of the blood pressure, and in one of these dogs, fatal ventricular fibrillation occurred suddenly. The authors suggested that these observations indicate that in most cases of sudden death in acute toluene intoxication, the cause is severe hypoxia during toluene narcosis, but in a few cases, it is fatal arrhythmia due to the direct effect of toluene on the heart muscle.

7.2 Short Term Toxicity

Short term exposure via inhalation to moderate concentrations of toluene in various animal species (principally rats and mice) has been associated with central nervous system depression. At lower concentrations (9.38 to 563 mg/m^3), subtle behavioural and neurological and unconfirmed immunological effects have been reported, which are addressed in Section 9.8. Exposure to moderate to high concentrations of toluene has caused slight adverse effects on the liver, kidneys and lungs. The lowest reported effect level for effects other than those on the immune system and neurobehavioural manifestations in short term studies, as reviewed in ATSDR (1989), was 320 ppm (1,200 mg/m^3) which induced decreases in the weights of the body, whole brain and cerebral cortex in rats following continuous exposure for 30 days (Kyrklund *et al.*, 1987). The total content of phospholipids in the cerebral cortex was also reduced and there was a slight increase in phosphatidic acid. There was no histopathological examination of tissues in this study.

Studies on effects following short-term ingestion of toluene were not identified.

7.3 Skin and Eye Irritation

Depending on the dose and the duration of application, toluene has been mildly to severely irritating to the eyes of rabbits at 870 μg for 72 h to 2 mg for 24 h and, slightly irritating to the skin of rabbits at 435 mg for 72 h and guinea pigs at 1 mL of undiluted toluene for 16 h (IPCS, 1985).

7.4 Sub-Chronic Toxicity

Protocols and results of available sub-chronic studies for toluene are presented in Table 7.1.

7.4.1 Inhalation

The lowest concentration at which effects have been reported in such studies following inhalation is 100 ppm (LOEL) which induced a decrease in body weight (7.5 and 12% reduction in final weight relative to controls in males and females, respectively) in a 14-week inhalation study in mice conducted by the National Toxicology Program (NTP) (Huff, 1990). Data on food consumption were not provided. This NTP inhalation bioassay is the best documented and only adequate sub-chronic study in which several doses were administered, though histopathological examinations were conducted at the two highest dose levels only. At concentrations of 625 ppm (2300 mg/m^3) and greater in mice in this bioassay, there was an increase in relative liver weights and at 1250 ppm (4700 mg/m^3) or greater, increases in relative kidney weights in females ($P < 0.05$) were also observed. The relative lung weights for male mice exposed to 2500 ppm (9400 mg/m^3) were greater than those for controls ($P < 0.05$). In female mice, marginally significant increases in relative lung weights were observed in groups exposed to 100, 625 and 1250 ppm ($P < 0.01$) but not in those exposed to the highest concentration (2500 ppm), though owing probably to the lack of a clear exposure-response relationship, the authors did not consider this effect to be treatment-related. In two higher dose groups for which histopathological examinations were conducted (2500 and 3000 ppm), centrilobular hepatocellular hypertrophy was also observed.

In rats exposed to concentrations of 1250 ppm or greater for 15 weeks in the NTP subchronic bioassay, the relative weights of the kidney and liver in males were increased and the leucocyte count in females was decreased (NOEL = 625 ppm or 2300 mg/m^3)(Huff, 1990).

7.4.2 Ingestion

Effects following ingestion of toluene in sub-chronic studies have also been reported and are summarized in Table 7.1. In the best documented and most complete study conducted to date (a recently reported NTP bioassay) which included full histopathological examination for the two highest dose groups (2,500 and 5,000 mg/kg b.w./d) and limited examinations for the three lower dose groups (312, 625, and 1,250 mg/kg b.w./d), there was myocardial fibre degeneration in mice ingesting 5000 mg/kg b.w. toluene by gavage in corn oil for 13 weeks (Huff, 1990); survival was reduced at 1250 mg/kg b.w./d (1/10 in females) and higher, and clinical signs were observed at 2,500 or 5,000 mg/kg b.w. Relative liver weights were increased at doses of 1,250 or 2,500 mg/kg b.w. in male mice and 312 mg/kg b.w. ($P<0.05$) (LOEL) or higher in the females.

In rats ingesting doses of 2500 mg/kg body weight of toluene or greater by gavage in corn oil, 5 days/wk for 13 weeks, survival was reduced, clinical signs were observed in both male and female rats, and haemorrhages were present in the urinary bladder, but only significant ($P<0.01$) in the male rats. In females ingesting 1,250 mg/kg b.w. and greater and in males receiving 625 mg/kg b.w. or greater, relative liver and kidney weights were increased. At 1,250 or 2,500 mg/kg b.w. there was also neuronal necrosis in the brain. The NOEL in this study is considered to be 312 mg/kg b.w. per day.

7.5 Chronic Toxicity and Carcinogenicity

The results of the only identified studies of the chronic toxicity and/or carcinogenicity of toluene are presented in Table 7.2. Toluene has not been carcinogenic in the most extensive of these studies conducted to date.

7.5.1 Inhalation

For inhalation, relevant bioassays are those conducted by the NTP (Huff, 1990) and the Chemical Industry Institute of Toxicology (CIIT, 1980).

In the CIIT bioassay, there were no treatment-related effects on haematological parameters, urinalysis or clinical chemistry following inhalation by male and female Fischer rats of 30 ppm (112.5 mg/m^3) toluene for 6 h/d, 5 d/wk for 24 months. Following exposure to 100 or 300 ppm (375 or 1125 mg/m^3), there was a decrease in the haematocrit of female rats but there was no exposure-response relationship. Upon histopathological examination which was limited to tissues from control rats and rats exposed to 300 ppm for up to 24 months, there was no increase in the incidence of neoplastic, proliferative, inflammatory or degenerative lesions (CIIT, 1980). However, failure to administer the maximum tolerated dose may have reduced the sensitivity of this carcinogenesis bioassay.

In another carcinogenesis bioassay conducted by the NTP (Huff, 1990), rats of both sexes inhaled 600 or 1,200 ppm (2250 or 4500 mg/m^3) toluene for 6.5 h/d, 5 d/wk for two years; male and female mice were exposed to 120, 600 or 1,200 ppm on the same schedule. There were no significant treatment-related effects on mean body weights or survival of male or female rats. The severity of nephropathy increased with administered concentration in exposed rats and was significantly higher than in controls at the highest concentration (1,200 ppm). A rare renal tubular cell carcinoma in a female rat (1/50, 2%) and an equally uncommon sarcoma of the kidney in another female rat were seen in the 1,200 ppm exposure group (1/50, 2%). Erosion of the olfactory epithelium and degeneration of the respiratory epithelium were significantly increased in exposed rats at all concentrations (600 ppm and above). Inflammation of the nasal mucosa and metaplasia of the olfactory epithelium were significantly increased in exposed female rats at all concentrations, but for the most part, were of mild severity. A squamous cell carcinoma of the nasal mucosa was seen in one female rat at 1,200 ppm (1/50, 2%). A squamous papilloma of the forestomach was observed in one female rat (1/50, 2%) and a squamous cell carcinoma of the forestomach (1/50, 2%) was observed in a second female rat at 1,200 ppm; however, these were not considered to be treatment-related. There were no compound-related neoplasms in male rats. It was concluded on the basis of these results that under the conditions of these 2-year inhalation studies, there was no evidence of carcinogenic activity for male or female F344/N rats.

There were no significant treatment-related effects on mean body weights or survival of male and female mice, though survival in all groups of male mice was lower than usual. There were also no neoplastic or non-neoplastic effects in female or male mice leading to some controversy in the NTP peer review group about the value of the study in mice in assessment of carcinogenicity, since the maximum tolerated dose may not have been achieved. It was concluded, however, that the dose selection was adequate and that under the conditions of these 2-year inhalation studies, there was no evidence of carcinogenic activity for male or female B6C3F1 mice.

7.5.2 Ingestion

In the only carcinogenesis bioassay by the oral route identified (Maltoni *et al.*, 1983; 1985), groups of 40 Sprague Dawley rats of each sex were administered by gavage in olive oil, 500 mg/kg b.w. of toluene (98.34% pure), once daily, 4-5 days per week for 104 weeks. At the end of the study (week 141), hemolymphoreticular neoplasms were reported in 3/37 (8%) and 7/40 (16%) toluene-exposed males and females, respectively, compared to 3/45 (7%) and 1/49 (2%) in male and female controls. The total number of animals bearing tumours was 39/80 (49%) for toluene-exposed as compared with 21/100 (21%) in the vehicle control group. Based on these results, the authors concluded that toluene increased the incidence of total malignant tumours, some of which rarely occurred. However, several limitations of this study including lack of statistical analyses, inadequate reporting of the incidence of various tumours and the

administration of a single dose limit its usefulness in assessing the carcinogenic potential of toluene.

7.5.3 Dermal Exposure

Data on the possible carcinogenic effects of dermal exposure to toluene have largely been limited to results in vehicle controls in investigations where it has been used as a solvent for lipophilic chemicals such as polycyclic aromatic hydrocarbons and in two-stage tumour initiation-promotion bioassays. When applied topically to the shaved skin of animals, toluene has not induced significant excesses in tumours though there have been some non-significant increases in some studies. For example, in one study (Lijinsky and Garcia, 1972, cited in IPCS, 1985), a skin papilloma in one mouse and a skin carcinoma in a second mouse from a group of 30 animals which received topical applications of 16 to 20 μL of toluene, twice a week, for 72 weeks were reported. In another limited study in mice, in which toluene (0.1 mL of 100%) was painted on the skin of mice twice weekly for 20 weeks, one permanent and one regressing tumour in 14 mice and six permanent and five regressing tumours in 35 mice following initiation with 7,12-dimethyl-benz(a)anthracene were observed (Frei and Kingsley, 1968). The authors concluded on the basis of these results that toluene has some weak promotor activity, though these results have not been confirmed in an additional study by the same group (Frei and Stephens, 1968). The incidence of tumours in the control groups was not reported in these studies.

7.6 Developmental and Reproductive Toxicity

7.6.1 Inhalation

In general, toluene has not been teratogenic in mice, rats or rabbits following inhalation, but has induced embryotoxic-foetotoxic effects (decreased foetal weight, delayed ossification and minor skeletal anomalies) at concentrations which, in some cases, were non-toxic to the mothers (*i.e.*, as low as 500 mg/m^3) (IPCS, 1985, ATSDR, 1989).

In a study by Hudak and Ungvary (1978), 19 pregnant CFY rats were exposed by inhalation to 1500 mg/m^3 (399 ppm) for 24 h/d from days 9 to 14 of pregnancy, 9 pregnant rats inhaled 1500 mg/m^3 for 24 h/d from days 1 to 8 of pregnancy, 10 rats inhaled 1000 mg/m^3 (266 ppm) 8 h/d from days 1 to 21 of pregnancy and 26 rats inhaled air for 24 h/d from days 9 10 14 of pregnancy. In addition, groups of 11 pregnant CFLP mice were exposed by inhalation to 500 mg/m^3 (133 ppm), 15 pregnant CFLP mice to 1500 mg/m^3 (399 ppm) for 24 h/d from days 6 to 13 of pregnancy and 14 mice inhaled air for 24 h/d from days 6 to 13 of pregnancy. In the rats exposed to 1500 mg/m^3 from days 9 to 14 of pregnancy, the body weight gain of the mothers, fetal loss and the mean fetal and placental weights were similar to those in the control group. However, there was an increase in the incidence of irregular sternebrae and extra ribs

in the offspring. For the group exposed continuously to 1500 mg/m^3 from days 1 to 8 of pregnancy, the average fetal, but not the placental weight decreased ($P < 0.01$). Retarded skeletal growth was more frequent than in the control group ($P < 0.05$). In rats exposed to 1000 mg/m^3, 8 h/d from days 1 to 21 of pregnancy, maternal weight gain, fetal loss, mean fetal and placental weights and percentage of weight retarded fetuses were similar to that in the control group. There was an increased frequency of signs of retarded skeletal development ($P < 0.05$), but no skeletal anomalies or malformations (LOAEL = 1000 mg/m^3). The group of CFLP mice exposed to 1500 mg/m^3 toluene died within 24 h. In the group of CFLP mice exposed continuously to 500 mg/m^3 toluene from days 6 to 13 of pregnancy, the average number of fetuses did not differ from that of the control group. The average fetal weight decreased and the number of fetuses with retarded growth increased (LOAEL = 500 mg/m^3). No adverse effects were observed in the mothers.

In another study by Ungvary and Tatrai (1985), groups of 15 CFLP mice were exposed by inhalation to 500 or 1000 mg/m^3 toluene for 4 hours, three times a day, days 6 to 15 of pregnancy and groups of 10 and 8 NZ rabbits for 24 h/d on days 7 to 20 of pregnancy. In mice, skeletal retardation in the fetuses and increased incidence of fetuses with retarded growth were observed at 1000 mg/m^3. Maternal toxicity was not observed (NOAEL = 500 mg/m^3, LOAEL = 1000 mg/m^3). In rabbits, there was a decrease in maternal weight gain, increased fetal loss by spontaneous abortion (4/8) and increased number of total resorptions (2/8) at 1000 mg/m^3. At 500 mg/m^3, there were no adverse effects in the mothers or offspring (NOAEL = 500 mg/m^3, LOAEL = 1000 mg/m^3).

In the offspring of pregnant CD-1 mice inhaling 400 ppm (1500 mg/m^3) toluene from days 7 to 16 of gestation for 7 h/d, there was a significant shift in the fetal rib profile (Courtney *et al.*, 1986). At 200 ppm (750 mg/m^3), there was a significant increase in the frequency of dilated renal pelves. The activity of lactic dehydrogenase (LDH) was significantly increased in the brains of dams exposed to 400 ppm during gestation while in nonpregnant adult mice exposed to this concentration concurrently, the activity of LDH was significantly increased in the liver and kidneys.

In a two-generation study (American Petroleum Institute, 1985), groups of 10 to 30 male and 19 to 60 female Sprague-Dawley derived albino rats in the F_0 and F_1 generations were exposed 6 h/d, 7d/wk during an 80 day premating period and a 15 day mating period; adult females of both generations were also exposed on days 1 through 20 of gestation and days 5 through 21 of lactation by whole body inhalation to concentrations of 100, 500 and 2,000 ppm toluene (375, 1875, 7500 mg/m^3). Additional groups of 10 males and 20 females were exposed to 2000 ppm (7500 mg/m^3) and bred with untreated counterparts in each of the two consecutive generations. Each generation was mated once and selected F_1 fetuses were examined for fetotoxic-teratogenic effects. No treatment-related effects on parental survival, appearance or behaviour in either generation were reported. At the highest concentration (2,000 ppm; 7500

mg/m^3), the fetal weight, uterine weight, and pup weight were significantly lower in the offspring in both generations when both sexes of parents were exposed. However, no effects were observed in the offspring when only the male parents were exposed to 2000 ppm. Thus, the no-observed-effect-level in this study was 500 ppm (1875 mg/m^3).

In a study on the effects of *in utero* exposure on the neurobehavioural development of rats and hamsters (Da-Silva *et al.*, 1990), 13 pregnant Wistar rats and 6 *Mesocricetus auratus* hamsters were exposed to 800 mg/m^3 (213 ppm) toluene, 6 h/d during days 14 to 20, and 6 to 11 of gestation, respectively. No overt maternal toxic effects were observed either in rats or hamsters. In toluene-exposed rats, the number of litters with low birth weight pups was increased ($P < 0.05$). Male rat offspring exposed to toluene *in utero* displayed shorter latencies to choose one side of a T maze in a spontaneous alteration test (225.7 vs. 28, $P < 0.05$), while hamsters of both sexes performed worse in a rotating rod test (91.3 vs 67.4, $P < 0.05$).

7.6.2 Ingestion

In a study reported only in the form of an abstract, an increased incidence of cleft palate was observed in CD-1 mice, following oral administration of 1.0 mL/kg toluene by gavage in cottonseed oil (equivalent to 870 mg/kg b.w./d), daily on days 6 through 15 of gestation (Nawrot and Staples, 1979). There was a significant increase in embryonic lethality at all dose levels (240, 430, and 870 mg/kg b.w./d), and a significant reduction in fetal weight at 430 and 870 mg/kg b.w., though the increased incidence of cleft palate did not appear to be due only to a general retardation in growth rate. There was no maternal toxicity following exposure to any of the concentrations. When toluene was administered at 870 mg/kg on days 12 to 15, there were no embryotoxic or fetotoxic effects, though decreased maternal weight gain was noted.

In another study reported by Seidenberg *et al.* (1986), groups of 30 pregnant ICR mice were administered 1800 mg/kg b.w./d toluene by gavage in corn oil on days 8 to 12 of gestation. No effects on the embryo/fetal viability, and/or postnatal growth and viability were observed. There was also no evidence of maternal toxicity other than slight depression or ataxia.

7.7 Mutagenicity and Related Endpoints

The genotoxicity of toluene has been examined in various assays with endpoints including reverse mutation, mitotic gene conversion, mitotic crossing-over, chromosome aberrations, forward mutation and tests for DNA damage in microbial and mammalian cell cultures *in vitro* as well as *in vivo*, as presented in Table 7.3. In general, results of both *in vivo* and *in vitro* studies have indicated that toluene is not genotoxic (ATSDR, 1989; IPCS, 1985; Huff, 1990). Positive results have been due most likely to impurities or artifacts of study protocols (IPCS, 1985; Huff, 1990).

For example, the detection of DNA single-strand breaks by Sina *et al.* (1983 in Huff, 1990) was probably a secondary effect of cell lysis rather than direct interaction of toluene with nuclear DNA since it occurred only when cytotoxicity was greater than 30% (Huff, 1990). Studies in which induction of chromosomal aberrations by toluene have been reported (Dobrokhotov, 1972; Lyapkalo, 1973; Dobrokhotov and Enikeev, 1977 in Huff, 1990) are difficult to evaluate since the purity of the compound tested was not specified, the types of aberrations scored were unclear, cells scored from a group of animals were pooled rather than analyzed individually and in one case (Dobrokhotov and Enikeev, 1977 in Huff, 1990), there was no indication of the actual numbers of cells scored (Huff, 1990).

In three experiments without S9 mix and one with S9 mix by McGregor *et al.* (1988), toluene induced statistically significant increases in the mutant fraction in the L5178Y tK+/tK- mouse lymphoma cell forward mutation assay. The authors considered these results questionable, however, owing to the possibility that toluene had come out of solution, due to its poor water solubility.

Induction of micronuclei in the bone marrow of NMRI and $B6C3F_1$ mice has been reported in two studies by one group of investigators (Mohtashamipur *et al.*, 1985; 1987) after i.p. injection of 0 to 865 mg/kg, and in a study reported only as an abstract where SHR male mice were administered 200 mg/kg by gavage (Feldt and Zhurkov, 1985). However, these results were not confirmed by Gad-El-Karim *et al.* (1984) and Kirkhart (1980 in Huff, 1990) who reported no micronuclei induction in mice after i.p. injection of 0 to 1,000 mg/kg or 860 to 1,720 mg/kg, respectively.

7.8 Special Studies

7.8.1 Neurotoxicity

Studies of the neurotoxic effects of toluene have generally involved examination of clinical signs, electrical activity in the brain or effects on neurotransmitters or behaviour. Results of these studies are summarized in Tables 7.4 to 7.6.

With the exception of some behavioural effects reported at very low concentrations in one study (Horiguchi and Inoue, 1977) and biochemical effects in the brain, the biological significance of which is unclear (Fuxe *et al.*, 1982; von Euler *et al.*, 1987, 1988, 1989; Hsieh *et al.*, 1990), neurotoxic effects have resulted only following exposure to levels greater than those reported to induce other effects in sub-chronic studies. Clinical signs such as increased spontaneous activity and sleep disturbances have been observed following single or repeated short term exposure to concentrations greater than 3750 mg/m^3; the lowest concentration at which EEG changes have been reported is 500 ppm (1,875 mg/m^3) (12 weeks) which induced disruptions and frequency changes in hippocampal theta wave activity (Naaisuno, 1986, in

ATSDR, 1989). Following single or repeated short term exposure to concentrations as low as 300 mg/m^3, dopamine concentrations in the brain were decreased (Fuxe *et al.*, 1982). More recently, augmentation of protein phosphorylation in the rat forebrain, in particular the striatum, and disturbance of receptor (neurotensin and vasoactive intestinal polypeptide) binding in the absence of behavioural effects have been observed following short-term and subchronic exposure to 80 ppm (330 mg/m^3) toluene, respectively (von Euler *et al.*, 1987; 1988). This group of investigators also reported that neonatal exposure of rats to 330 mg/m^3 toluene on days 1 to 7 after birth produced persistent changes in dopamine and noradrenaline neurons in the forebrain, hypothalamus and substantia nigra in the presence of a relatively intact neuroendocrine system. Neonatal exposure diminished or even counteracted the responses to short-term toluene exposure in adulthood (von Euler *et al.*, 1988). Hsieh *et al.* (1990) reported increased levels of some biogenic monoamines but not all of those examined in some regions of the brain in an unspecified number of rats exposed for 21 days to drinking water containing 17 and 80 mg/L (considered to be equivalent to doses on a body weight basis of 5 and 22 mg/kg/day), with increases being less at 405 mg/L (105 mg/kg/day).

In general, behavioural effects including deficits in conditioned avoidance response, simple behaviour or unconditioned reflexes have been observed only in rats and mice following exposure to concentrations greater than 3000 mg/m^3 for periods of 4 hours or more (Table 7.5). However, Geller *et al.* (1979) reported initial stimulation followed by depression in multiple fixed ratio-fixed interval (FR-FI) response schedule performance following inhalation by a small number of male Holtzman, Sprague-Dawley rats of 150 ppm (563 mg/m^3) for 4 hours. In addition, statistically significant decreases in cumulative wheel-turning activity in comparison with controls were reported at all doses in a study in which male NA 2 mice were exposed for 6 hours daily for 20 days to 1, 10, 100 or 1000 ppm (3.75 to 86,250 mg/m^3) toluene (Horiguchi and Inoue, 1977). However, there was no indication of the size of the experimental groups or the significance of the exposure-response trend in the published account of the study; moreover, animals were not chosen randomly but were selected for high wheel-turning activity. These results have not been confirmed by other investigators.

Toluene has also induced subtle changes in the auditory (ATSDR, 1989) and visual systems. Permanent high-frequency hearing loss in rats exposed to 1,000 ppm for 14 hours per day for 2 weeks has been reported though no effects were observed following exposure to lower concentrations (400 and 700 ppm) for periods up to 16 weeks (Pryor *et al.* 1984). In an English abstract of a study published in Japanese, Ikeda (1987) reported high concentrations of toluene in the optic nerve and reversible effects on electroretinography in rats following one or two weeks (12 h/d) exposure by inhalation to 90 ppm (340 mg/m^3) toluene.

7.8.2 Immunological Effects

Data on the immunological effects of toluene are limited. Increased susceptibility to respiratory infection upon challenge by *Streptococcus zooepidemicus* determined by mortality in the 14 day period following 3 hours of exposure of groups of 30 CD-1 mice to toluene concentrations of 2.5 to 500 ppm (9.38 to 1,875 mg/m^3) was observed in all dose groups, except those exposed to 10 ppm (37.5 mg/m^3) (Aranyi *et al.* 1985). There were, however, no measurable effects following a single 3 h or repeated exposures (3 h/d for 5 days, or 3 h/d, 5d/wk for 20 days) of similarly sized groups to 1 ppm. Decreases in pulmonary bactericidal activity 3 hours after infection with ^{35}S-labelled *Klebsiella pneumoniae* were observed after single 3 hour exposures to 2.5, 100, 250, and 500 ppm. Significant effects were not observed at 5, 10, 25 and 50 ppm. There was a decrease in bacterial activity following repeated exposure (3 h/d, for 5 days) to 1 ppm, but not following a single (3 h) or repeated exposures for a longer period (3 h/d, 5 d/wk for 20 days). Therefore, there was no consistent correlation between the two host resistance assays. The authors also noted the lack of a clear concentration response relationship in interpretation of the effects. The magnitude of the changes in bactericidal activity was also small with the mean percentages of bacteria killed in 3 hours being 71.9, 78.3, 73.4, 84.1, 90.8, 79.7, 84.1 and 79.2 corresponding to 500, 250, 100, 50, 25, 10, 5, and 2.5 ppm, respectively. The authors suggested on the basis of their results that toluene may affect alveolar macrophage function but concluded that this possibility needs to be further clarified in additional investigations.

In a study reported by Hsieh *et al.* (1989), small groups (n = 5) of male CD-1 mice ingested drinking water reported to contain 0, 17, 80, and 405 mg/L (considered to be equivalent to doses on a body weight basis of 5, 22 and 105 mg/kg/d) for 4 weeks. Mitogenesis by lipopolysaccharide, pokeweed mitogen, concanavalin A, and phytohemagglutinin was suppressed in splenocytes from exposed mice in all dose groups. Splenocyte lymphoproliferation to alloantigens and the numbers of sheep red blood cell-specific plague-forming cells were decreased in the high dose group of animals only. Interleukin-2 synthesis was also adversely affected in the high dose group (405 mg/L; 105 mg/kg/d). The authors concluded that further studies are needed to determine the precise biological significance of the effects of toluene on immune function.

7.9 Toxicity of Metabolites

The various metabolites of toluene have not been mutagenic or genotoxic in studies conducted to date (Huff, 1990) including benzyl alcohol in bacterial systems and human fibroblasts; benzoic acid in the *Salmonella* mutation assay, yeast gene conversion assay, chromosomal aberration in Chinese hamster ovary cells and human fibroblasts; hippuric acid in the *Salmonella* mutation assay; and m- and p-cresol in the *Salmonella* mutation assay, in human

fibroblasts and mouse fibroblasts *in vivo*. Results of carcinogenicity bioassays for benzyl alcohol and benzoic acid in rats have also been negative (NTP, 1989a, 1989b in Huff, 1990).

In the English abstract of a study published in Japanese, it was reported that visual toxicity was not observed in groups of five rats subcutaneously administered 2 mg/d of benzyl alcohol or 4 mg/d of benzaldehyde for two weeks (Ikeda, 1987).

8 EFFECTS ON HUMANS

Data on the health effects of toluene in humans are available from case reports of intentional abuse, clinical studies in human volunteers and epidemiological studies of occupationally exposed populations. Reports of effects following intentional abuse are not reviewed in detail here since the extremely high exposures (up to 112,500 mg/m^3; IPCS, 1985) are less relevant to assessment of the effects of toluene in the general environment. Moreover, reported cases of intentional abuse and epidemiological studies of occupationally exposed populations have generally involved exposures to complex mixtures with toluene as the principal constituent; they are, therefore, of less value than clinical studies in human volunteers in assessing exposure-response relationships for toluene itself.

8.1 Clinical Studies in Human Volunteers

Available data on effects of toluene in clinical studies in human volunteers are presented in Table 8.1. In general, studies have involved fairly short term single (20 minutes to 8 hours) or repeated exposures (6 to 7 hours per day for periods of 3 to 4 days or 8 hours biweekly for a period of 8 weeks) of a limited number of subjects (n=3 to 43) to concentrations ranging from 37.5 to 3000 mg/m^3. In well designed and documented studies, adverse effects have not been observed following exposure to 375 mg/m^3 or less for single periods of exposure of from 20 minutes to 3.5 hours (Gamberale and Hultengren, 1972, in IPCS, 1985; Winneke, 1982 in IPCS, 1985) or repeated exposures for 3 to 7 hours for periods up to 3 days (Echeverria *et al.* 1989; Ogata *et al.* 1970) based on a variety of tests of neurological function. However, Andersen *et al.* (1983) reported a decrease in neurological function as measured by a variety of tests, an increase in neurological symptoms and irritation of the respiratory tract following exposure of 16 volunteers to 375 mg/m^3 6 hours/day for 4 days. No adverse effects were seen at 150 mg/m^3 in this study. Dick *et al.* (1984) also reported adverse effects on visual vigilance following exposure of 18 to 30 volunteers to 375 mg/m^3 for 4 hours. Adverse effects on neurological function following single or repeated exposure to 375 mg/m^3 or less of toluene have also been reported in several other studies (Baelum *et al.* 1985; von Oettingen *et al.* 1942, in IPCS, 1985) which are less reliable owing to limitations of design (see Table 7.6). These effects are reversible on cessation of exposure; however, prolonged high level exposure has been reported to result in symptoms of permanent CNS damage, including impaired hearing, tremors, and behavioral changes.

8.2 Epidemiological Studies of Occupationally Exposed Populations

Epidemiological studies of populations occupationally exposed to toluene have been reviewed in IPCS (1985) and ATSDR (1989). These evaluations and the results of more recent investigations are reviewed here. In general in such studies, effects on the blood, liver, and central nervous system have been examined; there are also a few investigations in which

associations between exposure to toluene and reproductive, clastogenic or immunological effects have been examined. Furthermore, two studies of cancer mortality in workers exposed principally to toluene have been reported.

8.2.1 Systemic Effects

As reported in ATSDR (1989), available data on respiratory effects of chronic exposure to toluene in the occupational environment are inconclusive. Morphological changes in the nasal mucosa of 10 paint-sprayers exposed to 13 detected solvents (primarily toluene at concentrations ranging from 0.8 to 4.8 ppm and isobutylacetate) and dust have been reported (Hellquist *et al.*, 1983, in ATSDR, 1989); however, there was no conclusive association between duration of exposure and mucosal abnormalities (ATSDR, 1989). Symptoms of nasal irritation (in addition to eye irritation, nausea, skin conditions, dizziness and headaches) were reported in 42 workers exposed to mixtures of solvents, of which toluene was generally a major component (1 to 80 ppm) (Winchester and Madjar, 1986 in ATSDR, 1989); however, concurrent exposure to a mixture of solvents precludes establishing an unequivocal causal relationship between exposure to toluene and mucosal irritation (ATSDR, 1989).

Before the mid-1950s, haematological effects were reported to be associated with chronic occupational exposure to toluene; these effects are now attributed to concurrent exposure to benzene, a common contaminant of toluene at that time (ATSDR, 1989). Haematological effects have generally not been observed in recent studies of workers exposed for several years to concentrations which ranged up to 600 ppm toluene though these investigations have been limited by small cohort size and lack of individual exposure estimates (Banfer *et al.* 1961, in ATSDR, 1989; Matsushita *et al.* 1975, in ATSDR, 1989; Yin *et al.* 1987). However, Tahti *et al.* (1981) reported increased leucocyte counts in workers exposed for several years to toluene (20 to 200 ppm; benzene concentrations $<0.01\%$) in a factory manufacturing tarpaulins, but all mean counts were within the range of normal values. The cohort in this study was small, exposure to other solvents was not documented and there were few historical data on exposure; moreover, the toxicological significance of transitory changes in leukocyte counts is not clear (ATSDR, 1989).

Liver damage has generally not been observed in populations occupationally exposed to toluene; however, the available studies had only limited power to detect subtle adverse hepatic effects (ATSDR, 1989). Decreased serum levels of lactate-dehydrogenase were reported in female shoemakers exposed for several months to toluene (7 to 324 ppm) and other solvents (at concentrations that were generally less than one tenth of that of toluene) (Seiji *et al.* 1987 in ATSDR, 1989). However, since this enzyme is present in almost all tissues, this finding cannot be attributed to an effect on the liver with any certainty. Serum concentrations of liver enzymes in Swedish paint industry workers exposed for several years to several organic chemicals were

not increased when compared to nonexposed controls (Lundberg and Hakansson, 1985 in ATSDR, 1989).

More recently, mild hepatic effects have been reported in 3% of occupationally exposed workers hospitalized for solvent intoxication and dementia (Guzelian *et al.* 1988). In this epidemiological study of 289 print workers exposed primarily to less than 200 ppm toluene for 2 to 8 h/d (with minimal exposure to methyl alcohol, ethyl alcohol, trichloroethylene, lacquer thinners and diethyl ether), there was little difference between workers and controls in the prevalence of abnormal results of liver function tests, with the exception of eight workers for whom serum alanine transferase and/or alkaline phosphatase were repeatedly elevated. The eight men were not obese and generally healthy and had no history of taking medications or of drinking alcohol to excess. Six of them had hepatomegaly based on physical examination. For all eight, liver biopsy revealed mild, pericentral fatty change.

In a cross-sectional study of 181 male workers of a rotogravure printing plant (reported to be "in principle, all male workers in the plant"), 31 metal workers and electricians occasionally exposed to low levels of toluene ($<<$ 200 mg/m^3) were considered to be the reference group; the "exposed" group was 150 workers exposed for lengthy periods each day to $>$ 200 mg/m^3 (Boewer *et al.* 1988). Effects were assessed on the basis of physical examinations (including medical examination and histories) and laboratory tests (determination of serum aspartate aminotransferase, alanine aminotransferase, and gamma glutamyltransferase, blood glucose, oral glucose tolerance test, triglycerides, cholesterol, lipid electrophoresis, antinuclear factors, HB's-Ag, anti-HB's and abdnominal ultrasound). Alcohol consumption was characterized as minor, moderate or high based on responses to a questionnaire, a personal interview and corroboration with company medical and management personnel. Total body fat was estimated by the Broca index. Based on regression analysis including consideration of alcohol consumption, age, and body weight, toluene was not associated with liver damage, though the number of subjects particularly in the "reference group" was small. It should also be noted that the reference group was "occasionally" exposed to low levels of toluene.

Similarly, available data on renal effects in populations occupationally exposed to toluene are inconclusive. Significantly elevated excretion of albumin but not beta-2-microglobulin was reported in workers exposed to 80 to 107 ppm of toluene and unspecified concentrations of xylene, styrene and other chemicals (Askergren *et al.* 1981).

8.2.2 Carcinogenicity

Only two studies in which a potential association between occupational exposure to toluene and cancer has been investigated have been identified (Svensson *et al.* 1990; Wen *et al.* 1985). In a limited historical cohort study of 1,008 male oil refinery workers (who have been followed for a period of 43 years) exposed to approximately 1 ppm (8 h TWA) toluene and other

chemicals, mortality for all causes of death and cancer were lower than that in the general population (Wen *et al.* 1985). Although there was no excess mortality due to cancer, the risk appeared to increase with increasing duration of employment (ATSDR, 1989). However, the power of the study to detect a meaningful increase in cancer mortality was limited.

In another historical cohort study of 1020 rotogravure printers exposed to toluene and employed for a minimum period of three months in eight plants during 1925-85, exposure was estimated based on airborne concentrations of toluene measured since 1943 in one plant and 1969 in most, and on present concentrations of toluene in blood and subcutaneous fat (Svensson *et al.* 1990). Annual average concentrations in each plant were estimated to range from approximately 30 ppm (110 mg/m^3) in the mid-1980s to about 450 ppm (1700 mg/m^3) in the 1940s. There was some concomitant exposure to benzene up to the beginning of the 1960s. Compared with regional rates, total mortality did not increase during the observation period 1952-1986 (129 observed versus 125 expected). There was no increase in mortality from non-malignant diseases of the lungs, nervous system, or gastrointestinal and urinary tracts. There was no overall excess of tumours for the period 1958 to 1985 (68 vs. 54). Among the specific cancers considered which included leukaemias, lymphomas and myelomas, only those of the respiratory tract were significantly increased (Observed:Expected = 16:9). The increase was not statistically significant, however, in subjects with an exposure period of at least five years and a latency period of at least 10 years. Further, there was no relationship of the excess with estimated cumulated dose of toluene.

8.2.3 Genotoxicity

In several studies, increases in chromosomal aberrations or sister chromatid exchanges have been reported in toluene-exposed workers compared with unexposed populations (Bauchinger *et al.* 1982, in IPCS, 1985; Funes-Cravioto *et al.* 1977, in IPCS, 1985; Pelclova *et al.* 1990; Schmid *et al.* 1985, in ATSDR, 1989). The increase in sister chromatid exchange frequencies in toluene - exposed workers ceased to be statistically significant at periods greater than two years post-exposure (Schmid *et al.* 1985 in ATSDR, 1989). In these studies, however, there was a failure to adequately demonstrate that exposure was to toluene alone or, with the exception of the study by Schmid *et al.* (1985 in ATSDR, 1989), to consider the data from smokers separately from those of non-smokers, though smoking causes the same type of damage as that reported in some populations occupationally exposed to toluene (Huff, 1990; IPCS, 1985). In the most recent of these studies by Pelclova *et al.* (1990), an increased incidence of chromosome damage in the peripheral lymphocytes was reported in a group of 42 rotogravure printers exposed to a range of 104-1170 ppm (390-4380 mg/m^3) toluene for 12 years on average, and in a group of 28 other workers at the plant exposed to toluene concentrations in their offices of 2.1-4.3 ppm (8-16 mg/m^3) for 2 h/d, as compared with a control group of 32 persons working in offices near the plant. Although smoking and alcohol consumption were taken into account in the analyses, the influence of rotogravure printing dyes cannot be excluded. Other

investigators have found no correlation between occupational exposure to toluene and increased frequencies of either chromosome aberrations (Forni *et al.* 1971; Haglund *et al.* 1980; Maki-Paakkanen *et al.* 1980) or sister chromatid exchanges (Haglund *et al.* 1980), though this may have been a function of the limited power of the studies. For example, there was no increase in the frequency of stable (deletions, translocations, trisomies) and unstable (fragments, dicentric or ring chromosomes) chromosomal changes in peripheral lymphocytes of 24 workers exposed to 750 to 1500 mg/m^3 (200-400 ppm) toluene only for 7-15 years, compared to matched controls (Forni *et al.* 1971). There were no significant differences in the frequency of chromosomal aberrations and sister chromatid exchanges in 32 printers exposed to 26 to 420 mg/m^3 (7 to 112 ppm) pure toluene, 8h daily for an average of 14 years, compared to a group of 15 unexposed workers from a research institute (Maki-Paakkanen *et al.* 1980).

8.2.4 Reproductive and Developmental Effects

Available epidemiological data as summarized in IPCS (1985) and ATSDR (1989) and more recent studies are insufficient to serve as a basis for evaluation of the reproductive or developmental toxicity of toluene since in all of the studies conducted to date, subjects had also been exposed to other solvents. In a study of 14 women in Finland occupationally exposed to mixed solvents, some of which included toluene, and also exposed to various drugs including aspirin, vasodilators and diuretics, there was an increased risk of central nervous system anomalies and defects of neural tube closure in children exposed in utero (Holmberg, 1979 in ATSDR, 1989).

Michon *et al.* (1965 in IPCS, 1985), Matsushita *et al.*, (1975 in IPCS, 1985) and Syrovadko (1977 in IPCS, 1985; USEPA, 1985) reported complaints such as prolonged and intensive menstrual bleeding in women occupationally exposed to toluene, in combination with other aromatic hydrocarbons. Syrovadko (1977 in IPCS, 1985 and USEPA, 1985) also reported longer duration of labour and in babies born to these women, more frequent fetal asphyxia, higher prevalence of underweight babies, and poor nursing habits compared to control infants. In a case control study reported by Axelsson *et al.* (1984) of 745 women born after 1935 who had been engaged in laboratory work between 1968 and 1979, toluene exposure during the first trimester of pregnancy was reported by 140, 17 of whom (10.2%) had had a spontaneous abortion. The rate of spontaneous abortion among women who had not worked in a laboratory during the first trimester was 11.5% and for women who had worked in a laboratory but not with solvents during the first trimester, 9.5 %.

8.2.5 Neurotoxicity

Chronic occupational exposure to mixtures of solvents containing predominantly toluene has resulted in impaired performance on psychometric, motor and muscular function tests (ATSDR, 1989). Printers exposed to toluene and other solvents had poorer performance on tests

measuring cognitive ability. Differences in alcohol consumption could not explain the results based on an analysis of subgroups (Hanninen *et al.* 1976; 1987); however, the number of subjects examined was small.

In a cross-sectional study by Foo *et al.* (1990), neurobehavioural effects were examined in a group of 30 female workers exposed to toluene (8-h TWA 88 ppm = 330 mg/m^3) and a control group of 30 workers from a section of the same factory in which toluene-containing glue was not used, matched for age, sex, and ethnicity. All subjects were teetotallers, non-smokers, taking no medication and had no history of illness of the central or peripheral nervous systems or psychiatric disorders. The potential for exposure of the workers to other solvents was not addressed by the authors. There were statistically significant differences between workers exposed to toluene and controls in six out of eight neurobehavioural tests measuring manual dexterity, visual scanning and verbal memory, even though the controls were also exposed to low levels of toluene (13 ppm), due to cross contamination of work areas. Concentrations of toluene in the blood of exposed and control subjects averaged 1.25 and 0.16 mg/L, respectively.

In a recent study, 30 rotogravure printers (33 to 61 years of age) exposed to mean concentrations of 43 and 157 mg/m^3 toluene in two plants for 4 to 43 years, were interviewed and psychometric testing conducted (Orbaek and Nise, 1989). The potential for exposure to other solvents in the working environment was not reported by the authors. A high proportion of the printers reported significantly increased frequency of symptoms compared to control subjects including fatigue (60%), recent short-term memory problems (60%), concentration difficulties (40%), mood lability (27%) and other neurasthenic symptoms. In most of the psychometric tests, performance of the printers was poorer than that of the reference group (who had never been exposed to solvents). Although the number of workers examined in this study is small, the authors concluded that long-term exposure to concentrations less than 157 mg/m^3 induced neurasthenic symptoms and reduced performance on psychometric tests.

In 262 male employees of two Danish photographic printing plants (325 out of a total of 382 volunteered to participate, 59 of the 325 on night shift or holiday during the study period were excluded), exposure was scored based on information on six criteria (including some consideration of short term peaks) obtained in interviews (Morck *et al.* 1988). Concentrations of toluene ranged up to 1200 ppm before the 1950s, were 200 ppm in the 1950s and 50 to 100 ppm since the 1960s. Subjects answered standardized questionnaires on symptoms for all major organ systems and drug and alcohol consumption. Work foremen were also interviewed concerning alcohol consumption. Physical examinations (including blood pressure and reaction time determinations and lung function testing) and biochemical measurements (beta-haemoglobin and creatinine, urate, alanine aminotransferase, creatine kinase, thyroxin, triiodythyronin, estradiol follicle stimulating and luteinizing hormones, prolactin sexual hormone binding globulin and cortisole in serum and creatinine in urine) were conducted. Follow-up examinations of a subsample of 140 of the workers who had not worked for 6 weeks (due to a "lock-out") were

also conducted. Following adjustment for possible confounding factors (age, alcohol consumption, smoking, weight and height), a statistically significant correlation was observed between exposure and dizziness ($p<0.01$), subjective feeling of decreased memory ($p<0.001$), decreased ability to concentrate ($p<0.001$), fainting fit during the past two years ($p<0.01$), subjectively experienced abnormal defecation pattern ($p<0.01$), sexual problems experienced during the last few years ($p<0.001$), systolic blood pressure ($p<0.01$) and serum levels of follicle stimulating hormone (FSH) ($p<0.001$). Following six weeks without exposure, the plasma testosterone level increased significantly and the systolic blood pressure and alanine amino-transferase decreased significantly ($p<0.001$); only the latter correlated with the exposure score. The authors reported that other solvents such as petroleum and white spirit had been used by the workers examined, though to a rather limited extent.

The prevalence of slight to moderate "organic brain syndrome" was increased in a small number (22) of workers exposed to toluene for at least 12 years in two plants compared to 19 unexposed control subjects matched for age and employment status, as assessed by clinical psychiatric interview (conducted blindly). Testing of cognitive function was conducted though results were not reported. At the time of the investigation, eight-hour time weighted average concentrations of toluene in the plants were 50 to 80 ppm (188 to 300 mg/m^3); workers had also been exposed to white spirit, ethanol and trichloroethylene (Larsen and Leira, 1988).

Visual evoked potentials (VEPs) from stimulation by checkerboard pattern reversal were examined in 54 rotogravure printers exposed to toluene (all men, aged 22 to 64 years, duration of exposure 1 to 41 years to mean concentrations of 2000 mg/m^3) and a control group of 46 subjects (23 men and 23 women aged 22 to 54 years) (Urban and Lukas, 1990). All subjects had no history of illness known or assumed to influence VEPs. Reduced reproducibility or absence of some waves was more frequent in the exposed as compared to the control group. The VEPs were abnormal in 24% of workers which correlated positively with the duration of exposure to toluene and also with the degree of alcohol consumption. Results were similar two years later upon re-examination in 78% of the exposed workers, suggesting that the observed VEP changes were stable.

8.2.6 Immunotoxicity

Data available on the immunological effects of toluene in occupationally exposed populations are limited and confounded by concomitant exposure to other chemicals. Workers exposed to a mixture of toluene, benzene and xylene had significantly lower serum IgG and IgA levels (Lange *et al.* 1973 in ATSDR, 1989). Leukocyte agglutinins for autologous leukocytes and increased leukoagglutination titer in human sera after incubation with the solvents were also observed. These data suggest that workers exposed to these chemicals may exhibit allergic blood dyscrasias. A decrease in the T lymphocyte count of workers occupationally exposed to a mixture of benzene, toluene and xylene was observed (Moszczynski and Lisiewicz, 1984 in

ATSDR, 1989). However, there were no signs of diminished immunological function or disturbances in immune skin reactions against such antigens such as tuberculin or distreptase in these subjects. The reduction of T lymphocytes may have been the result of the depressive effect of benzene on the lymphocyte system.

8.3 Intentional Abuse

Cases of intentional abuse (*i.e.*, "glue sniffing") have generally involved exposure to complex mixtures, with toluene being the principal constituent. The concentrations of toluene inhaled under such circumstances are extremely high, approaching 112,500 mg/m^3 (*i.e.*, saturation concentration at 20°C). Such high exposures can result in gross disorientation and unconsciousness (IPCS, 1985).

Episodes of toluene abuse are characterized by the progressive development of CNS symptoms of dysfunction. Following repeated exposures for periods as long as 10 to 14 years, permanent encephalopathy, reversible hepatorenal damage, cerebral and cerebellar atrophy, impairment of neurological and neuropsychological function, dementia with cerebellar ataxia, optic atrophy with blindness, acquired pendular nystagmus, sensori-neural hearing loss, convulsions, haematological abnormalities and possible "fetal solvent syndrome" have been reported (Ikeda and Tsukagoshi, 1990; IPCS, 1985; Knox and Nelson, 1966, Low *et al.* 1988; Maas *et al.* 1991; Seppalainen, 1988; USEPA, 1989). In a recent report, a 14-year-old Caucasian boy with a toluene level in blood of 0.26 μg/L developed extensive hypothalamic dysfunction including diabetes insipidus, adipsia, hyperprolactinaemia, and poikiliothermia together with central sleep apnoea (Teelucksingh *et al.* 1991).

9 EFFECTS ON THE ECOSYSTEM

9.1 Aquatic Toxicity

The aquatic toxicology of toluene has been reviewed by a number of authors and agencies (USEPA, 1980; Gilbert *et al.*, 1983; Syracuse Research Corporation, 1983; IPCS, 1985; Nielsen and Howe, 1991).

Toluene is a volatile substance and disappears rapidly from solution. It is therefore difficult to maintain test concentrations for sufficient time to establish concentration-effects profiles for aquatic organisms. This is especially the case for studies under static conditions with open containers, and for studies of chronic or sublethal effects where prolonged exposure periods are required. While equipment and protocols are available for studying effects of volatile compounds, these have not been applied to toluene to any great extent and hence sublethal effects have not been widely determined.

Ward *et al.* (1981) determined that the average measured water concentrations of toluene in seawater ranged from 5-8% of the nominal concentration in a 96-hour acute test in an open container. Korn *et al.* (1979) found that concentrations of toluene in static test systems declined with time, either via volatilization or biodegradation, and that it did so in a temperature-dependent fashion. Toluene declined to non-detectable levels within 72 hours at 12°C, within 96 hours at 8°C, and to 25% of the initial concentration after 96 hours at 4°C. Toxicity data for volatile compounds such as toluene generated using static test systems are of questionable accuracy because volatilization results in actual test concentrations being well below the nominal concentrations (Buikema and Hendricks, 1980). Brenniman *et al.* (1976) observed that 96-hour LC_{50}s derived for toluene using static open systems generally are not lower than 24-hour LC_{50}s using the same system, indicating that most toluene had probably left the system by 24 hours. In contrast, Galassi *et al.* (1988) found mean measured concentrations to fluctuate by only 10% over 48 hours when using a closed static system.

These observations suggest that an assessment of the aquatic toxicity of toluene based on static and open systems and reporting nominal rather than measured concentrations could underestimate its hazard in the environment. This report therefore focuses on results from studies employing flow-through or static renewal conditions or where the concentrations in solution have been actually measured during the course of the tests.

Water hardness appears to have little effect on acute lethality (USEPA, 1980; NRC, 1980) although some effects due to temperature (DOE, 1984) and salinity (Dangé, 1986) have been reported. These effects on toxicity may be due to effects on the test organisms, effects on the physicochemical behaviour of toluene, and interactive effects of both. Toluene is less soluble

in saltwater than in fresh water and is both more soluble and more volatile at higher temperatures.

9.1.1 Effects on Algae

All of the tests for toxicity of toluene to algae have been conducted under static conditions, using either open or closed vessels (Table 9.1).

Galassi *et al.* (1988), using a closed system with measured concentrations, reported a 72-hour EC_{50} of 12.5 mg/L for *Selenastrum capricornutum*. Growth of *S. capricornutum* was reduced by 50% after 8 days at 9.4 mg/L (measured concentrations) (Herman *et al.*, 1990). Giddings (1979), in a closed vessel study with the same species, recorded 97% inhibition of photosynthesis after 8 hours exposure to 100 mg/L, based on nominal concentrations.

In saltwater, respiration of *Chlorella* sp. was inhibited by 62% after 12 hours exposure to 34 mg/L (measured) (Potera, 1975). The EC_{50} for inhibition of photosynthesis by the marine diatom *Dunaliella biocula* was approximately 10 mg/L (nominal) after 4 hours exposure in a closed vessel (Jensen *et al.*, 1984). Dunstan *et al.* (1975) demonstrated inhibition of growth for the marine diatoms *Skeletonema costatum*, *Amphidinium carterae*, *Cricosphaera carterae* and *Dunaliella tertiolecta* at concentrations of 10 mg/L (nominal). Growth rates for the latter two species were actually stimulated by 10-40% at toluene concentrations less than 1.0 mg/L. These authors concluded that differential growth of phytoplankton species could ultimately determine the community structure and its trophic relationships.

9.1.2 Effects on Invertebrates

Based on the limited data available, the toxicity of toluene to crustaceans and molluscs (Table 9.2) is similar to that reported for fish. Many of the studies were done with static, open systems and the toxicity may therefore be underestimated in those studies.

Among freshwater invertebrates, the 24-hour LC_{50} for the water flea, *Daphnia magna*, was 7 mg/L based on measured concentrations in closed vessels (Galassi *et al.*, 1988), while the 48-hour LC_{50} was 11.5 mg/L based on nominal concentrations in closed vessels (Bobra *et al.*, 1983).

The fourth instar larvae of the mosquito, *Aedes aegypti*, was found to have a 24-hour LC_{50} of 21.52 mg/L; the lowest concentration with no mortality was observed to be 9.95 mg/L (Berry and Brammer, 1977).

Valve closure of the zebra mussel, *Dreissena polymorpha*, was altered after 24-hour exposure to 9.4 mg/L (Sloof *et al.*, 1983). This is an exotic species imported to Canadian waters; data for native freshwater molluscs are not available.

The toxicity of toluene to marine invertebrates appears to be similar to that to freshwater species. The 96-hour LC_{50} for adult bay shrimp, *Crago franciscorum*, was 4.3 mg/L (Benville and Korn, 1977). For the grass shrimp, *Palaemonetes pugio*, the 24-hour LC_{50}s were 25.8 mg/L for larvae and 17.2 mg/L for adults (Potera, 1975). Toluene inhibited the filtration ability of mussels at 1 mg/L (SRI, 1980). Concentrations of 7.8 mg/L significantly reduced the respiration rate of the mussel *Mytilus californicus* when exposed for 24 hours; concentrations of 64-88 mg/L significantly reduced their heart rate (Sabourin and Tullis, 1981). The 96-hour LC_{50} for the larvae of the crab *Cancer magister* was 28 mg/L under static conditions with renewal of test solution every 24 hours (Caldwell *et al.*, 1976).

9.1.3 Effects on Fish and Amphibians

As with other organisms, there is a paucity of data on the toxicity of toluene to fish under flow-through, static with renewal or closed static systems where the toluene concentrations were actually measured (Tables 9.3, 9.4, 9.5).

As is frequently the case in testing toxicant effects on fish (Mayer and Ellersieck, 1986), some early life stages of salmonid species are most sensitive. McKim (1977) reviewed 56 life cycle toxicity tests involving 34 organic and inorganic chemicals and four species of fish, and found that the embryo-larval and early juvenile stages were generally the most sensitive. In 86% of the tests reviewed, the maximum acceptable toxicant concentration (MATC) estimated by embryo-larval or early juvenile exposures was identical to the MATC established in partial or complete life cycle tests. Water quality, species, type of toxicant, and parental exposure did not appear to affect this trend.

Moles *et al.* (1981) studied the growth of coho salmon (*Oncorhynchus kisutch*) fry exposed for 40 days to constant concentrations of toluene in freshwater under flow-through conditions. The 96-hour LC_{50} estimated by extrapolation was 5.5 mg/L. Growth per day, determined from weights and lengths, decreased linearly with increasing toluene concentrations. Weight differences in the 2.8 and 5.0 mg/L groups were significantly different from the control. At the highest test concentration (5.0 mg/L), growth stopped during the first 20 days of exposure. The NOEC was 1.4 mg/L.

In a 32-day exposure test with embryo-larvae of fathead minnows (*Pimephales promelas*), the lowest observable effect concentration (LOEC) for weight gain was 6 mg/L, based on exposure to measured concentrations of toluene under flow-through conditions (Devlin *et al.*, 1982). As shown by determinations of 96-hour LC_{50}s, 30 day old fish (26 mg/L) and pro-larvae

(29 mg/L) of fathead minnows were significantly more sensitive to the lethal effects of toluene than were the embryos (63 mg/L).

Ward *et al.* (1981) observed a 96-hour LC_{50} of 13 mg/L for the marine sheepshead minnows (*Cyprinodon variegatus*) exposed to measured concentrations of 1 - 19 mg/L toluene over the period from fertilization to 28 days post-hatch. Toluene concentrations equal to or greater than 7.7 mg/L (LOEC) caused significant decreases in the hatching success of embryos and increases in the mortality of juveniles; there was no significant effect on the growth of the surviving juveniles. The NOEC for hatching success and juvenile mortality was 3.2 mg/L. These authors estimated a maximum acceptable toxicant concentration (MATC) for survival, growth, reproduction, spawning, viability of embryos, and survival and growth of the F_1 generation to be 3.2-7.7 mg/L. This compares well with a value of 6 mg/L determined by Devlin *et al.* (1982) for fathead minnows.

Although carp (*Cyprinus carpio*) experienced changes in serum and tissue parameters, reflecting altered metabolism and depletion of energy stores, when exposed to toluene for 72 hours at 0.1 mg/L (Gluth and Hanke, 1985), the significance of these responses to growth and survival were not established.

Black *et al.* (1982) determined the toxicity of toluene to the early life stages of the rainbow trout (*Oncorhynchus mykiss*), leopard frog (*Rana pipiens*), and northeastern salamander (*Ambystoma gracile*) using a flow-through system designed specifically for testing the effects of volatile organic compounds. Exposure concentrations were confirmed by daily chemical analyses of test water, which was optimally reconstituted for embryo-larval tests and chemically monitored throughout the experiment. Eggs were exposed continually to toluene from within 30 minutes of fertilization (embryos) to 4 days post-hatch (larvae). Average hatching times were 23 days for trout, 5 days for frogs and 5.5 days for salamanders, resulting in total exposure times of 23 days for trout, 9.5 days for salamander, and 9 days for frog. The LC_{50}s (continuous exposure, from fertilization until 96-hours post-hatch) were 0.02 mg/L for trout, 0.39 mg/L for frog, and 0.85 mg/L for salamander.

In another study with adult rainbow trout, Galassi *et al.* (1988) report a 96-hour LC_{50} of 5.8 mg/L.

Slooff (1979) found that 2.5 mg/L toluene was the lowest concentration to cause a change in the respiration frequency of rainbow trout within 24 hours of exposure. Thomas and Rice (1979) found that toluene caused a linear increase in the breathing rate of pink salmon (*Oncorhynchus gorbuscha*) fry with increasing exposure concentrations. These increases in breathing rate were accompanied by increased oxygen consumption reflecting increased energy demands. Breathing rates increased by 10% at toluene concentrations of 2.5 mg/L and were doubled at 4.3 mg/L.

The studies of Maynard and Weber (1981), using a Y-maze, suggest that downstream migrating juvenile coho salmon would probably avoid acutely lethal concentrations of individual monocyclic aromatic hydrocarbons, but there is some question as to whether they would avoid toxic concentrations of mixtures of these compounds. Juvenile coho salmon were able to significantly avoid toluene concentrations in freshwater of 1.4 mg/L or greater, but no significant avoidance of 0.9 mg/L was observed. A greater percentage of early smolts than presmolts avoided 1.8 mg/L toluene. The EC_{50}(avoidance) (expressed as mg total hydrocarbons) for coho salmon for a mixture of 57% toluene, 26% xylenes, 8% benzene, 7% 1,2,4-trimethylbenzene, and 2% ethylbenzene, was 1.9 mg/L in June and July and 3.7 mg/L in January and February. During the peak spawning run at Chambers Creek, Washington, Weber *et al.* (1981) found that free-living, mature Pacific salmon avoided 3.2 mg/L and higher concentrations of this same mixture. Potential effects on upstream migration of toluene spills in streams and rivers are not known.

9.2 Toxicity to Terrestrial Organisms

The potential for toluene to affect terrestrial ecosystems has not been evaluated either in the field or in laboratory microcosms. Very little information is available on the effects of toluene on terrestrial organisms apart from experimental laboratory species.

9.2.1 Toxicity to Soil Microorganisms and Soil Processes

A temporary increase in the rate of bacterial growth in sewage sludge deposits, as measured by methane production, was observed at 20 mg/L toluene (Barash, 1957, cited in Miller *et al.*, 1976). The same system showed a sharp reduction in the rate when exposed to 200 mg/L.

Saturated levels of toluene (515 mg/L at 20°C) were found to be toxic to *Pseudomonas putida*, strain AB, although lower levels allowed growth (Gibson, 1975 cited in Syracuse Research Corporation, 1983). The 16-hour EC_{50} for cell multiplication of *P. putida* at 25°C was greater than 400 mg/L (Bringmann and Kühn, 1977).

The NOEC for toluene in relation to soil microbial respiration and ammonification ranged from 100 - 1300 mg/kg and was <26 mg/kg (dry) for nitrification (Sloof and Blokzijl, 1988). Walton *et al.*, (1989), in studies with soil moistened to 80% base saturation, found that microbial respiration was initially depressed at 1000 mg/kg (dry) as measured by the production of CO_2; respiration was unaffected at day 6, however.

9.2.2 Toxicity to Earthworms

In a 28-day test with earthworms (*Eisenia foetida*), toluene affected mortality, cocoon production, and appearance; appearance was the most sensitive parameter, with a NOEC of between 15 and 50 mg/kg soil (dry weight) (Sloof and Blokzijl, 1988). The LC_{50} was between 150 and 280 mg/kg. In a contact test with the same species, filter papers were impregnated with various amounts of toluene and a 48-hour lethal exposure value of 75 $\mu g/cm^2$ of filter paper was determined (Neuhauser *et al.*, 1985).

9.2.3 Toxicity to Plants

Effects of toluene on terrestrial plants have been reviewed by Miller *et al.* (1976), Syracuse Research Corporation (1983), Sloof and Blokzijl (1988), and Nielsen and Howe (1991). Toluene damages the plasma membrane of plants, entering readily through the stomata and the cuticle. According to Sloof and Blokzijl, (1988), chlorosis and growth inhibition were induced at levels of >6000 mg/m^3 air, 500 mg/L water, and 1000 mg/kg soil; growth stimulation may occur at 5 to 50 $\mu g/L$ water. Toluene vapours damaged the semi-permeability of sweet potato tubers and affected water intake by the seeds of *Lupinus*, *Zea* and *Pisum* (Miller *et al.*, 1976).

Other plants which were damaged by toluene vapours included young barley, tomato and carrot plants. Effects occurred after exposures of 0.25 to 2 hours at concentrations of 6,400 and 12,000 mg/m^3 (Currier, 1951). Barley and tomato were more sensitive than carrots at levels of 6,400 mg/m^3 and above. Damage to green leaves included leaf tip darkening, loss of turgor, and bleaching of chlorophyll in sunlight.

9.2.4 Toxicity to Birds and Mammals

There are no toxicity data available for birds or wild mammals. Tests with laboratory mammals have been reviewed in Chapter 7.

Because of toluene's volatility, inhalation of ambient air is considered the major source of exposure for terrestrial species. Laboratory studies using inhalation as the route of exposure are therefore those that are most relevant to the assessment of environmental effects. The lowest effect level for rats and mice under conditions of subchronic or chronic exposure by inhalation was 100 ppm (375 mg/m^3) (LOEL which induced a decrease in body weight in a 14-week inhalation study in mice [Huff, 1990]) (see Chapter 7).

Fetotoxic effects of toluene have been demonstrated in controlled studies with rats and mice (Donald *et al.*, 1991). Continuous inhalation exposures to toluene at 133 - 2000 ppm (500-7500 mg/m^3) during the critical period of fetal development were responsible for several negative effects. Intrauterine developmental retardation is the most clearly established effect,

as evidenced by decreased fetal weights and retarded skeletal development. There is also evidence of effects on postnatal and possibly neurological/behavioural development.

Effects following exposure by inhalation are therefore only experienced by laboratory mammals after lengthy periods of exposure to toluene concentrations greater than about 375 mg/m^3 in the air.

9.3 Abiotic Effects

Gases involved in enhanced global warming strongly absorb infrared radiation especially of wavelengths of 7 to 13 μm, enabling them to trap and re-radiate a portion of the Earth's thermal radiation (Wang *et al.*, 1976; Ramanathan *et al.*, 1985). Since toluene does not absorb at these wavelengths (Sadtler Research Laboratories, 1982), it is not considered as a direct contributor to global warming.

Substances involved in depletion of stratospheric ozone are generally halogenated, insoluble in water, and persistent in the atmosphere allowing movement to the stratosphere; in the stratosphere, they are degraded only by high energy, short wavelength ultraviolet radiation (Firor, 1989). Since toluene is a non-halogenated, water-soluble molecule of low persistence in the atmosphere, it is not associated with depletion of stratospheric ozone.

10 OTHER PERTINENT DATA

The St. Clair River - Lake St. Clair ecosystem has a diverse fish community including a total of 93 sport and forage fish, including rainbow trout and other salmonids, and provides spawning and nursery habitat for at least 46 species of fish (Edsall *et al.*, 1988). The area provides excellent habitat for amphibians and reptiles (including rare species), birds and mammals. The marshes and shallow waters of Lake St. Clair provide one of the most important resting and feeding areas for migrating waterfowl in Canada south of James Bay. Lake St. Clair National Wildlife Area is one of 30 Canadian sites designated by the Ramsar Convention as a Wetland of International Importance. The Walpole Island Indian Band occupies the St. Clair River delta area. The wetlands and the diverse fauna they support are important to the traditional values of the Band and provide food and wealth to their economy.

Between 1974 and 1985, there were 11 major oil spills of 10 tonnes or more (a total of 1,282 tonnes) and 21 major spills of other hazardous compounds (a total of 10,390 tonnes) in the St. Clair River system (Upper Great Lakes Connecting Channels Management Committee, 1988). The largest group of pollutants spilled into the St. Clair River are oil and gas products; between 1986 and 1989, the total mass of these substances spilled into the river was over 6,000 kg, along with 19 kg of isolated toluene in two spills. In January, 1992, there was a spill of 1,000 kg of a mixture of toluene (33%), benzene, and xylenes from an Ontario source, resulting in toluene concentrations in the river as high as 22 μg/L (MOE, 1992). While spills are occasional and transient in nature, environmental effects could be expected in areas of recurring spills. Such effects have not been clearly identified nor quantified, and the relative contribution of toluene to possible effects in the St. Clair River - Lake St. Clair ecosystem is not known.

11 CURRENT OBJECTIVES, GUIDELINES AND REGULATIONS

Table 11.1 lists many Canadian (including federal, provincial, territorial, and municipal), foreign, and international regulations, standards, recommendations and guidelines for toluene.

In Canada, a water quality guideline of 0.3 mg/L is recommended for the protection of aquatic biota (CCREM, 1987). An aesthetic objective of 0.024 mg/L is recommended for drinking water quality based on the odour threshold (NHW, 1989). The province of Ontario and the Montreal Urban Community limit point source emissions of toluene so that the calculated 30-minute maximum ground level concentration attributable to the source is 2 mg/m^3 (see Table 11.1); the basis for this standard is the prevention of odour. Occupational exposure limits at the federal and provincial levels are generally in line with recommendations of the American Conference of Governmental Industrial Hygienists; the Canadian Labour Code and corresponding provincial regulations have a TWA (time-weighted average) of 375 mg/m^3 and a STEL (short term exposure limit) of 560 mg/m^3 for toluene in the work place (Table 11.1).

The USEPA has included toluene in its List II of inert ingredients in pesticide products (Campt, 1989); products in this list are "potentially toxic inerts with high priority for testing", and pesticide registrants are encouraged to replace them with less toxic ingredients. In Canada, pesticides are regulated federally under the *Pest Control Products Act*, administered by Agriculture Canada. Recommendations have been made to establish three lists of formulants in Canada, and to deal with the formulants in a manner similar to that of the USEPA (Pesticide Registration Review Team, 1990). Adoption of such a policy could result in reduced use of toluene in pesticide formulations.

In the U.S.A., toluene is subject to the provisions of Section 112 of the 1990 *Clean Air Act* Amendments.

A Working group of the International Agency for Research on Cancer has concluded that toluene is not classifiable as to its carcinogenicity to humans (Group 3) (IARC, 1989). The USEPA has classified toluene as a Group D compound (not classifiable as to human carcinogenicity) (ATSDR, 1989). The reference dose proposed by USEPA was 21 mg/day (ATSDR, 1989).

"Safe" levels for exposure of biota have been calculated by government agencies, though the levels may not yet be formally adopted as guidelines or regulations. In the Netherlands, Sloof and Blokzijl (1988) proposed a safe level for fresh water and marine ecosystems of 0.05 mg/L, and noted that short term exposure (less than 24 hours) to peak levels of about 0.5 mg/L should not result in ecological damage. In the U.K., Nielsen and Howe (1991) calculated no effect levels in water ranging from 0.004 to 0.05 mg/L.

REFERENCES

Ameno, K., Fuke, C., Ameno, S., Kiriu, T., Sogo, K. and Ijiri, I. 1989. A fatal case of oral ingestion of toluene. Forensic Sci. Int. 41:255-260.

American Petroleum Institute. 1978. Mutagenicity evaluation of toluene. API Medical Research Publication. 26-60020.

American Petroleum Institute. 1981. Mutagenicity evaluation of toluene. Mouse dominant lethal assay. API Medical Research Publication. 28-31347.

American Petroleum Institute. 1985. Two-Generation Reproduction/Fertility Study on a Petroleum-Derived Hydrocarbon: Toluene. Volume 1. EPA Document No. FYI-AX-0885-0294.

Amlacher, E. and Rudolph, C. 1978. Nuclear DNA synthesis rate and labelling index: effects of carcinogenic and non-carcinogenic chemicals on its behaviour in the organism of growing CBA mice. The thymidine-incorporation-screening-system (TTS). Exp. Pathol. 16:69-82.

Amlacher, E. and Rudolph, C. 1981. The thymidine incorporation inhibiting screening system (TTS) to test carcinogenic substances (a nuclear DNA synthesis suppressive short term test). Archiv für Geschwulstforsch. 51:605-610.

Andersen, I., Lundqvist, G.R., Molhave, L., Pedersen, O.F., Procter, D.F., Vaeth, M. and Wyon, D.P. 1983. Human response to controlled levels of toluene in six-hour exposures. Scand. J. Work Environ. Health. 9:405-418.

Anderson, D. and Styles, J.A. 1978. An evaluation of 6 short-term tests for detecting organic chemical carcinogens. Appendix II. The bacterial mutation test. Br. J. Cancer. 37:924.

Andersson, K., Fuxe, K., Toftgard, R., Nilsen, O.G., Eneroth, P. and Gustafsson, J. 1980. Toluene-induced activation of certain hypothalamic and median eminence catecholamine nerve terminal systems of the male rat and its effects on anterior pituitary hormone secretion. Toxicol. Lett. 5:393-398.

Angerer, J. 1979. Occupational chronic exposure to organic solvents. VII. Metabolism of toluene in man. Int. Arch.Occup. Environ. Health. 43:63-67. (cited in IPCS, 1985).

Aranyi, C., O'Shea, W.J., Sherwood, R.L., Graham, J.A. and Miller, F.J. 1985. Effects of toluene inhalation on pulmonary host defenses of mice. Toxicol. Lett. 25:103-110.

Aristov, V.N., Red'kin, Y.V., Bruskin, Z.Z. and Ogleznev, G.A. 1981. Experimental data on the mutagenic effect of toluene, isopropyl alcohol and sulphur dioxide. Gigiena Truda i Professional'nye Zabolevaniya. 7:33-36.

Askergren, A., Allgen, L.G., Karlsson, C., Lungberg, I. and Nyberg, E. 1981. Studies on kidney function in subjects exposed to organic solvents. Acta Med. Scand. 209:479-483.

Astrand, I., Ehrner-Samuel, H., Kilbom, A. and Ovrum, P. 1972. Toluene exposure. I. Concentration in alveolar air and blood at rest and during exercise. Scand. J. Work Environ. Health. 72:119-130.

Atkinson, R. 1990. Gas-phase tropospheric chemistry of organic compounds: A review. Atmos. Environ. 24A:1-41.

ATSDR (Agency for Toxic Substances and Disease Registry). 1989. Toxicological Profile for Toluene. U.S. Public Health Service. 133 pp.

Axelsson, G., Lutz, C. and Rylander, R. 1984. Exposure to solvents and outcome of pregnancy in university laboratory employees. Br. J. Ind. Med. 41:305-312.

Baelum, J., Andersen, I., Lundqvist, G.R., Molhave, L., Pedersen, D.F., Vaeth, M. and Wyon, D.P. 1985. Response of solvent-exposed printers and unexposed controls to six-hour toluene exposure. Scand. J. Work. Environ. Health. 11:271-280.

Banfer, W. 1961. Studies on the effect of pure toluene on the blood picture of photograture printers and helper workers. Zentral fur Arbeitsmed. 11:35-40. (cited in ATSDR, 1989).

Barash, V.A. 1957. The influence of some mineral and organic substances on methane fermentation in sewage sludges. [Chemical Abstracts 52:75831, 1958]. Cited in Miller *et al.*, 1976.

Barker, J.F. 1987. Volatile aromatic and chlorinated organic contaminants in groundwater at six Ontario landfills. Water Pollut. Res. J. Can. 22:33-48.

Barker, J.F., Barbash, J.E. and Labonté, M. 1988. Groundwater contamination at a landfill sited on fractured carbonate and shale. J. Contam. Hydrol. 3:1-25

Battig, K. and Grandjean, E. (1964) Industrial solvents and avoidance conditioning in rats. Arch. Environ. Health. 9:475-749. (cited in IPCS, 1985).

Bauchinger, M., Schmid, E., Dresp, J., Kolin-Gerresheim, J., Hauf, R. and Suhr, E. 1982. Chromosome changes in lymphocytes after occupational exposure to toluene. Mutat. Res. 102:439-445. (cited in IPCS, 1985).

Baxter, L., Dennie, D., Schooler, S., Parham, S., Lyons, C., Wilson, A. and Washington, W. 1987. Dominant lethal mutations in Sprague-Dawley rats. Fed. Proceed. 46:1137.

Bayer, C.W., Black, M.S. and Galloway, L.M. 1988. Sampling and analysis techniques for trace volatile organic emissions from consumer products. J. Chromatogr. Sci. 26-168-173.

Benville, P.E. and Korn, S. 1977. The acute toxicity of six monocyclic aromatic crude oil components to striped bass (*Morone saxatilis*) and bay shrimp (*Crago franciscorum*). Calif. Fish Game 63(4):204-209.

Berry, W.O. 1980. A comparative study of the uptake of toluene by bluegill sunfish *Lepomis macrochirus* and crayfish *Orconectes rusticus*. Environ. Pollut. 21A:109-119.

Berry, W.O. and Brammer, J.D. 1977. Toxicity of water-soluble gasoline fractions of fourth-instar larvae of the mosquito *Aedes aegypti L.* Environ. Poll. 13:229-234.

Bjornaes, S. and Naalsund, L.U. 1988. Biochemical changes in different brain areas after toluene. Toxicology 49:367-374.

Black, F.M., High, L.E. and Lang, J.M. 1980. Composition of automobile evaporative and tailpipe hydrocarbon emissions. J. Air Pollut. Control Assoc. 30:1216.

Black, J.A., Birge, W.J., McDonnell, W.E., Westerman, A.G., Ramey, B.A. and Bruser, D.M. 1982. The aquatic toxicity of organic compounds to embryo-larval stages of fish and amphibians. Research Report No. 133. Project No. B-071-KY. United States Dept. of the Interior. Agreement No. 14-34-0001-0223(FY1980).

Bobra, A.M. 1991. Personal communication. Environment Canada, Commercial Chemicals Branch, Ottawa.

Bobra, A.M., Shiu, W.Y. and Mackay, D. 1983. A predictive correlation for the acute toxicity of hydrocarbons and chlorinated hydrocarbons to the water flea. Chemosphere 12:1121-1129.

Boewer, C., Enderlein, G., Wollgast, U., Nawka, S., Palowski, H. and Bleiber, R. 1988. Epidemiological study on the hepatotoxicity of occupational toluene exposure. Int. Arch. Occup. Environ. Health 60:181-186.

Bos, R.P., Brouns, R.M.E., van Doorn, R., Theuvs, J.L.G. and Henderson, R.T. 1981. Non-mutagenicity of toluene, o-,m-,and p-xylene,o-methylbenzylalcohol and o-methyl-benzylsulphate in the Ames assay. Mutat. Res. 88:273-279.

Brenniman, P., Hartung, R. and Weber, W.J. 1976. A continous-flow bioassay method to evaluate the effects of outboard motor exhaust and selected aromatic toxicants to fish. Water Res. 10:165-169.

Brien, E.D. 1991. Survey of Pesticide Registrants, unpublished data. Environment Canada, Commercial Chemicals Branch, Ottawa.

Bringmann, G. and Kühn, R. 1980. Comparison of the toxicity thresholds of water pollutants to bacteria, algae and protozoa in the cell multiplication inhibition test. Water Res. 14:231-241.

Bruckner, J.V. and Peterson, R.G. 1976. Evaluation of toluene toxicity utilizing the mouse as an animal model of human solvent abuse. Pharmacology. 18(2):244.

Bruckner, J.V. and Peterson, R.G. 1981. Evaluation of toluene and acetone inhalant abuse. II. Model development and toxicology. Toxicol. Appl. Pharmacol. 61:27-38.

Buccafusco, R.J., Ells, S.J. and LeBlanc, G.A. 1981. Acute toxicity of priority pollutants to bluegill (*Lepomis macrochirus*). Bull. Environ. Contam. Toxicol. 26:446-452.

Buikema, L.A. Jr. and Hendricks, A.C. 1980. Benzene, Xylene, and Toluene in aquatic Systems: A Review. American Petroleum Institute, Washington, D.C.

Bushnell, P.J., Evans, H.L. and Palmes, E.D. 1985. Effects of toluene inhalation on carbon dioxide production and locomotor activity in mice. Fundam. Appl. Toxicol. 5:971-977.

Buttery, R.G., Seifert, R.M. and Ling, L.C. 1975. Characterization of some volatile constituents of dry red beans. J Agric. Food Chem. 23:516-519.

Caldwell, R.S., Calderone, E.M. and Mallon, M.H. 1976. Effects of a seawater fraction of Cook Inlet crude oil and its major aromatic components on larval stages of the Dungeness crab, *Cancer magister dana*. In: Fate and effects of petroleum hydrocarbon in marine organisms and ecosystems. Pergamon Press, New York. Pp. 210-220.

Callahan, M.A., Slimak, M.W., Gabel, N.W., May, I.P., Fowler, C.F., Freed, J.R., Jennings, P., Durfee, R.L., Whitmore, F.C., Maestri, B., Mabey, W.R., Holt, B.R. and Gould, C. 1979. Water-Related Environmental Fate of 129 Priority Pollutants. Volume II. PB80-204381. National Technical Information Service, Springfield, VA.

Campt, D.D. 1989. Inert ingredients in pesticide products; policy statement; revision and modification of lists. Fed. Reg. 54:48314-48316.

Carlsson, A. and Ljunquist, E. 1982. Exposure to toluene: concentration in subcutaneous adipose tissue. Scand. J. Work Environ. Health 8:56-62.

Carpenter, C.P., Geary, D.L., Jr., Myers, R.C., Nachreiner, D.J., Sullivan, L.J. and King, J.M. 1976b. Petroleum hydrocarbon toxicity studies. XIII. Animal and human response to vapors of toluene concentrate. Toxicol. Appl. Pharmacol. 36:473-490. (cited in IPCS, 1985).

Casserly, D.M., Davis, E.M., Downs, T.D. and Guthrie, R.K. 1983. Sorption of organics by *Selenastrum capricornutum*. Water Res. 17:1591-1594.

CCME (Canadian Council of Ministers of the Environment). 1990. Management Plan for Nitrogen Oxides (NOx) and Volatile Organic Compounds (VOCs). Phase I. Canadian Council of Ministers of the Environment, Winnipeg. CCME-EPC/TRE-31E.

CCREM (Canadian Council of Resource and Environment Ministers). 1987. Canadian Water Quality Guidelines. Environment Canada, Water Quality Branch, Ottawa.

Chan, C.C., Valner, L., Martin, J.W. and Williams, D.T. 1990. Determination of organic contaminants in residential indoor air using an adsorption-thermal desorption technique. J. Air Waste Manage. Assoc. 40:62-67.

CHEM-INTELL (Chemical Intelligence Services). 1989. [Canadian toluene plant and production data]. File 318 available online on Dialog.

Chénier, R. 1992. Unpublished report. Environment Canada, Commercial Chemicals Branch, Ottawa.

Chung, T.Y., Hayase, F. and Kato, H. 1983. Volatile components of ripe tomatoes and their juices, purees and pastes. Agric. Biol. Chem. 47:343-351.

CIIT (Chemical Industry Institute of Toxicology). 1980. Final Report. A Twenty-Four Month Inhalation Toxicology Study in Fischer-344 Rats Exposed to Atmospheric Toluene. CIIT Docket No. 2200, CIIT/IBT Labs, Inc., Research Triangle Park, NC. 61 pp.

Coleman, E.C., Ho, C.T. and Chang, S.S. 1981. Isolation and identification of volatile compounds from baked potatoes. J. Agric. Food Chem. 29:42-48.

Comba, M.E. and Kaiser, K.L.E. 1987. Benzene and toluene levels in the upper St. Clair River. Water Poll. RRes. J. Can. 22:468-473.

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

Contreras, C.M., Gonzalez-Estrada, T., Zarabozo, D. and Fernandez-Guardiola, A. 1979. Petit mal and grand mal seizures produced by toluene or benzene intoxication in the cat. Electroencephalogr. Clin. Neurophysiol. 46(3):290-301.

Corpus Information Services. 1988. Toluene. CPI Product Profiles. Don Mills, Ontario.

Corpus Information Services. 1989. Toluene. CPI Product Profiles. Don Mills, Ontario.

Courtney, K.D., Andrews, J.E., Springer, J., Menache, M., Williams, T., Dalley, L. and Graham, J.A. 1986. A perinatal study of toluene in CD-1 mice. Fund. Appli. Toxicol. 6:145-154.

Currier, H.B. 1951. Herbicidal properties of benzene and certain methyl derivatives. Hilgardia 20:383-406.

Da-Silva, V.A., Malheiros, L.R. and Bueno, F.M.R. 1990. Effects of toluene exposure during gestation on neurobehavioural development of rats and hamsters. Brazilian J. Med. Biol. Res. 23:533-537.

Dangé, A.D. 1986. Branchial sodium potassium ATPase inhibition in a freshwater euryhaline teleost Tilapia (*Oreochromis mossambicus*) during short-term exposure to toluene or naphthalene. Influence of salinity. Environ. Poll. A42:311-324.

Dann, T. 1989. Speciation and Reactivity of volatile organic compounds in ambient air samples and emission inventories. Pollution Measurement Division, Conservation and Protection - Environment Canada. PMD 89-16.

Dann, T. and Gonthier, C. 1986. Measurement of volatile organics at an abandoned waste disposal site, Montreal, Quebec, Canada. Prepr. Pap. Natl. Meet. Div. Environ. Chem., Am. Chem. Soc. 26:390-393.

Dann, T. and Wang, D. 1989. Measurement of Volatile Organic Compounds in the Greater Vancouver Regional District (August - December, 1988). Pollution Measurement Division, Environment Canada. PMD89-15. 27 pp.

Dann, T., Wang, D. and Etlinger, A. 1989. Volatile organic compounds in Canadian ambient air: a new emphasis. Pollution Measurement Division, Conservation and Protection, Environment Canada. PMD 89-26.

Davis, T. 1991. Pesticides Directorate Pesticide Information Data Base, unpublished data. Agriculture Canada, Pesticides Directorate, Ottawa.

Dean, B.J. 1985. Recent findings on the genetic toxicology of benzene, toluene, xylenes and phenols. Mutat. Res. 154:153-181.

del Rosario, R., de Lumen, B.O., Habu, T., Flath, R.A., Mon, T.R. and Teranishi, R. 1984. Comparison of headspace volatiles from winged beans and soybeans. J. Agric. Food Chem. 32:1011-1015.

Dennie, D., Taylor, A., Wilson, A. and Washington, W.J. 1986. Dominant lethal mutations in Sprague-Dawley rats. Ohio Journal of Science. 86:34-35.

Devlin, E.W., Brammer, J.D. and Puyear, R.L. 1982. Acute toxicity of toluene to three age groups of fathead minnows (*Pimephales promelas*). Bull. Environ. Cont. Toxic. 29:12-17.

Dick, R.B., Setzer, J.V., Wait, R., Hayden, M.B., Taylor, B.J., Tolos, B. and Putz-Anderson, V. 1984. Effects of acute exposure of toluene and methyl ethyl ketone on psychomotor performance. Int. Arch. Occup. Environ. Health. 54:91-109.

Dobrokhotov, V.B. 1972. The mutagenic influence of benzene and toluene under experimental conditions. Gig. Sanit. 37:36-39.

Dobrokhotov, V.B. and Enikeev, M.I. 1977. The mutagenic effect of benzene, toluene, and a mixture of these hydrocarbons in a chronic experiment. Gig. Sanit. 41:32-34.

DOE (Environment Canada). 1984. Toluene: Environmental and Technical Information for Problem Spills. Environmental Protection Service, Environment Canada. Cat. No. En48-10/9-1984E. Canadian Government Publications Centre, Hull, Quebec. 104 pp.

DOE (Environment Canada). 1989a. Atlantic Region Federal-Provincial Toxic Chemical Survey of Municipal Drinking Water Sources, Data Summary Report, Province of Nova Scotia, 1985-1988. Environmental Protection Service, Environment Canada, Water Quality Branch, Atlantic Region. IWD-AR-WQB-89-154.

DOE (Environment Canada). 1989b. Atlantic Region Federal-Provincial Toxic Chemical Survey of Municipal Drinking Water Sources, Data Summary Report, Province of New

Brunswick, 1985-1988. Environmental Protection Service, Environment Canada, Water Quality Branch, Atlantic Region. IWD-AR-WQB-89-155.

DOE (Environment Canada). 1989c. Atlantic Region Federal-Provincial Toxic Chemical Survey of Municipal Drinking Water Sources, Data Summary Report, Province of Prince Edward Island, 1985-1988. Environmental Protection Service, Environment Canada, Water Quality Branch, Atlantic Region. IWD-AR-WQB-89-156.

DOE (Environment Canada). 1989d. Atlantic Region Federal-Provincial Toxic Chemical Survey of Municipal Drinking Water Sources, Data Summary Report, Province of Newfoundland, 1985-1988. Environmental Protection Service, Environment Canada, Water Quality Branch, Atlantic Region. IWD-AR-WQB-89-157.

Donald, J.M., Hooper, K., and Hopenhayn-Rich, C. 1991. Reproductive and developmental toxicity of toluene: a review. Environ. Health Persp. 94:237-244.

Donner, M., Husgafvel-Pursiainen, K., Maki-Paakkanen, J., Sorsa, M. and Vainio, H. 1981. Genetic effects of *in vivo* exposure to toluene. Mutat. Res. 85:293-294.

Dossing , M., Baelum, J., Hansen, S.H., and Lundqvist, G.R. 1984. Effect of ethanol, cimetidine and propranolol on toluene metabolism in man. Int. Arch. Occup. Environ. Health. 54:309-315.

Dossing, M., Arlien-Soborg, P., Petersen, L.M., Milling Pedersen, L., and Ranek, L. 1983. Liver damage associated with occupational exposure to organic solvents in house painters. Eur. J. Clin. Invest. 13:151-157.

Dumdei, B.E. and O'Brien, R.J. 1984. Toluene degradation products in simulated atmospheric conditions. Nature 311:248-250.

Dumdei, B.E., Kenny, D.V., Shepson, P.B., Kleindienst, T.E., Nero, C.M., Cupitt, L.T., and Claxton, L.D. 1988. MS/MS analysis of the products of toluene photooxidation and measurement of their mutagenic activity. Environ. Sci. Technol. 22:1493-1498.

Dunstan, W.M., Atkinson, L.P. and Natoli, J. 1975. Stimulation and inhibition of phytoplankton growth by low molecular weight hydrocarbons. Marine Biol. 31:305-310.

Dutkiewicz, T. and Tyras, H. 1968. The quantitative estimation of toluene skin absorption in man. Arch. Gewerbepath. Gewerbehyg. 24:253-257. (cited in USEPA, 1987).

Echeverria, D., Fine, L., Glangolf, G., Schork, A. and Sampaio, C. 1989. Acute neurobehavioural effects of toluene. Br. J. Ind. Med. 46:483-495.

Edsal, T.A., Manny, B.A. and Raphael, C.N. 1988. The St. Clair River and Lake St. Clair, Michigan: an Ecological Profile. U.S. Fish and Wildlife Service Biological Report 85(7.3). 130 pp.

EHD (Environmental Health Directorate). 1988. Reference Values for Canadian Populations. Draft Document.

Fel'dt, E.G. 1985. Evaluation of the mutagenic hazards of benzene and some of its derivatives. Gig. Sanit. 7:21-23.

Fel'dt, E.G. and Zhurkov, V.S. 1985. Study of the mutagenic effects of benzene and toluene in the mammalian somatic and germ cells. Mutat. Res. 147:294 (abstract).

Ferrario, J.B., Lawler, G.C., Deleon, I.R. and Laseter, J.L. 1985. Volatile organic pollutants in biota and sediments of Lake Pontchartain. Bull. Environ. Contam. Toxicol. 34:246-255.

Finlayson-Pitts, B.J.F. and Pitts, J.N. Jr. 1986. Atmospheric Chemistry: Fundamentals and Experimental Techniques. John Wiley & Sons Publication.

Firor, J. 1989. The Challenge of Global Warming. Ed. D.E. Abrahamson, Island Press, Washington, D.C.

Fishbein, L. 1985. An overview of environmental and toxicological aspects of aromatic hydrocarbons. II. Toluene. Sci. Tot. Environ. 42:267-288.

Florin, I., Rutberg, L., Curvalll, M. and Enzell, C.R. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology. 15:219-232.

Fluck, E.R., Poirier, L.A. and Rueluis, H.W. 1976. Evaluation of a DNA polymerase-deficient mutant of *E.coli* for the rapid detection of carcinogens. Chem.-Biol. Interactions. 15:219-231.

Fodor, G.C., Schlipkoeter, H.W. and Zimmermann, M. (1973). The objective study of sleeping behaviour in animals as a test of behavioural toxicity. In: Adverse effects of environmental chemicals and psychotropic drugs. Quantitative interpretation of functional tests. Germany, Elsevier Scientific Publishers, Vol. 1, 115-123 pp.

Foo, S.C., Jeyaratnam, J. and Koh, D. 1990. Chronic neurobehavioural effects of toluene. Br. J. Ind. Health. 47:480-484.

Forni, A., Pacifico, E. and Limonta, A. 1971. Chromosome studies in workers exposed to benzene or toluene or both. Arch. Environ. Health. 22:373-378.

Frei, J.V. and Kingsley, W.F. 1968. Observations on chemically induced regressing tumours of mouse epidermis. J. Natl. Cancer Inst. 41:1307-1313.

Frei, J.V. and Stephens, P. 1968. The correlation of promotion of tumour growth and of induction of hyperplasia in epidermal two-stage carcinogenesis. Br. J. Cancer. 22:83-92.

Freitag, D., Ballhorn, L., Geyer, H. and Korte, F. 1985. Environmental Hazard profile of organic chemicals. An experimental method for the assessment of the behaviour of organic chemicals in the ecosphere by means of simple laboratory tests with carbon-14-labeled chemicals. Chemosphere 14:1589-1616.

Funes-Cravioto, F., Zapata-Gayon, C., Kollmodin-Hedman, B., Lambert, B., Lindsten, J., Norberg, E., Nordenskjold, M., Olin, R. and Swensson, A. 1977. Chromosome aberrations and sister-chromatid exchange in workers in chemical laboratories and a rotoprinting factory and in children of women laboratory workers. Lancet. 13 August. 332-325 pp. (cited in IPCS, 1985).

Fuxe, K., Andersson, K., Nilsen, O.G., Toftgard, R., Eneroth, P. and Gustafsson, J. 1982. Toluene and telencephalic dopamine: selective reduction of amine turnover in discrete DA nerve terminal systems of the anterior caudate nucleus by low concentrations of toluene. Toxicol. Lett. 12:115-123.

Gad-El-Karim, M.M., Harper, B.L. and Legator, M.S. 1984. Modifications in the myeloclastogenic effect of benzene in mice with toluene, phenobarbital, 3-methylcholanthrene, Aroclor 1254 and SKF-525A. Mutat. Res. 135:225-243.

Gad-El-Karim, M.M., Harper, B.L., Sadagopa-Ramanujam, V.M. and Legator, M.S. 1982. Modifications in the metabolism and myeloclastogenic effect of benzene. Environ. Mutagen. 4:350-351.

Gad-El-Karim, M.M., Sadagopa-Ramanujam, V.M. and Legator, M.S. 1986. Correlation between the induction of micronuclei in bone marrow by benzene exposure and the excretion of metabolites in urine of CD-1 mice. Toxicol. Appl. Pharmacol. 85:464-477.

Galassi, S., Mingazzini, M., Vigano, L., Cesareo, D. and Tosato, M.L. 1988. Approaches to modelling toxic responses of quatic organisms to aromatic hydrocarbons. Ecotox. Environ. Safety. 16:158-169.

Gamberale, F. and Hultengren, M. 1972. Toluene exposure. II. Psychophysiological functions. Work Environ. Health. 9(3):131-139. (cited in IPCS, 1985).

Geller, I., Hartmann, R.J., Randle, S.R. and Gause, E.M. 1979. Effects of acetone and toluene vapours on multiple schedule performance of rats. Pharmacol. Biochem. Behav. 11:395-399.

Gerner-Smidt, P. and Friedrich, U. 1978. The mutagenic effect of benzene, toluene and xylene studied by the SCE technique. Mutat. Res. 58:313-316.

Geyer, H., Politzki, G. and Freitag, D. 1984. Prediction of ecotoxicological behaviour of chemicals: relationships between n-octanol/water partition coefficients and bioaccumulation of organic chemicals by alga *Chlorella*. Chemosphere. 13:269-284.

Gibson, D.T. 1975. Microbial degradation of hydrocarbon. Ed. E.D. Goldberg. The Nature of Sea Water: Report of the Dahlem Workshop on the Nature of Sea Water. Berlin, March 10-15, 1975. Published in Physical and Chemical Sciences Research Report No.1. Dahlem Conferences, Berlin. pp. 667-696.

Gibson, J.E. and Hardisty, J.F. 1983. Chronic toxicity and oncogenicity bioassay of inhaled toluene in Fischer-344 rats. Fundam. Appl. Toxicol. 3:315-319.

Giddings, J.M. 1979. Acute toxicity to *Selenastrum capricornutum* of aromatic compounds from coal conversion. Bull. Environ. Contam. Toxic. 23:360-364.

Gilbert, D., Woodruff, C., Preston, A., Thomas, R. and Wood, M. 1983. Exposure and Risk Assessment for Toluene. PB85-221505. National Technical Information Service, Springfield, VA, 182 pp.

Gluth, G. and Hanke, W. 1985. A comparison of physiological changes in carp, *Cyprinus carpio*, induced by several pollutants at sublethal concentrations. Ecotoxic. Environ. Saf. 9:179-188.

Gomez-Arroyo, S. and Castillo-Ruiz, P. 1985. Sister chromatid exchanges induced by thinner in *Vicia faba*. Contaminacion Ambiental. 1:17-23.

Gomez-Arroyo, S., Castillo-Ruiz, P. and Villalo-Bospietrini, R. 1986. Chromosomal alterations induced in *Vicia faba* by different industrial solvents: thinner, toluene, benzene, n-hexane, n-heptane and ethyl acetate. Cytologia. 51:133-142.

Gonthier, C. 1986. Étude de la qualité de l'air à l'intérieur des résidences construites sur le terrain de l'ancien dépotoir de la ville de LaSalle. Rapport final. Environnement Canada, Service de la protection de l'environnement, Région du Québec, Montréal, 1986.

Güsten, H., Klasinc, L. and Marić, D. 1984. Prediction of the abiotic degradability of organic compounds in the troposphere. J. Atmosph. Chem. 2:83-93.

Guzelian, P., Mills, S. and Fallon, H.J. 1988. Liver structure and function in print workers exposed to toluene. J. Occup. Med. 30:791-796.

Haglund, U., Lungberg, I. and Zech, L. 1980. Chromosome aberrations and sister chromatid exchanges in Swedish paint industry workers. Scand. J. Work Environ. Health 6:291-298.

Hampton, C.V., Plerson, W.R., Schuetzie, D. and Harvey, T.M. 1983. Hydrocarbon gases emitted from vehicles on the road. 2. Determination of emission rates from diesel and spark-ignition vehicles. Environ. Sci. Technol. 17:699.

Hanninen, H., Antii-Poika, M. and Savolainen, P. 1987. Psychological performance, toluene exposure and alcohol consumption. Int. Arch. Occup. Environ. Health 59:475-483.

Hanninen, H., Eskelinen, L., Husman, K. and Nurminen, M. 1976. Behavioral effects of long-term exposure to a mixture of organic solvents. Scand. J. Work Environ. Health 4:240-255.

Hansen, N., Jensen, V.B., Appelquist, J. and Morch, E. 1978. The uptake and release of petroleum hydrocarbons by the marine mussel *Mytil edulis*. Prog. Water Technol. 10:351-359.

Haworth, S., Lawlor, T., Mortelmans, K., Speck, W. and Zeiger, E. 1983. Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen. 5(Supplement 1):3-142.

Hawthorne, A.R., Gammage, R.B. and Dudney, C.S. 1986. An indoor air quality study of 40 east Tennessee homes. Environ. Int. 12:221-239.

Heitmuller, P.T., Hollister, T.A. and parrish, P.R. 1981. Acute toxicity of 54 industrial chemicals to sheephead minnow (*Cyprinodon variegatus*). Bull. Environ. Contam. Toxciol. 27:596-604.

Hellquist, H. Irander. K and Edling, C., et al. 1983. Nasal symptoms and histopathology in a group of spray-painters. Acta Otolaryngol. 96:495-500. (cited in ATSDR, 1989).

Herman, D.C., Inniss, W.E. and Mayfield, C.I. 1990. Impact of volatile aromatic hydrocarbons, alone and in combination, on growth of the freshwater alga *Selenastrum capricornutum*. Aquat. Toxicol. 18(2):87-100.

Hermens, J., Canton, H., Janssen, P. and de Jong, R. 1984. Quantitative structure-activity relationships and toxicity studies of mixtures of chemicals with anaesthetic potency: acute lethal and sublethal toxicity to *Daphnia magna*. Aquat. Toxicol. 5:143-154.

Hisanaga, N. and Takeuchi, Y. 1983. Changes in sleep cycle and EEG of rats exposed to 4000 ppm toluene for four weeks. Ind. Health. 21(3):153-164. (cited in IPCS, 1985).

Holmberg, P.C. 1979. Central nervous system defects in children born to mothers exposed to organic solvents during pregnancy. Lancet. 2:177. (cited in ATSDR, 1989).

Honma, T. 1983. Changes in acetylcholine metabolism in rat brain after a short-term exposure to toluene and n-hexane. Toxicol. Lett. 16:17-22. (cited in IPCS, 1985).

Honma, T., Miyagawa, M. Sato, M. and Hasegawa, H. 1982. Increase in glutamine content of rat midbrain induced by short-term exposure to toluene and hexane. Ind. Health. 20:109-115. (cited in IPCS, 1985).

Honma, T., Sudo, A., Miyagawa, M., Sato, M. and Hasegawa, H. 1983. Significant changes in the amounts of neurotransmitter and related substances in rat brain induced by subacute exposure to low levels of toluene and xylene. Ind. Health. 21:143-151. (cited in IPCS, 1985).

Horiguchi, S. and Inoue, K. 1977. Effects of toluene on the wheel-turning activity and peripheral blood findings in mice--an approach to the maximum allowable concentration of toluene. J. Toxicol. Sci. 2:363-372.

Hsieh, G.C., Sharma, R.P. and Parker, R.D.R. 1989. Immunotoxicological evaluation of toluene exposure via drinking water. Environ. Res. 49:93-103.

Hsieh, G.C., Sharma, R.P., Parker, R.D.R. and Coulombe, Jr., R.A. 1990. Evaluation of toluene exposure via drinking water on levels of regional brain biogenic monoamines and their metabolites in CD-1 mice. Ecotoxicol. Environ. Safety. 20:175-184.

Hudak, A. and Ungvary, G. 1978. Embryotoxic effects of benzene and its methyl derivatives: toluene and xylene. Toxicology. 11:55-63.

Huff, J. 1990. NTP (Technical Report on the Toxicology and Carcinogenesis Studies of Toluene (CAS No. 108-88-3) in F33/N Rats and B6C3F1 Mice (Inhalation Studies). Draft Report. NTP TR371, NIH Publication No. 90-2826, National Toxicology Program, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. 253 pp.

IARC (International Agency for Research on Cancer). 1989. Some organic solvents, resin monomers and related compounds, pigments and occupational exposures in paint manufacture and painting. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 47. Lyon, France, pp.79-123.

Ikeda, K. 1987. Visual toxicity of toluene - An experimental study. Acta Soc. Ophthalmol Jpn. (English Abstract) 91:903-910.

Ikeda, M. and Tsukagoshi, H. 1990. Encephalopathy due to toluene sniffing. Report of a case with magnetic resonance imaging. Eur. Neurol. 30:347-349.

Ikeda, N., Takahashi, H., Umetsu, K. and Suzuki, T. 1990. the course of respiration and circulation in "toluene-sniffing". Forensic Sci. Int. 44:151-158.

Ikeda, T. and Miyake, H. 1978. Decreased learning in rats following repeated exposure to toluene: preliminary report. Toxicol. Lett. 1(4):235-239.

Ikeda, T., Maehara, N., Sadmoto, T., Harabuchi, I., Yamamura, K. and Miyake, H. 1981. Effects of toluene exposure on the rest-activity cycle of rats. Toxicol. Lett. 9(3):255-266. (cited in IPCS, 1985).

Inoue, O., Seiji, K., Watanabe, T., Kasahara, M., Nakatsuka, H., Yin, S.N., Li, G.L., Cai, S.X., Jin, C., and Ikeda, M. 1988. Mutual metabolic suppression between benzene and toluene in man. Int. Arch. Occup. Environ. Health. 60:15-20.

IPCS (International Programme on Chemical Safety). 1985. Environmental Health Criteria 52. Toluene. IPCS. World Health Organization, Geneva, Switzerland, 146 pp.

Iregren, A. 1986. Subjective and objective signs of organic solvent toxicity among occupationally exposed workers. Scand. J. Work Environ. Health 12:469-475.

Ishikawa, T.T. and Schmidt, H., Jr. 1973. Forced turning induced by toluene. Pharmacol. Biochem. Behav. 1(5):593-595. (cited in IPCS, 1985).

Isidorov, V.A., Zenkevich, I.G. and Ioffe, B.V. 1990. Volatile organic compounds in solfataric gases. J. Atmos. Chem. 10:292-313.

Jenkins, L.J., Jr., Jones, R.A. and Siegel, J. 1970. Long-term inhalation screening studies of benzene, toluene, o-xylene and cumene on experimental animals. Toxicol. Appl. Pharmacol. 16:818-823.

Jensen, K., Mariager Pedersen, S. and Aertebjerg Nielen, G. 1984. The effect of aromatic hydrocarbons on the productivity of various marine planktonic algae. Limnology. 15:581-584.

Johnson, R.L., Cherry, J.A. and Pankow, J.F. 1989. Diffusive contaminant transport in natural clay: a field example and implications for clay-lined waste disposal sites. Environ. Sci. Technol. 23:340-349.

Kaiserman, M.J. and Allen, T.A. 1990. Trends in Canadian Tobacco Consumption, 1980-1989. Chronic Diseases in Canada 11:54-55.

Kauss, P.B. and Hutchinson, T.C. 1975. Effects of water-soluble petroleum components on the growth of *Chlorella vulgaris*. Environ. Pollut. 9:157-174.

Kirk, R.E., Othmer, D.F., Grayson, M. and Eckroth, D. 1983. Kirk-Othmer Encyclopedia of Chemical Technology. John Wiley, New York.

Kirkhart, B. 1980. Micronucleus Test on Toluene. USEPA Contract No. 68-02-2947. Menlo Park, CA: SRI International. Research Triangle Park, NC: U.S. Environmental Protection Agency. (cited in Huff, 1990).

Knox, J.W. and Nelson, J.R. 1966. Permanent encephalopathy from toluene inhalation. New England J. Med. 275:1494-1496.

Konemann, H. 1981. Quantitative structure-activity relationships in fish toxicity studies. Part 1: Relationship for 50 industrial pollutants. Toxicolgy 19:209.

Korn, S., Moles, D.A. and Rice, S.D. 1979. Effects of temperature on the median tolerance limit of pink salmon and shrimp exposed to toluene, naphthalene, and Cook Inlet crude oil. Bull. Environ. Contam. Toxicol. 21:521-525.

Krivanek, N. and Mullin, L.S. 1978. Comparison of conditioned avoidance and unconditioned reflex tests in rats exposed by inhalation to carbon monoxide, 1,1,1-trichloroethane, toluene, or ethanol. Toxicol. Appl. Pharmacol. 45(1):357-358. (cited in IPCS, 1985).

Kyrklund, T. Kjellstrand, P. and Haglid, K. 1987. Brain Lipid changes in rats exposed to xylene and toluene. Toxicology. 45:123-133.

Lange, A., Smolik, R. and Zatonski, W. et al. 1973. Leukocyte agglutinins in workers exposed to benzene toluene and xylene. Int. Arch. Arbeits. Med. 31:45-50. (cited in ATSDR, 1989).

Larsen, F. and Leira, H.L. 1988. Organic brain syndrome and long-term exposure to toluene: a clinical, psychiatric study of vocationally active printing workers. J. Occup. Med. 30:875-878.

LeBlanc, G.A. 1980. Acute toxicity of priority pollutants to water flea (*Daphnia magna*). Bull. Environ. Contam. Toxicol. 24:684-691.

Lebowitz, H., Brusick, D., Matheson, D., Jagannath, D.R., Reed, M., Goode, S. and Roy, G. 1979. Commonly used fuels and solvents evaluated in a battery of short-term bioassays. Environ. Mutagen. 1:172-173.

Lesage, S. and Lapcevic, P.A. 1990. Differentiation of the origins of BTX in ground water using multivariate plots. Ground Water Monit. Rev. (Spring 1990), 4 pp.

Lesage, S., Ritch, J.K. and Treciokas, E.J. 1990. Characterization of groundwater contaminants at Elmira, Ontario, by thermal desorption, solvent extraction GC-MS and HPLC. Water Poll. Res. J. Can. 25:275-292.

Levelton, B.H., and Associates Ltd. 1990. Reduction of VOC emissions from solvents by product substitution, process changes or add-on controls. Contract Report prepared for Environment Canada, Industrial Programs Branch.

Liang, J.C. and Hsu, T.C. 1983. A single cytogenetic assay for detecting mitotic-arresting effects of volatile liquids. Environ. Mutagen. 5:375.

Liang, J.C., Hsu, T.C. and Henry, J.E. 1983. Cytogenetic assays for mitotic poisons. The grasshopper embryo system for volatile liquids. Mutat. Res. 113:467-479.

Lijinsky, W. and Garcia, H. 1972. Skin carcinogenesis tests of hydrogenated derivatives of anthanthrene and other polynuclear hydrocarbons. Z. Krebsforsch. 77:226-230. (cited in IPCS, 1985).

Lonneman, W.A., Seila, R.L. and Meeks, S.A. 1986. Non-methane organic composition in the Lincoln Tunnel. Environ. Sci. Technol. 20:790-796.

Low, L.K., Meeks, J.R. and Mackerer, C.R. 1988. Health effects of the alkylbenzenes. I. Toluene. Toxicol. Ind. Health. 4:49-75.

Lowi, A., Jr. and Carter, W.P.L. 1990. A method for evaluating the atmospheric ozone impact of actual vehicle emissions. SAE Technical Paper Series, No. 900710. SAE International, Warrendale, Pa.

Lu, P.Y. and Metcalf, R.L. 1975. Environmental fate and biodegradability of benzene derivatives as studied in a model aquatic system. Environ. Health Persp. 10:269-284.

Lundberg, I. and Hakansson, M. 1985. Normal serum activities of liver enzymes in Swedish paint industry workers with heavy exposure to organic solvents. Br. J. Ind. Med. 42:596-600. (cited in ATSDR, 1989).

Lutz, W.K. 1979. *In vivo* covalent binding of organic chemicals to DNA as a quantitative indicator in the process of chemical carcinogenesis. Mutat. Res. 65:289-356.

Lutz, W.K. 1984. Structural characteristics of compounds that can be activated to chemically reactive metabolites: use for a prediction of a carcinogenic potential. Archives of Toxicology. Supplement 7:194-207.

Lutz, W.K. and Schlatter C. 1979. *In vivo* covalent binding of chemicals to DNA as a short-term test for carcinogenicity. Arch. Toxicol. Supplement 2:411-415.

Lyapkalo, A.A. 1973. Genetic activity of benzene and toluene. Gig. Tr. Prof. Zabol. 17:24-28.

Maas, E.F., Ashe, J., Spiegel, P., Zee, D.S. and Leigh, R.J. 1991. Acquired pendular nystagmus in toluene addiction. Neurology 41:282-285.

Mackay, D. and Leinonen, P.J. 1975. Rate of evaporation of low-solubility contaminants from water bodies to atmosphere. Env. Sci. Technol. 9:1178-1180.

Mackay, D., Shiu, W.Y. and Ma, K.C. 1992. Illustrated Handbook of Physical-Chemical Properties and Environmental Fate for Organic Chemicals. Volume I. Lewis Publishers, Boca Raton. 697 pp.

MacLeod, A.J. and Cave, S.J. 1976. Variations in the volatile flavour components of eggs. J. Sci. Fd. Agric. 27:799-806.

Madé, B. 1991. Unpublished data. Environment Canada, Industrial Programs Branch, Ottawa.

Maeda, K. 1970. Effects of toluene on higher nervous functions of rats. I. Effects of toluene exposure on conditioned behaviour of rats. Jpn. J. Ind. Health. 12:517-523. (cited in IPCS, 1985).

Maki-Paakkanen, J., Husgafvel-Pursiainen, K., Kalliomaki, P.L., Tuominen, J. and Sorsa, M. 1980. Toluene-exposed workers and chromosome aberrations. J. Toxicol. Environ. Health. 6:775-781.

Maltoni, C., Conti, B. and Cotti, G. 1983 Benzene: A multipotential carcinogen. Results of long-term bioassays performed at the Bologna Institute of Oncology. Am. J. Ind. Med. 4:589-630.

Maltoni, C., Conti, B., Cotti, G. and Belpoggi, F. 1985. Experimental studies on benzene carcinogenicity at the Bologna Institute of Oncology: current results and ongoing research. Am. J. Indust. Med. 7:415-446.

Matsushita, T., Arimatsu, Y. and Ueda, A., et al. 1975. Hematological and neuromuscular response of workers exposed to low concentration of toluene vapor. Ind. Health. 13:115-121. (cited in ATSDR, 1989).

Mayer, F.L. and Ellersieck, M.R. 1986. Manual of acute toxicity: interpretation and data base for 410 chemicals and 66 species of freshwater animals. U.S. Dept. Int., Fish and Widl. Serv., Res. Publ. 160. 460 pp.

Maynard, D.J. and Weber, D.D. 1981. Avoidance reactions of juvenile coho salmon (*Oncorhynchus kisutch*) to monocyclic aromatics. Can J. Fish Aquat. Sci. 38:772-778.

McAuliffe, C.D. 1977. Evaporation and solution of C_2 to C_{10} hydrocarbons from crude oils on the sea surface. In Fate and Effects of Petroeleum Hydrocarbons in Marine Organisms and Ecosystems (D.A. Wolfe, ed.). Pergamon, New York. Pp. 363-372.

McCarrol, N.E., Keech, B.H. and Piper, C.E. 1981b. A microsuspension adaptation of the *Bacillus subtilis* rec assay. Environ. Mutagen. 3:607-616.

McCarrol, N.E., Piper, C.E. and Keech, B.H. 1980. Bacterial microsuspension assays with benzene and other organic solvents. Environ. Mutagen. 2:281-282.

McCarrol, N.E., Piper, C.E. and Keech, B.H. 1981a. An *E.coli* microsuspension assay for the detection of DNA damage induced by direct-acting agents and promutagens. Environ. Mutagen. 3:429-444.

McGregor, D.B., Brown, A., Cattanach, P., Edwards, I., McBride, D., Riach, C. and Caspary, W.J. 1988. Responses of the L5178Y tK+/tK- mouse lymphoma cell forward mutation assay: III. 72 Coded Chemicals. Environ. Mol. Mutagen. 12:85-154.

McKim, J.M. 1977. Evaluation of tests with early life stages of fish for predicting long-term toxicity. J. Fish. Res. Board Can. 34:1148-1154.

Meinhart, E. and Schreier, P. 1986. Study of flavour compounds from Parmigiano Reggiano cheese. Milchwissenschaft 41:689-691.

Michon, S. 1965. [Disturbance of menstruation in women working in an atmosphere polluted with aromatic hydrocarbons.] Pol. Tyg. Lek. 20:1547-1649 (in Polish). (cited in IPCS, 1985).

Miller, T.A., Rosenblatt, D.H., Dacre, J.C., Pearson, J.G. and Kulkarni. 1976. Problem Definition Studies on Potential Environmental Pollutants. IV. Physical, Chemical, Toxicological, and Biological Properties of Benzene; Toluene; Xylenes; and para-Chlorphenyl Methyl Sulfide, Sulfoxide, and Sulfone. AD-A040 435. National Technical Information Service, Springfield, VA, 95 pp

MOE (Ontario Ministry of Environment). 1977. St.Clair River Organic Study: Fish Toxicity and Tainting Evaluation for Selected Industrial Effluents. Limnology and Toxicity Section, Water Resources Branch, Toronto, Ontario.

MOE (Ontario Ministry of Environment). 1989a. Preliminary Report for the First Six Months of Monitoring in the Petroleum Refining Sector. December 1989.

MOE (Ontario Ministry of Environment). 1989b. Drinking Water Surveillance Program. Overview annual report 1987.

MOE (Ontario Ministry of Environment). 1992. Unpublished report. Ontario Ministry of the Environment, Sarnia, Ontario.

Mohtashamipur, E., Norpoth, K., Woelke, U. and Huber, P. 1985. Effects of ethylbenzene, toluene, and xylene on the induction of micronuclei in bone marrow polychromatic erthrocytes of mice. Arch. Toxicol. 58:106-109.

Mohtashamipur, E., Strater, H., Triebel, R. and Norpoth, K. 1987. Effects of pretreatment of male NMRI mice with enzyme inducers or inhibitors on clastogenicity of toluene. Arch. Toxicol. 60:460-463.

Moles, A., Bates, S., Rice, S.D. and Korn, S. 1981. Reduced growth of coho salmon fry exposed to two petroleum components, toluene and naphthalene, in fresh water. Trans. Amer. Fish. Soc. 110:430-436.

Montgomery, D.D. and Kalman, D.A. 1989. Indoor/outdoor air quality: reference pollutant concentrations in complaint-free residences. Appl. Ind. Hyg. 4:17-20.

Morck, H.I., Winkel, P. and Gyntelberg, F. 1988. Health effects of toluene exposure. Dan. Med. Bull. 35:196-200.

Morrow, J.E., Gritz, R.L. and Kirton, M.P. 1975. Effects of some components of crude oil on young Coho salmon. Copeia 2:326.

Moszczynski, P. and Lisiewicz, J. 1984. Occupational exposure to benzene, toluene and xylene and the T lymphocyte functions. Haematologia. 17:449-453. (cited in ATSDR, 1989).

MRI (Midwest Research Institute). 1989. Critical literature review and summary on the potential environmental impacts and human health effects of toluene at levels occurring in the Canadian environment. Contract No. 2050. Contract Report for National Health and Welfare Canada, Environmental Health Directorate.

Mullin, L.S. and Krivanek, N.D. 1982. Comparison of unconditioned reflex and conditioned avoidance tests in rats exposed by inhalation to carbon monoxide, 1,1,1-trichloroethane, toluene or ethanol. Neurotoxicology. 3:126-137. (cited in IPCS, 1985).

Naaisuno, L.U. 1986. Chemically induced damage to the hippocampal formation. Forswarets Forskningsinstitutt. Norwegian Defense Research Establishment. NDRE/PUBL-86/1002. 103 pp. (cited in ATSDR, 1989).

Naalsund, L.U. 1986. Chemical Induced Damage to the Hippocampal Formation. Norwegian Defence Research Establishment, NDRE/PUBL-86/1002; AD-A168096. National Technical Information Service, Springfield, VA, pp. 89-104. (cited in IPCS, 1985).

Nakagaki, K., Arito, H. and Tsuruta, H. 1983. Changes in sleep-waking rhythms of rats following a single injection of toluene. Ind. Health. 21:165-174. (cited in IPCS, 1985).

Nakamura, S., Oda, Y., Shimada, T., Oki, I. and Sugimoto, K. 1978. SOS-inducing activity of chemical carcinogens and mutagens in *Salmonella typhimurium* TA1534/pSK 1002: examination with 151 chemicals. Mutat. Res. 192:239-246.

NAQUADAT. 1991. National Water Quality Data Bank. Water Quality Branch, Inland Waters Directorate. Environment Canada, Ottawa.

Nawrot, P.S. and Staples, P.E. 1979. Embryofetal toxicity and teratogenicity of benzene and toluene in the mouse. Teratology. 19:41A.

Nestmann, E.R., Lee, E.G.H., Matula, T.I., Douglas, G.R. and Mueller, J.C. 1980. Mutagenicity of constituents identified in pulp and paper mill effluents using the Salmonella/mammalian microsome assay. Mutat. Res. 79:203-212.

Neuhauser, E.F., Loehr, R.C. and Malecki, M.R. 1985. The toxicity of selected organic chemicals to the earthworm *Eisenia foetida*. J. Environ. Qual. 14:383-388.

NH&W (National Health and Welfare). 1977. Nutrition Canada Survey, food consumption patterns report 1970-1972. Bureau of Nutrition Services, Health Protection Branch, 248 pp.

Nielsen, I.R. and Howe, P. 1991. Environmental hazard assessment: Toluene. Toxic Substances Division, Directorate for Air, Climate and Toxic Sustances, Department of the Environment, United Kingdom.

NIOSH (National Institute for Occupational Safety and Health). 1973. Criteria for a Recommended Standard. Occupational Exposure to Toluene. NIOSH 73-11023. NTIS PB-222-219/8. 108 pp.

Nomiyama, K. and Nomiyama, H. 1974. Respiratory retention, uptake and excretion of organic solvents in man. Benzene, toluene, n-hexane, trichloroethylene, acetone, ethyl acetate and ethyl alcohol. Int. Arch. Arbeitsmed. 32:75-83. (cited in IPCS, 1985).

NRC (U.S. National Research Council). 1980. The Alkyl Benzenes. Committee on Alkyl Benzene Derivatives, Board of Toxicology and Environmental Health Hazards, Assembly of Life Sciences, National Academy Press, Washington, D.C.

NTP (National Toxicology Program). 1989a. Toxicology and Carcinogenesis Studies of Benzyl Alcohol in F344/N Rats and B6C3F$_1$ Mice. NTP Technical Report No. 343. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. 158 pp.

NTP (National Toxicology Program). 1989b. Toxicology and Carcinogenesis Studies of Benzaldehyde in F344/N Rats and B6C3F$_1$ Mice. NTP Technical Report No. 378. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC (in preparation).

Pelclova, D., Rossner, P. and Pickova, J. 1990. Chromosome aberrations in rotogravure printing plant workers. Mutat. Res. 245:299-303.

Pellizzari, E.D., Hartwell, T.D., Harris III, B.S.H., Waddell, R.D., Whitaker, D.A. and Erickson, M.D. 1982. Purgeable organic compounds in mother's milk. Bull. Environ. Contam. Toxicol. 28:322-328.

Pesticide Registration Review Team. 1990. Recommendations for a Revised Federal Pest Management Regulatory System - Final Report. Agriculture Canada, Ottawa. 71 pp.

Peterson, R.G. and Bruckner, J.V. 1978. Measurement of toluene levels in animal tissues. In: Sharp, C.W. and Carrol, L.T., ed. Voluntary Inhalations of Industrial Solvents, Rockville, Maryland, National Institute on Drug Abuse. 333-342 pp.

Pickering, Q.H. and Henderson, C. 1966. Acute toxicity of some important petrochemicals to fish. J. Wat. Pollut. Control Fed. 38:1419-1429.

Pilar, S. and Graydon, W.F. 1973. Benzene and toluene distribution in Toronto atmosphere. Environ. Sci. Technol. 7:628-631.

Potera, G.T. 1975. The effects of benzene, toluene, and ethyl benzene on several important members of the estuarine ecosystem. Ph.D. Thesis, Lehigh University, 117 pp. [Diss. Abstr. B.36(5):2010]

Pryor, G.T., Rebert, C.S., Dickinson, J. and Feeney, E.M. 1984. Factors affecting toluene-induced ototoxicity in rats. Neurobehav. Toxicol. Teratol. 6:223-238.

Pyykko, K., Tahti, H. and Vapaatalo. 1977. Toluene concentrations in various tissues of rats after inhalation and oral administration. Arch. Toxicol. 38:169-176.

Ramanathan, V., Cicerone, R.J., Singh, H.B. and Kiehl, J.T. 1985. Trace gases and their potential role in climate change. J. Geophys. Res. 90(D3):5547-5566.

Rea, T.M., Nash, J.F., Zabik, J.E., Born, G.S. and Kessler, W.V. 1984. Effects of toluene inhalation on brain biogenic amines in the rat. Toxicology. 31:143-150. (cited in IPCS, 1985).

Rickert, W.S. and LABSTAT Inc. 1988. Some considerations when estimating exposure to environmental tobacco smoke (ETS) with particular reference to the home environment. Can. J. Public Health 79:533-539.

Riihimaki, V. and Pfaffli, P. 1978. Percutaneous absorption of solvent vapors in man. Scand. J. Work Environ. Health. 4:73-85.

Rodriguez-Arnaiz, R. and Villalobos-Pietrini, R. 1985a. Genetic effects of thinner, benzene and toluene in *Drosophila melanogaster*. 1. Sex chromosome loss and non-disjunction. Contaminacion Ambiental. 1:35-43.

Rodriguez-Arnaiz, R. and Villalobos-Pietrini, R. 1985b. Genetic effects of thinner, benzene and toluene in *Drosophila melanogaster*. 2. Sex-linked recessive lethal mutations and translocations II-III. Contaminacion Ambiental. 1:45-49.

Sabourin, T.D. and Tullis, R.E. 1981. Effect of three aromatic hydrocarbons on respiration and heart rates of mussel, *Mytilus californianus*. Bull. Environ. Contam. Toxicol. 26:729-736.

Sadtler Research Laboratories. 1982. Infrared Spectra of Priority Pollutants and Toxic Chemicals. Sadtler Research Laboratories, Philadelphia, PA.

Sato, A. 1988. Toxicokinetics of benzene, toluene and xylenes. IARC Sci. Publ. France. Vol. 85, Ch. 3, pp. 47-64.

Scheff, P.A., Wadden, R.A., Bates, B.A. and Aronian, P.F. 1989. Source fingerprints for receptor modeling of volatile organics. J. Air Pollut. Control Assoc. 39:469-478.

Schmid, E., Bauchinger, M. and Hauf, R. 1985. Chromosome changes with time in lymphocytes after occupational exposure to toluene. Mutat. Res. 142:37-39. (cited in ATSDR, 1989).

Seidenberg, J.M., Anderson, D.G. and Becker, R.A. 1990. Validation of an in vivo developmental toxicity screen in the mouse. Teratogen. Carcinogen. Mutagen. 6:361-374.

Seiji, K., Inoque, O. and Nakatsuka, H., et al. 1987. No biologically significant changes in liver function after occupational exposure to toluene at over-OEL levels. Ind. Health. 25:163-168. (cited in ATSDR, 1989).

Seip, H.M., Alstad, J., Carlberg, G.E., Martinsen, K. and Skaane, R. 1986. Measurement of mobility of organic compounds in soils. Sci. Tot. Env. 50:87-101.

Seppalainen, A.M.H. 1988. Neurophysiological approaches to the detection of early neurotoxicity in humans. CRC Crit. Rev. Toxicol. 18:245-298.

Shah, J.J. and Heyerdahl, E.K. 1988. National Ambient Volatile Organic Compounds (VOCs) Data Base Update, Documentation. Pb88-195631. National Technical Information Service, Springfield, VA, 131 pp.

Shah J.J. and Singh H.B. 1988. Distribution of volatile organic chemicals in outdoor and indoor air. A national VOCs data base. Environ. Sci. Technol. 22:1381.

Shigeta, S., Aikawa, H., Mishawa, T. and Kondo, A. 1978. Effect of single exposure to toluene on Sidman avoidance response in rats. J. Toxicol. Sci. 3(4):305-312. (cited in IPCS, 1985).

Sigsby, J.E., Jr., Tejada, S., Ray, W., Lang, J.M. and Duncan, J.W. 1987. Volatile organic compound emissions from 46 in-use passenger cars. Environ. Sci. Technol. 21:466-475.

Sina, J.F., Bean, C.L., Dysart, G.R., Taylor, V.I. and Bradley, M.O. 1983. Evaluation of the alkaline elution/rat hepatocyte assay as a predicator of carcinogenic/mutagenic potential. Mutat. Res. 113:357-391. (cited in Huff, 1990).

Slaine, D.D. and Barker, J.F. 1990. The detection of naturally occurring BTX during a hydrogeologic investigation. Ground Water Monit. Rev. (Spring 1990):89-94.

Sloof, W. 1979. Detection limits of a biological monitoring system based on fish respiraton. Bull. Environ. Contam. Toxicol. 23:517-523.

Slooff, W. and Blokzijl, P.J. (ed.). 1988. Integrated Criteria Document Toluene. RIVM Research for Man and Environment. National Institute of Public Health and Environmental Protection. The Netherlands. Report Number: 758473010.

Slooff, W., de Zwart, D. and Marquenie, J.M. 1983. Detection limits of a biological monitoring system for chemical water pollution based on mussel activity. Bull. Environ. Contam. Toxic. 30:400-405.

Snyder, R.D. and Matheson D.W. 1985. Nick translation-a new assay for monitoring DNA damage and repair in cultured human fibroblasts. Environ. Mutagen. 7:267-279.

Spanggord, R.J., Mortelmans, K.E., Griffin, A.F. and Simmon, V.F. 1982. Mutagenicity in *Salmonella typhimurium* and structure-activity relationships of wastewater components emanating from the manufacture of trinitrotoluene. Environ. Mutagen. 4:163-179.

SRI. 1980. Health Effects of Chemicals Series: Toluene. R.L. Joiner, SRI International, Menlo Park, California.

Stanley, J.S. 1986. Broad Scan Analysis of Human Adipose Tissue: Volume II: Volatile Organic Compounds. Final Report. Prepared by Midwest Research Institute for Office of Pesticide and Toxic Substances, U.S. Environmental Protection Agency, Washington, D.C.

Stoss, F.W. and Haines, T.A. 1979. The effects of toluene on embryos and fry of the Japanese medaka *Oryzias latipes* with a proposal for rapid determination of maximum acceptable toxicant concentration. Environ. Poll. 20:139-148.

Strachan, W.M.J. 1991. Personal communication. Environment Canada, Canada Centre for Inland Waters, Burlington.

Styles, J.A. 1978. An evaluation of 6 short-term tests for detecting organic chemical carcinogens. Apendix III. Mammalian cell transformation in vitro. Br. J. Cancer. 37:931-936.

Suzuki, H. 1973. [Autonomic nervous responses to experimental toluene exposure in humans]. Jpn. J. Ind. Health. 15:379-384 (in Japanese). (cited in IPCS, 1985).

Svensson, B.G., Nise, G., Englander, V., Attewell, R., Skerfving, S. and Moller, T. 1990. Deaths and tumours among rotogravure printers exposed to toluene. Br. J. Ind. Med. 47:372-379.

Swindoll, C.M., Aelion, C.M., Dobbins, D.C., Jiang, O., Long, S.C. and Pfaender, 1988. Aerobic biodegradation of natural and xenobiotic organic compounds by subsurface microbial communities. Environ. Toxicol. Chem. 7:291-299.

Syracuse Research Corporation. 1983. Health Assessment Document for Toluene. Final Report. PB84-100056. National Technical Information Service, Springfield, VA, 427 pp.

Syrovadko, O.N. 1977. [Working conditions and health status of women handling organosiliceous varnishes containing toluene]. Gig. Tr. Prof. Zabol. 12:15-19 (in Russian with English summary). (cited in IPCS, 1985).

Tahti, H., Aaran, R.K. and Vapaatalo, H. 1983. An inhalation method for testing the toxicity of volatile compounds in small laboratory animals. A study on short-term and long-term toluene inhalation in rats. Meth. and Find. Exptl. Clin. Pharmacol. 5:667-671.

Tahti, H., Karkkainen, S., Pyykko, K., Kataja, M. and Vapaatalo, H. 1981. Chronic occupational exposure to toluene. Int. Arch. Occup. Environ. Health. 48:61-69.

Takeuchi, Y. and Hisanaga, N. 1977. The neurotoxicity of toluene. EEG changes in rats exposed to various concentrations. Br. J. Ind. Med. 34(4):314-324.

Takeuchi, Y. and Suzuki, H. 1975. Change of convulsion threshold in the rat exposed to toluene. Ind. Health. 13:109-114. (cited in IPCS, 1985).

Takeuchi, Y., Hisanaga, N. and Ono, Y. 1979. Changes of sleep cycles and EEG in rats chronically exposed to toluene vapour. Arch. Hig. Rada Toksikol. 30(Suppl.):467-475. (cited in IPCS, 1985).

Teelucksingh, S., Steer, C.R., Thompson, C.J., Seckl, J.R., Douglas, N.J. and Edwards, C.R.W. 1991. Hypothalamic Syndrome and central sleep apnoea associated with toluene exposure. Quart. J. Med. 78:185-190.

Thomas, R.E. and Rice, S.D. 1979. The effect of exposure temperature on oxygen consumption and opercular breathing rates of pink salmon fry exposed to toluene, naphthalene, and water-soluble fractions of Cook Inlet crude oil and No. 2 fuel oil. Marine Pollution: Functional Responses 79:39-52.

Tice, R.R., Vogt, T.F. and Costa, D.L. 1981. Cytogenetic effects of inhaled benzene in murine bone marrow. Environ. Sci. Res. 25:257-275.

Topham, J.C. 1980. Do induced sperm-head abnormalities in mice specifically identify mammalian mutagens rather than carcinogens. Mutat. Res. 74:379-387.

Ungvary, G. and Tatrai, E. 1985. On the embryotoxic effects of benzene and its alkyl derivatives in mice, rats and rabbits. Arch. Toxicol. Suppl. 8:425-430.

Ungvary, G., Manyai, S., Tatrai, E., Szebereny, S.Z., Cseh, R.J., Molnar, J. and Folly, G. 1980. Effect of toluene inhalation on the liver of rats: Dependence on sex, dose and exposure time. J. Hyg. Epidemiol. Microbiol. Immunol. 24:242-252.

Upper Great Lakes Connecting Channels Management Committee. 1988. Upper Great Lakes Connecting Channels Study. Volume 2. Final Report. Prepared jointly by Environment Canada, Ontario Ministry of the Environment, U.S. Environmental Protection Agency, Michigan Department of Natural Resources.

Urban, P. and Lukas, E. 1990. Visual evoked potentials in rotogravure printers exposed to toluene. Br. J. Ind. Health. 47:819-823.

USDHHS (U.S. Department of Health and Human Services). 1986. The Health Consequences of Involuntary Smoking: a report of the Surgeon General. Public Health Service, Centers for Diseases Control, Office on Smoking and Health. Rockville, Maryland.

USEPA (U.S. Environmental Protection Agency). 1980. Ambient Water Quality Criteria for: Toluene. PB81-117855. National Technical Information Service, Springfield, VA.

USEPA (U.S. Environmental Protection Agency). 1980a. *In vitro* microbiological genotoxicity assays of toluene. SRI International Project LSU-7558-30.

USEPA (U.S. Environmental Protection Agency). 1980b. An evaluation of the effect of toluene on sister chromatid exchange frequencies in cultured Chinese hamster ovary cells. SRI International Project LSU-7558.

USEPA (U.S. Environmental Protection Agency). 1980c. Micronucleus test on toluene. SRI International Project LSU 7558-32.

USEPA (U.S. Environmental Protection Agency). 1985. Drinking Water Criteria Document for Toluene. PB86-117975. National Technical Information Service, Springfield, VA, 190 pp.

USEPA (U.S. Environmental Protection Agency). 1987. Health Advisory: Toluene. Office of Drinking Water. Washington, D.C. 17 pp.

USEPA (U.S. Environmental Protection Agency). 1987a. Toluene. In: Occurrence of Synthetic Organic Chemicals in Drinking Water, Food, and Air. Office of Drinking Water. Washington, D.C.

USEPA (U.S. Environmental Protection Agency). 1989. 40 CFR Parts 141, 142, and 143 [WH-FRL-3380-1]. National Primary and Secondary Drinking Water Regulations. Proposed Rule. Fed. Regist. 54:22062-22160.

USEPA (U.S. Environmental Protection Agency). 1990. Air Emissions Species Manual. Volatile Organic Compound Species Profiles. Vol. I. Office of Air Quality Planning and Standards. Research Triangle Park. EPA-450/2-90-001a.

Veith, G.D., Macek, K.J., Petrocelli, S.R. and Carroll, J. 1980. An evaluation of using partition coefficients and water solubility to estimate bioconcentration factors for organic chemicals in fish. In Aquatic Toxicity. J.G. Eaton, P.R. Parish and A.C. Hendrieks (eds). American Society for Testing and Materials, ASTM STP 707: 116-129.

Veulemans, H. and Masschelein, R. 1978. Experimental human exposure to toluene. I. Factors influencing the individual respiratory uptake and elimination. Int. Arch. Occup. Environ. Health. 42:91-103. (cited in USEPA, 1985).

von Euler, G., Fuxe, K., Hansson, T., Ogren, S.O., Agnati, L.F., Eneroth, P., Harfstrand, A. and Gustafsson, J.A. 1988. Effects of chronic tolueneexposure on central monoamine and peptide receptors and their interactions in the adult male rat. Toxicology. 52:103-126.

von Euler, G., Fuxe, K., Hansson, T., Eneroth, P. and Gustafsson, J.A. 1989. Persistent effects of neonatal toluene exposure on regional brain catecholamine levels and turnover in the adult male rat. Toxicology. 54:1-16.

von Euler, G., Fuxe, K., Hansson, T., Benfenati, F., Agnati, L.F. and Gustafsson, J.A. 1987. Effects of subacute toluene exposure on protein phosphorylation levels in rat frontoparietal and striatal membranes. Acta Physiol. Scand. 131:113-118.

von Oettingen, W.F., Neal, P.A., Donahue, D.D., Svirbely, J.L., Baernstein, H.D., Monaco, A.R., Valaer, P.J. and Mitchell, J.L. 1942. The toxicity and potential dangers of toluene with special reference to its maximal permissible concentration. US Public Health Service, 50 pp. (Public Health Bulletin No. 279). (cited in IPCS, 1985).

Wakeham, S.G., Canuel, E.A., Doering, P.H., Hobbie, J.E., Helfrich, J.V.K. and Lough, R.G.R. 1985. The biogeochemistry of toluene in coastal seawater: radiotracer experiments in controlled ecosystems. Biogeochemistry 1:307-328.

Walton, B.T., Anderson, T.A., Hendricks, M.S. and Talmage, S.A. 1989. Physicochemical properties as predictors of organic chemical effects on soil microbial respiration. Environ.Toxicol. Chem. 8:53-63.

Wang, W.C., Yung, Y.L., Lacis, A.A., Mo, T. and Hansen, J.E. 1976. Greenhouse effects due to man-made perturbations of trace gases. Science 194(4266):685-690.

Ward, G.S., Parrish, P.R. and Rigby, R.A. 1981. Early life stage toxicity tests with a saltwater fish: Effects of eight chemicals on survival, growth and development of sheepshead minnows (*Cyprinodon variegatus*). J. Toxicol. Environ. Health 8:225-240.

Weber, D.D., Maynard, D.J., Gronlund, W.D., and Konchin, V. 1981. Avoidance reactions of migrating adult salmon to petroleum hydrocarbons. Can. J. Fish. Aquat. Sci. 38:779-781.

Wecher, R.A. and Scher S. 1982. Bioassay procedures for identifying genotoxic agents using light-emitting bacteria as indicator organisms. Serono Symposium Publications. Raven Press. 1:109-113.

Wen, C.P., Tsai, S.P., Weiss, N.S., Gibson, R.L., Wong, O. and McClellan, W.A. 1985. Long-term mortality study of oil refinery workers IV. Exposure to lubricating-dewaxing process. J. Natl. Cancer Inst. 74:11-18.

Whipple, J.A., Eldridge, M.B. and Benville, P., Jr. 1981. An ecological perspective of the effects of monocyclic aromatic hydrocarbons on fishes. In Biological Monitoring of Marine Pollutants, F.J. Vernberg, A. Calabrese, F.P. Thurberg and W.B. Vernberg (eds.). Academic Press, New York. Pp. 483-551.

Wilson, J.T., Enfield, C.G., Dunlap, W.J., Cosby, R.L., Foster, D.A. and Baskin, L.B. 1981. Transport and fate of selected organic pollutants in a sandy soil. J. Environ. Qual. 10:501-506.

Wilson, J.T., MacNabb, J.F., Wilson, B.H. and Noonan, M.J. 1983. Biotransformation of selected organic pollutants in ground water. Dev. Ind. Microbiol. 24:225-233.

Winchester, R.V. and Madjar, V.M. 1986. Solvent effects on workers in the paint, adhesive and printing industries. Ann. Occup. Hyg. 30:307-317. (cited in ATSDR, 1989).

Wineman, M.M., Kalman, D.A. and Larson, T.V. 1985. Selected trace gas atmospheric emission estimates from two municipal landfills with passive gas collection systems. Paper presented at the 1985 Annual PNWIS-APCA meeting. November 13-15, 1985. Calgary, Alberta.

Winneke, G. 1982. Acute behavioral effects of exposure to some organic solvents: psychophysiological aspects. Occup. Neurol. Acta Neurol. Scand. 66(Suppl. 92):117-129. (cited in IPCS, 1985).

Wolf, M.A., Rowe, V.K., McCollister, D.D., Hollingsworth, R.L. and Oyen, F. 1956. Toxicological studies of certain alkylated benzenes and benzene. Arch. Ind. Health. 14:387-398.

Wood, J.A. and Porter, M.L. 1986. Hazardous Pollutants in Class II Landfills. Paper Presented at the 79th Annual Meeting of the Air Pollution Control Association. June 22-27, 1986. Minneapolis, Minnesota.

Wood, R.W., Rees, D.C., and Laties, V.G. 1983. Behavioural effects of toluene are modulated by stimulus control. Toxicol. Appl. Pharmacol. 68:462-472.

Yamawaki, S., Segawa, T. and Sarai, K. 1982. Effects of acute and chronic toluene inhalation on behaviour and (^{3}H)-serotonin binding in rats. Life Sci. 30:1997-2002. (cited in IPCS, 1985).

Yin, S., Li, G., Hu, Y., Zhang, X., Jin, O., Inoue, K., Seiji, K., Kasahara, M., Nakatsuka, H. and Ikeda, M. 1987. Symptoms and signs of workers exposed to benzene, toluene, or the combination. Ind. Health 25:113-130.

Zafonte, L. and Lyons J.M. 1989. Benzene/aromatics measurements and exhaust emissions from gasoline vehicles. Paper presented at the 82nd Annual Meeting and Exhibition. Air and Waste Management Association. June 25-30, 1989. Anaheim, California.

Zhong, B. and Tang, Q. 1980. A comparative study of the cytogenetic effects of benzene, toluene and xylene. Hereditas. 2:29-31.

TABLES

Table 2.1. Physical and chemical properties of toluene [a]

Properties	Data
Molecular weight	92.15
Density	0.867 g/cm^3
Appearance	Colourless liquid
Melting/freezing point	-95°C
Boiling point	110.6°C
Vapour pressure	3.8 kPa (25°C) 7.9 kPa (40°C)
Solubility: in fresh water in sea water in other media	515 mg/L (25°C) 380 mg/L (25°C) Miscible in ethanol, diethyl ether, benzene; soluble in acetone and carbon disulphide
Log K_{ow} (octanol/water partition coefficient)	2.69 (25°C)
Log K_{oc} (sorption partition coefficient)	2.5
Henry's Law Constant	680 Pa·m^3·mol^{-1} (25°C)
Vapour weight to volume conversion factor at 25°C, 1 atm	1 ppm = 3.75 mg/m^3 1 mg/m^3 = 0.266 ppm
Olfactory threshold in air	9.4 mg/m^3
Olfactory threshold in water	1 mg/L

[a] Modified from DOE (1984), IPCS (1985), and Mackay *et al.* (1992)

Table 3.1. Canadian production capacity, supply, and demand for isolated toluene (from Corpus Information Services, 1989)

	1986	1987	1988	1989	1990[a]	1993[a]
			kilotonnes			
CAPACITY						
Sarnia / Corunna [b]	405.0	405.0	405.0	405.0	405.0	
Montreal [c]	175.0	225.0	225.0	225.0	225.0	
TOTAL CAPACITY	580.0	630.0	630.0	630.0	630.0	595
SUPPLY						
Production	393.3	395.8	416.5	438.0[a]		500
Import	33.3	104.0	74.2	45.0[a]		40
Inventory change		-53.8				
TOTAL SUPPLY	426.6	446.0	490.7	483.0[a]		540
DEMAND						
Benzene	83.1	180.0	175.0	180.0[a]		200
Benzoic acid / phenol	19.5	20.0	20.0	20.0[a]		20
Trinitrotoluene	5.0	5.0	5.0	5.0[a]		5
Solvents	53.0	56.0	58.0	58.0[a]		60
Misc.	4.0	5.0	5.0	5.0[a]		5
Total domestic	164.6	266.0	263.0	263.0[a]		290
Export sales	262.0	180.0	227.7	220.0[a]		250
TOTAL DEMAND	426.6	446.0	490.7	483.0[a]		540

[a] as forecast by Corpus Information Services (1989)
[b] Esso Chemical Canada/Sarnia; Polysar Energy and Chemical/Corunna; Shell Canada/Corunna; Sunchem/Sarnia
[c] Kemtec Petrochemical/Montreal; Petrocan Chemicals/Montreal

Table 3.2. Estimated atmospheric emissions of toluene in Canada

Sources	Estimated Atmospheric Emissions (kilotonnes/year)	% of Total Estimated Atmospheric Emissions	References
Industrial processes			
Toluene and other chemical production	0.2	0.2	MRI, 1989
Coke oven emissions	1.1	1.0	MRI, 1989
Solvents	54.0	51.0	Levelton and Associates Ltd., 1990
[Subtotal]	*[55.3]*	*[52.2]*	
Transportation sources			
Light duty vehicles	34.0	32.1	Madé, 1991; CCME, 1990; Zafonte and Lyons, 1989; Sigsby *et al.*, 1987; Black *et al.*, 1980
Heavy duty vehicles	1.0	1.0	Madé, 1991; CCME, 1990; Hampton *et al.*, 1983
Marine/Air/Rail	0.5	0.5	CCME, 1990; USEPA, 1990
Off-road	4.3	4.0	Madé, 1991; CCME, 1990
Gasoline marketing	3.3	3.1	Madé, 1991; CCME, 1990; USEPA, 1990; Scheff *et al.*, 1989
[Subtotal]	*[43.1]*	*[40.7]*	
Other sources			
Landfills	0.4	0.3	Wood and Porter, 1986; Wineman *et al.*, 1985
Forest fires	4.4	4.2	MRI, 1989
Other inadvertent releases	2.7	2.6	MRI, 1989
[Subtotal]	*[7.5]*	*[7.1]*	
TOTAL	**105.9**	**100.0**	

Table 4.1. Toluene concentrations in ambient air in Canada (based on 24-hour averaging time unless otherwise indicated) [a]

City	Dates	Number of sites	Number of samples	Toluene concentrations ($\mu g/m^3$)		
				Mean	Max	Min
Quebec						
Montreal (PT)	Sept. 83-Oct. 83	1	10	32.5	72.6	17.9
Montreal (PT)	Oct. 84-Oct. 85	1	49	14.8	47.8	2.1
Montreal (PT)	Aug. 86-Sept. 88	1	91	17.2	40.5	2.5
Montreal (PT)	Jan. 89-Jun. 89	1	26	14.7	45.3	5.0
Montreal	May 89-Jun. 89	1	8	10.6	20.1	3.4
Ontario						
Dorset/Egbert [b] 1-hr averaging	*Jul. 88-Aug. 88*	*2*	*30*	*1.1*	*4.6*	*0.2*
Toronto (JT)	Aug. 84-Aug. 85	1	105	30.7	145.0	5.0
Toronto 3-hr averaging	*Aug. 87-Oct. 87*	*3*	*36*	*53.4*	*415.0*	*4.0*
Toronto (JT)	Nov. 88-Feb. 89	1	9	15.5	37.3	6.9
Toronto (Edgar)	Nov. 88-Feb. 89	1	11	15.6	50.1	3.9
Toronto (STO)	Nov. 88-Feb. 89	1	10	5.4	9.0	2.1
Hamilton	Jan. 89-Jun. 89	1	21	13.8	59.3	3.6
Walpole Island [b]	Jan. 88-Sept. 88	1	33	5.0	17.9	0.8
Walpole Island [b]	Oct. 88-Oct. 89	1	20	3.5	7.1	1.8
Sarnia	Aug. 83-Sept. 83	1	13	14.2	53.8	2.1
Sarnia	Jan. 89-Jun. 89	1	27	5.2	15.1	1.2
Windsor	Jul. 87-Sept. 88	1	57	16.2	55.8	4.0
Windsor	Oct. 88-Oct. 89	1	57	12.5	59.0	3.7
British Columbia						
Vancouver (T9)	Nov. 83	1	9	14.7	31.9	1.4
Vancouver (T9)	Dec. 85-Jan. 86	1	9	40.7	70.7	12.3
Vancouver 3-hr averaging	*Aug. 87-Nov. 87*	*4*	*40*	*22.7*	*81.4*	*5.4*
Vancouver 3-hr averaging	*Aug. 88-Dec. 88*	*6*	*75*	*24.3*	*112.0*	*2.0*
Vancouver	Aug. 88-Dec. 88	5	17	44.2	127.0	2.0
Vancouver (T9)	Nov. 88-Apr. 89	1	21	18.7	68.3	0.9

[a] From Dann *et al.*, 1989.
[b] Rural sampling site

Table 5.1. Estimated daily intake of toluene by Canadians from various sources

Substrate/ Medium[a]	Estimated Intake micrograms per kilogram of body weight per day				
	0-0.5 yr[b]	0.5-4 yr[c]	5-11 yr[d]	12-19 yr[e]	20-70 yr[f]
Air (urban)	1.7 -14.7	2.0 - 17.0	2.4 - 20.4	2.1 - 17.5	1.5 - 12.6
(rural)	1.2 - 1.7	1.3 - 1.9	1.6 - 2.3	1.4 - 2.0	1.0 - 1.4
Water	0.03	0.1	0.08	0.04	0.04
Food (Fish)	0.04	0.1	0.2	0.1	0.1
Consumer Products	0	0	0	0.2 - 1.2	0.1 - 0.9
Self-serve gasoline station					
(summer)	0.7	0.8	0.9	0.8	0.6
(winter)	0.5	0.6	0.7	0.6	0.4
Total Estimated Intake	1.8 - 15.5	2.1 - 18.0	2.6 - 21.6	2.3 - 19.6	1.6 - 14.2
Cigarette smoking					
(main-stream)	0	0	0	45.2	57.1
(side-stream)[g]	0.04	0.05	0.06	0.05	0.04

[a] Mean concentrations in air are 5.2-44.2 $\mu g/m^3$ and 3.5-5.0 $\mu g/m^3$ for urban and rural locations, respectively (Dann *et al.*, 1989); mean concentration in drinking water is 2.0 $\mu g/L$ (Otson *et al.*, 1982) and in fish is 1 $\mu g/g$ (Gilbert *et al.*, 1983). It is assumed that consumer products contain 5% toluene, exposure lasts 5-30 min, once per week, and that toluene is absorbed through one hand at a rate of 20 mg/h (Gilbert *et al.*, 1983). For self-serve gasoline stations, the mean airborne concentrations are 2.55 mg/m^3 (PACE, 1987) and 1.88 mg/m^3 (PACE, 1989) in summer and winter, respectively. It is also assumed that the average driver spends 10 minutes per week at the gas station. Cigarettes are estimated to contain 160 μg toluene/cigarette, and side-stream smoke contains 960 μg/cigarette (USDHHS, 1986); it is assumed that adults aged 20-70 years smoke 25 cigarettes per day and those 12-19 years smoke 15 cigarettes per day.

[b] Weighs 6 kg, breathes 2 m^3 air, drinks 0.1 L water, (modified from EHD, 1988), and consumes 0.25 g fish daily (NH&W, 1977).

[c] Weighs 13 kg, breathes 5 m^3 air, drinks 0.8 L water, (modified from EHD, 1988), and consumes 1.52 g fish daily (NH&W, 1977).

[d] Weighs 26 kg, breathes 12 m^3 air, drinks 1.1 L water, (modified from EHD, 1988), and consumes 4.81 g fish daily (NH&W, 1977).

[e] Weighs 53 kg, breathes 21 m^3 air, drinks 1.1 L water, (modified from EHD, 1988), and consumes 5.06 g fish daily (NH&W, 1977).

[f] Weighs 70 kg, breathes 20 m^3 air, drinks 1.5 L water, (from EHD, 1988), and consumes 6.59 g fish daily (NH&W, 1977).

[g] It is assumed that the average home volume is 340 m^3 with one individual smoking 2 cigarettes per hour over a 5 hour period and a collection efficiency (CE) of 0.11 for tobacco smoke and based on a formula where dose = respiration rate/hour x duration x concentration x collection efficiency (Rickert and LABSTAT INC., 1988).

TABLE 7.1. Subchronic toxicity

Species	Protocol	Results	Effect Levels	References
Inhalation				
F344/N rats; 10 of each sex per group	0, 100, 625, 1250, 2500 and 3000 ppm, 6.5 h/d, 5 d/wk for 15 weeks. Histopathological examination limited to two highest dose groups.	Decreased survival at 3000 ppm; the final mean body weights of rats exposed to 2500 or 3000 ppm were 15% or 25% lower than that of controls for males or 15% or 18% lower for females. Clinical signs included dyspnea in all exposed groups except males exposed to 3000 ppm and females exposed to 1250 ppm and ataxia in rats exposed to 2500 or 3000 ppm. The relative weights of the heart, liver and kidney for female rats exposed to 2500 or 3000 ppm, of the kidney and liver for male rats exposed to 1250 or 2500 ppm, and of the heart for male rats exposed to 2500 ppm were increased as compared with those for controls. Plasma cholinesterase activity decreased as the exposure concentration increased, and the leukocyte count was decreased for female rats at 1250 ppm or higher.	625 ppm (2345 mg/m^3) (NOEL)	Huff (1990)

Table 7.1. (Continued)

Species	Protocol	Results	Effect Levels	References
$B6C3F_1$ mice, 10 of each sex per group	0, 100, 625, 1250, 2500 and 3000 ppm, 6.5 h/d, 5 d/wk for 14 weeks. Histopathological examination limited to two highest dose groups.	Final mean body weights of all exposed groups were 7.5% and 12% lower than those of controls in males and females, respectively. Dyspnea was observed primarily at 2500 and 3000 ppm. The relative liver weights for male and female mice exposed to 625 ppm or higher, and the relative kidney weights for male and female mice exposed to 1250 ppm or higher, and the relative lung weights for male mice exposed to 1250 ppm or higher were greater than those for controls. There was a significant increase ($P<0.01$) in the relative lung weights for female mice exposed to 100 to 1250 ppm, which was probably not treatment-related in view of the lack of dose-response. Centrilobular hepatocellular hypertrophy was observed in 10/10 male mice at 2500 ppm and 4/6 male mice at 3000 ppm.	100 ppm (375 mg/m^3) (LOEL)	Huff (1990)
Male Sprague Dawley Rats (16)	Rats were housed in a coupola-shaped inhalation chamber with eight separate compartments, each for one to two rats. 1,000 ppm, 8 h/d, 13 weeks. Psychomotor tests, blood glucose, serum alanine aminotransferase (S-ALAT) and aspartate aminotransferase (S-ASAT) values as well as hematocrit.	The development of body weights was retarded compared to that of the control animals; however, body weights between the control and the experimental animals did not differ significantly at the end of experiment. No effect on the neurological system as measured by the tilting plane and rotarod tests. No effect on the levels of blood glucose, S-ALAT and S-ASAT and hematocrit.	one dose only	Tahti et al., 1983
Male ICR mice (5)	4000 ppm, 3 h/d 5 times/wk for 8 weeks. No histopathological examination.	No manifestations of toxicity other than minor, transient elevations in serum glutamic-oxaloacetic transaminase (SGOT).	one dose only	Bruckner and Peterson (1981)

Table 7.1. (Continued)

Species	Protocol	Results	Effect Levels	References
Male ICR mice (6) and male Sprague-Dawley albino rats (4)	Seven consecutive inhalation cycles daily, each cycle consisting of a 10-min exposure to 12000 ppm followed by a 20-min, solvent free recovery, 5 d/wk for 8 weeks. Histopathological examination and clinical chemistry.	No effects based on clinical chemistry indices (i.e. serum glutamic-oxaloacetic transaminase, lactate dehydrogenase and blood urea nitrogen, lung fluid content, liver triglyceride content) and histopathological examination of tissues (i.e. lung, liver, brain, kidney and heart).	one dose only	Bruckner and Peterson (1981)
CFY rats (male and female) (Number unspecified)	Only males were exposed to 3500 mg/m^3, 8 h/d every day for 6 months; both males and females to 1000 mg/m^3, 6 h/d, 5 d/week for 6 months. Histology and histochemistry.	In females, 1000 mg/m^3 induced a retardation of growth and significantly increased the liver-to-body weight ratio. In male rats, body weight was depressed and relative liver weight was increased at 3500 mg/m^3. The changes in liver weight and body weight were not statistically significant. The serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) levels were not affected in rats exposed to 1000 mg/m^3; however, the cytochrome P-450 content of the liver was significantly increased in both low and high exposure group. No histological changes which might have been due to toluene inhalation occurred in any of the organs.	265 ppm (1000 mg/m^3) (LOAEL) Validity of the LOAEL unclear since number of animals in the experimental groups was not specified	Ungvary et al. (1980)
Rats (30), guinea-pigs (30), dogs (4), or monkeys (6)	Continuous exposure to 389 mg/m^3 (107 ppm) for 90 days.	No effects on liver, kidneys, lung, spleen, heart, or blood composition in any of the tested animals as assessed by histopathological examination. In addition, no effects of treatment in the brain or the spinal cord of dogs or monkeys. No significant changes in any of the haematological parameters (haemoglobin, haematocrit, or leucocyte count). All except 2 of 30 treated rats survived exposure.	One dose only	Jenkins et al. (1970)

Table 7.1. (Continued)

Species	Protocol	Results	Effect Levels	References
Ingestion				
F344/N rats, 10 of each sex per group	0, 312, 625, 1250, 2500 and 5000 mg/kg b.w./d for 13 weeks (gavage in corn oil). Full histopathological examination of 2500 and 5000 mg/kg b.w./d dose groups; limited number of tissues examined in lower dose groups.	All rats that received 5000 mg/kg b.w./d died during the first week; reduced survival at 2500 mg/kg b.w./d. Clinical signs included prostration, hypoactivity, ataxia, piloerection, lacrimation, and excessive salivation in the 2500 and 5000 mg/kg groups. The relative liver and kidney weights for female rats that received 1250 or 2500 mg/kg and for males that received 625 or 1250 mg/kg were increased relative to those for vehicle controls. In addition, the relative heart weights for female rats that received 1250 or 2500 mg/kg were increased compared with those for vehicle controls. Absolute brain weights were increased in males and females that received 2500 mg/kg b.w./d. Necrosis of the brain, consisting of neuronal necrosis in the dentate gyrus and fimmons horn of the hippocampus in male and female rats that received 1250 or 2500 mg/kg. Hemorrhage in the mucosa, submucosa, or muscularis of the urinary bladder of male and female rats in the two highest dose groups with no evidence of increase in hyaline droplets.	312 mg/kg b.w./d (NOEL) 625 mg/kg b.w./d (LOEL)	Huff (1990)

Table 7.1. (Continued)

Species	Protocol	Results	Effect Levels	References
B6C3F$_1$ mice, 10 of each sex per group	0, 312, 625, 1250, 2500 and 5000 mg/kg b.w./d for 13 weeks (gavage in corn oil). Full histopathological examination of 2500 and 5000 mg/kg b.w./d dose groups; limited number of tissues examined in lower dose groups.	Clinical signs included subconvulsive jerking, prostration, impaired grasping reflex, hypothermia, hypoactivity and ataxia in mice at the two highest doses. Relative liver weights were increased for male mice at 1250 or 2500 mg/kg b.w. and at 312 mg/kg b.w. or higher for female mice. Myocardial fiber degeneration in 3/10 males and 2/10 females at 5000 mg/kg; all animals in the highest dose group died during the first week of exposure; reduced survival at 2500 and 1250 mg/kg b.w./d.	312 mg/kg b.w./d (LOEL)	Huff (1990)
Female Wistar rats (10)	118, 354 and 590 mg/kg b.w./d, 5 d/wk fed in olive oil in diet for 6 months. The total volume administered daily was never greater than 2 to 3 mL. Group of 20 control rats were fed 2.5 mL of olive oil. Hematological examinations were made on selected animals of each group to determine the total erythrocytes and leucocytes, hemoglobin content and white blood cell count.	There were no adverse effects at any dose level based on clinical and gross inspection as well as histological evaluation of the kidney and liver.	590 mg/kg b.w./d (NOAEL) Limited haematological and histological examination	Wolf et al. (1956)

TABLE 7.2. Chronic toxicity and carcinogenicity

Species	Dose	Results	Effect Levels	References
Inhalation				
F344/N rats, 60 of each sex per group	0, 600 or 1200 ppm, 6.5 h/d, 5 d/wk for 103 weeks. Full histopathological and haematological examinations, survival, clinical signs and body weight of all animals.	Dose-related increase in nephropathy in male and female rats which was significant at 1200 ppm. A rare renal tubular cell carcinoma in a female rat and an equally uncommon sarcoma of the kidney in another female rat at 1200 ppm. Erosion of the olfactory epithelium and degeneration of the respiratory epithelium increased in females at 600 and 1200 ppm. Incidence of inflammation of the nasal mucosa and respiratory metaplasia of the olfactory epithelium significantly ($p<0.05$) increased in exposed females (inflammation of the nasal mucosa: 27/49; 42/50; 41/50; metaplasia of the olfactory epithelium: 0/49; 2/50; 6/50 for control, 600 and 1200 ppm, respectively). A rare squamous cell carcinoma of the nasal mucosa in one female rat at 1200 ppm. NTP concluded that there was no evidence of carcinogenic activity for male or female F344/N rats exposed to toluene at concentrations of 600 or 1200 ppm.	600 ppm (2250 mg/m^3) (LOAEL)	Huff, 1990
B6C3F$_1$ mice, 60 of each sex per group	0, 120, 600 or 1200 ppm, 6.5 h/d, 5 d/wk for 103 weeks. Full histopathological and haematological examinations, survival, clinical signs and body weight of all animals.	The mean body weights of male mice at 1200 ppm were generally comparable to those of controls; however, for female mice at this dose, the mean body weights were 4 to 9% lower than those of controls from week 36 to week 76 and from week 88 to week 96. No biologically important increases in nonneoplastic or neoplastic lesions. NTP concluded that there was no evidence of carcinogenic activity for male or female B6C3F$_1$ mice exposed to toluene at concentrations of 120, 600 or 1200 ppm for 2 years.	1200 ppm (4500 mg/m^3) (NOAEL)	Huff, 1990

Table 7.2. (Continued)

Species	Dose	Results	Effect Levels	References
F344/N rats, 120 of each sex per group	0, 30, 100, 300 ppm 6 h/d, 5 d/wk for up to 24 months. All animals were subjected to gross pathological examination. Histological examination of a battery of tissues from animals receiving the highest dose and controls. Ophthalmology, hematology, blood chemistry and urinalysis for selected animals at each sacrifice interval (6, 12, 18, and 24 months).	There were 140 unscheduled deaths (14.6% of 960 animals) over the 2 year study. The authors concluded that the distribution of these deaths was roughly equal in all treatment groups and was not significantly different from random. Gross pathological examination of rats dying during the course of the study, or that were sacrificed as scheduled, did not reveal any lesions attributable to toluene exposure. Histologically, a variety of proliferative, degenerative and inflammatory lesions were observed in the control and 300 ppm toluene-exposed group. These lesions were considered unrelated to toluene exposure. No differences in haematology, urinalysis, or clinical chemistry were observed between the treated or control groups. The authors concluded that the results provide no evidence that toluene causes chronic toxicity or oncogenicity in F344/N rats at these concentrations.	300 ppm (1125 mg/m^3) (NOAEL) No effects at any dose	CIIT (1980) Gibson and Hardisty (1983)
Oral Sprague-Dawley rats, 40 of each sex per group	Toluene (98.34%) was administered by ingestion (stomach tube) in olive oil at 500 mg/kg b.w./d, 4-5 d/wk for 104 weeks. The animals were then kept under observation until spontaneous death. The animals were examined and weighed every two weeks, pathological changes were recorded, and a complete autopsy was performed on each animal. Full histological examination of all animals.	Hemolymphoreticular neoplasms were reported in 3/37 exposed males and 7/40 exposed females compared with 3/45 and 1/49 in vehicle controls. The authors reported an increase in the total number of animals bearing malignant tumours (types unspecified) at 141 weeks: 39/80 as compared with 21/100 for the controls.	One dose only. No statistical analysis and inadequate reporting of incidence of various tumours	Maltoni et al., 1985

Table 7.3. Mutagenicity and other related endpoints

Test Organism	Species	Activation[a]	Endpoint	Result[b]	References
Bacteria	S.typhimurium	± S9	Point mutations	-	1, 5, 8, 9, 14, 18, 26, 27, 28, 42, 47
		± S9	DNA damage (differential cytotoxicity)	-	14
		± S9	DNA damage (SOS-induction)	-	41
	E.coli	± S9	Point mutations	-	14
		± S9	DNA damage (differential cytotoxicity)	-	14, 19, 36, 37
	B.Subtilis	± S9	DNA damage (differential cytotoxicity)	-	35, 36
	P.phosphoreum	Not stated	Point mutations	+	51
Yeast	S.cerevisiae	± S9	Point mutations	-	1, 14, 28
		± S9	Mitotic crossing over	-	14
		± S9	Gene conversions	-	14
Bean	V.faba	---	Chromosome aberrations	+	24, 25
Grasshopper	M.sanguinipes	---	Cell division abnormalities	+	29, 30
Fruit fly	D.melanogaster	---	Sex chromosome abnormalities	-	43
		---	Sex-linked recessive lethals	-	13, 44
		---	Translocations	-	44
Mammalian cells in vitro	Human	- S9	Chromosome aberrations	-	23
		- S9	Sister chromatid exchange	-	23
		- S9	DNA damage (Nick translation)	-	46
		± S9	Cell transformation	-	48
	Mouse	± S9	Point mutations	-	1, 28
		± S9	Point mutations	equivocal	27, 38
	Hamster	± S9	Chromosome aberrations	-	27
		± S9	Sister chromatid exchange	-	15, 27
		± S9	Cell transformation	-	48
	Rat	(Liver cells)	DNA damage (strand breaks)	+	45

Table 7.3 (Continued)

Test Organism	Species	Activation[a]	Endpoint	Result[b]	References
Mammals	Rat	Inhalation	Chromosome aberrations	-	6, 13
in vivo			Chromosome aberrations	+	12
			Micronuclei	-	52
			Sister chromatid exchange	?+	13
			DNA - binding	-	31, 32, 33
			Cell division abnormalities	+	6
		Intraperitoneal	Chromosome aberrations	-	1, 28
			Dominant lethal mutations	+	7
		Subcutaneous	Chromosome aberrations	+	11, 34
		"Injection"	Micronuclei	equivocal	52
	Mouse	Inhalation	Dominant lethal mutations	-	2
		Oral	Chromosome aberrations	-	17, 20, 21
			Micronuclei	?+	17
			Micronuclei	-	20, 21, 22
			Dominant lethal mutations	-	17
		Intraperitoneal	Micronuclei	-	16
			Micronuclei	+	39, 40
			Sister chromatid exchange	-	49
			DNA synthesis inhibition	-	3, 4
			Sperm head abnormalities	-	50

Legend

a) ± S9 With and without an added metabolic activation fraction derived from rodent liver (S9)
   - S9 Without S9

b) - Negative result
   + Positive result
   ?+ Positive result reported, of questionable significance
   equivocal Equivocal result

Table 7.3 (Continued)

Test system	Concentration/dose/ duration	Observation	References
1. Bacterial tests			
1.1. Tests for point mutations in Salmonella typhimurium			
TA 1535, TA 1537, TA 1538, TA 98, TA 100 Both in the presence and absence of liver S-9 mix from rats.	Concentration range used not stated (but up to at least 4,300 µg/plate).	Plate incorporation assay. A negative response was obtained when tested both with and without metabolic activation. Toxicity was observed at and above 4,300 µg per plate.	Nestmann E.R. et al. 1980 (42)
TA 1535, TA 1537, TA 1538, TA 98, TA 100. Both in the presence and absence of liver S-9 mix from Sprague-Dawley rats.	A range of concentrations from 10 to 5,000 µg/plate.	Plate incorporation assay. A negative result was obtained both in the presence and absence of metabolic activation. No bacterial toxicity was reported.	Spanggord R.J. et al. 1982 (47)
TA 1535, TA 1537, TA 1538, TA 98, TA 100. Both in the presence and absence of liver S-9 mix from rats.	A range of concentrations from 87 to 8,700 µg/plate.	Plate incorporation assay. A negative response was obtained both in the presence and absence of metabolic activation. The highest concentration tested produced some toxicity.	EPA 1980a (14)
TA 1535, TA 1537, TA 1538, TA 98, TA 100. Both in the presence and absence of liver S-9 mix from Sprague-Dawley rats.	A range of concentrations from 0.87 to 4,300 µg/plate.	Plate incorporation assay. A negative response was obtained both in the presence and absence of metabolic activation. At the maximum dose tested, survival was below 50%.	American Petroleum Institute 1978 (1) Lebowitz H. et al. 1979 (28)
TA 98, TA 100, UTH 8413, UTH 8414. Both in the presence and absence of liver S-9 mix from Sprague-Dawley rats.	A range of concentrations from 50 to 2,000 µg/plate.	Plate incorporation assay. A negative response was obtained both in the presence and absence of metabolic activation. No bacterial toxicity was reported.	Connor T.H. et al. 1985 (9)

Table 7.3 (Continued)

Test system	Concentration/dose/ duration	Observation	References
TA 1535, TA 1537, TA 98, TA 100. Both in the presence and absence of liver S-9 mix from Sprague-Dawley rats or Syrian hamsters.	A range of concentrations from 10 to 1,000 µg/plate.	Preincubation-plate incorporation assay. A negative response was obtained both in the presence and absence of metabolic activation. Slight bacterial toxicity was reported at the highest concentration.	Huff J. 1990 (27) Haworth S. et al. 1983 (26)
TA 1535, TA 1537, TA 98, TA 100. Both in the presence and absence of liver S-9 mix from Sprague-Dawley rats.	276 µg/plate.	Spot test. A negative response was obtained both in the presence and absence of metabolic activation.	Florin I. et al. 1980 (18)
TA 1535 TA 1538, TA 98, TA 100. Tested in the presence of liver S-9 mix from Sprague-Dawley rats.	A range of concentrations from 4 to 2,500 µg/plate.	Plate incorporation assay. A negative result was obtained with metabolic activation. Testing without activation was not carried out. No bacterial toxicity was reported.	Anderson D. & Styles J.A. 1978 (5)
TA 1535, TA 1537, TA 1538, TA 98, TA 100. Both in the presence and absence of liver S-9 mix from Sprague-Dawley rats.	The range of concentrations used was not clearly stated.	Suspension assay. A negative result was obtained in the presence and absence of metabolic activation. The results were somewhat variable due to the extreme toxicity of toluene (the maximum dose tested was above that reducing survival by approximately 50%).	American Petroleum Institute 1978 (1) Lebowitz H. et al. 1979 (28)
TA 98, TA 100. Both in the presence and absence of liver S-9 mix from Sprague-Dawley rats.	A range of concentrations from 2.76 to 2,760 µg/plate.	Test conditions were not stated (probably a plate incorporation assay). A negative response was obtained both in the presence and absence of metabolic activation. At 2,760 µg/plate, bacterial toxicity was noted.	Florin I. et al. 1980 (18)

Table 7.3 (Continued)

Test system	Concentration/dose/ duration	Observation	References
TA 1535, TA 1537, TA 1538, TA 100. Both in the presence and absence of liver S-9 mix prepared from untreated Aroclor-1254 treated Wistar rats.	A range of concentrations from 100 to 2,000 µg/plate.	Plate incorporation assay. A negative response was obtained when tested both with and without metabolic activation. The highest concentration tested resulted in or some bacterial toxicity.	Bos R.P. et al. 1981 (8)
1.2. Tests for point mutations in other bacteria			
Photobacterium phosphoreum strain PPL.	No details of concentration range used.	Spot test. An increase in the frequency of bright clones was observed. Thus toluene gave a positive response [and was classified by the authors as a carcinogen/mutagen].	Wecher R.A. & Scher S. 1982 (51)
Escherichia coli WP2. Both in the presence and absence of liver S-9 mix from rats.	A range of concentrations from 87 to 8,700 µg/plate.	Plate incorporation assay. A negative response was obtained both in the presence and absence of metabolic activation. No bacterial toxicity was observed.	EPA 1980a (14)
1.3. Differential cytotoxicity assays (indicators of DNA damage) with Salmonella typhimurium			
SL 4525 (rfa) (rec^+) SL 4700 (rfa) (rec derivative of SL 4525). Both in the presence and absence of liver S-9 mix from rats.	8,700 and 17,400 µg/plate.	Spot test. There was no effect on the size of the zone of inhibition of growth in the presence and absence of metabolic activation.	EPA 1980a (14)
SL 4525 (rfa) (rec^+) SL 4700 (rfa) (rec derivative of SL 4525). Both in the presence and absence of rat liver S-9 mix.	A range of concentrations from "0.87 to 8.7 µg/plate".	Microsuspension assay. No differential toxicity was observed in the presence or absence of metabolic activation.	EPA 1980a (14)

Table 7.3 (Continued)

Test system	Concentration/dose/ duration	Observation	References
1.4. Differential cytotoxicity assays with Escherichia coli			
W 3110 (pol A^+) P 3478 (pol A^- derivative of W 3110) Both in the presence and absence of liver S-9 mix from rats.	8,700 or 17,400 µg/plate.	Spot test. There was no effect on the size of the zone of inhibition of growth both in the presence and absence of metabolic activation.	EPA 1980a (14)
W 3110 (pol A^+) P 3478 (pol A^- derivative of W 3110) Both in the presence and absence of liver S-9 mix from rats.	A range of concentrations from "0.87 to 8.7 µg/plate".	Microsuspension assay. No differential toxicity was observed in the presence or absence of metabolic activation.	EPA 1980a (14)
W 3110 (pol A^+) P 3478 (pol A^- derivative of W 3110) in the presence and absence of liver S-9 mix from Charles River rats.	0 or 21,750 µg was applied to the central well.	Spot test. Toluene did not cause a zone of inhibition of the growth of either strain. Thus no conclusions can be drawn from this study.	Fluck E.R. et al. 1976 (19)
WP 2 (rec A^+, lex A^+, pol A^+, uVr A^+) (wild type) WP 2 uvr A^- (rec A^+, lex A^+, pol A^+, uvr A^-) (derived from WP 2) CM 611 (rec A^+, lex A^-, pol A^+, uvr A^-) WP 67 (rec A^+, lex A^+, pol A^- uvr A^-) WP 100 (rec A^-, lex A^+, pol A^+ uvr A^-) (all derived from WP 2 uvr A W 3110 (pol A^+) P 3478 (pol A^- derivative of W3110).	Concentration range not stated.	Microsuspension assay. The minimum inhibitory concentration for the growth of all strains, both in the presence and absence of S-9 mix, was 60,000 µg/well. Thus toluene was considered to be inactive in this test system.	McCarrol N.E. et al. 1980 (36) McCarrol N.E. et al. 1981a (37)

Table 7.3 (Continued)

Test system	Concentration/dose/ duration	Observation	References
1.5. Differential cytotoxicity assay with Bacillus subtilis			
H 17 (rec $^{+}$) M 45 (rec $^{-}$ derivative of H 17) Both in the presence and absence of liver S-9 mix from rats.	Concentration range not stated.	Microsuspension assay. The minimum inhibitory concentration for the growth of either strain, both in the presence and absence of S-9 mix, was 20,000 µg/well. Thus toluene was considered to be inactive in this test system.	McCarrol N.E. et al. 1980(36) McCarrol N.E. et al. 1981b (37)
1.6. SOS-induction assay with Salmonella typhimurium			
TA 1535/pSK1002 Both in the presence and absence of rat liver S-9 mix.	Tested at unspecified concentrations up to 100 µg/ml.	The ability to damage DNA was measured in a test measuring SOS induction, as measured by umu gene expression. Toluene gave a negative result in this test.	Nakamura S. et al. 1978 (41)
2. Yeast assays			
Tests for point mutations in Saccharomyces cerevisiae			
D 7. Both in the presence and absence of rat liver S-9 mix.	A range of concentrations from 8.7 to 4,350 µg/ml.	Reverse mutation (plate incorporation) assay. A negative result was obtained both in the presence and absence of metabolic ativation. A negative result was also obtained for mitotic crossing over and gene conversion, both in the presence and absence of metabolic activation. Complete cell killing was obtained at 870 µg/ml both with and without metabolic activation.	EPA 1980a (14)

Table 7.3 (Continued)

Test system	Concentration/dose/ duration	Observation	References
D 4. Both in the presence and absence of liver S-9 mix from Sprague-Dawley rats.	A range of concentrations from 0.87 to 4,300 µg/plate.	Reverse mutation (plate incorporation) assay. A negative result was obtained both in the presence and absence of metabolic activation. At the maximum concentration tested, survival was less than 50%.	American Petroleum Institute 1978 (1) Lebowitz H. et al. 1979 (28)
D 4. Both in the presence and absence of liver S-9 mix from Sprague-Dawley rats.	The range of concentrations used was not clearly stated.	Reverse mutation (suspension) assay. A negative result was obtained both in the presence and absence of metabolic activation. The maximum concentration tested killed approximately 50% of the yeast.	American Petroleum Institute 1978 (1) Lebowitz H. et al. 1979 (28)
3. Bean studies			
Broad bean Vicia faba Root meristem cells	0, 0.05, 0.10, 0.15 or 0.20% for 1, 2, 3 or 4 hr	Study of the effect of toluene on chromosome structure. Chromosome preparations were made immediately after the 1,2 or 3 hr exposures and 2, 14, 18, 42 and 44 hr after 4 hr exposure. The mitotic index showed a concentration-related decrease and no mitotic figures were observed at 0.20%. Subchromatid aberrations (subchromatid bridges) were seen during 1-2 hr exposures only. Chromatid aberrations (single fragments and bridges) were seen from the first hours of treatment. Chromosome aberrations (double fragments and bridges) were only seen after 4 hr treatment with 42-44 hr recovery. Alterations to the centromere, disturbances of the mitotic spindle and micronuclei were also observed. C-mitoses were only observed in the first 3 hr of treatment. The total incidence of aberrations increased with toluene concentration.	Gomez-Arroyo S. et al. 1986 (25)

Table 7.3 (Continued)

Test system	Concentration/dose/ duration	Observation	References
		Thus, in this study, toluene induced chromosome aberration and was considered to be an S-phase independent agent.	
Broad bean Vicia faba Root meristem cells 250 subacrocentric and 50 metacentric chromosomes scored at each dose level.	Root tips were exposed to 0, 0.003, 0.006 or 0.012% thinner for 1 hr. The thinner comprised 52.0% toluene, 25.5% n-hexane, 12.5% ethyl alcohol, 6.0% ethyl acetate, 2.0% isopropanol, 1% benzene and 1% n-heptane.	Study of the effects of thinner on the incidence of sister chromatid exchanges. There was a statistically significant dose related increase in the incidence of sister chromatid exchanges. As toluene represents only 52% of the thinner,and the effects of the other solvents comprising the thinner are unknown, the interpretation of this result is difficult.	Gomez-Arroyo S. & Castillo-Ruiz P. 1985 (24)
4. **Grasshopper** Melanoplus sanguinipes embryos Three embryos examined at each dose level.	0, 40,000, 200,000, 400,000 or 800,000 ppm vapour [estimated levels] for 16 hr.	Experiment to study the effect of toluene on the division processes of cells. The mitotic index (MI) and anaphase to metaphase (A/M) ratio were determined in squash preparations of embryos. 400,000 and 800,000 ppm toluene caused death of the embryos. The A/M ratio was zero (i.e. significantly reduced) at 200,000 ppm compared with controls and C-mitoses were observed. No effect was observed at 40,000 ppm. MI was not elevated, possibly due to toluene toxicity or to its preventing interphase cells from entering mitosis. It was concluded that the effect may be mediated by toluene interference with spindle microtubles.	Liang J.C. et al. 1983 (30) Liang J.C. & Hsu T.C. 1983 (29)

Table 7.3 (Continued)

Test system	Concentration/dose/ duration	Observation	References
5. Tests with <u>Drosophila melanogaster</u>			
Oster	0, 0.1, 0.25, 0.50, 0.75, 1.0, 1.25 or 1.5% in the food.	Study of effects on sex chromosome loss and non-disjunction. Males and females were allowed to mate for 3 days after treatment. 15 days later the F_1 emerged flies were recorded. Toluene caused a dose-related decrease in viability. The incidence of non-disjunction or X-Y chromosome loss in males was statistically significantly increased ($P<0.05$) at 1.0% (frequency 0.83%), 1.25% (frequency 0.99%) and 1.5% (frequency 1.41%) (control frequency 0.24%). However, the magnitude of the increase was very low, similar to that reported for benzene. No other positive control data were presented.	Rodriguez-Arnaiz R. & Villalobos-Pietrini R. 1985a (43)
Oster	0, 0.1, 0.25, 0.5, 0.75, 1.0, 1.25 or 1.5% in the food of males only.	Study of the effects of toluene on sex linked recessive lethal mutations and translocations II-III. Males and females were allowed to mate for 3 days after treatment. 15 days later the F_1 emerged flies were recorded. For the translocation II-III study a further F_1 mating was performed and the F_2 emerged flies scored 15 days later. Toluene caused a dose-related decrease in viability. Toluene had no effect on the incidence of sex linked recessive lethal mutations or translocations II-III. [A statistically significant increase in tranlocations II-III, but no effect on recessive lethal mutations, was reported for benzene.]	Rodriguez-Arnaiz R. & Villalobos-Pietrini R. 1985b (44)

Table 7.3 (Continued)

Test system	Concentration/dose/ duration	Observation	References
White strain	Males were fed 500 or 1,000 ppm in food for 24 hr.	Report in abstract form only. There was evidently no effect on recessive lethal mutation frequencies, though no figures were given.	Donner M. et al. 1981 (13)
6. In vitro assays with mammalian cells			
6.1. Assays for point mutations			
Mouse L5178Y TK^+/TK^- cells. Both in the presence and absence of mouse liver S-9 mix.	A range of concentrations from 43.5 to 261 µg/ml.	Forward mutation assay. A negative result was obtained both in the presence and absence of metabolic activation. Viability was approximately 70% of control at 43.5 and 87 µg/ml, 50% at 130.5 µg/ml, 37% at 174 µg/ml and 7% at 261 µg/ml.	American Petroleum Institute 1978 (1) Lebowitz H. et al. 1979 (28)
Mouse L5178Y TK^+/TK^- cells. Tested three times in the absence of metabolic activation and twice in the presence of liver S-9 mix from Fisher rats.	A range of concentrations from 31.25-500 µg/ml without activation. A range of concentrations from 6.25-250 µg/ml in the presence of S-9.	Decreased viability was observed at about 175 µg/ml and above. Two of the runs without S-9 and both runs with S-9 were judged positive while the other run without S-9 was considered equivocal. The investigators expressed concern that the results may have been unduly influenced by solubility problems and, overall, judged the assay questionable even though reproducible, significant responses were observed in all five experiments.	McGregor D.B. et al. 1988 (38) Huff J. 1990 (27)

Table 7.3 (Continued)

Test system	Concentration/dose/ duration	Observation	References
6.2. Assays for chromosome aberrations			
Chinese hamster ovary (CHO) cells. Tested both in the presence and absence of liver S-9 mix from Sprague-Dawley rats.	0, 50, 160, 500 or 1,600 µg/ml.	A negative response was obtained both in the presence and absence of metabolic activation. No cytotoxicity was reported at maximum concentration tested.	Huff J. 1990 (27)
Human lymphocytes. No activation system was included.	0, 15.2, 152 and 1,520 µg/ml for 3 days.	SCE, chromosome aberration and cell growth inhibition study. There was no effect on the incidence of chromosome aberrations. Significant cell growth inhibition was seen at 152 µg/ml and above. No positive control data were presented and only 60 metaphases per concentration were examined. The purity of toluene was not given.	Gerner-Smidt P. & Friedrich U. 1978 (23)
6.3. Assays for sister chromatid exchange			
CHO cells. Tested both in the presence and absence of of liver S-9 mix from Sprague-Dawley rats.	A range of concentrations from 50-5,000 µg/ml (without metabolic activation) and 16-1,600 µg/ml (with metabolic activation).	A negative result was obtained both in the presence and absence of metabolic activation. Toxicity was observed at concentrations above 400 µg/ml. The positive controls gave satisfactory responses.	Huff J. 1990 (27)
CHO cells. Tested both in the presence and absence of liver S-9 mix from Fischer F344 rats.	217-348 µg/ml without metabolic activation. 108-1,450 µg/ml with metabolic activation.	Toluene did not induce SCE in this experiment either with or without metabolic activation. 870 µg/ml (without metabolic activation) and 1,740 µg/ml (with metabolic activation) were cytotoxic. The positive controls gave satisfactory responses.	EPA 1980b (15)

Table 7.3 (Continued)

Test system	Concentration/dose/ duration	Observation	References
Human lymphocytes. No activation system was included.	0, 15.2, 152 and 1,520 µg/ml for 3 days.	SCE, chromosome aberration and cell growth inhibition study. There were no effects on the incidence of SCE in metaphases in first, second or third mitoses after the start of culture. Significant cell growth inhibition was seen at 152 and 1,520 µg/ml. No positive control data were presented and the purity of toluene was not specified.	Gerner-Smidt P. & Friedrich U. 1978 (23)
6.4. Assays for DNA damage			
Rat hepatocytes.	0, 2.8, 28 or 276 µg/ml for 3 hr.	Study to investigate the ability of toluene to induce single strand DNA breaks in hepatocytes (measured by alkaline elution). Decreased viability (increased asparate aminotransferase release) was observed at all dose levels and increased DNA damage at all dose levels, particularly 28 µg/ml. [The investigators considered this to be a false positive response with toluene, perhaps an example of those chemicals which induce DNA damage but do not cause detectable mutation or carcinogenicity.]	Sina J.F. et al. 1983 (45)
Human diploid fibroblasts. No metabolic activation system was included.	0 or 275 µg/ml for 2 hr.	Nick translation repair assay. DNA damage was monitored (using incorporation in the presence of E.coli DNA polymerase I) immediately after removal of toluene or following a 2 hr incubation period with or without added ara-C and hydroxyurea. Toluene did not cause DNA damage or strand-break repair or long-patch repair in this assay. The positive control (MNNG) gave adequate results.	Snyder R.D. & Matheson D.W. 1985 (46)

Table 7.3 (Continued)

Test system	Concentration/dose/ duration	Observation	References
6.5. Transformation assays			
BHK-21 C13 cells (baby Syrian hamster kidney cells) and W1-38(human lung cells) tested both in the presence and absence of rat liver S-9 mix.	A range of concentrations from 0.08 to 250 µg/ml.	A cell transformation assay. No increase in the spontaneous rate of transformations was seen in either cell type, either with or without added metabolic activation. No data on cell toxicity were given.	Styles J.A. 1978 (48)
7. **In vivo studies with mammalian cells**			
7.1. Chromosome effects using bone marrow cells			
Rat Charles River Five males per group per sampling time.	0, 21.8, 71.3 or 215 mg/kg bw intraperitoneally, as either a single dose or daily for 5 days. Animals were killed 6,24 or 48 hr after single dose treatment or 6 hr after the fifth dose.	Toluene did not increase the incidence of chromosomal abnormalities. The positive control (triethylene melamine) gave a satisfactory response. However, toluene did not have an effect on the mitotic index. The toluene was described as 'pure'.	American Petroleum Institute 1978 (1) Lebowitz H. et al. 1979 (28)
Rat White. Eight males per group.	Groups of animals were exposed, by inhalation, 4 hr/day, excluding holidays, for 4 months, to approx. 1.44 or 13.5 ppm toluene. The nature of exposure in the control group was not stated.	A combined study of cytogenetics and of damage to the mitotic apparatus in bone marrow cells. There were no differences in chromosomal aberrations at the anatelophase stage between the control and treated groups. Toluene induced a significant increase, in the treated groups, in the frequency of asymmetrical mitosis, C-mitosis, multipolar mitosis, mono-polar metaphase and the percentage of anatelophases with disturbances. The no-effect concentration for pure toluene was estimated to be 0.7 ppm. The incidence of these findings was low and no positive control data were presented. The purity of the toluene used was not stated.	Aristov V.N. et al. 1981 (6)

Table 7.3 (Continued)

Test system	Concentration/dose/ duration	Observation	References
Rat Albino. Six to eight males per group.	0 or 1,000 mg/kg bw, subcutaneously, daily for 12 days.	At this dose level toluene administration caused bone marrow hyperplasia. Toluene reportedly induced an increase in the numbers of chromosome aberrations in bone marrow cells. The types of aberrations included gaps, chromatid breaks and isochromatid breaks. There was an approximately 3 fold increase over control levels. (Benzene (1,000 mg/kg) caused an approximately 10 fold increase). The purity of the toluene used was not given.	Lyapkalo A.A. 1973 (34)
Rat Strain not stated. Five males per group.	0 or 800 mg/kg bw/day as a 10% solution in vegetable oil, subcutaneously for 12 days.	The incidence of chromosome rearrangements and average number of aberrations per bone marrow cell was reportedly increased in the toluene group. Chromosome breaks and cells with multiple chromosome damage were seen in the treated group but not in the control group. No statistical analysis was presented. The purity of the toluene was not given.	Dobrokhotov V.B. 1972 (11)
Rat Albino. 24 males per group.	0 or 163 ppm vapour 4 hr/day for 4 months.	Study of the effects of toluene on peripheral blood and bone marrow cell chromosomes. Assessments were made after 1, 2.5 and 4 months exposure and 30 days after termination of exposure. Peripheral red blood cell counts and haemoglobin levels were reduced in the group exposed to toluene. A moderate increase in peripheral white blood cell count was observed on exposure to toluene. These changes reversed during the 30-day exposure-free period. There was a high incidence (significant at the 0.001 level) of chromosome aberrations (both % metaphases with chromosome aberrations and number of aberrations per chromosome) in	Dobrokhotov V.B. & Enikeev M.I. 1977 (12)

Table 7.3 (Continued)

Test system	Concentration/dose/ duration	Observation	References
		the toluene treated group at each assessment time. The predominant changes were gaps and breaks. The purity of the toluene used was not given.	
Rat Wistar. An unspecified number of males.	0 or 300 ppm vapour 6 hr/day, 5 days/week for 15 weeks.	Report as abstract only. There was evidently no difference in the frequency of chromosome aberrations in bone marrow cells of control and treated animals, though no figures were given.	Donner M. et al. 1981 (13)
Mouse SHK. Five to eight males per group.	0, 1, 5, 25, 125, 250, 500 or 1,000 mg/kg bw, orally, daily for 10 days. The animals were killed 6 hr after the last dose.	Toluene did not increase the incidence of chromosomal abnormalities. No positive control data were presented and signs of toxicity (if any) were not reported.	Fel'dt E.G. 1985 (17)
Mouse CD-1 Five animals per sex per group.	Two oral doses of 0 or 1720 mg/kg bw given 24 hr apart.	Toluene did not increase the incidence of chromosome abnormalities, as evaluated 6 hr after the second dose. No signs of toxicity were reported.	Gad el Karim M.M. et al. 1982 (21) Gad el Karim M.M. et al. 1984 (20)
7.2. Micronucleus tests			
Rat No details of strain, sex or number of animals used.	Exposure was for 60 days. Exposure level and duration of daily exposure was not stated, but probably included 4,640 ppm vapour.	A study of the effect of toluene on peripheral lymphocyte micronuclei numbers. There was no effect on total leukocyte counts. Micronucleus numbers were not increased relative to pre-exposure values at any time after exposure to pure toluene but were increased after 60 days exposure to industrial grade toluene (containing less than 2% benzene). No positive control data were reported. There was no control group (results were compared with pre-exposure values)	Zhong B. et al. 1980 (52)

Table 7.3 (Continued)

Test system	Concentration/dose/ duration	Observation	References
		and the number of micronuclei observed was small. Consequently these results are of uncertain significance.	
Rat No details of strain, sex or number of animals used.	Doses given were not stated, but probably up 4,300 mg/kg bw. Route of exposure was not stated, but was 'by injection'.	A study of the effect of toluene on peripheral lymphocyte micronuclei numbers. An increased number of interphase cell micronuclei was reported. However, no positive control data were reported, the number of micronuclei observed was very small and a considerably higher number of micronuclei was observed in the control group for another study. The results of this study are therefore of uncertain significance.	Zhong B. et al. 1980 (52)
Mouse Swiss. 24 males (control) and 32 males (treated groups).	0, 250, 500 or 1,000 mg/kg bw intraperitoneally. 2 doses were given 24 hr apart.	Toluene did not increase the incidence of polychromatic bone marrow erythrocyte micronuclei in this test. No significant effect was observed on the PCE: RBC ratio. The positive control (trimethyl phosphate) gave a satisfactory response.	EPA 1980c (16)

Table 7.3 (Continued)

Test system	Concentration/dose/ duration	Observation	References
Mouse SHK. Six males per group.	0, 8, 40, 200 or 1,000 mg/kg bw orally, twice (30 and 6 hr before the animals were killed).	There was a statistically significant increase in the number of polychromatic bone marrow erythrocytes with micronuclei at 200 mg/kg bw and 1,000 mg/kg bw. There was no effect on the number of normochromatic erythrocytes containing micronuclei. The percentage of cells with micronuclei induced by toluene treatment was low and did not show a dose response. (Control 0.15%, 8 mg/kg bw 0.18%, 40 mg/kg bw 0.57% ($p>0.01$), 1,000 mg/kg bw 0.42% $p<0.01$)). [The incidence at 200 mg/kg bw is not known.] The percentage of cells with micronuclei in the control group of a parallel study with benzene (0.40%) was broadly similar to that seen with the highest toluene dose toluene (1,000 mg/kg). Consequently, in the absence of historical control data, this result must be interpreted with caution.	Fel'dt E.G. 1985 (17)
Mouse CD-1. Five males per group (treated) and five males and five females (controls).	0 or 860 mg/kg bw, single oral dose.	1000 polychromatic bone marrow erythrocytes were scored 30 hr after toluene administration. No toxicity was reported and the basis for the dose selection was not given. Toluene had no effect on the incidence of polychromatic erythrocyte micronuclei. Thus in this study toluene showed no myeloclastogenic activity.	Gad el Karim M.M. et al. 1986 (22)
Mouse NMRI and B6C3F1. Five males of each strain per group.	0, 2, 108, 217, 325 or 435 mg/kg bw. Two doses were given intraperitoneally 24 hr apart. Benzene, cyclophosphamide and 4-nitroquinoline-1-oxide were used as positive controls.	1000 polychromatic bone marrow eythrocytes were scored 6 hr after the second injection. Statistically significant dose-related increases in micronucleated polychromatic eythrocytes were seen at all dose levels (B6C3F1 strain) and at 217 mg/kg bw and above (NMRI strain). Thus in this study toluene had	Mohtashamipur E. et al. 1985 (39)

Table 7.3 (Continued)

Test system	Concentration/dose/ duration	Observation	References
		clastogenic activity. The number of micronuclei observed after toluene administration in NMRI mice was substantially lower than seen after treatment with positive controls. The dose levels in this study were set so as not to exceed 70% of the predetermined LD_{50}. The purity of the toluene was not specified.	
Mouse NMRI. Three males per group.	0, 218, 322 or 435 mg/kg bw intraperitoneally. Two doses given 24 hr apart. Subgroups were also treated with Aroclor 1254, phenobarbital, 3-methyl-cholanthrene or metyrapone prior to, or simutaneously with toluene.	In this study toluene (99.0% pure) administration resulted in a dose-related increase in the incidence of micronuclei in bone marrow polychromatic erythrocytes (1000 examined per smear). A satisfactory dose-related response was observed with the positive control, benzene. Pretreatment with enzyme inducers enhanced the clasogenicity of toluene. This enhancement was more evident following Aroclor 1254 pretreatment than following phenobarbital or 3-methylcholanthrene. Simultaneous treatment with toluene and enzyme inhibitors (alpha-naphthoflavone or metyrapone) reduced the clastogenicity of toluene. However, enhanced clastogenicity was observed when the enzyme inhibitor was given 24 hr before toluene. Doses were set so as not to exceed 70% of the predetermined LD_{50}.	Mohtashamipur E. et al. 1987 (40)
Mouse CD-1. Five animals per sex per group.	Two oral doses of 0 or 1,720 mg/kg bw given 24 hr apart.	A combined polychromatic bone marrow erythrocyte micronucleus test and metaphase analysis to study the clastogenic effect of toluene. Evaluations (on 1000 PCEs per animal) were performed 6 hr after the second dose. No signs of toxicity were reported on either	Gad el Karim M.M. et al. 1982 (21) Gad el Karim M.M. et al. 1984 (20)

Table 7.3 (Continued)

Test system	Concentration/dose/ duration	Observation	References
		MI or PCE:RBC ratios. Toluene administration did not increase the incidence of micronuclei.	
7.3. Sister chromatid exchange assays			
Rat Wistar. Males (number unspecified).	0 or 300 ppm vapour 6 hr/day, 5 days/week for 15 weeks.	Report in abstract form only. There was a statistically significant increase in SCE in bone marrow cells of toluene administered rats after 11 and 13 weeks exposure. The frequency was within the control range after 15 weeks exposure. No other time points were examined.	Donner M. et al. 1981 (13)
Mouse DBA/2. Four to six males per group.	0, 1,700 or 3,000 mg/kg bw intraperitoneally as a single dose.	Study of the effect of toluene on induced SCE and inhibition of cell proliferation in the bone marrow. Toluene did not induce SCE or inhibit cell proliferation.	Tice R.R. et al. 1981 (49)
7.4. Other in vivo studies indicative of damage to DNA			
Rat No details of strain, sex or numbers of animals used.	A dose of 64 mg/kg bw was given by inhalation over a 5-hr exposure period.	The Covalent Binding Index (a measure of the binding of toluene to DNA) in the liver was less than 0.04. This was very low and considered to be partly due to the incorporation of tritiated water.	Lutz W.K. & Schlatter C. 1979 (33) Lutz W.K. 1979 (31) Lutz W.K. 1984 (32)
Mouse CBA. Three suckling animals per group.	The dose given was not stated, but was 15 - 30% of the LD_{50}. Administration was by intraperitoneal injection.	A study of carcinogen-induced inhibition of nuclear DNA synthesis, measured by incorporation of [^{3}H] thymidine and autoradiography, in renal tubular cells. (The Thymidine Incorporation Inhibiting Screening Test (TSS)). Toluene had no effect in the kidney. Known carcinogens (e.g. diethylnitrosamine, 2-acetyl	Amlacher E. & Rudolph C. 1978 (3) Amlacher E. & Rudolph C. 1981 (4)

Table 7.3 (Continued)

Test system	Concentration/dose/ duration	Observation	References
		aminofluorence and benzidine) gave positive results.	
7.5. Dominant lethal assays			
Rat Sprague-Dawley. An unspecified number of males was used.	A dose of 0.4 of the LD_{50} or 1,166 mg/kg bw/day was given intraperitoneally for 5 days. The treated males were then mated with untreated females (one male to one female each week for 7 weeks).	Report, in abstract form only, of results for the first 3 weeks' matings. Females were killed on day 14 after mating and their uteri and contents examined. After 3 weeks of mating there was no difference between control and treated groups for total number of implants or number of dead implants per female. These data suggests that toluene had no effect on the mature sperm or the spermatid - the stages of spermatogenesis assessed using this treatment schedule. No conclusions can be drawn from this study as it is a preliminary summary with no data.	Dennie D. et al. 1986 (10)
Rat Sprague-Dawley. An unspecified number of males were used.	A dose of 0.4 of the LD_{50} or 1,166 mg/kg bw/day was given intraperitoneally for 5 days. The treated males were then mated with untreated females (one male to one female each week for 7 weeks).	This appears to be a later report of Dennie D et al. 1986. Report in abstract form only. Females were killed 14 days after mating and their uterine contents examined. Total number of implants, the number of dead implants and the number of live fetuses per pregnant female were determined. No data were presented but it was stated that the spermatids and spermatocytes were more sensitive to the mutagenic action of toluene than are other stages of spermatogenesis. The percentage of dominant lethal mutations	Baxter L. et al. 1987 (7)

Table 7.3 (Continued)

Test system	Concentration/dose/ duration	Observation	References
		induced in these stages was greater than 10%. The investigators concluded that a positive result had been obtained but no independent verification can be made because the full data were not available.	
Mouse CD-1. 12 males per group.	0, 100 or 400 ppm vapour 6 hr/day, 5 days/week for 8 weeks. The treated males were then mated with untreated females (1 male to 2 females) for 1 week. Each male was mated with 2 sets of females.	No toxicologically important observations were made on the male animals during the exposure period. The females were killed 14 days after the midweek of mating and their uteri and contents examined. Toluene administration did not reduce fertility in the males or pre or post-implantation loss in the females.	American Petroleum Institute 1981 (2)
Mouse CBA x C57BL/6 17-20 per dosed group.	0, 25, 125 and 375 mg/kg bw, orally daily, for 5 weeks. The treated males were then mated with untreated females (1 male to 3 females) for 1 week.	Females were killed on days 15-17 of gestation. None of the indices studied (post-implantational lethality, number of implantations and of live and dead embryos per pregnant female) revealed any differences between the control and treated groups. The value of this study is limited by the short dosing schedule (5 instead of 8 weeks).	Fel'dt E.G. 1985 (17)
7.6. Sperm head abnormality assay			
Mouse CBA x BALB/c F1 Five males per group.	0, 87, 218, 435, 870 or 1,305 mg/kg bw/day, for 5 days, by intraperitoneal injection.	1,305 mg/kg was a lethal dose. No increase in sperm head abnormalities was observed in the other groups when sperm were examined 5 weeks after the last dose. No actual figures for frequencies of abnomalties were given.	Topham J.C. 1980 (50)

Table 7.4. Effects of toluene on the central nervous system[a]

Species	Protocol	Effects	Reference
Inhalation			
Cat	25500 mg/m^3,10 min/d for 40 days	restlessness, tachypnoea, coughing , sneezing, salivation, mydriassis, and lachrymation	Contreras et al. (1979 in IPCS, 1985)
	153500 mg/m^3,10 min/d for 40 days.	ataxia, collapse; EEG changes in cerebellum, amygdala and visual cortex; seizures with repeated high-level exposure; recovery occurred 12 min after exposure	
rat	3750; 7500 mg/m^3, 4h/d	EEG changes (decreased cortical and hippocampal components)	Takeuchi and Hisanaga (1977 in IPCS, 1985)
	15000 mg/m^3, 4h/d	increased excitability followed by depression and inability to stand; changed sleep cycle myoclonic seizures; increased pulse rate	
rat	7500 mg/m^3,8h/d for 8 weeks	decreased threshold for Bemegride-induced convulsions	Takeuchi and Suzuki (1975 in IPCS, 1985)
rat	3750 mg/m^3, 6h/d, 6 d/wk, for 4 weeks	increased spontaneous activity during light period after repeated exposure; single exposure did not influence circadian rhythm	Ikeda et al. (1981 in IPCS, 1985)
rat	7500 mg/m^3, 4h/d for 24 weeks	interrupted sleep cycle; decreased duration of REM sleep	Takeuchi et al. (1979 in IPCS, 1985)
rat	26250 mg/m^3, 15 min for 1, 7, or 14 days	hind-limb abduction, resting tremor, head weaving; ataxia, tachypnoea, salivation, diarrhoea, and convulsions; frequency unchanged after 2 weeks of exposure	Yamawaki et al. (1982 in IPCS, 1985)
rat	15000 mg/m^3, 4h/d for 4 weeks	changes in sleep cycle and EEGs continued 1 week after exposure	Hisanaga and Takeuchi (1983 in IPCS, 1985)
rat	3750 mg/m^3 for 24 hours	increased REM sleep	Fodor et al. (1973 in IPCS, 1985)

Table 7.4 (continued)

Species	Protocol	Effects	Reference
mouse	375, 3750 and 11250 mg/m^3, 5h/d for 8 days	no effect on locomotor activity at 375 mg/m^3; at the two higher dose levels, decreased locomotor activity was observed	Bushnell et al. (1985)
rat	1875 mg/m^3, 8 to 16h/d, 5d/wk for 12 weeks	disruptions and frequency changes in hippocampal theta wave activity, changes in EEGs	Naaisuno (1986 in ATSDR, 1986)
rat	1200 mg/m^3 for 30 days	decreased weight of the brain and cerebral cortex, decreased in the total phospholipid content of the cerebral cortex accompanied by a small increase in phosphatidic acid levels	Kyrklund et al. (1987)
ip injection rat	single dose of 200, 400, or 600 mg/kg b.w.	no effect on circadian sleep-waking rhythm; rhythm of paradoxical sleep and wakefulness were changed; at 600 mg/kg, EEG was abnormal; on second day, 200 mg/kg exposed group showed increase in paradoxical sleep phase during dark period; sleep-waking rhythm returned to normal by third day	Nakagaki et al. (1983 in IPCS, 1985)

[a] modified from IPCS (1985)

Table 7.5. Changes in neurotransmitters after toluene exposure[a]

Species	Protocol	Effects	Reference
Inhalation			
Rat	26250 mg/m^3, 15 min/d for 14 days	decrease in 5-hydroxytryptaline (5HT) binding in whole brain, especially hippocampus, pons, and medulla	Yamawaki et al. (1982 in IPCS, 1985)
Rat	375 or 1125 mg/m^3, for 8 hours 3750 mg/m^3 for 8 hours	increased dopamine (DA) levels increased DA levels in striatum; increased noradrenaline (NA) in medulla and midbrain; increased 5HT in cerebellum, medulla, and striatum	Rea et al. (1983 in IPCS, 1985)
Rat	750, 1500, or 3000 mg/m^3 continuous exposure for 30 days	increased DA in striatum (dose dependent); reduced 5HT in cortex and hippocampus, NA in hypothalamus, cortex, and hippocampus; reduced acetylcholine (Ach) in striatum and whole brain; cyclic 3',5'-adenosine monophosphate (cAMP) in striatum; amino acids: gama-aminobutyric acid (GABA) increased by mid and highest doses while glycine was reduced by the low dose exposure	Honma et al. (1983 in IPCS, 1985)
Rat	15000 mg/m^3 for 8 hours	glutamine levels in mid brain increased significantly	Honma et al. (1982 in IPCS, 1985)
Rat	3750 - 30000 mg/m^3 for 8 hours	ACh increased at low dose and reduced at high dose; acetylcholinesterase (AChE) elevated at both exposures; choline acetyltransferase (ChAT) activity reduced was dose dependent	Honma (1983 in IPCS, 1985)
Rat (Sprague Dawley)	1875 mg/m^3, 6h/d for 3 days; killed 16 - 18 h after exposure	increase in catecholamines (DA + NA) in lateral palisade zone of median eminence	Andersson et al. (1980)

Table 7.5 (continued)

Species	Protocol	Effects	Reference
Rat	300 mg/m^3, 6h/d for 3 days 1875 mg/m^3, 6h/d for 3 days 5625 mg/m^3, 6h/d for 3 days 11250 mg/m3, 6h/d for 3 days	decreased DA levels in marginal zone of nucleus caudatus, and anterior nucleus accumbens; DA turnover significantly reduced in all parts of anterior caudate nucleus reduction in DA turnover in anterior nucleus accumbens effects on DA in anterior nucleus accumbers disappeared, while a selective increase in DA in the DA-cholecystokinin (CCK) immunoreactive nerve terminals significantly increased DA turnover in tuberculum olfactorium; significant increases in amine levels in DA-CCK immunoreactive-nerve terminals in the nucleus accumbens,especially in the tuberculum olfactorium	Fuxe et al. (1982)
Male Wistar rats (randomly divided into groups of 6 to 10 rats)	500 ppm (1875 mg/m^3), 16 h/d for 12 weeks.	Increase in activity of neurotransmitter synthesizing enzymes glutamic acid decarboxylase (GAD) in the brain stem, choline acetyltransferase (ELAT) in the hippocampus and cerebellar vermis and aromatic amino acid decarboxylase (AAD) in the hippocampus, septum and hypothalamus. Results did not confirm those of four week studies in which activities of neurotransmitter synthesizing enzymes in the brain stem were reduced.	Bjornaes and Naalsund (1988)

Table 7.5 (continued)

Species	Protocol	Effects	Reference
Rat (Sprague-Dawley, n= 5)	88 ppm (330 mg/m^3), 6 h/d from day 1 to 7 and for 3 days in the 8th week.	Neonatal toluene exposure produced persistent changes in dopamine and noradrenaline neurons of the forebrain, hypothalamus and substantia nigra in the presence of a relatively intact neuroendocrine system. In addition, neonatal toluene exposure was found to alter the responses of the catecholamine neurons and appeared to diminish or even counteract the responses to short-term toluene exposure in adulthood.	von Euler et al. (1989)
Rat (Sprague-Dawley, n = 12)	80 ppm (330 mg/m^3), 6 h/d, 5+4 days for 2 weeks.	Toluene exposure increased membrane protein phosphorylation levels in the rat forebrain and especially in the striatum, probably leading to changes in information handling and/or metabolic changes.	von Euler et al. (1987)
Rat (male 12 months old Sprague-Dawley, n = 6)	80 ppm (330 mg/m^3), 6 h/d, 5 d/wk., for 3 months.	Toluene exposure induced region-specific effects on pre-and postsynaptic parameters of catecholamine and neuropeptide neurotransmission based on receptor-binding which might in part be due to the high vulnerability of the intramembrane receptor-receptor interactions in these regions; no behavioural effects.	von Euler et al. (1988)

Table 7.5 (continued)

Species	Protocol	Effects	Reference
Ingestion			
Mouse (groups of 5 adult male CD-1)	fed drinking water ad libitum containing 0, 17, 80 and 405 mg/L toluene (corresponded to 0, 5, 22 and 105 mg/kg b.w./d).	In the hypothalamus, a major norepinephrine (NE)-containing compartment, the concentrations of NE were significantly increased by 51, 63, and 34% in groups ingesting 5, 22, and 105 mg/kg b.w./d, respectively. Significant increases of NE were also observed in the medullar oblongata and mid-brain. Concentrations of its metabolites (3-methoxy-4-hydroxymandelic acid) also increased in various brain regions. Concentrations of dopamine were significantly higher in the corpus striatum and hypothalamus whereas alterations in levels of its metabolites were marginal. Toluene significantly increased the concentrations of serotonin in all dissected brain regions, except the cerebellum; greatest increase observed in mid-dose group.	Hsieh et al. (1990)

[a] modified from IPCS (1985)

Table 7.6. Behavioural effects of different doses of toluene[a]

Species	Protocol	Effects	References
Inhalation Rat (Sprague Dawley)	563 mg/m^3 for 0.5, 1, 2, or 4 hours	initial stimulation followed by depression in multiple fixed ratio-fixed interval (FR-FI) response schedule performance	Geller et al. (1979)
Rat	375, 668, 2100 mg/m^3 for 4 hours 3750, 6675, 11250 mg/m^3 for 4 hours	no-observed adverse-effect-level deficit in conditioned reflex; less when external signal cued response	Wood et al. (1983)
Rat (male)	2063 - 3000 mg/m^3, 4h/d for 3 weeks	no effect on avoidance response	Battig and Grandjean (1964 in IPCS, 1985)
Rat (male)	7500 mg/m^3, 8h/d for 52 days	process of extinction in conditioned avoidance response	Maeda (1970 in IPCS, 1985)
Rat (male)	3750 or 11250 mg/m^3 for 4 hours	no effects were observed in low dose group; at high dose level, deficit in conditioned avoidance response was observed	Shigeta et al. (1978 in IPCS, 1985)
Rat (male)	12000 and 24000 mg/m^3 for 4 hours 3000 and 6000 mg/m^3 for 4 hours 3000 mg/m3 for 4 hours	deficit in conditioned avoidance response no effect deficit in unconditioned reflexes and simple behaviour	Krivanek and Mullin (1978 in IPCS, 1985); Mullin and Krivanek (1982 in IPCS, 1985)
Rat	15000 mg/m^3, 2h/d for 60 days	multiple response schedule;no effect on CRF or FR30; deficit in DRL in 12-second schedule	Ikeda and Miyake (1978 in IPCS, 1985)
Rat (Sprague Dawley)	86250 mg/m^3, 30 min/d for 7.6 days	induced forced turning	Ishikawa and Schmidt (1973 in IPCS, 1985)

Table 7.6 (continued)

Species	Protocol	Effects	References
Rat (male Fischer), forty-eight rats were housed in the 4-chamber exposure system	0, 400, 700 and 1000 ppm, 14 h/d, 7 d/wk for 16 weeks; changed to 0, 850, 1000, 1200 for an additional five weeks.	Hearing loss, measured by behavioral and electrophysiologic methods, was repeatedly observed after as few as 2 weeks of exposure to 1000 ppm toluene for 14 hours per day, but lower concentrations (400 and 700 ppm) were without effect even after 16 weeks of exposure.	Pryor et al. (1984)
Rat (male pigmented DA-HAN)	1000 ppm, 21 h/d, 7 d/wk for 6 or 11 weeks	reduced optokinetic gain and a slight reduction in gain during sinusoidal oscillatory vestibular stimulation; caused a possibly permanent lesion within the vestibulo-cerebellum.	Nylen et al. (1991)
Rat (male Wistar)	90 ppm, 12 h/d, for one to two weeks	initial depression of the amplitudes of both a- and b-waves of electroretinogram at one week after the initiation of exposure, but was completely normalized six weeks after withdrawal. Prolonged latency time of the N_2 component of visual evoked potential two weeks after inhalation which did not improve even 4 weeks afterwards suggested that the involvement of visual pathway was located mainly at the optic nerve.	Ikeda (1987)
Mouse (male)	3.75, 37.5, 375, 3750 mg/m^3, 6h/d for 10 days	deficit in wheel-turning	Horiguchi and Inoue (1977)
Mouse	15000 mg/m^3 for 3 hours or 40000 mg/m^3 for 10 min	deficit in visual placing, grip strength, wire manoeuvre tail pinch, righting reflex	Peterson and Bruckner (1978 in IPCS, 1985)
Mouse	45000 mg/m^3, 3h/d, 5d/wk for 8 weeks	deficit in performance tests	Bruckner and Peterson (1976 in IPCS, 1985)

[a] modified from IPCS (1985)

Table 8.1 (Continued)

Study Protocol	Results	Comments	Reference
Twenty three Japanese volunteers were exposed to 375 and 750 mg/m^3 toluene for 3 h or 3 h and 1 h break followed by an additional 4-h exposure.	A prolonged eye-to-hand reaction time, but no effect on critical flicker fusion frequency was observed after exposure to 750 mg/m^3. No changes in either reaction time or flicker value were observed after exposure to toluene at 375 mg/m^3.	The NOAEL is 350 mg/m^3.	Ogata et al. (1970)
Twelve healthy male volunteers were exposed to toluene at concentrations of 375, 1125, 1875 and 2625 mg/m^3 (100, 300, 500 and 700 ppm) for 20 minutes.	There was significant impairment of reaction time at 1125 mg/m^3, which was further impaired at 1875 and 2625 mg/m^3. No impairment was observed at 375 mg/m^3. Perceptual speed was unaffected at exposure levels below 2625 mg/m^3. No effect on heart rate was observed at 375 mg/m^3.	The number of subjects is small. The NOAEL is 375 mg/m^3 and the LOAEL is 1125 mg/m^3.	Gamberale and Hultengren (1972, in IPCS 1985)
Eighteen volunteers were exposed to 375, 1125 and 1875 mg/m^3 (100, 300 and 500 ppm) for 3.5 hours.	Complex reaction time in audio/visual bisensory vigilance task, psychomotor performance, critical flicker fusion frequency and auditory evoked potentials only at 1875 mg/m^3. Simple reaction time began to increase at 1125 mg/m^3. No effects on simple reaction time, rotary pursuit and tapping test were observed at 375 mg/m^3.	The NOAEL is 375 mg/m^3 and the LOAEL is 1125 mg/m^3.	Winneke (1982, in IPCS, 1985)
Sixteen healthy male volunteers were exposed to increasing concentrations of toluene ranging from 37.5, 150 to 375 mg/m^3 (10, 40 and 100 ppm) by inhalation 6 h/d, for 4 days.	At 375 mg/m^3, multiplication errors, Landolt's rings, and screw plate tests were significantly affected in addition to increased occurrence of headache, dizziness, sensation intoxication and irritation of respiratory tract. The two lower levels, 37.5 and 150 mg/m^3 did not produce any adverse effect.	Battery of 8 tests of visual perception, psychomotor functions and higher cortical functions: rotary pursuit, screw plate, Landolt's ring, Bowdon Wiersma, multiplication, sentence comprehension and word memory tests. The NOAEL is 150 mg/m^3 and the LOAEL is 375 mg/m^3.	Andersen et al. (1983)

Table 8.1. Inhalation toxicity in humans - Clinical studies

Study Protocol	Results	Comments	Reference
Three human volunteers were exposed repeatedly to toluene (benzene ≤ 0.01%) for 8-h periods at concentrations of 0, 188, 375, 750, 1125, 1500, 2250 and 3000 mg/m^3 (i.e. 0, 50, 100, 200, 300, 400, 600 and 800 ppm, respectively), in an exposure chamber. A maximum of 2 exposures a week was maintained to allow sufficient time for recovery between exposures. A total of 22 exposures was performed over an 8-week period.	Drowsiness with a very mild headache in 1 subject was noted but no after effects were observed after exposure to 188 mg/m^3. Subjective complaints of fatigue, muscular weakness, confusion, impaired coordination, enlarged pupils, and accommodation disturbances were reported at 750 mg/m^3. These effects increased in severity with increases in toluene concentration until, at 3000 mg/m^3, the subjects experienced rapid onset of severe fatigue and, after 3 h, pronounced nausea, confusion, lack of self-control, and considerable incoordination and staggering gait in all 3 subjects. Considerable after-effects, lasting at least several days, which included severe nervousness, muscular fatigue and insomnia were observed. In addition, pupillary light reflex was strongly impaired in one subject and optic discs were pale in two subjects.	The design of the study is complex and not clear. For example, the number of hours per day is different for the several groups. Seven of the 22 exposures were controls and exposures to particular levels of toluene were replicated only 1-4 times. Further, the number of subjects in this study is small. The NOAEL is 188 mg/m^3.	Von Oettingen et al. (1942, in IPCS, 1985)
Six volunteers were exposed to 750 and 1500 mg/m^3 for 8-h periods.	Mild eye and throat irritation was noted after exposure to 750 mg/m^3 and lachrymation occurred at 1500 mg/m^3. Based on sensory thresholds for irritation (eye, nose, throat), dizziness, taste, and olfactory fatigue, 6 out of 6 volunteers indicated their willingness to work for 8 h exposed to a concentration of 825 mg/m^3.	The LOAEL is 750 mg/m^3. Small number of subjects.	Carpenter et al. (1976b in IPCS, 1985)
Five male volunteers were exposed to 750 mg/m^3 for 6 h compared with controls.	An effect on heart rate was observed. A mean decrease of 7 beats/min. was noted.	Small number of subjects. One dose only.	Suzuki (1973, in IPCS, 1975)

Table 8.1 (Continued)

Study Protocol	Results	Comments	Reference
Forty-three volunteer male printers, aged 29 to 50 years who had been exposed to solvents for 9 to 25 years during employment were exposed once in a climate chamber to 100 ppm (375 mg/m^3) of toluene for 6.5 h. 43 control subjects matched for sex, age, educational level and smoking habits were exposed to clean air for 6.5 h.	Exposure to 375 mg/m^3 of toluene caused discomfort with complaints of low air quality, strong odor, fatigue, sleepiness, a feeling of intoxication, and irritation of the eyes, nose and throat. Furthermore, the subjects exposed to toluene had decreased manual dexterity, decreased color discrimination, and decreased accuracy in visual perception. No effect was observed in more complicated visuomotor tests.	Previous exposure for 9 to 25 years to solvents. The LOAEL is 375 mg/m^3.	Baelum et al. (1985)
A total of 74 volunteers aged 18 to 38 years were exposed to 100 ppm (375 mg/m^3) toluene for 8 h in an exposure chamber. The subjects were divided into groups of 30 , 26, and 18 for choice reaction time, for visual-vigilance, and for pattern recognition tasks, respectively. The control group consisted of 6 to 12 subjects. The subjects were tested before, during, and after the treatment or under control conditions.	The effect on the visual-vigilance test was most pronounced during the first two hours of exposure and the reduction in correct detections occurred primarily during the first measured exposure period. A similar trend was found in the pattern recognition test although the results were not statistically significant ($P = 0.07$). None of the choice reaction time measures were significantly affected by the exposure to toluene.	Effects were not as great as those of ingested ethanol at 0.8 mL/kg. One dose only.	Dick et al. (1984)

Table 8.1 (Continued)

Study Protocol	Results	Comments	Reference
From 152/225 male spray painter respondents to a questionnaire, two extreme groups, namely the sensitive (14 subjects) and the insensitive (12 subjects) groups, were chosen and matched with respect to age and number of years employed as a painter. These subjects were experimentally exposed for 4 h to 300 mg/m^3 of toluene or air in an exposure chamber. Effects on performance were determined by a battery of four tests including choice reaction time, simple reaction time, colour vigilance and memory reproduction.	There were no indications of effects on performance, nor was there any correlation between symptom frequencies and performance levels. The only difference found between the two groups was a higher frequency of symptoms of local irritation in the group which had reported high symptom frequencies on the questionnaire.	One dose only. Previous exposure to other solvents likely.	Iregren (1986)
A total of 42 college students were exposed 7 h/d, for 3 days to 0, 75 and 150 ppm (0, 281 and 563 mg/m^3) of toluene and changes in their central nervous system function and symptoms were assessed.	Adverse performance at 150 ppm with reduction of verbal and visual short-term memory (6.0% for digit span, 5.0% for short-term memory), perception (12.1% for pattern recognition), manual dexterity (6.5%) and psychomotor skill (3.0% for critical tracking). The number of headaches and eye irritation also increased in a dose response manner. The greatest effect was found for an increasing number of observations of sleep. No clear pattern of neurobehavioural effects consistent with the "type 1 central nervous system" classification of the World Health Organization. However, subtle acute effects were found just below and above the 100 ppm toluene level.	The LOAEL is 150 ppm (563 mg/m^3) and NOAEL is 75 ppm (281 mg/m^3).	Echeverria et al. (1989)

Table 9.1. Effects of toluene on aquatic plants

Species	Static / flow-through [a]	Temp. °C	Hardness mg/L or Salinity %	pH	Response	Concentration, mg/L	Nominal or Measured [b]	Reference
FRESHWATER								
Chlorella vulgaris	stat open	20			24h-EC50 cell number inhibition	245	n	Kauss and Hutchinson, 1975
Selenastrum capricornutum	stat closed	24			8h-97% inhibition of photosynthesis	100	n	Giddings, 1979
	stat closed			7.0	8d-EC50 growth	9.4	n	Herman *et al.*, 1990
	stat closed				72h-EC50	12.5	m	Galassi *et al.*, 1988
Scenedesmus quadricauda	stat closed	27			Toxicity threshold	>400	n	Bringman and Kühn, 1978
SALTWATER								
Chlorella sp.	closed				12h-inhibition of respiration (62%)	34	m	Potera, 1975
Dunaliella biocula	stat closed		sea water	sea water	4h-EC50 photosynthesis	10	n	Jensen *et al.*, 1984
Diatoms	closed	18	sea water	sea water	Growth inhibition	10	n	Dunstan *et al.*, 1975

[a] flow = flow-through ren = renewal stat = static
[b] n = nominal concentration m = measured concentration

Table 9.2. Effects of toluene on invertebrates

Species	Size / age	Static / flow-through [a]	Temp. °C	Hardness mg/L or Salinity %	pH	Response	Concentration, mg/L	Nominal or measured [b]	Reference
FRESHWATER									
Water flea	<24 h	stat	21-23	72	6.7-8.1	48h-LC50 [c]	310	n	LeBlanc, 1980
Daphnia magna						48h-NOEC	28	n	LeBlanc, 1980
	<48 h	stat	22	100		48h-EC50 immobility	15.0	n	Hermens *et al.*, 1984
		QSAR [d]	19	100		16d-EC50 reproduction	1.4	n	Hermens *et al.*, 1984
		QSAR [d]	19	100		16d-LC50	3.8	n	Hermens *et al.*, 1984
	4-6 day	stat closed	23		6-7	48h-LC50	11.5	n	Bobra *et al.*, 1983
		stat closed				24h-LC50	7	m	Galassi *et al.*, 1988
Zebra mussel *Dreissena polymorpha*	adult	flow	18			valve closure	9.4	n	Sloof *et al.*, 1983
Yellowfever mosquito *Aedes aegypti*	larvae	stat	24-26			24h-LC50	21.5	m	Berry and Brammer, 1977
SALTWATER									
Copepod *Nitocra spinipes*						24h-LC50	24.2-74.2	m	Potera, 1975
Crab *Cancer magister*	larvae	ren	13	3.0%		96h-LC50	28	n	Caldwell *et al.*, 1976
Bay shrimp	adult	stat open	16	2.5%		24h-LC50	12.0	n	Benville and Korn, 1977
Crago franciscorum	adult	stat open	16	2.5%		96h-LC50	4.3	n	Benville and Korn, 1977
Grass shrimp	larvae					24h-LC50	25.8	m	Potera, 1975
Palaemonetes pugio	adult					24h-LC50	17.2	m	Potera, 1975

Table 9.2 (concluded)

Species	Size / age	Static / flow-through [a]	Temp. °C	Hardness mg/L or Salinity %	pH	Response	Concentration, mg/L	Nominal or measured [b]	Reference
Shrimp	0.8 g	stat	4	2.6-2.8%		96h-LC50	21.4	n[c]	Korn *et al.*, 1979
Eualus sp.	0.8 g	stat	8	2.6-2.8%		96h-LC50	20.2	n[c]	Korn *et al.*, 1979
	0.8 g	stat	12	2.6-2.8%		96h-LC50	14.7	n[c]	Korn *et al.*, 1979
Mussel *Mytilus californicus*	0.4 - 1.2 g	stat	11	3.2		24h respir. reduction	7.8	n	Sabourin and Tullis, 1981

[a] flow = flow-through ren = renewal stat = static
[b] n = nominal concentration m = measured concentration
[c] concentration is the same as that given for the 24h-LC50
[d] QSARS: quantitative structure-activity relationships were used to determine the toxicity thrseholds from selected experimental results
[e] measurements indicated that toluene was not detectable within 72 h at 12°C, 96 h at 8°C, and was at 25% of nominal concentration after 96 h at 4°C

Table 9.3 (concluded)

Species	Size / age	Static / flow-through [a]	Temp. °C	Hardness mg/L	pH	Response	Concentration, mg/L	Nominal or measured [b]	Reference
Rainbow trout	2.4 g	stat	12	44	7.4	96h-LC50 [c]	24	n	Mayer and Ellersieck, 1986
Oncorhynchus mykiss	adult	ren closed	12			96h-LC50	5.8	m	Galassi *et al.*, 1988
	embryo-larvae	flow	14.3	106	7.8	23d + 96h-LC50	0.02	m	Black *et al.*, 1982
Coho salmon	fry	flow	7.6			96h-LC50	5.5	m	Moles *et al.*, 1981
Oncorhynchus kisutch									

[a] flow = flow-through ren = renewal stat = static
[b] n = nominal concentration m = measured concentration
[c] concentration is the same as that given for the 24h-LC50

Table 9.3. Lethal effects of toluene on freshwater fish

Species	Size / age	Static / flow-through [a]	Temp. °C	Hardness mg/L	pH	Response	Concentration, mg/L	Nominal or measured [b]	Reference
Fathead minnow *Pimaphales promelas*	1-2 g	stat	25	20	7.5	96h-LC50	34.3	n	Pickering and Henderson, 1966
	1-2 g	stat	25	360	8.2	96h-LC50	42.3	n	Pickering and Henderson, 1966
	embryo	flow	25	80	8.3	96h-LC50	63	m	Devlin *et al.*, 1982
	1 d	flow	25	80	8.3	96h-LC50	29	m	Devlin *et al.*, 1982
	juv	flow	25	80	8.3	96h-LC50	26	m	Devlin *et al.*, 1982
Bluegill sunfish *Lepomis macrochirus*	1-2 g	stat	25	20	7.5	96h-LC50 [c]	24	n	Pickering and Henderson, 1966
	0.32-1 g	stat	20-24	28-44	6.7-7.4	96h-LC50	13	n	Buccafusco *et al.*, 1981
	0.5 g	stat	17	12	8	96h-LC50	240	n	Mayer and Ellersieck, 1986
	0.5 g	stat	17	44	8	96h-LC50	135	n	Mayer and Ellersieck, 1986
	0.5 g	stat	17	162	8	96h-LC50	74	n	Mayer and Ellersieck, 1986
	0.5 g	stat	17	300	8	96h-LC50	135	n	Mayer and Ellersieck, 1986
Channel catfish *Ictalurus punctatus*	0.1 g	stat	22	44	7.4	96h-LC50 [c]	240	n	Mayer and Ellersieck, 1986
Japanese medaka *Oryzias latipes*	embryo	stat	23-27			96h-LC50	54	n	Stoss and Haines, 1979
Zebra fish *Brachydanio rerio*		flow	20			48h-LC50	25	n	Sloof, 1979
Goldfish *Carassius auratus*	1-2 g	stat	25	20	7.5	96h-LC50 [c]	57.7	n	Pickering and Henderson, 1966
	20-80 g	flow	18		7.0	96h-LC50	23	m	Brenniman *et al.*, 1976
Guppy *Poecilia reticulata*	0.1-0.2 g	stat	25	20	7.5	96h-LC50	59.3	n	Pickering and Henderson, 1966
	2-3 months	ren	22	soft		14d-LC50	68	n	Könemann, 1981
	fry	ren closed	21			96h-LC50	28.2	m	Galassi *et al.*, 1988

Table 9.4. Lethal effects of toluene on estuarine and marine fish

Species	Size / age	Static / flow-through [a]	Temp. °C	Salinity %	pH	Response	Concentration, mg/L	Nominal or measured [b]	Reference
Striped bass *Morone saxatilis*	6 g	stat	16	2.5		96h-LC50[c]	7.3	n	Benville and Korn, 1977
Sheepshead minnow *Cyprinodon variegatus*	juv	stat	25-31	1.0-3.1		96h-LC50[c]	>280 <480	n	Heitmuller *et al.*, 1981
	juv	flow+	29	1.5		96h-LC50	13	m	Ward *et al.*, 1981
Pink salmon	fry	stat	4	2.6-2.8		96h-LC50	6.41	n[d]	Korn *et al.*, 1979
Oncorhynchus gorbuscha	fry	stat	8	2.6-2.8		96h-LC50	7.63	n[d]	Korn *et al.*, 1979
	fry	stat	12	2.6-2.8		96h-LC50	8.09	n[d]	Korn *et al.*, 1979
	1-2 g	flow	12			24h-LC50	5.4	m	Thomas and Rice, 1979
Coho salmon *Oncorhynchus kisutch*	5-40 g	stat	8	3.0	8.1	96h-LC50	22 (>10<50)	n	Morrow *et al.*, 1975

[a] flow = flow-through flow+ = intermittent flow-through stat = static
[b] n = nominal concentration m = measured concentration
[c] concentration is the same as that given for the 24h-LC50
[d] measurements indicated that toluene was not detectable within 72 h at 12°C, 96 h at 8°C, and was at 25% of nominal concentration after 96 h at 4°C

Table 9.5. Sub-lethal effects of toluene on fish

Species	Size / age	Static / flow-through [a]	Temp. °C	Hardness mg/L or Salinity %	pH	Response	Concentration, mg/L	Nominal or measured [b]	Reference
FRESHWATER									
Rainbow trout *Oncorhynchus mykiss*	yearling	flow	19-20	180	8.0	24h-respiration	2.5	m	Sloof, 1979
Coho salmon	fry	flow	7.6-10.4			40d-NOEC	1.4-2.8	m	Moles *et al.*, 1981
Oncorhynchus kisutch	juv	stat	5-17			70 min-avoidance behaviour	1.4	m	Maynard and Weber, 1981
Fathead minnow *Pimaphales promelas*	embryo-larval	flow	25	45	7.6	32d-LOEC growth	6	m	Devlin *et al.*, 1982
Carp *Cyprinus carpio*	12-17 cm	ren	17			72h-biochemical	0.1	n	Gluth and Hanke, 1985
Tilapia *Oreochromis mossambicus*						biochemical	25	n	Dangé, 1986
SALTWATER									
Sheepshead minnow *Cyprinodon variegatus*	embryo-larvae	flow +	29	2.5%	7.8-8.5	28d-growth	>3.2<7.7	m	Ward *et al.*, 1981
Pink salmon *Oncorhynchus gorbuscha*	fry	flow	12			15h-NOEC-rate of breathing	2.4	m	Thomas and Rice, 1979

[a] flow = flow-through flow + = intermittent flow-through ren = renewal stat = static
[b] n = nominal concentration m = measured concentration

Table 11.1 (continued)

Geographic area	Status	Medium	Description	Levels	Act / Reference [b]	Date
	Recommend.	Air	Ambient Air Quality Criterion	MAC: 2mg/m^3	O.R. 308	
	Recommend.	Air	Occupational - TLV	TWA: skin 375mg/m^3 STEL: skin 560mg/m^3 (excludes farms, private homes, and teachers)	Occupational Health and Safety Act of Ontario	1980
	Recommend.	Water	Drinking, Surface and Ground Water Quality	MAC organics: 96 hr LC50 < 10mg/L for fish (prohibitions against polluting surface and ground waters)	Not legally enforceable; applied under Ontario Water Resources Act	May 1984
Manitoba	Recommend.	Air	Occupational - TLV	TWA: 375mg/m^3 STEL: 560mg/m^3	Workplace Safety and Health Act	1976
Saskatchewan	Regulation	Air	Occupational - TLV	TWA: 8 hr 375mg/m^3 STEL: 15 min 560mg/m^3	Occupational Health and Safety Act / Regulations, s. 70, 71, 73	13 Mar. 1986
Alberta	Regulation	Air	Occupational - TLV	TWA: 8hr 375mg/m^3 STEL: 15min 560mg/m^3	Occupational Health and Safety Act, s. 2(1), 6, 7	7 Jul. 1983
British Columbia	Recommend.	Air	Industrial emissions	LEVELS: A - objective for new discharges: 3750mg/m^3 B - intermediate objective for existing discharges: 3750mg/m^3 C - immediate objective for all existing chemical and petroleum industries: 37,500mg/m^3	Waste Management Act	Mar. 1974
	Regulation	Air	Industrial occupational - MPC and TLV	MPC: 8 hr 375mg/m^3 15 min 560mg/m^3	Workers' Compensation Act of B.C.	1 Oct. 1979

Table 11.1. Canadian, foreign, and international regulations, standards, and guidelines for toluene [a]

Geographic area	Status	Medium	Description	Levels	Act / Reference [b]	Date
CANADA - Federal						
	Regulation	Air	Occupational - TLV	TWA: 377 mg/m^3 STEL: 565mg/m^3	Canada Labour Code	13 Mar. 1986
	Recommend.	Drinking water	Aesthetic objective	MAC: 0.024 mg/L	Guidelines for Drinking Water Quality	1989
	Recommend.	Surface water	Protection of freshwater aquatic life	MAC: 0.3mg/L	Canadian Water Quality Guidelines	1989
CANADA - Provincial						
Newfoundland	Regulation	Air	Occupational - TLV	TWA: 375 mg/m^3 STEL: 560 mg/m^3	Newfoundland Occupational Health and Safety Act / Regulations, s. 2(2), 25(5)(A)	29 Jun. 1979
Nova Scotia	Regulation	Air	Occupational - MXL	TWA: skin 375mg/m^3 STEL: skin 560mg/m^3	Health Act of Nova Scotia / Regulations, s. 4(1), 6	1967
Prince Edward Island	Recommend.	Air	Occupational - TLV	TWA: 375mg/m^3 STEL: skin 560mg/m^3	Occupational Health and Safety Act	28 May 1985
New Brunswick	Regulation	Air	Occupational - TLV	TWA: 375mg/m^3 STEL: skin 560mg/m^3	Mining Act of New Brunswick / Regulations, s. 288	1977
Quebec	Regulation	Air	Occupational - Emissions	Levels not to exceed: Av. Conc. 375mg/m^3 Max. Conc. 560mg/m^3	Occupational Health and Safety Act of Quebec, s. 5	19 Dec. 1979
Ontario	Regulation	Air	Industrial Ambient Air Emissions - MPC	MPC: 2mg/m^3 (at point of impingement)	Environmental Protection Act of Ontario	1985

Table 11.1 (continued)

Geographic area	Status	Medium	Description	Levels	Act / Reference[b]	Date
	Recommend.	Water		Class II - harmful	GMBL* v11,p 173	1985
Great Britain	Recommend.	Air	Occupational - OES	8 hr TWA: 375mg/m^3 10 min TWA: 560mg/m^3	GNHSE*,vEH40/ 87, p8	1987
Hungary	Regulation	Air	Occupational - MAC	TWA: 100mg/m^3 STEL: 500mg/m^3 30 min	HSMSZ* 21461-78	1978
Italy	Recommend.	Air	Occupational - TLV	300-800mg/m^3 skin absorption	TLVIT* p.20	Mar. 1985
Japan	Recommend.	Air	Occupational - MAC	TWA: 375mg/m^3	SAIGLB* v29,	1987
Netherlands	Recommend.	Air	Occupational - MXL	TWA skin: 375mg/m^3	NMACN* p24	1986
	N/A	Water	Median water quality limit	0.001mg/L	N/A	N/A
	N/A	Water	Limit for fish tainting	0.25mg/L	N/A	N/A
Poland	Regulation	Air	Occupational - MPC	TWA: 100mg/m^3	OMLWS*	1982
Romania	Regulation	Air	Occupational - MPC	TWA: 300mg/m^3 CLV: 400mg/m^3	OMHRO*	1975
U.S.A.	Recommend.	Air	Occupational - TLV	TWA: 375mg/m^3 STEL: 560mg/m^3	ACGIH*	1987
	Regulation	Air	Occupational Restriction	Total exhaust air conc. must be < 1.4% by vol. air	Federal Register 40(180.1001)	1981
	Regulation	Air	Occupational - PEL	TWA: 753mg/m^3 CLV: 1130mg/m^3 Max. peak during 10 min. of 8 hr shift 1830mg/m^3	Federal Register 29(1910)	1986
	Regulation	Water	Emission standards - MXL	Effluent limitations, level not stated	Federal Register 47,28260.	1982
	Regulation	Hazardous waste	Notification requirement	Notification requirement (domestic waste is exempt)	Federal Register 40(261)	1981

Table 11.1 (continued)

Geographic area	Status	Medium	Description	Levels	Act / Reference [b]	Date
	Regulation	Air	Occupational - TLV and MPC	MPC: 8 hr 375mg/m^3 15 min 560mg/m^3 (applies to all mines other than coal mines)	Mines Act B.C. / Regulations, s. 99(2)	30 Jun. 1983
CANADA - other						
North West Territories	Regulation	Air	Occupational TLV	TWA: 375mg/m^3 STEL: skin 560mg/m^3	Safety Ordinances of NWT, s. 31	1980
Yukon Territory	Regulation	Air	Occupational	8hr skin 375mg/m^3 15min skin 560mg/m^3	Occupational Health and Safety Act of YT / Regulations s. (27)1	
Montreal	By-law	Air	Ambient air quality - stack emissions	MAC, 0.25hr 2mg/m^3 MAC, 8hr 2mg/m^3	Montreal Urban Community By-Law 90	
FOREIGN						
Belgium	Recommend.	Air	Occupational - TLV	TWA: 375mg/m^3 STEL: 560mg/m^3	TLVBE* p1	1988
	Recommend.	Air	Occupational - Biological Effect Indicator	2.5 g/g creatinine at the end of shift 3 mg/ml - last 4 hours of shift	TLVBE* p1	1988
Bulgaria	Regulation	Air	Occupational - MPC	50mg/m^3	OJBGR* v88	1971
Czechoslovakia	Regulation	Air	Occupational - MAC	TWA: 200mg/m^3 CLV: 1000mg/m^3	HPMZC*v.58, p12	Aug. 1985
Finland	Recommend.	Air	Occupational - MPC	TWA: 375mg/m^3 STEL: 565mg/m^3	APWFI* v 25,p10	1988
	Regulation	Air	Emissions - MXL	Class II 100mg/m^3 [at a mass flow 2 kg/hr must not be exceeded]	GMBL*v.7 p93-143	1986
	Recommend.	Air	Occupational - MAC	8h TWA 380mg/m^3 30 min STEL: 1900mg/m^3	DFSK* vol XXIV, p16	1988

Table 11.1 (continued)

Geographic area	Status	Medium	Description	Levels	Act / Reference[b]	Date
INTERNATIONAL						
WHO	Recommend.	Air	Occupational - MXL	TWA: 200mg/m^3, 375mg/m^3 STEL: 600mg/m^3, 800mg/m^3 (two values for each; further studies recommended)	WHOTAC* 664,3	1981
WHO	Recommend.	Ambient air	MAC	MAC: 30 min 1mg/m^3 24 hr 8mg/m^3	N/A	N/A
FAO/WHO	Recommend.	Food	Additive	Establishment as an additive not deemed necessary	N/A	N/A

* Modified from IRPTC-Legal data base [DSLEGSTM.IRPTC]

Abbreviations/acronyms:

ACGIH = American Conference of Governmental Industrial Hygienists
MAC = Maximum Acceptable Concentration
MPC = Maximum Permissable Concentration
MXL = Maximum Exposure Limit
N/A = Not Available
Recommend. = Recommendation
STEL = Short Term Exposure Limit
TLV = Threshold Limit Value
TWA = Time Weighted Average
WHMIS = Workplace Hazardous Materials Information System

[b] For all references to International Statutes and Instruments, see IRPTC-Legal, file name REFER.IRPTC

Table 11.1 (continued)

Geographic area	Status	Medium	Description	Levels	Act / Reference[b]	Date
	Regulation	Hazardous waste	Requirement	99.99% must be destroyed in incinerators	Federal Register 40(264)	1981
	Regulation	Water	Classification	Designated as a hazardous substance for the purpose of discharge (including spills, leaks, ships)	Water Pollution Control Act	1981
	Regulation	Water	Requirement	Permits are needed for any discharge into USA waters	Water Pollution Control Act	1981
	Regulation	Water - marine	Prohibition MPC	Prohibits ocean dumping, unless conc. < solub.	Federal Register 40(227)	1981
	Regulation	Surface water	Aquatic life protection	MAC: 17.5mg/L	USEPA	
	Regulation	Waste	Classification	Identifies toluene as one of 400 priority substances	Federal Register 47(31219)	
U.S.S.R. (former)	Regulation	Air	Occupational - MAC & Class	CLV: 50mg/m^3 Hazard class III	GOSTS*	1988
	Regulation	Air	Ambient air concentration	MAC: 0.6mg/m^3 daily average	PDKAV*	Aug. 1984
	Regulation	Water	Surface water quality - MAC	MAC 0.5mg/L Class IV	SPNPV*	1988
	Regulation	Water	Domestic water - MAC	MAC: 0.5mg/L	N/A	N/A
	Regulation	Water	Surface water for fishing - MAC	MAC 0.5mg/L	PDKTV*	1978
	Regulation	Soil		MAC: 0.3mg/kg	PDKCP*	1985
	Regulation	Water	Occupational - MAC	MAC: 50 g/L skin contact	PDUZK*	1988
Yugoslavia	Regulation	Air	Occupational - MAC	MAC: 200mg/m^3	ORYUG*	1971