

VINYL TOLUENE

1. Exposure Data

1.1 Chemical and physical data

Commercial vinyl toluene is a mixture of *meta* and *para* isomers with small amounts of *ortho* isomer. Chemical and physical data are given for the individual isomers and for the commercial mixture, when available.

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 25013-15-4

Replaced CAS Reg. No.: 1321-45-5

Chem. Abstr. Name: Ethenylmethylbenzene

IUPAC Systematic Name: *ar*-Methylstyrene

Synonyms: Methylstyrene; methylvinylbenzene; tolylethylene

Chem. Abstr. Serv. Reg. No.: 611-15-4

Chem. Abstr. Name: 1-Ethenyl-2-methylbenzene

IUPAC Systematic Name: *ortho*-Methylstyrene

Synonyms: 2-Ethenylmethylbenzene; 2-methylstyrene; 1-methyl-2-vinylbenzene; 2-vinyltoluene; *ortho*-vinyltoluene

Chem. Abstr. Serv. Reg. No.: 100-80-1

Chem. Abstr. Name: 1-Ethenyl-3-methylbenzene

IUPAC Systematic Name: *meta*-Methylstyrene

Synonyms: 3-Ethenylmethylbenzene; 3-methylstyrene; 1-methyl-3-vinylbenzene; 3-vinyltoluene; *meta*-vinyltoluene

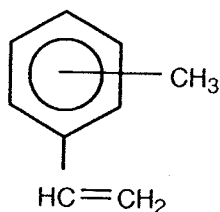
Chem. Abstr. Serv. Reg. No.: 622-97-9

Chem. Abstr. Name: 1-Ethenyl-4-methylbenzene

IUPAC Systematic Name: *para*-Methylstyrene

Synonyms: 4-Ethenylmethylbenzene; 4-methylstyrene; 1-methyl-4-vinylbenzene; 1-*para*-tolylethene; 4-vinyltoluene; *para*-vinyltoluene

1.1.2 Structural and molecular formulae and relative molecular mass



C_9H_{10}

Relative molecular mass: 118.18

1.1.3 Chemical and physical properties of the pure substance

- (a) *Description*: Colourless liquid (Dow Chemical Co., 1991), with a strong disagreeable odour (US National Library of Medicine, 1993)
- (b) *Boiling-point*: 167.7 °C (commercial mixture, *meta* and *para*); 169.8 °C (*ortho*); 171.6 °C (*meta*); 172.8 °C (*para*) (Eller, 1984)
- (c) *Freezing-point*: -77 °C (commercial mixture) (Deltech Corp., 1992)
- (d) *Density*: 0.898 g/ml at 20 °C (commercial mixture, *meta* and *para*); 0.904 g/ml at 20 °C (*ortho*); 0.911 g/ml at 20 °C (*meta* and *para*) (Eller, 1984)
- (e) *Spectroscopy data*: Infrared [D1711 (mixed isomers), 15063 (*meta*), 21205 (*para*)], ultraviolet [4418 (*meta*), 8303 (*para*)], nuclear magnetic resonance and mass [450 (*meta*), 185 (*para*)] spectral data have been reported (US National Toxicology Program, 1990; Sadtler Research Laboratories, 1991; US National Library of Medicine, 1993)
- (f) *Solubility*: Insoluble in water (89 mg/L) (commercial mixture) (Dow Chemical Co., 1991); completely soluble in acetone, benzene, carbon tetrachloride, diethyl ether, ethanol and *n*-heptane (US National Library of Medicine, 1993)
- (g) *Volatility*: Vapour pressure, 1.6 mm Hg [220 Pa] at 25 °C (commercial mixture, *meta* and *para*); 1.8 mm Hg [240 Pa] at 25 °C (*ortho* and *para*); 1.9 mm Hg [260 Pa] at 25 °C (*meta*) (Eller, 1984); 1.1 mm Hg [147 Pa] at 20 °C; relative vapour density (air = 1), 4.08 (commercial mixture) (Dow Chemical Co., 1991)
- (h) *Stability*: Lower explosive limit, 1.1%; polymerizes slowly at room temperature (Deltech Corp., 1991, 1992)
- (i) *Conversion factor*: $\text{mg/m}^3 = 4.83 \times \text{ppm}^a$

1.1.4 Technical products and impurities

Commercial vinyl toluene is primarily a mixture of *meta*- and *para*-vinyl toluene, usually with 56–60% *meta*, 40–45% *para* and 1% *ortho*. It is available as a commercial product with the following characteristics: purity, 99.2 wt% min.; polymer, 25 ppm max.; and *para-tert*-butylcatechol (inhibitor), 10–15 ppm or 45–55 ppm (Dow Chemical Co., 1988, 1989; Deltech Corp., 1991; Dow Chemical Co., 1991; Deltech Corp., 1992).

1.1.5 Analysis

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

^aCalculated from: $\text{mg/m}^3 = (\text{molecular weight}/24.45) \times \text{ppm}$, assuming normal temperature (25 °C) and pressure (101.3 kPa)

1.2 Production and use

1.2.1 Production

Vinyl toluene has been produced commercially in the USA since the late 1940s by the dehydrogenation of *meta*- and *para*-ethyl toluene with zinc oxide catalyst and by catalytic reforming (Kniel *et al.*, 1980; US National Toxicology Program, 1990). In 1992, vinyl toluene (mixed isomers) was produced or distributed in laboratory and larger quantities by seven companies in the USA and one company each in France, Japan, Switzerland and the United Kingdom (Directories Publishing Co., 1994).

1.2.2 Use

Vinyl toluene is a reactive monomer which polymerizes to form a clear, colourless polymer. Like styrene, vinyl toluene can be polymerized by any of the conventional methods of initiation and in the presence of inert materials such as fillers, dyes, solvents, resins, rubbers and plasticizers. Copolymers of vinyl toluene and other monomers such as acrylate, acrylonitrile, 1,3-butadiene, divinylbenzene, methacrylate and maleic anhydride are used in products with widely different physical properties (Dow Chemical Co., 1989; Deltech Corp., 1992).

Vinyl toluene is used in the coatings industry as a modifier for drying oils and oil-modified alkyds. It is also used as a replacement for styrene in unsaturated polyester resins where high-temperature cures and little shrinkage are desired. When used in this way, vinyl toluene contributes a lower vapour pressure at a given temperature and a higher flash-point (Deltech Corp., 1992). As a copolymer with styrene, it is used to increase the operating temperature range of paints, coatings and varnishes (Lewis *et al.*, 1983).

1.3 Occurrence

Vinyl toluene isomers may be released to the environment in wastewater and in atmospheric emissions resulting from its manufacture or use in resin production and plastics (Liepins *et al.*, 1977; Perry *et al.*, 1979; Sandmeyer, 1981). Vinyl toluene isomers may also be released to the environment in engine exhaust (Fleming, 1970; US National Library of Medicine, 1993), wood smoke (Kleindienst *et al.*, 1986) and emissions from the combustion of polyethylene and polystyrene polymers (Hawley-Fedder *et al.*, 1984a,b). Exhaust gas from motor boat engines has been found to pollute waterways with vinyl toluene isomers (Jüttner, 1988). *ortho*-Vinyl toluene has been identified as a biodegradation product of *ortho*-ethyl toluene (Kappeler & Wuhrmann, 1978).

1.3.1 Natural occurrence

ortho-Vinyl toluene has been identified in the essential oil of *Distichlis spicata*, a marsh grass found in Mississippi salt marshes in the USA (Mody *et al.*, 1975).

1.3.2 Occupational exposure

The National Occupational Exposure Survey conducted by the National Institute for Occupational Safety and Health between 1981 and 1983 indicated that 25 400 employees

were potentially exposed to vinyl toluene in the USA (US National Institute for Occupational Safety and Health, 1993). Of this number 1% were estimated to be exposed to vinyl toluene and 99% to materials containing vinyl toluene. The estimate is based on a survey of US companies and did not involve measurements of actual exposures.

Few data have been published on levels of vinyl toluene vapour in the workplace. It was below detection levels in personal and area samples taken at a plant where polyester resin spray-up, lay-up and moulding processes were used. Vinyl toluene was included in the analysis because of the presence of empty containers indicating its use in the past (Rosensteel, 1979). Similarly, vinyl toluene was not detected (< 0.05 ppm [< 0.24 mg/m³]) in seven full-shift area samples taken in a mine where roof bolting was done with a resin containing vinyl toluene as one of the main ingredients (Cornwell & Stark, 1987).

1.3.3 Air

ortho-Vinyl toluene was identified in indoor air of houses in Washington DC and Chicago, IL, USA (Jarke *et al.*, 1981). Trace levels of vinyl toluene [isomer unspecified] were detected in air samples collected in Nitro, WV, USA (Erickson & Pellizzari, 1978).

Vinyl toluene has been detected in exhaust emissions from spark-ignition engines (*ortho*, *meta* and *para* isomers) (Fleming, 1970; US National Library of Medicine, 1993), wood smoke (*meta* isomer) (Kleindienst *et al.*, 1986), emissions from the incineration of polyethylene and polystyrene polymers (*ortho*, *meta* and *para* isomers) (Hawley-Fedder *et al.*, 1984a,b) and volatile emissions from polychloroprene-based building materials (*ortho* isomer) (Kiselev *et al.*, 1983).

1.3.4 Water

Vinyl toluene [isomer unspecified] was identified in water samples collected from the River Lee in the United Kingdom (Waggott, 1981), and *ortho*, *meta* and *para* isomers were identified in water samples collected in August 1984 from Lake Constance (Germany) after a period of heavy boat traffic. The concentration of *ortho*-vinyl toluene in water samples collected throughout the day varied between 3 and 72 mg/L. Emissions from motor boat engines were identified as the primary source of the volatile organic compounds found in the water (Jüttner, 1988).

ortho-Vinyl toluene was tentatively identified in concentrates of effluents from wastewater treatment plants in Lake Tahoe, Pomona and Orange County, CA, USA (Lucas, 1984). Vinyl toluene [isomer unspecified] was detected in effluents from six of 63 US industrial plants at concentrations ranging from < 10 to > 100 µg/L (Perry *et al.*, 1979).

1.4 Regulations and guidelines

Occupational exposure limits and guidelines for vinyl toluene in 18 countries are presented in Table 1.

The US Food and Drug Administration (1993) established regulations for the use of monomers, polymers, copolymers and homopolymers of vinyl toluene (methylstyrene) in products in contact with food, including food packaging adhesives (21 CFR 175.105),

Table 1. Occupational exposure limits and guidelines for vinyl toluene (all isomers, unless otherwise noted)

Country	Year	Concentration (mg/m ³)	Interpretation
Argentina	1991	240	TWA
		485	STEL (15 min)
Australia	1983	240	TWA
		485	STEL
Austria	1982	480	TWA
Belgium	1984	240	TWA
		485	STEL
Canada	1986	240	TWA
		485	STEL
Denmark	1988	120 ^a	TWA
Finland	1993	240	TWA
		480	STEL
France	1993	240	TWA
Germany	1993	480	TWA (MAK); substance with intense odour ^b
Indonesia	1978	480	TWA
Mexico	1984	240	TWA
		485	STEL
Netherlands	1986	240	TWA
Romania	1975	300	Average
		400	Maximum
Sweden	1991	120	TWA; skin
		350	STEL (15 min)
Switzerland	1987	240	TWA
United Kingdom	1992	480	TWA
		720	STEL (10 min)
USA			
ACGIH	1994	242	TWA
		483	STEL
OSHA	1992	480	TWA
NIOSH (REL)	1990	480	TWA
Venezuela	1978	480	TWA
		720	Ceiling

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

TWA, time-weighted average; STEL, short-term exposure limit; TLV, threshold limit value; PEL, permissible exposure level; REL, recommended exposure level; MAK, maximale arbeitsplatzkonzentration (maximal workplace concentration); skin, absorption through the skin may be a significant source of exposure

^aIncludes mixed isomers and each isomer

^bConcentration that should never be exceeded is twice the MAK for 10 min, four times per shift

resinous and polymeric coatings for polyolefin films (21 CFR 175.300, 175.320), paper and paperboard in contact with dry food (21 CFR 176.180), cellophane (21 CFR 177.1200), poly(*para*-vinyltoluene) and rubber-modified poly(*para*-vinyltoluene) (21 CFR 176.1635), rubber articles intended for repeated use (21 CFR 177.2600) and a component of polyolefin film (21 CFR 178.3610).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

3.1.1 *Mouse*

Groups of 60 male and 60 female Swiss mice, six weeks old, were administered 0 (control), 10, 50 or 250 mg/kg bw vinyl toluene (purity, > 99%; 96.8% *para* isomer and 3% *meta* isomer) by gastric intubation in olive oil once a day on five days a week for 78 weeks. The study was terminated at 83 weeks, when the survival rate was reduced to less than 50% in at least one group. There was no treatment-related effect on survival of female mice or on body weight in mice of either sex; survival of male mice was reduced in treated groups, but the authors concluded that both the chemical and amyloidosis were causal factors in the increased mortality [survival data not provided]. There was no significant treatment-related increase in either the percentage of mice with malignant tumours or with benign and malignant tumours combined or in the number of malignant tumours per mouse (Conti *et al.*, 1988).

3.1.2 *Rat*

Groups of 60 or 90 male and 60 or 90 female Sprague-Dawley rats, six weeks old, were administered 10, 50, 250 or 500 mg/kg bw vinyl toluene (purity, > 99%; 96.8% *para* isomer and 3% *meta* isomer) by gastric intubation in olive oil once a day on five days a week for 108 weeks. Control groups of 60 male and 60 female rats received olive oil alone. Five rats from the 500-mg/kg group were killed at 54 and 107 weeks. The study was terminated at 123 weeks when the survival rate was reduced to less than 50% in at least one group. Survival of male rats receiving 250 and 500 mg/kg bw was reduced [exact data not provided]. There was no treatment-related effect on survival in female rats or on body weights of male or female rats and no treatment-related increase in either the percentage of rats with malignant tumours or with benign and malignant tumours combined nor in the number of malignant tumours per rat (Conti *et al.*, 1988).

3.2 Inhalation

3.2.1 *Mouse*

Groups of 50 male and 50 female B6C3F1 mice, eight to nine weeks old, were exposed by whole-body inhalation to 0 (control), 10 or 25 ppm [48.2 or 120.5 mg/m³] vinyl toluene

(approximately 99% pure; 65–71% *meta* and 32–35% *para* isomers) for 6 h per day on five days a week for 103 weeks and were sacrificed one week following the last exposure. Complete gross and microscopic examination was performed on all high-dose and control mice at terminal sacrifice and on all mice that died or were sacrificed when moribund prior to the end of the study. Mice in the mid-dose groups were examined microscopically for gross lesions and for alterations in lung and nasal passages. There was a dose-related decrease in body weights in animals of each sex. Survival at termination of the experiment was 33/50, 40/50 and 41/50 for male mice and 36/50, 37/50 and 34/50 for female mice in the control, low- and high-dose groups, respectively. There was no treatment-related increase in the incidence of any tumour in male or female mice. There were significant (logistic regression test) treatment-related decreases in the incidences of lymphoma (7/50, 2/50, 0/50; $p = 0.006$) and alveolar–bronchiolar tumours (12/50, 5/50, 2/50; $p = 0.003$) in male mice and of liver tumours (9/50, 5/50, 2/50; $p = 0.021$) in female mice. Hyperplasia of the respiratory epithelium and inflammation of the nasal mucosa and lung were observed in all treated groups (US National Toxicology Program, 1990).

3.2.2 Rat

Groups of 49 or 50 male and 50 female Fischer 334/N rats, 9–10 weeks old, were exposed by whole-body inhalation to 0 (control), 100 or 300 ppm [482 or 1447 mg/m³] vinyl toluene (purity, approximately 99%; 65–71% *meta* and 32–35% *para* isomers) for 6 h per day on five days a week for 103 weeks and sacrificed one week after the last exposure. Body weights of high-dose males and low-dose females were decreased. Survival at termination of the experiment was 19/49, 17/50 and 19/50 for males and 31/50, 28/50 and 26/50 for female rats in the control, low- and high-dose groups, respectively. There was no treatment-related change in the incidence of any type of tumour in male or female rats. A dose-related increase in the incidence of hyperplasia of the respiratory epithelium of the nasal passages was observed in animals of each sex (US National Toxicology Program, 1990).

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 Humans

No data were available to the Working Group.

4.1.2 Experimental systems

para-Vinyl toluene was oxidized to the side-chain diol by the cytochrome P450-mediated system in rat liver microsomes *in vitro* at a rate similar to that of styrene. Protein binding by the two analogues *in vitro* was also similar (Hanzlik *et al.*, 1978).

In a series of experiments on vinyl toluene (60% *meta* and 40% *para* isomer), both short-term intraperitoneal injection of 100 or 500 mg/kg bw and inhalation of 50, 100 and

300 ppm [240, 480 and 1450 mg/m³] (6 h/day, five days/week) for up to 15 weeks caused dose- and time-dependent decreases in non-protein sulfhydryl groups and increases in the activities of 7-ethoxycoumarin *O*-deethylase and UDP-glucuronosyl transferase in the livers and kidneys of male Wistar rats, C57Bl/6 mice and Chinese hamsters. Vinyl toluene was found to bind to hepatic cytochrome P450 and to decrease the reduced glutathione content (Heinonen & Vainio, 1980, 1981; Heinonen *et al.*, 1982a,b; Heinonen, 1984).

Male Wistar rats inhaling 300 ppm [1450 mg/m³] vinyl toluene for one week or 50, 100 and 300 ppm [240, 480 and 1450 mg/m³] for 8–12 weeks showed a dose-dependent increase in the urinary excretion of thioethers (Heinonen *et al.*, 1982a,b).

After *ortho*-, *meta*- and *para*-vinyl toluenes were injected intraperitoneally into male albino Wistar rats, 11 urinary metabolites were distinguished (Fig. 1). The main metabolites were similar to the corresponding styrene metabolites and included ethylene glycol, mandelic acid, glyoxylic acid derivatives and *N*-acetylcysteine and glucuronide conjugates. Over 90% of the recovered metabolites were excreted within 24 h (Bergemalm-Rynell & Steen, 1982). *N*-Acetylcysteine derivatives substituted at carbon 8 greatly exceeded (> 80%) those substituted at carbon 9 in Sprague-Dawley rats, in spite of steric hindrance by the methyl group (Kühler, 1984).

After a single intraperitoneal dose of *para*-vinyl toluene at 50 mg/kg bw, 55% was recovered in urine within 23 h, but mainly within the first 6 h, and the main metabolites were quantified (Fig. 1). Saturation of metabolic pathways began at a dose of 250 mg/kg bw. Excretion of all metabolites of *para*-vinyl toluene was prevented by 1-phenylimidazole, an inhibitor of cytochrome P450 monooxygenases, while the excretion rates of the metabolites were increased by prior treatment with polychlorinated biphenyls (Heinonen, 1984).

4.2 Toxic effects

4.2.1 Humans

The odour threshold for vinyl toluene (55–70% *meta* and 30–45% *para* isomer) was reported to be similar to that for styrene, i.e. 50 ppm [240 mg/m³] (Wolf *et al.*, 1956). This value is much higher than the threshold cited for styrene by other sources (70 µg/m³ as a 30-min average; WHO, 1987). Strong eye and nasal irritation was observed at 400 ppm [1930 mg/m³] (Wolf *et al.*, 1956).

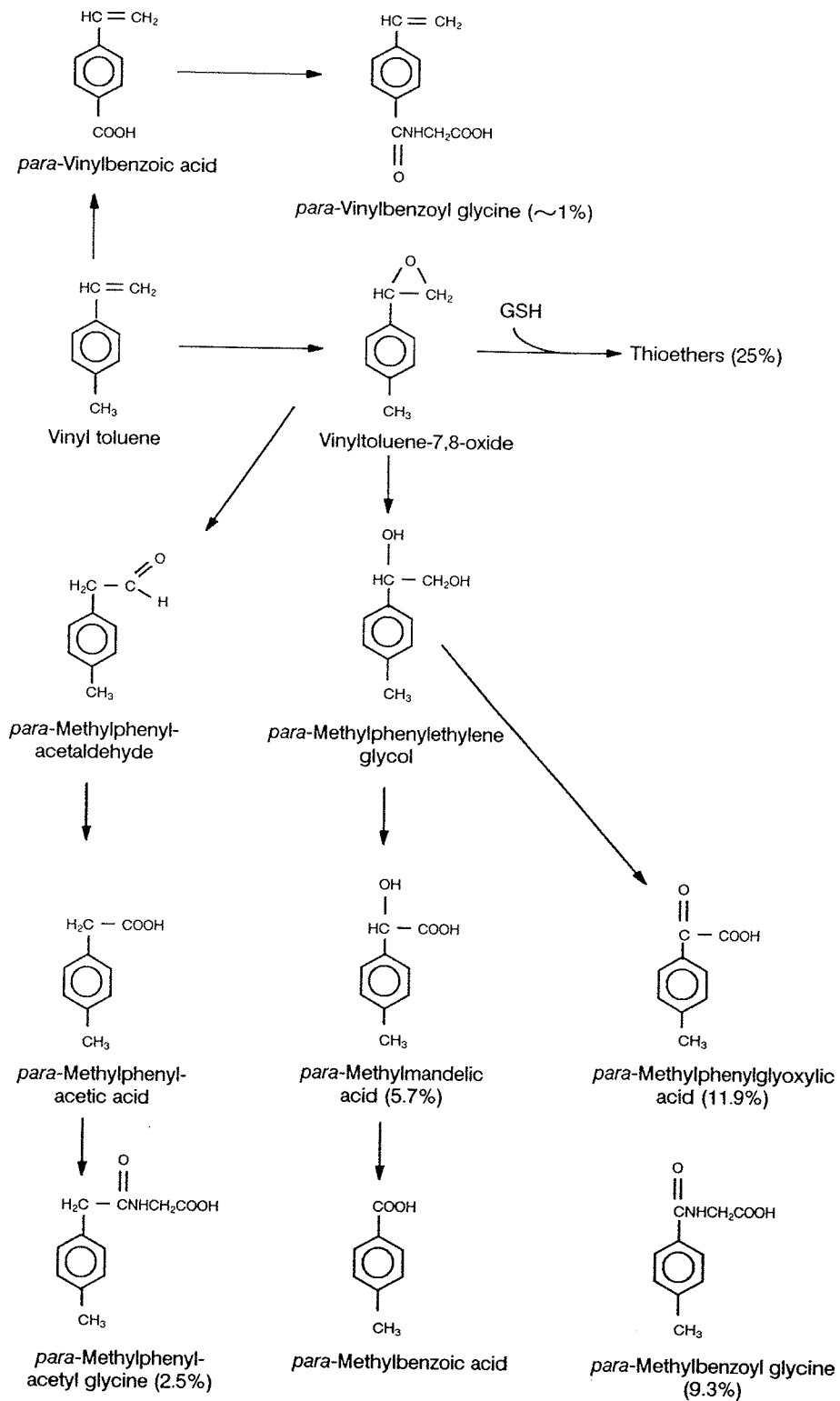
Central nervous system effects, such as depression, poor memory, slow visuomotor performance and electrophysiological changes, have often been associated with heavy occupational exposures to vinyl toluenes (Mutti & Franchini, 1987). Information is not available on human exposure to vinyl toluene alone.

In a case report on an individual with contact allergy to styrene, a cross-reaction was described with all three isomers of vinyl toluenes (Sjöborg *et al.*, 1982, 1984).

4.2.2 Experimental systems

The results of studies in experimental animals provide support for the neurotoxicity of vinyl toluene. In male Wistar and Sprague-Dawley rats exposed by inhalation to up to 300 ppm [1450 mg/m³] vinyl toluene (60–70% *meta* and 30–70% *para* isomer) for a

Fig. 1. The main metabolic pathways of vinyl toluene in rats



From Heinonen (1984). Amounts of metabolites are expressed as per cent of one intraperitoneal dose of 50 mg/kg bw

maximum of 15 weeks, decreased motor conduction velocity was observed within 12 weeks (Seppäläinen & Savolainen, 1982; Gagnaire *et al.*, 1986). Specific depletion of brain dopamine levels has been described in New Zealand rabbits (Romanelli *et al.*, 1986; Mutti *et al.*, 1988), and that is suggested to be the neurotoxic mechanism for a number of compounds with a reactive carbonyl group that can condense with dopamine to form tetrahydroisoquinolines (Mutti *et al.*, 1988; see the monograph on styrene). This effect may induce other hormonal changes that are under hypothalamic regulation which affect reproduction. Other neurochemical changes that have been observed include the release of lysosomal proteases in rat brain (Savolainen & Pfäffli, 1981).

In the subchronic studies cited above, vinyl toluene also caused cellular growth depression and hepatotoxicity in rats (Wolf *et al.*, 1956; Heinonen *et al.*, 1982b). In a chronic two-year study, rats and mice had hyperplasia of the respiratory epithelium and erosion and cyst formation in the olfactory epithelium; in mice, inflammation of the nasal passages and bronchioles was also described (US National Toxicology Program, 1990).

4.3 Reproductive and prenatal effects

No data were available to the Working Group.

4.4 Genetic and related effects

4.4.1 Humans

No data were available to the Working Group.

4.4.2 Experimental systems (see also Table 2 and Appendices 1 and 2)

Vinyl toluene was not mutagenic to *Salmonella typhimurium*. It did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster*, treated either by feeding liquid vinyl toluene (up to 500 ppm [mg/kg] for one or three days) or by exposure to the gas at up to 300 ppm [1450 mg/m³] for five days.

Vinyl toluene induced forward mutations at the *tk* locus of mouse L5178Y lymphoma cells in the absence of an exogenous metabolic activation system, but only at a single, highly toxic dose.

It induced neither sister chromatid exchange nor chromosomal aberrations in Chinese hamster ovary cells; however, in human lymphocytes exposed in whole blood cultures, vinyl toluene induced both sister chromatid exchange and chromosomal aberrations in a dose-dependent manner, in the absence of exogenous metabolic activation. The induction of sister chromatid exchange was dependent on the number of erythrocytes present. Significant increases in the frequencies of sister chromatid exchange were observed in human lymphocytes exposed in whole blood cultures to *ortho*, *meta* and *para* isomers. The strongest responses were seen with the *meta* and *para* isomers, which are the dominant species in vinyl toluene (Norppa & Vainio, 1983; Norppa & Tursi, 1984).

Vinyl toluene increased the frequency of micronuclei in mouse bone-marrow erythrocytes *in vivo*.

Table 2. Genetic and related effects of vinyl toluene

Test system	Result ^a		Dose ^b (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	-	-	590.0000	Norppa <i>et al.</i> (1981) (abstract)
SA0, <i>Salmonella typhimurium</i> TA100, reverse mutation	-	-	167.0000	Zeiger <i>et al.</i> (1987)
SA5, <i>Salmonella typhimurium</i> TA1535, reverse mutation	-	-	590.0000	Norppa <i>et al.</i> (1981) (abstract)
SA5, <i>Salmonella typhimurium</i> TA1535, reverse mutation	-	-	167.0000	Zeiger <i>et al.</i> (1987)
SA7, <i>Salmonella typhimurium</i> TA1537, reverse mutation	-	-	590.0000	Norppa <i>et al.</i> (1981) (abstract)
SA7, <i>Salmonella typhimurium</i> TA1537, reverse mutation	-	-	167.0000	Zeiger <i>et al.</i> (1987)
SA8, <i>Salmonella typhimurium</i> TA1538, reverse mutation	-	-	590.0000	Norppa <i>et al.</i> (1981) (abstract)
SA8, <i>Salmonella typhimurium</i> TA1538, reverse mutation	-	-	590.0000	Norppa <i>et al.</i> (1981) (abstract)
SA9, <i>Salmonella typhimurium</i> TA98, reverse mutation	-	-	167.0000	Zeiger <i>et al.</i> (1987)
DMX, <i>Drosophila melanogaster</i> , sex-linked recessive lethal mutation	-	-	450.0000 feeding	Norppa <i>et al.</i> (1981) (abstract)
DMX, <i>Drosophila melanogaster</i> , sex-linked recessive lethal mutation	-	-	300.0000 inhal.	Norppa <i>et al.</i> (1981) (abstract)
G5T, Gene mutation, mouse lymphoma L5178Y cells <i>in vitro</i>	(+)	0	60.0000	McGregor <i>et al.</i> (1988)
SIC, Sister chromatid exchange, Chinese hamster ovary cells <i>in vitro</i>	-	-	75.0000	US National Toxicology Program (1990)
CIC, Chromosomal aberrations, Chinese hamster ovary cells <i>in vitro</i>	-	-	50.0000	US National Toxicology Program (1990)
SHL, Sister chromatid exchange, human whole blood lymphocytes <i>in vitro</i>	+	0	40.0000	Norppa (1981a)
SHL, Sister chromatid exchange, human whole blood lymphocytes <i>in vitro</i>	+	0	118.0000	Norppa & Tursi (1984)
CHL, Chromosomal aberrations, human lymphocytes <i>in vitro</i>	+	0	320.0000	Norppa (1981a)
MVM, Micronucleus formation, mouse bone-marrow cells <i>in vivo</i>	+	-	200 bw × 1 ip	Norppa (1981b)
meta-Vinyl toluene				
SHL, Sister chromatid exchange, human whole blood lymphocytes <i>in vitro</i>	+	0	118.0000	Norppa & Vainio (1983)
para-Vinyl toluene				
SHL, Sister chromatid exchange, human whole blood lymphocytes <i>in vitro</i>	+	0	118.0000	Norppa & Vainio (1983)

^a+, positive; (+), weak positive; -, negative; 0, not tested

^bIn-vitro tests, µg/ml; in-vivo tests, mg/kg bw

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Vinyl toluene has been produced since the 1940s, as a mixture mainly of *meta* and *para* isomers, by dehydrogenation of *meta*- and *para*-ethyl toluene. It is used as a reactive monomer in the production of polymers and coatings. Few data are available on levels of occupational or environmental exposures to vinyl toluene.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Vinyl toluene (predominantly *para* isomer) was tested for carcinogenicity in one experiment in mice and one experiment in rats by intragastric intubation. The mixed isomers were tested in one experiment in mice and one experiment in rats exposed by inhalation. No increase in the incidence of tumours was observed in any of the experiments.

5.4 Other relevant data

Vinyl toluene is absorbed in rats exposed by inhalation; its neurotoxicity indicates that is distributed to the brain in both man and rat. The vinyl moiety is first metabolized to form an epoxide, which is either conjugated with glutathione or further oxidized to a number of products, including carboxylic acids, which are conjugated with glycine. The methyl group can also be oxidized to a carboxylic acid and subsequently conjugated with glycine. Saturation of metabolic pathways in rats commences at a dose of 250 mg/kg bw.

No data were available on the genetic and related effects of vinyl toluene in humans.

Vinyl toluene induces sister chromatid exchange and chromosomal aberrations in cultured human lymphocytes and micronuclei in mouse bone-marrow cells *in vivo*.

5.5 Evaluation¹

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

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

Overall evaluation

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

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

6. References

- American Conference of Governmental Industrial Hygienists (1993) *1993-1994 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices*, Cincinnati, OH, p. 35
- Arbejdstilsynet [Labour Inspection] (1988) *Graensevaerdier for Stoffer og Materialer* [Limit Values for Compounds and Materials] (No. 3.1.0.2), Copenhagen, p. 32
- Bergemalm-Rynell, K. & Steen, G. (1982) Urinary metabolites of vinyltoluene in the rat. *Toxicol. appl. Pharmacol.*, **62**, 19-31
- Conti, B., Maltoni, C., Perino, G. & Ciliberti, A. (1988) Long-term carcinogenicity bioassays on styrene administered by inhalation, ingestion and injection and styrene oxide administered by ingestion in Sprague-Dawley rats, and *para*-methylstyrene administered by ingestion in Sprague-Dawley rats and Swiss mice. *Ann. N.Y. Acad. Sci.*, **534**, 203-234
- Cook, W.A., ed. (1987) *Occupational Exposure Limits—Worldwide*, Akron, OH, American Industrial Hygiene Association, pp. 157, 224
- Cornwell, R. & Stark, G. (1987) *Health Hazard Evaluation Report, Freeman United Coal Mining, Frankfort, IL* (Report No. HETA-87-040-1838), Cincinnati, OH, National Institute for Occupational Safety and Health
- Deltech Corp. (1991) *Vinyl Toluene Sales Specifications*, Baton Rouge, LA
- Deltech Corp. (1992) *Technical Bulletin: VT* Monomer (*Vinyltoluene)*, Baton Rouge, LA
- Deutsche Forschungsgemeinschaft (1993) *MAK and BAT Values 1993* (Report No. 29), Weinheim, VCH Verlagsgesellschaft, p. 59
- Directories Publishing Co. (1994) *Chem. Sources—USA & International*, Clemson, SC
- Dow Chemical Co. (1988) *Sales Specification: Vinyltoluene 50T* (Product No. 91606), Midland, MI
- Dow Chemical Co. (1989) *The Dow Family of Styrenic Monomers*, Midland, MI
- Dow Chemical Co. (1991) *Material Safety Data Sheet: Vinyltoluene 12T* (Product No. 11393), Midland, MI
- Eller, P.M., ed. (1984) *NIOSH Manual of Analytical Methods*, 3rd Ed., Vol. 1 (DHHS (NIOSH) Publ. No. 84-100), Washington DC, US Government Printing Office, pp. 1501-1-1501-7
- Erickson, M.D. & Pellizzari, E.D. (1978) *Analysis of Organic Air Pollutants in the Kanawha Valley, WV and the Shenandoah Valley, VA* (US EPA Report No. EPA-903/9-78-007; US NTIS PB-286141), Philadelphia, PA, US Environmental Protection Agency, pp. 17, 47
- Fleming, R.D. (1970) *Effect of Fuel Composition on Exhaust Emissions from a Spark-ignition Engine* (US NTIS PB-194942), Washington DC, US Department of the Interior, Bureau of Mines
- Gagnaire, F., Nicot, T., Zissu, D., Bonnet, P. & de Ceaurriz, J. (1986) Assessment of tail nerve function in rats chronically exposed to vinyltoluene. *Toxicol. Lett.*, **30**, 27-34
- Hanzlik, R.P., Shearer, G.O., Hamburg, A. & Gillesse, T. (1978) Metabolism *in vitro* of *para*-substituted styrenes. *Biochem. Pharmacol.*, **27**, 1435-1439
- Hawley-Fedder, R.A., Parsons, M.L. & Karasek, F.W. (1984a) Products obtained during combustion of polymers under simulated incinerator conditions. I. Polyethylene. *J. Chromatogr.*, **314**, 263-273
- Hawley-Fedder, R.A., Parsons, M.L. & Karasek, F.W. (1984b) Products obtained during combustion of polymers under simulated incinerator conditions. II. Polystyrene. *J. Chromatogr.*, **315**, 201-210
- Heinonen, T. (1984) Metabolism of vinyltoluene in the rat: effect of induction and inhibition of the cytochrome P-450. *Biochem. Pharmacol.*, **33**, 1585-1593

- Heinonen, T. & Vainio, H. (1980) Vinyltoluene induced changes in xenobiotic-metabolizing enzyme activities and tissue glutathione content in various rodent species. *Biochem. Pharmacol.*, **29**, 2675-2679
- Heinonen, T. & Vainio, H. (1981) Dose-dependent effects of vinyltoluene inhalation on non-protein thiols and drug biotransformation in liver and kidneys of the rat. *Xenobiotica*, **11**, 285-289
- Heinonen, T., Vainio, H. & Nickels, J. (1982a) Effects of vinyltoluene alone and after pretreatments with polychlorinated biphenyls on hepatocellular morphology and enzyme activities in liver and kidneys in rats. *Toxicology*, **22**, 297-310
- Heinonen, T., Nickels, J. & Vainio, H. (1982b) Subacute toxicity of vinyltoluene vapour: effects on the hepatic and renal drug biotransformation and the urinary excretion of thioether. *Acta pharmacol. toxicol.*, **51**, 69-75
- ILO (1991) *Occupational Exposure Limits for Airborne Toxic Substances: Values of Selected Countries* (Occupational Safety and Health Series No. 37), 3rd Ed., Geneva, pp. 274-277 (Substance Nos 1368, 1370, 1371, 1372)
- Institut National de Recherche et de Sécurité (1993) *Limit Values for Dangerous Substances in Work Place Air* (ND 1609-125-93), Paris
- Jarke, F.M., Dravnieks, A. & Gordon, S.M. (1981) Organic contaminants in indoor air and their relation to outdoor contaminants. *Am. Soc. Heating Refrigerating Air Conditioning Eng. Trans.*, **87**, 153-165
- Jüttner, F. (1988) Motor-boat-derived volatile organic compounds (VOC) in lakewater. *Z. Wasser. Abwasser Forsch.*, **21**, 36-39
- Kappeler, T. & Wuhrmann, K. (1978) Microbial degradation of the water-soluble fraction of gas oil—II. Bioassays with pure strains. *Water Res.*, **12**, 335-342
- Kiselev, A.V., Maltsev, V.V., Saada, B. & Valovoy, V.A. (1983) Gas chromatography-mass spectrometry of volatiles released from plastics used as building materials. *Chromatographia*, **17**, 539-544
- Kleindienst, T.E., Shepson, P.B., Edney, E.O., Claxton, L.D. & Cupitt, L.T. (1986) Wood smoke: measurement of the mutagenic activities of its gas- and particulate phase photooxidation products. *Environ. Sci. Technol.*, **20**, 493-501
- Kniel, L., Winter, O. & Tsai, C.-H. (1980) Ethylene. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, M., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd Ed., Vol. 9, New York, John Wiley & Sons, pp. 393-431
- Kühler, T. (1984) Mercapturic acid metabolites from 2-, 3-, and 4-ethenyl-methylbenzenes in the rat. *Xenobiotica*, **14**, 417-428
- Lewis, P.J., Hagopian, C. & Koch, P. (1983) Styrene. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, M., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd Ed., Vol. 21, New York, John Wiley & Sons, pp. 770-801
- Liepins, B., Mixon, F., Hudak, C. & Parsons, T.B. (1977) The industrial organic chemicals industry. In: *Industrial Process Profiles for Environmental Use* (US EPA Report No. EPA-600/2-77-023f; US NTIS PB-281478), Cincinnati, OH, US Environmental Protection Agency, pp. 337-338
- Lucas, S.V. (1984) *GC/MS (Gas Chromatography-Mass Spectrometry) Analysis of Organics in Drinking Water Concentrates and Advanced Waste Treatment Concentrates*, Vol. 2, *Computer-printed Tabulations of Compound Identification Results for Large-volume Concentrates* (US EPA Report No. EPA-600/1-84-020b; US NTIS PB85-128239), Research Triangle Park, NC, US Environmental Protection Agency, pp. 124, 149, 174

- McGregor, D.B., Brown, A., Cattanach, P., Edwards, I., McBride, D., Riach, C. & Caspary, W.J. (1988) Responses of the L5178Y tk⁺/tk⁻ mouse lymphoma cell forward mutation assay: III. 72 coded chemicals. *Environ. mol. Mutag.*, **12**, 85-154
- Mody, N.V., de la Cruz, A.A., Miles, D.H. & Hedin, P.A. (1975) The essential oil of *Distichlis spicata*. *Phytochemistry*, **14**, 599-601
- Mutti, A. & Franchini, I. (1987) Toxicity of metabolites to dopaminergic systems and the behavioural effects of organic solvents. *Br. J. ind. Med.*, **44**, 721-723
- Mutti, A., Falzoi, M., Romanelli, A., Bocchi, M.C., Ferroni, C. & Franchini, I. (1988) Brain dopamine as a target for solvent toxicity: effects of some monocyclic aromatic hydrocarbons. *Toxicology*, **49**, 77-82
- Norppa, H. (1981a) The in vitro induction of sister chromatid exchanges and chromosome aberrations in human lymphocytes by styrene derivatives. *Carcinogenesis*, **2**, 237-242
- Norppa, H. (1981b) Styrene and vinyltoluene induce micronuclei in mouse bone marrow. *Toxicol. Lett.*, **8**, 247-251
- Norppa, H. & Tursi, F. (1984) Erythrocyte-mediated metabolic activation detected by SCE. *Basic Life Sci.*, **29 B**, 547-559
- Norppa, H. & Vainio, H. (1983) Induction of sister-chromatid exchanges by styrene analogues in cultured human lymphocytes. *Mutat. Res.*, **116**, 379-387
- Norppa, H., Skyttä, M., Donner, M., Sorsa, M. & Vainio, H. (1981) Mutagenicity of vinyl toluene (Abstract). *Mutat. Res.*, **85**, 294
- Perry, D.L., Chuang, C.C., Jungclaus, G.A. & Warner, J.S. (1979) *Identification of Organic Compounds in Industrial Effluent Discharges*. (US EPA Report No. EPA-600/4-79-016; US NTIS PB-294794), Athens, GA, US Environmental Protection Agency, p. 42
- Romanelli, A., Falzoi, M., Mutti, A., Bergamaschi, E. & Franchini, I. (1986) Effects of some monocyclic aromatic solvents and their metabolites on brain dopamine in rabbits. *J. appl. Toxicol.*, **6**, 431-435
- Rosensteel, R.E. (1979) *Health Hazard Evaluation Determination, Warminster Fiberglass, Southampton, PA* (Report No. HE-78-3-555), Cincinnati, OH, National Institute for Occupational Safety and Health
- Sadtler Research Laboratories (1991) *Sadtler Standard Spectra. 1981-1991 Supplementary Index*, Philadelphia, PA
- Sandmeyer, E.E. (1981) Aromatic hydrocarbons. In: Clayton, G.D. & Clayton, F.E., eds, *Patty's Industrial Hygiene and Toxicology*, 3rd Ed., Vol. 2B, New York, John Wiley & Sons, pp. 3319-3323
- Savolainen, H. & Pfäffli, P. (1981) Neurochemical effects of short-term inhalation exposure to vinyltoluene vapor. *Arch. environ. Contam. Toxicol.*, **10**, 511-517
- Seppäläinen, A.M. & Savolainen, H. (1982) Dose-dependent neurophysiological and biochemical effects of prolonged vinyltoluene vapor inhalation in rat. *NeuroTox.*, **3**, 36-43
- Sjöborg, S., Dahlquist, I., Fregert, S. & Trulsson, L. (1982) Contact allergy to styrene with cross reaction to vinyltoluene (Short communication). *Contact Derm.*, **8**, 207-208
- Sjöborg, S., Fregert, S. & Trulsson, L. (1984) Contact allergy to styrene and related chemicals. *Contact Derm.*, **10**, 94-96
- Työministeriö [Ministry of Labour] (1993) *Limit Values 1993*, Helsinki, p. 19
- UNEP (1993) *IRPTC Data Profiles on Vinyl Toluene*, Geneva
- US Food and Drug Administration (1993) Food and drugs. *US Code fed. Regul.*, **Title 21**, Parts 175.105, 175.300, 175.320, 176.180, 177.1200, 176.1635, 177.2600, 178.3610, pp. 129-144, 147-167, 196-200, 219-222, 274-275, 309-313, 358-359

- US National Institute for Occupational Safety and Health (1992) *NIOSH Recommendations for Occupational Safety and Health. Compendium of Policy Documents and Statements* (DHHS (NIOSH) Publ. No. 92-100), Cincinnati, OH, Division of Standards Development and Technology Transfer, p. 132
- US National Institute for Occupational Safety and Health (1993) *National Occupational Exposure Survey (1981-1983)*, Cincinnati, OH
- US National Library of Medicine (1993) *Hazardous Substances Data Bank (HSDB)*, Bethesda, MD
- US National Toxicology Program (1990) *Toxicology and Carcinogenesis Studies of Vinyl Toluene (Mixed Isomers) (65%-71% meta-Isomer and 32%-35% para-Isomer) (CAS No. 25013-15-4) in F344/N Rats and B6C3F₁ Mice (Inhalation Studies)* (Technical Report Series No. 375; NIH Publ. No. 90-2830), Research Triangle Park, NC
- US Occupational Safety and Health Administration (1992) Air contaminants. *US Code fed. Regul., Title 29*, Part 1910.1000, p. 29
- Waggott, A. (1981) Trace organic substances in the River Lee. In: Cooper, W.J., ed., *Chemistry in Water Reuse*, Vol. 2, Ann Arbor, MI, Ann Arbor Science, pp. 55-99
- WHO (1987) *Air Quality Guidelines for Europe* (WHO Regional Publications, European Series No 23), Copenhagen, pp. 118-125
- Wolf, M.A., Rowe, V.K., McCollister, D.D., Hollingsworth, R.L. & Oyen, F. (1956) Toxicological studies of certain alkylated benzenes and benzene. Experiments on laboratory animals. *Arch. ind. Health*, **14**, 387-398
- Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K. & Speck, W. (1987) *Salmonella* mutagenicity tests: III. Results from the testing of 255 chemicals. *Environ. Mutag.*, **9** (Suppl. 9), 1-110