TOLUENE DIISOCYANATES

Data were last reviewed in IARC (1986) and the compounds were classified in *IARC Monographs* Supplement 7 (1987).

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Commercial toluene diisocyanate mixtures

Chem. Abstr. Serv. Reg. No.: 26471-62-5
Chem. Abstr. Name: 1,3-Diisocyanatomethylbenzene
IUPAC Systematic Name: Isocyanic acid, methyl-*meta*-phenylene ester
Synonyms: Diisocyanatotoluene; TDI; toluene diisocyanate

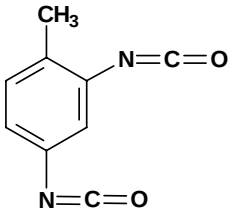
2,4-Toluene diisocyanate

Chem. Abstr. Serv. Reg. No.: 584-84-9
Chem. Abstr. Name: 2,4-Diisocyanato-1-methylbenzene
IUPAC Systematic Name: Isocyanic acid, 4-methyl-*meta*-phenylene ester
Synonyms: 2,4-Diisocyanatotoluene; 2,4-TDI; 2,4-toluene diisocyanate

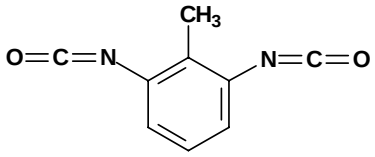
2,6-Toluene diisocyanate

Chem. Abstr. Serv. Reg. No: 91-08-7
Chem. Abstr. Name: 1,3-Diisocyanato-2-methylbenzene
IUPAC Systematic Name: Isocyanic acid, 2-methyl-*meta*-phenylene ester
Synonyms: 2,6-Diisocyanatotoluene; 2,6-TDI; 2,6-toluene diisocyanate

1.1.2 *Structural and molecular formulae and relative molecular mass*



2,4-Toluene diisocyanate



2,6-Toluene diisocyanate

$C_9H_6N_2O_2$ Relative molecular mass: 174.16

1.1.3 *Chemical and physical properties of the pure substances*

(*a*) *Description*: Colourless to pale yellow liquid with pungent odour (United States National Library of Medicine, 1997)
(*b*) *Boiling-point*: 251°C (2,4-isomer) (Lide, 1997)
(*c*) *Melting-point*: 20°C (2,4-isomer); 18°C (2,6-isomer) (Lide, 1997)
(*d*) *Solubility*: 2,4- and 2,6-Toluene diisocyanates decompose in water and are very soluble in acetone and benzene (Lide, 1997)
(*e*) *Vapour pressure*: 1.3 Pa at 20°C (2,4-isomer) (Lewis, 1993)
(*f*) *Flash point*: 132°C (2,4-isomer) (Lewis, 1993)
(*g*) *Conversion factor*: $mg/m^3 = 7.1 \times ppm$

1.2 Production and use

Worldwide production capacities for toluene diisocyanates in 1987 were reported as (thousand tonnes): western hemisphere, 356; eastern Europe, 46; western Europe, 380; and Japan and the Far East, 88 (Ulrich, 1989). Worldwide production capacities in 1993 were reported as (thousand tonnes): North America, 485; Europe, 530; Pacific region, 308; and Latin America, 102.5 (Anon., 1995).

Toluene diisocyanate is commonly produced as a mixture of the 2,4- and 2,6-isomers, that is used as a monomer in the preparation of polyurethane foams, elastomers and coatings, as a cross-linking agent for nylon-6, and as a hardener in polyurethane adhesives and finishes. Polyurethane elastomers made from toluene diisocyanates are used in coated fabrics and clay-pipe seals. Polyurethane coatings made from toluene diisocyanates are used in floor finishes, wood finishes and sealers, and in coatings for aircraft, tank trucks, truck trailers and truck fleets (United States National Library of Medicine, 1997).

1.3 Occurrence

1.3.1 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES, 1997), approximately 40 000 workers in the United States were potentially exposed to toluene diisocyanates (see General Remarks). Occupational exposures to toluene diisocyanates may occur during their production and in the production of polyurethane foams, elastomers, coatings, adhesives and finishes. Exposure may also occur in the use of some polyurethane products. Data on occupational exposure levels have been presented in a previous monograph (IARC, 1986). More recent exposure levels have been reported in connection with epidemiological (Section 2) and toxicological (Section 4) studies.

1.3.2 *Environmental occurrence*

Toluene diisocyanates may be released to the environment as fugitive emissions and from stack exhaust during the production, transport and use of toluene diisocyanate in the manufacture of polyurethane foam products and coatings. They have been detected at low levels in wastewater samples (United States National Library of Medicine, 1997).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 0.036 mg/m^3 as the 8-h time-weighted average threshold limit value for occupational exposures to 2,4-toluene diisocyanate in workplace air. Similar values have been used as standards or guidelines for 2,4- or 2,6-toluene diisocyanates in several countries. In some other countries, values ranging from 0.04 to 0.14 mg/m^3 for mixed isomers have been used (International Labour Office, 1991).

No international guideline for toluene diisocyanates in drinking-water has been established (WHO, 1993).

2. Studies of Cancer in Humans

2.1 Cohort studies

Sorahan and Pope (1993) studied 5824 men and 2465 women who had been employed for at least six months during 1958–79 at 11 factories in England and Wales which made polyurethane foams. Exposures to isocyanates were classified by an occupational hygienist on the basis of recorded job titles. The highest-exposure category comprised jobs in which either the 8-h time-weighted average exposure during 1978–86 was greater than 4 ppb [28.4 µg/m^3] or peak exposures exceeded 10 ppb [71 µg/m^3] on most days. Cohort members were followed up through National Health Service records, and their mortality during 1958–88 and cancer incidence during 1971–86 were compared with national rates by the person–years method. In addition, internal comparisons of risk according to exposure were carried out by Poisson regression analysis, and through a nested case–control study. Overall mortality in the cohort was close to expectation (816 deaths; standardized mortality ratio (SMR), 0.97), as was total mortality from cancer (221 deaths; SMR, 0.9). In men, no notable elevation of mortality was recorded for any specific cancer. In women, significant excesses of deaths were observed for cancers of the pancreas (6 versus 2.2 expected; SMR, 2.7; 95% confidence interval (CI), 1.0–6.0) and lung (16 versus 9.1 expected; SMR, 1.8; 95% CI, 1.0–2.9). However, there was no significant elevation of mortality from these tumours in both sexes combined (pancreas, 14 deaths versus 10.3 expected; lung, 81 deaths versus 81.3 expected), and in the internal analyses, risk was not related to isocyanate exposure. Mortality from rectal cancer was low (5 deaths versus 10.2 expected in men and women combined). In female workers, high rates of pancreatic (standard rate ratio (SRR), 3.2) and lung cancer (SRR, 2.3) were seen, as well as increased incidence of cancers of the larynx (3 cases versus 0.3 expected) and kidney (4 versus 0.9), but all of the cases were classified as having minimal or zero exposure to isocyanates. An earlier survey in the industry had indicated a high prevalence of smoking among female employees, and the authors concluded that this may have contributed to the increased frequency of some cancers in women.

In Sweden, a cohort study was carried out at nine factories manufacturing polyurethane foam that incorporated toluene diisocyanates or methylenediphenyl diiso-

cyanate (see this volume) (Hagmar *et al*., 1993a). Exposures to airborne isocyanates had been monitored at all of the plants since 1965. Time-weighted average concentrations of toluene diisocyanates had generally been below 100 μg/m^3, and those of methylenediphenyl diisocyanate below 10 μg/m^3, but with peaks up to 3 mg/m^3 and 0.35 mg/m^3, respectively. Other potential exposures included freons, silicone oils and waxes, amine accelerators, ethanolamine, methylene-bis-(2-chloroaniline) (MOCA) (see IARC, 1993), triethylamine, triethylene diamine, styrene (see IARC, 1994) and various other organic solvents. The cohort comprised 4154 workers who were employed during 1958–87 at a time when personnel records were complete, and who had worked for at least one year by 1987. The vital status of all subjects at 31 December 1987 was ascertained, and information about those who had died and about incident cancers was obtained from Statistics Sweden and the National Tumour Registry. Rates of death and cancer incidence were compared with those in the national population by the person–years method. There were fewer deaths in total than expected (130 deaths; SMR, 0.8; 95% CI, 0.7–0.9); mortality from cancer (33 deaths; SMR, 0.8; 95% CI, 0.5–1.1) and overall cancer incidence (72 cases; standardized incidence ratio (SIR), 0.8; 95% CI, 0.6–1.0) were also below expectation. Among the subset of subjects classified as exposed to toluene diisocyanates or methylenediphenyl diisocyanate, there were 39 incident cancers (45.8 expected) including five cases of rectal cancer (1.8 expected) and no cases of lung cancer (4.0 expected). With allowance for a minimum latency of 10 years, the SIR for rectal cancer was 3.2 (3 cases).

A nested case–control study was carried out in an expanded cohort of 7023 men and women from the same factories (Hagmar *et al*., 1993b). The subjects had worked during 1958–87, but unlike in the cohort study, no minimum period of employment was specified. Each of 119 subjects with a cancer registered during 1959–87 was matched with three controls of the same sex and age (to within six years), who were under follow-up at the time the cancer occurred. Because of missing information, the final analysis was based on 114 cases and 313 referents. Exposures were rated by an occupational hygienist who was unaware of subjects' disease status, and risks were estimated by conditional logistic regression. No association was found between exposure to isocyanates and overall cancer incidence (odds ratio, 0.9; 90% CI, 0.6–1.3). Nor was there any association with rectal cancer. Among subjects with high exposure there was a non-significant increase in prostate cancer (4 cases; odds ratio, 2.7; 95% CI, 0.4–18.1).

Schnorr *et al*. (1996) studied 2717 male and 1893 female employees from four polyurethane foam plants in the United States, all of whom had worked for at least three months during 1958–84 in a department or job in which exposure to toluene diisocyanates occurred. Airborne concentrations of toluene diisocyanates had been greater than 0.2 mg/m^3 at one of the plants during 1965–69, but personal monitoring in 1984–85 at the three plants which were still then operating indicated 4-h time-weighted average exposures below 0.04 mg/m^3. Other potential exposures included dichloromethane (see this volume) , aliphatic amines, nitrogen dioxide, acrolein (see IARC, 1995) and acrylonitrile (see this volume). The cohort was followed through the National Death Index,

social security and internal revenue records, and state bureaux of motor vehicles; vital status was determined for 96.9% of subjects at 31 December 1993. Their mortality was compared with that of the national population by the person–years method, with adjustment for sex, race, age and calendar period. Mortality from all causes was close to expectation (316 deaths; SMR, 0.95; 95% CI, 0.85–1.1) as was mortality from all cancers (71 deaths; SMR, 1.0; 95% CI, 0.8–1.3) and from lung cancer (20 deaths; SMR, 1.0; 95% CI, 0.6–1.6). There were small excesses of deaths from rectal cancer (3 versus 1.1 expected) and Hodgkin's disease (2 versus 0.9), but these were not significant, and there was no tendency for risk of cancer mortality to rise with increasing duration of exposure.

2.2 Case–control study

In the Montreal case–control study carried out by Siemiatycki (1991) (see monograph on dichloromethane in this volume), the investigators estimated the associations between 293 workplace substances and several types of cancer. Isocyanates were one of the substances, and it was stated that the most common form in this study was toluene diisocyanates. The main occupations to which isocyanate exposure was attributed in this study were motor vehicle refinishers, motor vehicle mechanics and foundry workers. Only 0.8% of the study subjects had ever been exposed to isocyanates. For most types of cancer examined (oesophagus, stomach, colon, rectum, pancreas, prostate, bladder, kidney, skin melanoma, lymphoma), there was no indication of an excess risk due to isocyanates. For lung cancer, in the population subgroup of French Canadians (the majority ethnic group in this region), based on 10 cases exposed at any level, the odds ratio was 2.2 (90% CI, 0.9–5.3). [The interpretation of the null results has to take into account the small numbers and presumably low exposure levels. Workers had multiple exposures.]

3. Studies of Cancer in Experimental Animals

Commercial mixtures of 2,4- and 2,6-toluene diisocyanates administered by gavage induced a dose-related increase in the incidence of subcutaneous fibromas and fibrosarcomas (combined) in male rats, together with an increase in the incidence of pancreatic acinar-cell adenomas in male rats and of pancreatic islet-cell adenomas, neoplastic nodules of the liver and mammary gland fibroadenomas in female rats. In female mice, dose-related increases in the combined incidence of haemangiomas and haemangiosarcomas and of hepatocellular adenomas were observed after gavage administration. No treatment-related tumour was observed after exposure of mice or rats to commercial toluene diisocyanates by inhalation, although the results of the study with rats have not been reported fully (IARC, 1986).

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

4.1 Absorption, distribution, metabolism and excretion

Toluene diisocyanates are reactive molecules that combine readily with nucleophiles, and as such have a propensity to react with proteins at the site of application to animals, in other tissues and with plasma (Kennedy *et al*., 1994). They are hydrolysed in aqueous media to the corresponding diamines, which can react with unchanged toluene diisocyanates to form polymeric ureas (Chadwick & Cleveland, 1981; Ulrich, 1983).

The major metabolites of toluene diisocyanates in both animals and humans are toluene diamines and their acetylated products (Rosenberg & Savolainen, 1985; Bartels *et al.*, 1993; Lind *et al*., 1996).

4.1.1 *Humans*

The toxicokinetics of 2,4- and 2,6-toluenediisocyanates in 11 chronically exposed workers at two flexible foam polyurethane production plants have been reported. The toluene diisocyanate concentrations in air varied between 0.4 and 4 μg/m^3 in one plant and in the other between 10 and 120 μg/m^3. In one of the plants, the plasma 2,4-toluene diamine levels were 0.4–1 ng/mL before a 4–5-week holiday and 0.2–0.5 ng/mL afterwards. The corresponding plasma levels of 2,6-toluene diamine were 2–6 and 0.5–2 ng/mL, respectively. In the other plant, the plasma 2,4-toluene diamine concentrations were 2–23 ng/mL before the holiday and 0.5–6 ng/mL afterwards and those of 2,6-toluene diamine were 7–24 ng/mL before and 3–6 ng/mL afterwards. The plasma concentrations of 2,4-toluene diamine were 2–24 ng/mL before a 12-day holiday, and 1–14 ng/mL afterwards. The corresponding values for plasma 2,6-toluene diamine were 12–29 and 8–17 ng/mL, respectively. The urinary elimination rates for 2,4-toluene diamine before the holiday were 0.04–0.54 and 0.02–0.18 μg/h afterwards. The corresponding values for 2,6-toluene diamine were 0.18–0.76 μg/h before and 0.09–0.27 μg/h after the holiday. The half-life in urine ranged from 5.8 to 11 days for 2,4- and 2,6-toluene diamines. The differences in exposure were reflected by the plasma toluene diamine concentrations. The mean half-life in plasma was 21 (range, 14–34) days for 2,4-toluene diamine and 21 (16–26) days for 2,6-toluene diamine. The study showed that the half-life in plasma of chronically exposed workers for 2,4- and 2,6-toluene diamine was twice as long as for volunteers with short-term exposure. An indication of a two-phase elimination pattern in urine was found. The first phase was related to the more recent exposure and the second, much slower one was probably related to release of toluene diamines in urine from toluene diisocyanate adducts in the body (Lind *et al.*, 1996).

The average air concentration of toluene diisocyanates at a toluene diisocyanate flexible foam plant was 29.8 μg/m^3 (12.5–19.9; n = 12). The highest exposure measured was approximately 3 mg/m^3 toluene diisocyanates. 2,4- and 2,6-Toluene diamine levels in urine and in plasma from four exposed workers and one volunteer were determined

after strong acid hydrolysis. The plasma toluene diamine concentrations among the workers were 1–38 g/L and 7–24 µg/L for 2,4- and 2,6-toluene diamine, respectively. The individual plasma levels among the workers over the three-day periods varied from 7 to 73%. For a volunteer, plasma concentration reached a maximum about 24 hours after the last exposure. The half-time of plasma toluene diamines for the volunteer was about 10 days. The urine levels varied greatly with time and exposure. High levels were found during or shortly after the exposure (Tinnerberg *et al.*, 1997).

4.1.2 *Experimental systems*

Timchalk *et al*. (1994) examined the route-dependent metabolism of [^{14}C]toluene 2,4-diisocyanate and [^{14}C]toluene 2,4-diamine in Fischer 344 rats. Forty-eight hours after an oral dose of 60 mg [^{14}C]toluene 2,4-diisocyanate/kg bw, 81%, 8% and 4% of the radioactivity was found in the faeces, urine and tissue/carcass/gastrointestinal tract contents, respectively. Markedly different results were obtained following inhalation exposure of rats to 2 ppm [14.2 mg/m^3] [^{14}C]toluene 2,4-diisocyanate for 2 h. Forty-eight hours after exposure, 47%, 15% and 34% of the recovered radioactivity was in the faeces, urine and tissue/carcass/gastrointestinal tract contents, respectively.

In comparative studies, [^{14}C]toluene 2,4-diamine, the hydrolysis product of [^{14}C]-toluene 2,4-diisocyanate, was administered to rats at doses of 3 mg/kg bw (orally or intravenously) and 60 mg/kg bw orally. After 48 h, the distribution of radioactivity was similar in all cases (urine, 64–72%; faeces, 20–31%; and tissue/carcass/gastrointestinal tract, 2–5%). Comparison of the toluene 2,4-diisocyanate inhalation group with the oral toluene 2,4-diisocyanate and toluene 2,4-diamine treatment groups indicated that a larger percentage of the inhaled radioactivity was in the tissues/carcass and that excretion of radioactivity into the urine was slower following toluene 2,4-diisocyanate inhalation.

Following inhalation or oral exposure to [^{14}C]toluene 2,4-diisocyanate, about 90% and 65% of the quantitated urinary metabolites were acid-labile conjugates. In contrast, only 16–39% of the urinary metabolites were conjugated following oral administration of [^{14}C]toluene 2,4-diamine.

Inhalation exposure to toluene 2,4-diisocyanate results primarily in the formation of acid-labile conjugates, with little or no toluene 2,4-diamine being formed. This suggests that the disposition of inhaled toluene 2,4-diisocyanate is quite different from that of orally administered toluene 2,4-diisocyanate or of intravenously or orally administered toluene 2,4-diamine.

4.2 Toxic effects

The toxicity of toluene diisocyanates has been reviewed (WHO, 1987).

4.2.1 *Humans*

Toluene diisocyanates are potent respiratory irritants and sensitizers, even at low air-borne concentrations. Chronic bronchitis, chronic restrictive pulmonary disease and

hypersensitivity pneumonitis have also been described among toluene diisocyanate-exposed people (IARC, 1986).

A follow-up study (Pisati *et al*., 1993) of patients with toluene diisocyanate-induced asthma suggested that a short period of exposure and a short duration of symptoms before diagnosis, followed by complete cessation of exposure, are likely to lead to improvement of the symptoms and lung function. A decrease only of the exposure led to deterioration of lung function, and long exposure and duration of symptoms were unfavourable prognostically.

No deterioration of lung function, but an increased frequency of respiratory symptoms were observed in a follow-up study among non-sensitized workers with a mean exposure to toluene diisocyanates of 3 ppb [21.3 μg/m^3] (Omae *et al*., 1992a). This study also suggested that among workers with a mean exposure of 8 ppb [57 μg/m^3], peak exposures to 30 ppb [213 μg/m^3] and above were associated with a loss of ventilatory function among employees not sensitized to toluene diisocyanates (Omae *et al*., 1992b).

4.2.2 *Experimental systems*

Inhalation exposure to toluene diisocyanates is irritating to the eyes and respiratory tract, and induced chronic rhinitis, interstitial pneumonia and catarrhal bronchitis after long-term exposure. Respiratory sensitization to toluene diisocyanate developed in guinea-pigs after inhalation but also after dermal exposure (IARC, 1986).

Toluene diisocyanates induced respiratory epithelial inflammation, metaplasia and necrosis in mice at the lowest concentration tested (0.71 mg/m^3) after the shortest exposure period studied (6 h per day for four days). The reaction became more severe when the exposure period was extended to 9 or 14 days. No effects were observed in the olfactory epithelium, trachea or lungs (Zissu, 1995)

In-vitro tracheal hyperreactivity to carbachol was induced in mice by cutaneous application of toluene diisocyanates (isomeric composition not indicated), followed by nasal toluene diisocyanate challenge; this was not accompanied by an elevation of toluene diisocyanate-specific IgE. The reaction could be transferred to naive recipient mice by transfusion of lymphoid cells from sensitized mice (Scheerens *et al*., 1996).

Inhalation exposure of guinea-pigs to toluene diisocyanates (3 h per day on five consecutive days) led to sensitization (antibody formation, pulmonary reactiveness to toluene diisocyanate-albumin conjugate), at exposure levels ≥ 0.14 mg/m^3 (Huang *et al*., 1993).

When guinea-pigs were sensitized to toluene diisocyanates by daily instillations for one week on the nasal mucosa and further exposed nasally once a week for four weeks, pulmonary alveolitis, characterized by infiltration of mononuclear cells and eosinophils, was observed. Vasculitis was not found, and fibrosis was negligible, but small non-necrotizing granulomas, containing epithelioid histiocytes, multinucleated giant cells, lymphocytes and eosinophils were also observed. The histological picture was thus reminiscent of the hypersensitivity pneumonitis described in humans after exposure to toluene diisocyanates (Yamada *et al*., 1995).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

When female Wistar rats were exposed by inhalation to toluene diisocyanates (nominal concentrations 1, 3 or 9 mg/m^3, 6 h per day) on days 6 through 15 of gestation, a slight increase of asymmetric sternebrae was observed at the highest dose, but no adverse effect on maternal weight gain, number of corpora lutea, implantation sites, pre- and postimplantation loss, fetal or placental weight, gross and visceral anomalies or degree of ossification was detected (Buschmann *et al*., 1996).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

Unless otherwise indicated, studies were carried out with an 80/20 mixture of 2,4/2,6-toluene diisocyanates. In one of two studies, toluene diisocyanate induced mutations in *Salmonella typhimurium* strains TA100, TA1538, and TA98 in the presence of an exogenous metabolic activation system only. It induced sex-linked recessive lethal mutations in *Drosophila* in a single study.

Toluene diisocyanate did not induce unscheduled DNA synthesis in rat primary hepatocytes. 2,4-Toluene diisocyanate induced mutations in mouse lymphoma L5178Y cells at the *tk* locus in the presence of exogenous metabolic activation and increased the frequency of sister chromatid exchanges but not chromosomal aberrations in Chinese hamster ovary cells. 2,6-Toluene diisocyanate induced gene mutations in L5178Y cells in the presence of an exogenous metabolic activation system and induced sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cell cultures.

In human lymphocyte cultures prepared from a male donor, toluene diisocyanate induced DNA single-strand breaks and chromosomal aberrations, but not sister chromatid exchanges.

Micronuclei were not induced in erythrocytes of mice or rats exposed to atmospheric concentrations of 1.1 mg/m^3 toluene diisocyanate for 6 h per day on five days per week for four weeks.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Toluene diisocyanates are industrial chemicals produced in large volumes. Exposure to toluene diisocyanates may occur during their production and in the processing and handling of polyurethane foams.

Table 1. Genetic and related effects of toluene diisocyanates

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	NG	Andersen *et al*. (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	NT	–	1250	Anderson & Styles (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	NT	–	1250	Anderson & Styles (1978)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NG	Andersen *et al*. (1980)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	+	NG	Andersen *et al*. (1980)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	NT	–	1250	Anderson & Styles (1978)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	+	NG	Andersen *et al*. (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	NT	–	1250	Anderson & Styles (1978)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		15000 ppm feed	Foureman *et al*. (1994)
URP, Unscheduled DNA synthesis, rat primary hepatocytes, *in vitro*	–	NT	50	Shaddock *et al*. (1990)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*[c]	?	+	75	McGregor *et al*. (1991)
GST, Gene mutation, mouse lymphama L5178Y cells, *tk* locus *in vitro*[d]	–	+	25	McGregor *et al.* (1991)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*[c]	+	–	300	Gulati *et al*. (1989)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*[d]	+	–	50	Gulati *et al*. (1989)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*[c]	–	–	1000	Gulati *et al*. (1989)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*[d]	+	–	600	Gulati *et al*. (1989)

Table 1 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic activation	With exogenous metabolic activation		
DIH, DNA single-strand breaks, human lymphocytes *in vitro*[e]	+	NT	2400	Marczynski *et al*. (1992)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*[e]	–	–	90	Mäki-Paakkanen & Norppa (1987)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*[e]	(+)	+	45	Mäki-Paakkanen & Norppa (1987)
MVM, Micronucleus test, CD-1 mouse erythrocytes *in vivo*	–		1.1 mg/m^3 inh 6 h/d, 5 d/wk, 4 wk	Loeser (1983)
MVR, Micronucleus test, Sprague-Dawley CD rat erythrocytes *in vivo*	–		1.1 mg/m^3 inh 6 h/d, 5 d/wk, 4 wk	Loeser (1983)

[a] +, positive; (+), weakly positive; –, negative; ?, inconclusive; NT, not tested
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; NG, not given; inh, inhalation. All data are from tests using an 80:20 mixture of 2,4-toluene diisocyanate:2,6-toluene diisocyanate unless otherwise indicated.
[c] Test using 2,4-toluene diisocyanate
[d] Test using 2,6-toluene diisocyanate
[e] Results are from cultures of peripheral blood lymphocytes obtained from one donor for each study.

5.2 Human carcinogenicity data

The risk of cancer associated with occupational exposure to isocyanates has been examined in three industrial cohort studies and in a population-based case–control study of several types of cancer. No strong association or consistent pattern has emerged.

5.3 Experimental data

Commercial mixtures of 2,4- and 2,6-toluene diisocyanates were tested for carcinogenicity in mice and rats by gavage and by inhalation exposure. Administration by gavage induced a dose-related increase in the incidence of subcutaneous fibromas and fibrosarcomas (combined) in male rats, together with an increase in the incidence of pancreatic acinar-cell adenomas in male rats and in pancreatic islet-cell adenomas, neoplastic nodules of the liver and mammary gland fibroadenomas in female rats. In female mice, dose-related increases in the combined incidence of haemangiomas and haemangiosarcomas and of hepatocellular adenomas were observed; no treatment-related tumour was seen in male mice, possibly due to poor survival. No treatment-related tumour was observed after exposure of mice or rats to commercial toluene diisocyanate by inhalation, although the results of the study with rats have not been reported fully.

5.4 Other relevant data

Toluene diisocyanates are metabolized to toluene diamines in humans and rats. Toluene diisocyanates are irritants and respiratory sensitizers in humans and rats.

Toluene diisocyanate did not induce micronuclei in mammalian erythrocytes *in vivo*. It induced DNA damage and chromosomal aberrations but not sister chromatid exchanges in human lymphocytes *in vitro*. It induced gene mutation and sister chromatid exchanges but not DNA damage or chromosomal aberrations in rodent cells *in vitro*. It induced sex-linked mutations in *Drosophila* and in some experiments was mutagenic in bacteria. The presence of an exogenous metabolic activation system led to inconsistent results, sometimes enhancing and at other times eliminating the genotoxic effects of toluene diisocyanate.

5.5 Evaluation

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

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

Overall evaluation

Toluene diisocyanates are *possibly carcinogenic to humans (Group 2B)*.

6. References

American Conference of Governmental Industrial Hygienists (1997) *1997 TLVs®* and *BEIs®*, Cincinnati, OH, p. 38

Andersen, M., Binderup, M.-L., Kiel, P., Larsen H. & Maxild, J. (1980) Mutagenic action of isocyanates used in the production of polyurethanes. *Scand. J. Work Environ. Health*, **6**, 221–226

Anderson, D. & Styles J.A. (1978) The bacterial mutation test. Six tests for carcinogenicity. *Br. J. Cancer*, **37**, 924–930

Anon. (1995) Isocyanates, organic. In: Kroschwitz, J.I. & Howe-Grant, M., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th Ed., Vol. 14, New York, John Wiley, pp. 902–934

Bartels, M.J., Timchalk, C. & Smith, F.A. (1993) Gas chromatographic/tandem mass spectrometric identification and quantitation of metabolic 4-acetyltoluene-2,4-diamine from the F344 rat. *Biol. Mass Spectrom.*, **22,** 194–200

Buschmann, J., Koch, W., Fuhst, R. & Heinrich, U. (1996) Embryotoxicity study of monomeric 4,4′-methylenediphenyl diisocyanate (MDI) aerosol after inhalation exposure in Wistar rats. *Fundam. appl. Toxicol.,* **32**, 96–101

Chadwick, D.H. & Cleveland, T.H. (1981) Isocyanates, organic. In: Mark, H.F., Othmer, D.F., Overberger, C.G. & Seaborg, G.T., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 13, New York, John Wiley, pp. 789–818

Foureman, P., Mason, J.M., Valencia, R. & Zimmering, S. (1994) Chemical mutagenesis testing in *Drosophila*. X. Results of 70 coded chemicals tested for the National Toxicology Program. *Environ. mol. Mutag.,* **23**, 208–227

Gulati, D.K., Witt, K., Anderson, B., Zeiger, E. & Shelby, M.D. (1989) Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells *in vitro* III. Results with 27 chemicals. *Environ. mol. Mutag.*, **13**, 133–193

Hagmar, L., Welinder, H. & Mikoczy, Z. (1993a) Cancer incidence and mortality in the Swedish polyurethane foam manufacturing industry. *Br. J. ind. Med*., **50**, 537–543

Hagmar, L., Strömberg, U., Welinder, H. & Mikoczy, Z. (1993b) Incidence of cancer and exposure to toluene diisocyanate and methylene diphenyldiisocyanate: a cohort based case–reference study in the polyurethane foam manufacturing industry. *Br. J. ind. Med*., **50**, 1003–1007

Huang, J., Aoyama, K. & Ueda, A. (1993) Experimental study on respiratory sensitivity to inhaled toluene diisocyanate. *Arch. Toxicol.,* **67**, 373–378

IARC (1986) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*. Volume 39, *Some Chemicals Used in Plastics and Elastomers*, Lyon, pp. 287–323

IARC (1987) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, p. 72

IARC (1993) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 57, *Occupational Exposures of Hairdressers and Barbers and Personal Use of Hair Colourants; Some Hair Dyes, Cosmetic Colourants, Industrial Dyestuffs and Aromatic Amines*, Lyon, pp. 271–303

IARC (1994) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 60, *Some Industrial Chemicals*, Lyon, pp. 233–320

IARC (1995) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 63, *Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals*, Lyon, pp. 337–372

International Labour Office (1991) *Occupational Exposure Limits for Airborne Toxic Substances*, 3rd Ed. (Occupational Safety and Health Series No. 37), Geneva, pp. 160–161

Kennedy, A.L., Wilson, T.R., Stock, M.F., Alarie, Y. & Brown, W.E. (1994) Distribution and reactivity of inhaled ^{14}C-labeled toluene diisocyanate (TDI) in rats. *Arch. Toxicol*., **68,** 434–443

Lewis, R.J., Jr (1993) *Hawley's Condensed Chemical Dictionary*, 12th Ed., New York, Van Nostrand Reinhold, pp. 1157–1158

Lide, D.R., ed. (1997) *CRC Handbook of Chemistry and Physics*, 78th Ed., Boca Raton, FL, CRC Press, p. 3-41

Lind, P., Dalene, M., Skarping, G. & Hagmar, L. (1996) Toxicokinetics of 2,4- and 2,6-toluenediamine in hydrolysed urine and plasma after occupational exposure to 2,4- and 2,6-toluene diisocyanate. *Occup. environ. Med*., **53**, 94–99

Loeser E. (1983) Long-term toxicity and carcinogenicity studies with 2,4/2,6-toluene-diisocyanate (80/20) in rats and mice. *Toxicol. Lett.*, **15**, 71–81

Mäki-Paakkanen, J. & Norppa, H. (1987) Chromosome aberrations and sister-chromatid exchanges induced by technical grade toluene diisocyanate and methylenediphenyl diisocyanate in cultured human lymphocytes. *Toxicol. Lett.*, **36**, 37–43

Marczynski, B., Czuppon, A.B., Marek, W. & Baur, X. (1992) Indication of DNA strand breaks in human white blood cells after in vitro exposure to toluene diisocyanate (TDI). *Toxicol. ind. Health*, **8**, 157–169

McGregor, D.B., Brown, A.G., Howgate, S., McBride, D., Riach, C. & Caspary, W.J. (1991) Responses of the L5178Y mouse lymphoma cell forward mutation assay. V. 27 coded chemicals. *Environ. mol. Mutag.*, **17**, 196–219

NOES (1997) *National Occupational Exposure Survey 1981-83*, Unpublished data as of November 1997, Cincinnati, OH, United States Department of Health and Human Services, Public Health Service, National Institute for Occupational Safety and Health

Omae, K., Nakadate, T., Higashi, T., Nakaza, M., Aizawa, Y. & Sakurai, H. (1992a) Four-year follow-up of effects of toluene diisocyanate exposure on the respiratory system in polyurethane foam manufacturing workers I. Study design and results of the first cross-sectional observation. *Int. Arch. occup. environ. Health,* **63**, 559–564

Omae, K., Higashi, T., Nakadate, T., Tsugane, S., Nakaza, M. & Sakurai, H. (1992b) Four-year follow-up of effects of toluene diisocyanate exposure on the respiratory system in polyurethane foam manufacturing workers II. Four-year changes in the effects on the respiratory system. *Int. Arch. occup. environ, Health,* **63**, 565–569

Pisati, G., Barufini, A. & Zedda, S. (1993) Toluene diisocyanate induced asthma: outcome according to persistence or cessation of exposure. *Br. J. ind. Med.,* **50**, 60-64

Rosenberg, C. & Savolainen, H. (1985) Detection of urinary metabolites in toluene diisocyanate exposed rats. *J. Chromatogr*., **323**, 429–433

Scheerens, H., Buckley, T.L., Davidse, E.M., Garssen, J., Nijkamp, F.P. & Van Loveren, H. (1996) Toluene diisocyanate-induced *in vitro* tracheal hyperreactivity in mice. *Am. J. respir. Crit. Care Med.*, **154**, 858–865

Schnorr, T.M., Steenland, K., Egeland, G.M., Boeniger, M. & Egilman, D. (1996) Mortality of workers exposed to toluene diisocyanate in the polyurethane foam industry. *Occup. environ. Med*., **53**, 703–707

Shaddock, J.G., Robinson, B.Y. & Casciano, D.A. (1990) Effect of pretreatment with hepatic mixed-function oxidase inducers on the genotoxicity of four rat carcinogens in the hepatocyte/DNA repair assay. *Mutagenesis*, **5**, 387–391

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

Sorahan, T. & Pope, D. (1993) Mortality and cancer morbidity of production workers in the United Kingdom flexible polyurethane foam industry. *Br. J. ind. Med*., **50**, 528–536

Timchalk, C., Smith, F.A. & Bartels, M.J. (1994) Route-dependent comparative metabolism of [^{14}C]toluene 2,4-diisocyanate and [^{14}C]toluene 2,4-diamine in Fischer 344 rats. *Toxicol. appl. Pharmacol.*, **124**, 181–190

Tinnerberg, H., Dalene, M. & Skarping, G. (1997) Air and biological monitoring of toluene diisocyanate in a flexible foam plant. *Am. ind. Hyg. Assoc. J.*, **58**, 229–235

Ulrich, H. (1983) Urethane polymers: In: Mark, H.F., Othmer, D.F., Overberger, C.G. & Seaborg, G.T., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd Ed., Vol. 23, New York, John Wiley, pp. 576–608

Ulrich, H. (1989) Isocyanates, organic. In: Gerhartz, W. & Yamamoto, Y.S., eds, *Ullmann's Encyclopedia of Industrial Chemistry*, 5th rev. Ed., Vol. A14, Weinheim, VCH Publishers, pp. 611–625

United States National Library of Medicine (1997*) Hazardous Substances Data Bank (HSDB)*, Bethesda, MD [Record No. 6003]

WHO (1987) *Toluene Diisocyanates* (Environmental Health Criteria 75), Geneva, International Programme on Chemical Safety

WHO (1993) *Guidelines for Drinking Water Quality*, 2nd Ed., Vol. 1, *Recommendations*, Geneva

Yamada, K., Amitani, R., Niimi, A. & Kuze, F. (1995) Interstitial pneumonitis-like lesions in guinea-pigs following repeated exposure to toluene diisocyanate. *Eur. Respir. J.*, **8**, 1300–1306

Zissu, D. (1995) Histopathological changes in the respiratory tract of mice exposed to ten families of airborne chemicals. *J. appl. Toxicol.*, **15**, 207–213