4,4′-METHYLENEDIPHENYL DIISOCYANATE AND POLYMERIC 4,4′-METHYLENEDIPHENYL DIISOCYANATE

Data were last reviewed in IARC (1979) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

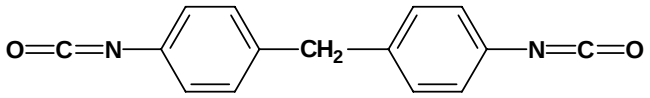
Chem. Abstr. Serv. Reg. No.: (a) 101-68-8 (monomer) and (b) 26447-40-5

Chem. Abstr. Name: 1,1′-Methylenebis(4-isocyanatobenzene)

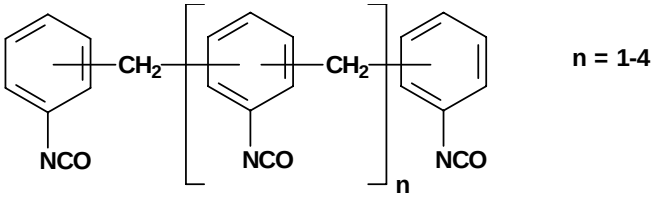
IUPAC Systematic Names: For 101-68-8: isocyanic acid, methylenedi-*para*-phenylene ester

Synonyms: Bis(1,4-isocyanatophenyl)methane; diphenylmethane diisocyanate; MDI; methylenedi-*para*-phenylene isocyanate and for 26447-40-5: crude MDI; polymeric MDI; PMDI; generic MDI; non-isomeric-specific MDI

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_{15}H_{10}N_2O_2$ Relative molecular mass: 250.27



$C_{15}H_{10}N_2O_2.[C_8H_5NO]_n$ (polymeric)

1.1.3 *Chemical and physical properties of the pure substance*

(from United States National Library of Medicine (1997a), unless otherwise stated)

(*a*) *Description*: White to light yellow odourless flakes

(*b*) *Boiling-point*: 196°C at 665 Pa

(*c*) *Melting-point*: 38°C

(*d*) *Solubility*: Soluble in acetone, benzene, kerosene and nitrobenzene
(*e*) *Vapour pressure*: 0.13 Pa at 40°C

1.1.4 *'Polymeric MDI'*

The principal material of commerce is not pure 4,4′-methylenediphenyl diisocyanate but is a mixture containing 4,4′-methylenediphenyl diisocyanate, other methylenediphenyl diisocyanate isomers, and low oligomers of the general structure shown above.

This dark amber mixture is commonly called polymeric, or generic, or non-isomer-specific methylenediphenyl diisocyanate. Its composition is variable but typically is in the range of 40–50% 4,4′-methylenediphenyl diisocyanate, 2.5–4.0% 2,4′-methylenediphenyl diisocyanate, 0.1–0.2% 2,2′-methylenediphenyl diisocyanate, and the remainder (50–60%) higher homologues (Woods, 1990; European Union, 1999).

1.2 Production and use

The world production of methylenediphenyl diisocyanate all types included was 1200 thousand tonnes in 1991. In the European Union, approximately 790 thousand tonnes were manufactured in 1996, compared with 540 thousand tonnes in 1991 and 267 thousand tonnes in 1980; 215 thousand tonnes were processed in 1980 (European Union, 1999).

It is mainly used in the industrial production of rigid polyurethane foams. Many other uses are in the fields of coatings, adhesives, sealants and elastomers such as paints, adhesives, weather-resistant sealing materials and footwear. There is use also in the production of particle board (bonding of wood) and mould cores for the foundry industry (European Union, 1999).

1.3 Occurrence

1.3.1 *Occupational exposure*

Some data on levels of occupational exposure to 4,4′-methylenediphenyl diisocyanate have been presented in a previous *IARC Monograph* (IARC, 1979).

1.3.2 *Environmental occurrence*

4,4′-Methylenediphenyl diisocyanate can be released to the environment in waste stream emissions from sites of industrial manufacture and use. Toxic Release Inventory reports to the United States Environmental Protection Agency before at least the mid-1990s were subject to serious overestimation of the releases to the environment, because of errors in the way that the figures were calculated by industry. Within the European Union, total emissions from production sites in 1996 were about 43 kg and emissions from processing plants in the same year were about 7100 kg (European Union, 1999).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 0.051 mg/m^3 as the threshold limit value for occupational exposure to

4,4′-methylenediphenyl diisocyanate in the workplace air. Similar values have been used as standards or guidelines in many countries (International Labour Office, 1991).

No international guideline for 4,4′-methylenediphenyl diisocyanate in drinking-water has been established (WHO, 1993).

2. Studies of Cancer in Humans

See monograph on toluene diisocyanate.

3. Studies of Cancer in Experimental Animals

No data were available to the Working Group with regard to preparations of monomeric 4,4′-methylenediphenyl diisocyanate alone. The following is a study of a preparation containing both monomeric and polymeric 4,4′-methylenediphenyl diisocyanate.

3.1 Inhalation

3.1.1 *Rat*

Groups of 60 male and 60 female Wistar rats, six weeks of age, were exposed to target concentrations of 0 (controls), 0.2, 1.0 or 6.0 mg/m^3 (analytical value, 0.19, 0.98 or 6.03 mg/m^3) respirable (particle size, 93.5% < 4.2 μm) polymeric 4,4′-methylenediphenyl diisocyanate aerosol (31.0–31.7% (w/w) isocyanate content, 0.06–0.12% hydrolysable chlorine, 0.20–0.37% total chlorine, 0.0001–0.0069% chlorobenzene, 0.003–0.005% phenyl isocyanate, 44.8–50.2% monomeric 4,4′-methylenediphenyl diisocyanate, 0.01% sediment content) for 6 h per day on five days per week for two years. The exposure concentrations were selected based on results of a 13-week study. Complete histological examination was performed and almost all organs and all grossly observed lesions were examined histologically. Survival at 104 weeks of study was 38/60, 38/60, 42/60 and 36/60 control, low-dose, mid-dose and high-dose males and 41/60, 42/60, 48/60 and 50/60 control, low-dose, mid-dose and high-dose females. In the high-dose group, pulmonary adenomas were found in 6/60 males ($p < 0.05$ by two-sided Fisher's exact test) and 2/59 females, and pulmonary adenocarcinoma was found in 1/60 males. No lung tumours were found in other groups. Accumulation of alveolar macrophages containing polymeric 4,4′-methylenediphenyl diisocyanate-associated refractile yellowish material, localized fibrosis, alveolar duct epithelialization and increased incidences of calcareous deposits and localized alveolar bronchiolization were observed in the lungs of the high-dose group (Reuzel *et al.*, 1994). [The Working Group noted that the effects observed could not be attributed confidently either to a non-specific small inhaled particle effect or to the chemical composition of the particles.]

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

The air levels of 4,4′-methylenediphenyl diisocyanate in a factory manufacturing polyurethane products were measured using personal, work-room and work-station monitors. In most cases, the levels were below detection limits. Using gas chromatography/mass spectrometry methods, urinary base-extractable metabolites were above control levels in 15 of the 20 workers and ranged from 0.035 to 0.83 pmol/mL 4,4′-methylenedianiline. The level of the acetylated metabolite, *N*-acetyl-4,4′-methylenedianiline, ranged from 0.13 to 7.61 pmol/mL. The amount of 4,4′-methylenedianiline released after acid hydrolysis was on average 6.5 times higher than the amount of free 4,4′-methylenedianiline and *N*-acetyl-4,4′-methylenedianiline present in urine. 4,4′-Methylenedianiline was present as a haemoglobin adduct in all of the 20 subjects at levels ranging from 70 to 710 fmol/g haemoglobin. In one individual, the haemoglobin adduct of *N*-acetyl-4,4′-methylenedianiline was detected. Plasma 4,4′-methylenedianiline levels ranged from 0.25 to 5.4 pmol/mL; up to 120 fmol/mg were covalently bound to albumin (Sepai *et al*., 1995a).

4.1.2 *Experimental data*

Following topical administration of [^{14}C]4,4′-methylenediphenyl diisocyanate in acetone to female Wistar rats, 20% of the administered dose was eliminated in the faeces within 24 h, while less than 1% appeared in the urine (Vock & Lutz, 1997).

After inhalation exposure of female Wistar rats to 4,4′-methylene diisocyanate aerosols (0.26, 0.70 and 2.06 mg/m^3 chronically for three and 12 months), 4,4′-methylenedianiline and *N*-acetyl-4,4′-methylenedianiline were the major urinary metabolites. Haemoglobin adducts of these metabolites were also detected. The dose–response relationships for haemoglobin adducts and urinary metabolites were non-linear over this dose range. The amounts of 4,4′-methylenedianiline and, to a lesser extent, *N*-acetyl-4,4′-methylenedianiline found in urine correlated well with the corresponding amount determined as haemoglobin adducts for all dose groups. Similar results were obtained with rats exposed for three and 12 months, indicating that a steady state had been reached by three months. Haemoglobin adducts from rats after a one-week recovery period decreased by approximately 40% for all dosed groups, suggesting that erythrocytes containing modified haemoglobin have a shorter lifespan (Sepai *et al.*, 1995b).

4.2 Toxic effects

4.2.1 *Humans*

4,4′-Methylenediphenyl diisocyanate is irritating to the skin, eyes and respiratory tract and induces asthma in humans (IARC, 1979).

Isocyanate-induced asthma and hypersensitivity pneumonitis in humans have been reviewed (Baur, 1995; Bernstein, 1996). A case of fatal asthma of a 4,4′-methylenediphenyl diisocyanate-sensitized subject has been described (Carino *et al*., 1997). Exposure to 4,4′-methylenediphenyl diisocyanate is a frequent cause of occupational asthma (Liss *et al*., 1988; Vogelmeier *et al*., 1991; Bernstein *et al*., 1993) but may also induce hypersensitivity pneumonitis (Malo & Zeiss, 1982; Vandenplas *et al*., 1993) and inflammatory upper respiratory tract diseases (Liss *et al*., 1988; Littorin *et al*., 1994). Most patients with 4,4′-methylenediphenyl diisocyanate-induced asthma have elevated levels of IgG-class antibodies towards 4,4′-methylenediphenyl diisocyanate–albumin conjugates in the plasma, while IgE-class antibodies are rare (Liss *et al*., 1988).

4.2.2 *Experimental systems*

Intradermal injection and topical cutaneous administration of 4,4′-methylenediphenyl diisocyanate induced IgG1 antibodies towards 4,4′-methylenediphenyl diisocyanate and an acute pulmonary response towards inhalation challenge to a non-irritating concentration of 4,4′-methylenediphenyl diisocyanate in guinea-pigs, while no such reaction was observed after inhalation treatment (approximately 21.5 mg/m^3 for 3 h per day on five consecutive days) (Rattray *et al*., 1994). However, when guinea-pigs were exposed to a high concentration of 4,4′-methylenediphenyl diisocyanate (135 or 360 mg/m^3) once for 15 min, an immediate-onset respiratory sensitivity response was observed after challenge to a low (3.4 mg/m^3) concentration of 4,4′-methylenediphenyl diisocyanate; after intradermal sensitization, such a reaction was observed only upon challenge with an irritating concentration (60 mg/m^3) of 4,4′-methylenediphenyl diisocyanate (Pauluhn & Mohr, 1994). C57BL/6 mice injected intradermally with 4,4′-methylenediphenyl diisocyanate responded to local 4,4′-methylenediphenyl diisocyanate administration by ear swelling; this reaction could be transferred by transfusion of syngeneic mouse lymph node-derived T cells (Tanaka *et al*., 1987). Total IgE concentration in blood was elevated in a dose-dependent manner in BALB/c mice after dermal instillation of 4,4′-methylenediphenyl diisocyanate; the elevation became significant when the dose reached 1.35 mg (Potter & Wederbrand, 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 4,4′-methylenediphenyl diisocyanate (nominal concentrations of 1, 3 or 9 mg/m^3, 6 h per day) on days 6 through 15 of gestation, a slight increase of asymmetric sternebrae appeared at the highest dose but no adverse effect was observed 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 (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)

In one study, 4,4′-methylenediphenyl diisocyanate induced mutations in *Salmonella typhimurium* strain TA100 in the presence of exogenous metabolic activation but not in its absence. It induced a weak mutagenic response in *S. typhimurium* strain TA98 with exogenous metabolic activation but was not mutagenic in strains TA1535, TA1537, TA1538 or in *Escherichia coli* WP2 *uvrA*.

A second study reported that technical-grade 4,4′-methylenediphenyl diisocyanate (containing 25% 4,4′-methylenediphenyl triisocyanate and 30% unspecified higher molecular weight compounds) increased the frequency of sister chromatid exchanges and chromosomal aberrations in human lymphocytes in the presence or absence of exogenous metabolic activation.

Results from an inhalation study showed that a low level (5–10 adducts/10^9 nucleotides) of arylamine-derived DNA adducts was formed in the olfactory epithelium of female Wistar rats exposed to an average atmospheric concentration of 0.7–2.0 mg/m^3 4,4′-methylenediphenyl diisocyanate for 17 h per day on five days per week for one year. Adducts were not detected in DNA from lung, liver, bladder, kidney, respiratory epithelium or peripheral blood lymphocytes of exposed animals (Vock *et al*., 1996).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

4,4′-Methylenediphenyl diisocyanate is used for the production of polyurethane coatings and elastomers.

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 Animal carcinogenicity data

Polymeric 4,4′-methylenediphenyl diisocyanate containing 44.8–50.2% monomeric 4,4′-methylenediphenyl diisocyanate was tested for carcinogenicity by inhalation in rats. An increased incidence of lung tumours was observed.

5.4 Other relevant data

The major urinary metabolites of 4,4′-methylenediphenyl diisocyanate are 4,4′-methylenedianiline and *N*-acetyl-4,4′-methylenedianiline, both of which also form haemoglobin

Table 1. Genetic and related effects of 4,4′-methylenediphenyl diisocyanate

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	370	Shimizu *et al*. (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1850	Shimizu *et al*. (1985)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1850	Shimizu *et al*. (1985)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	1850	Shimizu *et al*. (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	(+)	185	Shimizu *et al*. (1985)
ECW, *Escherichia coli* WP2 *uvrA*, reverse mutation	–	–	1850	Shimizu *et al*. (1985)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*[c]	(+)	(+)	2600	Mäki-Paakkanen & Norppa (1987)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*[c]	+	(+)	650	Mäki-Paakkanen & Norppa (1987)

[a] +, positive; (+), weakly positive;–, negative
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL
[c] Technical-grade product was tested

adducts in exposed workers and rats. 4,4′-Methylenediphenyl diisocyanate is an irritant and a sensitizer; exposure by inhalation produces asthma among workers.

4,4′-Methylenediphenyl diisocyanate forms low-level DNA adducts *in vivo* and induces mutations in bacteria and chromosomal aberrations and sister chromatid exchanges in human lymphocyte cultures.

5.5 Evaluation

There is *inadequate evidence* for the carcinogenicity of 4,4′-methylenediphenyl diisocyanate or polymeric 4,4′-methylenediphenyl diisocyanate in humans.

There is *limited evidence* in experimental animals for the carcinogenicity of a mixture containing monomeric and polymeric 4,4′-methylenediphenyl diisocyanate.

Overall evaluation

4,4′-Methylenediphenyl diisocyanate (industrial preparation) is *not classifiable as to its carcinogenicity to humans (Group 3).*

6. References

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