# Methylene Diphenyl Diisocyanate (monomeric MDI) and polymeric MDI (PMDI); CASRN 101-68-8, 9016-87-9

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Methylene Diphenyl Diisocyanate (monomeric MDI) and polymeric MDI (PMDI)

**File First On-Line 05/01/1994**

| Category (section) | Assessment Available? | Last Revised |
|---|---|---|
| **Oral RfD (I.A.)** | not evaluated | |
| **Inhalation RfC (I.B.)** | yes | 02/07/1998 |
| **Carcinogenicity Assessment (II.)** | yes | 02/07/1998 |

## I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

### I.A. Reference Dose for Chronic Oral Exposure (RfD)

Methylene Diphenyl Diisocyanate (monomeric MDI) and polymeric MDI (PMDI)
CASRN — 101-68-8, 9016-87-9
Last Revised — 02/07/1998

Not available at this time.

## I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Methylene Diphenyl Diisocyanate (monomeric MDI) and polymeric MDI (PMDI)
CASRN — 101-68-8, 9016-87-9
Primary Synonym — Diphenylmethane Diisocyanate
Last Revised — 02/07/1998

### I.B.1. Inhalation RfC Summary

| Critical Effect | Exposures* | UF | MF | RfC |
|---|---|---|---|---|
| **Hyperplasia of the olfactory epithelium**<br><br>**Reuzel et al., 1990, 1994b** | Benchmark concentration (BMC):<br>BMC10 (ADJ): 0.14 mg/cu.m<br>BMC10 (HEC): 0.06 mg/cu.m | 100 | 1 | 6E-4 mg/cu.m |

*Conversion Factors: MW=250.26 (monomeric MDI). BMC10 (ADJ) was obtained by running the BMC software program using concentrations from the Reuzel et al. (1994b) study adjusted for 24 hours/day and 7 days per week. The THRESH polynomial regression model, developed by Clement International (1990), specific for quantal endpoints, was used in the BMC analysis. The BMC10 (HEC) was calculated for a particle: respiratory effect in the extrathoracic (ET) region. The RDDR (ET) with a particle MMAD of 0.68 um and sigma g of 2.93, based on particle deposition modeling as described in U.S. EPA (1994), Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity, was calculated using current RDDR software as 0.453. The default body weight (462 gm) for the male Wistar rat was taken from Table 4.5 (U.S. EPA, 1994a), Methods for Derivation of Inhalation Reference Concentrations and Applications of Inhalation Dosimetry, and used as input to the RDDR program. BMC10 (HEC) = BMC10 (ADJ) RDDR (ET) = 0.06 mg/cu.m. For further discussion of the RDDR and derivation of the RfC see Sections 5.2.2 and 5.2.3 of the Toxicological Review (US EPA 1998).

### I.B.2. Principal and Supporting Studies (Inhalation RfC)

Reuzel, P.G.J., J.H.E. Arts, L.G. Lomax, et al. 1994b. Chronic inhalation and carcinogenicity study of respirable polymeric methylene diphenyl diisocyanate (polymeric MDI) aerosol in rats. Fundam. Appl. Toxicol. 22: 195-210.

Reuzel, P.G.J., J.H.E. Arts, M.H.M. Kuypers, and C.F. Kuper. 1990. Chronic toxicity/carcinogenicity inhalation study of polymeric methylene diphenyl diisocyanate aerosol in rats (Final Report). Prepared by Civo Institute for the International Isocyanate Institute. Report No. V88.122.

Specific-pathogen-free (SPF)-bred Wistar rats of the Cpb: WU strain (60/sex/exposure level) were exposed whole-body to aerosols of polymeric methylene diphenyl diisocyanate (PMDI). The test material was a dark brown liquid with an average molecular weight of about 400 and each batch received from the manufacturer contained 47% monomeric MDI. The remaining 53% was described as "polymeric" MDI. [Note: PMDI refers to a mixture containing about 50% monomeric MDI and 50% trimeric species and higher molecular weight oligomers (Ulrich, 1983); this composition, which is very similar to that used in the workplace, renders the material semisolid and suitable for aerosol generation.] The test material was kept at room temperature under "common laboratory conditions." This is interpreted to mean that the test material was stored under an inert gas. If unprotected, MDI reacts with water to form carbon dioxide.

The rats were exposed for 6 h/day, 5 days/week, for 24 mo to nominal exposure levels of 0, 0.2, 1.0, and 6.0 mg/cu.m. A satellite group of rats (10/sex/exposure level) was exposed similarly for 12 mo and examined histopathologically at the end of exposure. The mean actual values as measured by gravimetry were within plus or minus 10% of nominal values. Thus, nominal values will be used in the following discussion. The duration-adjusted exposure levels are 0, 0.036, 0.18, and 1.1 mg/cu.m. Particle size determinations were made weekly with a cascade impactor. The mass median aerodynamic diameter (MMAD) and geometric standard deviation (in parenthesis) corresponding to the exposure levels were 0, 0.68 um (2.93), 0.70 um (2.46), and 0.74 um (2.31), respectively. Gross observations and organ weights were obtained on all animals. Histological observations were made on the lungs, mediastinal lymph nodes, and nasal cavity (six levels) on all animals and in Forty-three other tissues in controls and animals exposed to 6 mg/cu.m.

Histologic evidence of damage at the 24-month necropsy of the main group involved the same tissues as at 12 months, although the severity had increased in nasal and pulmonary tissues. Basal cell hyperplasia was evident in the olfactory epithelium of the nasal tract of males (14/60, 13/60, 26/60, and 32/60 at 0, 0.2, 1.0, and 6.0 mg/cu.m, respectively) and females (4/60, 8/60, 8/60, and 49/59 at 0, 0.2, 1.0, and 6.0 mg/cu.m, respectively). Statistical significance was reached in males at the mid and high concentrations and only at the high concentration in females. It was often accompanied by Bowman's gland hyperplasia, which was significant in males at 1 and 6 mg/cu.m. Olfactory epithelial degeneration was elevated significantly in males and females only at 6 mg/cu.m. In the lung, there was increased severity in the accumulation of pigment-laden macrophage in alveolar duct lumina (incidence in males:

0/60, 3/60, 21/60, and 60/60; females: 0/59, 1/60, 23/60, and 59/59) and in localized fibrotic changes (males: 1/60, 0/60, 9/60, and 44/60; females: 0/59, 0/60, 4/60, and 48/60). Localized alveolar duct epithelialization was increased significantly in both males and females exposed to 1 and 6 mg/cu.m. Localized alveolar bronchiolization was significant in both sexes exposed to 6 mg/cu.m. Accumulation of yellow pigment in the mediastinal lymph nodes was noted in males (incidence: 0/59, 0/53, 9/51, and 50/58) and females (incidence: 0/53, 1/57, 3/50, and 43/55). The accumulation of macrophage and the localization of tissue damage in the area of macrophage accumulation suggest that the lung effect is due primarily to toxicity of the macrophage (with secondary damage), although some of the effects were described as being distributed evenly throughout the lungs. There were no histological effects in any of the other organ systems examined.

The information obtained in this chronic study suggests that the NOAEL is 0.2 mg/cu.m (duration-adjusted concentration = 0.036 mg/cu.m) and a LOAEL of 1.0 mg/cu.m (duration-adjusted concentration = 0.18 mg/cu.m) for respiratory tract effects in both pulmonary and extrathoracic regions. The RfC was derived using benchmark concentration (BMC) analysis on basal cell hyperplasia of the olfactory epithelium (males only). The BMC approach was used because it takes into consideration the shape of the concentration-response curve, whereas the NOAEL selection is based solely on study concentrations employed. Given the apparent sensitivity of the male to basal cell hyperplasia and the expression of an elevated incidence of both basal cell hyperplasia and olfactory degeneration at both the mid and high concentrations, it is not possible to differentiate basal cell hyperplasia, on the basis of either the interim or final sacrifice histopathological results, as a compensatory response to olfactory degeneration. Thus, it is prudent to regard basal cell hyperplasia as an adverse response. This critical effect was chosen over localized pulmonary fibrosis because, after HECs are compared, the nasal effects would yield a more conservative RfC. Because the test mixture in the Reuzel et al. study (1990, 1994b) was of a composition that is typically used during polyurethane foam manufacturing, the results of this study are more relevant to potential exposure of individuals in ambient environments than are those associated with the pure MDI used by Hoymann et al. (1995), whose study description and evaluation follows. For this reason, the results of the Reuzel study were used in RfC derivation.

The THRESH polynomial regression model, developed by Clement International specifically for quantal endpoints was used in the BMC analysis. The model was used to calculate extra risk, defined as the fraction of animals that would respond to a dose among animals who otherwise would not respond. The model was run at two specified levels of risk, 5% and 10%, using the concentrations and responses for nasal olfactory basal cell hyperplasia in male rats from the Reuzel et al. (1994b) study. Maximum likelihood estimates (MLE) and BMC values (i.e., lower 95% confidence bound on MLE) were derived for each risk level. With both models at the 5% and 10% risk levels, the MLEs were 0.10 and 0.22 mg/cu.m, respectively.

Results from both models indicated that the BMCs provided acceptable fits to the data. The goodness-of-fit p value was 0.09. The BMCs were 0.07 and 0.14 mg/cu.m, respectively. The BMC10 values for nasal olfactory degeneration and for basal cell hyperplasia were nearly identical (0.14 mg/cu.m versus 0.18 mg/cu.m, respectively).

The regional deposited dose ratio (RDDR) was calculated for each region of the respiratory system according to a computer program based on the rationale and empirical data described in U.S. EPA (1994b). The RDDRs for the particles having a MMAD = 0.68 um and sigma g = 2.93 are 0.453 for the extrathoracic and 0.910 for the thoracic regions. The resulting BMC10 (HEC) associated with nasal effects is 0.06 mg/cu.m.

A chronic toxicity study also was conducted in female Wistar rats (80/exposure group) exposed to monomeric MDI in aerosol form to gravimetrically determined levels of 0.23, 0.70, and 2.05 mg/cu.m for 17 h/day, 5 days/week for 24 mo (Hoymann et al., 1995). The amount of monomer in each of the three groups, determined by chemical analysis, was 0.097, 0.549, and 1.75 mg/cu.m, respectively. It is likely that monomeric MDI reacted with water in the exposure atmosphere to form oligoureas, amines, and carbon dioxide. The nominal levels were used for calculation purposes because the exposure levels in the Reuzel et al. (1994b) study were based on gravimetric analysis. The duration-adjusted values are 0.12, 0.35, and 1.04 mg/cu.m, respectively. The MMAD of the exposure particles was about 1 um in each of the three exposure groups. Treatment-related and statistically significant pulmonary lesions found in animals exposed for two years were similar in nature to those found in the Reuzel et al. (1990, 1994b) study. They included: (1) dose-related increase in focal/multifocal alveolar and bronchioalveolar hyperplasia, (2) dose- related increase in incidence of focal/multifocal interstitial fibrosis of lungs, and (3) dose-related multifocal accumulation of particle-laden and pigmented macrophage. Goblet cell hyperplasia in the nose and focal/multifocal mucosal inflammatory cell infiltration was significantly elevated above controls for the high-exposure group only. No other significant nasal effects were observed. The histopathologic effects correlated with a number of pulmonary function effects, particularly in the high-exposure group. Histopathologic observations in a satellite group examined at 1 year were consistent with the effects reported at 2 years.

A study LOAEL of 0.23 mg/cu.m is identified in this study for pulmonary effects only. There is no NOAEL

### I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF = 100.

Three uncertainty factors (UF) were applied to the BMC10 (HEC): a 10 for intraindividual variation, 3 for the lack of reproductive data, and a 3 for interspecies variation inasmuch as dosimetric adjustments had been made. The two UFs of 3 each coalesce to a 10, yielding a total UF of 100.

MF = 1.

### I.B.4. Additional Studies/Comments (Inhalation RfC)

In a 13-week study, SPF-bred Wistar rats (30/sex/exposure level) were exposed to polymeric MDI aerosol (Reuzel et al., 1985b, 1994a). Polymeric MDI was in the form of a dark brown liquid that contained 52% monomeric MDI. Rats were exposed to 4, 8, or 12 mg/cu.m of an aerosol of this liquid for 6 h/day, 5 days/week, for 13 weeks. This study demonstrated adverse effects in the lungs and nasal cavity at levels of 4 mg/cu.m and above. However, because of a lack of data on aerosol sizes, a quantitative LOAEL(HEC) cannot be derived. In addition, Wistar rats (15/sex/exposure level) were exposed to PMDI aerosol at actual levels of 0.35, 1.4, or 7.2 mg/cu.m for 6 h/day, 5 days/week for 13 weeks (Reuzel et al., 1985a, 1990, 1994a). The only exposure-related observation was an increase in yellowish-colored alveolar macrophages in all animals of the high-exposure group, but there was no tissue reaction evident. The results of these shorter-term studies are consistent with the findings of the chronic study that subsequently was performed (Reuzel et al., 1990, 1994b).

Exposure to isocyanates is a leading cause of occupational asthma worldwide (Mapp, 1988). Because PMDI is used extensively in making flexible polyurethane foam, there have been a number of case reports describing occupational asthma and hypersensitivity pneumonitis, but exposure levels are unknown (Zammit-Tabona et al., 1983; Konzen et al., 1966; Tanser et al., 1973; Zeiss et al., 1980; Malo and Zeiss, 1982; O'Brien et al., 1979; Mapp et al., 1985; Lob and Boillat, 1981; Baur et al., 1984; Vandenplas et al., 1993). Specific immunoglobulin E and G antibodies have been demonstrated in some occupationally exposed workers with a diagnosis of occupational asthma, but the presence of antibodies can occur without asthmatic symptoms (Cartier et al, 1989; Liss et al., 1988; Pezzini et al., 1984; and Tse et al., 1985). High exposure concentrations, such as might occur during a spill (Brooks, 1982), likely are a risk factor in human sensitization. The available human data concerning occupational exposure to PMDI/MDI, coupled with lack of knowledge about mechanism of action, are insufficient to identify exposure levels and scenarios responsible for isocyanate-induced sensitization. For this reason, PMDI/MDI-induced asthma could not be selected as an endpoint for RfC derivation. Few occupational studies have examined exposure-response relationships with respect to pulmonary function decline as a result of PMDI/MDI exposure. This endpoint is of concern given the demonstration of chronic pulmonary function decline in workers

exposed to TDI (Diem et al., 1982) and derivation of an RfC for TDI based on this study (IRIS, 1994).

Musk et al. (1982), in a longitudinal study, followed for 5 years 107 workers from two plants in a polyurethane manufacturing facility in which both TDI and MDI were present in the air. MDI was used only in the last 2 years of the study. The geometric mean of the MDI measurements was reported as 0.0003 and 0.0006 ppm in each of the two plants. The TDI levels were about twice the levels of MDI. However, MDI levels may have been much higher, as it has been demonstrated that MDI exists as an aerosol, not a vapor (Dharmarajan and Weill, 1978). No adverse effects on pulmonary function, measured according to applicable criteria of the American Thoracic Society (ATS), were detected during the course of the study as measured by FEV1. Reanalysis of the data (Musk et al., 1985) confirmed the results and conclusions.

Pham et al. (1988) prospectively studied a group of workers from two polyurethane manufacturing facilities in 1976 and 1981. Exposure levels were not well characterized and criteria for pulmonary function testing were not cited. Attrition of females was high as 64% were lost to follow-up in 1981. Exposure categories were classified as: A--unexposed in both studies, B--indirectly exposed, C--directly exposed, and D-- exposed in 1976 but removed from contact with MDI in 1981. Although the number of workers with asthma or chronic bronchitis increased in all groups and functional impairment was observed in vital capacity and FEV1 in group C, the lack of exposure characterization, attrition, and inclusion of asthmatics preclude any conclusions with respect to MDI.

The potential of PMDI to cause developmental effects was examined in two inhalation studies. Buschmann et al. (1996) reported a possible developmental effect when gravid Wistar rats were exposed to 1, 3, or 9 mg monomeric MDI/cu.m for 6 h/day from days 6-15 post conception, after which surviving animals were necropsied on day 20. A significant increase in asymmetric sternebrae in fetuses from the high-exposure group was observed and regarded as a possible developmental effect. A quasi-monodisperse MDI aerosol was generated by a evaporation-condensation technique. The particles had a MMAD of 1.1 æm and a geometric standard deviation of 1.37. Polymerization was precluded by exposing MDI droplets to temperatures above 50øC to a period of 1.5 sec only during droplet evaporation. Prenatal toxicity was also evaluated in pregnant Wistar rats exposed to respirable PMDI from days 6-15 of gestation (Gamer et al., 1994). Rats (25/exposure level) were exposed to 1, 4, and 12 mg PMDI/cu.m with a MMAD below 2.8 um. Two treatment-related deaths occurred in the high-exposure group and some survivors in this group exhibited respiratory symptoms. No treatment- related effects on gestational or fetal parameters occurred in the two lowest exposure groups. However, the increase in maternal lung weights in these groups warrants concern about developmental effects postnatally.

While the Gamer et al. (1994) study suggests that the potential of PMDI to cause prenatal toxicity in this strain is low, studies in other laboratory animal species and a multigenerational study would be needed to ascertain the potential to cause functional deficits or altered development in the postnatal period. PMDI/MDI may have potential to reach extrarespiratory sites such as the testes and ovaries. Measurable radioactivity was found to reach extrathoracic tissues and body fluids of guinea pigs exposed for 1 h to radiolabeled TDI levels as low as 4 ppb (Kennedy et al., 1989).

***For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF)***.

### I.B.5. Confidence in the Inhalation RfC

Study — High
Database — Medium
RfC — Medium

Confidence in the principal study is high because the study was well designed, performed in an adequate number of animals, and indicated a concentration-response relationship for the critical effect. Confidence in the database is medium because of data limitations regarding (1) developmental effects in the postnatal period and reproductive parameters in laboratory animals, (2) incomplete characterization of active agent(s) in test atmospheres, and (3) exposure-response data for PMDI/MDI-induced asthma. Although studies with TDI have not shown any reproductive or developmental effects (Tyl, 1988; Tyl and Neeper-Bradley, 1989), the potential for PMDI/MDI to cause such effects has not been established. The RfC is given a medium confidence rating because (1) confidence in the database takes precedence and (2) may not be sufficiently protective against isocyanate-induced asthma in individuals already sensitized to isocyanates.

***For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF)***.

### I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document: Toxicological Review of Methylene diphenyl diisocyanate in Support of Summary Information on Integrated Risk Information System (IRIS). (US EPA 1998)

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to the Toxicological Review of Methylene Diphenyl

Diisocyanate (MDI) US EPA 1998. ***To review this appendix, exit to the toxicological review, Appendix B, Summary of and Response to External Peer Review Comments (PDF)***.

Other EPA Documentation None

Agency Consensus Date — 10/20/1997

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Methylene Diphenyl Diisocyanate (monomeric MDI) and polymeric MDI (PMDI) conducted in November 2001 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

### I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (Internet address).

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## II. Carcinogenicity Assessment for Lifetime Exposure

Methylene Diphenyl Diisocyanate (Monomeric MDI) and Polymeric MDI (PMDI)
CASRN —101-68-8, 9016-87-9
Last Revised: 02/07/1998

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimated in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in the Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where

indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

## II.A. Evidence for Human Carcinogenicity

### II.A.1. Weight-of-Evidence Characterization

Under U.S. EPA's 1986 Guidelines for Carcinogen Risk Assessment, monomeric MDI or polymeric MDI (PMDI) would be classified as not classifiable or a Group D chemical. Under U.S. EPA's 1996 Proposed Guidelines for Carcinogen Risk Assessment, the carcinogenic potential of MDI/PMDI would be characterized as "cannot be determined, but for which there is suggestive evidence that raises concern for carcinogenic effects" on the following basis. The increased incidence of pulmonary adenomas in male (6/60) and female (2/59) Wistar rats (strain Cpu:WU) and one pulmonary adenocarcinoma in a male rat, all exposed to the highest concentration in a lifetime chronic inhalation study involving PMDI, suggest that PMDI has tumorigenic potential. However, the finding of one pulmonary adenocarcinoma in a chronic study is not clear evidence of carcinogenic potential. However, the tumorigenic results, coupled with evidence that methylene diphenyl aniline (MDA), a known animal carcinogen and the principal reaction product of MDI, is found in blood of MDI-exposed rats and nonhydrolyzed urine of PMDI/MDI-exposed humans increases concern about the carcinogenic potential of PMDI/MDI. The available human evidence is inadequate to describe the carcinogenic potential of PMDI/MDI.

***For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).***

***For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).***

### II.A.2. Human Carcinogenicity Data

Inadequate. Two retrospective cohort mortality/cancer incidence studies were conducted to investigate associations between increased cancer risk and exposure to chemicals in polyurethane foam production workers (Sorahan and Pope, 1993; Hagmar et al., 1993a,b). Both populations were exposed to toluene diisocyanate (TDI), MDI, and other chemicals. No increased cancer risks attributed to isocyanate exposure were observed. Exposure to isocyanates was not well characterized and the study cohorts were exposed to a variety of other chemicals. The average duration of employment in the Hagmar et al. (1993a) study was 6.5 years with an average follow-up of 10.6 years. In the Sorahan and Pope (1993) study, the

minimum length of follow-up was 9 years. The young age of the cohorts and the short follow-up time limit a full evaluation of the carcinogenic potential of this exposure environment.

### II.A.3. Animal Carcinogenicity Data

Limited. Four groups of 60 Wistar rats (strain Cpb:WU) of each sex were exposed whole-body by inhalation to nominal levels of 0, 0.2, 1.0, or 6.0 mg/cu.m of PMDI aerosol for 6 h/day, 5 days/week for 24 mo (Reuzel et al., 1990, 1994a). [Note: PMDI refers to a mixture containing about 50% monomeric MDI and 50% trimeric species and higher molecular weight oligomers (Ulrich, 1983); this composition, which is very similar to that used in the workplace, renders the material semisolid and suitable for aerosol generation]. The selection of 6 mg/cu.m as the high dose was based on a steep dose-response curve identified in a 13-week study (Reuzel et al., 1994b). In the latter study, severe respiratory effects, including mortality, was observed at 12.3 mg/cu.m whereas similar, but much less severe, clinical effects were seen at the next lowest dose, 8.4 mg/cu.m. These observations, coupled with significant increases in absolute and relative lung weights in the chronic study, are consistent with 6.0 mg/cu.m in the chronic study as approaching a maximum tolerated dose.

Mean actual values were within ñ 10% of nominal values. The MDI test material was a dark brown viscous material, of which 47% was monomeric MDI. The remaining 53% was described as polymeric MDI. The material was stored under "common laboratory conditions," which is interpreted to mean under an inert gas to prevent reaction with water. The mass mean aerodynamic diameter (MMAD) and geometric standard deviation or sigma g (in parenthesis) corresponding to the exposure levels were 0, 0.68 um (2.93), 0.70 um (2.46), and 0.74 um (2.31), respectively. Forty-three different organs or tissues and all grossly visible lesions were examined by light microscopy of control and all high-concentration animals and of decedents of the other concentration groups. Survivors of the low- and mid- concentration groups were subjected to histopathological examination of the nose, lungs, mediastinal lymph nodes, and all gross lesions. Although olfactory epithelial degeneration was elevated significantly in both sexes at 6 mg/cu.m and concentration-related increase basal cell hyperplasia was evident in males, there were no compound-related nasal tumors. Pulmonary adenomas were observed in males (6/60) and females (2/59) exposed to 6 mg/cu.m compared with controls (0/120). Also, one pulmonary adenocarcinoma (approximately 10 mm in size) was observed in one male exposed to 6 mg/cu.m. The adenomas were only a few millimeters in size and were located adjacent to areas in which hemorrhage, macrophage accumulations, and fibroblastic reactions were observed. These data suggest that recurrent tissue injury may be requisite for the induction of tumors.

A chronic toxicity/carcinogenicity study also has been conducted in female Wistar rats, strain Crl:[WI]BR (Hoymann et al. 1995). In this unpublished study, rats were exposed to mean

concentrations of monomeric MDI in aerosol form of 0.23, 0.70, and 2.05 mg/cu.m. The MMAD was determined to be about 1 um in each of the three exposed groups. The selection of exposure levels was based on results of a previous 90-day study. The highest concentration can be considered a maximum tolerated dose inasmuch as the body weight gain for this group after 17 months of exposure was 11% less than that of controls. Proliferation of the alveolar epithelium, considered preneoplastic, was observed along with bronchiolar- alveolar adenomas in the high-concentration group. Neither MDI- nor MDA-DNA adducts were found in the lungs; however, the high dilution inherent in the techniques used may have been responsible for this "negative" finding.

Under the conditions of the Hoymann et al. (1995) study, in which about 85% of the material inhaled by the animals in the high-concentration group was monomeric MDI, there was no evidence of a tumorigenic response in the lungs. Only one bronchioalveolar adenoma was found in 1/80 rats in the high-concentration group. The low incidence in females from the Reuzel et al. (1994) study and the lack of a response in females from the Hoymann et al. (1995) study may indicate that the female Wistar rat is not the most appropriate test species for determination of the carcinogenic potential of PMDI or monomeric MDI. The difference in monomeric MDI content of inhaled material between the two studies also represents a confounding factor.

### II.A.4. Supporting Data for Carcinogenicity

Pulmonary adenomas have also been observed in mice, but not rats, exposed to TDI. Loeser (1983) exposed groups of Sprague-Dawley rats and CD-1 mice to 0, 0.05, or 0.15 ppm TDI (80:20 mixture of the 2,4 and 2,6 isomers, respectively) for 6 h/day, 5 days/week, for 2 years. No treatment-related tumors were observed in rats. Although there was no difference in survival or body weight changes between controls and exposed animals, rhinitis suggests that the maximum tolerated dose was approached. Although there was no dose-response trend, multiple pulmonary adenomas were elevated in male mice at 0.05 ppm (9/90, p=0.01, Fishers exact test; controls 1/90) and at 0.15 ppm ( 6/90, p=0.06, Fishers exact test). The incidence of pulmonary carcinomas in male exposed mice was less than that of controls. Lymphomas of the haematopoietic/lymphoreticular system was also elevated in male, but not female, mice. The incidence in the 0.05 ppm group was 12/90 compared with 2/90 in controls and in the 0.15 ppm group, 5/90. The investigators did not consider the lymphomas to be treatment- related. Although there was a variety of noncarcinogenic nasal lesions in both sexes upon histopathology, no nasal tumors were observed. Mortality in mice at study termination was high in both sexes, but no treatment- related effects in this regard were discerned.

MDI yielded mixed results in genotoxicity tests. Technical-grade monomeric MDI was positive in the Salmonella reverse mutation plate- incorporation assay in strains TA98 and

TA100 only in the presence of exogenous metabolic activation and negative in strain TA1537 (Anderson et al, 1980). A prepolymer [liquified, branched-chain MDI material formed by reaction of MDI with small amounts of glycols] of MDI tested similarly although activity was much less than with the technical-grade material. Using a plate-incorporation assay, Haskell Laboratories (1976) also found monomeric MDI in the presence of metabolic activation to test positive with strains TA98 and TA100, but not TA1535 or TA1537. However, Zeiger et al. (1987) found MDI to test negative both with and without exogenous at concentrations up to 10,000 ug per plate in strains TA98, TA100, TA1535, and TA1537. All test substances in the above-mentioned studies had been dissolved in dimethylsulfoxide (DMSO), a solvent in which MDI (and TDI) are unstable and may lead to genotoxic degradation products (Gahlmann et al., 1993). Hengler and Slesinski (1982) also reported negative results for a "prepolymer" of MDI in these four strains in a plate-incorporation assay; however, concentrations appear to have been considerable lower than those in the other studies. Positive controls tested appropriately for all strains.

A commercial grade of MDI (45% by weight MDI) without exogenous activation was found to induce chromosome aberrations in human whole-blood lymphocyte cultures after 24-hr treatment; addition of exogenous metabolic activation significantly increases aberration frequency only at the highest concentration tested (Maki-Paakenen and Norpa, 1987).

## II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

No data available.

## II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

No data available.

### II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

The mechanism by which PMDI/MDI causes benign pulmonary tumors in Wistar rats (principally in males), a strain in which such tumors are rare, chronically exposed to 6 mg/cu.m for 2 years is unknown. MDA may be a causative agent. This reaction product has been detected after acid hydrolysis in blood and amniotic fluid of pregnant rats exposed to MDI (Bartsch et al., 1996) and in blood and nonhydrolyzed urine of PMDI-exposed workers (Sepai et al., 1995). It has been shown to result in pulmonary adenomas (and tumors at remote sites) when MDA was administered to female mice in drinking water (Lamb et al., 1986). In

addition, the pulmonary adenomas associated with TDI exposure (Loeser, 1983), an isocyanate of similar reactivity, occurred in mice, but not rats. In the absence of toxicity/carcinogenicity studies of mice exposed to PMDI/MDI, it is unclear if mice are simply more sensitive than rats to the effects of such compounds. If so, the carcinogenic potential of polymeric MDI as reflected by the results of the studies in rats may be underestimated. On the other hand, Reuzel and coworkers, as well as Hoymann et al. (1995), suggest that these adenomas (and preneoplastic lesions observed by Hoymann et al.) may be the result of recurrent tissue damage since effects were seen in high- dose animals. This hypothesis finds support in the observation by Reuzel and coworkers that the adenomas are adjacent to areas of tissue damage.

### II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

From a qualitative perspective, the animal evidence for PMDI and MDA raises concern that PMDI/MDI may have tumorigenic/carcinogenic potential in human exposure scenarios. The inconclusive results associating lung cancer in occupational populations with exposure to TDI/MDI does not diminish this concern. The limitations of the human studies, particularly the purportedly low levels of exposure and the short duration of exposure of the cohorts, preclude a more definitive assessment.

The two lifetime inhalation studies in which an appropriate number of rats were exposed to respirable PMDI and monomeric MDI yielded results that were similar in nature. Thus, confidence is high that the pulmonary effects observed were treatment-related. However, uncertainties surrounding mechanism and dose preclude extrapolation to humans inasmuch as the agent (PMDI, monomeric MDI, or MDA) responsible for the tumorigenic response in the principal study is unknown.

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## II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

### II.D.1. EPA Documentation

Source Document — Toxicological Review of Diphenylmethane Diisocyanate in Support of Summary Information on Integrated Risk Information System (IRIS) (US EPA 1998).

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to Toxicological Review of Methylene Diphenyl Diisocyanate (MDI) in support of summary information on Integrated Risk Information

System (IRIS). ***To review this appendix, exit to the toxicological review, Appendix B, Summary of and Response to External Peer Review Comments (PDF)***.

### II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date — 10/20/1997

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Methylene Diphenyl Diisocyanate (monomeric MDI) and polymeric MDI (PMDI) conducted in November 2001 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

### II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (Internet address).

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## III. [reserved]
## IV. [reserved]
## V. [reserved]

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## VI. Bibliography

Methylene Diphenyl Diisocyanate (monomeric MDI) and polymeric MDI (PMDI); CASRN 101-68-8, 9016-87-9

### VI.A. Oral RfD References

Not applicable.

## VI.B. Inhalation RfC References

Baur, X., M. Dewair, and H. Rommelt. 1984. Acute airway obstruction followed by hypersensitivity pneumonitis in an isocyanate (MDI) worker. J. Occup. Med. 26(4): 285-287.

Brooks, S.M. 1982. The evaluation of occupational airways disease in the laboratory and workplace. J. Allergy Clin. Immunol. 70: 56-66.

Buschmann, J., W. Koch, R. Fuhst, and U. Heinrich. 1996. Embryotoxicity study of monomeric 4,4'-Methylenediphenyl Diisocyanate (MDI) aerosol after inhalation exposure in Wistar rats. Fund. Appl. Toxicol. 32: 96-101

Cartier, A., L. Gammer, J.-L. Malo, F. Lagier, H. Ghezzo, K. Harris, and R. Patterson. 1989. Specific serum antibodies against isocyanates: Association with occupational asthma. J. Allergy Clin. Immunol. 84: 507-514.

Clement International. 1990. THC: A computer program to compute a reference dose from quantal animal toxicity data using the benchmark dose method. K.S. Crump Division, Ruston, LA.

Dharmarajan, V. and H. Weill. 1978. Physical state of airborne p,p'- diphenylmethane diisocyanate (MDI) and its measurement. Am. Ind. Hyg. Assoc. J. 39: 737-744.

Gamer, A.O., J. Hellwig, K. Kuttler, and B. Hildebrand. 1994. Prenatal toxicity of polymeric MDI in rats: aerosol inhalation. BASF Aktiengesellschaft, Ludwigshafen/Rhein, FRG. Project No. 31R0354/92046.

Hoymann, H.-G., J. Buschmann, and U. Heinrich. 1995. Examinations about the chronic toxicity/carcinogenicity of 4,4'-methylene diphenyl diisocyanate (MDI). Fraunhofer-Institut fur Toxikologie and Aerosolforschung, Hannover, Germany. Report No. 116-06-084 (in German).

Kennedy, A. L., M. F. Stock, Y. Alarie, and W.R. Brown. 1989. Uptake and distribution of 14C during and following inhalation exposure to radioactive toluene diisocyanate. Toxicol. Appl. Pharmacol. 100: 280-292.

Konzen, R. B., B.F. Craft, L.D. Scheel, and C.H. Gorski. 1966. Human response to low concentrations of p,p'-diphenylmethane diisocyanate (MDI). Am. Ind. Hyg. Assoc. J. 27(2): 121-127.

Liss, G.M., D.I. Bernstein, D.R. Moller, J.S. Gallagher, R.L. Stephenson, and I.L. Bernstein. 1988. Pulmonary and immunologic evaluation of foundry workers exposed to methylene diphenyldiisocyanate (MDI). J. Allergy Clin. Immunol. 82(1): 55-61.

Lob, M. and M.-A. Boillat. 1981. Asthme retarde au diphenylmethane diisocyanate (MDI). Schweiz. Med. Wschr. 111: 150-154.

Malo, J.-L. and C.R. Zeiss. 1982. Occupational hypersensitivity pneumonitis after exposure to diphenylmethane diisocyanate. Am. Rev. Respir. Dis. 125: 113-116.

Mapp, C.E., L. Dal Vecchio, P. Boschetto, and L.M. Fabbri. 1985. Combined asthma and alveolitis due to diphenylmethane diisocyanate (MDI) with demonstration of no crossed respiratory reactivity to toluene diisocyanate (TDI). Ann. Allergy 54: 424-429.

Mapp, C.E., P. Boschetto, L. Dal Vecchio, P. Maestrelli, and L.M. Fabbri. 1988. Occupational asthma due to isocyanates. Eur. Resp. J. 1: 273-279.

Musk, A.W., J.M. Peters, L. DiBerardinis, and R.L.H. Murphy. 1982. Absence of respiratory effects in subjects exposed to low concentrations of TDI and MDI. J. Occup. Med. 24(10): 746-750.

Musk, A.W., J.M. Peters, and L. Bernstein. 1985. Absence of respiratory effects in subjects exposed to low concentrations of TDI and MDI: A reevaluation. J. Occup. Med. 27(12): 917-920.

O'Brien, I.M., A.J. Newman-Taylor, P.S. Burge, M.G. Harries, I.W. Fawcett, and J. Pepys. 1979. Toluene diisocyanate-induced asthma: II. Inhalation challenge tests and bronchial reactivity studies. Clin. Allergy 9: 7-15.

Pezzini, A., A. Riviera, P. Paggiaro, A. Spiazzi, F. Gerosa, M. Filieri, G. Toma, and G. Trident. 1984. Specific IgE antibodies in twenty-eight workers with diisocyanate-induced bronchial asthma. Clin. Allergy 14: 453-461.

Pham, Q.T., D. Teculescu, C. Meyer-Bisch, and J.M. Mur. 1988. Effects of chronic exposure to diisocyanates. Bull. Eur. Physiopathol. Respir. 23: 561-564.

Reuzel, P.G.J., J.H.E. Arts, M.H.M. Kuypers, and C.F. Kuper. 1990. Chronic toxicity/carcinogenicity inhalation study of polymeric methylene diphenyl diisocyanate aerosol in rats. Prepared by the Civo Institute for the International Isocyanate Institute. Report No. V 88.122, 1990.

Reuzel, P.G.J., M.S. Bosland, L.M. Appelman, A.W.J. de Jong, and J.P. Bruyntjes. 1985a. Sub-chronic (13 week) inhalation toxicity study of polymeric MDI aerosol in rats (part B1) (Final Report). Prepared by Civo Institute for the International Isocyanate Institute. January 1985. Report No. V83.290/220758.

Reuzel, P.G.J., C.F. Kuper, L.M. Appelman, and R.N. Hooftman. 1985b. Sub-chronic (13 week) inhalation toxicity study of polymeric MDI aerosol in rats (part B2) (Final report). Prepared by the Civo Institute for the International Isocyanate Institute. January 1985. Report No. V85.023/240158.

Reuzel, P.G.J., J.H.E. Arts, L.G. Lomax, et al. 1994b. Chronic inhalation and carcinogenicity study of respirable polymeric methylene diphenyl diisocyanate (polymeric MDI) aerosol in rats. Fundam. Appl. Toxicol. 22: 195-210.

Reuzel, P.G.J., C.F. Kuper, V.J. Feron, L.M. Appelman, and E. Loser. 1994a. Acute, subacute, and subchronic inhalation toxicity studies of respirable polymeric methylene diphenyl diisocyanate (polymeric MDI) aerosol in rats. Fundam. Appl. Toxicol. 22: 186-194.

Tanser, A.R., M.P. Bourke, and A.G. Blandford. 1973. Isocyanate asthma: respiratory symptoms caused by diphenyl-methane di-isocyanate. Thorax 28: 596-600.

Tse, K.S., A. Johnson, H. Chan, and M. Chan-Yeung. 1985. A study of serum antibody activity in workers with occupational exposure to diphenyl methane diisocyanate. Allergy 40: 314-320.

Tyl, R.W. 1988. Developmental toxicity study of inhaled toluene diisocyanate vapor in CD (Sprague-Dawley) rats. Union Carbide, Bushy Run Research Center. Revised Project Report 50-592.

Tyl, R.W., and T.L. Neeper-Bradley. 1989. Two-generation reproduction study of inhaled toluene diisocyanate in CD (Sprague-Dawley) rats. Union Carbide, Bushy Run Research Center. Project Number 86-33-90704.

Ulrich, H. 1983. Urethane polymers. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., Vol 23. pp. 576-608.

U.S. EPA. 1994. Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity: Notice of Availability, dated October 26, 1994. Fed. Reg. 59 (206):53799.

U.S. EPA. 1994a. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry, EPA/600/8-90/066F, dated October 1994.

U.S. EPA. 1998. Toxicological Review of Methylene Diphenyl Diisocyanate. For Internet access see www.epa.gov/iris, or contact the IRIS Hotline at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (Internet address).

Vandenplas, O., J.-L. Malo, M. Saetta, C.E. Mapp, and L.M. Fabbri. 1993 Occupational asthma and extrinsic alveolitis due to isocyanates: current status and perspectives. Br. J. Ind. Med. 50: 213-228.

Zammit-Tabona, M., M. Sherkin, K. Kijek, H. Chan, and M. Chan-Yeung. 1983. Asthma caused by diphenylmethane diisocyanate in foundry workers. Am. Rev. Respir. Dis. 128: 226-230.

Zeiss, C.R., T.M. Kannellakes, J.D. Bellone, D. Levitz, J.J. Pruzansky, and R. Patterson. 1980. Immunoglobulin E-mediated asthma and hypersensitivity pneumonitis with precipitating anti-hapten antibodies due to diphenylmethane diisocyanate (MDI) exposure. J. Allergy Clin. Immunol. 65(5): 346-352.

## VI.C. Carcinogenicity Assessment References

Andersen, M., M.-L. Binderup, P. Kiel, H. Larsen and J. Maxild. 1980. Mutagenic action of isocyanates used in the production of polyurethanes. Scand. J. Work environ. Health 6: 221-226.

Gahlmann, R., B. Herbold, A. Ruckes and K. Seel. Untersuchungen zur Stabilitat aromatischer Diisocyanate in dimethylsulfoxid (DMSO): Toluylendiisocynat (TDI) und Diphenylmethandiisocyanat (MDI) im Ames-Test. Zbl. Arbeitsmed. 43: 34-38.

Hagmar, L., H. Welinder, and Z. Mikoczy. 1993a. Cancer incidence and mortality in the Swedish polyurethane foam manufacturing industry. Br. J. Ind. Med. 50: 537-543.

Hagmar, L., U. Stromberg, H. Welinder, and Z. Mikoczy. 1993b. Incidence of cancer and exposure to toluene diisocyanate and methylene diphenyldiisocyanate; a cohort based case-referent study in the polyurethane foam manufacturing industry. Br. J. Ind. Med. 50: 1003-1007.

Hengler, W.C. and R.S. Slesinski. 1982. Diphenylmethane diisocyanate prepolymer. Salmonella/microsome (Ames) bacterial mutagenicity assay. Bushy Run Research Center, Union Carbide. Project Report 45-65.

Haskell Laboratory. 1976. In vitro microbial mutagenicity studies of isocyanic acid, methylenedi-para-phenylene ester. E.I. du Pont de Nemours and Company. Haskell Laboratory Report No. 463-76.

Hoymann, H.-G., J. Buschmann, and U. Heinrich. 1995. Examinations about the chronic toxicity/carcinogenicity of 4,4'-methylene diphenyl diisocyanate (MDI). Fraunhofer-Institut fur Toxikologie and Aerosolforshung, Hannover, Germany. Report No. 116-06-084.

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.

Maki-Paakkenen, J. and H. Norppa. 1987. Chromosome aberrations and sister- chromatid exchanges induced by technical grade toluene diisocyanate and methylene diphenyl diisocyanate in cultured human lymphocytes. Toxicol. Lett. 36: 37-43.

Marczynski, B., A.B. Czuppon, H.P. Hoffarth, W. Marek and X. Baur. 1992. DNA damage in human white blood cells after inhalation exposure to methylene diphenyl diisocyanate (MDI) - case report. Toxicol. Lett. 60: 131-138.

Reuzel, P.G.J., J.H.E. Arts, L.G. Lomax, M.H.M. Kuijpers, C.F. Kuper, C. Gembardt, V.J. Feron and E. Loser. 1994a. Chronic inhalation and carcinogenicity study of respirable polymeric methylene diphenyl diisocyanate (polymeric MDI) aerosol in rats. Fundam. Appl. Toxicol. 22: 195-210.

Reuzel, P.G.J., C.F. Kuper, V.J. Feron, L.M. Appelman, and E. Loser. 1994b. Acute, subacute, and subchronic inhalation toxicity studies of respirable polymeric methylene diphenyl diisocyanate (polymeric MDI) aerosol in rats. Fundam. Appl. Toxicol. 22: 186-194.

Reuzel, P.G.J., J.H.E. Arts, M.H.M. Kuypers, and C.F. Kuper. 1990. Chronic toxicity/carcinogenicity inhalation study of polymeric methylene diphenyl diisocyanate aerosol in rats. Prepared by the Civo Institute for the International Isocyanate Institute. Report No. V 88.122, 1990.

Sepai, O., D. Henschler and G. Sabbioni. 1995. Albumin adducts, hemoglobin adducts and urinary metabolites in workers exposed to 4,4'-methylenediphenyl diisocyanate. Carcinogenesis 16(10): 2583-2587.

Sorahan, T. and D. Pope. 1993. Mortality and cancer morbidity of production workers in the United Kingdom flexible polyurethane foam industry. Br. J. Ind. Med. 50: 528-536.

Ulrich, H. 1983. Urethane Polymers. Kirk-Othmer encyclopedia of chemical technology, 3rd Ed., Vol. 23. pp. 576-608.

U.S. Environmental Protection Agency. 1996. Proposed guidelines for carcinogen risk assessment. Federal Register 61(79): 17960-18011.

U.S. Environmental Protection Agency. 1986. Risk assessment guidelines of 1986. Office of Health and Environmental Assessment, Washington, DC. EPA/600/8-87/045.

## VII. Revision History

Methylene Diphenyl (monomeric MDI) and polymeric MDI (PMDI)
CASRN — 101-68-8, 9016-87-9

| Date | Section | Description |
|---|---|---|
| **05/01/1994** | I.B. | Inhalation RfC now on-line |
| **02/07/1998** | I.B., II., VI. | Revised RfC, new carcinogenicity assessment |
| **12/03/2002** | I.B.6., II.D.2. | Screening-Level Literature Review Findings message has been added. |

## VIII. Synonyms

Methylene Diphenyl Diisocyanate (monomeric MDI) and polymeric MDI (PMDI)
CASRN — 101-68-8, 9016-87-9
Last Revised —02/07/1998

- 101-68-8
- 1,1' - METHYLENEBIS (4-ISOCYANATOBENZENE)
- 4,4' - DIISOCIANATO DE DIFENILMETANO (SPANISH)
- 4,4' - DIISOCYANATE DE DIPHENYLMETHANE (FRENCH)
- 4,4' - DIISOCYANATHODIPHENYLMETHANE
- 4,4' - DIPHENYLMETHANE DILSOCYANATE
- 4,4' - METHYLENEBIS (PHENYL ISOCYANATE)
- 4,4' - METHYLENEDIPHENYL DIISOCYANATE
- 4,4' - METHYLENEDIPHENYLENE ISOCYANATE
- 4,4' - METHYLENEDI - P- PHENYLENE DIISOCYANATE
- BENZENE, 1,1' -METHYLENEBIS(4-ISOCYANATO-
- BIS (1,4-ISOCYANATHOPHENYL) METHANE
- BIS (4-ISOCYANATOPHENYL) METHANE
- BIS (P-ISOCYANATOPHENYL) METHANE
- CARADATE 30
- DESMODUR 44
- DI-(4-ISOCYANATOPHENYL) METHANE
- DIFENIL-METHAN-DIISOCIANATO (ITALIAN)
- DIFENYLMETHAAN-DISSOCYANAAT (DUTCH)
- DIISOCYANATE DE DIOPHENYLMETHANE-4,4' (FRENCH)
- DIPHENYLMETHAN-4,4' -DIISOCYANAT (GERMAN)
- DIPHENYLMETHANE 4,4' -DIISOCYANATE
- DIPHENYLMETHANE-4,4' -DIISOCYANATE
- DIPHENYL METHANE DIISOCYANATE
- DIPHENYLMETHANE DIISOCYANATE
- HSDB 2630
- HYLENE M50
- ISOCYANIC ACID
- ISONATE 125M
- ISONATE 125 MF
- MDI
- METHYLENEBIS (4-ISOCYANATOBENENE)
- METHYLENEBIS (4-PHENYLENE ISOCYANATE)
- METHYLENEBIS (4-PHENYL ISOCYANATE)
- METHYLENEBIS (4-PHENYLISOCYANATE)
- METHYLENEBIS (P-PHENYLENE ISOCYANATE)
- METHYLENEBIS (P-PHENYL ISOCYANATE)
- METHYLENE DI (PHENYLENE ISOCYANATE)
- METHYLENEDI-P-PHENYLENE DIISOCYANATE
- METHYLENEDI-P-PHENYLENE ESTER
- METHYLENEDI-P-PHENYLENE ISOCYANATE
- NACCONATE 300
- NCI-C50668
- NSC 9596
- P,P' -DIPOHENYLMETHANE DIISOCYANATE

- P,P' -METHYLENEBIS (PHENYL ISOCYANATE)
- UN 2489