

## 1,6-Hexamethylene diisocyanate; CASRN 822-06-0

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 1,6-Hexamethylene diisocyanate

**File First On-Line 09/01/1994**

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	yes	09/01/1994
Carcinogenicity Assessment (II.)	not evaluated	

### I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — 1,6-Hexamethylene diisocyanate  
CASRN — 822-06-0

Not available at this time.

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

Substance Name — 1,6-Hexamethylene diisocyanate  
CASRN — 822-06-0  
Last Revised — 09/01/1994

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrathoracic effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

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

Critical Effect	Exposures*	UF	MF	RfC
<b>Degeneration of olfactory epithelium</b>	NOAEL: 0.005 ppm (0.035 mg/cu.m)	100	1	1E-5 mg/cu.m
<b>Rat Chronic Inhalation Study</b>	NOAEL(ADJ): 0.006 mg/cu.m NOAEL(HEC): 0.001 mg/cu.m			
<b>Mobay, Inc., 1989</b>	LOAEL: 0.025 ppm (0.175 mg/cu.m) LOAEL(ADJ): 0.03 mg/cu.m LOAEL(HEC): 0.005 mg/cu.m			

\*Conversion Factors and Assumptions — MW = 168.2. At 23 C and assuming 760 mmHg, NOAEL (mg/cu.m) = 0.005 ppm x 168.2/24.3 = 0.035 mg/cu.m. NOAEL(ADJ) = 0.035 x 6 hours/24 hours x 5 days/7 days = 0.006 mg/cu.m. The NOAEL(HEC) was calculated for a gas:respiratory effect in the extrathoracic region. MVa = 0.24 cu.m/day, MVh = 20 cu.m/day, Sa

= 11.6 sq.cm, Sh = 177 sq.cm. RGDR = (MVa/Sa)/(MVh/Sh) = 0.183. NOAEL(HEC) = NOAEL(ADJ) x RGDR = 0.001 mg/cu.m.

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

Mobay, Inc. 1989. Chronic inhalation toxicity and oncogenicity study with 1,6-hexamethylene diisocyanate (HDI) in rats (Final Report) with attached appendices and cover letter dated 12/20/1989. TSCATS/405187. EPA/OTS Doc. No. 86-900000055.

Fischer 344 rats (60/sex/group) were exposed to analytical concentrations of 0, 0.005, 0.025, or 0.164 ppm (0, 0.035, 0.17, or 1.14 mg/cu.m) HDI for 6 hours/day, 5 days/week for 2 years. The duration-adjusted values are 0, 0.006, 0.03, or 0.2 mg/cu.m, respectively. Satellite groups of rats (10/sex/group) were exposed similarly for 1 year. Those in the high-exposure group were exposed to a mean analytical concentration of 0.126 ppm for the first 127 days, then was increased to a mean analytical concentration of 0.172 ppm because of a lack of overt signs of toxicity at the lower concentration. The overall mean analytical concentration was 0.164 ppm. Rats were monitored for clinical signs of toxicity, mortality, body weight/organ weight change, ophthalmology, hematology, clinical chemistry, urinalysis parameters, and gross and microscopic lesions. The study met U.S. EPA TSCA guidelines for toxicity and oncogenicity studies (Stern, 1990). Histopathology included examination of the lungs and seven levels of the nasal cavity.

There were no significant differences in mortality between treated and control groups. A statistically significant decrease in the body weights of high-exposure females was observed in the second year, but was low in magnitude (5%). Clinical observations included exposure-related eye irritation in high-exposure males (during the first year only). There were no compound-related lesions of the eye detected by ophthalmologic examination. Increased incidence of purile penis discharge and preputial gland mass at the high concentration was not correlated with any gross or histopathological lesions and was not considered exposure related. Hematological findings included increased numbers of reticulocytes in high-exposure males and females at several intervals, which may indicate borderline anemia. There were few statistically significant differences in RBC count, HCT, and Hgb between exposed and control animals. There were no biologically significant differences between exposed and control groups in clinical chemistry or urinalysis parameters.

Observations of the lungs of main-group animals included minimal-to-mild, focal-to-multifocal lesions characterized as epithelialization, interstitial pneumonia, and histiocyte accumulation. These effects were seen in the two highest exposure groups. There was no clear indication of a concentration- response relationship. Lung lesions were not observed in the satellite groups after 1 year of exposure. A NOAEL for lung effects of 0.005 ppm is identified. The NOAEL(HEC) is 0.01 mg/cu.m. The LOAEL is 0.025 ppm. The LOAEL(HEC) is 0.44 mg/cu.m.

Compound-related histopathological changes were limited to the respiratory tract, principally the nasal cavity. Lesions judged to be evidence of severe toxicity noted in high-exposure animals included degeneration of the olfactory epithelium, hyperkeratosis, occasional atrophy, and focal erosion or ulceration (olfactory epithelium). These lesions were not seen in the low-exposure group or in controls. Erosion was observed in several regions (i.e., vestibule, prepapilla, posterior incisor, and first palatal ridge). Erosion was increased in incidence, but not severity, at levels 2-6. Degeneration of the olfactory epithelium in animals of the high-concentration group occurred at the first molar and first palatal ridge section levels. Degeneration of the olfactory epithelium increased in both severity and incidence with increasing concentration at the level of the first palatal ridge. The occurrence of this lesion in the mid-exposure group (males and females) at an elevated incidence and severity relative to that at the lowest concentration group was judged a LOAEL. Erosion at the level of the first palatal ridge occurred only at the high concentration. Other nasal lesions occurred at increased incidence compared with controls in both the low- and mid-exposure groups, but the severity was either lower or unchanged. These lesions include hyperplasia/metaplasia, mucus hyperplasia, and inflammation. The incidence of hyperplasia/metaplasia in some regions (e.g., posterior incisor) was reduced in the high-exposure group, perhaps being masked by erosion and hyperkeratosis. Although hyaline droplet degeneration was an observation in several regions of the nasal tract and occurred at increased incidence in the low-exposure group compared with controls, its toxicological significance is unclear because it is a common physiologic finding in rats and may relate to mucus hyperplasia (Monticello et al., 1990). Lesions similar to those in the main group were also observed in satellite animals at 1 year, but were not as extensive nor severe and occurred primarily in animals in the two highest exposure groups. Thus, the NOAEL for nasal effects is 0.005 ppm. The NOAEL(HEC) is 0.001 mg/cu.m. The LOAEL for nasal effects is 0.025 ppm. The LOAEL(HEC) is 0.005 mg/cu.m.

Fischer 344 rats (20/sex/group) were exposed to analytical concentrations of 0, 0.01, 0.04, or 0.14 ppm (0, 0.07, 0.28, or 1 mg/cu.m) HDI vapor (average temperature, 22 degrees C) for 6 hours/day, 5 days/week for 13 weeks (Mobay, Inc., 1988). The duration-adjusted values are 0, 0.01, 0.05, or 0.18 mg/cu.m, respectively. Parameters monitored included clinical signs of toxicity, body weight, hematology, clinical chemistry, urinalysis, organ weights, and gross and microscopic pathology. The respiratory tract, including six levels of the nasal region, was examined. Increased ocular irritation relative to controls was observed in all groups.

Degenerative changes in the olfactory epithelium, described as minimal, were observed in 2/20 male rats exposed to the highest concentration. Inflammation occurred in all groups, including controls, but neither incidence nor severity were related to concentration. Likewise, mucus hyperplasia was present in some animals, but neither incidence nor severity of this lesion was related to the concentration. Squamous metaplasia of the respiratory epithelium was observed in all exposure groups of both sexes and, unlike in the chronic 2-year study, occurred in a

concentration-related manner for both incidence and severity. This lesion was not noted in any control animal. Epithelial cells within this lesion were described as disorganized. Keratin covered these lesions in some animals exposed to the middle and high concentrations. Although the nature of squamous metaplasia in the nasal tract has both adaptive and adverse interpretations, the concentration-related increases in incidence and severity of this lesion as well as its absence in control animals justify its characterization as predominantly adverse. Because the lesion was noted as minimal in severity in 11/40 animals at the lowest concentration, 0.01 ppm is a mild LOAEL, and the LOAEL(HEC) is 0.23 mg/cu.m. Because squamous metaplasia occurred only at the highest concentration in the chronic study and did not appear to progress, the significance of these findings is unclear.

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

UF — A UF of 10 was used to account for intraspecies extrapolation, a UF of 3 to adjust for interspecies conversion because dosimetric adjustments are used, and a UF of 3 for the absence of developmental/reproductive studies. Although there are no data relating to systemic distribution of HDI or its conversion products, the lack of remote distribution of toluene diisocyanate (TDI) and its conversion products in inhalation studies suggests that it is unlikely that HDI is distributed to extrarespiratory sites in significant amounts. Both HDI and TDI are considered to be very reactive chemically and there are no data to indicate that one is more persistent in the body than the other. Thus, 3 seems appropriate as a UF for developmental/reproductive endpoints, even though there are no developmental/reproductive studies.

MF — None

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

Sprague-Dawley rats (10/sex/group) were exposed (head only) to 0, 0.005, 0.0175, 0.15, or 0.3 ppm (0, 0.03, 0.1, 1, or 2.1 mg/cu.m) for 5 hours/day, 5 days/week for 3 weeks (Mobay, Inc., 1984). Five animals were sacrificed at the end of the exposure period, and five were sacrificed after a 2-week recovery period. Body weight and food consumption were monitored, and hematology, blood chemistry, urinalysis, necropsy, and microscopic examination of tissues were performed. Concentration related irritation of the eyes and nose were observed at concentrations of 0.1 mg/cu.m and greater. Absolute kidney weight was significantly decreased in females exposed to concentrations of 0.0175 ppm or above and in males at the highest concentration. The decrease in females was concentration related. Relative kidney weights were also decreased in both sexes at the highest concentration. Liver weights (absolute and relative) were significantly decreased in females at 0.0175 and 0.3 ppm. Histologic examination of the nasal turbinates revealed an increase in the incidence of (1) hemorrhage in males only at the two highest concentrations (5/10), (2) acute inflammation in both sexes at the two highest concentrations, (3)

squamous metaplasia (both sexes) at the three highest concentrations, and (4) in epithelial necrosis (males at all four concentrations and females at the two highest concentrations. There was an increase in incidence of inflammation in the trachea, compared with controls, in males at the two highest concentrations and in females at all concentrations. The LOAEL (nasal epithelial necrosis) is 0.005 ppm.

Male Wistar II rats (20/group) were exposed to target concentrations of 0, 0.2, or 2 ppm HDI for 4 hours/day, 5 days/week for 4 weeks (Mobay, Inc., 1970). The actual concentrations to which animals were exposed is questionable because it was not clear in the limited description of experimental procedures if vapors or aerosols were used. There was no information to judge whether target concentrations were achieved. No histopathology was performed. The information presented indicated that clinical signs of toxicity and changes in body weight occurred in animals exposed to the highest concentration only. Acute and subacute inhalation studies in mice, rats, and guinea pigs indicate that HDI adversely affects the respiratory system. The LD(50) for rats ranged from 290 for a 1-hour exposure to >28.5 for five repeated 4-hour exposures (Mobay, Inc., 1970). Mice, rats, and guinea pigs showed variable sensitivity to the lethal effects of HDI vapor (Mobay, Inc., 1971). Exposure to 2 ppm (13.8 mg/cu.m) for 6 hours/day for 5 days killed 6/10 mice, 1/10 rats, and 4/5 guinea pigs. Exposure of rats to 1.17 ppm (8 mg/cu.m) HDI for 3 hours/day for 5 days did not result in death, but did result in a decreased respiratory rate that did not return to baseline levels after 2 days of no exposure (Mobay, Inc., 1987). Additional symptoms included dyspnea and rales. Respiratory effects seen in dead animals and animals exposed to potentially lethal concentrations included symptoms of severe respiratory irritation including respiratory distress, bronchopneumonia, and hemorrhagic lungs (Karol et al., 1984; Mobay, Inc., 1970, 1971; Mobay, Inc., 1987). Guinea pigs may be more sensitive to HDI than either rats or mice. Of four guinea pigs exposed to 4 ppm (27.5 mg/cu.m) HDI for 2-6 hours, two animals died within 1 hour, and surviving animals exhibited severe respiratory distress (Karol et al., 1984). Animals exposed to 1.8 ppm (12.4 mg/cu.m) displayed severe respiratory irritation.

Respiratory sensitization (e.g., isocyanate asthma) to HDI is well documented and has been associated with immunologic lung disease such as hypersensitivity pneumonitis (Zeiss et al., 1983; Malo et al., 1983). Zeiss et al. (1983) reported, in an abstract, that one car painter developed hypersensitivity pneumonitis with late-onset asthma (specific IgG antibody to HDI was detected), and another worker developed immediate-onset asthma with both HDI-specific IgG and IgE antibodies. Hypersensitivity pneumonitis also was diagnosed in the case report by Malo et al. (1983) in which one car painter had been exposed to a paint mixture containing 7% polymeric HDI for at least 6 years. Other investigators that have detected increased levels of HDI-specific IgE or IgG antibodies in exposed workers include Cartier et al. (1989), Grammer et al. (1988, 1990), and Welinder et al. (1988). Exposure data in the aforementioned studies are limited and identification of an exposure-response relationship for respiratory sensitization is precluded.

As with other isocyanates (e.g., TDI), sensitization can result in immediate, dual, or isolated late asthmatic reactions (O'Brien et al., 1987; Malo et al., 1983; Zeiss et al., 1983). Challenge with an aerosol or vapor of HDI usually elicits an asthmatic response in sensitized individuals. Symptoms experienced by sensitized workers include shortness of breath, wheezing, cough, malaise, fever, and leukocytosis (Cartier et al., 1989; Innocenti et al., 1986; Welinder et al., 1988). The exposure parameters that cause sensitization or elicit asthmatic reactions in individuals already sensitized are unknown. Symptom surveys pertaining to occupational exposure to TDI, an isocyanate for which there is a larger database than for HDI, is consistent with the view that isocyanate-asthma may occur as a result of "massive or high exposure" typified by accidental spills (Brooks, 1982; Karol, 1981). This view is supported by evidence in exposures of guinea pigs to TDI (Karol, 1983; Aoyama et al., 1994). However, the potential of "low-level" exposures to cause sensitization cannot be discounted. Although the guinea pig is a model for human asthma, the extent to which the dose-response relationships observed with TDI (Karol, 1983) are representative of isocyanate-induced asthma is unclear.

There is limited information pertaining to the inhalation potency of HDI. Exposure (10 minutes) of mice in a sensory irritation model indicated that the concentration required to cause a decrease of 50% in the respiratory rate (RD50) was 0.96 ppm for HDI; lower levels resulted as duration of exposure increased. The lack of a plateau in the RD50 is a factor that limits the usefulness of this approach in extrapolating results to the human (Bos et al., 1992). Additional confounding factors include pulmonary irritation and interspecies variation. Weyel et al. (1982) examined HDI-biuret in the mouse sensory irritation model. The HDI-biuret was aerosolized, and the mean aerodynamic diameter and sigma g were determined. It was found that the RD50 value was considerably higher than the values for either free HDI or TDI. It is noted that HDI-biuret contains three free isocyanate groups, compared with two groups for TDI and monomeric HDI.

The effect of exposure to HDI on lung function has been studied to a limited extent. Information pertaining to TDI (Diem et al., 1982) suggests that long-term occupational exposure can lead to chronic lung function decrements in never-smokers at low levels (e.g., <5 ppb). Lung function in car painters exposed to HDI or HDI-containing materials has been evaluated by Alexandersson et al. (1987) and Tornling et al. (1990) in a prospective cohort study with a 6-year follow-up. In the initial study (Alexandersson et al., 1987), the lung function of 41 male car painters exposed to HDI and HDI-biuret trimer were compared with a control group exposed to the same solvents and dust as the painters and to another control group from the same garages who had not been exposed "to any great extent" to any of the agents (HDI, dust, or solvents). Exposure was re-created after study completion, and levels of HDI and HDI-biuret were estimated, taking into account mask wearing and job classification. There were no statistically significant spirometric changes observed during a workweek (between measurements on Monday morning and Friday afternoon). However, closing volume relative to vital capacity increased in painters during the workweek. This is suggestive of small airways disease. In a follow-up investigation, 36 car

painters and a total of 142 controls were reevaluated. Exposure measurements were made at the 14 car painting shops still in operation, taking into account job classification and respirator usage. Exposure data were estimated from 11 shops that had closed since the original study. The calculated time-weighted-average exposure for car painters was 0.0015 mg/m<sup>3</sup> HDI and 0.09 mg/m<sup>3</sup> HDI-biuret. HDI-biuret is a prepolymeric form of HDI and predominates in occupational environments. Attempts were made to estimate peak exposure according to job classification. There were no statistically significant decrements in lung function parameters between nonsmoking car painters and nonsmoking controls. There was a significant smoking effect observed. A cross-sectional study (Diller et al., 1985) indicated normal lung function in 81 HDI production workers compared with 86 controls. Exposure levels were not measured by the study investigators. Plant records indicated levels associated with shift supervisors during a 1-month period at study inception were about 1 ppb. There was a high percentage of smokers in both exposure categories. Smoking may have obscured any effects of HDI on lung function. Average exposures were not provided.

There is limited information on the distribution of inhaled HDI. Brorson et al. (1990) exposed five male volunteers in a chamber for 7.5 hours. The inhaled dose was estimated at 100 ug. The hydrolysis product of HDI, 1,6- hexamethylene diamine (HDA), was measured in urine. The cumulated urinary excretion of HDA ranged between 11 and 21% of the inhaled dose. The half-time in urine was calculated at 1.2 hours.

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

Study — High  
Database — Medium  
RfC — Medium

The principal study was well conducted in an adequate number of animals and placed particular emphasis on possible effects on the upper, as well as the lower, respiratory tract. Both a NOAEL and a LOAEL were identified. The confidence level for the principal study is therefore rated as high. The types of effects seen were consistent between the chronic and 90-day studies. The database is judged to be medium because of the absence of reproductive/ developmental and metabolic studies. Accordingly, the RfC is assigned a confidence of medium.

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

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — None



Agency Work Group Review — 03/26/1992, 05/28/1992, 09/23/1992

Verification Date — 09/23/1992

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 1,6-Hexamethylene diisocyanate conducted in September 2002 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](mailto: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](mailto:hotline.iris@epa.gov) (internet address).

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## **II. Carcinogenicity Assessment for Lifetime Exposure**

Substance Name — 1,6-Hexamethylene diisocyanate  
CASRN — 822-06-0

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

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**III. [reserved]**

**IV. [reserved]**

**V. [reserved]**

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## **VI. Bibliography**

Substance Name — 1,6-Hexamethylene diisocyanate  
CASRN — 822-06-0

## VI.A. Oral RfD References

None

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## VI.B. Inhalation RfC References

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## **VI.C. Carcinogenicity Assessment References**

None

## VII. Revision History

Substance Name — 1,6-Hexamethylene diisocyanate  
CASRN — 822-06-0

Date	Section	Description
09/01/1994	I.B.	Inhalation RfC on-line
12/03/2002	I.B.6.	Screening-Level Literature Review Findings message has been added.

## VIII. Synonyms

Substance Name — 1,6-Hexamethylene diisocyanate  
CASRN — 822-06-0  
Last Revised — 06/01/1992

- 822-06-0
- Hexane, 1,6-diisocyanato-
- Hexamethylene diisocyanate
- 1,6-hexamethylene diisocyanate
- AI3-28285
- Diisocyanate d'hexamethylene [French]
- HDI
- Hexamethylendiisokyanat [Czech]
- Hexamethylene diisocyanate
- Hexamethylenediisocyanate
- Hexametilendilsocianato [Spanish]
- HEXANE 1,6-DIISOCYANATE
- HMDI
- HSDB 6134
- ISOCYANIC ACID, DIESTER with 1,6-HEXANEDIOL
- Isocyanic acid, hexamethylene ester
- METYLENO-BIS-FENYLOIZOCYJANIAN [Polish]
- Szesciometylenodwuizocyjanian [Polish]

- TL 78
- 1,6-DIISOCYANATOHEXANE
- 1,6-HEXANEDIOL DIISOCYANATE
- 1,6-HEXYLENE DIISOCYANATE