2,4-/2,6-Toluene diisocyanate mixture (TDI) ; CASRN 26471-62-5

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 TDI

File First On-Line 09/01/1995

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	yes	09/01/1995
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — 2,4-/2,6-Toluene diisocyanate mixture (TDI)
CASRN — 26471-62-5

Not available at this time.

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

Substance Name — 2,4-/2,6-Toluene diisocyanate mixture (TDI)
CASRN — 26471-62-5
Last Revised — 09/01/1995

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 (extrarespiratory 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
Chronic lung-function decline **Prospective Occupational Study** **Diem et al., 1982**	NOAEL: 0.006 mg/cu.m (0.0009 ppm) NOAEL (ADJ) : 0.006 mg/cu.m NOAEL (HEC) : 0.002 mg/cu.m LOAEL: 0.014 mg/cu.m (0.0019 ppm) LOEAL (ADJ) : 0.014 mg/cu.m LOAEL (HEC) : 0.005 mg/cu.m	30	1	7E-5 mg/cu.m

*Conversion Factors and Assumptions — MW = 174.16. Assuming 25 C and 760 mmHg, NOAEL(mg/cu.m) = 0.0009 ppm x MW/24.45 = 0.006 mg/cu.m. This is an extrarespiratory

effect of a gas. The NOAEL is based on an 8-hour TWA occupational exposure. MVho = 10 cu.m/day, MVh = 20 cu.m/day. The NOAEL(HEC) = 0.006 mg/cu.m x (MVho/MVh) x 5 days/7 days = 0.002 mg/cu.m.

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

Diem, J.E., R.N. Jones, D.J. Hendrick, et al. 1982. Five-year longitudinal study of workers employed in a new toluene diisocyanate manufacturing plant. Am. Rev. Resp. Dis. 126: 420-428.

A number of occupational studies have evaluated chronic lung-function decline in workers exposed to toluene diisocynate (TDI). With one exception, that of Diem et al. (1982), these studies involved polyurethane foam production workers, a group exposed not only to TDI, but also to a variety of other substances with unknown potential to cause lung-function decline (Kaufman and Overcash, 1993; Omae et al., 1992a). Although some of these occupational studies demonstrated longitudinal lung-function decline, there are a number of confounding factors, in addition to the complex exposure environment, that preclude the use of these studies in identifying exposure- response relationships for TDI. Principal confounding factors include (1) study designs that do not account for smoking status, (2) sampling and analytical schemes that have limited ability to accurately detect and quantify both TDI isomers, (3) high rates of annual forced expiratory volume in 1 second (FEV1) decline in minimally exposed and referent populations, and (4) high intra- and interindividual variation in lung-function testing. When these factors are taken into account, only the Diem et al. (1982) study provides sufficient data from which both a NOAEL and a LOAEL can be identified.

This study has several strengths not ordinarily found in investigations of this type: (1) baseline FEV1 values were established for each individual before commencement of TDI production; (2) parallel internal comparisons between study groups of annual FEV1 declines were made; (3) statistical techniques assessed true annual change and interindividual variability in measurements; (4) an extensive number of breathing zone samples were analyzed by the paper-tape method, a method with greater capability than the Marcali (1957) method for measurement of peak exposures, and accurate measurements of both TDI isomers; and (5) a significant decrease in FEV1 due to smoking. The principal deficiency is the lack of breathing-zone measurements in the first 2 years of plant operation.

TDI production workers (277 males) were followed prospectively over a 5- year period for evidence of respiratory tract dysfunction. Pulmonary-function measurements taken at nine survey points over a period of 5 years, with baseline pulmonary-function measurements taken in 168 individuals with no previous exposure to TDI approximately 6 months before manufacturing (and TDI exposure) started. Pulmonary-function measurements included spirometry, single-breath diffusing capacity, and residual volumes (nitrogen washout technique). For inclusion in

the longitudinal analysis of pulmonary-function measurements, a worker was required to have three or more pulmonary-function tests. Of the 277 workers, 223 qualified. A Medical Research Council questionnaire was administered at each survey point to assess smoking habits and respiratory symptoms. Pulmonary-function testing was conducted according to American Thoracic Society criteria. Atopy was assessed in all participants by skin-prick tests for 16 common aeroallergens and defined as two or more positive skin-prick tests. Atopy is generally addressed to determine if individuals known to be allergic to aeroallergens are more susceptible to TDI than are those who are not allergic. Neither the time of day nor the day of the work week in which the tests were administered was indicated. As a result of attrition, 109 workers with some TDI exposure prior to entry into the study were enrolled up to survey 5. Forty-nine of the original 168 had left the study by the last site visit.

Although the study was initiated in April 1973, personal sampling results were taken and reported only from June of 1975 onward (when personal continuous-tape monitors became available commercially). This sampling and detection method is considered to be accurate for measuring both isomers of TDI and for detecting short-term peaks in exposure. A total of 2093 samples from 143 workers from all workshifts were collected. However, no reliable exposure data are available during the initial 2 years of manufacturing (when levels commonly fluctuate the most). It is, therefore, likely that the true exposure levels during these initial 2 years were appreciably higher than those measured during the subsequent study years. Workers were dichotomized into two cumulative exposure groups: (1) below 68.2 ppb-months (which represents the cumulative exposure of an individual who spent the entire 62 months of the study in the low-exposure area; 62 x the geometric mean of 1.1 ppb = 68.2) and (2) above 68.2 ppb-months. The two cumulative exposure groups were further subdivided into two groups whose mean ratios of FEV1 to height were (1) low or (2) normal; the former group was excluded from the analyses. The group with normal FEV1 level was then normalized for age and a 5.8-mL increase in FEV1 annual decline for each decade of age. The two cumulative exposure groups also were characterized and analyzed as to the amount of time spent above 20 ppb.

A maximum likelihood weighted regression approach was used to account for variability in the interindividual precision of the measurements (Diem and Liukkonen, 1988).

After subdivision of the high- and low-cumulative-exposure groups into smoking categories of never, previous, or current, it was found that never- smokers in the high-cumulative-exposure category (n = 21) had a significant decline of 38 mL/year FEV1 (one-tailed p = 0.001) over never-smokers in the low category (n = 35). Similar results were observed in the forced expiratory flow at 25-75% (FEF25-75). Among the never-smokers, the mean annual decline for the high-exposure group was significantly larger (113 mL/second-year) than that of the low-exposure group (81 mL/second-year). When the same groups were recategorized based on time spent above 20 ppb, similar significant declines in FEV1 were noted with the addition of an

FEV1 decline of 18 mL/year in current smokers. A significant decline in FEV1 between never- and current- smokers in the low-exposure group was observed, confirming expectations of a smoking effect. Respiratory symptoms and atopy were not related to exposure, and there was no effect of exposure on the diffusing capacity of carbon monoxide, nitrogen washout, or prevalence of respiratory symptoms.

Hughes (1993) provided both geometric and arithmetic 8-hour TWA means of TDI air levels for the never-smokers in the two cumulative exposure groups. The choice of which mean to use in epidemiological studies in which cumulative exposure is lognormally distributed (whereas the health endpoint is assumed to be linearly related to exposure) has been an area of considerable discussion (Seixas et al., 1988). Because both the geometric and arithmetic means for cumulative exposure of never-smokers in the low- and high-exposure groups of the Diem et al. (1982) study were nearly identical (Hughes, 1993), a normal distribution is indicated. Assuming lung-function decline is linearly related to exposure, the arithmetic mean would be the measure of choice (Hassleblad, 1993). The arithmetic means for never-smokers in the low and high categories were 0.9 [standard deviation (SD) = 0.3] and 1.9 ppb (SD = 0.8), respectively. The corresponding geometric means were 0.9 (SD = 1.3) and 1.8 ppb (SD = 1.5). Although the mean exposure values determined in this study are close to the detection limit of the sampling and detection method, the values are considered accurate because they were obtained by continuous monitoring over the entire workday (Dharmarajan, 1990). FEV1 decline also showed high correlation with time spent in peak exposure categories. Those in the high- cumulative-exposure group (74) spent 15% of their work time at levels above 5 ppb, whereas those in the low category (149) spent only 2% of their time above 5 ppb. Despite these correlations with peak exposure, there is no a priori evidence that they provide a better measure of a concentration-response relationship than do mean exposures.

Data for never-smokers in this study suggest that an increase in annual FEV1 and an FEF25-75 decline in excess of that due to aging are caused by long-term exposure to an arithmetic mean TDI concentration of 1.9 ppb. Thus, the LOAEL is designated as 1.9 ppb. The LOAEL(HEC)is 0.014 mg/cu.m, the NOAEL is 0.9 ppb, and the NOAEL(HEC), based on an adjustment for TWA occupational exposures, is 0.002 mg/cu.m.

Jones et al. (1992) did not find a relationship between TDI exposure and annual declines in FEV1 and other lung-function parameters in polyurethane foam workers in a 5-year longitudinal study of lung function. The work environment differs substantially from that of Diem et al. (1982) in that many other chemicals (e.g., catalysts, surfactants, blowing agents, and others) are used in foam manufacture. Foam finishers also were exposed to suspended particulates. Because of high attrition due to refusal to participate, inclusion of other workers was permitted through the fourth year, at which time 435 workers were enrolled. Annual lung-function changes were determined from spirometric data collected on 227 individuals (181 males and 46 females) who,

during the course of the study, had three or more spirometric examinations. The results from two acceptable maneuvers with the highest combined percent of predicted values for the FEV1 and FVC were averaged. Mean annual lung-function declines were determined by calculating slopes for each of the 227 individuals, using weighted, stepwise multiple linear regression techniques as described by Diem and Liukkonen (1988). There was no study bias due to attrition; lung function of those with one or two lung function measurements was similar to those of individuals who had three or more lung function measurements. Asthmatics (17/227) were not included in the stepwise linear regression.

TDI levels were measured by personal monitors (lower detection limit of 0.5 to 1.0 ppb) worn by 258 workers on 507 workshifts, producing a total of 4,845 measurements. The personal monitors (lower detection limit = 1 ppb) were modified after year 1 to have a lower detection limit of 0.5 ppb during 1983-1987 and produced up to 14 evenly-spaced, 12-minute exposure samples over an 8-hour workshift. This sequential monitor was adopted to improve accuracy in recording peak exposure and TWA under varying exposure conditions. Samples with no detectable TDI were assigned a value of one-half the lower detection limit; in 1983-1987, this value was 0.25 ppb.

Based on these measurements, arithmetic mean TWA concentrations were assigned to groups of jobs with similar average exposure and cumulative exposure, further segregated by smoking categories (never-, ex-, and current smokers). Average exposure was defined as cumulative exposure divided by length of employment. Cumulative exposure from "hire-to-start" (utilizing estimates of past exposure) was used in assessing effects of TDI exposure on a cross-sectional analysis of lung-function values, whereas exposure from "start-to-end" was used in the longitudinal analyses.

Annual declines in FEV1 by cumulative exposure and smoking groups for this study were provided in the Mobay (1991) submission to U.S. EPA. The cumulative exposure groups (males) from start-to-end of the study were <31 ppb-month, >31<54 ppb-month, and >54 ppb-month. The arithmetic mean concentrations (and SDs) for males in each of the low-cumulative-exposure groups of never-smokers (n = 25), ex-smokers (n = 14), and current smokers (n = 12) were 0.3 (0.3), 0.4 (0.2), and 0.4 (0.2) ppb, respectively (Hughes, 1993). Arithmetic mean concentrations in the high-cumulative-exposure groups for never-smokers (n = 24), ex-smokers (n = 17), and current smokers (n = 24) were 1.3 (0.4), 1.2 (0.5), and 1.2 (0.5) ppb, respectively. The geometric and arithmetic means, with the exception of never-smokers in the low-exposure category, were nearly identical. Thus, the arithmetic mean was considered the measure of choice. Neither a smoking effect nor an effect of exposure (hire- to-end or start-to-end) was observed in any of the exposure groups. There were no significant differences in FEV1 between those with adequate slopes (n = 227) and those without (n = 137).

The mean annual declines for the 227 participants were uncharacteristically large (71 mL/year for males and 43 mL/year for females) in comparison with expected values in cross-sectional analysis and in other longitudinal studies (e.g., Diem et al., 1982; Sherman et al., 1992). The low-measured-air concentrations, the close spacing of the exposure gradient between exposure groups, the relatively small number of individuals in each smoking category by exposure grouping, and the large annual declines in FEV1 all may be factors in the inability of the investigators to detect statistically significant lung-function annual-change differences between TDI exposure groups.

There was no correlation between methacholine responsiveness and exposure or atopy in this study. Regression analysis showed a significant association of prevalence of chronic bronchitis with exposure after controlling for age, smoking, and sex. However, the numbers of individuals with chronic bronchitis was small (28/380).

Populations and some exposure characteristics did differ from those in the Diem et al. (1982) study, where a significant number of individuals had not been exposed to TDI previous to study inception, and 44% of the air samples from the high-TWA-exposure group exceeded 20 ppb for 10 minutes or longer. In contrast, the population examined by Jones et al. (1992) previously was exposed for many years, and <5% of air samples from high-exposure job categories exceeded 20 ppb.

A consortium of British industrial concerns, in cooperation with the Medical Research Council of Great Britain, instituted a 5-year longitudinal study designed to evaluate the relationship between TDI exposure to lung function in polyurethane foam workers. The results of this study are unpublished (Bugler et al., 1991). For most plants, all available isocyanate- exposed workers were included in the study population. The number of individuals followed longitudinally was 780 (649 men and 131 women). Of the total, 157 or 20% had never previously been exposed to TDI. Controls, which included a group that handled only cold urethane products, were selected, taking into account sex, age, ethnic origin, and smoking status.

The final population was trained prior to the study in the techniques of performing lung function tests that were made at the same time of day, on the same day of the week, and in the same month of the year to exclude seasonal, in-shift, and other cyclical effects. A complete occupational history, beginning at the time an individual left school, was obtained from each worker.

Environmental sampling was performed with personal monitors (continuous- tape method) with a limit of detection of 1 ppb. During the course of the study, 2732 measurements were made. The majority of control-worker exposures was <1 ppb. The mean 8-hour TWA exposure of the group handling cold urethane products was 0.6 ppb. Of the 780 individuals in the study, 521 were in the

exposed group with a mean exposure of 1.2 ppb (SD = 1.1). The mean 8-hour TWA exposure of the 136 in the minimally exposed group was 0.3 ppb (SD = 0.18) (Allport, 1993). Although cumulative exposure of the 780 individuals was lognormally distributed, exposures in this study were characterized only by the arithmetic mean.

Regression analysis revealed no significant exposure-related longitudinal changes in FEV1 among any of the categories, including nonsmokers, a group that Diem et al. (1982) indicated had experienced deficits in lung function due to TDI exposure. The ability to detect any FEV1 differences between exposed groups may have been masked by the high annual decline (37 mL/year) observed in the minimally exposed workers. The prevalence of respiratory symptoms reported by this group on initial and final questionnaires did not suggest that these workers had preexisting impairments (Allport, 1993). A significant increase in some symptoms in both males and females was noted in both the handling and exposed groups. Allport (1993) surmised that these symptoms may have been caused by exposure to solvent-based adhesives used in the foam fabrication process. Of the 780 individuals in the study population, 24 had symptoms suggestive of TDI sensitization (Allport, 1993). Of these 24, 20 were in the exposed group. The mean FEV1 decline for these individuals was 49 mL/year.

The high level of annual FEV1 decline in minimally exposed workers (controls), the low exposure levels in all categories, and the absence of an expected effect due to smoking indicate that the study may have limited ability to detect a response to TDI.

In order to determine the extent to which the results of the Jones et al. (1992) and Bugler et al. (1991) could influence interpretation of the positive association between exposure and lung function in the Diem et al. (1982) study, a meta-analysis (Hassleblad, 1993) was performed on the three data sets. This approach utilized arithmetic means of exposure by smoking groups because arithmetic means were established by protocol in each of the three studies. Maximum likelihood functions (expressed in slope units of milliliters of FEV1 decline per parts per billion TDI) were developed for individual data sets from each study and for combined data sets for smokers and never-smokers. Likelihood functions for the slopes of each group (smokers and nonsmokers) from all three studies were combined using an inverse variance weighting formula (Hasselblad, 1993). The likelihood functions for male never-smokers and smokers show that they have similar probability densities, and all are shifted to the right, a direction toward decreased lung function with exposure. The combined maximum likelihood estimate for never-smokers in the high-exposure group is 23.6 mL FEV1 decline/ppb TDI with 95% confidence limits of 3.9 to 43.0. The 38-mL/year decline observed in the Diem et al. (1982) study falls within these confidence limits. Although the combined never-smoker slope is statistically significant compared with the smoker slope (point estimate = 11.8), the relative difference between the two slopes may be more of a chance variation than a meaningful difference. Because inverse variance weighting was used, the combined variance data from the Jones et al. (1992) and Bugler et al.

(1991) studies made only a small contribution to the combined results; the variance in the Diem et al. (1982) study was much smaller than that in the other studies. Thus, the "negative" findings from these studies were not inconsistent with the "positive" results of Diem et al. (1982).

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

UF — This uncertainty factor includes a factor of 10 to account for intrahuman variability and a factor of 3 to account both for subchronic to chronic extrapolation and the lack of developmental toxicity data in a second species.

MF — None

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

The respiratory tract is the critical target tissue for both acute and chronic TDI exposures. Effects include primary irritation, sensitization (e.g., "isocyanate asthma"), and progressive impairment of lung function as a result of long-term exposures. Asthmatic symptoms may occur immediately on exposure, be delayed for several hours after exposure, or consist of both an immediate and delayed reaction (Moscato et al., 1991). Sensitization generally refers to induction of heightened airways responsiveness that results in the development of a hypersensitive state, characterized by abnormal respiratory responses, such as asthmatic symptoms, to low, nonirritating concentrations of a substance. Little is known about exposure conditions that lead to development of sensitization to TDI or to its symptomatic sequelae, including occupational asthma. Spill surveys (Brooks, 1982; Karol, 1981, 1983) suggest that occupational asthma may occur as a result of "massive or high" exposure typified by accidental spills, although it is not known if "low-level" exposure has the same potential. Identification of TDI-specific antibodies in serum is an approach often used in both human and laboratory animal studies to determine if exposure to TDI has taken place and to assess the relationship between asthmatic responses and antibody titer. Despite evidence that TDI-induced asthma is, in part, immunologically mediated, elicitation of TDI-specific immunoglobulin E (IgE) is found in only a small percentage of individuals with symptoms (Baur et al., 1994).

Other features also may play important roles in isocyanate-induced asthma. Histamine-releasing factor has been suggested as a possible biomarker of diisocyanate-induced asthma, although there was no correlation with IgE (Herd and Bernstein, 1994). Genetic predisposition also may play a role in pathogenesis (Bignon et al., 1994). Asthmatic responses are associated with airway eosinophilia and inflammation related, in part, to T-cell responses to TDI (Maestrelli et al., 1994) and subepithelial fibrosis in the airway wall (Saetta et al., 1995).

Peters et al. (1968, 1969, 1970), Peters and Wegman (1975), and Peters (1970, 1974) studied pulmonary function in a group of 38 polyurethane foam workers (31 males and 7 females) at 6-month intervals for 3 years. Area sampling, not breathing-zone measurement, was used. The Marcali (1957) method was used for detection. The annual rate of FEV1 decline in each of the 3 years was 120 mL/year. There was no relationship between cumulative exposure and FEV1 annual decline. Although this rate of decline is clearly excessive, it is not possible to delineate a specific exposure level due to the limitations of the sampling and analytical methodologies and because of the possibility that substances other than TDI in this environment may have been responsible for the lung-function decline.

Wegman et al. (1974, 1977, 1982) followed polyurethane production workers exposed to TDI prospectively for 4 years. At 4-year follow-up, only 37/111 had acceptable spirograms. These workers were classified into three exposure categories, but TWAs were not provided. Only a few samples (138) were taken, and none in the interval between the last 2 years of the study. Although large declines in FEV1 were observed in the two highest categories, limitations discussed for the studies by Peters and colleagues confound interpretation of the study results.

Musk et al. (1982, 1985) followed polyurethane foam workers for 5 years in which air levels (2043 measurements) of TDI in the breathing zone were measured by the Marcali (1957) method during the last 4 years. During the last 2 years, diphenylmethane diisocyanate also was present in the air. Only 94 (54 males and 40 females) from the original 259 were available for reexamination at the 5-year follow-up (Musk et al., 1985). It is stated in the discussion that this group did not include any subject with symptoms suggesting hypersensitivity to isocyanates, but the criteria for this determination were not provided. There was no evidence of bias introduced by the selective retirement of subjects from the cohort, as evaluated by the similarity of the mean FEV1 value of the original cohort with that of those who remained in the study. The exposure category for each subject was determined from these measurements and occupational history. The geometric mean for TDI in the two plants studied were 1.0 ppb in one and 1.5 ppb in the other, levels similar to those in the Diem et al. (1982) study. There were no statistically significant differences in the total 5-year decrement in FEV1 (Musk et al., 1982) between those workers (42) with no exposure and those (17) exposed to TDI alone. The average annual FEV1 decline was 20-25 mL, based on analysis of original data and after reanalysis, respectively. Regression analysis showed that the 5-year decrement was significantly related only to smoking. A NOAEL cannot be demonstrated conclusively due to sampling and analytical limitations, the lack of a comparison of FEV1 decline between never- and current-smokers, and the small cohort. Musk et al. (1985) also stated that the annual FEV1 declines were similar to cross-sectional age regression coefficients of predicted normal populations, although these data were not provided. It has been noted elsewhere that these regression coefficients are inaccurate gauges for the evaluation of longitudinal spirometric data (Glindmeyer et al., 1982).

Although the results of the Musk et al. (1982, 1985, 1988) and Wegman et al. (1974, 1977, 1982) studies are expressed relative to isocyanate exposure data measured by the conventional impinger method of Marcali (1957) and, thus, are not directly comparable with those of Diem et al. (1982), who used paper- tape monitors and expressed concentrations as an 8-hour TWA, cumulative exposure, and time above 0.02 ppm, their results are consistent with those reported by Diem et al. (1982). Wegman et al. (1974, 1977, 1982) demonstrated a concentration-response relationship for annual FEV1 changes and, together with Peters et al. (1968, 1969), Peters (1974), and Peters and Wegman (1975), provide a correlation between workshift FEV1 changes and annual FEV1 declines. Musk et al. (1982, 1985, 1988) provide a supportive NOAEL level that ties into the concentration-response established in the Wegman et al. (1974, 1977, 1982) studies. Important limitations of the studies by Musk et al. (1982, 1985, 1988) and by Wegman et al. (1974, 1977, 1982) include (1) low power because few individuals were available for follow-up; (2) breathing zone concentrations were unknown because area monitors generally were used; (3) the wet colorimetric methods used are capable of TWA measurements only, and sampling generally was only 20-90 minutes in duration; (4) the likelihood that other chemicals were present in the exposure environments; and (5) levels of the 2,6-isomer were probably underestimated in polyurethane production situations because methods based on the Marcali (1957) procedure are known to underestimate levels by 47% when compared with the standards of the 2,4- isomer. When arrayed, the results from these support a concentration-response relationship for annual FEV1 changes, so these studies are used to support the NOAEL demonstrated in the Diem et al. (1982) study.

In the prospective study by Adams (1975), no association was found between duration of exposure and FEV1; however, deficiencies in study detail and design (e.g., no breathing-zone exposure data) preclude the use of this study in exposure-response identification.

Cross-sectional studies (Holness et al., 1984; Alexandersson et al., 1985) have not found correlations between duration of exposure and lung function in TDI workers compared with referents. Omae (1984) also found no relation between exposure of TDI production workers (mean duration of exposure at 2- year follow-up was 11 years) to a TWA of 1 ppm TDI and lung function. The intermittent nature of exposure (plant was automated) may have been a confounder in the negative findings.

Omae et al. (1992a,b) also examined pulmonary function in polyurethane foam workers from seven Japanese factories (average duration of employment = 13.3 years) in relation to TDI exposure over a 4-year period. Workers in some factories were exposed concurrently to other reactive chemicals and gases. Exposure was assessed by means of personal monitors worn by each worker during working hours. Only 159 breathing-zone samples were taken during the study period. Referents were described as working in the same factories, but were not exposed to TDI. At the 4-year follow-up, there were 57 exposed workers and 24 referents common to all

three surveys for which there were valid spirometric data. Low power due to small sample size and the high rates of annual lung- function decline observed in minimally exposed workers, workers exposed to a TWA of about 6 ppb, and referents preclude identification of either a NOAEL or LOAEL.

Karol (1981) investigated concentration-response relationships for serum antibody titers and lung function decline in workers (n = 20) exposed to TDI as a result of acute exposures and those (n = 96) exposed to stable levels. Specific and total IgE values remained unchanged in workers exposed to stable TDI environments of 0.02 ppm or lower for 6 to 24 months, and no change was seen in their pulmonary function. In contrast, pulmonary function was depressed (FEV1 decline of greater than or equal to 20%) in 4/20 involved in acute exposure episodes, and 3/4 had positive antibody titers. Of nine cases of acute exposure resulting in immediate symptoms with no change in pulmonary function, high titers were detected in one instance. This study showed that workers exposed to ambient levels of TDI at 0.02 ppm or lower did not develop specific IgE titers in contrast to increased antibody production in workers having acute TDI exposures sufficient to produce short-term decreases in pulmonary function. Karol et al. (1994), during an investigation of predictive factors in TDI asthmatics, found that increases in serum IgE titers were most likely to occur in individuals experiencing early-onset asthmatic reactions.

Banks et al. (1989) reported on the results of TDI challenge testing performed on 59/63 workers referred with a diagnosis of probable isocyanate- induced asthma. It was concluded that an exposure of 0.02 ppm of a commercial TDI mixture for up to 15 minutes provoked asthma in nearly all of the challenge-positive workers. The nature of the isomer (2,4- or 2,6-TDI) also was a determinant of whether the asthmatic reaction occurred immediately or was delayed.

Clinical studies suggest that total dose may be more important than concentration in eliciting TDI-asthma (Vandenplas et al., 1993), whereas studies with guinea pigs suggest the opposite (Karol, 1983). The extent to which studies in guinea pigs are surrogates for human asthma is unclear, inasmuch as the experimental animals do not exhibit asthmatic symptoms exhibited by humans with isocyanate-induced asthma. Studies with guinea pigs typically assess respiratory rate increases on exposure as indicative of a hypersensitive response.

Sangha and Alarie (1979) exposed mice for 3 hours/day for 5 consecutive days at concentrations of TDI ranging from 0.007 to 1.180 ppm. At levels of 0.023 ppm and above, reduction in respiratory rate was observed. Two other groups (4/group) were exposed to 0.031 and 0.250 ppm for 3 hours/day for 3 days to assess histopathology in the nasal mucosa. No remarkable lesions were noted in the 0.031-ppm group. Damage to the external nares and respiratory epithelium, but not olfactory epithelium, was noted in the 0.250-ppm group.

Using a protocol designed to examine the role of concentration x time vs. concentration alone in eliciting TDI pulmonary sensitization, Karol (1983) found that, at least for guinea pigs, concentration was the important factor. Female English, smooth-hair guinea pigs were exposed head-only for 3 hours/day for 5 consecutive days at levels from 0.12-10.00 ppm or exposed whole-body 6 hours/day, 5 days/week for 70 days to 0.02 and 0 ppm. Two hours into these exposures a concentration-dependent decrease in respiration rate (a result of sensory irritation) was noted at levels above 0.12 ppm. All animals expired at 10.00 ppm. All animals exposed to 0.960 ppm or greater developed a cytophilic antibody response in a passive cutaneous anaphylaxis assay, whereas none developed in animals exposed to 0.12 ppm. Although a linear relationship between exposure and the incidence of animals in which the antibody was present, as well as in antibody titer, was observed in animals exposed to 0.12-0.96 ppm in the short protocol, no antibody response developed in animals exposed to 0.02 ppm for 70 days. Dermal sensitivity was apparent in animals exposed to 0.12-7.60 ppm for 5 days but negative in animals exposed to 0.02 ppm for 70 days. Pulmonary sensitivity, assessed by increases in the respiratory rate after bronchial provocation challenge, was elicited in animals exposed to 0.36, 0.61, and 0.96 ppm, but not in either of the two higher exposure groups, in spite of high antibody titers or in the group exposed for 70 days. Antibody response and pulmonary sensitivity in animals exposed to 1.60 ppm for 3 hours/day on days 1 and 3 were lower than in those exposed to 0.61 ppm for 3 hours/day, 5 days/week, although these groups were equivalent in ppm x hours. It was concluded that exposure regimen and concentration, rather than total dose, are important for immune response, and 0.02 ppm (0.14 mg/cu.m) is identified as a NOAEL in this species for antibody response and dermal and respiratory sensitivity. The NOAEL(HEC) for sensitization (assumed to involve extrarespiratory phenomena) is 0.14 mg/cu.m.

In a protocol similar to that of Karol (1983), Wong et al. (1985) exposed eight female English, smooth-haired guinea pigs, head-only, to a mixture of TDI isomers at 1.40 ppm for 3 hours/day for 4 consecutive days or to 0.02 ppm for 6 hours/day, 4 days/week for 70 days (whole-body, n = 24). The duration- adjusted value is 0.02 mg/cu.m. Control animals (n = 8) were exposed to room air in a similar time schedule to the 0.02-ppm group. Body weight monitoring, immunologic evaluations, and histopathology of the lungs were performed. TDI- specific IgE antibodies were detected in all animals exposed to 1.40 ppm, but in no animals exposed to 0.02 ppm. Sensitivity to TDI was assessed by bronchial provocation challenge on days 37 and 38. Pulmonary hypersensitivity was indicated in 4/8 animals exposed to 1.40 ppm and none in the 0.02-ppm group. Pulmonary performance during and after TDI exposure was assessed by the ventilatory response to carbon dioxide. Indices assessed were tidal volume changes and respiration frequency. In contrast to animals exposed to 1.40 ppm, no effects on baseline tidal volumes, ventilatory response to carbon dioxide, or respiration frequency were elicited in the 0.02-ppm animals. Histopathology showed multifocal interstitial inflammation (7/8), localized pleural thickening (4/8), and peripheral lymphoid hyperplasia (3/8) in animals of the 1.40-ppm group. The only histopathology noted in the 0.02-ppm group was patchy interstitial inflammation in

2/24 animals. The results of this study, which support those found by Karol (1983), indicate neither impairment of pulmonary function nor pulmonary sensitization at 0.02 ppm (0.14 mg/cu.m). The RGDR for the pulmonary-function effect is 0.8. The NOAEL(HEC) for pulmonary function and histopathology is 0.11 mg/cu.m. The NOAEL(HEC) for pulmonary hypersensitivity (assumed to involve extrarespiratory phenomena) is 0.11 mg/cu.m.

Loeser (1983) exposed CD-l mice (30/sex/group) and SD rats (21/sex/group) to a production-grade TDI isomeric mixture at measured levels of 0.05 and 0.15 ppm (0.36 and 1.06 mg/cu.m) for 5 days/week, 6 hours/day, for 104 weeks (mice) or 108-110 weeks (rats). The duration-adjusted concentrations are 0.064 and 0.189 mg/cu.m, respectively. Organ weights were recorded at all scheduled necropsies, and 34 tissues were examined histologically, including the lungs (infused) and nasal turbinates (two levels). No exposure-related effects were observed on mortality, organ weights, hematological parameters, blood chemistry, or urinalysis parameters in rats or mice. The results of the histopathological findings from the rat nasal passages are reported by Owen (1984). Concentration-related increases in incidence and severity of chronic or necrotic rhinitis with epithelial atrophy, metaplasia and inflammation were observed in male and female rats. This effect was observed in males at the high concentration and in females at both exposure levels. The proportion of female rats with rhinitis at grades 1-4 (minimal to marked) were 18, 43, and 70% for control and 0.05- and 0.15-ppm groups, respectively, and, with rhinitis at grades 2-4 (slight to marked), the percent incidence was 3, 12, and 23, respectively. Similar lesions were reported in mice, although details were not sufficient to define effect levels. This study identifies a LOAEL for respiratory system effects in the ET region in rats. The RGDR for the ET region is 0.22 for the rat. The LOAEL(HEC) is 0.01 mg/cu.m.

Several studies using ring-labeled TDI have investigated the distribution of labeled material after inhalation of TDI by guinea pigs and rats (Kennedy et al., 1989a,b, 1994). The findings indicate that radioactivity is associated with conjugated proteins (e.g., albumin), laminin, and all organs and tissues examined, including blood, liver, kidney, and spleen. Levels in kidney, liver, and spleen were about 10-fold less than the amount of label in the lungs at the highest concentration of TDI. The testes were not examined. These results indicate that at least portions of the original TDI molecule are transported to extrarespiratory sites. Evidence that some form of TDI is either translocated or hydrolyzed is supported by the finding of toluene diamine, its metabolite, in the urine of TDI-exposed individuals (Maitre et al., 1993) and of rats exposed to 2,4-TDI (Timchalk et al., 1994).

Tyl (1988) exposed timed-pregnant Sprague-Dawley rats (25/exposure group) to mean TDI concentrations of 0, 0.021, 0.120, and 0.480 ppm for 6 hours/day on gestational days 6-15. At necropsy on gestational day 21, body and organ weights were measured and tissues retained for histopathological examination. A total of 21-23 litters were examined in each exposure group. Intact fetuses in each litter were examined for external, visceral, and skeletal malformations and

variations. Indications of maternal toxicity at 0.480 ppm included significant reductions in body weight and food consumption and rales. There were no treatment-related effects on corpora lutea; total, nonviable, or viable implantations per litter; or sex ratio or fetal body weights per litter. No embryotoxicity or teratogenicity was observed at any exposure concentration. There was no mortality, nor were there early or aborted deliveries. Of 111 skeletal variants observed in the study, only one, poorly ossified cervical centrum 5, exhibited a statistically significant increased incidence in the 0.480-ppm group relative to controls. This variation was described as a common rat skeletal variation. The NOAEL for reproductive and developmental effects is 0.12 ppm. The NOAEL(HEC) is 0.85 mg/cu.m. The LOAEL, based on maternal toxicity, is 0.48 ppm. The LOAEL(HEC) is 3.4 mg/cu.m.

In a two-generation reproduction study, male and female Sprague-Dawley weanling rats (28/sex/group) were exposed to mean TDI concentrations of 0, 0.020, 0.079, and 0.290 ppm, 6 hours/day, 5 days/week, for 10 weeks (Tyl and Neeper-Bradley, 1989). They then were paired randomly within groups for 3 weeks to produce the F1 generation. Exposures of females continued through mating and the first 19 days of gestation and were discontinued from gestation day 20 through the fourth day postpartum. Exposures of females resumed on day 5 postpartum and continued through postnatal day 20. Exposures of P0 males were continuous from the mating period through delivery of the first F1 litters.

At weaning, 28 weanlings/sex/group were randomly selected to produce the F2 generation. F1 weanlings were exposed to the same TDI protocol as the P0 generation. In addition, 10 F1 weanlings/sex/group were necropsied for gross lesions. P0 males were necropsied following delivery of the first F1 litters. F0 females were necropsied after the F1 pups were weaned. Selected tissues from 10 P0 animals/sex/group in the high exposure and control groups were examined for histopathological lesions. Tissues from the upper respiratory tract from 10 animals/sex from the mid- and low-exposure groups also were examined for histopathological lesions.

Clinical signs of toxicity (nasal discharge in males and red-tinged fur in females) were observed in the high-exposure P0 group, but there were no effects on body weight. Histopathology revealed a significant increase in the incidence of rhinitis in the nasal turbinates of P0 animals (both sexes) exposed to 0.079 and 0.290 ppm and hyperplasia and dysplasia of the respiratory epithelium of P0 males at 0.290 ppm. The incidence of hyperplasia was significantly increased in P0 females at 0.290 ppm. There were no treatment-related gross lesions in F1 animals that were necropsied. F1 males had a significant increase in the incidence of rhinitis at all exposure concentrations; in females, this increase was apparent only at the two higher doses. In the high-exposure group (males), there was a significant increase in the incidence of submucosal lymphoid infiltrates in both the larynx and the trachea as well as a significant increase in the

incidence of intracellular eosinophilic droplets. There were no treatment-related effects in the trachea or larynx of F1 females.

During the 12-week prebreed exposure of F1 animals, animals from the 0.290-ppm group exhibited reduced body weights (both sexes) and weight gain (males only). The only treatment-related clinical signs were observed in F1 females and included perinasal encrustation and red-tinged fur. F2 pup body weights and weight gain per litter were reduced at 0.079 and 0.290 ppm during lactation.

In this study, there was no effect of exposure on any of the reproduction parameters evaluated. The LOAEL, based on an increased incidence of rhinitis in F1 males, is 0.02 ppm (0.14 mg/cu.m). The LOAEL(HEC), based on a RGDR of 0.18 for this extrathoracic effect, is 0.02 mg/cu.m.

I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Medium
RfC — Medium

Confidence in the Diem et al. (1982) study is medium. Although the study was prospective and used appropriate endpoints and state-of-the-art methods in monitoring, the lack of exposure characterization in the first 2 years and the unknown relationship of peak exposures to lung function decline detract from clear identification of the NOAEL and LOAEL. The database is given a medium confidence rating because of limitations in monitoring and analytical procedures in the majority of occupational studies cited and the uncertainties associated with peak vs. TWA exposures as determinants of toxicity. In addition, developmental toxicity data from a second species are lacking. Medium confidence in the RfC results.

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.

This assessment was peer reviewed by external scientists. This review was completed on May 18, 1995. Their comments have been carefully evaluated and considered in the revision and finalization of this IRIS Summary. A record of these comments is included in the IRIS documentation files.

Other EPA Documentation — U.S. EPA, 1988, 1989

Agency Work Group Review — 04/21/1988, 12/18/1990, 09/11/1991, 09/24/1993, 05/11/1995

Verification Date — 05/11/1995

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 2,4-/2,6-Toluene diisocyanate mixture (TDI) conducted in August 2003 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).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 2,4-/2,6-Toluene diisocyanate mixture (TDI)
CASRN — 26471-62-5

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

VI. Bibliography

Substance Name — 2,4-/2,6-Toluene diisocyanate mixture (TDI)
CASRN — 26471-62-5

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

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VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — 2,4-/2,6-Toluene diisocyanate mixture (TDI)
CASRN — 26471-62-5

Date	Section	Description
09/01/1995	I.B.	Inhalation RfC summary on-line
10/28/2003	I.B.6	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — 2,4-/2,6-Toluene diisocyanate mixture (TDI)
CASRN — 26471-62-5
Last Revised — 06/01/1995

- 26471-62-5
- 584-84-9
- 91-08-7
- 1,3-DIISOCYANATO-2-METHYLBENZENE
- 2,4-DIISOCYANATO-1-METHYLBENZENE
- 2,4-DIISOCYANATOTOLUENE
- 2,4-TDI
- 2,4-TOLUENE DIISOCYANATE
- 2,4-TOLUYLENE DIISOCYANATE
- 2,4-TOLYLENE DIISOCYANATE

- 2,6-DIISOCYANATO-1-METHYLBENZENE
- 2,6-DIISOCYANATOTOLUENE
- 2,6-TDI
- 2,6-TOLUENE DIISOCYANATE
- 2-METHYL-META-PHENYLENE DIISOCYANATE
- 2-METHYL-META-PHENYLENE ISOCYANATE
- 2-METHYL-M-PHENYLENE ISOCYANATE
- 4-METHYL-META-PHENYLENE DIISOCYANATE
- 4-METHYL-M-PHENYLENE ISOCYANATE
- 4-METHYL-PHENYLENE DIISOCYANATE
- 4-METHYL-PHENYLENE ISOCYANATE
- DIISOCYANATOTOLUENE
- METHYLPHENYLENE ISOCYANATE
- AI3-15101
- BENZENE, 1,3-DIISOCYANATO-2-METHYL-
- BENZENE, 1,3-DIISOCYANATOMETHYL-
- BENZENE, 2,4-DIISOCYANATO-1-METHYL-
- BENZENE, 2,6-DIISOCYANATO-1-METHYL-
- CRESORCINOL DIISOCYANATE
- DESMODUR T80
- DI-ISOCYANATE DE TOLUYLENE [FRENCH]
- DI-ISO-CYANATOLUENE
- DIISOCYANAT-TOLUOL [GERMAN]
- HYLENE T
- HYLENE TCPA
- HYLENE TIC
- HYLENE TLC
- HYLENE TM
- HYLENE TM-65
- HYLENE TRF
- ISOCYANIC ACID, 2-METHYL-META-PHENYLENE ESTER
- ISOCYANIC ACID, 2-METHYL-M-PHENYLENE ESTER
- ISOCYANIC ACID, 4-METHYL-M-PHENYLENE ESTER
- ISOCYANIC ACID, METHYLPHENYLENE ESTER
- META-TOLUENE DIISOCYANATE
- META-TOLYLENE DIISOCYANATE
- MONDUR TD
- MONDUR TD-80
- MONDUR TDS
- M-TOLYLENE DIISOCYANATE
- NACCONATE IOO
- NCI-C50533
- NIAX TDI
- NIAX TDI-P
- RCRA WASTE NO. U223

- RUBINATE TDI 80/20
- TDI
- TDI-80
- TOLUEEN-DIISOCYANAAT [DUTCH]
- TOLUEN-DISOCIANATO [ITALIAN]
- TOLUENE 2,4-DIISOCYANATE
- TOLUENE, 2,4-DIISOCYANATO-
- TOLUENE 2,6-DIISOCYANATE
- TOLUENE DIISOCYANATE
- TOLUILENODWUIZOCYJANIAN [POLISH]
- TOLUYLENE-2,4-DIISOCYANATE
- TOLYENE 2,4-DIISOCYANATE
- TOLYLENE 2,4-DIISOCYANATE
- TOLYLENE 2,6-DIISOCYANATE
- TOLYLENE DIISOCYANATE
- TULUYLENDIISOCYANAT [GERMAN]