CHRONIC TOXICITY SUMMARY

2,4- AND 2,6-TOLUENE DIISOCYANATE

(2,4- and 2,6-TDI; 2,4- and 2,6-diisocyanato-1-methylbenzene; 2,4- and 2,6-diisocyanatoluene)

CAS Registry Number: 584-84-9 or 26471-62-5 (mixture)

I. Chronic Toxicity Summary

Inhalation reference exposure level	**0.07 µg/m^3** (0.01 ppb)
Critical effect(s)	Decreased lung function in occupationally exposed workers
Hazard index target(s)	Respiratory system

II. Chemical Property Summary (HSDB, 1995; CRC, 1994)

Description	Colorless to pale yellow liquid
Molecular formula	$C_9H_6N_2O_2$
Molecular weight	174.15 g/mol
Boiling point	2,4-TDI: 251°C
Melting point	2,4-TDI: 20.5°C 2,6-TDI: 18.3°C
Vapor pressure	2,4-TDI: 0.008 torr @ 20°C
Solubility	Miscible with ether, acetone, benzene, carbon tetrachloride, chlorobenzene, diglycol monomethyl ether, kerosene, olive oil, alcohol; soluble in ethyl acetate
Conversion factor	7.1 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Commercial toluene diisocyanate is comprised of approximately 80% 2,4-TDI and 20% 2,6-TDI. TDI is used in the manufacture of polyurethane foams, elastomers, and coatings (HSDB, 1995; Howard, 1989). It is also used in the manufacture of floor and wood finishes, lacquers, foam plastics, polyurethane foam coated fabrics, and insulation materials (HSDB, 1995; Howard, 1989; Duncan *et al.*, 1962). Emissions of TDI to the atmosphere can occur during production, handling, and processing of polyurethane foam (Howard, 1989) and coatings. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 13,223 pounds of toluene diisocyanates, 35,663 pounds of toluene-2,4-diisocyanate, and 754 pounds of toluene-2,6-diisocyanate (CARB, 1999).

IV. Effects of Human Exposures

Diem *et al.* (1982) conducted a prospective study beginning in 1973 of 277 male workers involved in the production of TDI. The study examined pulmonary function, with nine examinations conducted over a five year period. A large group of workers (168) with no previously reported TDI exposure was examined 6 months prior to TDI production in the plant to provide baseline pulmonary function measurements. Personal sampling by continuous tape monitors provided exposure levels, but was not used until 2 years after the study was initiated. Sampling information resulted in a division of the workers into two groups: those exposed to levels below 68.2 ppb-months (which reflects the level of exposure of a worker for the entire 5 year duration in the low-exposure area (geometric mean = 1.1 ppb)) and those above this level. The arithmetic mean exposure level for the non-smokers was 1.9 ppb TDI in the high-exposure group and 0.9 ppb TDI in the low-exposure group (calculated by Hughes, 1993). The higher exposure group was further limited to those individuals who showed a normal FEV_1 to height ratio. Data were analyzed by the maximum likelihood weighted regression approach (Diem and Liukkonen, 1988). Both FEV_1 and forced expiratory flow (25-75%) [FEF (25-75%)] among workers who never smoked were found to be significantly reduced in the high-exposure group (n = 21) compared to the low-exposure group (n = 35). Categorizing workers based on time spent at exposure levels above 20 ppb demonstrated a significant difference in FEV_1 and FEF(25-75%) and this effect was also observed among current smokers. Among low-exposure workers, a smoking effect was observed, with smokers showing a significant decline in FEV_1.

A similar longitudinal study of lung function was conducted among workers exposed to TDI during the course of polyurethane foam production (Jones *et al.*, 1992). Participants (181 males and 46 females) were required to have 3 or more spirometric examinations over the 5 year study period. Exposure of males was evaluated by personal monitors and resulted in arithmetic mean low exposure levels of 0.3, 0.4, and 0.4 ppb TDI for never-smokers, ex-smokers, and current smokers, respectively. Among workers with high-level exposure, mean TDI levels were reported to be 1.3, 1.2, and 1.2 ppb for never-, ex-, and current smokers, respectively. Stepwise multiple linear regression methods (excluding asthmatics) were used in evaluating the data (Diem and Liukkonen, 1988). No relationship between TDI exposure and change in lung function was observed, although the prevalence of chronic bronchitis was significantly associated with exposure.

A longitudinal study of 780 workers exposed to TDI in the production of polyurethane foam was also conducted (Bugler *et al.*, 1991; unpublished). Exposure levels were established using continuous-tape personal monitoring devices. The mean exposure level was 1.2 ± 1.1 (SD) ppb TDI among 521 workers and 0.3 ± 0.18 ppb TDI in the control group. Another control group who handled cold urethane products had an 8 hour time-weighted average exposure of 0.6 ppb TDI. No significant longitudinal changes in FEV_1 were found after regression analysis, although FEV_1 decline was high among the control group. Exposure levels among the different groups were close, limiting the power of the study to detect changes. Approximately 3% of the 780 workers showed signs of TDI sensitization and, of these, over 80% were in the group exposed to 1.2 ppb.

Meta-analysis of the three data sets (Jones *et al.*, 1992; Bugler *et al.*, 1991; Diem *et al.*, 1982) showed that the difference in significance among the findings of each of the studies could have been due to chance. The change in the probability density for the decline in FEV_1 shifted in the same direction for all data sets and the smoker/non-smoker slope difference became less meaningful with the data set combination (Hasselblad, 1993).

Another toxicological area of concern with exposure to TDI is the development of sensitization, resulting in a well-documented condition known as "isocyanate asthma" of either immediate or delayed-type onset (Moscato *et al.*, 1991). The level of exposure required to either develop or trigger a sensitization reaction is not well documented, however. Weaknesses of studies showing pulmonary effects of TDI exposure include use of area sampling vs. breathing-zone measurement of exposure, poor statement of criteria for evaluating hypersensitivity, and the presence of other compounds in the environment which may influence lung function.

V. Effects of Animal Exposures

Mice were exposed to TDI concentrations ranging from 0.007 to 1.18 ppm for 3 hours/day for 5 days consecutively (Sangha and Alarie, 1979); decreased respiratory rate was observed in groups exposed to levels higher than 0.023 ppm TDI. Groups of four mice were also exposed to 0.031 and 0.250 ppm TDI for 3 hours/day for 3 days. Lesions of the external nares and respiratory epithelium were observed in the high dose group.

Female guinea pigs were exposed to 0.12, 0.36, 0.61, 0.96, and 10.00 ppm TDI (head-only) for 3 hours/day for 5 consecutive days (short protocol) or to 0.02 ppm TDI (whole body) plus controls for 6 hours/day, 5 days/week for 70 days (long protocol). The animals showed decreased respiration rate two hours into exposure at levels above 0.12 ppm TDI and had a cytophilic antibody response at 0.96 ppm and above (Karol, 1983). All animals exposed to 10 ppm died. Dermal sensitivity was evident among animals in the short protocol down to 0.12 ppm TDI. No antibody response or dermal sensitivity developed in the animals exposed to 0.02 ppm TDI in the long protocol.

Similarly, guinea pigs (8 females) were exposed head only to 1.40 ppm TDI for 3 hours/day for 4 days (no control group). In a second exposure regimen, animals (n = 24) were exposed to 0.02 ppm TDI for 6 hours/day, 4 days/week for 70 days (whole body) including a control group (n = 8) exposed to room air in a similar manner (Wong *et al.*, 1985). Half the animals (4/8) exposed to 1.40 ppm TDI showed pulmonary hypersensitivity (measured on days 37 and 38) and all developed TDI-specific IgE antibodies, whereas none of the animals in the 0.02 ppm TDI group showed either of these effects. Histopathological effects in the 1.40 ppm TDI group included interstitial inflammation, pleural thickening, and peripheral lymphoid hyperplasia. Interstitial inflammation was noted in 2/24 animals exposed to 0.02 ppm TDI.

SD rats and CD-1 mice were exposed to 0.05 or 0.15 ppm TDI for 6 hours/day, 5 days/week for 2 years (Loeser, 1983; nasal histopathology reported by Owen, 1984). Among female rats at both dose levels and male rats at the high dose level, histopathological effects observed included necrotic rhinitis, metaplasia, and inflammation of the respiratory epithelium. Female animals

showed dose-dependent increases in incidence and severity of this effect. Similar lesions were reported in mice, although they were not well characterized.

Reproductive toxicity of TDI was evaluated in a two-generation study conducted in rats (Tyl and Neeper-Bradley, 1989). Weanling rats (28/sex/dose) were exposed to 0, 0.020, 0.079, and 0.290 ppm TDI for 6 hours/day, 5 days/week, for 10 weeks, at which time the animals were randomly mated. Exposure of the females continued through gestation (excepting gestational day 20 through the fourth day postpartum), and exposure of the males continued only until the delivery of the F_1 generation. Weanlings in the F_1 generation were exposed in a manner similar to the parental (P_0) generation and bred after weaning to produce the F_2 generation. Body weights were significantly reduced among animals of both sexes in the highest dose group and weight gain was reduced among males in the highest dose group. Effects on the respiratory system in the P_0 generation animals included rhinitis of the epithelium in the two highest dose groups of both male and female animals. Hyperplasia of the respiratory epithelium was also increased in the high dose groups of both sexes among P_0 animals. Among males in the F_1 generation, the incidence of rhinitis was significantly increased at all exposure levels and the incidence of submucosal lymphoid infiltrates of the larynx and trachea was increased in the highest dose group. F_2 generation animals showed reduced pup weight and weight gain during the lactation period in the two highest dose groups.

Developmental toxicity of TDI was evaluated by exposing pregnant Sprague-Dawley rats (25/group) for 6 hours/day on gestational days 6-15 to 0, 0.021, 0.120, or 0.48 ppm TDI (Tyl, 1988). Reduced maternal body weight, decreased food consumption, and rales occurred among the dams in the 0.48 ppm TDI dose group. A significant fetal effect, a statistically significant increase in a specific skeletal malformation, was reported in the highest dose group.

VI. Derivation of the Chronic Reference Exposure Level

Study	Diem *et al.*, 1982
Study population	Human TDI production workers (n = 168)
Exposure method	Occupational inhalation exposure
Critical effects	Decreased lung function
LOAEL	0.014 mg/m^3 (1.9 ppb)
NOAEL	0.006 mg/m^3 (0.9 ppb) (non-smokers)
Exposure continuity	8 h/day (10 m^3/day occupational exposure), 5 d/wk
Exposure duration	5 years
Average occupational exposure	0.002 mg/m^3 for NOAEL group (0.006 x 10/20 x 5/7)
Human equivalent concentration	0.002 mg/m^3 for NOAEL group
LOAEL uncertainty factor	1
Subchronic uncertainty factor	3
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference exposure level	0.00007 mg/m^3 (0.07 $\mu g/m^3$; 0.01 ppb)

The chronic REL is equivalent to the U.S. EPA RfC. OEHHA agreed with the U.S. EPA analysis and the selection of Diem *et al*. (1982) as the most appropriate study to use for the REL. The rationale for selection of this study is as follows. This study presented evidence of a decline in lung function, as indicated by decrements in FEV_1, among workers involved in TDI production. Other factors supporting its quality include:
(1) the absence of other confounding compounds in the work environment,
(2) the establishment of baseline lung function prior to exposure to TDI,
(3) a "parallel internal comparison" of study groups for lung function,
(4) an appropriate statistical analysis which took into account interindividual variability,
(5) breathing zone measurement of TDI (although commenced 2 years into the study), and
(6) a smoking effect on lung function.

VII. Data Strengths and Limitations for Development of the REL

The major strengths of the chronic REL for TDI are the use of human exposure data from workers exposed over a period of years and the observation of a NOAEL. The major weaknesses are the uncertainty in estimating exposure, the potential variability in exposure concentration, and the limited nature of the study that focused on lung effects.

VIII. References

Bugler J, Clark RL, Hill ID, and McDermott M. 1991. The acute and long-term respiratory effects of aromatic di-isocyanates. A five year longitudinal study of polyurethane foam workers. Study sponsored by the British Rubber Manufacturers Association, the International Isocyanate Institute, and the Health and Safety Executive, UK.

CARB. 2000. California Air Resources Board. California Emissions Inventory Development and Reporting System (CEIDARS). Data from Data Base Year 1998. February 12, 2000.

CRC. 1994. CRC Handbook of Chemistry and Physics, 75th edition. Lide DR, ed. Boca Raton, FL: CRC Press Inc.

Diem JE, Jones RN, Hendrick DJ, Glindmeyer HW, Dharmarajan V, Butcher BT, Salvaggio JE, and Weill H. 1982. Five-year longitudinal study of workers employed in a new toluene diisocyanate manufacturing plant. Am. Rev. Respir. Dis. 126:420-428.

Diem JE, and Liukkonen JR. 1988. A comparative study of three methods for analyzing longitudinal pulmonary function data. Stat. Med. 7:19-28.

Duncan B, Scheel LD, Fairchild EJ, Killens R, and Graham S. 1962. Toluene diisocyanate inhalation toxicity: pathology and mortality. Am. Ind. Hyg. Assoc. J. 23:447-456.

Hasselblad V. 1993. Analysis of studies of workers exposed to toluene diisocyanate. Report prepared for U.S. EPA, Environmental Criteria and Assessment Office, Research Triangle Park, NC.

Howard PH. (ed) 1989. Handbook of environmental fate and exposure data for organic chemicals. Vol. I. Large production and priority pollutants. Chelsea, MI: Lewis Publishers, Inc.

HSDB. 1995. Hazardous Substances Data Bank. National Library of Medicine, Bethesda, MD (TOMES® CD-ROM Version). Denver, CO: Micromedex, Inc. (Edition expires 7/31/96).

Hughes J. April and November, 1993. Memoranda from Janet Hughes, Tulane Medical Center, to Mark Greenburg, U.S. EPA.

Jones RN, Rando RJ, Glindmeyer, Foster TA, Hughes JM, O'Neil CE, and Weill H. 1992. Abnormal lung function in polyurethane foam producers: weak relationship to toluene diisocyanate exposures. Am. Rev. Respir. Dis. 148:671-677.

Karol MH. 1983. Concentration-dependent immunologic response to toluene diisocyanate (TDI) following inhalation exposure. Toxicol. Appl. Pharmacol. 68:229-241.

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.

Moscato G, Dellabianca A, Vinci G, Candura SM, and Bossi MC. 1991. Toluene diisocyanate-induced asthma: clinical findings and bronchial responsiveness in 113 exposed subjects with work-related respiratory symptoms. J. Occup. Med. 33:720-725.

Owen PE. 1984. The toxicity and carcinogenicity to rat of toluene diisocyanate vapour administered by inhalation for a period of 113 weeks. Addendum report. Volume 2. Hazelton Laboratories Europe.

Sangha GK, and Alarie Y. 1979. Sensory irritation by toluene diisocyanate in single and repeated exposures. Toxicol. Appl. Pharmacol. 50:533-547.

Tyl RW. 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 RW, and Neeper-Bradley TL. 1989. Two-generation reproduction study of inhaled toluene diisocyanate in CD (Sprague-Dawley) rats. Union Carbide, Bushy Run Research Center. Project No. 86-33-90704.

U.S. EPA. 1995. United States Environmental Protection Agency. Documentation of the reference concentration for chronic inhalation exposure (RfC) for 2,4-/2,6-toluene diisocyanate mixture. Integrated Risk Information System (IRIS on-line). Washington, DC: U.S. EPA. Available online at http://www.epa.gov/ngispgm3/iris

Wong KL, Karol MH, and Alarie Y. 1985. Use of repeated CO_2 challenges to evaluate the pulmonary performance of guinea pigs exposed to toluene diisocyanate. J. Toxicol. Environ. Health 15:137-148.