CHRONIC TOXICITY SUMMARY

METHYLENE DIPHENYL ISOCYANATE

(diphenylmethane diisocyanate)

CAS Registry Number: 101-68-8

I. Chronic Reference Exposure Level

Inhalation reference exposure level	**0.7 µg/m^3**
Critical effect(s)	Hyperplasia of the olfactory epithelium in rats
Hazard index target(s)	Respiratory system

II. Physical and Chemical Properties (HSDB, 1995)

Description	Light yellow solid
Molecular formula	$C_{15}H_{10}N_2O_2$ (monomer)
Molecular weight	Variable (monomer = 250.27 g/mol)
Density	1.197 g/cm^3 @ 70°C (monomer)
Boiling point	196°C (monomer)
Melting point	37°C (monomer)
Vapor pressure	0.001 torr @ 40°C (monomer)
Solubility	Soluble in acetone, benzene, kerosene, and nitrobenzene (monomer)
Conversion factor	Monomer: 1 ppm = 10.2 mg/m^3 at 25°C; Not applicable for polymer

III. Major Uses or Sources

Methylene diphenyl isocyanate (MDI) is used for bonding rubber to nylon. MDI is also used in the manufacture of lacquer coatings and in the production of polyurethane resins and spandex fibers (HSDB, 1995). It is often handled in a partially polymerized form ("MDI polymer"), which has a much lower vapor pressure than the monomer. 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 30,398 pounds of MDI (CARB, 2000).

IV. Effects of Human Exposure

A 5-year occupational study of 107 workers from a polyurethane plastic manufacturing plant examined pulmonary function, respiratory symptoms, and smoking habits (Musk *et al.*, 1982, 1985). No significant changes in pulmonary function or respiratory symptoms were observed

when controlled for smoking. Mean MDI concentrations measured ranged from 0.0003 to 0.0006 ppm.

Significantly increased prevalence of asthma in female workers and of chronic bronchitis in male and female workers was observed following occupational exposure to low levels of MDI (<0.02 ppm) (Pham *et al.*, 1988). Workers from two plants were grouped by job classification and evaluated in this study conducted in 1976; workers were grouped as unexposed (62 men, 21 women), indirectly exposed (61 men, 56 women), or directly exposed (91 men, 27 women). Further characterization of the exposure groups was not presented. Decrements in pulmonary function (measured by VC, FEV_1 and single-breath carbon monoxide diffusion tests) were observed in men in the direct and indirect exposure groups: decrements in men with a history of direct exposure to MDI were statistically significant. Workers were also grouped by duration of occupational exposure (<20 months, 20-60 months, >60 months). Workers with known (direct or indirect) occupational exposure to MDI for greater than 60 months exhibited statistically significant decrements in pulmonary function tests. The follow-up examination of this study describes data from male workers only. At the time of the 5-year follow-up, air levels had been reduced to below the maximum allowed air concentration of 0.005 ppm by a modification of the ventilation system. Statistically significant decrements in pulmonary function were observed again in workers with known direct occupational exposure to MDI. Workers who were exposed at the time of the 1976 study but had since been removed from exposure did not exhibit decrements in pulmonary function, leading the authors to conclude that the effects of low-level exposure to MDI are to some extent reversible. Flaws in study design, including lack of exposure characterization, attrition, and inclusion of asthmatics in cohorts, preclude a quantitative assessment of MDI exposure on lung function.

An epidemiologic study of foundry workers reported more respiratory symptoms and significantly lower mean FEV_1 and maximum mid-expiratory flow at 25-75% in exposed workers compared to controls (Johnson *et al.*, 1985). However, MDI-exposed workers also had unquantified exposure to silica, metal dust, phenol formaldehyde, and a pyridine derivative precluding the evaluation of respiratory effects resulting from MDI exposure.

A worker with 5 years occupational exposure and suspected MDI hypersensitivity was exposed continuously in a controlled chamber to 5 ppb for 15 minutes, then 10 ppb for 30 minutes, and 20 ppb for 15 minutes (Marczynski *et al.*, 1992). The worker had not been exposed to MDI in the workplace for 5 days prior to the test challenge. Exposure to MDI resulted in an immediate, moderate, asthmatic reaction associated with significant hypoxemia.

IgG antibodies recognizing MDI-human serum albumin conjugates were detected in 4 of 5 MDI-exposed workers (Aul *et al*., 1999). The levels of specific IgG antibodies were more elevated with polymeric MDI compared with monomeric MDI.

A workplace death of a 39-year-old foundry worker was ascribed to occupational asthma induced by MDI exposure (Carnio *et al*., 1997). Postmortem pulmonary findings included epithelial desquamation, mucosal eosinophilic/neutrophilic infiltration, bronchial vessel dilatation, and edema and hypertrophy of smooth muscle.

V. Effects of Animal Exposure

Rats were exposed to 0.2, 1.0, and 6.0 mg/m^3 aerosolized MDI polymer 6 hours per day, 5 days per week for 24 months (Reuzel *et al.*, 1990; 1994). Statistically significant increased incidences of basal cell hyperplasia, olfactory epithelial degeneration, alveolar duct epithelialization, localized alveolar bronchiolization, and adenomas were observed in male and female rats exposed to 6.0 mg/m^3 MDI. An accumulation of macrophages with yellow pigment was also noted in the lungs and mediastinal lymph nodes. Male rats exposed to this concentration also exhibited a statistically significant increase in the incidence of Bowman's gland hyperplasia. Male rats exposed to 1 mg/m^3 MDI also exhibited statistically significant increased incidences of basal cell hyperplasia and Bowman's gland hyperplasia. An accumulation of macrophages with yellow pigment was observed in the lungs of female rats and the lungs and mediastinal lymph nodes of male rats exposed to 1 mg/m^3. No adverse effects were noted in rats exposed to 0.2 mg/m^3 MDI.

Hyperplasia of the olfactory epithelium with MDI exposure (Reuzel *et al.*, 1990; 1994)

Concentration (mg/m^3)	*Males*			*Females*			*Combined*		
	Responders	*N*	*Incidence*	*Responders*	*N*	*Incidence*	*Responders*	*N*	*Incidence*
0	14	60	0.23	4	60	0.067	18	120	0.15
0.2	13	60	0.22	8	60	0.13	21	120	0.18
1	26	60	0.43	8	60	0.13	34	120	0.28
6	32	60	0.53	49	59	0.83	81	119	0.68

Guinea pigs were exposed to 2 ppm MDI 3 hours per day for 5 days (Aizicovici *et al.*, 1990). Qualitative immunostaining techniques indicated that MDI was localized in the respiratory tract. The spleen, lymph nodes, and thymus had very little staining. However, another study exposed guinea pigs to 4 ppb radiolabelled toluene diisocyanate (TDI) for 1-hour and found measurable radioactivity in extrathoracic tissues and body fluids (Kennedy *et al.*, 1989). Therefore, there is a possibility that MDI may be transported to sites other than the respiratory tract, such as the ovaries and testes, following inhalation exposure.

Gravid Wistar rats, Crl:(WI)BR, were exposed by whole-body inhalation to clean air (control) and to 1, 3, and 9 mg/m^3 MDI, respectively, for 6 hr per day from days 6 to 15 post conception (Buschmann *et al.*, 1996). Rats were killed on day 20. The lung weights in the high-dose group were significantly increased compared to the sham-treated control animals. Treatment did not influence any other maternal and/or fetal parameters investigated (including maternal weight gain, number of corpora lutea, implantation sites, pre-and postimplantation loss, fetal and placental weights, gross and visceral anomalies, and degree of ossification). A slight but significant increase in litters with fetuses displaying asymmetric sternebra(e) was observed after

treatment with the highest dose. Although the relevance of an increase of this minor anomaly in doses which maternal toxicity is limited and within the limits of biological variability, a substance-induced effect in the high-dose group cannot be excluded with certainty. Thus, the authors reported a NOAEL of 3 mg/m^3 for embryotoxic effects.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Reuzel *et al.*, 1990; 1994
Study population	Rats
Exposure method	Inhalation of polymeric aerosolized MDI (0, 0.2, 1.0, and 6.0 mg/m^3)
Critical effects	Hyperplasia of the olfactory epithelium
LOAEL	1 mg/m^3
NOAEL	0.2 mg/m^3
Benchmark Concentration (BMC_{05})	0.25 mg/m^3 (95% lower confidence limit on concentration for a 5% incidence of response based on analysis of the combined male and female data with a linear model, the best-fitting of 6 models examined, p = 0.99)
Study continuity	6 hours per day, 5 days per week
Study duration	24 months
Average experimental exposure	0.046 mg/m^3 for BMC_{05} group (0.25 x 6/24 x 5/7)
Human equivalent concentration	0.020 mg/m^3 for BMC_{05} group (particle with extrathoracic respiratory effects, RDDR = 0.453, based on MMAD = 0.68 µm and sigma g = 2.93)
LOAEL uncertainty factor	1
Subchronic uncertainty factor	1
Interspecies uncertainty factor	3
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	30
Inhalation reference concentration	0.7 µg/m^3

The data of Reuzel *et al*. (1990, 1994) were examined with six quantal dose-response models (linear, log-normal, Weibull, logistic, quadratic, gamma) using USEPA BMDS 1.2. All models except the quadratic gave a good fit to the combined male and female data set. The linear model was selected as the best-fitting model. Possible differences between male and female susceptibility are suggested by the gender-specific data, although the significance of these differences is uncertain.

USEPA used the same two studies and a BMC_{10} approach to develop an RfC of 0.6 µg/m^3. Since USEPA used a 3-fold database uncertainty factor, their BMC_{10}-based RfC is comparable to the BMC_{05}-based OEHHA REL.

VII. Data Strengths and Limitations for Development of the REL

Strengths of the REL for MDI include the use of a well-conducted, long-term inhalation study, the observation of a NOAEL, and the estimation of a benchmark concentration. A limitation of the REL is that it is based on data on exposures to MDI "polymer" which actually contains nearly 50% monomer. Monomers may in some cases be more toxic than polymers. Thus, effects of pure monomeric MDI may occur at concentrations somewhat lower than observed in the reported study on MDI polymer. However, the capacity of MDI polymer to induce immunologic sensitization is greater than that of MDI monomer (Aul *et al*., 1999). The relative potential of MDI monomer and polymer to induce hyperplasia of the olfactory epithelium is unknown.

VIII. References

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CHRONIC TOXICITY SUMMARY

PHTHALIC ANHYDRIDE

(1,3-isobenzofurandione; phthalic acid anhydride)

CAS Registry Number: 85-44-9

I. Chronic Toxicity Summary

Inhalation reference exposure level	**20 mg/m^3**
Critical effect(s)	Eye and respiratory irritation, asthma, and bronchitis in occupationally exposed workers
Hazard index target(s)	Respiratory system

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

Description	White or pale yellow crystals
Molecular formula	$C_8H_4O_3$
Molecular weight	148.11 g/mol
Boiling point	295°C
Melting point	130.8°C
Vapor pressure	5.14×10^{-4} torr @ 25°C; 1 torr @ 96.5°C
Solubility	Soluble in 162 parts water, 125 parts carbon disulfide; soluble in hot benzene
Conversion factor	1 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

The primary use of phthalic anhydride (PA) is as a chemical intermediate in the production of plastics from vinyl chloride. Phthalate esters, which function as plasticizers, are derived from phthalic anhydride. Phthalic anhydride has another major use in the production of polyester resins and other minor uses in the production of alkyd resins used in paints and lacquers, certain dyes (anthraquinone, phthalein, rhodamine, phthalocyanine, fluorescein, and xanthene dyes), insect repellents, and urethane polyester polyols. It has also been used as a rubber scorch inhibitor and retarder (HSDB, 1995; National Cancer Institute (NCI), 1979). 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 11,442 pounds of phthalic anhydride (CARB, 2000).

IV. Effects of Human Exposure

Symptoms in workers exposed to phthalic anhydride by inhalation in two plants (A and B) manufacturing alkyd and unsaturated polyester resins were studied (Nielsen *et al.*, 1988). Two groups of exposed workers were identified in each plant. One group worked directly loading the reactors from bags of phthalic anhydride ("heavy" exposure – 35 workers) and the other group was involved with "other work" which led to "low" exposure (25 workers). Mean employment times for the "heavy" and "low" exposure groups were 13.3 and 11.9 years, respectively. Time-weighted average air concentrations for workers from the loading of PA was 6.1 (range: 1.8-14.9) and 6.8 mg PA/m^3 (range: 1.5-17.4) in plants A and B, respectively. Similar exposure levels in both plants led to pooling of data. The exposure duration of the "heavy" group was estimated at approximately 30 minutes two times a day, corresponding to the time of loading, and resulted in a full-day time weighted exposure estimate of 0.4 mg PA/m^3. For those engaged in "other work" exposure levels were estimated at < 0.1 mg PA/m^3 (the limit of detection). Other chemicals in use in smaller amounts included maleic anhydride, isophthalic anhydride, and trimellitic anhydride. Comparison of symptom incidence between the "heavy" and "low" exposure groups included conjunctivitis (46% vs. 20%), rhinitis (40% vs. 20%), rhinoconjunctivitis (17% vs. 12%), asthma (17% vs. 0%), and chronic bronchitis (17% vs. 4%). Serum antibodies were measured in both groups of workers and compared to 22 nonexposed workers (employed at a food processing factory). The only significantly changed level was an increase in specific IgG in the "heavy" exposure group. A correlation was also noted between specific IgG level and exposure level, although not all individuals with elevated specific IgG reported symptoms.

In a study conducted at another plant manufacturing alkyd and/or unsaturated polyester resins, serum immunoglobulins and lung function were examined in 23 workers exposed to phthalic anhydride and 18 control subjects (Nielsen *et al.*, 1991). Estimated exposure levels were 6.6 mg PA/m^3 (range: 1.5-17) (Nielsen *et al.*, 1988). Workers were examined for sensitization to PA and other allergens and possible development of small airways disease. Among the exposed workers, there was significantly increased reporting of conjunctivitis and rhinoconjunctivitis. One worker showed an asthmatic response to anhydrides. No significant differences in lung function tests were observed between exposed and unexposed groups.

Symptoms in workers occupationally exposed to PA during the course of producing alkyd and/or polyunsaturated polyester resins were described (Wernfors *et al.*, 1986). Exposure estimates of breathing zone PA levels ranged from 3 to 13 mg/m^3 for workers engaged directly with the handling of PA. In other areas the estimated level was <0.3 mg/m^3. The study examined 48 workers who were employed at the time of the study and 70 former employees who responded to a survey of symptoms related to exposure. No unexposed control group was included in the study. Workers who were employed for at least two months reported symptoms of rhinitis (28%), chronic bronchitis (11%), and asthma (28%). Among a subset of 11 workers with asthma, 3 had positive skin tests for PA sensitivity. Bronchial provocation tests with 6 or 0.5 mg/m^3 PA for 5 or 10 minutes were positive in 2 workers.

V. Effects of Animal Exposure

Male albino rats (6/treatment group) were exposed to phthalic anhydride vapors at 0, 0.02, 0.2, and 1 mg/m^3 continuously for 45 days (Protsenko, 1970). After a two week recovery period the testes were examined for spermatozoa motility time as well as for ascorbic acid, dehydroascorbic acid, and nucleic acid content. Motility time was defined as the time it took for spermatozoa to cease motion completely under microscopic examination. Spermatozoa motility time was decreased ~50% in the 1 mg/m^3 dose group and ~25% in the 0.2 mg/m^3 dose group. Significant decreases in ascorbic acid and dehydroascorbic acid levels were found in animals exposed to 0.2 and 1.0 mg/m^3 phthalic anhydride, and dehydroascorbic acid levels were decreased in the 0.02 mg/m^3 dose group. At 1 mg/m^3, RNA levels and combined RNA and DNA levels were significantly increased over controls. No significant changes were observed in the 0.02 mg/m^3 dose group.

Five and six female Hartley guinea pigs were exposed to 0.05-0.2 mg/m^3 and 0.6-6 mg/m^3 phthalic anhydride dust, respectively, for 3 hours/day for 5 consecutive days (Sarlo and Clark, 1992). Exposures were expressed as ranges due to difficulty in regulating dust levels in the chambers. Sampling of dust showed particles were 65-80% < 10 μm diameter and had a mean mass diameter of 5.8-9.8 μm. Eight control animals were exposed to filtered air only. Two weeks after the last exposure, animals were challenged for 30 minutes with aerosolized PA-guinea pig serum albumin conjugate. All animals in the "high" dose group showed immediate bronchoconstriction and transiently increased respiratory rate. Animals in this dose group also showed elevated IgG antibody titers. No detectable increase in antibody levels was found in the "low" dose group.

Type I hypersensitivity was examined in female Hartley guinea pigs exposed to phthalic anhydride dust (Sarlo *et al.*, 1994). Two groups of 8 animals were exposed to 0.5 or 1.0 mg/m^3, and two groups of 16 animals were exposed to 0 (filtered air only) or 5.0 mg/m^3 phthalic anhydride dust (respirable size – 5 μm) in stainless steel chambers for 3 hours/day for 5 consecutive days. Groups of 8 animals from the control and 5 mg/m^3 groups were challenged after a two week recovery period for 30 minutes with 5.0 mg/m^3 phthalic anhydride dust. Respiratory data were collected using a plethysmograph from 30 minutes before the exposure to 60 minutes after the exposure. No significant difference (defined as a change of 3 standard deviations from the same parameter in the control animals) in respiration rate or plethysmograph pressures was found between the exposed and unexposed animals. Eight animals in each of the four exposure groups were also challenged after two weeks of recovery with 2.0 mg/m^3 aerosolized PA-guinea pig serum albumin (GPSA) conjugate as described above. Respiratory rate was increased in 4/8 of the high-dose group animals and 1/8 of the low-dose animals. Plethysmograph pressures were increased in 3/8 animals in the high-dose group and one animal each in the low- and mid-dose groups. Serum IgG antibodies to PA-GPSA were elevated in all exposed animal groups and the effect showed a dose-response. Passive cutaneous anaphylaxis testing for anti-phthalic anhydride-GPSA IgG1a immunoglobulins showed positive results for 3/8, 1/8, and 5/8 animals in the 0.5, 1.0, and 5.0 mg/m^3 dose groups, respectively. Results in control animals were not described. Three of eight animals in the highest dose group had >189 hemorrhagic foci in their lungs. No control animal had more than 2 such foci. No foci were

observed in animals challenged with albumin conjugate. Serum IgG titer correlated with the presence of these foci.

Slavgorodskiy (1969) studied the toxicity of phthalic anhydride to animals from inhalation exposure. Sixty white male rats (strain not reported; group distribution not stated, but presumed to be 15 animals/treatment group) were exposed in 100 L chambers to 0, 0.18, 0.54, and 1.52 mg PA/m^3 aerosol continuously for 70 days. General condition and behavior, body weight, motor chronaxy of flexor and extensor muscles (every 10 days), cholinesterase activity (every two weeks), and hematological parameters were monitored during the course of the study. (Chronaxy is the minimum time for which a current must flow, at a voltage twice the minimal current necessary to produce muscle stimulation, in order to cause a muscle to contract.) No changes in body weight or behavior were observed in the treated animals. In animals in the high-dose group, the chronaxy ratio of flexors and extensors differed from the controls beginning on day 31 of exposure and continued until two weeks after exposure ceased. Significantly decreased whole blood cholinesterase activity occurred in the high- and mid-dose groups, with the change occurring after 42 days of exposure. An increase in thrombocyte count occurred in the high- and mid-dose groups after 70 days of exposure, but returned to normal during the two-week recovery period. Thus, 0.18 mg/m^3 PA appears to be a NOAEL in this study.

A chronic feeding study was conducted with phthalic anhydride in rats and mice to evaluate the carcinogenicity of the compound (National Cancer Institute (NCI), 1979). F344 rats (50/sex/dose group plus 20/sex control animals) were treated with diet containing 0, 7500, or 15,000 ppm phthalic anhydride for 105 weeks (which corresponds to approximately 0, 300, and 600 mg/kg-day, assuming that food consumption is 4% body weight/day). Animals were monitored for changes in body weight and for survival, and, upon death or the end of the study, were examined histopathologically. The only group showing significantly lower body weights was male rats in the high-dose group after week 13. No significant change in mortality was observed. Adverse non-cancer effects observed in the dosed groups, but not in the control animals, included “arched back, rough hair coat, ulceration, and corneal opacity”, however, incidences were described as “low”. No significant histopathological effects were found to be associated with exposure to phthalic anhydride. $B6C3F_1$ mice (50/sex/dose group plus 20/sex control animals) were initially treated with diet containing 0, 25,000, or 50,000 ppm phthalic anhydride (approximately 0, 3000, and 6000 mg/kg-day, assuming that food consumption is 12% body weight/day). Because of excessive weight loss after week 32, exposure levels were reduced during the course of the study such that the time-weighted average exposure for males was 16,346 and 32,692 ppm and for females was 12,019 and 24,038 ppm phthalic anhydride. Evaluation of toxicity was conducted at 104 weeks as with the rats. Mean body weight was reduced in male and female mice in a dose-related manner. No other significant treatment-related adverse effects were observed in the mice.

Pregnant female CD-1 mice (10/dose group) were treated intraperitoneally with phthalic anhydride in 0.5%(w/v) carboxymethyl cellulose solution on gestational days 8-10 (Fabro *et al.*, 1982). Dosing was variable, beginning within the 95% confidence limits of the LD_{01} and progressing geometrically downward until no effect was observed. Animals were terminated on Day 18 and examined for teratogenic effects including fetal viability and number, resorption, and gross malformations. The 95% lower confidence limit on the dose producing teratogenicity

(grossly observable malformations and fetal internal malformations) in 5% and 50% of animals were 0.40 and 1.37 mmol/kg-day (59 and 203 mg/kg-day), respectively.

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Neilsen *et al.* (1988; 1991)
Study population	23 occupationally-exposed workers
Exposure method	Discontinuous occupational inhalation exposures
Critical effects	Increased incidence of conjunctivitis, rhinitis, asthma, and chronic bronchitis
LOAEL	6.5 mg/m^3 (mean of 6.1 and 6.8)
NOAEL	Not observed
Exposure continuity	8 hours/day, 5 days/week
Exposure duration	Mean of 13.3 years
Average experimental exposure	2.3 mg/m^3 for LOAEL group (6.5 mg/m^3 $\times$ 10/20 $\times$ 5/7)
LOAEL uncertainty factor	10
Subchronic uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Inhalation reference exposure level	0.02 mg/m^3 (20 μg/m^3)

Adverse effects were demonstrated to occur in humans occupationally exposed to phthalic anhydride in the workplace over long periods of time (Nielsen *et al.*, 1988). The symptoms reported primarily affected the respiratory system, with increased incidence of rhinitis, rhinoconjunctivitis, asthma, and chronic bronchitis. Conjunctivitis was also reported in exposed workers. Specific anti-PA IgG was significantly elevated compared to a non-exposed group. Increased incidences of rhinoconjunctivitis, conjunctivitis, or chronic bronchitis have also been reported in workers exposed to similar levels of PA dust (Nielsen *et al.*, 1991; Wernfors *et al.*, 1986). In these reports, adverse effects were clearly observed at the exposure level reported (6.5 mg PA/m^3; full-day time weighted exposure of 0.4 mg PA/m^3). Although symptoms were reported by Nielsen (1988) in the lower exposure level group, the significance is not clear since a true control group (unexposed workers) was not included in the symptomatology section of the study. The low exposure group's level of exposure was less than the detection limit for phthalic anhydride cited in the study, and this group was considered as a control group.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for phthalic anhydride include the use of human exposure data from workers exposed over a period of years. Major areas of uncertainty are (1) the uncertainty in estimating exposure, (2) the potential variability in exposure concentration, (3) the

potential low exposures of the group considered as controls, (4) potential confounding by exposures to other chemicals, (5) the limited nature of the study, (6) the lack of reproductive and developmental toxicity studies, and (6) the lack of observation of a NOAEL in the key study. Another area of uncertainty is the apparent 10-fold greater sensitivity to bronchoconstriction from PA exposure in guinea pigs (a model for human asthmatics) in comparison to occupationally exposed workers.

The study in rats by Protsenko (1970) identified a LOAEL of 0.2 mg/m^3 and a NOAEL of 0.02 mg/m^3 for decreased sperm motility. However, this result from 1970 has not been verified or further explored in more recent toxicological or epidemiological studies. The small sample size of 6/group further weakens confidence in this result. Therefore, the study in workers by Nielson *et al.* (1988, 1991) was chosen as the basis for the REL for PA.

VIII. References

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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 µg/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

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