

Air Toxics Hot Spots Program

Introduction to Noncancer Reference Exposure Levels for

- ***Toluene Diisocyanate (TDI)***
- ***Methylene Diphenyl Diisocyanate (MDI)***

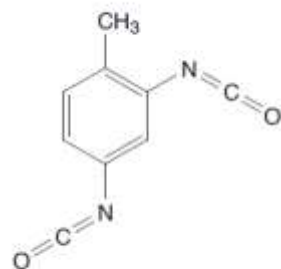
**Office of Environmental Health Hazard
Assessment**

**Scientific Review Panel Presentation
November 2014**

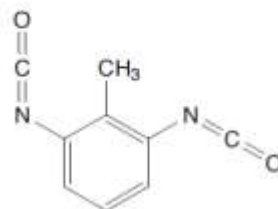
Office of Environmental Health Hazard Assessment



Toluene Diisocyanate (TDI)



2,4-Toluene diisocyanate
CAS No. 584-84-9



2,6-Toluene diisocyanate
CAS No. 91-08-7

- ◆ TDI monomer used in flexible polyurethane foams adhesives and coatings
- ◆ Volatile: vapor pressure 0.023 mm Hg 25°C
- ◆ Highly reactive N=C=O groups react with lung tissue and macromolecules
- ◆ One of the most potent LMW sensitizers



Brief Overview of Toxicity of TDI

Acute exposure in animals and humans:

- ◆ Sensory irritation
- ◆ Eye, nose, throat irritation
- ◆ Pulmonary irritation and tissue damage (dose dependent)
- ◆ Airways hyperresponsiveness

Chronic exposure:

- ◆ Sensitizer via inhalation and dermal exposure – Occupational Asthmagen
- ◆ chronic bronchitis, rhinitis, conjunctivitis in workers
- ◆ Accelerated decline in lung function (in absence of asthma)



Toluene Diisocyanate (TDI)

Draft Acute REL based on:

- ◆ **Acute exposure caused sensory irritation in normal subjects at 50 ppb and above (Henschler et al., 1962)**
- ◆ **Asthmatic responses in nonsensitized human asthmatic subjects at 10 ppb and above for 1 hr (Baur et al. 1994; Vogelmeier et al. 1991; Fruhmann et al., 1991)**
- ◆ **≥100% increase in airway resistance (Raw) in 1/15 asthmatic subjects at 10 ppb and another at 20 ppb**



TDI 8-Hour & Chronic RELs

- ◆ **Based on decreased lung function (FEV₁) in TDI workers (Diem et al., 1982)**
 - ◆ **5 year prospective study in 277 workers**
 - ◆ **detailed longitudinal analysis of workers from the start of exposure in a new TDI production facility, lung function measured prior to starting work at new facility and multiple measures over 5 years after start of employment**
 - ◆ **Sensitizing incidence: 12/277 (0.9%/yr)**



Methylene Diphenyl Diisocyanate (MDI)

Reference Exposure Levels



- ◆ **MDI and polymeric MDI (PMDI) used mainly in rigid polyurethane foams**
- ◆ **Lower VP than TDI (5×10^{-6} mm Hg @ 25°C)**
- ◆ **Exposure during spraying applications or heating**
- ◆ **Dermal contact a concern in workers**



Brief Overview of Toxicity of MDI

Toxicity qualitatively similar to TDI

Acute exposure:

- ◆ **irritation of the lungs and upper respiratory tract with symptoms including headache, sore throat, cough, and chest tightness**
- ◆ **Animal studies – respiratory epithelial damage, pulmonary edema**
- ◆ **If exposure high, reactive airways dysfunction**

Chronic exposure:

- ◆ **Sensitization**
- ◆ **Occupational asthma with a latency period**
- ◆ **hypersensitivity pneumonitis**



MDI Acute REL

Acute REL based on MDI rodent inhalation study

- ◆ **Critical effect: increased total protein in BALF in female Wistar rats (Pauluhn, 2002)**
 - ◆ 6 hr exposure, increased protein 3 hrs post-exposure
 - ◆ No NOAEL, LOAEL 0.7 mg/m³, no BMC modeling

| MDI (mg/m ³) | Total Protein Content in BALF (mg/m ³) | Standard Deviation |
|--------------------------|--|--------------------|
| 0 | 0.152 | ±0.034 |
| 0.7 | 0.224 | ±0.021 |
| 2.3 | 0.215 | ±0.037 |
| 8 | 0.363 | ±0.062 |
| 20 | 0.484 | ±0.131 |



MDI 8-Hour REL

- ◆ 8-Hour REL based on PMDI rodent inhalation study
 - ◆ Critical effect: Increased incidence of bronchiolo-alveolar hyperplasia and pulmonary fibrosis
 - ◆ Re-exam of Reuzel et al. (1994) data by Feron et al. (2001)
 - ◆ Two year study in adult female Wistar rats
 - ◆ 60 per group, exposure 6 hr/d, 5 d/wk
 - ◆ NOAEL 0.19 mg/m³ , LOAEL 0.98 mg/m³

| PMDI (mg/m ³) | Hyperplasia |
|---------------------------|--------------|
| 0 | 11/59 (19%) |
| 0.19 | 10/60 (17%) |
| 0.98 | 25/60 (42%) |
| 6.03 | 59/59 (100%) |



MDI Chronic REL

Chronic REL Derivation based on MDI rodent study:

- ◆ **Critical effect: Increased incidence and severity of interstitial fibrosis**
- ◆ **Reanalysis of Hoymann et al. (1998) by Feron et al. (2001)**
- ◆ **Two year study in adult female Wistar rats**
- ◆ **80 per group, 18 hours/day, 5 days/week**
- ◆ **No NOAEL, LOAEL 0.23 mg/m³**

| MDI (mg/m ³) | Interstitial Fibrosis |
|--------------------------|-----------------------|
| 0 | 10/80 (13%) |
| 0.23 | 63/80 (79%) |
| 0.7 | 77/80 (96%) |
| 2.05 | 79/80 (99%) |



Next Steps

- ◆ **OEHHA has received public comments, and developed responses**
- ◆ **OEHHA has revised document in response to public comments**
- ◆ **Panel will receive SRP review draft of document, public comments, and OEHHA's responses to comments very soon**
- ◆ **RELs will be reviewed at the next SRP meeting, December 12th**

