MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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January 13, 2014

To: File for 2,4-Toluene Diisocyanate (CAS No. 584-84-9); 2,6-Toluene Diisocyanate (CAS No. 91-08-7); or as a mixture (CAS No. 26471-62-5)

From: Michael Depa, Air Quality Division, Toxics Unit

Subject: Screening Level Update

This memo describes a screening level update for toluene diisocyanate (TDI). TDI refers to 2,4-toluene diisocyanate (CAS# 584-84-9), 2,6-toluene diisocyanate (CAS# 91-08-7), and the commercially available 80/20 mixture of 2,4-TDI and 2,6-TDI (CAS# 26471-62-5). The American Conference of Governmental Industrial Hygienists (ACGIH, 2004) states that there are, "no important toxicologic distinctions recognized between the isomers."

- The Initial Threshold Screening Level (ITSL) for TDI is 0.07 µg/m³ (annual average).
- The Second ITSL for TDI is 0.4 µg/m³ (8-hr average).
- The Initial Risk Screening Level for TDI is 0.03 µg/m³ (annual average).
- The Secondary Risk Screening Level for TDI is 0.3 µg/m³ (annual average).

Derivation of Chronic ITSL

The ITSL is based on the U.S. Environmental Protection Agency (EPA) Reference Concentration (RfC) of 0.07 µg/m³ (US EPA, 1995). EPA based the RfC on a 5-year occupational inhalation study (Diem, et al. ,1982) which identified chronic lung function decline as the critical effect of exposure to commercial grade TDI (80/20 mixture of 2,4- and 2,6-TDI). The study established a no-observed-adverse-effect-level (NOAEL) of 6 µg/m³ and a lowest-observed-adverse-effect-level (LOAEL) of 14 µg/m³. The NOAEL human equivalent concentration ($NOAEL_{HEC}$) = 0.006 mg/m³ x (MVho/MVh) x 5 days/7 days per week = 0.002 mg/m³, where the volume of air breathed in 8 hours occupationally (MVho) is 10 m³, and the volume of air breathed per day in non-occupational settings is 20 m³. A total uncertainty factor of 30 was used, which includes an uncertainty factor of 10 to account for intrahuman variability (i.e., sensitive individuals) and a factor of 3 to account both for subchronic to chronic extrapolation and the lack of developmental toxicity data in a second species.

Chronic ITSLs that are based on an RfC are typically assigned an averaging time of 24-hrs pursuant to Rule 232(2)(b). However, if the RfC-based ITSL is established in conjunction with an acute ITSL, the chronic RfC-based ITSL can more appropriately have an annual averaging time, pursuant to Rule 229. ITSLs based on a chronic inhalation study are adjusted for continuous exposure and derived using uncertainty factors to adjust for lifetime exposure and are typically associated with long averaging times such as an annual average. Coupling a chronic ITSL with an acute ITSL ensures that exposure levels below both ITSLs will provide effective health protection.

Derivation of Acute (Second) ITSL
A Second ITSL for TDI was derived based on the American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 0.005 ppm (0.036 mg/m^3). The TLV was developed to protect against respiratory sensitization. The Second ITSL was calculated pursuant to R336.1232(c) where ITSL = OEL/100, where "OEL" stands for occupational exposure limit. OEL based ITSLs are assigned an averaging time of 8-hrs pursuant to Rule 232(2)(a). In establishing a second ITSL with a short average time (e.g., 8-hr), the averaging time for the chronic ITSL has been revised from 24-hours to annual. It should be noted that the TLV is currently on the ACGIH Notice of Intended Changes (NIC) list to be lowered from 0.005 ppm to 0.001 ppm. While all NICs are not necessarily adopted, they are listed as intended changes to solicit comment from interested parties.

Derivation of the IRSL
TDI meets the definition of a carcinogen because oral dosing in animals was associated with the appearance of tumors at multiple sites. The International Agency for Research on Cancer IARC has classified TDI as a Group 2B, possible human carcinogen (IARC, 1987). US EPA has not classified TDI for carcinogenicity. NIOSH considers TDI to be an occupational carcinogen and recommends exposure reduction to the lowest feasible minimum. The National Toxicology Program (NTP) lists TDI as, "reasonably anticipated to be a human carcinogen" based on "sufficient evidence of carcinogenicity from studies in experimental animals" (NTP, 2011).

The Air Quality Division (AQD, 1987) previously derived an Initial Risk Screening Level (IRSL) of 0.03 $\mu g/m^3$ based on the oral slope factor of 1.04E-1 per mg/kg/day from a 1986 National Toxicology Program (NTP) carcinogenesis study of the commercial grade mixture (80%/20%) of toluene 2,4- and 2,6-diisocyanate. The inhalation unit risk derived from the slope factor is 3E-5 per $\mu g/m^3$. The results of the gavage exposure study showed an increase in tumors of subcutaneous tissues in male and female rats, the pancreas in male rats, mammary gland and liver in female rats, and liver and circulatory system in female mice. (NTP, 1986). No epidemiological studies were found during this review that showed an increased occurrence of cancer in humans.

Other Information
In the stomach, TDI undergoes hydrolysis to form toluene diamine (TDA), a known carcinogen. However, by inhalation exposure, the TDI is absorbed in the upper respiratory tract and results in the formation of acid-labile conjugates with little TDA formed. The differential formation of TDA via the two routes of exposure may contribute to the mechanism by which TDI was carcinogenic in mice and rats by oral but not by inhalation exposure.

The available human epidemiological data and experimental animal inhalation data are equivocal and inadequate to quantitate carcinogenic risk by inhalation exposure to TDI in humans. California adopted an inhalation unit risk factor of 1.1E-5 per $\mu g/m^3$ for TDI, however, the calculation steps were not presented (Cal OEHHA, 2009). An inhalation unit risk factor of 1.1E-5 per $\mu g/m^3$ would result in a cancer based screening level of 0.09 $\mu g/m^3$ associated with a risk of 1 per million.

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