MICHIGAN DEPARTMENT OF ENVIRONMENT, GREAT LAKES, AND ENERGY

INTEROFFICE COMMUNICATION

May 26, 2022

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: Carcinogenicity of TDI Via Inhalation Route of Exposure

After evaluating the available data, it was determined that inhalation exposure to TDI poses a plausible human health risk of carcinogenic effects. The Initial Risk Screening Level (IRSL) and Secondary Risk Screening Level (SRSL) for Toluene Diisocyante (TDI, mixture and 2,6- and 2,4- isomers) are affirmed. The IRSL and SRSL for TDI are 0.03 micrograms per cubic meter (µg/m³) and 0.3 µg/m³, respectively, both with annual averaging time.

Background

In 1987, the AQD derived an oral slope factor of 1.04E-1 $(mg/kg\text{-}day)^{-1}$ (AQD, 1987) using cancer incidence data from a rodent oral bioassay performed by the National Toxicology Program (NTP, 1986). At that time the oral slope factor was deemed appropriate to derive an inhalation unit risk (IUR) of 3E-5 per µg/m³. This IUR was used to derive the IRSL and SRSL.

TDI meets the definition of a carcinogen[1] because chronic oral and inhalation studies in animals produced statistically increased incidence of tumors at multiple sites (NTP, 1986; Loeser, 1983). The International Agency for Research on Cancer has classified TDI as a Group 2B, possible human carcinogen (IARC, 1987). US EPA has not classified TDI for carcinogenicity. However, EPA's Office of Air Quality Planning and Standards uses an inhalation unit risk to assess population cancer risk from inhalation exposure to TDI released into the air from industrial sources subject to Maximum Achievable Control Technology[2] (EPA, 2021). California's Office of Environmental Health Hazard Assessment (OEHHA) uses "Unit Risk and Cancer Potency Values" for TDI of 1.1E-5 $(\mu g/m^3)^{-1}$, and 3.92E-2 $(mg/kg\text{-}day)^{-1}$ (OEHHA, 2020). 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

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[1] Rule 103(c). Air Pollution Control Rules. Rule 336.1103(c) et seq. of the Michigan Administrative Code promulgated pursuant to Part 55, Air Pollution Control, of the Natural Resources and Environmental Protection Act (NREPA), 1994 PA 451, as amended.

[2] EPA is mandated under Section 112(f) of the Clean Air Act to conduct residual risk assessments for major sources of hazardous air pollutants (HAPs) eight years after Maximum Achievable Control Technology Standards have been promulgated and to evaluate HAP effects on public health and the environment.

to be a human carcinogen" based on, "sufficient evidence of carcinogenicity from studies in experimental animals" (NTP, 2011).

Oral exposure to toluene diisocyanates caused tumors at several different tissue sites in rats and mice (NTP,1986). Administration of commercial-grade TDI (analyzed as 85% 2,4- isomer and 15% 2,6- isomer) by stomach tube caused liver tumors (hepatocellular adenoma) in female rats and mice, benign tumors of the mammary gland (fibroadenoma) and pancreas (islet-cell adenoma) in female rats, and benign tumors of the pancreas (acinar-cell adenoma) in male rats. It also increased the combined incidences of benign and malignant tumors of subcutaneous tissue (fibroma and fibrosarcoma) in rats of both sexes and of the blood vessels (hemangioma and hemangiosarcoma) in female mice (NTP 1986).

The Air Quality Division (MDNR, 1987) derived an Initial Risk Screening Level (IRSL) of 0.03 µg/m³ based on the oral slope factor of 1.04E-1 per mg/kg/day from data published in a 1986 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 µg/m³ using the default human weight of 70 kg and default human inhalation rate of 20 m³ per day. 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 due to TDI exposure. However, occupational studies in the United Kingdom, Sweden and the U.S. showed an increased risk of lung cancer death in women in the polyurethane foam industry (Sorahan and Nichols, 2002; Mikoczy et al., 2003; Schnorr et al., 1996), although there was no positive trend when durations of "lower" or "higher" exposures to diisocyanates were examined. Pinkerton et al. (2016) found that laryngeal cancer mortality may be associated with TDI exposure.

Previously AQD has reviewed the science on TDI and concluded that TDI has the potential to cause cancer via the inhalation route of exposure (MDEQ, 2014; see attached memo below). The AQD's position on the inhalation carcinogenicity issue may have changed at one point; however, the current conclusion is that a quantitative estimate of inhalation carcinogenicity is appropriate (discussed further below). AQD is consistent with other authorities. AQD uses a similar health-based inhalation standard to the US Environmental Protection Agency (EPA) and California Office of Environmental Health Hazard and Assessment (OEHHA). EPA, OEHHA and AQD regulate TDI as a potential human inhalation carcinogen. Both EPA and OEHHA quantitate potential human cancer risk due to inhalation exposure to TDI.

Current Evaluation of Evidence for Carcinogenicity of TDI Via Inhalation Route

In the only chronic animal inhalation study available, Löser (1983) exposed groups of 90 male and female rats (Sprague-Dawley) and mice (CD-1) to 0, 0.05, and 0.15 ppm (0, 0.35 mg/m³, 1.1 mg/m³) TDI for 6 hours/day, 5 days/week for approximately 2 years. The incidence of multiple lung adenomas in male mice was 0/90, 9/90 and 6/90 in control, 0.05 ppm, and 0.15 ppm, respectively. The low and high dose incidence rates of cancer are statistically elevated compared to control at $p<=0.01$ and $p<=0.05$, respectively.

Unfortunately, because of a decreased incidence in the high dose compared to the low dose group, a dose-response curve that includes the two dose groups could not be used to derive a quantitative risk value for lung tumors from Löser (1983). A standard protocol for chronic animal testing studies states that, "At least three dose levels and a concurrent control should be used" (OECD, 2018). It should be noted that Löser (1983) categorized adenoma tumors as "adenoma/microadenoma" or "multiple adenoma." If both single and multiple adenomas are combined there is no statistical difference between the high-dose group and control animals, although the low-dose remains statistically elevated ($p<=0.01$) (Muller, 2008). The categories of multiple vs. single adenoma of the lung in mice are not typically reported in toxicological studies. For example, both single and multiple bronchioalveolar adenomas are combined when the National Toxicology Program publishes inhalation bioassays (NTP, 2011). Nonetheless, it is conceivable that mice having more than one adenoma could be seen as a more serious occurrence of tumors, especially since CD-1 mice may have as much as 13% spontaneous incidence of lung adenomas (Son and Gopinath, 2004). Muller (2008) showed contemporaneous historical incidence[3] as percent in male mice with multiple adenomas. Twelve studies were available that showed historical incidences of multiple adenomas in male mice control groups: 8, 2, 2, 4, 0, 4, 0, 4, 0, 8, 4, and 2%. Using a hypothetical incidence multiple adenomas in the control mice of 1 per 90 mice would result in the high dose (6 per 90) not being significantly elevated as measured by Fisher exact test with a value of $p=0.1177$. However, using multiple adenoma incidence in the control mice of 2 per 90 mice, the low dose (10 per 90) is still statistically elevated compared to control mice with a Fisher exact test value of 0.0144. Although the historical incidence of multiple adenomas in male mice is enlightening, the concurrent control incidence rate should weigh more than historical controls from different time periods. As noted above, both the low and high dose groups from Löser (1983) had statistically elevated lung tumors in male mice compared to the concurrent control mice which has zero incidence of multiple adenomas.

The MOA for carcinogenicity of TDI has not been established. AQD is aware of the hypothesis that hydrolysis of TDI to TDA is a necessary precursor to cancer lesions. Studies have shown that inhaled TDI is absorbed and distributed throughout the body (see below). After inhalation some TDI may be swallowed and re-enter the body from the digestive tract. Since TDI exposure via inhalation is absorbed and distributed, and that it may be swallowed after inhalation supports the use of the route-to-route extrapolation (e.g., oral-to-inhalation).

The results of a study in male F344 rats exposed to ^{14}C ring-labeled 2,4-TDI vapor (2 ppm) via inhalation for 4 hours suggest that approximately 61–90% of the radioactivity was absorbed; the remaining radioactivity was likely rapidly cleared from the respiratory tract and/or swallowed (Timchalk et al. 1994). When examined 48 hours later, the highest percentage of the recovered dose was found in the gastrointestinal contents (~17%), followed by the carcass (10%) and skin (6%) (Timchalk et al. 1994). While most inhaled TDI passes through GI tract, this transit does not convert TDI to TDA (Timchalk et al., 1994). However, a small amount of acetylated TDA was found in urine after inhalation exposure (Timchalk et al., 1994).

[3] Muller (2008) reported, "In 1998, Bayer has asked the Hazleton laboratory about historic control data with respect to the TDI rat and mouse studies. Hazleton then provided some data including some control data, as percentages, for mouse tumors 'from the same time period as the studies'."

Kennedy et al. (1994) quantified the distribution of radioactivity in blood components after a 4-hour inhalation exposure of rats to ^{14}C-2,4-TDI. Radioactivity was primarily recovered from the plasma (74– 87%), but radioactivity was also detected in the cell pellet. The plasma was fractionated by molecular weight, showing that the vast majority of the radioactivity (97–100%) was associated with high molecular weight (>10 kDa) components; electrophoresis was then used to demonstrate that the majority of the radioactivity was associated with a 70 kDa protein, which the authors suggested was likely albumin. Analysis of stomach contents by fractionation and electrophoresis showed that a higher proportion of the radioactivity in the stomach (28%) was in the low molecular weight fraction (<10 kDa) compared with the fraction in plasma. High performance liquid chromatography (HPLC) analysis of the low molecular weight fraction showed a TDA peak in addition to other products, demonstrating that TDA is not the primary reaction product after inhalation exposure.

TDI is absorbed and distributed systemically via inhalation and is biologically reactive. Day et al. (1996) analyzed hemoglobin adducts of TDI in guinea pigs exposed to 1 ppm 2,4-TDI for 3 hours/day on 5 consecutive days, and identified several TDI-derived adducts that demonstrated that the isocyanate moiety was capable being transported from the lung into the blood and across the erythrocyte membrane to form a hemoglobin adduct. From this data it is possible to infer that TDI could cross the nuclear membrane and form DNA-adducts, which could result in gene mutations.

TDA was measured in human plasma at levels up to 27.2 ng/mL for 2,4-TDA and 62.1 ng/mL for 2,6-TDA (Tinnerberg and Mattsson 2008). The form of TDA and TDI in blood could be “acid-labile conjugates.” The definition of “labile” means liable to change or easily broken down or displaced. It is possible these molecules could be involved in carcinogenesis, because a carcinogenic MOA is not known. Additional data on this subject is available in occupationally exposed Swedish workers manufacturing polyurethane products. Workers excreted 53.2 to 259.6 nmol of TDA per gram of creatinine (Bolognesi et al. 2001). Concentrations of toluene diisocyanate in urine of occupationally exposed workers ranged from 0 to 76 µg/L for the 2,4 isomer and from 0 to 31 µg/L for the 2,6 isomer (Bolognesi et al. 2001).

Bilban (2004) examined mutagenic markers in workers exposed to TDI. Twenty-six workers were exposed to TDI ranging from 0.007 mg/m^3 to 0.016 mg/m^3 at a plastics production facility in southeaster Slovenia in the year 2000. The control group consisted of twenty-one individuals from the same geographic area. Chromosomes from peripheral blood lymphocytes were used to assess structural chromosome aberrations, sister chromatid exchange (SCE), and micronucleus (MN). Structural chromosome aberrations (SCAs) were evaluated in peripheral blood lymphocytes of exposed workers, with an average value of 2.6. The number of sister chromatid exchanges (SCE) were evaluated in 50 cells per exposed worker with an average of 8.1. The number of induced micronuclei (MN) was evaluated in 500 cytokinesis blocked cells per exposed worker with an average of 12.07. The averages of the control group were 1.89 (SCA), 5.52 (SCE), and 4.38 (MN). The difference between the groups is of statistical significance. The author concluded that the results point to mutagenic activity of TDI or its metabolic products (Bilban, 2004). Whatever the MOA turns out to be, the results from Bilban (2004) provide evidence that inhalation of TDI results in increased mutagenic activity after occupational exposure.

The epidemiological database does not demonstrate strong association with cancer risk.

Lung Cancer Incidence and Mortality –Swedish cohort (MDI and TDI)

- Hagmar et al (1993) –no increase in lung cancer incidence in workers with apparent exposure
- Mikoczy et al (2004) update –increased lung cancer incidence and mortality in female workers (not males) but unrelated to exposure

Lung Cancer Incidence and Mortality –UK cohort (MDI and TDI)

- Sorahan & Pope (1993) -increase in lung cancer incidence and mortality in female workers (not males); all deaths occurred in females with minimal exposure
- Sorahan & Nichols (2002) update -increase in lung cancer incidence and mortality in female (not male) workers; all female lung cases occurred in women with minimal exposure

Lung Cancer Mortality –US cohort (TDI)

- Schnorr et al (1996) –mortality from lung cancer in cohort, males, or females unrelated to exposure
- Pinkerton et al (2016) update -increases in mortality from all causes, all cancers and respiratory tract cancers in cohort, males, and females; respiratory tract cancers were unrelated to exposure

One updated study (Sorahan & Nichols, 2002) showed increase incidence of lung cancer occurred in women with minimal exposure, but there was no positive trend when durations of “lower” or “higher” exposures to diisocyanates were examined. Pinkerton et al. (2016) concluded:

> We found a statistically significant increase in all cause and all cancer mortality as well as laryngeal and lung cancer mortality. Lung cancer mortality was not related to exposure duration or cumulative TDI exposure, but was associated with employment duration in finishing jobs, which suggests that dermal exposure may play a role. Our ability to detect an association with cumulative TDI exposure may have been hampered by the lack of smoking data, a healthy worker survivor effect, uncertainty in the exposure estimates, and the use of exposure estimates that reflected inhalational exposure only. The excess in laryngeal cancer mortality was large and unlikely to be explained by smoking alone.

Discussion

During inhalation to TDI, TDI deposits in the trachea and lung (Kennedy et al., 1994), which happens to be where tumors were formed in male mice after a two-year inhalation study (Löser, 1983). Pinkerton et al. (2016) stated that after occupational exposure laryngeal cancer mortality was large, and suggested that inhalation exposure to TDI may be carcinogenic to humans. Both Löser (1983) and Pinkerton et al. (2016) imply that TDI is carcinogenic in the respiratory tract. Interestingly, a surprising amount of inhaled TDI finds its way into the digestive tract, likely swallowed after mucociliary clearance from the lungs or via the bile duct from liver metabolism. Timchalk et al. (1994) stated that 47% of the inhaled dose of TDI was accounted for in the feces and 15% in the urine. The authors stated that 34% of the recovered radioactivity was found in the carcass, with one-half of that associated with the gastrointestinal tract contents. In the same study by Timchalk et al. (1994) using oral dosing, 81% of TDI was eliminated in the feces, and only 8% was eliminated via the urine. One can hypothesize that inhalation exposure to TDI is

more effectively absorbed systemically than oral dose because of the differential urinary elimination (15% via inhalation, and 8% via oral dosing).

The urinary excretion of TDA differs depending on the route of exposure of TDI. TDA is produced at a higher amount after oral exposure to 60 mg/kg/BW than 2 ppm TDI (5.12 vs 0.16 µg equivalents) (Timchalk et al., 1994). The significance of this different excretion rate of TDA from oral and inhalation exposure could be due to dose quantity, different metabolism or pharmacokinetic processes that are exposure route specific. Bilban (2004) showed that occupational inhalation exposure to TDI causes increased mutagenic activity as assessed by structural chromosome aberrations. Notwithstanding the differential metabolism of oral and inhalation exposure to TDI, the relevance of metabolism of TDI to TDA remains ambiguous as a carcinogenic MOA and has not been established for either route of exposure.

Based on the information provided above, it likely that inhalation exposure to TDI poses a plausible human health risk of carcinogenic effects. The quantitative risk from oral exposure to TDI also provides a reasonable basis for evaluating inhalation risk and the default route-to-route extrapolation of oral-to-inhalation cancer risk is appropriate to protect public health in this case.

Conclusion

Since the available evidence indicates that TDI is a probable human inhalation carcinogen, AQD has reestablished the IRSL and SRSL for TDI at 0.03 micrograms per cubic meter (µg/m³) and 0.3 µg/m³, respectively, both with annual averaging time.

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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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