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Response to Public Comments for 2,4-Toluene Diisocyanate (CAS No. 584-84-9)

Summary:

Based on public comments, the Air Quality Division (AQD) has reviewed the Initial Risk Screening Level (IRSL[1]) and Secondary Risk Screening Level (SRSL[2]) for 2,4-toluene diisocyanate (TDI). As a result of that review, the AQD has determined that the current IRSL and SRSL are appropriate and defensible, and the current screening levels will be retained.

Background:

Revisions to the Air Pollution Control Rules[3] were promulgated December 22, 2016. Subsequently, the Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD) published toxic air contaminant screening levels and their basis as required by Rule 230(1). Pursuant to Rule 230(2), the AQD solicited and received public comments on these screening levels for 60 days: February 14 through April 14, 2017. The AQD must respond to these comments within 180 days; the latest date for response is October 11, 2017.

[1] Risk of cancer at 1 per million

[2] Risk of cancer at 1 per one hundred thousand

[3] Air Pollution Control Rules in Michigan Administrative Code promulgated pursuant to Article II Pollution Control, Part 55 (Sections 324.5501-324.5542), Air Pollution Control, of the Natural Resources And Environmental Protection Act, 1994.PA 451, as amended (NREPA).

Comment and Response:

Comment:
There is not a justifiable biological or toxicological rationale for using an oral cancer slope factor based on a flawed NTP study in rodents to derive or extrapolate to an inhalation unit risk factor in humans. The AQD should withdraw the IRSL and SRSL values derived for TDI.

Response:
In 1987 the AQD derived an oral slope factor (1.04E-1 per mg/kg/day) and an inhalation unit risk (IUR; 3E-5 per µg/m³) based on the increased incidence of fibromas and fibrosarcomas in male rats exposed orally (NTP, 1986) to the commercial mixture of TDI (2,4-TDI and 2,6-TDI) (CAS No. 26471-62-5). From the IUR for the TDI mixture, the AQD calculated an IRSL and SRSL for the TDI mixture. Later, the AQD applied the same IUR to derive IRSLs and SRSLs for the individual isomers of TDI: 2,6-toluene diisocyanate (CAS No. 91-08-7) and 2,4-toluene diisocyanate (CAS No. 584-84-9). The oral carcinogenicity study was summarized by the National Toxicology Program (NTP, 2016):

> Oral exposure to toluene diisocyanates caused tumors at several different tissue sites in rats and mice. Administration of commercial-grade toluene diisocyanate (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 NTP (2016) classifies TDI as reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals.

The International Agency for Research on Cancer (IARC, 1986) classifies TDI as Group 2B: The agent (mixture) is "possibly carcinogenic to humans". There is inadequate evidence of carcinogenicity in humans but there is sufficient evidence of carcinogenicity in experimental animals.

Isocyanates are highly reactive, and are polymerized with alcohols to create polyurethanes. Sometimes TDI is processed so that some of the TDI molecules link together to form homopolymers (dimers, trimers and oligomers). Concerning the reactivity of TDI, IARC (1986) states:

> Reacts readily with compounds containing active hydrogens, such as water, acids and alcohols; contact with bases, such as caustic soda and tertiary amines, may cause uncontrollable polymerization and the rapid evolution of heat

It is estimated that during inhalation exposure, essentially all of the inhaled 2,4-[^{14}C]TDI is retained by the animal (Timchalk et al., 1994). At 48 hr post-inhalation exposure approximately 15 and 47% of the recovered radioactivity was in the urine and feces,

respectively. The amount recovered in the feces is noteworthy, because it suggests that even with inhalation exposure there is some mechanism in which TDI is transferred into the digestive tract.

It has been hypothesized that tumors observed after oral gavage exposure are most likely due to the conversion of TDI to toluene diamine (TDA), a known rodent carcinogen. The Agency for Toxic Substances and Disease Registry (ATSDR, 2015) describes the metabolism of TDI to TDA as:

> After oral exposure, TDI is hydrolyzed in the gastrointestinal tract to TDA, which may be absorbed and metabolized further (acetylated, conjugated, or metabolized to aminophenolic or aminobenzoic acid compounds) (Timchalk et al. 1994). In the gut, TDA may also react with unhydrolyzed TDI to form polyurea polymers that pass unabsorbed through the gastrointestinal tract. In contrast, after inhalation exposure, little TDI, if any, is hydrolyzed to TDA; conjugation reactions are believed to represent be [sic] the primary fate of inhaled TDI. These route-specific differences in the fate of TDI were observed when rat urine was analyzed after oral and inhalation exposure; after oral exposure to TDI, 35% of the detected metabolites were free or acetylated TDA (the balance reflected acid-labile conjugates of TDI or TDA), while only 10% of the metabolites detected after inhalation exposure were acetylated TDA (Timchalk et al. 1994).

TDA is sparingly formed in humans as measured in plasma and urine.

> Toluenediamine, a metabolite of toluene diisocyanate, has been measured in the plasma at levels up to 27.2 ng/mL for 2,4-toluenediamine and 62.1 ng/mL for 2,6-toluenediamine (Tinnerberg and Mattsson, 2008). Swedish workers manufacturing polyurethane products excreted 53.2 to 259.6 nmol of toluenediamine per gram of creatinine. (NTP 2016)

Other than the oral gavage study using TDI, AQD was not able to find any other isocyanate that was classified as a carcinogen by a national or international agency. Inhalation exposure of 0.05 and 0.15 ppm TDI (commercial mixture); 360 and 1070 µg/m³, respectively, for 6 hrs/day, 5 days/week for approximately 2 years to TDI was not reported to induce tumors in rats or mice (Loeser et al., 1983). However, it is possible that the exposure concentrations used in Loeser et al. (1983) were too low to elicit a response in rats because the maximum tolerated dose (MTD) was not achieved[4], although the MTD was achieved in mice. A couple of mutagenicity studies using TDI in vitro have shown both positive and negative results. NTP (1983) states, "Differences in the results from the two [in vitro] studies are probably due to differences in the test conditions." Müller (2008)[5] re-examined the histopathology specimens from Loeser et al. (1983) and determined through subsequent statistical analyses that the increased incidences of two tumor types were statistically significant. (see Table 1 and 2; adapted from Prueitt et al., 2013).

[4] For the rats, Loeser et al. (1983) stated, "Statistical analysis indicated the TDI did not significantly affect mortality. Body weight gain was similar in all groups". Achievement of MTD would be indicated by a 10% decrease in body weight or a 10% increase in mortality in the high dose-group animals.

[5] The report by Müller (2008) was not available from primary sources. Two sources summarized and referenced the Müller (2008) report: Prueitt et al. (2013), and ECHA (2013).

Table 1. Male Mouse Incidence of lymphoma

Dose (ppm)	Incidence	rate
0	2/90	2.2%
0.05	12/90	13.3%*
0.15	5/90	5.6%

*p<0.01, Fisher's exact test; alpha=0.05, Yates' Chi-square test; both as determined by Muller (2008).

Table 2. Male Mouse Incidence of multiple lung adenoma

Dose (ppm)	Incidence	rate
0	0/90	0%
0.05	12/90	10%*
0.15	5/90	6.7%**

*p<0.01 as determined by Muller (2008)
*p<0.05, as determined by Muller (2008)

Concerning epidemiological evidence of cancer from TDI exposure, increased risks of lung cancer was observed in female, but not male, workers, and was a consistent finding across three of the six studies (summarized by Prueitt et al., 2013). However, there was no exposure-response relationship in any of the studies. Prueitt et al. (2013) stated:

> ...[W]e found that the epidemiology data are not sufficiently robust to support TDI as a human carcinogen. The available studies do not report consistent results, and there were no positive exposure–response relationships for any of the reported cancer outcomes. Because of the many limitations of these studies, the few positive findings may be a result of other factors or statistical anomalies.

With respect to the weight of evidence for inhalation carcinogenicity of TDI, there are several shortcomings of the toxicological database, notably the poor reporting of the Loeser et al. (1983) rodent inhalation study. This is especially apparent in light of the subsequent re-evaluation of Loeser et al. (1983) histopathology of the lung and lymphoma data reported by Müller (2008). The inconclusive epidemiology database (summarized by Prueitt et al., 2013) showed equivocal carcinogenic activity in female workers. TDI is completely systemically absorbed via inhalation into the human body, yet very sparingly transformed into TDA (Tinnerberg and Mattsson, 2008). Because it has not been conclusively demonstrated that metabolism of TDI into TDA is the carcinogenic mode of action of orally TDI-dosed rats and mice, it remains possible that TDI is carcinogenic to humans via the inhalation pathway. AQD concludes that a causal association between TDI inhalation exposure and carcinogenic effects is plausible in humans.

Summary and Conclusions:

The Inhalation Unit Risk for TDI was based on a rodent oral study where an increased incidence of tumors was observed in rats and mice. Although the route of administration was oral instead of the preferred inhalation route, the absorption and distribution of TDI via inhalation is strong enough evidence that the oral route systemic cancer risk is relevant in assessing the quantitative cancer risk from inhalation

exposures. Therefore, the current IRSL and SRSL are appropriate and defensible, and the current screening levels will be retained.

The primary AQD reviewer for these comments was Mike Depa, AQD Toxics Unit Toxicologist. The secondary (peer) reviewer was Robert Sills, AQD Toxics Unit Supervisor.

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