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Response to Public Comments for Toluene Diisocyanate (CAS No. 26471-62-5) 2,4-Toluene Diisocyante (CAS No. 584-84-9) 2,6-Toluene Diisocyante (CAS No. 91-08-7)

Summary:

Based on public comments, the Air Quality Division (AQD) has reviewed the Initial Risk Screening Level (IRSL) and Secondary Risk Level (SRSL) for toluene diisocyante (TDI). As a result of that review, the AQD will retain the IRSL and SRSL for TDI; therefore, the IRSL is 0.03 micrograms per cubic meter (µg/m³) and the SRSL is 0.3 µg/m³ (both with annual averaging time).

Background:

Pursuant to the Air Pollution Control Rules[1] 230(2), the AQD solicited comments on the derivation of the IRSL for TDI from June 15, 2022, through July 15, 2022.

[1] 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).

Comments and Responses:

Comment:
The study AQD used to derive the cancer risk screening level administered TDI by gavage into the acidic environment of the rodent stomach. This environment, found nowhere else in the body, favors transformation of TDI into toluene diamine, a known rodent carcinogen. The route-to-route extrapolation is not justified because there is very little toluene diamine (TDA) formed after inhalation exposure and subsequent ingestion.
Response:
Timchalk et al. (1994) exposed rats to radiolabeled 2,4-TDI via gavage and inhalation and found that free + acetyled TDA metabolites were in the urine from both exposures, indicating that both exposure pathways have similar pharmacokinetics.

Comment:
Only benign tumors were observed in one sex and one species of mice exposed by inhalation to TDI for 2 years. Without a patho-physiological reason for the single sex response it does not reflect that TDI acts as a carcinogen upon inhalation exposure.
Response:
Increased incidences of lung multiple adenoma after inhalation exposure to TDI were observed in male mice at 0.05 and 0.15 ppm TDI after two years (Loeser, 1983). The relevant portion of the Air Pollution Control Rules (R 336.1103) defines carcinogen as, "(iii) Group C -- Any substance for which there is limited evidence of carcinogenicity in animals in the absence of human data and which causes a significant increased incidence of benign or malignant tumors in a single, well-conducted animal bioassay."

Comment: EPA and OEHHA set noncancer risk levels for TDI, but there are no set cancer risk levels by either agency.
Response:
This is not true: both the United States Environmental Protection Agency (USEPA, 2021) and California's Office of Environmental Health Hazard Assessment (OEHHA, 2020) use an inhalation unit risk (IUR) level of 1.1E-5 $(\mu g/m^3)^{-1}$ for TDI, which yields in an IRSL air concentration of 0.09 $\mu g/m^3$. This IUR was derived by California OEHHA based on the National Toxicology Program study (NTP, 1983). USEPA adopted OEHHA's IUR. Note that Michigan used the same study USEPA and OEHHA used to calculate their unit risk level but with slightly different calculations to derive an IRSL of 0.03 $\mu g/m^3$ (annual averaging time).

Comment:
Loeser has demonstrated that inhalation exposure (which may result in subsequent oral exposure) does not result in carcinogenicity.
Response:
Loeser (1983) exposed groups of 90 male and female rats (Sprague-Dawley) and mice (CD-1) via inhalation to TDI at doses of 0, 0.05, and 0.15 ppm (0, 0.35 mg/m^3, 1.1 mg/m^3) 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 lung cancer are statistically elevated compared to control at p<=0.01 and p<=0.05, respectively.

Comment: There are currently no identified publications proposing a mode of action other than conversion of TDI to TDA.

Response:

Regardless of the lack of investigations into alternative modes of action, the study by Loeser (1983) demonstrates that TDI is carcinogenic via inhalation. Timchalk et al. (1994) also supports the conversion of TDI to TDA via inhalation.

Comment:

Several longitudinal epidemiological studies have extensively assessed the effects of occupational exposure to TDI and the available data show TDI is not linked to occupational carcinogenicity.

Response:

Pinkerton et al. (2016) found a statistically significant increase in all cause and all cancer mortality as well as laryngeal and lung cancer mortality. It was also reported that, "Lung cancer mortality was not related to exposure duration or cumulative TDI exposure but was associated with employment duration in finishing jobs." Pinkerton et al. (2016) stated that the excess in laryngeal cancer mortality was large and unlikely to be explained by smoking alone. A recent publication by Park (2021) re-analyzed the mortality from lung cancer reported by Pinkerton (2016) and Sorahan (2002) and accounted for smoking. Furthermore, Park extracted exposure and outcome data from these published studies and found that after controlling for survivor bias there was an excess of risk of mortality from lung cancer that was comparable to that of sensitization (e.g., asthma). Park (2021) states:

> At 18 ppt TDI, in the range of concentration for 1/1000 risk of sensitization, and making important assumptions such as the independence of employment duration and exposure intensity, the approximate excess lifetime risk for lung cancer mortality in women is estimated to be on the order of 50 per 1000.

Park's estimate that exposure to TDI at 18 ppt (0.13 µg/m³) may equate to a lifetime cancer risk of 50 per 1000 strongly suggests that AQD's IRSL of 0.03 µg/m³ at 1 per million cancer risk is not health protective.

Comment:

The Bilban (2004) study consisted of a small sample size, and lacked consideration of the exposure characterization method, serum levels of TDI/TDA, and the external/ background exposure factors that could have influenced the study results. In the Bilban study, 69% of the participants were identified as smokers, which have significantly higher sister chromatid exchange (SCE) levels that non-smokers.

Response:

AQD acknowledges that the Bilban (2004) study was a relatively small sized study (26 in exposure group and 21 in the control group); however, the author specifically controlled for smoking. As to the other problems with the study (exposure characterization, background, serum levels, etc.) it is not known how these affect the results. The

conclusion of the Bilban (2004) is strong evidence that TDI or its conjugates causes genetic toxicity: compared to non-exposed workers, workers that were exposed to TDI had statistically elevated SCE and micronucleus levels. Bilban (2004) states that TDI or its metabolic products show mutagenic activity. Furthermore, inhalation of TDI is genotoxic via inhalation whether TDA is formed or not.

Comment:
The work of Lindberg et al. (2011) demonstrated that exposure to levels of TDI at levels that induce toxic effects does not have detectable genotoxic effects in mice.
Response:
TDI does not appear to have a systemic genotoxic effect in mice. However, these findings are not in agreement with the increase in chromosomal damage observed in polyurethane workers exposed to TDI (Bilban, 2004).

Comment:
There is no justification to conclude that putative increases in lung cancer are related to TDI exposures.
Response:
Park (2021) extracted TDI exposure and outcome data from published occupational exposure studies and found that after controlling for survivor bias, there was an excess of risk of mortality from lung cancer comparable to that of sensitization.

Summary and Conclusions:

Since the available evidence indicates that TDI is a possible human inhalation carcinogen, AQD has re-established the IRSL and SRSL for TDI at 0.03 µg/m^3 and 0.3 µg/m^3, respectively, both with annual averaging time.

The primary AQD reviewer for these comments was Michael Depa, AQD Toxics Unit Toxicologist. The secondary (peer) reviewer was Dr. Brian Hughes, AQD Toxics Unit Supervisor.

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