TDI-induced Asthma: Reanalysing Data to Find Hidden Trends

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TDI-induced Asthma: Reanalysing Data to Find Hidden Trends

Even if you've never heard of them, you've used polyurethanes. Producing them requires toluene diisocyanates, which may/can induce asthma when inhaled. A 5-year study claimed to conclude that cumulative TDI exposure over time was indicative of asthma incidence. However, a reanalysis by a team at the International Isocyanate Institute points the finger instead at the frequency of unprotected high-exposure events, like accidental spills or plant maintenance. This finding guides the way for future advances in worker safety.

Toluene Diisocyanates

Polyurethanes comprise a class of synthetic materials that are near-ubiquitous in modern life. First synthesised in the 1930s, their use has expanded widely. Flexible foam in bedding and furnishings, building insulation materials, stretch fibres and waterproof coatings in clothing are all made from polyurethanes. Consumer demand fuels a growing manufacturing industry valued at over $70 billion.

The synthesis of polyurethanes involves various materials, including a class of compounds called isocyanates. Two compounds within this class, 2,4-toluene diisocyanate and 2,6-toluene diisocyanate (TDIs), are associated with the onset of occupational asthma among factory workers exposed to them in the air.

Amidst a quorum of evidence, these concerns have led to improved precautions in manufacturing facilities to limit worker exposure to TDIs and reduce occupational asthma. Improved air ventilation, work procedures, and respiratory protection are among the steps taken to safeguard workers.

A Question of Safety

It is generally agreed that some link exists between TDI exposure and respiratory issues, which justifies these precautions. However, the cohort of research on this subject is unclear and contradictory. A major reason for this is that studies have largely failed to account for the diversity of roles and associated TDI exposures within manufacturing facilities. While they might share a break room, an administrative supervisor and a factory floor worker could have similar TDI exposures, or they may diverge completely.

One question in particular remains open, which is whether occupational asthma and respiratory issues should be attributed to long-term, low-level TDI exposure or to infrequent, concentrated exposures as they happen during leaks or maintenance. Far from trivial, the answer to this question may be vital to protecting workers from the adverse consequences of TDI exposure in a properly informed way.

A Reanalysis with Important Findings

This question is the focus of research by the team at the International Isocyanate Institute III that conducted a reanalysis of a five-year-long study carried out through collaboration between the National Institute for Occupational Safety and Health (NIOSH), the American Chemistry Council (ACC), and the International Chemical Workers Union. The III team noticed issues that were overlooked in the study, the scrutiny of which they believe yields conclusions instrumental to future worker safety.

To understand this work, let's first explore the ACC-NIOSH study. For five years, TDI exposures and respiratory health data were collected for workers across three TDI production plants in the USA. The results were published as four papers in the *Journal of Occupational and Environmental Medicine*.

ACC-NIOSH: TDI Exposure

In their first paper, the researchers described how they collected air samples from workers' breathing zones to measure TDI levels. TDI exposure was characterised as Time-Weighted Averages (TWA) throughout the work shift to determine background, long-term exposure, and exposure during High Potential Exposure Tasks (HPET) to assess high-level, short-term exposure.

With information on worker's roles and relative exposure protections, these data were grouped into Similar Exposure Groups (SEGs). This grouped workers in each plant together who had similar work tasks and would, therefore, be expected to have comparable TDI exposures.

Among both sets, they found that workers involved in drumming and loading work or in incident response experienced significantly higher exposure than others. This was true both for cumulative TDI exposure, calculated as parts-per-billion (ppb)-years, and as the number of HPETs which exceeded the Short-Term Exposure Limit of the short-term exposure limit at the time, 20 ppb.

ACC-NIOSH: Respiratory Health

In their second paper, the researchers outlined their data on worker respiratory health. They investigated health outcomes such as forced expiratory volume (FEV) decline, symptoms consistent with TDI-induced asthma, symptoms consistent with general asthma, and symptoms which justified further clinical evaluation.

The data on each were then compared with cumulative TDI exposure and peak TDI exposure (defined as the 95th percentile of TWA measurements). These comparisons were made using logistic regression models.

Results showed that for all health outcomes, cumulative exposure was more closely associated than peak exposure. Cumulative exposure correlated most closely with TDI-induced asthma, followed by general asthma, FEV decline, and then symptoms justifying clinical evaluation. This suggested to the authors that cumulative TDI exposure is a good predictor of occupational asthma development.

The researchers followed this by calculating the predictive strengths of exposures ranging from 5 to 20 ppb and ppb-years, for peak and cumulative TDI exposure, respectively, on each health outcome. This, they claimed, offers an objective basis to predict how likely a worker is to suffer deteriorating respiratory health or develop asthma given TDI exposure.

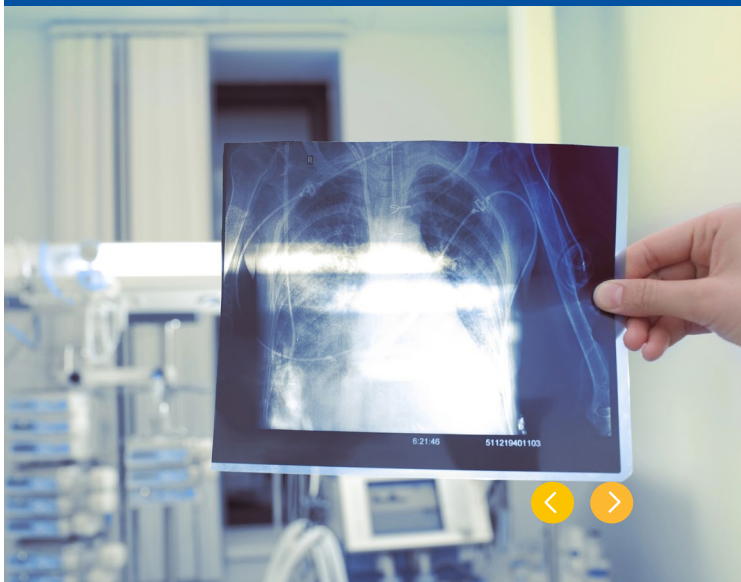
The Reanalysis

This conclusion would seem to offer a definitive model of cumulative TDI-exposure causing occupational asthma, one which is theoretically sound and built upon robust data. However, the real test of a model is how it fares under scrutiny, which is what the III team sought to find out.

- The (geometric) average and 95-percentile values are correlated. It is, therefore, unlikely that looking at 'peaks' this way would lead to a different outcome than looking at the average.
- The use of highest-integrity respiratory protective equipment (RPE) in the TDI production facilities puts serious doubt on 'gross' exposures (i.e., measured work atmosphere concentrations without taking into account protection afforded by wearing RPE) being the trigger for induction of asthma.
- Inconsistent use of exposure and risk time periods (for a subset of personnel, up to 30 years of exposure were considered but treated as if the risk were present for the 5-year duration of the study), which could have skewed conclusions.

The team conducted a reanalysis of the ACC-NIOSH study, aiming to independently identify where to best focus exposure reduction efforts to counteract occupational asthma risks.

> One question in particular remains open, which is whether occupational asthma and respiratory issues should be attributed to long-term, low-level TDI exposure or to infrequent, concentrated exposures as they happen during leaks or maintenance.



> In other words, cumulative TDI exposure was not, in fact, a good predictor of occupational asthma development.

V Polyurethane foam.

They started by verifying that the exposure measurements made in the study were consistent with published information and then recalculating cumulative exposures and putting these into relation to asthma incidence.

The Reanalysis: Cumulative TDI Exposure

The team first verified the integrity of the data set by recalculating exposure values for the SEGs and then attempted to link gross exposure during study duration with risk.

This verification showed that exposure data were consistent with the original study. The NIOSH researchers categorised workers into gross cumulative exposure groups (not adjusted for respiratory protection) and found that the use of average TWA values in the original study overweighed the impact of low background exposures while underrepresenting the impact of peak exposure events. Aligning exposure and risk time periods, the team found that asthma incidence was more evenly distributed across gross cumulative exposure groups than was concluded from the ACC-NIOSH study model. Logistic regression showed no significant association between the two variables.

The team also performed the same analysis for net cumulative exposure groups (adjusted for respiratory protection). This also found that asthma incidence was more evenly distributed across exposure groups, and logistic regression yielded no significant relationship either. In other words, cumulative TDI exposure was not, in fact, a good predictor of occupational asthma development.

The Reanalysis: Peak TDI Exposure

The team then explored other factors that might fulfil this predictive role. They identified important considerations which may have masked the answer, the resolution of which might point to it.

First, they pointed out that in the ACC-NIOSH cohort, whenever respiratory protection was used, it was of the highest protective quality, meaning that net rather than gross exposures should be considered.

Second, they noted that TDI-processing plants operate as closed systems continuously with steady, low background TDI levels. TWA values above background mainly occur when some part of this closed system is opened, such as during maintenance, leaks, or loading. This means that the values of time-weighted averages over time do not give direct information about the intensity of exposure events, which is lost in the surrounding background levels of brief exposure events.

What these considerations point to is that, in addition to the aforementioned misalignment of the exposure and risk time periods, the original study failed to consider net exposure, and to separate peak and cumulative exposures. As such, it failed to explore the role of peak exposures in asthma incidence properly. The team sought to investigate this potential correlation more thoroughly.

They derived a potential alternative model in which the frequency of unprotected TWA-8 exposures of 3ppb TDI or more was taken as a net exposure measure. This held a clear, positive relationship with TDI-induced asthma incidence. Linear and logarithmic logistic regression both met significance parameters. Finally, net exposure was shown to predict asthma incidence reliably.

Safeguarding Worker Safety in the Future

The strengths of this key reanalysis are severalfold. It distinguished raw (gross) exposure data from that which took the use of respiratory protection equipment into account. Net exposure was calculated, allowing an accurate representation of peak exposure events. But most importantly, the team looked beyond the data to find hidden trends.

This finding is not merely academic. Safety standards for polyurethane plant workers have been improved in recent decades, but they are still exposed to TDI, which, as demonstrated in these data, can lead to sensitisation and asthma. This work could prove pivotal to efforts toward safeguarding worker safety in the future.

MEET THE RESEARCHERS

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The International Isocyanate Institute is a not-for-profit association dedicated to evaluating and promoting the safe handling of MDI and TDI, with respect to the workplace, the community and the environment. The activities of the Institute are focused in a variety of ways, including laboratory and workplace studies and sharing safety information on the production of MDI, TDI and their precursors. Studies are carried out in member companies, in the workplaces of MDI and TDI users, and in the laboratories of contract research organisations or academic knowledge centres such as universities. There is liaison between industry and other experts to ensure that studies are as meaningful as possible in terms of real-life situations.

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FURTHER READING

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