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The relationship between toluene diisocyanate exposure and respiratory health problems: A meta-analysis of epidemiological studies

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Abstract

Human epidemiological studies have shown inconclusive results over the effects of diisocyanates on respiratory health problems. A meta-analysis combined evidence on the association between occupational asthma (OA), respiratory function, and toluene diisocyanate (TDI) inhalation exposure. Sixty-one articles on occupational toluene diisocyanate exposure were identified via two databases. Fourteen studies were included in the meta-analysis. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the studies. Odds ratios (OR_{asthma}) for the association between TDI exposure compared to non-exposure and OA were calculated. The difference in mean differences (MD) of forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC), and the annual mean change differences—in milliliters per year (mL/yr)—in FEV_1 and FVC pulmonary function between TDI exposed and non-exposed, were calculated. When applicable, a random effects meta-analysis was performed. The overall summary OR_{asthma} for TDI exposed versus non-exposed was 1.18 (95% CI = 0.78–1.79). The summary of the predicted mean percentage difference ($MD_{\%predicted}$) between exposed versus non-exposed was 2.96% for FEV_1 and 3.75% for FVC. A very small decrease of 5 mL/yr for FEV_1 and 10 mL/yr for FVC, respectively, was observed between the exposed and the non-exposed groups. There was moderate to low heterogeneity between study results, and most studies were evaluated as high-quality. This meta-analysis found no statistically significant adverse association between TDI occupational exposure and OA. No meaningful differences in lung function were detected between exposed and unexposed groups.

Keywords

Diisocyanates, respiratory, meta-analysis, toluene, pulmonary function

Introduction

Diisocyanates are important industrial chemicals used as raw materials for manufacturing polyurethane products such as sealants, surface coatings, and adhesives (Klees and Ott, 1999). The most commonly used diisocyanates include methylene diphenyl diisocyanate (MDI), toluene diisocyanate (TDI), naphthalene diisocyanate (NDI), and the non-aromatic hexamethylene diisocyanate (HDI).

Toluene diisocyanate is typically used as a mixture of 2,4'-TDI and 2,6'-TDI (80/20 or 65/35). Several human epidemiological studies have been conducted over the years to evaluate the respiratory health effects of TDI exposure. These studies have either used pulmonary indices such as the forced expiratory volume in 1 s (FEV_1) and the forced vital capacity (FVC) to measure airflow limitation or focused on asthmatic reactions or diagnosis. TDI-induced occupational asthma can be defined as a condition of bronchial inflammation and bronchial hyperresponsiveness induced by TDI exposure, and it manifests itself as transient symptomatic narrowing of

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the bronchi after re-exposure to low TDI concentrations (Ott et al., 2003).

The early human studies (Adams, 1975; Peters et al., 1970; Wegman et al., 1977) conducted in the 1970s suggested that exposure to TDI may indeed induce acute pulmonary effects such as occupational asthma (OA), and they also showed a decrease in pulmonary function after long-term inhalation even at low levels of exposure (Omae, 1984). In contrast, two studies reported mixed results and were not able to confirm the relationships observed in the aforementioned studies (Butcher et al., 1977; Ott et al., 2000). A possible explanation for this variability could be the different study designs that were used. Some studies investigated chronic low dose exposure whereas a limited number of others studied single exposures at high doses. Moreover, most of the studies were of longitudinal design without a control group.

It has been observed that lung function can fully recover over a period of 4–6 years after a single high dose of TDI (Weill, 1996). Often, earlier studies had not used control (non-exposed) groups with which to compare exposed groups, making it difficult to interpret the effects relative to normal healthy participants. In addition, there exists a large diversity in the methods of measurement of exposure and the ascertainment of occupational asthma as the outcome.

Therefore, the aim of this meta-analysis was to combine evidence on the association between OA, respiratory function, and isocyanate inhalation exposure by synthesizing the results of existing studies that have used a non-exposed control group, and by investigating potential variability caused by differences in study design and other important factors that may affect this association.

Methods

Search strategy

Available databases from STN International, which is a single source for scientific and technical research, were systematically searched to retrieve relevant articles published up to September 2021. Moreover, the Pubmed/Medline search engine was used to identify relevant literature using the following search string: (asthma*[Title/Abstract] OR bronchial*[Title/Abstract] OR respirat*[Title/Abstract] OR lung*[Title/Abstract]) AND (sensitis*[Title/Abstract] OR sensitiz*[Title/Abstract] OR concentrat*[Title/Abstract] OR threshold*[Title/Abstract] OR "exposure limit*"[Title/Abstract] OR "forced expiratory volume"[Title/Abstract] OR "FEV1"[Title/Abstract]) AND (diisocyanate*[Title/Abstract] OR isocyanate*[Title/Abstract]) AND (diisocyanate*[Title/Abstract] OR isocyanate*[Title/Abstract] OR tdi[Title/Abstract] OR mdi[Title/Abstract] OR hdi[Title/Abstract]) AND (worker*[Title/Abstract] OR workplace*[Title/Abstract] OR "occupational asthma"[Title/Abstract] OR "occupational exposure"[Title/Abstract] OR human*[Title/Abstract] OR consumer*[Title/Abstract] OR employee*[Title/Abstract]). The search was then further restricted to scientific manuscripts about human studies published in the English-language peer-reviewed literature. In addition, we investigated the references of the retrieved articles related to the topic to ensure no article was missed.

Study selection

Articles were searched in the databases and were screened by title/abstract. The articles that met the following eligibility criteria were screened and full texts were accessed and read. The criteria for inclusion were as follows: (1) studies about human subjects, (2) studies including subjects exposed to TDI, HDI, MDI or NDI, and (3) studies reporting on occupational asthma, asthma-like symptoms, or lung function. The exclusion criteria were as follows: (1) studies that did not report quantitative exposure data, (2) studies without a concurrent control group, and (3) studies not reported in the peer-reviewed English-language literature. Because of the limited data available on HDI, MDI, and NDI, we decided to focus this paper on TDI only. A brief description of the studies that reported on HDI, MDI, and NDI exposures is found in the Supplemental Information - 1.

Qualitative data extraction

The first authors' names, year of publication, study design, the numbers of workers exposed to TDI and those of healthy controls, and the means, minimum, and maximum values of TDI exposure (in ppm) were extracted from each article. OA and respiratory function was based on either (1) a validated medical questionnaire (e.g., Medical Research Council (MRC) Questionnaire (Cotes, 1987), (2) a decision by an occupational medicine professional, or (3) the outcome (i.e., sum/mean or best recording) of the three highest values of FEV_1 and/or FVC. Values were judged to be acceptable when the forced vital

capacities of three recordings varied less than 5% of each other.

Exposure measurement was categorized as "area" or "personal," although different analytical methodologies were described. The most frequently used methods for area sampling for isocyanates were continuous paper tape monitors (Reilly, 1968) or the Marcali method (Marcali, 1957). In a few instances, air samples were taken by midget impingers at different locations in a factory (Puscasu et al., 2015).

The most common method for personal exposure measurement was also the use of continuous paper tape (MCM type 4000) worn on the chest that measured breathing zone concentrations during work (Reilly, 1968).

The Newcastle-Ottawa Quality Assessment Scale (NOS) (Stang, 2010) was used to assess each article with a total score of 10 points for cross-sectional and 9 points for longitudinal studies, respectively. A total quality score >7 indicated a high-quality study. The quality evaluation was independently performed by the authors. Scoring inconsistencies were discussed until consensus was reached. Three broad perspectives were examined and scored in each study. (1) For the selection of the study groups each study could be awarded maximum 4 points (longitudinal studies) and maximum of 5 points (cross-sectional studies). (2) For the comparability between the groups a maximum of 2 points could be awarded for each study, and (3) for the ascertainment of the exposure of interest a maximum of 3 points were awarded for each study. More detailed explanation can be found in Tables S2-1 and S2-2 of the Supplemental Information - 2).

Quantitative data extraction

First, the odds ratios (OR_{asthma}) for the association between TDI exposure and OA in exposed compared to non-exposed workers were extracted from the studies or were recalculated for the 11 studies where the odds ratios (ORs) were not published. To calculate the same effect across studies, we recategorized exposure data into exposed versus not exposed and calculated the odds ratio for OA in each study. When needed, standard errors were calculated using the method of Woolf (Bertell, 1975).

Second, the difference in mean differences (MD) of FEV_1 and FVC between exposed and non-exposed individuals based on TDI exposure, as well as their associated standard errors, were extracted or recalculated. This mean difference was rescaled as a percentage of the normal predicted values ($MD_{\%predicted}$). The predicted normal values for FEV_1 and FVC were calculated in each study based on prediction equations after adjusting for age and height of similar samples of non-exposed subjects.

Third, the annual mean change differences—in mL/yr—in FEV_1 and FVC pulmonary function between the exposed and the non-exposed were calculated ($MD_{/year}$).

Meta-analysis

A random effects meta-analysis was performed for $\ln(OR_{asthma})$, $MD_{\%predicted}$ and $MD_{/year}$, considering potential variation (heterogeneity) in study outcome between the studies included. The I^2 (I-squared statistic) was used to describe the percentage of variation in study results across studies due to heterogeneity (Ioannidis, 2008) and was categorized as low (<25%), moderate (25–75%), or high (>75%). In a meta-regression analysis, we tested the null hypothesis that potential sources of heterogeneity, such as mean TDI exposure, study design, quality of study (NOS total score), and type of outcome ascertainment, have no influence on the outcome.

Results

Literature search and study selection

A total of 545 articles were retrieved from STN and 387 from Pubmed/Medline. After removing the duplicates, 590 articles remained and were screened (Figure 1). Of those, 462 articles were excluded based on their title/abstract as not relevant to the subject. The remaining 128 articles were assessed for eligibility, of which 61 full-text articles were read and reviewed for the quantitative meta-analysis. Of those, 47 articles were excluded as they did not include a non-exposed control group or were lacking sufficient data for the analysis.

Twenty studies on isocyanate exposure matched the selection criteria (14 on TDI, three on HDI, two on MDI, and one on NDI). Because of the heterogeneity of the statistical information and the methodology used in the studies on MDI, HDI, and NDI, a meta-analysis could not be performed on these studies. A short review of these studies is provided in Supplemental Information - 1. Finally, 14 studies on TDI were included in this meta-analysis. The additional studies mentioned in the discussion, and which are not part of

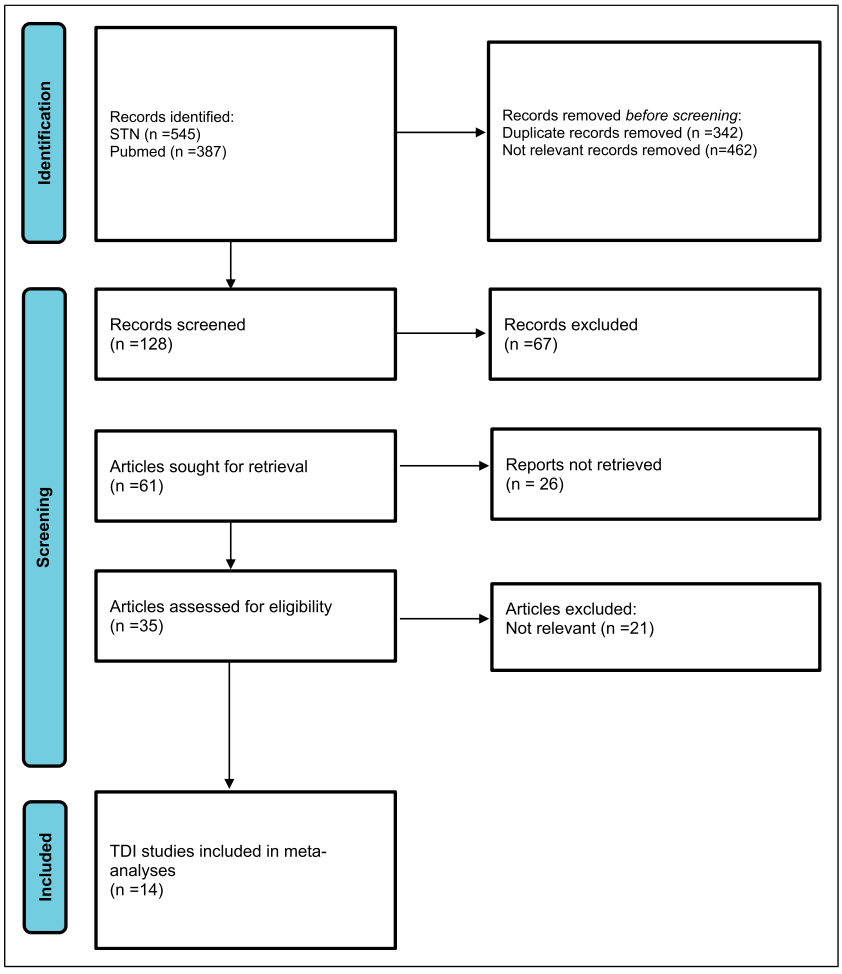

Figure 1. Selection of studies for meta-analyses.

the meta-analysis, were used only as additional information on the topic.

Characteristics of studies included in the meta-analysis

The studies included in the meta-analysis were published between 1975 and 2007. The author, year of publication, study design, exposure measurement, ascertainment method, average TDI level, and range of exposure are presented in Table 1. The average TDI exposures ranged from 0.001 to 0.027 ppm. Approximately 36% of the studies reported area air sampling, 57% reported personal air sampling, and 7% of the studies reported a combination of both. The diagnosis of asthma was reported in 57% of the studies based on a validated medical questionnaire (mainly, the MRC questionnaire), and 43% of the studies reported a clinical diagnosis of asthma. Results of pulmonary function tests were reported in 57% of the studies.

Scoring of selected studies

For the 14 selected studies, the overall quality scores ranged from 7 to 10 points, indicating high-quality studies. All studies (except one) scored high on the selection of study groups scale (score ≥4). Ten (71%) studies scored high on the comparability scale (score ≥2); the remaining four studies (29%) had a lower but still good quality score on comparability. On the outcome scale, 11 studies (79%) scored high (score ≥3) and the other 3 (21%) still had an acceptable score (individual study scores are reported in Table S2-3 of Supplemental Information - 2).

Meta-analysis results

The relationship between TDI exposure and OA in exposed compared to non-exposed workers (OR_{asthma}) was investigated (Figure 2). The overall OR_{asthma} across all studies was 1.18 (95% confidence interval (CI): 0.78–1.79, p-value = 0.44) with moderate (33%)

Table 1. Characteristics of studies included in meta-analysis.

Reference	Study design	Exposed/ non-exposed (n)	Exposure measurement[a]	Ascertainment method[b]	Average TDI level (ppm)	Range of exposure (ppm)	% of samplings > TLV)
Adams (1975)	Longitudinal	76/76	1	1	0.02		1/72%>0.02 ppm
Bodner et al. (2001)	Longitudinal	240/408	1	1,2,3	0.002	0.013->0.12	
Butcher et al. (1977)	Longitudinal	89/14	1	1	0.027	0.003–0.054	
Clark et al. (1998)	Longitudinal	508/136	2	3	0.001		33% of 8 h samples>0.02 ppm
Holness et al. (1984)	Cross-sectional	95/37	1,2	2	0.001		
Huang et al. (1991)	Cross-sectional	15/20	1	1,2,3		0.03–0.21	
Lee and Phoon (1992)	Cross-sectional	26/26	2	1,3		0.035–0.37	
Littorin et al. (2007)	Cross-sectional	136/118	2	2	0.001		
Meredith et al. (2000)	Cross-sectional	27/51	2	2	0.001		
Olsen et al. (1989)	Cross-sectional	10/89	1	1		0.005–0.02	
Omae (1984)	Longitudinal	64/24	2	1,3	0.001		
Omae et al. (1992)	Cross-sectional	90/44	2	1,3	0.005		
Ott et al. (2000)	Longitudinal	313/158	2	2,3	0.004		
Wang et al. (1988)	Cross-sectional	14/20	1	2,3	0.02	0.012->-0.047	

TLV: threshold limit value.
[a]Measure of exposure: 1 = area sampling, 2 = personal sampling.
[b]Case decision/decreased lung function based on: 1 = validated medical questionnaire (e.g., Medical Research Center's Respiratory Questionnaire for chronic bronchitis, 2 = decision by occupational medicine clinician, 3 = clinical test (e.g., pulmonary function: FEV_1 and FVC).

heterogeneity among studies. Three studies reported data on $MD_{\%predicted}$ for FEV_1 and FVC. The results of the respective meta-analyses are presented in Figure 3 (FEV_1) and Figure 4 (FVC), respectively. The overall $MD_{\%predicted}$ was 2.96 (95% CI: −5.69 - +11.62, p-value = 0.67) for FEV_1 and 3.75 (95%CI: −3.41-+10.90, p-value = 0.58 for FVC. In both cases, no heterogeneity in study results was identified (Figure 4).

The estimates for the annual mean differences ($MD_{/year}$) between the two groups for FEV_1 and FVC function tests are shown in Figure 5 (FEV_1) and Figure 6 (FVC), respectively. A decrease of 5.16 and 10.33 mL/yr (95% CI: −34.27 - +23.96, p-value = 0.55 for FEV1; 95% CI: −27.05 - +6.39, p-value = 0.44 for FVC, respectively) was observed between the exposed and the non-exposed groups. The mean difference between the two groups was not statistically significant (p-value > 0.05).

Sources of heterogeneity

The meta-regression analysis suggested that there was no significant source of variation when the mean TDI exposure, the study design, the quality of the study, and method of ascertainment of occupational asthma were considered as potential confounders (Table 2).

Discussion

The present meta-analysis compiled existing evidence on the association between TDI exposure and occupational asthma from six longitudinal and eight cross-sectional studies. So far, comprehensive narrative reviews have been published (Daniels, 2018; Diller, 2002; Ott, 2002) with each of them highlighting numerous limitations regarding the evaluation of this association (Figure 6).

Inconsistencies between previous studies, however, did not preclude meta-analysis. On the contrary, consistency of results among studies with different study designs and varying populations would be a positive sign that a true result was being found. In the present analysis, studies were in part harmonized by selecting primary studies that had both exposed and non-exposed groups to be able to compare OA rates. Subsequently, the potential impact of the different ways these studies were conducted was explored.

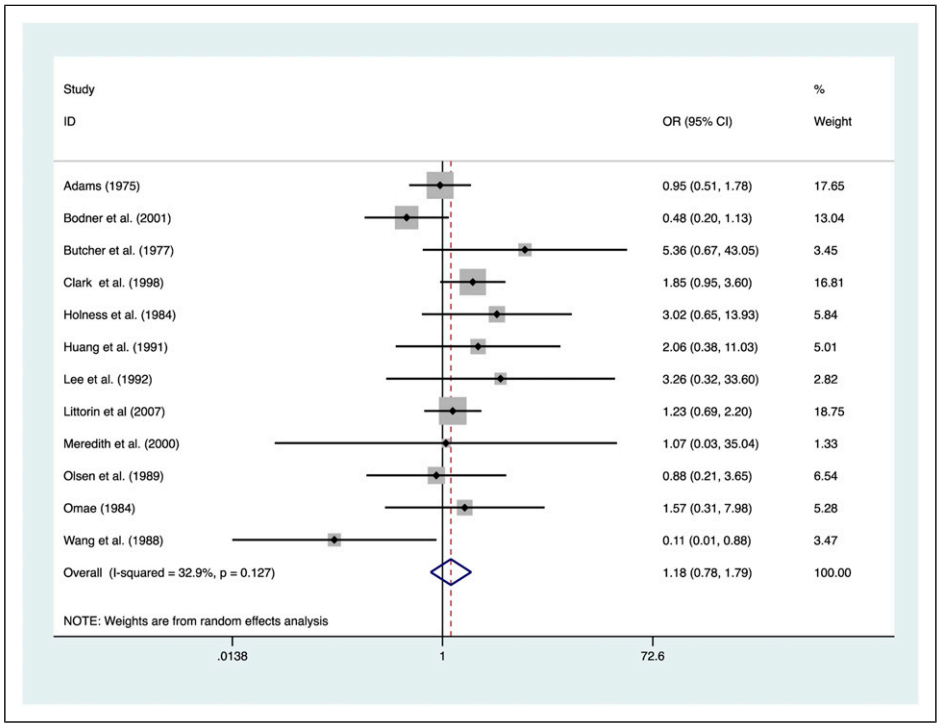

Figure 2. Forest plot depicting odds ratios for asthma (OR_{asthma}) for workers exposed versus workers not exposed to toluene diisocyanate after random effects meta-analyses. The quantitative weight was based on the inverse variance of each study. ES = 1.18; 95% CI = 0.78–1.79; *p*-value = 0.44). OR: odds ratio, ES; effect size, CI: confidence internal.

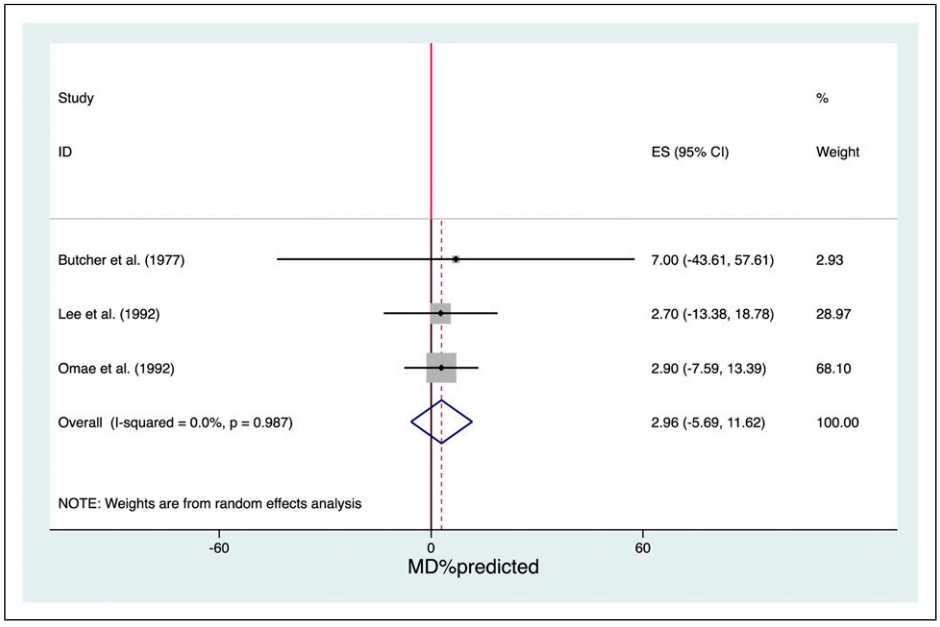

Figure 3. Forest plot depicting mean FEV1 differences—expressed as % of the predicted value—(MD%predicted) for workers exposed versus workers not exposed to toluene diisocyanate after random effects meta-analyses. The quantitative weight was based on the inverse variance of each study. (ES = 2.96; 95. 95% CI = −5.69- +11.62; *p* = 0.67). MD; mean difference, ES; effect size, CI: confidence internal.

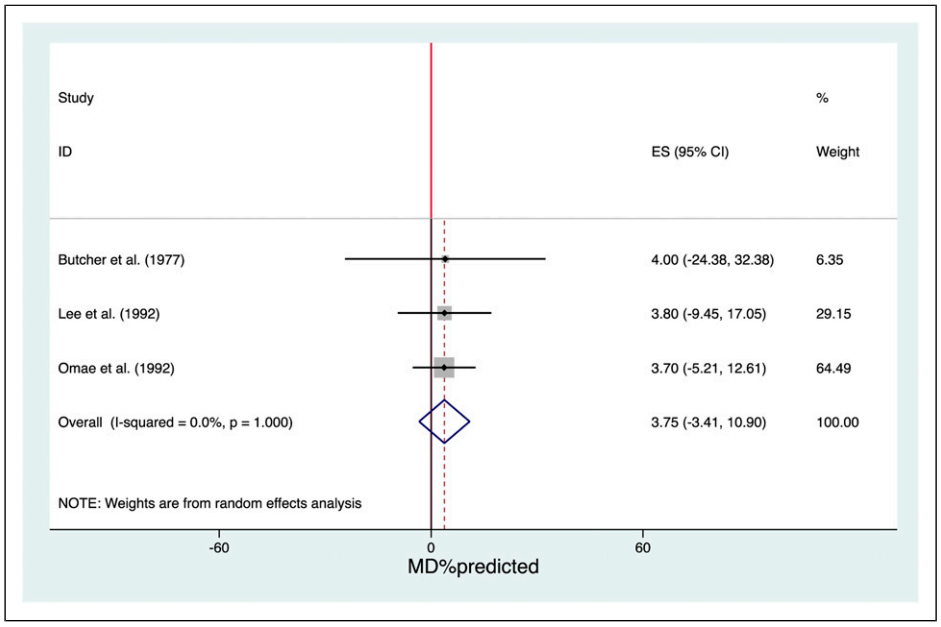

Figure 4. Forest plot depicting mean FVC differences—expressed as % of the predicted value—($MD_{\%predicted}$) for workers exposed versus workers not exposed to toluene diisocyanate after random effects meta-analyses. The quantitative weight was based on the inverse variance of each study. (ES = 3.75; 95%CI = −3.41- +10.90; $p = 0.58$). MD: mean difference; ES: effect size; CI: confidence internal.

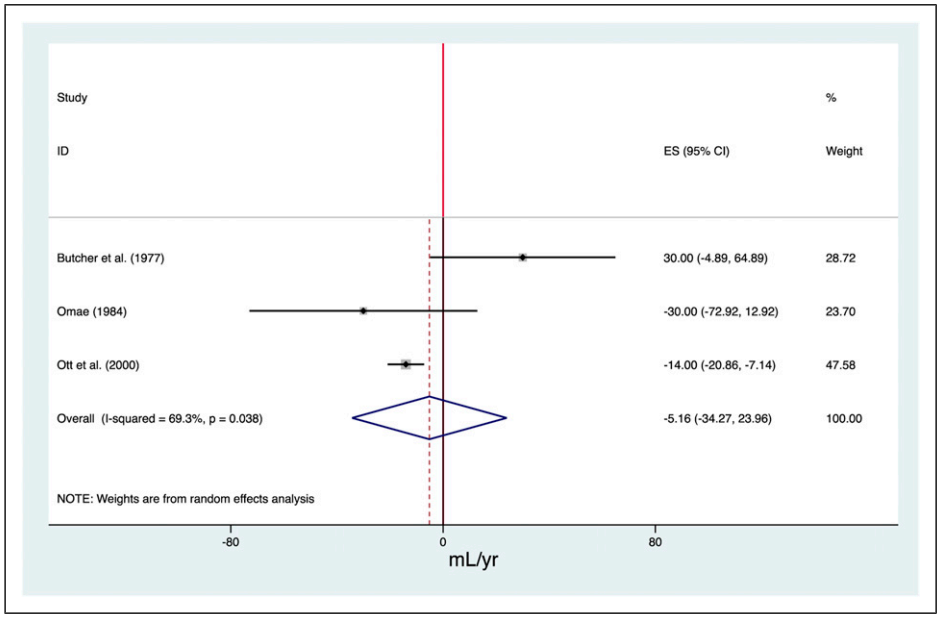

Figure 5. Forest plot depicting mean FEV_1 differences in mL/yr per year ($MD_{/year}$) for workers exposed versus workers not exposed to toluene diisocyanate after random effects meta-analyses. The quantitative weight was based on the inverse variance of each study. (ES = −5.16; 95%CI = −34.27- +23.96; $p = 0.55$). The unit of measurement is in mL/yr. MD: mean difference; ES: effect size; CI: confidence internal.

Table 2. *p*-values for potential sources of heterogeneity for epidemiological studies of TDI exposure and OA in exposed compared to non-exposed workers.

Effects on	OA	FEV_1 annual change	FVC annual change	$\%FEV_1$ predicted	% FVC predicted
Sources of heterogeneity	*p*-value	*p*-value	*p*-value	*p*-value	*p*-value
Mean TDI exposure	0.31	0.24	0.33	Insufficient data	Insufficient data
Study design	0.08	0.25	0.32	0.57	0.41
Quality of study	0.48	0.49	0.34	0.90	0.98
Type of diagnosis	0.26	NA	NA	NA	NA

OA: occupational asthma; NA: not applicable.

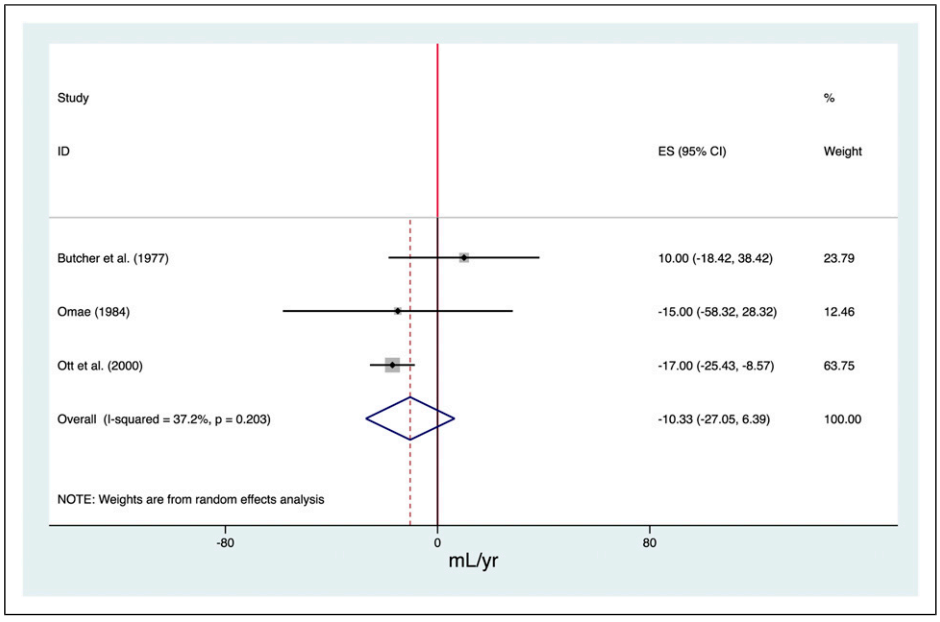

Figure 6. Forest plot depicting mean FVC differences in mL/yr per year (MD/year) for workers exposed versus workers not exposed to toluene diisocyanate after random effects meta-analyses. The quantitative weight was based on the inverse variance of each study. (ES = −10.33; 95% CI = −27.05-+6.39; $p = 0.44$). MD: mean difference; ES: effect size; CI: confidence internal.

Occupational asthma

The overall results from this meta-analysis showed that there was no statistically significant difference between TDI exposed and non-exposed workers for developing asthma, which was consistently found across studies (with a moderate heterogeneity of 33%). A possible explanation for this non-effect could be the very low range of TDI exposure observed in the investigated studies and the limited data available on dose-response assessments. In addition, in a review of nine longitudinal studies from 1954 to 1992, the authors concluded a downward trend of OA incidence over the past half century (Diller, 2002). Another issue that could potentially influence the exposure-outcome relationship is selection bias. Susceptible individuals to health problems are more likely not to be employed in positions involving exposure to chemicals. Self-selection of workers is likely as individuals with respiratory problems may not apply for work at a chemical plant. Therefore, the studied workers are mostly populations that were "healthier" in terms of respiratory diseases. The selective loss of exposed individuals with symptoms is especially important in cross-sectional studies on diisocyanate-related health effects. These studies likely underestimate the risk for workers, because those with symptoms may already have left their jobs making them unavailable for study. Cross-sectional occupational studies therefore are prone to both "healthy worker hire bias" and "healthy worker survivor bias" (Le Moual et al., 2008). The potential for this kind of bias may be reduced in prospective longitudinal studies, but these may also

miss workers with health problems who have left before the start of the study as well as those who are lost to follow-up.

FEV_1 and FVC

In an early longitudinal study, no evidence of decrease in FEV_1 was detected among 180 asymptomatic employees that were followed over a 9-year period (Adams, 1975). Further analyses showed no relationship of FEV_1 decrement to duration of exposure and comparable age-related effects (Adams, 1975). Cigarette smoking was not taken into consideration as a potential confounder and the data were analyzed as cross-sectional (FEV_1 was measured at one time point) rather than longitudinal; thus, estimates of average annual decline in FEV_1 were unavailable.

Decreased FEV_1 and FVC may be considered a consequence of severe asthma (Ott et al., 2003) and are therefore relevant in this context. However, a decrease in these values may not only be related to asthma. Many asthmatics, for instance, retain normal or close to normal lung function throughout life, showing reversibility from acute onset and return to previous function (Sears, 2007). Similarly, other factors, possibly genetic ones, may influence the decrease in respiratory function in healthy individuals with no evident asthma (Masuko et al., 2011).

While we found a negligible difference in annual decline between exposed versus unexposed groups, Diem et al. (1982) did find a difference, but only when comparing high (≥68.2 ppb-months versus low cumulative exposure without including a control group in the analysis. Holness et al. (1984) observed a larger decrease in mean FEV_1 (measured as a difference during a work shift) of approximately 50 mL between exposed and non-exposed.

On the other hand, Omae et al. (1992) did not observe a difference between exposed and controls during a work shift (cross-shift) in FEV_1. A possible explanation for this could be that a cross-shift change is more sensitive to picking up an acute response, rather than a chronic effect, which is likely to differ more between studies.

We therefore concluded that, based on the results from 14 studies, this meta-analysis did not find an association between occupational TDI exposure and lung function, at least for the low range of mean TDI reported (0.001–0.027 ppm) at the workplaces investigated. The negligible differences in FEV_1 and FVC between exposed versus unexposed groups confirmed this observation.

Limitations

A limitation of these meta-analyses is that little information on TDI dose was available for those studies that included a non-exposed control group. In addition, exposure categories were not comparable across studies. For example, one study reported low/medium/high exposures (Wegman et al., 1977) while others used measured exposure in ppm groups (Bodner et al., 2001). Also, few studies were available that investigated the potential effect of the duration of exposure. Adams (1975) found no support for a relationship between the length of TDI exposure and a decrease in ventilatory capacity and neither did Clark et al. (1998). Even though cumulative exposure seemed appropriate for the evaluation of asthma as a chronic disease, peak exposures and dose response analyses could influence the outcome as has been suggested by a recent review (Daniels, 2018). Indeed, in a longitudinal analysis, Collins et al. (2017) studied 197 TDI-exposed workers for 5 years and found an increased risk of cases consistent with TDI-induced OA with both cumulative and peak exposures. However, the use of the 95th percentile of cumulative exposure as an indicator of the potential peak exposures rather than individual measurements may have underestimated the actual peak exposures. Moreover, the analysis to assess the impact of dose was reported as the predicted probability of being a case based on median age of the workers for various levels of cumulative and peak exposures. In contrast, in a study included in this meta-analysis, no difference in peak exposures was found between workers exposed and not-exposed to TDI in either of the two monitored manufacturing companies (Meredith et al., 2000), but in both companies, TWA exposures at the time of onset of asthma were slightly higher for cases (mean TWA was 1.5 ppb) compared to referents (mean TWA was 1.2 ppb). The authors concluded that the risk of asthma was greater when the exposure was higher even though concentration of isocyanates exposure may be similar. The results of the study by Littorin et al. (2007) showed an increase in the reported symptoms in the eyes and lower airways among workers exposed to low levels of TDI (mean <1 ppb) compared with those of unexposed workers. Insufficient studies were available to evaluate the effect of peak exposure. Moreover, even when the average and range of TDI exposures were reported, lack

of more detailed information did not allow for further analysis. (Huang et al., 1991; Wang et al., 1988).

Another limitation may be in the assessment of OA. Almost half of the studies included in this analysis used the MRC Questionnaire on Respiratory Symptoms (Cotes, 1987) to infer OA. Although it may be argued that respiratory symptoms assessed by self-reporting may not constitute an objective measure, this is a validated questionnaire used by most, if not all, of the studies. We have used the group category "lower respiratory symptoms" or otherwise the indication of "wheezing" as an indication for OA. Selecting these symptoms from all those reported may have impacted the estimation of asthma frequency, albeit with an equal bias for exposed versus unexposed subjects.

Future work and conclusion

To obtain more insight into the association between TDI exposure and respiratory health problems, especially due to a lack of recent studies, it is important to see more studies with longitudinal designs, having both exposed and non-exposed subjects and with a focus on collecting more extensive dose, duration, and peak exposure data and identifying possible confounders for all personnel working in potentially exposed areas. In addition, most of the available studies analyzed the effects of a single chemical, even though, in reality, subjects are exposed to a mixture of various chemicals (Masoli et al., 2004). This adds complexity to investigating associations between isocyanate exposure and health effects. In addition, future studies should include a clinically verified OA diagnosis, and if workers leave the company, reasons for resignation should be assessed and a continued follow-up routine for OA after resignation should be set up to avoid information bias. Finally, since all eligible studies were conducted many years ago, recent developments in use of protective equipment and measurement of exposure at the workplace could be considered. Since the use of diisocyanates has been recently proposed to be restricted in the EU unless specific conditions for workers' training and risk management should become applicable in the workplace (Delfino, 2002), it is imperative to follow new guidelines for the correct use of these chemicals.

In conclusion, based on the results of this systematic review and meta-analysis, there seems to be no meaningful association between TDI exposure, OA, and lung function when comparing exposed to non-exposed individuals. Considering all methodological limitations, the results of the existing human epidemiological studies should be interpreted and used with caution.

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Supplemental Material

Supplemental material for this article is available online.

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