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Original article

Risk Assessment for Toluene Diisocyanate and Respiratory Disease Human Studies

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ABSTRACT

Background: Toluene diisocyanate (TDI) is a highly reactive chemical that causes sensitization and has also been associated with increased lung cancer. A risk assessment was conducted based on occupational epidemiologic estimates for several health outcomes.

Methods: Exposure and outcome details were extracted from published studies and a NIOSH Health Hazard Evaluation for new onset asthma, pulmonary function measurements, symptom prevalence, and mortality from lung cancer and respiratory disease. Summary exposure–response estimates were calculated taking into account relative precision and possible survivor selection effects. Attributable incidence of sensitization was estimated as were annual proportional losses of pulmonary function. Excess lifetime risks and benchmark doses were calculated.

Results: Respiratory outcomes exhibited strong survivor bias. Asthma/sensitization exposure response decreased with increasing facility-average TDI air concentration as did TDI-associated pulmonary impairment. In a mortality cohort where mean employment duration was less than 1 year, survivor bias pre-empted estimation of lung cancer and respiratory disease exposure response.

Conclusion: Controlling for survivor bias and assuming a linear dose–response with facility-average TDI concentrations, excess lifetime risks exceeding one per thousand occurred at about 2 ppt TDI for sensitization and respiratory impairment. Under alternate assumptions regarding stationary and cumulative effects, one per thousand excess risks were estimated at TDI concentrations of 10 – 30 ppt. The unexplained reported excess mortality from lung cancer and other lung diseases, if attributable to TDI or associated emissions, could represent a lifetime risk comparable to that of sensitization.

1. Introduction

Toluene diisocyanate (TDI) is a high-volume chemical used in the manufacture of polyurethane (PU). It appears as mixtures of the 2,4- and 2,6- isomers. In industrial environments it induces a TDI-specific adult-onset asthma, diminishing pulmonary function, and respiratory symptoms [1–9]. Three studies show an excess of lung cancer in women workers exposed to TDI or associated intermediates and degradation products [10–12] (below 1.5 ppb time-weighted average TDI in one plant [12]). A challenge in describing TDI adverse effects arises from the apparent selection of sensitized workers out of TDI exposure as the adverse effects appear, and possibly declining susceptibility. This *healthy worker survivor effect* (HWSE) for asthma has been reviewed in detail [13]. In this TDI risk assessment based on a thorough search of the published literature (SOM 6), exposure–responses were estimated under conditions corresponding to minimal survivor selection.

2. Materials and methods

2.1. Environmental toluene diisocyanate measurement

Early determinations of airborne TDI concentrations used the Marcali impinger/colorimetric method. A paper tape method ("MCM") for continuous real-time recording used in several studies was inaccurate at low TDI concentrations [14–18]; a review concluded that there is a positive bias by a factor of 1.5 – 2.0 in measurements below <– 10 ppb [16,17] (see SOM 1; Figs. S1-S6, Table S1). Other methods involved derivatization and high-performance liquid chromatography. The exposure assessments for

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Table 1
Pulmonary function: calculation for of excess annual proportional loss per ppb toluene diisocyanate (TDI) (EAPLX): for FEV_1

	Study design	EAPLX (FEV_1)
1	Cross-sectional group comparison of % predicted value	$(\%FEV_1(0) - (\%FEV_1(TDI))/cumTDI$
2	Cross-sectional group comparison of adjusted-value, L	$(FEV_1(0) - FEV_1(TDI))/(cumTDI \times FEV_1(0))$
3	Cross-sectional regression of % predicted value on cumTDI	beta(TDI)
4	Cross-sectional regression of adjusted-value, L, on cumTDI	$beta(TDI)/FEV_1(0)$
5	Average annual loss %	%AAL/meanTDI
6	Average annual loss, L	$AAL/(meanTDI \times FEV_1(0))$

where, $FEV_1(0)$ – in unexposed (if regression: intercept), if $FEV_1(0)$ not reported, stipulate = 3.8 L $FEV_1(TDI)$ – in TDI-exposed cumTDI – cumulative TDI exposure meanTDI – average TDI exposure beta(TDI) – regression coefficient for cumTDI term AAL – average annual loss (age-adjusted).

this risk assessment were limited: often a simple facility average concentration possibly within time periods. Concentrations in 24 asthma study populations (1968–2001) ranged 0.2, to 112 ppb TDI (median: 10 ppb) (SOM 2, Table S2) and in 18 pulmonary function studies (1982–2003) ranged 0.1 to 5.7 ppb TDI (median: 2.5 ppb) (SOM 3, Table S3). In a TDI mortality study [12] job exposure estimates ranged 1 to 13.5 ppb in one plant, 0.4 to 6.8 ppb in a second plant, and 0.1 to 2.3 ppb in a third. Facility-averages represent a) periodic process events (e.g., opening molds, unloading ovens, accessing curing areas, cleaning lines, nozzles, etc.), b) continuous emissions (partially cured product, spraying and leaks), and c) episodic excursions due to breakdowns (e.g., seal failures, spills, etc.).

2.2. Toluene diisocyanate–induced adult-onset asthma or sensitization

Research on TDI-sensitization mechanisms [19] has implications for assumptions made in epidemiological analyses regarding thresholds and linearity of exposure response. Studies have investigated regulatory T-cells in the draining lymph nodes in response to dermal exposure [20] and tissue localization of TDI-haptenized proteins accessible to dendritic cells [21]. Expression of micro messenger RNA and transcription factors has been observed 1 hour after dermal TDI exposure [22]. A role for inhalation following dermal exposure has been observed in rats [23]. Manifestations of sensitization form a continuum in animal studies. In inbred guinea pigs, respiratory hypersensitivity, and anti-TDI-GSA titer responses to challenge vary widely [24,25], as does local lymph node stimulation [26] or, in rats, cytokine (interleukin-4) response [27]. However, one important assessment criterion (exceeding a minimum wheal diameter) is dichotomous even though dose-dependent. Of necessity, the clinical diagnosis of occupational asthma is also a binary decision based on continuous response measures such as challenge or pulmonary function as well as exposure experience. Complicating matters, chronically exposed workers can tolerate symptoms for years: in a large survey of 780 flexible foam manufacturing workers over 5 years, 17 of 24 incident cases of TDI-sensitization remained in their jobs [28].

Sensitization after brief exposure is often observed. In a Velcro tape manufacturing plant with relatively high TDI concentrations (>25 ppb) and less than 2 years of operation, 14 of 34 were diagnosed with TDI-related asthma [29]. In a new facility producing PU foam with relatively low TDI exposures (maximum concentrations of 10 ppb), when evaluated at 6 months, 7 of 49 workers had new asthma symptoms, airway obstruction, or TDI-specific IgG levels [30]. In contrast, Adams identified new sensitization annually following TDI workers over 9 years [31].

In animal studies, sensitizing exposures are typically administered over one or several days and immunologic responses evaluated within 3 to 30 days of exposure [1,26,32–35]. In contrast, workplace TDI exposures extend for long periods punctuated with occasional peak levels and dermal contact. Effects can accumulate over time. In one human study, 5-min dermal sensitizer exposures over 6 days produced the same response as a single 30-min exposure [36]. Other studies suggest slow clearance from the dermal compartment [23,35] for which an extrapolation factor of 10 was proposed for cumulative effects [35].

Here asthma onset, pulmonary function changes, and symptoms are viewed as simultaneous sensitization and elicitation in a possibly steady-state process. Although the mechanistic literature commonly presumes a threshold in animal studies, it has not been clearly demonstrated in occupational populations, particularly with respect to facility-average TDI air concentrations. Contribution of both dermal and inhalation exposures would further disperse the sensitization response.

The following assumptions are made for health outcomes related to TDI-sensitization:

1. The immune responses and other effects reflect degrees of sensitization.
2. Exposure-induced immunological changes occur after brief delays (<than 1 month).
3. Effects of chronic low level exposures may accumulate over weeks or months.
4. Effects of exposures (as vapor, aerosol or dermal contact) in a given process environment can be roughly predicted by facility average air concentrations.
5. There is a linear exposure-response for asthma/sensitization incidence and TDI concentration considerably below 5 ppb (without linearity, different studies could not be meta-summarized based on facility average environmental assessments).
6. There was minimal impact of MDI in mixed TDI/MDI exposures in the studies used.

From 17 studies published between 1968 and 2001, 24 worker populations provided estimates of incidence [28,29,31,37–52] (SOM 2, Table S2). These studies reported sufficient steps taken to identify TDI-sensitization using such criteria as: symptom onset with exposure, pulmonary function assessment, TDI challenge, and evaluation by occupational physician. For two studies missing information for duration of observation a plausible value of 5 years was stipulated. Of the 24 populations analyzed, 14 were in TDI manufacturing; 8 produced products using PU foam, or adhesives or varnishes; 2 manufactured bulk PU foam. The mean number of new onset asthma/sensitization cases was 13.8, mean population size was 182, and mean TDI air concentration was 20.6 ppm, ranging from 0.23 to 112 ppm. The mean annual incidence rate was 0.047 (SOM 2, Table S2).

Underestimation of incidence would result if cases were leaving the workplace without being ascertained, or prior to the observation period (left-truncation bias [53]). An estimate of (linear) exposure response (XR) was calculated as the observed incidence

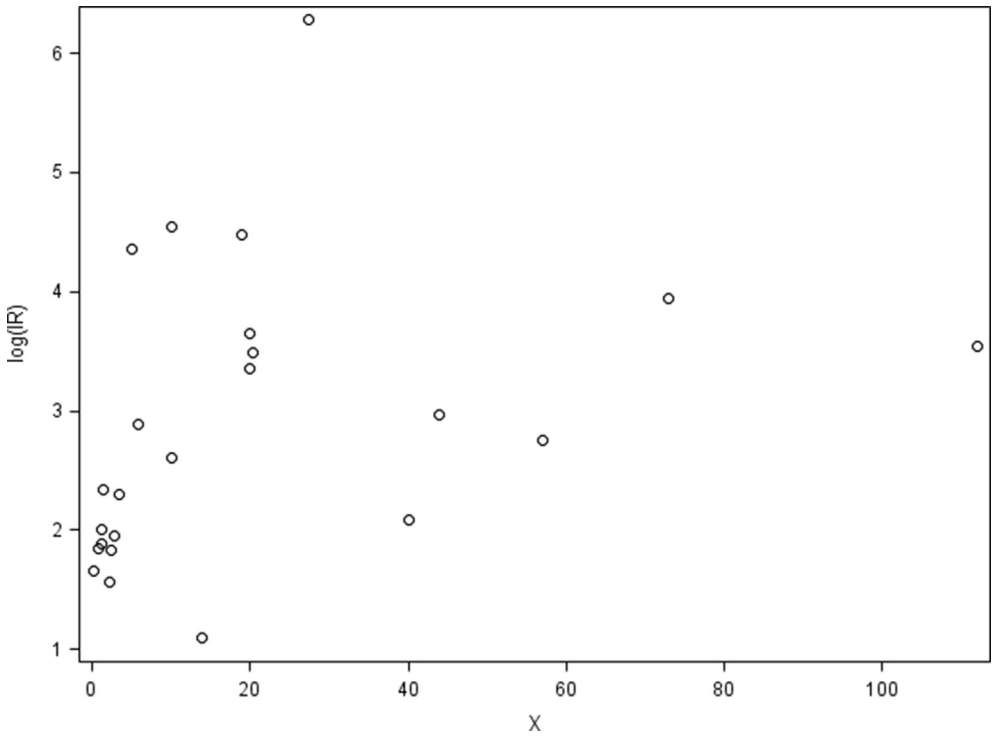

Fig. 1. Asthma incidence rate (IR) on average prevailing toluene diisocyanate (TDI).

rate of attributable asthma or sensitization divided by facility average TDI exposure. Correction for survivor bias arising from removal of symptomatic workers or declining susceptibility was sought using an iteratively weighted non-linear regression model of XR on facility-average TDI concentration, modeled as a simple exponential decline [54] (SAS: proc nlin; SOM 2). The weights were the inverse variance of the predicted incidence rates. From this analysis, the intercept was interpreted as the XR with the least survivor bias. Excess lifetime risk was calculated using the BEIR VII lifetable procedure [55], applying the estimated XR for asthma/sensitization incidence, assuming 45-year exposures (age 20 to 65) and lifetime through age 85.

2.3. Toluene diisocyanate–associated pulmonary function changes

Assessments of pulmonary function in 18 populations permitted calculating a common measure of decline (SOM 3, Table S3) [28,40,43,56–61]. Six different measurement approaches had been used for FEV_1 (Table 1) and/or FVC. Each outcome was expressed as the *excess annual proportional loss per ppb TDI current exposure* (EAPLX; Table 1; SOM 3). Most PFT studies did not report FEV_1/FVC results. In some cases, baseline FEV_1 or FVC values, needed to calculate proportional loss, were not reported and so were stipulated based on typical worker population values (FEV_1 = 3.8 L, FVC = 4.3 L). Diem et al. [62] were excluded because only dichotomized exposure levels were used and the studies of Musk et al. [63,64] were incompatible with the EAPLX estimation. The small group included from Clark et al. [57] followed for 17 years overlapped with the much larger group (n = 780) from Clark et al. [28] followed for 5 years.

When EAPLX was observed to systematically decline with facility-average TDI exposure, a non-iterative weighted non-linear regression was performed (weights: inverse variance of the reported annual proportional loss, using confidence intervals, *p*-values or standard errors) and the intercept interpreted as the XR. Impairment was defined as falling below the *lower limit of normal* (LLN), defined for healthy non-smoking individuals in NHANES III [65]. Using XR the additional proportion falling below the LLN in NHANES III over a 45-year working life at fixed TDI concentrations was calculated [66] (SOM 3). This benchmark dose procedure assumes a) the effect on pulmonary function is cumulative, b) a cumulative exposure dose results in the same loss whether it occurred over 1 year or 5 years, and c) the distribution of percent of predicted FEV_1 in the NHANES III population remains the same with increasing age. Declining pulmonary function is a risk factor for mortality independent of age, gender, race, smoking, and body-mass index (BMI) [67–71]. Three studies provide statistically significant estimates of rate ratios relating all-cause mortality to FEV_1 loss (1.010, 1.016, 1.015) [resp., 67, 69, 70]. For this risk assessment, a mortality rate ratio of 1.015 per percent loss in FEV_1 was applied in a life-table calculation (SOM 3).

2.4. Toluene diisocyanate–attributable mortality from lung cancer and non-malignant respiratory disease

Pinkerton et al. analyzed mortality in a NIOSH TDI cohort updated through 2011, which was available for this work; their analyses revealed statistically significant excesses for lung cancer and non-malignant respiratory diseases (NMRDs) compared with the general population, especially for women, but no significant positive associations with duration of, or cumulative, exposure to TDI [12]. A significant trend was observed for female breast cancer mortality on TDI cumulative exposure ($p = 0.02$) and TDI duration ($p = 0.017$) [12]. Because a strong HWSE was observed for asthma incidence in other studies, and in view of high workforce turnover in the NIOSH TDI cohort (median employment < 1.0 year) the employment termination rate in that cohort was modelled in relation to TDI exposure. Two other TDI studies found elevated mortality for NMRD, especially for women [11,12], compared with that typically observed in industrial populations [72]. Using the

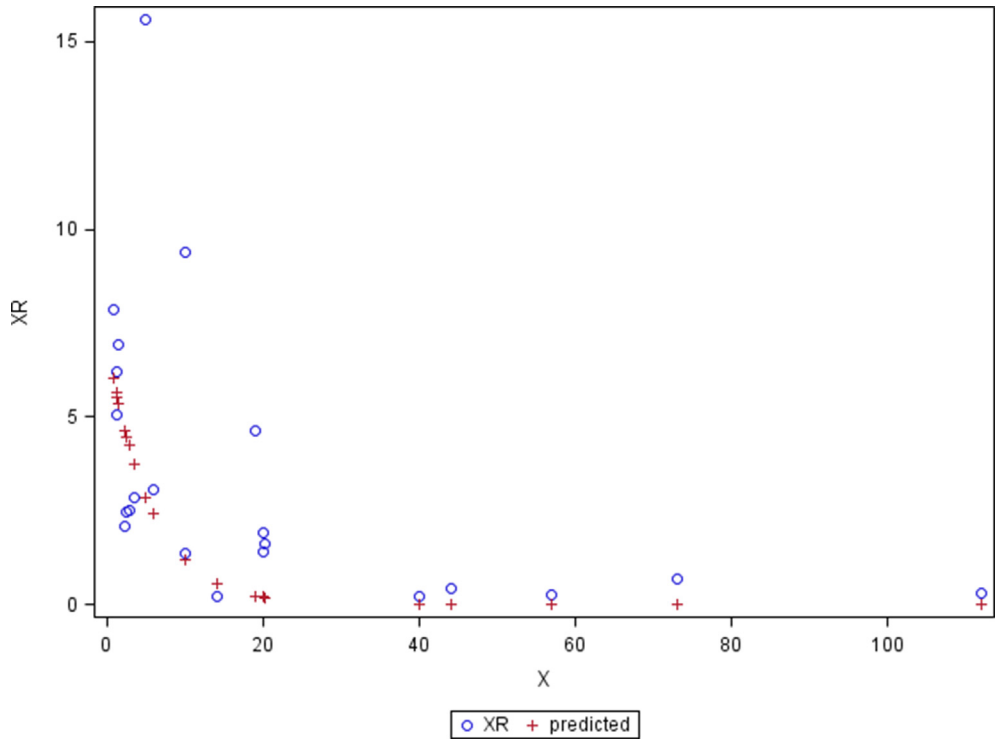

Fig. 2. Asthma exposure response (XR), as incidence rate per ppb toluene diisocyanate (TDI), on average prevailing TDI exposure (×) (per 1000 person-years; excluding two outliers).

NIOSH TDI cohort data, applying US mortality rates [73] in Poisson regression analysis, the overall NMRD SMR was calculated. Assuming a) excess NMRD deaths were attributable to TDI-related exposures and b) a predicted NMRD SMR of about 0.75 for unexposed industrial workers [72] to account for the healthy worker effect (HWE), an approximate *excess relative rate* (ERR) was calculated: ERR = SMR/0.75−1. NMRD mortality was also investigated with models incorporating individual time-dependent employment duration and cumulative exposures attempting to correct HWSE bias.

Three TDI mortality studies observed statistically significant elevated lung cancer in women PU foam workers [10–12]. In the NIOSH Pinkerton mortality study smoking history was unavailable for an analysis stratified on smoking [12]; however, other smoking-related causes of death in women (oral, bladder, and pancreas cancer; leukemia) exhibited an SMR deficit (SMR = 5/10.5 = 0.48). Therefore, it is appropriate to assume that smoking prevalence among women in that study was not higher than in the national reference population. In the Sorahan study [11], women in finishing jobs were assumed to have minimal airborne TDI exposure and quantitative exposure was not available for the Mikoczy study [10]. Using NIOSH TDI cohort data [12], assuming the predicted lung cancer SMR would be about 0.93 for unexposed workers [72], the ERR was calculated: ERR = SMR/0.93−1. As with NMRD Poisson regression models were used to investigate lung cancer mortality correcting for HWSE.

2.5. Toluene diisocyanate–associated symptoms

Respiratory symptoms were reported in 15 studies in TDI exposed workers and, in most cases, in unexposed groups [28,37,39,42,45,46,49,56–58,74–78]. Sixty estimates of excess symptom prevalence were extracted (SOM 5, Table S7). There were likely non-TDI exposures that could also cause symptoms (latex, fabrics, plasticizers); it was assumed that half of the symptoms reported by non-TDI exposed workers were work-related, the other half representing background rates. In the few studies without comparison groups, investigators reported symptoms judged to be TDI related. Excess symptom prevalence per ppb of TDI was calculated as an XR. A non-linear regression model was fit to obtain the intercept representing the least selected population risk. Inverse variance weights were calculated based on binomial variances for proportions derived from one (exposed) or two (exposed and controls) groups (SOM 5). Because excess prevalence, at low TDI concentrations, was a good approximation of the odds of attributable symptoms, the excess prevalence at higher exposures was obtained by linearly extrapolating the odds to higher exposures and then evaluating prevalence as odds/(1+odds).

3. Results

3.1. Toluene diisocyanate–induced adult onset asthma

The asthma incidence rate (per person-yr) showed little association with average TDI concentration across study populations (Fig. 1) and the XR ranged from 0.2 10^{-3} to 23 10^{-3} per year per ppb TDI (SOM 2, Table S2). When XR was plotted against average exposure, considerable structure emerged (Fig. 2). Two outlying points were: 1) a plant with low levels (0.23 ppb) and a stable workforce [49] and 2) a study in which the observation time was recent (prior 9 mo.) with rigorous follow-up of workers [29]. This downward trend of XR with TDI level indicates survivor bias that could arise, e.g., because: a) workers sensitized at higher exposures leaving employment more rapidly and before ascertainment, or b) declining susceptibility. In the regression model to minimize survivor bias the two outliers (XR > 17 10^{-3} per ppb-yr TDI) were excluded (Fig. 2; SOM 2) resulting in a model intercept of 7.0 10^{-3} or 0.7% per ppb-yr TDI. For TDI levels of 1, 5 or 10 ppb, the model

Table 2
Excess lifetime risk of new onset asthma per thousand with 45 years of toluene diisocyanate (TDI) exposure or with incidence limited to the first 9 or 4.5 years, as predicted from constant non-cumulative current exposures

TDI conc. (ppb)	Excess lifetime risk of asthma onset (per 1000)		
	45 years	9 years	4.5 years
1	260	54	28
0.5	140	28	14
0.2	59	11	5.6
0.1	30	5.6	2.8
0.05	15	2.8	1.4
0.02	6.0	1.1	0.56
0.01	3.0	0.56	0.28
0.005	1.5	0.28	0.14

1 ppb = 7.4 μg/m^3 TDI.

predicts XR: 5.9, 2.8 and 1.1 10^{-3} per ppb-yr, respectively. Applying the estimated XR in a life-table calculation (assuming constant susceptibility) yielded estimates of excess lifetime risk (Table 2): at 1 ppb the proportion becoming sensitized after 45 years is 260 per 1000 or 26%. One per thousand excess risk is estimated to occur over a working lifetime at about 0.003 ppb or 3 ppt.

3.2. Toluene diisocyanate–associated pulmonary function changes

The range of values for EAPLX was 0.00033 to 0.038, that is, 0.03% to 3.8% loss per year per ppb TDI, over a range of 0.1 to 5.7 ppb TDI (SOM 3, Table S3). These measures of PFT-TDI XR also showed a diminishing pattern in relation to TDI concentrations (Fig. 3). A fixed effect, non-linear weighted regression fit produced an estimate of XR at low exposures (from intercept) of: 0.0077, or 0.8% per ppb; at 1 ppb the estimated XR was 0.53% (see SOM 3). A random mixed-effect model addressing interstudy variability, produced a larger, more statistically significant estimate of the XR intercept: 0.0155, or 1.55% per ppb; at 1 ppb the estimated XR was 0.8% (see SOM 3). The TDI exposure over 45 years estimated of give 1/1000 excess impairment (by benchmark dose procedure) was 0.0017 ppb (0.005/2.9, Table 3). For increased mortality resulting from impaired pulmonary function, the estimated exposure conferring 1/1000 excess lifetime mortality risk was 0.0015 ppb TDI (Table 3).

Table 3
Excess prevalence per thousand of impaired pulmonary function (FEV_1 and FVC) over 45-year working lifetime at constant toluene diisocyanate (TDI) exposure and all-cause mortality associated with FEV_1 changes, for effective exposure durations of 45, 9, and 4.5 years

	Excess prevalence below lower limit of normal (per 1000)			Excess lifetime risk of mortality associated with reduced FEV_1 (per 1000)		
TDI conc. (ppb)	45 years	9 years	4.5 years	45 years	9 years	4.5 years
0.5	—	87	34	273	76	39
0.2	249	26	12	124	31	16
0.1	87	12	6.1	65	16	7.9
0.05	34	6.1	2.9	33	7.9	4.0
0.02	12	2.5	1.2	13	3.2	1.6
0.01	6.1	1.2	0.44	6.8	1.6	0.80
0.005	2.9	0.44	0.18	3.4	0.80	0.40

Impairment estimates based on common exposure response estimates for FEV_1 and FVC.

3.3. Toluene diisocyanate–attributable employment termination, non-malignant respiratory disease, and lung cancer mortality

In the Pinkerton mortality cohort (three plants with exposure history) [12], there was a high termination rate in the first 3 months

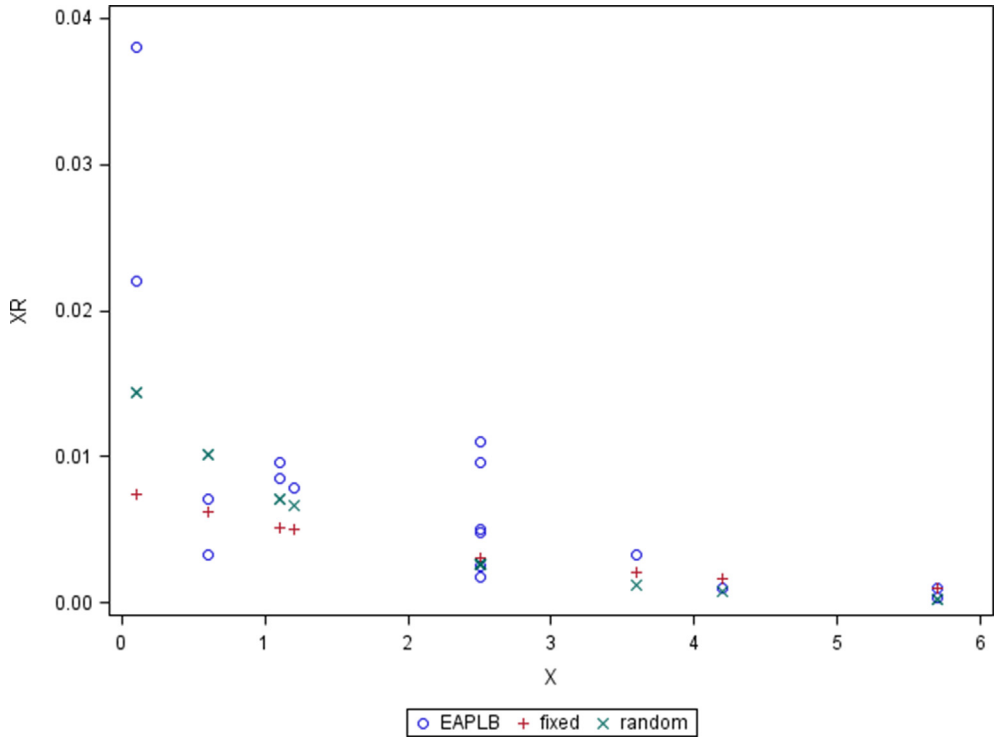

Fig. 3. Pulmonary function exposure response (XR, excess annual proportional loss per ppb toluene diisocyanate [TDI]) on facility average TDI concentration (per ppb): fixed- and random-effect models.

Table 4
Standardized mortality ratios (SMRs), excess rate ratios (ERRs), and exposure response (XR) for NMRD and lung cancer in three polyurethane foam plants, making assumptions of linearity of response and attributability exclusively to toluene diisocyanate/polyurethane production, using mean. lagged cumulative exposure over all observation time

	SMR (RR)	95% CI	ERR	Mean cumulative toluene diisocyanate exposure (ppb-yr)
Non-malignant respiratory disease (NMRD)				
All	1.46	1.18, 1.82	0.95	4.20
Men	1.39	1.05, 1.84	0.85	4.21
Women	1.59	1.13, 2.23	1.12	4.19
Lung cancer				
All	1.57	1.29, 1.88	0.68	2.63
Men	1.27	0.99, 1.62	0.37	2.87
Women	2.25	1.70, 2.97	1.42	2.31
Women in finishing	2.48	1.85, 3.32	1.66	2.32

SMR by Poisson regression (SAS proc nlin); model: cases = exp(a0) × expt; SMR = cases/expt.
expt = expected deaths from US specific rates; separate models by sex.
For NMRD: ERR = SMR/0.75−1; for lung cancer: ERR = SMR/0.93−1.
Person−time-weighted mean cumulative exposure from original exposure matrix over observation time of model; 10-year lag for lung cancer, 90-day lag for NMRD.

of follow-up, at an annual rate of 58%, which by 10 years of employment declined to 3% per year (SOM 4, Table S4). Statistical models revealed this negative association with duration and a positive association with 10-year lagged cumulative TDI exposure that was higher in finishing jobs (termination rate ratio: 27.8, 95% CI: 21.2−34.5, per mg/m^3-yr) than in other jobs (10.9, 95%CI: 7.2−14.6) (average finishing cumulative exposure across observation time after 10 years was 0.016 mg/m^3; SOM 4, Table S5). The TDI dependence was higher in women especially black women who, at low TDI concentrations, had the lowest termination rate (SOM 4, Figs S7-S10).

The overall NMRD SMRs calculated here for the Pinkerton cohort [12] (using different methods) for all workers, men, and women in the three plants with exposure history were 1.46 (95% CI = 1.18, 1.82), 1.39 (95%CI = 1.05, 1.84), and 1.59 (95%CI = 1.13, 2.23), respectively (Table 4), and very close to those reported [12]. The ERRs, adjusted for HWE, were 0.85 and 1.12, for men and women, respectively (Table 4). Models of NMRD mortality using individual time-dependent cumulative TDI exposures exhibited negative non-significant associations with employment duration and TDI exposure and elevated intercepts (corresponding to SMR = 2.05, data not shown). For lung cancer, the SMRs were 1.57 (95%CI = 1.29, 1.88), 1.27 (95%CI = 0.99, 1.62), and 2.25 (95% CI = 1.70, 2.97), respectively, for all workers, men, and women (Table 4). The ERRs were 0.37 and 1.42, respectively, for men and women, corresponding to person-time-weighted average cumulative exposures of 2.87 and 2.31 ppb-yr. For women in finishing jobs the SMR (2.48, 95%CI = 1.85, 3.32) and ERR (1.67) were larger (Table 4). Models of lung cancer mortality with TDI cumulative exposures showed non-significant negative associations, consistent with a strong HWSE in the mortality analyses as observed with employment duration.

3.4. Toluene diisocyanate−associated symptoms

Excess symptom prevalence varied from 0.01 to 0.96 over an exposure range of 0.23 to 160 ppb TDI (SOM 5, Table S7, Fig. S11) with no increase above 5 ppb. The decline in the XR (excess prevalence per ppb TDI) with increasing exposure (Fig. 4) (a direct consequence of the boundedness of prevalence) also reflects a selection/survivor effect. Comparing the observed excess prevalence with that predicted based on linear extrapolation of the excess odds suggests the magnitude of the survivor effect (SOM 5, Fig. S11). The intercept of the non-linear regression model of XR corresponded to an excess symptom prevalence per ppb of 1.02 at very low exposures (Fig. 4); at 1 ppb the predicted excess prevalence per ppb was

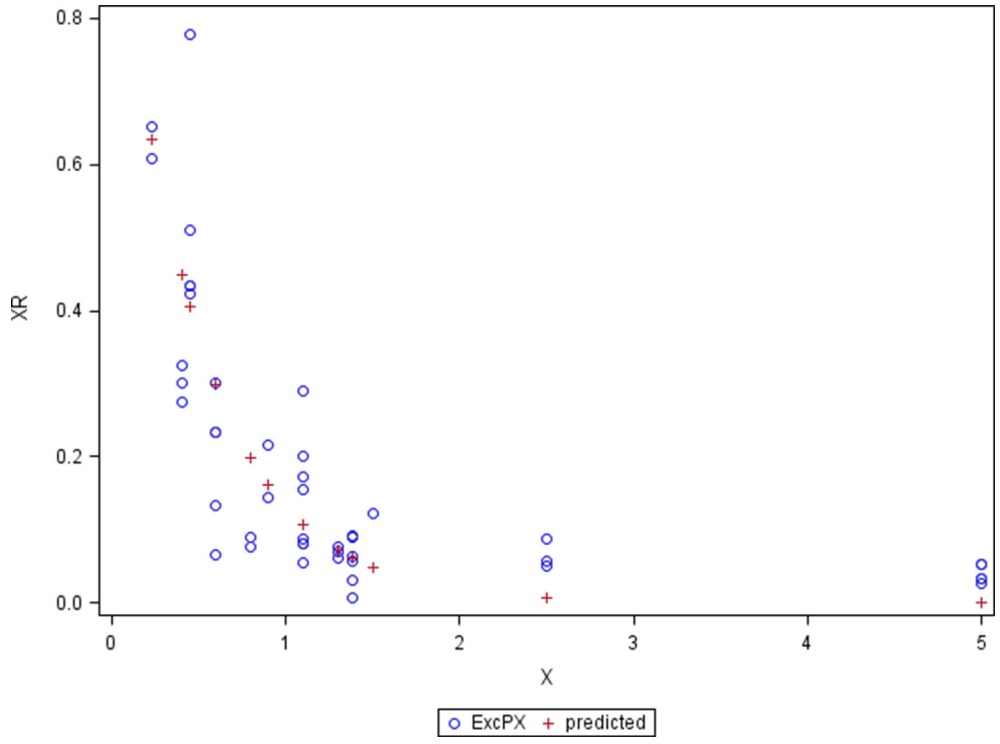

Fig. 4. Attributable symptom prevalence exposure response in relation to facility average toluene diisocyanate concentration (per ppb).

Table 5
Predicted prevalence, per thousand, of an attributable symptom in relation to current exposure correcting for survivor bias

Toluene diisocyanate conc. (ppb)	Excess prevalence (per 1000)					
	All	Shortness of breath	Cough	Wheeze	All but irritation, chronic bronchitis	Irritation*
1.0	504	459	514	468	473	452
0.5	337	298	346	305	309	292
0.2	169	145	175	150	152	141
0.1	92	78	96	81	82	76
0.05	48	41	50	42	43	40
0.02	20	17	21	17	18	16
0.01	10	8.4	11	8.7	8.9	8.2
0.005	5.1	4.2	5.3	4.4	4.5	4.1

Estimated excess prevalence at low MWF concentrations was estimate of odds from which excess prevalence at higher exposures was obtained as odds/(1+odds) by linear extrapolation of odds.

* Reported as: any irritation, throat irritation, eye irritation, rhinitis, runny nose, stuffed nose, or dermal irritation.

0.13 (SOM 5). Linear extrapolation (as odds) of the XR estimate (1.02) yielded an excess average risk of a respiratory symptom of about 20 per 1000, or 2%, at 0.02 ppb TDI which was similar in the individual symptom classes (Table 5). To the extent different symptoms are statistically independent, the risk of symptoms would be greater than 2%.

3.5. Summary risk assessment

The excess risk estimates across the various outcomes varied within a factor of 3 at 0.05 ppb TDI (Table 6). Excess lifetime risks of one per thousand occurred at 0.003 or 0.0015 ppb TDI, respectively, for asthma onset and respiratory impairment (Table 7). This risk assessment did not use the supporting symptom analyses because of unknown severities and subjective and unstandardized assessments. Mortality related to declining FEV_1 was not included because it represents an upper bound of risk to which other conditions may have contributed. Limitations in the different estimates could have resulted from extrapolation to a working lifetime of 45 years. With maximal or steady-state effects after only 9 or 4.5 years 1/1000 excess risks for asthma/sensitization would occur at 0.018 ppb (18 ppt) and 0.032 (32 ppt), respectively and, for respiratory impairment, at 0.0063 ppb (6.3 ppt) and 0.012 (12 ppt), respectively (Tables 2, 3, and 7).

Table 6
Excess lifetime risk (asthma, mortality) or excess prevalence (pulmonary impairment, attributable symptoms), per thousand, with a 45-year working life at fixed toluene diisocyanate (TDI) airborne concentration

TDI conc. (ppb)	Excess risk (per 1000)			
	Asthma onset*	PFT impairment	Associated symptom prevalence*	FEV_1 – related mortality
0.5	140	—	337	273
0.2	59	249	169	124
0.1	30	87	92	65
0.05	15	34	48	33
0.02	6.0	12	20	13
0.01	3.0	6.1	10	6.8
0.005	1.5	2.9	5.1	3.4

* In relation to current exposure.

Table 7
Toluene diisocyanate (TDI) exposure (ppt) conferring excess lifetime risk (asthma) or excess prevalence. (PFT) of one per thousand, with 45 years TDI exposure or with effects limited to the first 9 or 4.5 years of exposure

End-point	Asthma	PFT
TDI concentration with 45 years exposure, ppt	3	1.5
TDI concentration with 9 years exposure, ppt	18	6.3
TDI concentration with 4.5 years exposure, ppt	32	12

4. Discussion

4.1. Findings

There was a striking reduction in the XR with increasing facility-average TDI exposure across studies, which appears to be a survival phenomenon. Whether it results from changing intrinsic susceptibility, diminishing ascertainment of cases or some other mechanism such as immune tolerance or a countervailing reduction in dermal exposure (improbable) cannot be determined with the available data. A method was used to correct for survivor effects, but these may have occurred even in populations with low average exposures due to exposure variability within studies. Few studies described or discussed the reasons for employment termination; two studies performed careful case ascertainment over time [29,31].

Prior employment in isocyanate-sensitizing environments could have contributed what appeared to be new cases in some studies. However, in studies where an employer or medical doctor assessed respiratory cases one would assume that work prior to current employment, an important diagnostic issue, would have been queried but whether or not this was done was rarely and not systematically reported. The exposure–response for new sensitization is generally understood to be weaker (responses at higher exposures) than for elicitation of responses in sensitized individuals. Previously sensitized workers would be expected to become symptomatic rather quickly and at almost all levels of ambient TDI concentrations. Although possible, it is unlikely that prior sensitization could account for much of the observed pattern of incidence, PFT changes or symptoms.

In a recent study at three TDI production facilities (after the 2017 literature search), the annual incidence rate for asthma/sensitization was 0.9% [79] with mean TDI exposures of 0.65 ppb (1,594 full-shift routine air samples) [80] for a XR of 0.9%/0.65 = 1.4% per ppb-year. The observations were based on medical surveillance over 6 years with relatively low turnover [81]. The 73% potentially selective participation by symptomatic workers would imply an XR as low as of 1.4% × 0.73 = 1.0% per ppb-year, similar to the XR estimated here (0.7%).

For asthma and PFT impairment, considering maximal effects attained by 9 or 4.5 years, the TDI exposures conferring 1/1000 excess lifetime risk or prevalence (6.3–32 ppt) are 100-fold below typical TDI manufacturing activities at 4 ppb (4000 ppt) and above. Excess lifetime risks of 1/100 correspond to estimated TDI exposures of 0.063–0.32 ppb. Respiratory and other symptoms exhibited the same pattern of diminishing prevalence with increasing average TDI exposure. In some studies, the symptoms reported could have included those arising from irritant effects. The symptom associations supported but were not basis for this risk assessment. One study investigated the possible role in sensitization of the concomitant high amine exposures in PU production [37]. In that study, a visual “blue haze” was reported, a known consequence of corneal edema from amine exposures, but this complaint was not associated with the reported respiratory symptoms.

In manufacturing environments, TDI is often accompanied by other isocyanate moieties arising as feedstock mixtures, intermediates, and volatile reaction products in polymerization or as degradation products from high temperature applications (hot knife-cutting, flame bonding, lamination, etc.). For TDI-associated health effects, the available studies do not distinguish these exposures. The role of dermal exposures remains unquantified. In a facility manufacturing PU blocks, in workers exposed to 0.8 ppb TDI, Austin [83] observed higher levels of the biomarker urinary toluenediamine (uTDA) in jobs handling partially cured foam versus jobs with no physical contact (resp., 2.1, 0.11 μmol uTDA/mol creatinine). In manufacturing final products such as auto parts, women are over-represented in jobs handling recently cured PU foam [12,46] such as gluing, sewing, and laminating. This is the group where excess lung cancer was observed in three mortality studies [10–12].

The unexplained excesses in lung cancer and NMRD mortality in the Pinkerton cohort [12] are concerning, and any exposure dependence appears to be affected by healthy worker survivor bias. If a substantial part of the lung cancer excess were attributable to TDI-related process emissions, the excess risk could be comparable with or exceed that of asthma onset. 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 (See SOM 4). The concentrations of actual lung carcinogens that could be associated with TDI (rather than TDI itself), and conferring 1/1000 risk could be much higher than 18 ppt.

If dermal exposure plays a major role in sensitization, the contributions of TDI inhalation exposures to risk could be substantially less that estimated here. The sequence of events in sensitization may involve patterns of skin contact followed by brief elevated airborne levels [23]. Mice were sensitized by application of 1% TDI to the skin at Day 1 followed by intratracheal instillation of 0.2% TDI at Day 6 [84]. Recently, Pollaris et al. [85] observed a pronounced airway hyperactivity in mice following repeated intranasal exposures only with prior dermal sensitization. With reduced or avoided dermal sensitization, 1/1000 risk may be achievable with TDI air levels considerably above those identified here.

4.2. Other risk assessments

Another quantitative risk assessment for TDI was performed by Daniels [82] based on a subset of 8 employers identified in the same literature search used here but with lower TDI air concentrations (<5 ppb), whereas in the present analysis 14 of the 24 populations had average TDI exposures ranging 5.9 to 112 ppb (mean: 33.8). In the Daniels analysis, a pattern consistent with HWSE was not observed and the TDI exposure estimate for 1/1000 lifetime risk based on a linear model, was 17 ppt (or 0.17 ppb for 1/100 risk), which was about midrange for the estimates produced here under different assumptions regarding relevant exposure periods, ranging 3–32 ppt (Table 7).

In 2019, the European Chemicals Agency (ECHA) provided a comprehensive review of isocyanate health effects [86], discussing HWSE in some detail, and concluding that there is insufficient human data to address the issues of thresholds or quantifying the role of dermal exposures. ECHA compiled current global occupational exposure limits (OELs), which largely center on 5 ppb TDI with some ranging 1–10 ppb. These OELs are more than a factor of 100 higher than those based on risk estimates of Daniels [82] or in the present analysis.

4.3. Conclusions

The likely presence of some form of strong survivor effect in TDI-exposed workers is problematic for XR estimation. This investigation demonstrates that examination of the dependence of XR estimates on average air concentrations of irritant or sensitizing exposures offers some control of survivor bias and permits an assessment of risk. In clinical and investigational settings the importance of distinguishing irritant and early manifestations of sensitization effects was affirmed. When possible, a clinical opinion on whether sensitization-related health effects played a role in a worker's leaving employment should be recorded (anonymously) for assisting risk management. Lau and Tarlo have reviewed current issues in the diagnosis and management of work-related sensitization [87]; they affirm the importance of primary prevention given the complex exposure environments where sensitizers occur and the likely under-ascertainment of new cases. The analyses of exposure response and risk assessment in the present work support this view.

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Disclaimer

The findings and conclusions in this article are those of the author and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

Conflicts of interest

The author declares no conflicts of interest.

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Appendix A. Supplementary data

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