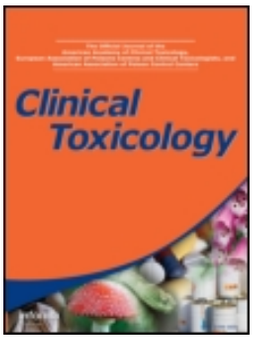

Clinical Toxicology

ISSN: 1556-3650 (Print) 1556-9519 (Online) Journal homepage: https://www.tandfonline.com/loi/ictx20

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To cite this article: M. A. Hughes, M. Carson, M. A. Collins, A. T. Jolly, D. M. Molenaar, W. Steffens & G. M. H. Swaen (2014) Does diisocyanate exposure result in neurotoxicity?, Clinical Toxicology, 52:4, 242-257, DOI: 10.3109/15563650.2014.898769

To link to this article: https://doi.org/10.3109/15563650.2014.898769

Clinical Toxicology (2014), **52**, 242–257

ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.3109/15563650.2014.898769

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REVIEW

Does diisocyanate exposure result in neurotoxicity?

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Context. Diisocyanates have been associated with respiratory and dermal sensitization. Limited number of case reports, and a few case studies, media, and other references suggest potential neurotoxic effects from exposures to toluene diisocyanate (TDI), 1,6 hexamethylene diisocyanate (HDI), and methylene diisocyanate (MDI). However, a systematic review of the literature evaluating the causal association on humans does not exist to support this alleged association. *Objective.* To perform systematic review examining the body of epidemiologic evidence and provide assessment of causal association based on principles of the Sir Austin Bradford Hill criteria or considerations for causal analysis. *Methods.* A comprehensive search of public databases for published abstracts, case reports, cross-sectional surveys, and cohort studies using key search terms was conducted. Additional searches included regulatory reviews, EU IUCLID and EU Risk Assessment databases, and unpublished reports in the International Isocyanate Institute database. An expert panel consisting of physicians, toxicologists, and an epidemiologist critically reviewed accepted papers, providing examination of epidemiologic evidence of each report. Finally, the Hill criteria for causation were applied to the summative analysis of identified reports to estimate probability of causal association. *Results.* Twelve papers reporting exposed populations with a variety of neurological symptoms or findings suitable for analysis were identified, including eleven case or case series reports, and one cross-sectional study. Three papers reported on the same population. Each of the papers was limited by paucity of diisocyanate exposure estimates, the presence of confounding exposures to known or suspected neurotoxicants, a lack of objective biological measures of exposure or neurotoxic effects, and lack of relative strength of association measures. Additionally, reported health symptoms and syndromes lacked consistency or specificity. No plausible mechanism of toxicity was found. Application of a predictive mathematical model for determining probability of causal association for neurotoxicity was calculated to be 21%. *Conclusion.* There is insufficient evidence for a causal association of neurotoxic effects and diisocyanate exposure based on lack of evidence in all categories of the Hill criteria for causality except for temporal association of reported symptoms and alleged exposure. Future reports should attempt to address more rigorous exposure assessment and control for confounding exposures.

Keywords Diisocyanate; Neurotoxicity; Peripheral nervous system; TDI; MDI; HDI; Central Nervous System; Sir Bradford Hill Criteria

Introduction

Diisocyanates, a group of chemical intermediates used predominantly in the production of polyurethanes, are widely recognized as having properties that may result in respiratory and dermal irritation and/or sensitization manifest as reversible obstructive lung disease (occupational asthma) or contact dermatitis. Recent case reports of diisocyanates, and in particular reviews of toluene diisocyanate (TDI), have suggested these agents as having an association and possible causal relationship of both central and peripheral nerve toxicity. Additionally, media reports[1] and the US Environmental Protection Agency (EPA)[2] now references 2,4 TDI as an agent that "affects the central nervous system", although citations for these assertions are not provided.

The mechanism for toxicity of diisocyanates particularly as it relates to occupational asthma, is yet to be clearly defined.[3] The potential for respiratory sensitization has led to stringent controls in workplace air, with typical regulatory occupational exposure limits being 5 ppb for an 8-hour time-weighted average and 20 ppb for a short-term exposure level.[4] With proper and appropriate protective equipment and adherence to the occupational exposure limits, occupational asthma, or irritative effects from diisocyanates are preventable.[5]

Diisocyanate compounds contain two isocyanate groups with a structure of R-C-N = C = O, and can be aliphatic such as 1,6 hexamethylene diisocyanate (HDI), or aromatic such as 2,4 or 2,6 TDI and methylene diphenyl diisocyanate (MDI) (Fig. 1). Metabolism of diisocyanates in humans is not well defined but studies in animals suggest the major

Received 11 August 2013; accepted 21 February 2014.

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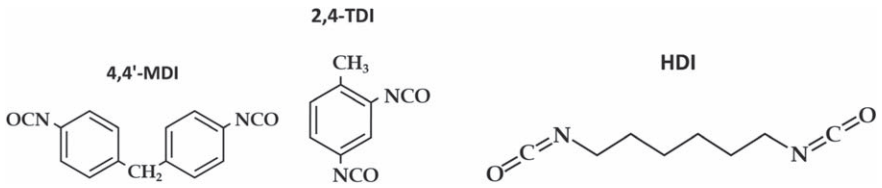

Fig. 1. Chemical structure of diisocyanates.

metabolic pathways to involve adduct formation with proteins and a smaller fraction of inhaled diisocyanates forming diacetylated products without formation of a free diamine.[6] Biological monitoring methods now available include analysis of hexamethylene diamine, toluene diamine, and methylenediamine formed after hydrolysis of isocyanate-protein adducts in urine or blood.[7] Because such hydrolytic analytical methods are not specific to diisocyanates, other methods with a high degree of specificity have been developed.[8–10]

Effects of diisocyanates have been studied extensively in animals using inhalation and dermal exposures. Local irritative effects to the skin and respiratory system and their sequelae remain the primary described effect, consistent with human toxicology. However, no robust and confirmed evidence of any primary peripheral or central nervous system neurotoxic effect from diisocyanates has been reported in experimental animal studies. Two-year inhalation studies on both MDI[11] and TDI[12] have been conducted, in which daily observations of clinical signs were made. There were no reports of clinical signs indicative of neurotoxicity. In short term investigatory studies conducted at higher exposure concentrations than the chronic studies, clinical signs related to respiratory irritation were reported with no indications of neurotoxic effects of MDI[13,14] or TDI.[15] Finally, one subchronic study with HDI[16] included a neurobehavioral testing segment, which was negative for such effects. Overall, the animal toxicology test data give no indication of neurotoxic effects from diisocyanates. To our knowledge, there are no agents that are established as neurotoxicants in humans that have not been established as neurotoxicants in animal studies, suggesting a priori association prematurely proposed without careful analysis of the data.

The purpose of this review is to identify and critically review published reports that describe or suggest a neurotoxic effect in humans from exposure to diisocyanates. Each report is independently assessed based on study type, exposure assessment, diagnostic studies, objective findings, and strengths and weakness of the author's conclusions. Using the sum of evidence, strength of causality assessment is made through consideration of the epidemiologic principles proposed by Sir Austin Bradford Hill, often referred to as the Hill criteria.

Materials and methods

Systematic search for publications

Publications relating to diisocyanates were identified through exhaustive literature searches of public databases (Medline, Biosis, CSNB, Embase and ULIDAT) using CAS numbers for 18 diisocyanates of commerce and their chemical and common names and abbreviations, such as "diisocyanates", "TDI", and "MDI". For the purposes of this work, further selection was applied using terms including "neuro*", "CNS", "PNS", "worker symptoms" "health effects", and "clinical signs". Additionally, unpublished studies by the International Isocyanate Institute (III), expert regulatory reviews including the EU IUCLID 2000 dataset, EU Risk assessment on MDI, SIDS submissions to ICCA, and various national regulatory exposure limit documentation sources were similarly searched for relevant reports or studies. Finally, Internet-based search engines were utilized for identification of regulatory material, trade publications and standards on TDI and MDI. The search was updated last on May 30, 2013.

Review process

The research panel included physicians experienced in making occupational health and toxicological assessments, clinical toxicologists, and an epidemiologist. Papers not appropriate for scientific assessment (i.e., press articles) were excluded from analysis. Peer-reviewed papers received an in-depth review and analysis of study type, detail of reported symptoms or physical findings and any diagnoses, suspected agent(s) resulting in symptoms, exposure assessment, type of population exposed, potential confounders, and other notable circumstances related to the report. Results were summarized into an evidence table for analysis.

Assessment for causal inference was performed using the Hill[17] considerations in the evaluation of causation. Application of these criteria is a generally accepted instrument to evaluate the total body of evidence consisting of all accumulated case reports. The nine considerations or criteria utilized include: strength of the association; consistency; specificity; temporality; biological gradient; biological plausibility; coherence; experimental evidence; and analogy. A narrative summary of all studies for each Hill criteria provide basis for analysis of causal association.

Finally, utilizing the narrative summary for each Hill consideration, we use a predictive mathematical model using a weight of evidence approach to causal inference for determining probability estimate of causal association based on the nine Hill criteria. This model presented by Swaen and van Amelsvoort[18] has previously been validated on analysis of 159 IARC category 1 and 2A agents. The model specifies that each Hill criterion be assigned a probability of being true. For example, considering the criterion "strength of association", if the overall risk ratio reported in the literature

is greater than 5, a 95% probability is assigned to the criterion, whereas it would be 80% for risk ratio between 2 and 5, and 60% if between 1 and 2. Space does not allow for full explanation of numerical assignment process for the other criteria, and the reader is referred to the original work by Swaen and van Amelsvoort. The strength of probability from 0 to 100% that the data presented in these reports satisfies a specific Hill consideration is assigned to each criterion. The individual criterion probabilities are then combined to obtain an estimate of overall probability.

Results

Over 100 articles or reports were examined for clinical relevance to the subject. Twelve reports were accepted as clinically relevant with substantive content to be included in the assessment. Excluded reports[19–31] are listed online at (Supplementary Table 1 to be found online at http://informahealthcare.com/doi/abs/10.3109/15563650.2014.898769). The papers selected for review were organized into the following categories: Exposure to diisocyanates only; Mixed exposures to diisocyanates with other chemicals and exposure to thermal decomposition of polyurethane foam. Of these, three papers[32–34] were found to be reports of the same exposed population of firefighters, and therefore are considered together. Thus, 10 study populations are available for analysis. Discussion of each report follows below. Results of each critique are summarized in Table 1.

Mastromatteo et al. 1965[35]

This case series describes 24 workers contracted to clean the pipes and storage tanks of a TDI manufacturing facility. Exposure occurred over a four- to five-day period. The work was performed due to the presence of contaminants in the system. Of the 24 workers, 12 did not use personal protective equipment (PPE), and this subset all developed respiratory symptoms, with five also reporting neuropsychiatric symptoms. Four of the five workers were described to have "anxiety neurosis", while one worker was diagnosed with "acute psychosis" during hospitalized treatment for respiratory symptoms, which the author attributed to an adverse reaction from corticosteroid therapy, and which resolved quickly when the therapy was discontinued. There were no reports of peripheral or central nervous system conditions. No long-term follow-up of these individuals has been reported. The author concluded that there was no evidence of psychiatric disability as a consequence of TDI exposure, attributing the neurosis symptoms to anxiety related to having acute respiratory symptoms.

This report is from a published brief providing synopsis of notable occupational incidents that occurred in a Canadian province during the year of 1965. A primary weakness is the lack of exposure data to diisocyanates or other potential substances (e.g., unspecified contaminants in manufacturing process and cleaning solvents) that were likely present but not described. Additionally, details regarding symptoms, physical examination, diagnostic testing performed, treatment and follow-up are lacking. Anxiety neurosis, the diagnosis given to four workers, is not further defined, but appears to describe an anxiety reaction related to developing acute respiratory distress and appears to have resolved quickly. There is no strength of association provided, although none in the group wearing PPE became symptomatic, suggesting some increased risk of ill health from exposure. However, symptoms are nonspecific. The lack of exposure data inhibits analysis of biological gradient. No mechanism for effect is proposed. There is insufficient evidence for making causal association of neurological effects from this report.

Singer et al. 1987[29]

This case series report describes three dockworkers exposed to liquid TDI from a punctured storage drum. The first worker was splashed with TDI on the face, arm and leg, and developed immediate respiratory symptoms and nausea. The two other workers assisting the first were also directly splashed with TDI. Total exposure appears limited to the short interval of removing themselves from the drum vicinity, although the author indicates dermal exposure from clothing could have been prolonged up to 4 hours. The workers reported chronic symptoms including headache, fatigue, concentration problems, irritability, depression, sleep disturbance, memory, and sexual dysfunction. The authors conducted neuropsychological testing at 2 and 16 months post-exposure. Testing at these intervals appears to include different batteries of tests, with the 16-month session being much more comprehensive, including nerve conduction and multiple psychometric tests. The authors report a decrement in Total IQ of an average of 23 points at 16 months post-exposure using the WAIS-R scale compared to that of the WAIS IQ scale used at the earlier evaluation. Reduced retention on Benton and Wechsler Memory Scale was also observed. Two of the workers exhibited sensory peripheral nerve conduction velocity impairment, one with bilateral median nerve slowing, and another with sural nerve slowing. The authors concluded that the delayed decline in mental function over 16 months post-exposure could be due to "(a) the gradual death of brain tissues that was injured by the initial exposure; (b) the release of TDI stored in body fat as the fat was mobilized, or the breakdown of other chemical storage sites; (c) the toxicity of TDI metabolites when they are cleared from the blood, liver, or other organs". The authors inferred metabolites of TDI to be cyanide and toluene, and therefore could have resulted in hypoxia and delayed neurological deterioration. The authors by analogy relate the effects of these three workers to effects of methyl isocyanate exposure as observed from victims of the Bhopal, India incident methyl isocyanate disaster. They reported that the causative role of the nerve conduction velocity test results was not determined. Although litigation was ongoing at the time of the second evaluation, results were similar 11 months post settlement. They also discount the confounding effect of anxiety and depression symptoms, which are prevalent in the general population and more likely to emerge with respiratory symptoms.[36]

Table 1. Evidence summary of reports meeting inclusion criteria.

Reference & Study type	Study size	Diisocyanate exposure	Co-exposure	Subjective symptoms	Objective findings	Diagnostic studies	Author's conclusions	Analysis
Exposure to Diisocyantaes Only								
Mastromateo 1965 Case Series	Twenty-four workers cleaning pipes and vessels for TDI manufacturing facility. Twelve not wearing proper PPE developed symptoms over 4-to 5-day period	TDI—Dermal and Respiratory	Only TDI was mentioned. Work was being done because system became contaminated (not specified)	Primary: 12/24 with upper or lower respiratory complaints. Secondary: (1/12)"acute psychosis" 1/12; 4/12 with anxiety neurosis with strong overtones of psychosomatic complaints	6 of 12 hospitalized for various respiratory symptoms, including pneumonia. 1 worker diagnosed with delusional psychosis - 48 hours after given corticosteroid therapy, resolved in 24 hours after medications stopped	Not mentioned in case report	Workers with proper PPE had no complaints. Noted anxiety with respiratory distress is common. "Highly motivated workers were able to return to full time employment. Workers with little or no motivation, in whom no permanent physical impairment could be found, have not yet returned to full employment"	Analysis of diagnosis and treatment is difficult due to sparse details and must be considered in context of medical system of 1965 Canada. Symptoms of anxiety are non-specific. No definition of "acute psychosis". Likely that exposure included other contaminants of TDI manufacturing process
Singer 1987 Case Series	Three wharf workers	TDI—punctured drum—Dermal and Respiratory	Not specified	Neurasthenia, emotional lability, headaches, depression, irritability, forgetfullness, disorientation, decreased concentration, hypesthesia stocking/glove	One subject had mild sensory peripheral neuropathy (bilateral median nerves), another had mild sural nerve sensory neuropathy. IQ testing showed progressive decrement ranging from 20–26 points between 2-month and 16-month period	Neurobehavioral testing at 2 and 16 months. Different tests used at intervals. WAIS score at 2 mos, WAIS-R at 16 mos. Nerve conduction studies	Progressive decrement of mental function due to "(a) gradual death of brain tissues that was injured by the initial exposure, (b) the release of TDI stored in body fat as the fat was mobilized…(c) the toxicity of TDI metabolites when they are cleared from the blood, liver, or other organs"	Author incorrectly infers toxic effects of TDI are from toluene and cyanates. Author used different testing methods between intervals, WAIS and WAIS-R scales not fully comparable. Litigation effect may have been present. Author used unvalidated malingering assessment to determine litigation effect unlikely

(*Continued*)

Table 1. (*Continued*)

Reference & Study type	Study size	Diisocyanate exposure	Co-exposure	Subjective symptoms	Objective findings	Diagnostic studies	Author's conclusions	Analysis
Mixed Exposure to Diisocyanates and Other Chemicals								
Thrasher 1989 Case Series	Fifteen workers in two small offices with complaints after office was remodeled	TDI—adhesive source from remodeling	Volatile organic chemicals (VOCs), formaldehyde (F), trimellitic anhydride (TMA) as "reactive chemicals" associated with building related illness	All subjected reported multiple symptoms involving mucous membranes, lungs, musculoskeletal, and CNS (headaches, memory problems), chronic malaise/fatigue, nausea, dizziness, irritability, altered olfaction (increased sensitivity to chemicals, smells). 100% reported headaches, memory difficulties, malaise. 87% reported flu-like illness	No over exposures found on air sampling (conducted 2-years after construction). TDI was below limits of detection. Positive antibody to albumin conjugate of F-IgE: 4/12, F-IgG 11/12; TDI-IgE: 5/12, TDI-IgG 9/12. Correlation of symptoms to antibody titers: F-IgE ($r = .33, p > 0.05$) F-IgG ($r = .24$, $p > 0.05$), TDI-IgE ($r = .48$, $p > 0.05$), TDI-IgG ($r = .48$, $P < 0.05$)	Building-related illness questionnaire; albumin conjugates of formaldehyde, TDI, trimellitic anhydride (TMA), VOCs; IgE and IgG antibodies to same substances	"Immunologic mechanisms may explain the existence of hypersensitivity pneumonitis, allergic rhinitis, asthma, and skin eruptions that have been reported in tight building syndrome"	Small sample size with no control population. Data suggest poor correlation of immunologic testing with symptoms. No objective physical findings in this population, yet author infers data may explain objective findings in other reports of "tight building syndrome"
Müeller 1989 Case Series	Forty workers in East Germany in polyurethane production	Diisocyanates	Dimethyl formamide, trichloromethane, phosphoric acid esters, trichlorofluormethane, tertiary amines, organic tin-compounds. Most with exposures for > 5 years	Nine workers (22%) with nonspecific neurasthenic symptoms. Nine workers (22%) with symptoms of peripheral neuropathy	EEG—No differences from age adjusted norms. PNF—11 with abnormalities (neurasthenia). MMA 11/40 with abnormalities (27.5%) EMG—11 with mild NCV slowing peripherally. PNF—11 with abnormalities	Physical Exam, ESR, Blood Count, liver enzymes, urine, respiratory evaluation, EMG, EEG, Mean momentary Arrhythmia (MMA) electrocardiogram(MMA and neurospsychological testing (PNF)	Findings considered nonspecific, as neuropsychological testing results may have been explained by age dependent decrease rather than toxic encephalopathy. Recommend against use of EEG for screening. Symptoms of neurasathenia, peripheral neuropathy may be explained by the co-exposures. No specific findings with diisocyanates	Workers in the polyurethane plant have multiple potential exposures. No specific exposure data presented on any substance. Data suggest no specific role of diisocyanates and neurotoxic effects

Reidy 1994 Case Series	Five workers allegedly exposed to MDI over 2-year period—facility type or industrial process not described	MDI—No workplace monitoring data, lack of details on task-specific exposure circumstances	Hydrocarbon vapors	All subjects diagnosed with occupational asthma (surrogate for exposure measures). "All... reported high incidence of vague subjective complaints…such as headaches, mood alterations, forgetfulness and decreased concentrations"	No deficits in Neuropsychological testing for: psychomotor, psychosensory, visuographic, language functions, mental efficiency, rate of information processing, learning ability and abstract reasoning	Neuropsychological testing	"[p]resent results do not clearly identify a single pattern of neuropsychological deficits associated with MDI exposure, the data do suggest the presence of compromised cognitive functions characteristic of CNS involvement"	All subjects unemployed, testing obtained by litigating attorneys. Unknown number of co-workers did not seek testing. Exposure suggested by diagnosis of occupational asthma, although no supporting data presented. Overall, data suggest limited. Conclusion of toxic encephalopathy from MDI with no exposure data and co-exposure to hydrocarbon vapors in undescribed process is speculative
Herbert 1995 Case Report, Series	Single subject as sentinel case, 40 union workers in prevalence study	HDI	Multiple solvents including toluene, xylene, and n-hexane	Case report—lightheadedness, loss of balance, headache, irritability, fatigue, and symmetrical paraesthesias in feet and hands	Case—Symmetrical distal mixed polyneuropathy demonstrated by NCV. Prevalence—great toe vibrotactile threshold testing 42% abnormal dominant, 36.4% nondominant toe in roofers ($p < 0.001$)	Tactile Threshold testing	"The results of this series of roofers suggest a previously unreported health hazard for roofing workers. [W]e maintain the results of this series should be considered as hypothesis generating, at best"	Exploratory study to determine prevalence of abnormal tactile response. Possible selection bias of union workers (15% of eligible population). Data suggest higher percentage of abnormal vibrotactile threshold testing. No correlation with exposure data. Data does not suggest causative link with diisocyanates. Abnormalities most likely associated with organic solvents

(*Continued*)

Table 1. (*Continued*)

Reference & Study type	Study size	Diisocyanate exposure	Co-exposure	Subjective symptoms	Objective findings	Diagnostic studies	Author's conclusions	Analysis
Nijem 2001 Cross Sectional Survey	One hundred and sixty-seven workers nonrandomly selected from 20 shoe factories in Palestine	Diisocyanates—nonspecified (use in curing of soles)	n-Hexane, toluene, dichloromethane, polyvinyl chloride	Neurasthenia, parethesias, sore eyes, breathing, difficulties	Prevalence Ratio: >1 month exposure compared to no exposure (from process involving diisocyanate and n-hexane): Sore eyes PR = 1.7 (1.1–2.7), tingling PR = 1.8 (1.2–2.9) No significant association with headache, breathing difficulty, mental irritability	Q16 Swedish neuropsychiatric symptom questionnaire	"Cumulative exposure in plastic molding was associated with sore eyes and tingling of limbs. Workers in this task could be exposed to diisocyanates, a strong irritant compound that produces eye and airway inflammation and to different solvents such as n-hexane that are responsible for toxic neuropathy"	Participants were recruited from factories in Palestine. Factory owners selected participants, introducing large bias. No exposure data. Analysis of symptoms by job task (and thus exposure) suggest no neurologic effects from diisocyanate, but suggests association with n-Hexane and other solvents
Moshe 2002 Case Report	Single Subject—61-y/o artist with 30 years painting in home studio	TDI	Toluene, xylene, benzene, methyl ethyl ketone, acetone, thinner	Intention tremor, parasthesia hands and feet, memory and concentration difficulties	Peripheral neuropathy, central neuropathy, ototoxic hearing loss, brakykinesis, cognitive impairment, attention and memory problems, decreased executive function compatible with solvent intoxication	Scalp somatoseneory evoked potentials, nerve conduction studies, neurobehavioral testing (limited battery of tests)	"The artist…suffered from sensory-motor peripheral polyneuropathy that was not explained by his diabetes (or alcohol, drugs, head trauma, or Alzheimer's). These exclusions supported a diagnosis of solvent-induced neuropathy"	Type of Diabetes or treatment details missing. No data on TDI or extent of exposure. Description of painting method indicates heavy exposure to organic solvents listed. Data suggest in this individual symptoms and objective findings most consistent with organic solvent peripheral neuropathy and encephalopathy

Exposures to Diisocyanates and Thermal Decomposition Products of Polyurethane								
McKerrow 1970 Axford 1976 LeQuesne 1976 Three case-series reports of the same firefighter population with 4-year follow-up	36 Firefighters in 1967 mattress manufacturing fire LeQuesne reports comparison with population of 15 fireman McKerrow reports Group 1:36 Fireman Group 2: 25 Factory workers	TDI—leaking vessel from fire, 1000 gallon spill	Pyrolysis products of polyurethane foam mattress factory—over 100 chemicals(Paabo 1987) McKerrow—Group 1: Pyrolysis products of polyurethane foam mattress factory; Group 2: Non-descript industrial process	LeQuesne: 23/36 reported "neurological" symptoms at some time during 4-year-period post fire. 5 men with acute N/V, euphoria (drunk) during fire. 14 men with variety of sx such as headache, difficulty concentrating, poor memory, irritability or depression at 3 weeks, 13 with some symptoms at 4 years McKerrow: Group 1: Acute—6/36 (two lost consciousness), euphoria, ataxia. Delayed/chronic: late memory and concentration difficulties in 14/36	LeQuesne Report Examination: 6/36 slight ataxia of gait, 1/36 with subjective parasthesia (pinprick). EEG normal. At 4-yr follow-up, 1 man with persistent sensory impairment, no other physical findings. Memory testing showed difference in long term recall mean score 33.2 vs. 27.0 in control vs. exposed and still affected ($p < 0.02$), no difference in control vs. all exposed ($p > 0.1$) McKerrow Report: No objective results provided	LeQuesne Report: Wechsler memory Scale. EEG, Physical Exam. CXR and Spirometry for pulmonary effects McKerrow Report: Not specified	LeQuesne Report: "Although proof that TDI was responsible for the neurological syndrome described is lacking, it appears that the men affected had in common a greater exposure to TDI than those unaffected" McKerrow Report: "Neurological symptoms including euphoria and ataxia occurred acutely in a few men and difficulty in concentration and a memory defect persisted in 14"	Lack of baseline comparison data for controls presented, therefore may not be representative. Significant age difference apparent in control (younger). Data suggest subset of exposed firefighters with persistent subjective symptoms, but no significant support for TDI exposure vs. other fire related exposures. Pyrolysis of polyurethane foam may release HCN, CO, benzonitrile, acryolonitrile, and many other organic solvents that are more consistent with symptoms described, including acute euphoria

There are multiple limitations in this case series report. The authors incorrectly speculate that TDI toxicity is similar to the effects of toluene and cyanide as independent agents as support for biological plausibility. This postulated biological mechanism for neurotoxicity is inconsistent with TDI toxicology. Gradual and delayed brain tissue necrosis, delayed release of stored TDI in body fat, or delayed persistent circulating metabolites has not been demonstrated. The observation of neuropsychological effects is also limited by several factors including absence of an appropriate control group, the small number of cases, lack of baseline outcome measures for IQ testing, use of non-validated comparison data from different test methodologies between evaluations, and significant delay between exposure and evaluation. These limitations of coherence, biologic gradient, specificity, consistency, and plausibility prevent supporting causal association of TDI and encephalopathy or progressive neurotoxicity, and therefore do not provide sufficient evidence for a causal association of diisocyanates and neurotoxicity.

Thrasher et al. 1989[37]

This is a case series report of 15 workers with onset of health effects after their office underwent renovation and remodeling. All employees reported widely variable combinations of symptoms involving mucous membranes, respiratory, musculoskeletal, and the central nervous systems. These symptoms included headaches, memory problems, chronic malaise or fatigue, nausea, dizziness, irritability, and altered olfaction. The report includes an investigation of biologic markers for exposure to formaldehyde, trimellitic anhydride, volatile organic chemicals (VOCs) and TDI through air sampling, a written questionnaire, and blood antibody testing by ELISA. TDI exposure was postulated based on use of TDI-containing adhesives. Indoor air concentration sampling measurements were taken 2 years after exposure began, demonstrating each substance below permissible standards. Antibodies to formaldehyde, TDI and trimellitic anhydride conjugates were also determined. The correlation between symptoms and the geometric mean titers to the conjugates were non-significant. The authors concluded that there might be a synergistic immunological response to airborne chemicals, which included TDI, and recommended immunological monitoring as a potential test for investigating future building-related illness.

Investigation of building-related illnesses is complex, controversial, and most often without specific identification of a causal agent. In this investigation, the authors do not attempt to attribute specific symptoms to the chemicals involved, but rather use antibody testing to correlate symptoms with putative exposure to TDI and the other agents. The absence of asymptomatic controls from the same or another building constitutes a major weakness and limits conclusions on strength of association. Further, the utility of diisocyanate antibody testing as evidence of exposure or disease is very limited due to lack of method standardization and lack of population normative data,[38,39] and consequently the validity of the method is limited. There is little consistency and no specificity of reported symptoms. Thus, there is insufficient data supporting diisocyanate neurotoxicity.

Müller et al. 1989[40]

This is a case series report of 40 workers (28 women and 12 men, aged 20–63 years) from an East German polyurethane production facility with 5 or more years at the plant. The authors report undefined workplace exposures to diisocyanates, dimethyl formamide, trichloromethane, phosphoric acid esters, trichlorofluoromethane, tertiary amines, and organic tin-compounds. Nine workers (22.5%) showed "unspecified neurasthenic symptoms", a term used to describe a constellation of symptoms such as fatigue, fearfulness, headaches, impotence, neuralgias, and melancholia; two had "neurological abnormalities (unspecified)", which in one case prompted a change of workplace. Results of psychological–neurological questionnaire (PNF) demonstrated nondescript abnormalities in eleven workers described as "neurasthenia". Mean Momentary Arrythmia (MMA) analysis to determine functional abnormalities of the visceral parasympathetic system demonstrated abnormality in 11 workers (27.5%). EEG studies demonstrated the borderline findings in 11 workers. Compared to an age-adjusted normal population there was no statistically significant difference in EEG findings. Seven workers had mild neurophysiological abnormalities in the EMG indicating a slight demyelinating neuropathy although data were not well described. The authors make no conclusions regarding the symptoms described and particular exposures.

The lack of a comparison group from a cohort of employees is a major limitation of this case series. The selection method of the 40 employees included is not well described. The number of potentially exposed and unexposed persons at the facility is not defined, but is likely much higher than the described population. Results of this case series indicate nonspecific findings or findings of undefined significance. The clinical significance of MMA test and findings are not defined. The psychological testing tool and significance of "abnormalities" are also not well defined. Electromyography results were nondescript other than mild slowing peripherally. Potential confounders are not well controlled. Age and alcohol use were not controlled for in the analysis. Workers with longer exposure times were significantly older than those with less exposure (42.7 vs. 27.7 years).

The observation that workers exposed to several substances in polyurethane production suggests, but does not demonstrate, an association between effect and exposure to chemicals in the workplace. Of those described, several are suspected neurotoxicants like halogenated organic solvents. There are however no actual exposure data, limiting efforts to demonstrate a positive relationship between symptoms and specific agents. Any positive correlation of polyneuropathy or encephalopathy to diisocyanates in this population is confounded by age, personal risk factors, and potential exposure to known neurotoxicants such as organic solvents. There is no indication of any specific involvement of diisocyanates

in the signs and symptoms reported. Thus, there is insufficient evidence to support a causal neurotoxicant effect from diisocyanates from this study.

Reidy et al. 1994[41]

This series presents results of neuropsychological evaluations on five workers referred by workers compensation attorneys who were allegedly exposed to MDI over a 2-year period. All subjects were diagnosed with isocyanate-induced occupational asthma and allergic rhinitis. Symptoms reported were flu-like symptoms, headaches, respiratory distress, depression, irritability, forgetfulness, disorientation, decreased calculating ability, word-finding and concentration, numbness of the hands and feet, altered sense of smell, chronic fatigue, decreased libido, decreased exercise tolerance, and skin rash. WAIS-R IQ did not reveal an abnormal pattern, although four of the five had weakness on the Digit Symbol subtest. Weaknesses were observed in attention–concentration testing. Generally normal memory learning testing was reported, although the authors concluded the majority had poor learning capacity. The primary finding was psychopathology with all subjects showing clinically significant depression scales, three on psychasthenia and three on schizophrenia.

Major limitations of this report include strong selection bias, lack of comparison with other exposed workers, and a lack of quantitative data on exposure to MDI, and other concomitant agents. Potential confounders also limit conclusions, as the authors concede findings could be due to emotional stress and potential impact of compensation bias in the test results. These factors as well as pre-morbid personality traits and interaction among plantiffs have been reported to lead to exaggerated health concerns.[42] Regardless, testing was largely normal except for the presence of mood disorder in all subjects and mild abnormalities in memory learning. Thus, given these extensive limitations and the lack of specific findings, the data presented does not provide evidence of MDI neurotoxicity.

Herbert et al. 1995[43]

This paper consists of a case report and a screening prevalence study of roofing workers. The authors describe a sentinel case of a 52-year-old roofer with 16-year exposure to multiple solvents such as toluene, xylene, and n-hexane as well as HDI. The roofer presented with light-headedness, loss of balance, headache, irritability, fatigue and symmetrical paraesthesias in feet and hands. Nerve conduction velocities demonstrated symmetrical distal mixed polyneuropathy. Based on this case report, the authors examined 40 roofers (15% of local union) exposed to various roofing systems for "neuritic" symptoms. Examination for neuropathy using vibrotactile thresholds of the dominant great toe demonstrated abnormalities in 42%. The authors attributed this finding to distal axonal neuropathy, likely a result of exposure to hexacarbon solvents such as n-hexane, concluding the study is hypothesis generating at best, that roofing workers may be at increased risk of peripheral neuropathy from exposure to solvents, particularly n-hexane.

Symptoms and findings from the sentinel case and the screened workers are consistent with demonstrated effects associated with n-hexane and other organic solvents. With no comparison group and lack of exposure data for diisocyanates, information on the strength of association is lacking. There is lack of evidence that directly associates diisocyanate (HDI) with neurotoxicity in this report, and thus putative exposure to HDI is an incidental finding and does not support neurotoxicity from diisocyanates.

Nijem et al. 2001[44]

This is a cross-sectional survey of 167 workers drawn from 20 shoe factories across Palestine. Health complaints were investigated through the use of the Q16 Swedish neuropsychiatric symptom questionnaire measuring symptoms of headache, mental irritability, painful tingling of limbs, and in addition asking about mucous membrane irritation, sore eyes, and breathing difficulties. Work exposures were stratified based on work task activity and months of exposure. No actual area or personal monitoring data, nor quantification of exposure was presented. Job categories surrogate for specific exposure (in parentheses) included plastic sole curing (TDI), molding (PVC), cleaning (dichloromethane), adhesive work (n-hexane), and varnishing (toluene), although the authors indicate n-hexane, toluene, and other solvents were present in many of the processes. Prevalence rates for most reported symptoms were high. Prevalence ratios (PR) were all nonsignificant except for tingling of limbs in plastics molding and curing group [PR = 1.8, 95% C.I. 1.2–2.9] that the authors state is associated with exposure to neurotoxic solvents such as n-hexane and dichloromethane; sore eyes were associated with exposure to organic solvents and diisocyanates [PR = 1.7, 95% C.I. 1.1–2.7]; and breathing difficulties associated with solvents during cleaning tasks and toluene during varnishing [PR = 1.9, 95% C.I. 1.1–3.5].

There are a number of biases and methodological weaknesses that limit the interpretation of the results of this study. Subjects included only males, and were a small subset of workers that were nonrandomly selected by the owners of each factory, introducing a significant potential for selection bias. The owners held the total number of eligible workers' secret. Thus, any measure of relative risk is imperfect in this population. Other weaknesses include lack of baseline characteristics of the comparison groups, and lack of exposure data for workers or job categories preventing analysis of biologic gradient. The proximity of the various manufacturing processes in the factories was also not described, and therefore exposures may not have been isolated by job category. The author indicates potential confounding as the workers with exposures to diisocyanates (TDI) also had exposure to PVC and n-hexane. The authors report that both tasks were associated with eye irritation but not with neurotoxicity symptoms such as tingling of limbs, although the data tables indicate a significant association with tingling of limbs in this job category. Ergonomic factors, a potential

confounder for tingling of limbs, were not described. Given these severe limitations and the confusion of stated results, no conclusion can be satisfactorily drawn, and therefore there is insufficient evidence of a causal association of diisocyanates and neurotoxicity.

Moshe et al. 2002[45]

This is a case report of a 60-year-old Israeli painter/artist with central and peripheral neuropathic findings. His work as a painter involved preparing mixtures of many compounds for painting, silk screen-printing, and the use of large quantities of hydrocarbons to clean brushes and surfaces. Substances used included organic solvents such as turpentine, methyl ethyl ketone (MEK), Stoddard solvent (white spirit), aromatic pigments, and dyes including those with lead or titanium base, TDI resins, antioxidants, preservatives, and stabilizers. Exposure to diisocyanates (TDI) is cited but not quantified. He did not utilize any PPE. After some 30 years as a painter, he developed weakness and paraesthesias of the hands and feet, intention tremor, and difficulty concentrating with memory deficits. He had mild atrophy and distal weakness of both upper and lower limbs and demonstrated bradykinesia. Nerve conduction studies for conduction velocities of upper and lower extremities and scalp somatosensory-evoked potentials demonstrated increased latencies suggesting a conduction defect in the large fiber sensory system as well as the median and ulnar nerves. Neurobehavioral testing demonstrated cognitive impairment with attention and memory deficits.

Application of these reported findings with diisocyanates however is limited due to the lack of exposure data for TDI and concomitant exposure to known neurotoxicants for both central and peripheral nervous system effects. The described symptoms and objective findings are most consistent with organic solvent-related peripheral neuropathy (MEK) and encephalopathy (toluene and xylene). Although air monitoring was not conducted, the described lack of workspace ventilation and PPE strongly suggests overexposure to solvents. In addition, this individual was reported to have diabetes mellitus (type not described), a significant confounder for peripheral neuropathy. Thus, there is insufficient evidence from this paper to positively associate neurotoxicity with diisocyanate exposure.

Le Quesne et al. 1976, Axford et al. 1976, McKerrow et al. 1970[32–34]

Three case series reports are considered together as each describes the same population. This cohort consists of 36 firemen who were involved in a 1967 fire at a polyurethane block foam manufacturing plant. The fire started in a part of the factory where finished blocks of foam were stored, and spread rapidly to the production area where several tanks of TDI and other chemicals used in the manufacturing process were stored. Firefighters did not use respiratory protection until the fire had been in progress for about an hour, when the smoke assumed a distinctive metallic taste and smell. The intense heat of the fire deformed valves on the storage tanks, resulting in one tank leaking an estimated 4500 liters (1200 gallons) of TDI. After the fire several of the men involved in removing fire-fighting hoses soaked in the spilled fluids described a white powdery coating of "polyurethane" upon drying of their uniforms, suggesting the fluid was in part TDI.

McKerrow et al.[34] initially reported on these fire fighters, describing acute and delayed respiratory and neurologic symptoms, including two experienced lost consciousness, four experienced euphoria or ataxia, and fourteen experienced delayed memory and concentration difficulties. Of note, the author also compared these symptoms to those of 25 workers from the plant with a mean of 2.7 years exposure to TDI who were not exposed to the fire but were symptomatic at some point in their employment, although did not present any data on their neurological symptoms. Axford et al.[32] in a subsequent paper focused his effort on the effects of the fire-related exposure to the respiratory system. Neurologic effects were not described. Le Quesne et al.[33] reported 23 men involved in the fire experienced neurological symptoms either acutely or in a four-year period after the fire. Neurologic symptoms were categorized according to temporal relation to the fire onset. Acute effects: Five men said that they felt as if they were drunk and were staggering about, three men transiently lost consciousness. Delayed effects: Three weeks after the fire incident 17 men were seen and complained of difficulty in concentration, confusion, poor memory, headache, irritability, or depression. Symptoms were at their worst during the second week after the fire. Abnormalities on neurological examination included six men with slight ataxia. Two patients, who complained of paraesthesias and sensory loss in the limbs, had subjective alteration to pin prick over the hands and feet. Electroencephalograms were recorded in nine men during the two weeks after the fire incident. Records from eight men were normal and the other were marginally abnormal. Long-term effects (3 weeks to 4 years): Four years later 18 men were evaluated, only 12 of whom were part of the first review. The most common complaint was poor memory (sole complaint of 10 men). Others complained of personality change, difficulty in concentration and work, irritability, or depression. Four of the original twelve had become symptom-free during periods ranging from 6 months to 3 years. On neurological examination no abnormal physical findings were detected, except persistent distal sensory impairment in one man.

Pertaining to exposure assessment, the authors asserted that there is no evidence that the fumes from the fire were sufficiently dense for any of the men to have become anoxic. The authors acknowledge that while several other chemicals were stored in the plant, which could have contributed to the clinical findings and symptoms, their analysis of the firemen's movements and the leakage of a large quantity of TDI caused them to determine that TDI was likely responsible. They also reported presence of pooled TDI the day following the fire on the plant grounds/floor, and that exposures were to high concentrations of TDI. However, they conceded that a toxic combination of chemicals or their breakdown products might have occurred and cannot be excluded due to the intense heat of the fire.

The primary weakness for this analysis is the lack of exposure assessment, and the assumption that TDI was the primary exposure. The authors did not include discussion of confounders such as toxic pyrolysis products of polyurethane foam or combustion products of the structure fire. Pyrolysis products of solid polyurethane foams are well described, including the release of hydrogen cyanide (HCN), carbon monoxide (CO), benzonitrile, acrylonitrile, oxides of nitrogen, hydrogen fluoride, hydrogen bromide, and over 100 other compounds.[46] Pyrolysis products of polyurethane are reported to result in neurologic symptoms consistent with those in the Le Quesne study.[21,30] Many of the symptoms described in this report may also be observed in CO poisoning: headache, dizziness, weakness, nausea, poor concentration, confusion, shortness of breath, numbness, tingling, and ataxia.[47–50]

Based on description of the fire and lack of PPE, the likelihood that firefighters were exposed to many of these compounds is very high. TDI has been reported to have a pungent or musty smell, but has not been described as a metallic taste or smell, further indicating other exposure besides TDI. The prevalence of acute respiratory symptoms (89%) and their persistence among this cohort are more consistent for a significant exposure to toxic fire gases rather than exposure to TDI. In response to exposure of TDI liquid, there appeared to be a large amount of water sprayed on the tanks and perhaps pooling on the floor from fighting the fire. TDI when mixed with water rapidly reacts to form polyureas and carbon dioxide that would effectively reduce exposure to TDI in this event.[51] This is evidenced by reports of firefighters reporting white plastic powder on their coats and equipment upon drying. Thus, the conclusion that the described symptoms are solely a result of TDI exposure is unsupported. Other study weaknesses include a lack of baseline comparison data, with apparent younger age distribution in controls. Psychometric testing compared to a control group of asymptomatic firefighters not involved in the incident may therefore be invalid, even though no significant differences were found except in long-term memory scores. Overall, there is insufficient evidence of a causal association between TDI exposure and neurotoxicity from this case series report.

Application of the Hill considerations for causality

Strength of association

There are no randomized trials or longitudinal cohort studies. Only one of these reports[44] included a relative risk ratio that was 1.7. Thus, the strength of association is not provided in most studies, with a weak association in one report. Based on the Swaen model, the probability of this criterion being true is assigned at 60%, or slightly higher than chance.

Consistency

The symptoms presented in each of the case reports were variable. Six reports included complaints with memory, eight reported headaches, four reported irritability, six reported depression, four reported paraesthesias, and four reported objective neurological findings. Thus, consistency of reported symptoms related to neurotoxicity from diisocyanates is mixed, with the more consistent symptoms also being nonspecific, see below. The probability of this criterion being true is assigned 50%, although we acknowledge it could be lower.

Specificity

None of the reported symptoms or objective findings reported in these case series is specific to diisocyanate exposure. Anxiety symptoms are quite common in respiratory distressed patients with respiratory symptoms such as COPD patients.[36] Other reported health outcomes such as memory loss and depression may be associated with a wide variety of agents and most importantly, various toxic fire combustion products.[52–56] Thus, there is lack of specificity for diisocyanates and the neurological effects described in these reports, and the probability of this criterion being true is assigned 40%.

Temporality

In each of the studies included, the onset of symptoms appears to have been preceded by potential exposure to diisocyanates, although baseline comparison and exposure data are lacking in most cases. The assigned probability this criterion is true is 100%.

Biological gradient

There is no clear dose response demonstrated in any of the reviewed papers, and therefore biological gradient remains undefined but potentially exists. The assigned probability this criterion is true is 50%.

Biological plausibility

One author proposed biologic plausibility based on diisocyanates metabolism into cyanide. Metabolic studies, however, have not shown a pathway for this type of metabolism. There are no other mechanisms of toxicity described or proposed in the reviewed studies, and thus biological plausibility remains undefined. Diisocyanates are not classified as organic solvents and have not been described to result in general anesthetic effects similar to hydrocarbon anesthetic effects. The assigned probability of this criterion being true is 0%.

Coherence

There are no early objective effects or other abnormalities that have been measured as a result of measured or known exposures. Each of the studies reported subjective effects. No specific physiological or biological testing specific to diisocyanates has been presented. Thus, there is lack of coherence. The assigned probability of this criterion being true is 0%.

Experimental evidence

Animal studies have not demonstrated neurotoxicity from diisocyanate exposure. Thus, experimental evidence is lacking. The assigned probability of this criterion being true is 0%.

Analogy

Diisocyanates are a group of low-molecular weight aromatic and aliphatic compounds. Except for one author who inaccurately proposed analogy to the Bhopal disaster and exposure to methyl-isocyanate, that is not an analog of diisocyanates, there are no reports of similar compounds or agents found that result in neurotoxicity. The assigned probability of this criterion being true is 50%, although we acknowledge it could be lower.

Using these assigned probabilities from the summary of available evidence identified, the mathematical model predicts the probability of causality of 21% (Table 2), supporting the argument that there is a lack of evidence linking diisocyanates and neurological health effects. This weighted model has been determined to be most sensitive for the variables of *strength of association, consistency*, and *experimental evidence* by Swaen. If assignment of probability for *strength* is assigned to be 50%, the probability of association drops to 14.8%., or if *consistency* is assigned 40%, the probability of association drops to 17.6%, thus demonstrating the importance of these factors in this model.

Discussion

In response to recent inferences that diisocyanates may be causal of short- and long-term neurological deficits, we provide a systematic review of the available literature of human data, with consideration of causal association based on the Hill considerations for causality. Our analysis found no quality epidemiological studies, but rather a collection of case and case series reports, considered the lowest level of epidemiological evidence suitable only for hypothesis generation.

Each of the included reports has serious limitations, particularly related to exposure assessment and control for confounding exposures to known neurotoxicants such as n-hexane, toluene, xylene, and asphyxiants such as CO and HCN.

The quality of clinical evaluation in each of the papers is very limited. The symptoms generally reported are variable across studies and no consistent syndrome is evident. Symptoms reported are often of the psychological type, relating to insufficiently described symptom complexes such as "neurasthenia", "neurosis", and "vegetative dystonia", as compared with the various specific effects from recognized neurotoxicants. These are historical terms that have been described as "functional somatic syndromes" that are more characterized by symptoms than by consistently described tissue abnormality.[57] These psychological symptoms are nonspecific and are most consistent with psychogenic reactions and in some cases authors have indicated may be related to compensation issues. These ill-defined neurological syndromes are therefore inconclusive as evidence for neurotoxic effect of diisocyanates.

Additionally, no dose-response association is described in the reviewed papers. For example it might be hypothesized that populations with significant respiratory symptoms—which would reflect high exposure—should also have reported the most neurological symptoms. However no assessment of subgroups is presented in any of the papers published.

Table 2. Mathematical model for probability of causality.

Hill's Criterion	Evidence Summary	Probability (%) of criterion being true	Product of discriminant function$^{\pm}$ and probability, (C1)	Product of discriminant function$^{\pm}$ and probability, (C2A)
Constant			− 14.7799	− 10.0835
1. Strength	One study (Nijem) presented relative risk ratio of 1.7*	60	3.7338 (0.06223 × 60)	1.1538 (0.01923 × 60)
2. Consistency	Studies varied in symptoms and findings**	50	2.0305 (0.04061 × 50)	0.9015 (0.01803 × 50)
3. Specificity	No findings specific to diisocyanates	40	− 1.1148 (− 0.02787 × 0)	− 1.5508 (− 0.03877 × 0)
4. Temporality	All case reports preceded by diisocyanates exposure	100	7.657 (0.07657 × 100)	8.281 (0.08281 × 100)
5. Biologic gradient	Dose-response data lacking**	50	− 1.764 (− 0.03528 × 50)	− 1.767 (− 0.03534 × 50)
6. Plausibility	No mechanism of toxicity found	0	0.00 (0.23025 × 0)	0.00 (0.21689 × 0)
7. Coherence	No early objective effects or other abnormalities were measured as a result of exposures	0	0.00 (0.009621 × 0)	0.00 (− 0.00334 × 0)
8. Experimental evidence	Animal studies have not demonstrated neurotoxicity from diisocyanate exposure	0	0.00 (0.00843 × 0)	0.00 (− 0.00659 × 0)
9. Analogy	Data to similar class of agents lacking**	50	− 0.6470 (− 0.01294 × 50)	− 0.5055 (− 0.01011 × 50)
		Sum	C1 = − 4.8844	C2A = − 3.5705
Probability of causality		$e^{C1}/(e^{C1} + e^{C2A})$ 21.2%		

*1 > RR < 2 assumes probability of 60%.
** Assumes 50% probability if data exists but undefined, otherwise assume 0%.
$^{\pm}$Discriminant function values defined by Swaen (from Swaen 09, Table 1).

There is one group of fire-fighters potentially exposed to very large amounts of liquid TDI addressed by three separate authors. Neuro-psychological symptoms observed even after 4 years are purported to be due to TDI exposure. However, other chemicals were also involved, and exposures to CO and other fire gases occurred. The included comparative study is inappropriately designed and the statistical significance of long-term effects is questionable. Thermal decomposition of diisocyanates can result in the formation of toxic gases like CO and HCN. In these cases it is not possible to ascribe symptoms to diisocyanates exposure alone, especially as symptoms reported are well described sequelae of CO poisoning.[58] Others have reported concerns regarding the methodology or level of evidence for the conclusions presented by these authors.[59–61]

There is weak evidence that described decline in mental function and effects on memory are explained by aging, a confounding factor that was not taken into account. Moreover, the central hypothesis of neurotoxicity as evidenced by memory difficulties (which was reported to be more prominent among those with persisting CNS symptoms) suffers from the confounding influences of responder symptomatic status, lack of reference to exposure risk, lenient statistical maneuvers with wide statistical errors, and lack of explicit supportive documentation. In addition the non-specificity of the specific reported health outcomes (memory loss/depression, and headache), may be associated with a wide variety of agents, personal risk factors, and most importantly, various toxic fire combustion products.[52–56]

Our inclusion of a mathematical model for predicting probability is a unique attempt to provide quantification of the available evidence based on the Hill criteria. This model has been shown to be a reasonable method for quantification of probability using Hill criteria on the body of the literature that a particular substance is a carcinogen, validated on established IARC category 1 and 2A agents. However, there are many limitations to using this model. Particularly, this model has not been demonstrated for use with non IARC category 1 and 2A agents, such that the applicability is unknown. Further validation using randomized trial databases or other non-carcinogen datasets are needed to determine if this model is applicable to this type of analysis. Additionally, there is a lack of standardization for assessors to assign likelihood that an overall assessment meets the criterion and therefore remains a matter of expert judgment. Thus, the probability calculated for causality cannot be considered an absolute number, but an indicator and should be a potential tool for future research considerations.

Conclusion

This systematic review demonstrated a lack of quality epidemiological studies in the literature on neurotoxic health effects and exposure to diisocyanates. The available evidence consists mostly of case reports and case series. Using the Hill criteria or considerations for causality, we found limited evidence for strength of association and consistency. There is a lack of or no evidence regarding specificity, biologic plausibility, coherence, and analogy. The literature particularly lacks specificity of symptoms and material exposure data to establish biologic dose. We conclude there is insufficient evidence to establish a causal association between diisocyanates and both acute and chronic neurologic health effects.

Acknowledgments

Special thanks to Irina Kolesnikova for assistance in translation of Russian and Bulgarian language articles (Artamonova and Cherednik 1971, Hristevo and Bainova 1977, Nakamura and Ogura 2004, Pokrovskaia et al. 1986).

Declaration of interest

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Donald M. Molenaar, MD, MPH was employed by Bayer Corporation, a diisocyanate manufacturer at the time this research was being conducted.

Dr. Wilfried Steffens is employed by a Bayer Crop Sciences. Dr. Steffens contributed to this work as a clinical toxicologist.

Gerard Swaen, PhD was employed by The Dow Chemical Company, a diisocyanate manufacturer at the time this research was conducted.

The International Isocyanate Institute (III) is a non-profit industry association whose members are producers of MDI and TDI. The purpose of the Institute is to develop scientific data in support of programs relating to the protection of the public, manufacturers, their employees, their customers, and the environment in the production and safe use of diisocyanate products.

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Supplementary material available online

Supplementary Table 1.