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Costs of isocyanate-related occupational diseases: A systematic review

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ABSTRACT

Although isocyanates are increasingly used in manufacturing and workplace exposure to isocyanates is widely recognized as one of the most frequent causes for occupational lung and skin diseases, little is known about the economic burden on the affected individual and the society. This study provides an overview on costs of occupational diseases related to isocyanates. We performed a systematic literature search of studies in the electronic databases of the German Institute of Medical Documentation and Information, and the Canadian Centre for Occupational Health and Safety. We extracted the key characteristics of the studies and performed a study quality assessment. We identified eight studies on the costs of illness, of which five focused on occupational lung diseases and three on occupational skin diseases. Further, eight studies calculated loss of income/compensation payments. Out of the 16 identified articles, only two reported costs directly attributable to isocyanate-induced diseases (asthma). Studies were hardly comparable because they differed substantially in their methodological approaches. Moreover, the quality assessment of the studies revealed substantial limitations. While a wide range of isocyanate-related costs was identified, consequences of isocyanate-related occupational diseases were considerable in terms of societal costs and loss of income. In most studies, indirect costs were the main cost driver. There is a need for high-quality cost of illness studies on isocyanate-induced diseases stratified by degree of severity and sex. Such studies provide valuable information to develop preventive strategies and set priorities for measures to lower the burden of professional health risks.

KEYWORDS

Costs of illness; economic consequences; isocyanates; loss of income; occupational attributable health costs; occupational respiratory disease; occupational skin diseases

Introduction

According to Article 1b of the Protocol to the Occupational Safety and Health Convention (1981), “the term ‘occupational disease’ covers any disease contracted as a result of an exposure to risk factors arising from work activity.”^[1] Thus, for a disease to be confirmed and recognized as occupational in origin, evidence concerning the causal relationship between work, exposure, and disease is required. This may be particularly challenging in cases with a long latency between exposure and initial symptom onset.^[2,3] Worldwide, there are many national laws and regulations for the recognition and compensation of occupational diseases; however, disorders due to chemical, physical, or biological agents registered on the “List of Occupational Diseases”^[4] of the International Labour Organization are recognized by all member states.

As an internationally recognized causative agent of occupational diseases, isocyanates belong to the category of highly reactive, low molecular weight chemicals. They can be classified as mono-, di-, and polyisocyanates depending on the number of isocyanate-groups. The most common type of isocyanates in workplaces are diisocyanates, which contain two isocyanate groups (NCO) and oligomers/polyisocyanates derived thereof. The predominant use of isocyanates (>90%) is in the direct manufacture of polyurethane plastic materials (PUs, also PURs), where diisocyanates are reacted with polyols and/or other nucleophiles like polyamines. Diisocyanates are also utilized in preparations, with the final reaction occurring at a later stage (coatings, adhesives, sealants and binders). In the last 50 years, isocyanates have been increasingly used in the industrial production and application of different kinds of polyurethane foams, flexible and

rigid polyurethanes, polyurethane fibers, coatings, elastomers, sealants, and adhesives. Areas of application include inter alia, the automotive industry, auto-body repair, construction insulation materials, and metal treatment.^[5]

According to the duration and extent of workplace exposure to isocyanates and their major products (polyurethanes) during the manufacturing process and their application in the workplace, inhalation and direct skin contact can cause toxic/allergic reactions, resulting in the development of specific lung and skin diseases. Typical disorders affecting the lungs are mainly asthma,^[5–9] and less frequently hypersensitivity pneumonitis (extrinsic allergic alveolitis),^[6–8,10–14] while isocyanate-induced skin diseases include allergic and irritant contact dermatitis. Moreover, recent studies emphasize the important role of skin exposure in the development of asthma. According to this theory, loss of skin barrier function due to acute exposure to high levels or continuous exposure to low levels of isocyanates can cause systemic allergen sensitization and lead to an increased risk of atopic dermatitis and atopic asthma.^[15–17]

Workplace exposure to isocyanates is widely recognized as one of the most frequent causes of occupational lung disease (with isocyanate-asthma being the major health problem^[5]) and skin diseases, which, in turn, are ranked among the most common occupational diseases in industrialized countries.^[18] Some countries only register cases of occupational disease if compensation is awarded or do not register them at all; therefore, information on the prevalence of occupational diseases is scarce, outdated, and varies significantly among countries.^[2,3,19–21] This particularly applies to isocyanate-induced lung and skin diseases. As reported recently, it is estimated that isocyanate-related occupational diseases affect between five hundred and a few thousand workers per year in the EU-28.^[22]

Isocyanate exposures can cause acute asthma symptoms requiring emergency services or even be fatal but cases are rather rare. Although isocyanate-induced occupational diseases usually do not result in hospitalization, they result in serious health problems and have significant socioeconomic implications for affected workers, placing a considerable burden on society. Occupational skin and respiratory diseases are often chronic conditions. During the early stages of the disease, symptoms (e.g., respiratory symptoms) may be reversed following removal from exposure; however, with continued exposure, an irreversible remodeling of the airways will eventually occur.^[23] Therefore, even after terminating employment, the prognosis, particularly of severe forms of disease, is often very poor,

resulting in long-term medical treatment and prolonged sick-leave. Further costs can accrue with retraining, rehabilitation, and pensions.^[24] In Europe it is estimated that, in 2003, the cost of compensation to the industrial economy due to isocyanate-induced occupational diseases was €21.5 million.^[25]

In Europe exposure prevalence to isocyanates continues to increase in the workplace,^[2] therefore, it is crucial to analyze the costs of illness and identify the main cost drivers. The aim of this article is to conduct a systematic literature search to provide an overview of the costs of occupational lung and skin disease caused by isocyanates. For a comprehensive overview, we present studies estimating typical costs of illness (COI), as well as studies reporting compensation payments and those calculating loss of income, reflecting the perspective of patients.

Methods

Data sources and search strategy

In order to identify studies concerning COI and loss of income/compensation payments related to occupational lung and skin diseases, we performed a systematic literature review according to the PRISMA guidelines.^[26] In terms of health economic studies, we searched a number of electronic databases, including Medline, EMBASE, and SciSearch, of the German Institute of Medical Documentation and Information (DIMDI).^[27] We also searched the OSH Reference Databases as they combine many specific databases related to occupational health and safety, including OSHLINE, HSELINE, NIOSHTIC, and CISILO. For a detailed overview on included databases, see [Figure 1](#).

We defined English search terms for the OSH Reference Databases as well as English and German search terms for the DIMDI Database using MESH-terms (see [Appendix A](#)). We anticipated finding few publications directly referring to the costs of isocyanate-induced diseases; therefore, we broadened our search strategy to also identify cost studies focusing on typical occupational lung and skin diseases that can be caused by isocyanates. We searched both databases with the term “isocyanate” and provided it with an or-connection for different combinations of terms for the following lung and skin diseases that can be triggered by isocyanates: asthma, hypersensitivity pneumonitis (extrinsic allergic alveolitis), chronic obstructive pulmonary disease (COPD), allergic contact dermatitis, irritant dermatitis, occupational dermatitis. The causal relationship between isocyanates and asthma^[5–9] and isocyanates and hypersensitivity pneumonitis^[6–8,10–14]

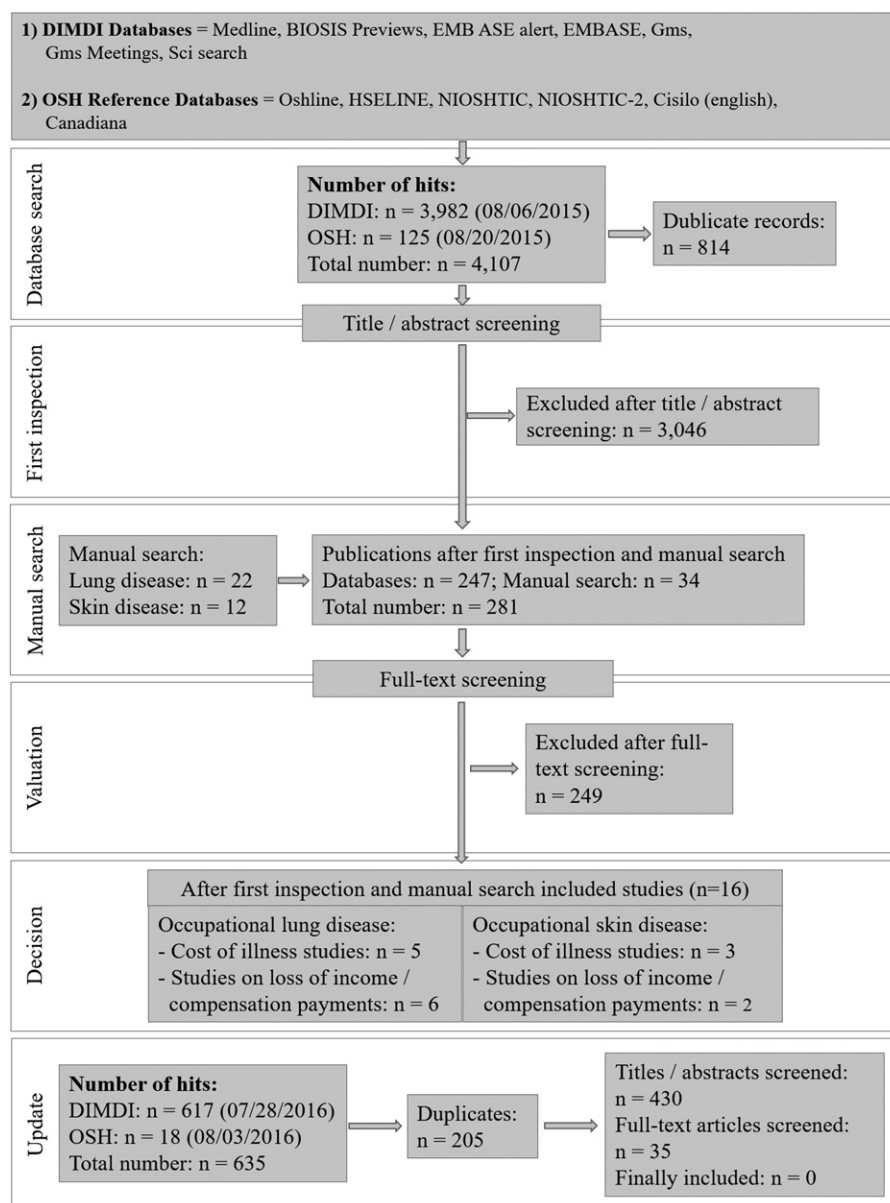


Figure 1. Selection process of studies.

has been firmly documented, albeit isocyanate-induced hypersensitivity pneumonitis has a very low frequency in the world.^[7,11] The association between isocyanates and COPD is less clear in the scientific literature. Even though only reported incidentally, isocyanates have also been described to cause COPD.^[9,28,29] Moreover, some overlap in symptoms and/or diagnoses between OA and occupational COPD has been documented.^[2,28] We decided to include COPD and hypersensitivity pneumonitis in our research strategy to provide a comprehensive picture of COI for respiratory diseases that might be induced by isocyanates.

All former terms were combined with “and” using various synonyms of costs “or” severity/duration of the illness. As our aim was to identify studies with a focus

on costs of work-related or occupational diseases, we further narrowed our research by using the sensitive string for occupation developed by Mattioli et al.^[30] In order to include studies not identified by the automated search, we further carried out a manual search using google scholar and the reference lists of studies identified in our search. The systematic literature search was performed in August 2015 and updated in August 2016.

Study identification and data extraction

We exported titles and abstracts (if available) of all identified articles to a literature administration program. First, after duplicate records were removed, two researchers independently screened titles and abstracts

for eligibility. Two reviewers then independently assessed the eligibility of the full-text publications meeting the inclusion criteria in the first step. Disagreements between the researchers were discussed and resolved by consensus. We included only those studies that were written in German or English language, but we did not limit our research in terms of publication date. Moreover, to be included in this review, studies had to fulfill the following criteria: (1) include confirmed/recognized occupational disease cases, i.e., cases of illness induced by the workplace; (2) include patients with occupational disease suffering from either illnesses demonstrably induced by isocyanates or from the aforementioned lung and skin diseases that may be caused by isocyanates; (3) estimate COI or loss of income/compensation payments; (4) focus on the working population (age over 17 years); and (5) involve industrialized countries, in order to provide a basis for the international comparison of COI. We excluded studies according to the following criteria: if they did not focus on our target indications or isocyanate-induced diseases; did not clearly define or report the causal link between work and lung/skin disease (e.g., studies focusing on diseases aggravated by work, but not induced by work); took into account the non-working population, specifically children and adolescents; and/or did not calculate costs deriving from work-related diseases.

From all studies meeting the inclusion criteria, information on the authors/country, study population, study design, data sources, study perspective, and results was abstracted in a tabular form. The term “study perspective” describes the perspective from which costs have been analyzed (e.g., from the patient, the employer, the payer or the society). Depending on the study perspective, different types of costs (direct, indirect, tangible) are included. While from the health insurance payer perspective only direct healthcare costs incurred by the payer are considered, the societal perspective additionally takes indirect costs and out-of-pocket costs into account.

In order to obtain comparable results, we standardized costs by converting them to euros (if necessary) according to the exchange rate of the price-year for which cost data was reported and inflated the costs to the base-year 2015, using the harmonized consumer price index.^[31] If details on the price-year were missing, we used the last year of the observation period.

Quality assessment

We further evaluated the quality of the COI studies. However, there is no international standard

methodology available for assessing COI studies. As various indication-specific checklists for COI analyses have been established (e.g., for prostate cancer,^[32] Alzheimer’s disease,^[33] eating disorders,^[34] bipolar disorders^[35]), we critically compared these for suitability to the objectives of our study. Finally, we decided to use the checklist developed by Kleine-Budde et al. (2014)^[35] because it comprehensively presents the central components of COI analysis. We evaluated each COI study, according to the following four aspects, covering in total 20 components: (1) aims and methods of the study, (2) calculation of costs, (3) presentation of results, and (4) discussion.^[35] Two researchers independently characterized the presence of each criterion as “yes”, “no”, or “non-applicable”. Disagreements were settled through discussion. Moreover, due to the heterogeneity of studies on loss of income/compensation payments and the lack of assessment instruments for this kind of studies, we excluded them from standardized quality evaluation.

Results

Study selection

As shown in Figure 1, a literature search performed in August 2015 identified 4,107 records derived from the two databases. Following deletion of duplicates, and screening of titles/abstracts for retrieval, we classified 247 articles as potentially relevant. Following the manual search, we additionally identified 22 references for costs of occupational lung and 12 records for occupational skin diseases. Finally, 16 studies fulfilled the inclusion criteria, of these, 8 were COI studies, including 5 studies focusing on occupational lung and 3 focusing on occupational skin diseases. The remaining eight studies focused on the loss of income or compensation payments. The research update performed in August 2016 we did not find further articles meeting the inclusion criteria. In sum, of the 16 identified articles, only 2 estimated COI directly attributable to isocyanate-induced respiratory diseases. The remaining studies either did not report the causative agents or included, inter alia, isocyanate-induced disease cases but did not calculate costs stratified by causative agent.

Methodological characteristics and costs

Occupational lung diseases

Through the systematic literature search we identified 11 studies dealing with the burden of occupational respiratory diseases; 5 of these belong to the category

of COI studies, and 6 studies examining compensation payments and/or loss of income. All studies except two focused solely on occupational asthma (OA). Six studies reported having included, *inter alia*, disease cases caused by isocyanates.^[36–41] Of these, two calculated COI separately for isocyanate-induced diseases (OA).^[36,37] No study reported COI of occupational COPD or hypersensitivity pneumonitis resulting directly from isocyanate exposure.

Table 1 illustrates the methodological characteristics and results of included COI studies due to occupational lung diseases. Of the COI studies, two were conducted in Europe (Spain^[42] and the UK^[37]) and focused on OA and three in the US^[36,43,44] focusing on OA alone or both, OA and COPD. Two studies also differentiated between several causative agents for OA.^[36,37]

In Europe, the most recent COI study focusing on both direct and indirect costs was performed by Ayres et al.^[37] in the UK. Estimates were based on six hypothetical patients, each exposed to isocyanates (1), latex and biocides (2), or flour (3). Direct costs covered all costs affecting society, including healthcare resources from the taxpayer perspective (e.g., outpatient care and inpatient care) and from the perspective of the individual patient (e.g., prescription charges, commuting, or additional transport). The authors also calculated indirect costs, including payments from the statutory health insurance (taxpayer perspective), reduction in net income, and human costs of ill health (individual perspective), as well as costs resulting from loss of productivity (employer perspective). The estimation of indirect costs was based on four theoretical assumptions derived from a literature review. The scenarios include different probabilities of remaining in the labor market, remaining with the same employer, performing the same job and experiencing changes in net salary. Total direct and indirect costs from the societal perspective, as well as lifetime costs, were calculated for the three different sensitizing agents. Cost calculation resulted in very small distinctions in annual direct costs between male and female OA cases and was equal, irrespective of sensitizing agent. In contrast to that, indirect costs per year differed strongly depending on the causative agent. In both male and female workers, OA cases induced by latex/glutaraldehyde resulted in the highest yearly indirect costs of €13,652–13,979 per male and €7,694–7,947 per female case, with indirect costs being 6–14 times higher than direct costs. By comparison, isocyanate-induced OA was reported to lead to indirect annual costs of €8,600–8,870 per male worker and

€6,368–6,609 per female worker. Of all causative agents, OA induced by isocyanates resulted in the highest lifetime costs in male workers (€23,027–24,764 per patient). In female workers, the highest lifetime costs were calculated for disease caused by flour (€4,574–5,023 compared with €672–738 in isocyanate-induced cases). Of total costs of all incident OA cases in the UK, approximately 49% were borne by the individual, 48% by the state, and 3% by the employer.^[37]

In the second COI study from Europe, García Gomez et al.^[42] took only direct costs caused by OA in Spain into account, irrespective of the triggering agent. First, the authors estimated the prevalence of OA by applying the attributable risk from exposure in the workplace to the number of prevalent asthma cases in Spain. Using data from the National Health System and further secondary data sources on costs of asthma, García Gomez et al.^[42] estimated direct costs that might be attributable to OA. The costs may have been calculated from a third payer perspective, although this was not stated by the authors. While the analysis of García Gomez et al.^[42] revealed direct annual costs of €1,685–1,884 per case, Ayres et al.^[37] reported a range of direct yearly costs between €926–1,241 for male and €930–1,240 for female OA cases.

Stratifying costs by causative agent, for the period between 1999 and 2010 in the US, Reeb-Whitaker et al.^[36] reported median medical-only costs of €882 for patients with OA caused by isocyanates and €299 for OA cases induced by all other agents. In their cost analysis, they included both compensable (e.g., wage costs, vocational rehabilitation costs, permanent partial disability, pension) and medical-only (non-compensable) claims, whereas indirect costs to workers and employers and administrative costs were not taken into account. On the basis of workers' compensation claim costs, results revealed that while there was no significant difference in medical-only costs between both groups, major differences were visible in compensable median costs of €36,176 for isocyanate-induced asthma cases and €2,531 for all other OA cases, over the study period.

In the US, a more comprehensive COI analysis was performed by Leigh et al.^[43] and Leigh et al.^[44] On the basis of several secondary data sources, they estimated costs in the US of prevalent cases of OA and COPD, irrespective of causative agent in 1996^[43] and 1999,^[44] respectively. While the first study took both direct costs (derived from medical and administrative expenses) and indirect costs (including lost wages,

Table 1. COI studies on occupational lung disease.

Author, country	Study population	Study design	Data sources	Study perspective	Results (direct / indirect / total costs)
Reeb-Whitaker et al. (2013) ⁽³⁶⁾ US	N = 27 (a) isocyanate-induced OA cases; (b) 839 OA cases caused by all other agents	Cross-sectional study: - Identification of OA cases (from 1999 through 2010) in the Washington State's Work-Related Asthma Surveillance system - Review of claims data: claim costs represent costs paid to date (12/15/2011) and expected future claim costs - Questionnaire administered via telephone with injured worker concerning workplace exposure and medical history	- Washington State's Work-Related Asthma Surveillance system - Workers' Compensation database - Medical records - Self-collected data	not mentioned	Total costs (1999-2010): (a) €1,296,181 (14% of total claim costs for asthma); Median total cost = €17,207 (b) Median total cost = €391 Median medical-only costs (1999-2010): (a) €882; (b) €299 Median compensable costs (1999-2010): (a) €36,176; (b) €2,531 Median time loss (1999-2010): (a) 367 days; (b) 39 days
García Gomez et al. (2012) ⁽⁴²⁾ Spain	OA (>20 years; CIE-9-MC diagnosis: CIE-9 493.0)	- Costs from specialized care (2008): Calculation of costs for hospital admission and specialized outpatient care; costs for primary care and medication were taken from secondary data sources - Global health expenses (2008): Based on the total expenses per patient with asthma	- National Health Systems (NHS) - Further secondary data sources	not mentioned	(a) Direct costs from specialized care (in-hospital and specialized outpatient care) for all patients per year: €9,921,083 (b) Primary Care cost = €4,990,305; Medication = €4,722,392 - Total health cost by disease (a + b) = €19,633,824 - Total direct costs per patient/year = €1,685 - €1,884
Ayres et al. (2010) ⁽³⁷⁾ UK	N = 6 hypothetical patients (m/f) with OA exposed to (1) isocyanates, (2) latex and biocides or (3) flour	- Literature research to identify COI studies on Asthma and OA - COI study (2003/2004): calculation of costs on the basis of different scenarios - Direct costs = resource consumption to diagnose, treat, rehabilitate OA cases, incl. governmental benefits - Indirect costs = based on four scenarios: same employer / same job; same employer / job switch; employer switch; retirement	- Survey of Work-related and Occupational Respiratory Disease - Costs are based on previously published literature	societal	Costs of isocyanate-induced OA: - Direct cost (society) per year/patient = €926-€1,241 (m) and €930-€1,240 (f) - Indirect cost (society) per year/patient = €8,600 - €8,870 (m) and €6,368 - €6,609 (f) - Total societal lifetime costs per patient = €23,027 - €24,764 (m) and €672 - €738 (f)
Leigh et al. (2003) ⁽⁴⁴⁾ USA	14 prevalent occupational diseases in the US (i.e. asthma and COPD)	- Estimation of medical costs of 14 prevalent occupational diseases (i.e. asthma cases aged 20+ and COPD cases aged 25+) in the US in 1999 using the top-down approach - Medical costs = payments to hospitals, physicians, pharmaceutical companies, nursing homes, vendors of medical supply	- National Center for Health Statistics - Health Care Financing Administration - Agency for Healthcare Research and Quality	not mentioned	Medical costs of OA: - Men: €0.36 billion - Women: €1.23 billion - Total: €1.59 billion Medical costs of occupational COPD: - Men: €2.00 billion - Women: €0.37 billion - Total: €2.37 billion

(Continued)

Table 1. Continued.

Author, country	Study population	Study design	Data sources	Study perspective	Results (direct / indirect / total costs)
Leigh et al. (2002) [43] US	Prevalent occupational asthma cases aged 20+ and COPD cases (ICD9-CM 490, 491, 492, 494, 496) aged 35+	Cross-sectional study: • Estimation of annual deaths and costs of prevalent cases of occupational asthma and COPD occurring in 1996 in the US using the human capital method (top-down approach) • Direct costs = medical and administrative expenses • Indirect costs = lost wages, lost fringe benefits, lost home production	• National Hospital Discharge Survey • Healthcare Cost and Utilization Project Nationwide Inpatient Sample • National Center for Health Statistics • Health Care Financing Administration • Other government bureaus / private firms	not mentioned	Costs of OA: • Direct = €1.13 billion (74%; of which medical-only costs = €0.98 billion) • Indirect = €0.39 billion (26%) • Total = €1.51 billion Costs of occupational COPD: • Direct = €2.73 billion (56%; of which medical-only costs = €2.33 billion) • Indirect = €2.06 billion (44%) • Total = €4.79 billion Grand total (Asthma and COPD): €6.30 billion

Abbreviations: OA = occupational asthma; COPD = chronic obstructive pulmonary disease; COI = cost of illness; m = male; f = female

fringe benefits, and home production) into account, the second study focused only on medical costs. Direct costs (e.g., inpatient care, outpatient care, pharmaceuticals) were estimated using a top-down approach, by multiplying total U.S. health-care spending with the ratio of hospital stays attributed to asthma/COPD on all hospital stays and the percentage of occupational asthma/COPD cases attributable to occupational hazards. Moreover, the authors adjusted for the inpatient/outpatient mix of costs, because the proportion of inpatient and outpatient care (and costs) is not equal in asthma and COPD.

Assuming a population attributed risk of 15% for both diseases in the US, according to the first study direct, indirect and total costs of all-cause OA were €1.13 billion, €0.39 billion, and €1.51 billion, respectively. For occupational COPD the authors reported much higher costs of €2.73 billion (direct costs), €2.06 billion (indirect costs), and €4.79 billion (total costs).^[43] Thus, in contrast to Ayres et al.,^[37] Leigh et al.^[43] calculated higher direct than indirect costs for OA.

Focusing only on medical costs, the first study reported costs of €2.33 billion for occupational COPD.^[43] This value has been confirmed by the second study estimating costs of €2.37 billion.^[44] However, with regard to OA, results of both studies differ substantially. While the first study calculated medical costs of €0.98 billion, according to the second study costs were €1.59 billion. The reason for this difference may be that the second study calculated medical costs for male and female workers separately, by assigning sex-specific days of care and proportionate attributable risk of developing occupational disease, and finally added up values to obtain total medical costs. As male and female workers have similar attributable risks of developing OA, but days of care are more than three times higher in women than men, this might result in higher total medical costs.^[44]

Due to divergent methodological approaches, a comparison of the studies that estimated COI for OA directly induced by isocyanates to those that analyzed all-cause OA is challenging. Broken down to the individual level, medical costs for all-cause OA reported by Leigh et al.^[43] and Leigh et al.^[44] might be similar to those reported for isocyanate-induced OA,^[36,37] but average medical costs reported by García-Gómez et al.^[42] are approximately twice as high. With regard to indirect costs, the economic burden of isocyanate-induced OA^[37] was reported to be considerably higher compared to all-cause OA.^[43] While for isocyanate-induced OA indirect costs were identified as

the main cost driver (accounting for more than 85% of total costs),^[37] in all-cause OA only 26% of total costs were reported to be attributable to indirect costs.^[43]

Apart from the COI studies, through the systematic literature search we also identified six studies focusing on loss of income (patients perspective) and/or financial compensation, of which four were conducted in Europe and two derived from Canada (see [Appendix B](#) for an overview). Four out of six studies reported isocyanates to be one of the most frequent causative agents in their study population suffering from OA (the remaining studies did not report causative agents), although none of the studies reported costs stratified by agent.

With the aim of investigating changes in employment status and income, Ameille et al.^[40] performed follow-up interviews (via telephone or posted questionnaire) with 209 OA patients, referred to occupational medicine departments in Paris one year after the initial diagnosis. The authors calculated the average loss of income, depending on the employment status (same employer vs. unemployed/other employer). Concerning employment status, 56% of patients reported still working for the same employer (of which approximately one third remained exposed to the causative agent), 16% had a new employer, 25% were still unemployed, and 3% retired. In the whole study population, nearly half of the patients reported a loss of income due to OA, with a mean reduction by 50% per year. Reduced income was significantly more frequent (80%) in patients having switched their employer.

On the basis of a comparable study design, Moscato et al.^[39] estimated monthly and annual income, as well as disease-related costs (including only medication) of 25 patients with OA in Italy. They concluded that termination of exposure in individuals with OA lead to a reduction in asthma severity and costs of medication, compared with baseline visits, and OA cases remained exposed. However, due to professional downgrading (i.e., change of workplace), it also results in a significant decrease in income. For patients who remain exposed, no significant change in the income was found.

The negative impact of job change due to OA on income has also been examined by Gannon et al.^[41] and Leira et al.^[45] Using medical records and self-collected data from questionnaires for workers in the UK, Gannon et al.^[41] estimated that the median perceived loss of yearly income was 54% in subjects removed from exposure and 35% in individuals

remaining exposed. Leira et al.^[45] reported that 39% of workers with OA from the aluminium industry in Norway and 55% from other industries had experienced a loss of annual income. Reduced income was only temporary in 3% of workers from the aluminium industry and 5% of workers from other industries. A reduction in annual income by more than €6,825 was reported by 16% of workers diagnosed with OA from the aluminum industry and 33% of workers from other industries.

Moreover, compensation payments, which refer to loss of income and functional impairment, could represent a significant variable in COI due to occupational lung disease. Malo et al.^[38] and Miedinger et al.^[46] analyzed costs of accepted claims for compensation in Quebec of 140 workers with OA between 1988 and 2002^[38] vs. 60 workers with OA between 2004 and 2006.^[46] According to Malo et al.,^[38] median costs for compensation for loss of income, functional impairment, and total costs were €31,502, €5,883, and €47,447, respectively. In comparison, Miedinger et al.^[46] reported higher median costs of €44,444, €9,592, and €55,312, respectively.

In summary, publications differ with respect to the method of cost calculation, the inclusion of cost categories, and the overall perspective, therefore the comparison of costs is challenging.

Occupational skin diseases

The database search revealed three studies focusing on COI caused by occupational skin diseases, two studies in Germany^[47,48] and one study in Denmark.^[49] Moreover, we identified two studies performed in the US/Australia focusing solely on workers' compensation payments.^[50,51] As the majority of the studies did not report the type of causative agent, we were not able to assess whether the study populations exclusively consisted of disease cases caused by isocyanates.

All COI studies were performed from the perspective of the society, including direct medical costs and indirect costs attributable to prolonged sick-leave and loss of productivity. As illustrated in [Table 2](#), COI studies differ substantially in the estimated yearly societal costs due to occupational skin diseases, ranging from approximately €417–3,587, for direct costs, and €3,710–6,669, for indirect costs. However, all studies identified indirect costs (approximately 52–95%) as the main cost driver.

While all studies included patients suffering from occupational skin diseases (i.e., contact dermatitis (CD)^[49] and hand eczema (HE)^[47,48]), they focused on groups with different degrees of severity. The COI

Table 2. COI studies on occupational skin diseases.

Author, country	Study population	Study design	Data sources	Study perspective	Results (direct / indirect / total costs)
Satterstrom et al. (2014) ^[49] , Denmark	N = 21,441 incident patients with CD (patch tested) in the period 2004-2009	- Register-based COI study with case-control design (propensity score matching) - Calculation of 'attributable' healthcare costs of (a) children (0-15 years), (b) OCD (16-65 years), (c) non-OCD (>15 years) - Healthcare costs: include drugs, primary + outpatient + inpatient care - Productivity loss: long-term sick leave (>24 days), vocational rehabilitation for OCD cases	- National Allergy Research Centre - Danish National Health Service Registry, Patient Registry, Prescription Registry - National Labour Market Authority's database DREAM	societal	Total healthcare costs per year/case: (b) OCD: before recognition: €49 (year 1)- €166 (year 4); after recognition: €417 (year 5) (c) non-OCD: before recognition: €230 (year 1)- €521 (year 4); after recognition: €600 (year 5) Productivity loss per case (year 1-5): (b) OCD: Sickness: €9,084; Vocational rehabilitation: €2,378 (c) non-OCD: Sickness: €3,286 Direct (healthcare) costs per patient/year: - SHI-1: €1,378 - SHI-2: €1,563 - SHI-3: €3,430 - OHI: €3,587 Indirect costs (productivity loss) per patient/year: - SHI-3: €2,029 - OHI: €3,710
Diepgen et al. (2013a) ^[48] , Germany	N = 310 patients with chronic HE insured by SHI or OHI	- First survey (2008): At 24 dermatology practices and clinics across Germany; included patients insured by SHI: SHI-1: non-working patients, SHI-2: work-unaffected patients, SHI-3: work-impaired patients - Second survey (2008): At two specialized centers linked with OHI system; included only patients insured by OHI (=work-diseased)	Two virtually identical cross-sectional surveys	societal	Direct (medical) costs per patient / year: - All patients: €2,868 - Severity group A: €2,932 - Severity group B: €2,829 Productivity loss per patient/year: - All patients: €6,669 - Severity group A: €5,550 - Severity group B: €7,367 Total annual societal costs per patient: - All patients: €9,538 - Severity group A: €8,482 - Severity group B: €10,196
Diepgen et al. (2013b) ^[47] , Germany	N = 151 OHE patients (physician diagnosed) recruited in one specialized hand eczema clinic in Germany	- Medical-record- and interview-based COI analysis of OHE patients (2006/2007) 12 months prior to inclusion in inpatient rehabilitation program - As not all data was available, some data were estimated by using assumptions - Two severity groups: Severity group A: no signs/mild, Severity group B: moderate to severe	- Medical records (medical history, diagnostic and therapeutic procedures) 1-hr structured interview	societal	Direct (medical) costs per patient / year: - All patients: €2,868 - Severity group A: €2,932 - Severity group B: €2,829 Productivity loss per patient/year: - All patients: €6,669 - Severity group A: €5,550 - Severity group B: €7,367 Total annual societal costs per patient: - All patients: €9,538 - Severity group A: €8,482 - Severity group B: €10,196

Abbreviations: CD = contact dermatitis; OCD = occupational contact dermatitis; HE = hand eczema, OHE = occupational hand eczema; SHI = statutory health insurance; OHI = occupational health insurance; COI = cost of illness

analysis of Satterstrom et al. (2014)^[49] involved patients with CD irrespective of severity group, i.e., also those with minor or no current symptoms. In contrast to that, Diepgen et al.^[47] distinguished two groups of HE severity (A=no signs/mild; B=moderate to severe), based on physician assessment and Diepgen et al.^[48] included only patients suffering from refractory chronic HE.

Besides the study population, the three studies differ with regard to the methods and data sources. In order to examine the influence of CD on societal costs and labor market affiliation, Satterstrom et al.^[49] linked information from 21,441 patients with CD, identified in a clinical database in Denmark, to health-care service, prescription and labor market registries. To receive costs attributable to CD, Satterstrom et al.^[49] applied a control group design in which five controls were assigned to each case of CD by means of the propensity score matching. Controls were derived from a 30% random sample of the total population. COI were estimated on an annual basis, from four years prior to recognition of occupational disease until one year after recognition, as a result from the difference between the costs of cases and controls.

Results show that for occupational CD patients attributable direct costs, including primary and secondary healthcare services and pharmaceuticals, remained almost stable over the first three years prior to recognition. However, one year before recognition and one year after recognition, there was a sharp increase in costs resulting a €417 per case and year after recognition. The development of indirect costs followed a similar trend leading to €9,084 per case due to productivity loss for the whole study period. However, due to limitations in the register, there was only information available for long-term sick leave (over 24 days in a row per year), underestimating indirect costs. Regarding the comparison of COI of patients suffering from occupational versus non-occupational CD, results revealed substantially higher attributable COI for non-occupational compared to occupational CD cases.^[49]

In comparison, the aim of Diepgen et al.^[48] was to compare COI of patients suffering from refractory chronic HE, dependent on the impact of work on the manifestation/aggravation of the disease. Using information from a cross-sectional data survey among publicly insured HE patients performed by Augustin et al.,^[52] Diepgen et al.^[48] conducted a second virtually identical study, focusing on HE patients insured by the occupational health insurance (OHI). To enable direct comparison of patients groups from both

surveys, the authors used the same approach in the recruitment, inclusion/exclusion criteria, and survey methods, as well as instruments, compared with Augustin et al.^[52] Direct costs included all resources relevant to the disease: ambulant honoraria, emollients, drug expenses, UV therapy, inpatient treatment, and patients' out-of-pocket expenses. Indirect costs were defined as costs caused by sick leave. In the course of the examination, Diepgen et al.^[48] defined the following groups of chronic HE patients according to the association between work and disease: non-working (SHI-1), work-unaffected (SHI-2), work-impaired (SHI-3) and work-diseased (OHI). While the groups "SHI-1" and "SHI-2" included cases for which chronic HE was not considered to be related to work, in patients belonging to group "SHI-3", HE causes days of absence from work and may be aggravated by occupational exposure (although occupational HE is unconfirmed). Conversely, group "OHI" comprises only cases for which the causal relationship between work and disease has been confirmed and recognized by the OHI.^[48] Diepgen et al.^[48] evaluated 310 patients and concluded that direct healthcare costs of work-impaired (SHI-3) and work-diseased (OHI) patients are more than twice as high compared with the group of non-working (SHI-1) and work-unaffected (SHI-2) chronic HE cases. Taking both direct and indirect costs derived from loss of productivity into consideration, overall yearly costs per case of chronic HE are approximately 4–5 times higher for work-diseased patients (€7,297) compared with non-working (€1,378) or cases unaffected by work (€1,563).^[48] This discrepancy in costs results more from loss of productivity due to long periods of sickness absence than from healthcare costs between occupational and non-occupational disease cases.

On the basis of the medical records (including medical history and diagnostic/therapeutic procedures) and 1-hr structured interviews conducted in a specialized hand eczema clinic in Germany, Diepgen et al.^[47] analyzed direct and indirect costs caused by occupational HE of 151 patients, 12 months prior to the inclusion in an inpatient rehabilitation program. Included direct costs are comparable to the previous study. As noted above, the authors stratified their analyses according to severity, into group A (no signs/mild) and B (moderate to severe). As some data relevant to the calculation of the overall economic burden were unavailable, the authors estimated COI on the basis of rather conservative assumptions, i.e., underestimating costs. Results revealed no significant difference in healthcare costs between both severity groups

(A = €2,932; B = €2,829). However, patients suffering from moderate to severe occupational HE reported a longer duration of incapacity for work (A = 40 days vs. B = 53 days per patient) in the past year and thus, tends to have higher indirect costs compared to cases with no or mild signs. In summary, total societal costs per year were higher in severity group B (€10,196) than in group A (€8,482).

Two studies focused exclusively on compensation payments (see [Appendix C](#) for an overview). Analyzing workers' compensation claims from 1993–2009 in Australia, Lyons et al.^[50] reported a median cost per claim of €871 on the basis of 156 hairdressers with occupational CD. Including costs of total temporary disability, medical treatment, partial permanent disability, and vocational rehabilitation, McCall et al.^[51] calculated mean total costs per OD claim of €4,062, based on 611 workers in Oregon between 1990 and 1997.

Quality assessment

The description above shows that there are studies examining the costs of occupational lung and skin diseases caused by isocyanates. However, to give an overview of the current state of research in this area and make suggestions on further fields of research, it is important to evaluate the quality of the included COI studies. Furthermore, quality assessment of the included studies is critical to adequately judge the validity of their findings.

Occupational lung diseases

As shown in [Table 3](#), in all COI studies on occupational lung disease the study objective and the inclusion/exclusion criteria of the study population were described clearly. However, only one out of five studies calculated costs directly attributable to the target disease. Using data from Washington State's work-related asthma surveillance system, Reeb-Whitaker et al.^[36] identified isocyanate-induced OA cases as those receiving compensation payments linked to the word "asthma". In contrast, other studies used data from primary and secondary sources, calculating costs for one patient and adopting them according to the prevalence of OA or occupational COPD. Although in most studies the adaption of costs was based on theoretical assumptions and may be subject to a high level uncertainty, only two out of five studies^[43,44] performed sensitivity analyses. In their top-down approach, based on national expenditures on medical care, the authors applied different values of

population attributable risk of occupational asthma/COPD, ranging from 10–20%.^[43,44]

With regards to the calculation of costs, only Ayres et al.^[37] directly reported estimating costs from the perspective of society, while in the remaining publications the study perspective can only be assumed. Moreover, all studies clearly documented the data sources used and the method of cost calculation, although the studies differ widely in the scope of calculated costs. While Ayres et al.^[37] and Leigh et al.^[43] took both, direct and indirect costs into account, García Gomez et al.^[42] and Leigh et al.^[44] focused only on direct costs. Apart from healthcare costs, the COI study performed Reeb-Whitaker et al.^[36] also included compensation payments. Thus, the latter three studies do not provide a complete picture of COI.

Concerning the presentation of results, most studies addressed the issue of sample sizes, but demographics, arithmetic mean costs and standard deviation were only reported in one of the five studies. As mentioned above, this may be due to the fact that most studies calculated societal, direct, and/or indirect costs based on highly aggregated economic data, but did not break down these costs according to the individual patient^[42–44] or presented only median costs.^[36] Moreover, all studies discussed their results in the context of other studies and addressed study limitations, although there was a lack of discussion on the study representativeness.

Occupational skin diseases

The systematic literature search identified three European COI studies examining occupational skin disease.^[47–49] As illustrated in [Table 3](#), for the three studies quality assessment revealed a clear description of the study objective and inclusion/exclusion criteria, as well as the calculation of disease-specific costs (on the basis of a control group design or by focusing on specific diagnostic codes). However, none of the studies reported the performance of sensitivity analyses in order to address parameter uncertainties. The COI study performed by Diepgen et al.^[47] was the only study acknowledging the use of a conservative approach in handling missing data, thus rather underestimating COI.

Concerning the estimation of COI, the study quality assessment showed that data sources, study perspective, cost categories, and inflation/discount rate (if necessary) were reported adequately in all studies; however, we observed deficits in the documentation of the cost calculation methods in Diepgen et al.^[48]

Table 3. Quality assessment of COI studies on occupational lung and skin diseases.

	Aims and methods of the study	Occupational lung diseases				Occupational skin diseases			
		Reeb-Whitaker et al. (2013) ^[36]	García Gomez et al. (2012) ^[42]	Ayres et al. (2010) ^[37]	Leigh et al. (2003) ^[44]	Leigh et al. (2002) ^[43]	Satterstrom et al. (2014) ^[49]	Diepgen et al. (2013a) ^[48]	Diepgen et al. (2013b) ^[47]
Study objective	The objective(s) and research question(s) of the study was (were) described clearly.	+	+	+	+	+	+	+	+
Inclusion and exclusion criteria	At least the objective diagnostic criteria (e.g., ICD code and DSM-IV) used to identify eligible patients were reported. The study population was specified.	+	+	+	+	+	+	+	+
Non-diseases comparison group or disease-specific costs	The study included a non-diseased control group in order to calculate excess costs or, if no control group was involved, the costs were due to the disease of interest (e.g., diagnostic codes).	+	-	-	-	-	+	+	+
Matching or regression analysis	If comparison groups were used: (a) they were matched, at least in terms of age and/or gender, to allow a direct comparison between equally dispersed groups with regard to their characteristics or (b) regression analysis was carried out in order to control differences.	n. a.	n. a.	n. a.	n. a.	n. a.	+	n. a.	n. a.
Sensitivity analysis	Relevant parameters were varied in univariate and/or in probabilistic sensitive analyses in order to address parameter uncertainties (e.g., different unit costs).	-	-	-	+	+	-	-	-
Calculation of costs									
Data sources	The source of information on healthcare utilization or costs was reported and mentioned specifically.	+	+	+	+	+	+	+	+
Perspective	The perspective of the cost calculation was reported (e.g., from payer, employer, or societal perspective).	-	-	+	-	-	+	+	+
Cost calculation	The method of cost calculation was clearly documented	+	+	+	+	+	+	-	+
Cost categories	The study estimated costs from the utilization of different kinds of healthcare services or areas, which meant that more than one category was given, in order to consider, at best, all costs that accrued from the disease under study.	-	+	+	+	+	+	+	+
Reference year (price)	All costs were valued at the price level of a stated base year.	-	+	+	+	+	+	+	-
Currency	The currency of calculated costs was reported.	+	+	+	+	+	+	+	+
Inflation rate and/or discount rate	If data were collected from or estimated for a period longer than one year, costs were adjusted for differential timing and the inflation rate/discount rate was mentioned.	-	n. a.	+	n. a.	n. a.	+	n. a.	n. a.
Monetary valuing of resource utilization	If data on resource utilization were collected that were valued with unit costs, the latter were reported; if cost data were used, these reflected actual charges.	+	+	+	+	+	-	-	+
Presentation of results									
Sample size	The sample size was reported.	+	+	+	-	+	+	+	+
Demographics	The characteristics of the sample were described; at least (mean) age and gender were reported.	-	-	+	-	-	+	+	+
Arithmetic mean costs	The cost estimates were (partly) presented as arithmetic means.	-	+	-	-	-	+	+	+
Standard deviations	Standard deviations of cost estimates were (partly) reported as a measure of variability.	-	-	+	-	-	-	-	-
Separate information	Separate information about the number of (health) services and cost were given for all cost categories that were described.	-	+	-	+	+	-	-	-
Discussion									
Other studies	The results were discussed in relation to other studies on the same topic.	+	+	+	+	+	+	+	+
Limitations	The limitations regarding the calculation of costs and the representativeness of the study population, in particular, were discussed in detail.	-	-	-	-	-	-	-	+

Abbreviation: + = yes, - = no, n. a. = non-applicable

and the valuation of costs at the price level of a stated base year in Diepgen et al.^[47] Moreover, Satterstrom et al.^[49] and Diepgen et al.^[48] did not report the unit costs by which resource utilization was valued. Showing a lack of methodological transparency, these shortcomings limit the possibility to replicate results. Nevertheless, all studies calculated direct and indirect costs, even if direct costs included different types of healthcare costs.

With regard to the presentation of results, the sample size and demographics of the study population were reported in all studies. Although arithmetic mean costs were also presented, none of the studies stated standard deviations as a measure of variability. Similarly, either separate information on the number of health services was provided, as by Diepgen et al.^[48] and Diepgen et al.,^[47] or the costs were reported for all described cost categories, as by Satterstrom et al.,^[49] although no study provided information on both aspects. Furthermore, all studies discussed their results in the context of related articles. However, only Diepgen et al.^[47] discussed limitations concerning both cost calculation and representativeness of the study population. Satterstrom et al.^[49] only addressed limitations concerning cost estimation and Diepgen et al.^[48] did not report any limitations.

Discussion

To our knowledge, this is the first systematic review considering costs of occupational lung and skin diseases potentially caused by isocyanates. To provide a complete picture of costs, we included not only classical COI studies, but also studies focusing on loss of income and compensation payments. For inclusion in this review, we identified 16 articles; of these, 11 focused on occupational lung disease and five on occupational skin disease. Overall, 50% of all identified studies calculated classical COI. Moreover, most studies estimated costs irrespective of the type of causative agent. Only two studies reported costs directly attributable to isocyanate-induced OA cases.

Although the review found substantial heterogeneity in reported direct and indirect COI, most studies reported that occupational lung and skin diseases resulted in a high economic burden for the individual patient and society. In all COI studies from Europe indirect costs were identified as the main cost driver, although one COI study in the US concluded differently. However, although we standardized costs, values can scarcely be compared because most studies differ

with respect to the underlying health care system (country), study population (i.e., disease cases with different grades of severity or causative agents), study design and data sources, study perspective/extent of included cost components, and the presentation of results. Concerning the quality assessment no study met all criteria.

With regard to occupational lung disease, the evidence on COI is limited. All identified studies focused on OA and two studies also examined occupational COPD. All studies on loss of income concluded that the development of OA was associated with long-term sick leave and a substantial decrease in annual income, with patients removing themselves from exposure and switching job and/or employer being worse off financially. However, results on COI varied substantially. In addition to the differences discussed above, the most common methodological shortcomings, according to the study quality assessment, were the lack of sensitivity analysis, the lack of discussion with respect to the representativeness of the study population, the reporting of aggregated costs rather than patient level costs as well as the inclusion of partial costs (direct or indirect) rather than a calculation of all costs attributable to the disease. Furthermore, the majority of costs in COI studies were derived from previously published literature, surveys or statistics, largely focusing on non-occupational asthma, and adapted to the target population based on theoretical assumptions (population attributable risks). However, it remains unclear whether COI differ between occupational asthma, work-exacerbated asthma, and asthma unrelated to work. Moreover, some studies indicated that costs of occupational lung disease may differ according to sex and causative agent, but it remains unclear whether COI depend on the degree of severity. We did not find any study focusing on COI of occupational COPD or hypersensitivity pneumonitis directly induced by isocyanates.

Similarly, studies concerning occupational skin diseases, particularly OHE and OCD, showed a wide range of estimated COI. In line with COI studies on occupational lung diseases, studies differed with regards to the study population (including occupational hand eczema or contact dermatitis patients with different grades of severity), study design, and data sources. Although we only identified three COI studies and we do not know if/how many isocyanate-induced cases were included in these studies, they are of higher quality as they showed fewer excessive methodological deficits compared to occupational lung diseases. Thus, these studies may be more

comparable as they share more common characteristics: all three studies were conducted in Europe (two of them in Germany), estimated costs from the societal perspective and thus, calculated both, direct and indirect costs, and presented them as patient-level annual costs.

Furthermore, these studies provide initial guidance that COI may differ according to severity and origin of disease (occupational vs. non-occupational). Differentiating between two severity groups, Diepgen et al.^[47] showed that higher indirect costs were incurred with OHE patients with moderate to severe symptoms, compared with patients with no or mild symptoms, but direct medical costs were similar in both groups. Conversely, Satterstrom et al.^[49] and Diepgen et al.^[48] compared patients with skin diseases related and unrelated to work showing contrasting results. While Diepgen et al.^[48] reported higher direct and indirect costs in work-impaired and work-disabled HE patients compared to work-unaffected patients, Satterstrom et al.^[49] only confirmed these results in terms of productivity loss. However, it remains unknown, whether costs of occupational skin diseases may depend on the causative agent (e.g., isocyanates).

Implications

Although there is much variation in estimations, the present review shows that the consequences of occupational diseases that may be caused by isocyanates are considerable in terms of societal costs and loss of income. As it is estimated that occupational diseases are under-reported, the total COI attributable to isocyanates, presented here, may have been considerably underestimated. As occupational lung and skin diseases place a heavy burden on the statutory health and accident insurance and the affected worker, the performance of comprehensive and high quality COI analyses constitutes an important element for the implementation of preventive measures. Therefore, the most important implication of this review is that there is a need for high-quality COI studies, in terms of methodological and reporting quality.

In order to calculate costs of occupational lung and skin diseases, studies calculating societal costs and stratifying by degree of severity, causative agent and sex, are required. Therefore, it would be desirable to combine secondary and primary data sources, for example by linking claims data from occupational health insurances, which could reflect real world evidence on paid costs, to medical records or to self-

collected data from a survey. This is particular relevant for some isocyanate-induced diseases, for example hypersensitivity pneumonitis/extrinsic allergic alveolitis, which to date have received insufficient attention.

Another option for estimating COI, often used in the identified publications, for example in studies on asthma, would be to multiply costs of general asthma by the attributable risk that the diseases have been induced by the workplace. However, there is no consensus that lung/skin diseases induced by work lead to similar COI compared with lung/skin diseases unrelated to work. Further COI studies focusing on this association are required. Therefore, it would be necessary to conduct two identical studies from the same study perspective, stratifying by degree of severity and triggering agent. This may allow the determination of transfer of costs.

Evidence on the disease burden and costs of isocyanate-induced occupational lung and skin diseases is important in supporting healthcare stakeholders and policy decision makers as they weigh up limiting/banning the industrial and/or professional use of harmful agents, while guaranteeing free movement of chemicals and supporting competitiveness and innovation, set out, for example, in the European Regulation for the Registration, Evaluation, Authorization in Chemicals (REACH).^[53] COI studies may also provide evidence for the health benefits of further preventive measures in occupational safety and health. Therefore, they may contribute to minimizing the risk of occupational exposure, for example with regards to protective clothing and training measures to improve correct handling of chemicals. As action generally occurs at the European level, international studies, based on a comparable study design and comparing COI of isocyanate-induced occupational lung and skin diseases, are required.

Limitations

There are some limitations to our study. First, as we limited our literature search to two databases, it may be possible that relevant publications not being included in these databases were missed. However, it is known that DIMDI and OSHLINE constitute the primary reference databases in the field of health economic studies and occupational diseases.

Second, we decided to search not only for COI studies on isocyanate-induced diseases but also for studies on typical occupational lung and skin diseases that can be caused by isocyanates; however, it remains

unclear whether pathogenesis and COI differ by occupational agent. Through the systematic literature search, we only identified few COI studies focusing directly on isocyanate-induced occupational disorders. Moreover, we also searched for COI studies on isocyanate-induced occupational COPD even if the causal relationship is less well documented compared with asthma. This was the only strategy that allowed us to gain an insight into the economic burden of isocyanate-related diseases.

Third, as there is no international standardized instrument for quality assessment of COI studies, we evaluated the quality of publications using the checklist developed by Kleine-Budde et al.^[35] as this checklist fitted our research question. However, for certain points, the use of the checklist was subject to some uncertainties. For example, it is unclear if the criterion “cost categories” calling for extensive cost analysis, is only fulfilled if direct and indirect costs are calculated, or whether the estimation of costs from different healthcare sectors is sufficient. Moreover, the checklist only requires clear documentation of the cost analysis methods, but not their appropriateness. With regard to the presentation of costs, cost data with a highly skewed distribution is better represented by median or quartiles rather than arithmetic mean. In summary, this checklist focuses more on reporting quality than on methodological quality. Despite this, the checklist provides a sound basis for the extraction of the most important components of a COI analysis as the basis of the discussion on quality.

Conclusion

Evidence on costs of occupational lung and skin diseases that are caused by exposure to isocyanates is low. Only a few studies were identified, and these studies presented with limitations in reporting/methodological quality. Despite these limitations and the substantial differences in their methodological approach, the identified studies concluded that occupational lung and skin diseases resulted in a significant economic burden for the patient and the society. Considering that exposure prevalence to isocyanates continues to increase in Europe, further studies in order to reflect real COI and stimulate preventive measures are warranted.

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Appendix A: Search terms and strategy

Category	German search terms	English search terms
Selected databases (DIMDI): Medline, BIOSIS Previews, EMBASE alert, EMBASE, Gms, Gms Meetings, SciSearch		
Isocyanate	FT = Isocyanat? CTG D "ISOCYANATE"	FT = Isocyanat? FT = Isothiocyanat? CT D "Isocyanate"
	Results= 50,955 (Nr. 5)	
Linkage with OR (Nr. 5)		
Isocyanate-induced diseases	Asthma CTG D ("ASTHMA"; "ASTHMA BRONCHIALE")	CT D ("ASTHMA"; "ASTHMA BRONCHIALE") CT D "BRONCHIAL ASTHMA"
	Pulmonary Disease, Chronic Obstructive CTG D ("CHRONISCH OBSTRUKTIVE LUNGENKRANKHEIT"; "CHRONISCH OBSTRUKTIVE PULMONALE ERKRANKUNG"; "CHRONISCH OBSTRUKTIVE PULMONALE KRANKHEIT")	CT D COPD CT D ("CHRONIC OBSTRUCTIVE PULMONARY DISEASE"; "CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)") CT D COAD CT D ("CHRONIC OBSTRUCTIVE AIRWAY DISEASE"; "CHRONIC OBSTRUCTIVE AIRWAYS DISEASE"; "CHRONIC OBSTRUCTIVE LUNG DISEASE") CT D ("AIRFLOW OBSTRUCTION, CHRONIC"; "AIRFLOW OBSTRUCTIONS, CHRONIC") CT D ("CHRONIC AIRFLOW OBSTRUCTION"; "CHRONIC AIRFLOW OBSTRUCTIONS")
	Alveolitis, Extrinsic Allergic FT = Exogen allergische alveolitis CTG D "EXOGEN-ALLERGISCHE ALVEOLITIS"	FT = extrinsic allergic alveoliti? CT D ("HYPERSENSITIVITY PNEUMONITIS"; "HYPERSENSITIVITY PNEUMONITIDES") CT D ("PNEUMONITIDES, HYPERSENSITIVITY"; "PNEUMONITIS, HYPERSENSITIVITY") CT D ("ALLERGIC ALVEOLITIS, EXTRINSIC"; "ALLERGIC ALVEOLITIS, EXTRINSIC") CT D "ALVEOLITIDES, EXTRINSIC ALLERGIC" CT D ("EXTRINSIC ALLERGIC ALVEOLITIDES"; "EXTRINSIC ALLERGIC ALVEOLITIS")
	CTG D "ALLERGISCHE ALVEOLITIS, EXOGENE"	
	Dermatitis, Allergic Contact CTG D ("DERMATITIS, KONTAKT-"; "DERMATITIS, KONTAKT-, ALLERGISCHE")	CT D ("DERMATITIS, ALLERGIC CONTACT"; "DERMATITIS, ALLERGIC ECZEMATOUS"; "DERMATITIS, CONTACT, ALLERGIC") CT D "DERMATITIDES, ALLERGIC ECZEMATOUS" CT D ("ALLERGIC ECZEMATOUS DERMATITIDES"; "ALLERGIC ECZEMATOUS DERMATITIS") CT D ("ECZEMATOUS DERMATITIDES, ALLERGIC"; "ECZEMATOUS DERMATITIS, ALLERGIC") CT D "ALLERGIC CONTACT DERMATITIS" CT D "ALLERGIC CONTACT DERMATITIDES" CT D ("CONTACT DERMATITIDES, ALLERGIC"; "CONTACT DERMATITIS, ALLERGIC")
	CTG D "ALLERGISCHE KONTAKTDERMATITIS"	
	Dermatitis, Irritant FT = Toxisches Kontaktekzem	FT = Irritant contact dermati? FT = Primary Irritant Dermatiti? CT D "IRRITANT CONTACT DERMATITIS" CT D "DERMATITIS, PRIMARY IRRITANT"
	FT = Toxische Kontaktdermatitis CTG D ("DERMATITIS, IRRITATIONS-"; "DERMATITIS, KONTAKT-"; "DERMATITIS, KONTAKT-, ALLERGISCHE")	CT D ("DERMATITIDES, IRRITANT"; "DERMATITIDES, PRIMARY IRRITANT") CT D ("IRRITANT DERMATITIDES"; "IRRITANT DERMATITIDES, PRIMARY"; "IRRITANT DERMATITIS"; "IRRITANT DERMATITIS, PRIMARY") CT D "PRIMARY IRRITANT DERMATITIS"
	Dermatitis, Occupational CTG D "BERUFSBEDINGTE DERMATOSE"	CT D ("OCCUPATIONAL DERMATITIDES"; "OCCUPATIONAL DERMATITIS") CT D ("INDUSTRIAL DERMATOSES"; "INDUSTRIAL DERMATOSIS") CT D "DERMATITIDES, OCCUPATIONAL" CT D ("DERMATOSES, INDUSTRIAL"; "DERMATOSIS, INDUSTRIAL")
	CTG D "DERMATITIS, BERUFSBEDINGTE"	
	Results: 266,220 (Nr. 44) With Isocyanate 316,351 (Nr. 45)	

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Category	German search terms		English search terms
Linkage with AND			
Cost	FT = Kosten FT = Kost? CTG D ("KOSTEN UND KOSTENANALYSE"; "KOSTEN, KRANKHEITS-")		FT = Cost FT = Cost? FT = Los* productivity CT D "PRODUCTIVITY LOSS" CT D "LOSS OF PRODUCTIVITY" CT D "ABSENTEEISM" CT D ("HEALTH CARE COSTS"; "HEALTH CARE COSTS/*") CT D ("COST OF ILLNESS"; "COST OF ILLNESS ANALYSIS"; "COST, COST ANALYSIS") CT D ("ECONOMIC"; "ECONOMIC ANALYSES"; " ECONOMIC ANALYSIS"; "ECONOMIC ASPECTS OF ILLNESS"; "ECONOMIC BURDEN OF DISEASE")
	Results= 1,317,348 (Nr. 54)		
Linkage with OR			
Severity and duration of illness	FT = Dauer der Erkrankung FT = Krankheitslast FT = Krankheitsschwere FT = Schwere der Erkrankung FT = Schweregrad Results= 82,187 (Nr. 59) Linkage with Cost= 1,396,967 (Nr.60) language: German and English		FT = Sickness duration FT = Illness duration CT D ("SEVERITY"; "SEVERITY OF ILLNESS") CT D ("DURATION OF ILLNESS"; "DURATION,DISEASE")
Limitations			
Linkage with „AND“			
Sensitive String occupation	FT = Beruf? FT = Arbeit? FT = Betrieb?	FT = work FT = Works? FT = work'? FT = worka? FT = worke? FT = workg? FT = worki? FT = workl? FT = workp? FT = occupation? FT = prevention? FT = protect?	
	Results: 5,635,163 (Nr. 68)		
Results			
Results DIMDI	N = 3,732 (sensitive string for occupation)		
Search terms	(Isocyanate OR Asthma OR "Chronic obstructive pulmonary disease" OR COPD OR (Airflow obstruction Chronic) OR "Chronic airflow obstruction" OR "Chronic Obstructive Airway Disease" OR "Pulmonary Emphysema" OR (Lung diseases obstructive) OR COAD OR "extrinsic allergic alveolitis" OR "Allergic contact dermatitis" OR "Irritant contact dermatitis") AND ("Cost of illness" OR cost* OR economic* OR "burden of disease" OR "Burden of Illness" OR (productivity loss*) OR (Los* productivity) OR absenteeism OR "sickness duration" OR "illness duration" OR "duration of illness" OR "severity of the disease" OR "Severity of illness") AND (Work-related OR (Working environment) OR (Work environment) OR Workload OR Occupation? OR Prevention)		
OSH References Databases			
Search terms	N= 260		
OSH References Databases			
Results DIMDI and OSH			
Results DIMDI and OSH N = 3,982 (sensitive string for occupation)			
Explanation: ? replaces any number of characters; FT = free text, all fields; CT = Controlled Terms; N = number of records			

Appendix B: Studies on loss of income/compensation payments due to occupational lung diseases

Author, country	Study population	Study design	Data sources	Results (direct / indirect / total costs)
Miedinger et al. (2011), Quebec	N = 60 OA subjects (diagnosis: inhalation testing) claiming compensation in Quebec	Longitudinal study (2004-2006): - Clinical examination and questionnaire concerning employment status, participation in rehabilitation programs and quality of life on two occasions - Costs = compensation for loss of income and functional impairment	- Workers' Compensation Board of the Workers' Compensation Agency of Quebec - Self-collected data	- Compensations for loss of income: Median: €44,444 - Compensations for functional impairment: Median: €9,592 - Total costs for compensation: Median: €55,315
Malo et al. (2008), Quebec	N = 140 OA worker with accepted claims for compensation	Cross-sectional study (1988-2002): - Drawing of a random sample of 8 to 10 subjects with accepted claims for compensations for OA per year from 1988 to 2002 - Costs = compensation for loss of income and functional impairment	Quebec Commission de la santé et de la sécurité du travail	- Compensations for loss of income: Mean: €56,116; Median: €31,502 - Compensations for functional impairment: Mean: €9,056; Median: €5,883 - Total compensations for loss of income and functional impairment: Mean: €71,828; Median: €47,447
Leira et al. (2005), Norway	N = 723 workers (Aluminium and other industries) with physician's diagnosis of OA	Cross sectional study: - Study period: 1995-99 - Questionnaire: information on working situation, symptoms, symptom-work-relationship, smoking, and socioeconomic consequences of the disease - As data on exposure coded by the doctor varied, the job was used as proxy for the exposure	- Notification of occupational diseases obtained from the registry of the Labor Inspection Authority - Self-collected data	- Loss of income: - Aluminium industry: 39% had a reduction in annual income; 3% temporarily reduction - Other industries: 55% had a reduction in annual income; 5% temporarily reduction - Financial compensation from Occupational Injury Insurance Act: - Aluminum industry: 26% <€13,650; 8% €13,650 - €68,252; 0,4% = > €68,252 - Other industries: 10% < €13,650; 11% €13,650 - €68,252; 4% = > €68,252
Moscato et al. (1999), Italy	N = 25 patients with OA; diagnosis confirmed by specific inhalation challenge	Longitudinal study: - Baseline diagnosis (1992-1995): peak expiratory flow rate, symptoms, drug consumption, direct or indirect disease expenses socioeconomic status - Follow-up visits (1, 3, 6, 12 months): Clinical examination, spirometry, methacholine challenge. Assessment of diary-derived parameters, asthma severity and socioeconomic status	Self-collected data	12 months after diagnosis 13 patients had ceased exposure (group A) and 12 patients continued to be exposed (group B) - Loss of income: A significant loss of income was registered in patients of group A (€11,042 - €16,857 on the year preceding diagnosis and €6,958 - €13,778 on the year after diagnosis; $p < 0.01$); no significant change was seen for patients in group B
Ameille et al. (1997), Paris	N = 209 OA patients; diagnosis based on medical history and confirmatory investigation	Follow Up Study: - Baseline (1989-93): Lung function test, sociodemographic information, medical information, severity of asthma, additional information: e.g. type of employment, number of employees 1 year later: Interviews via telephone or self-administered questionnaire by post. Information on working status, financial situation and compensation claim	Self-collected data at the occupational medicine departments for OA	- Financial consequences of OA: 46% of patients had suffered from a reduction of income with a mean reduction of 50% per year - Mean loss of annual income were significantly higher in subjects who left their employer than in those who remained in the same company - Of the 103 workers whose claim for compensation was accepted, 58 (56%) suffered from a reduction of income.
Gannon et al. (1993), UK	N = 112 workers with OA; diagnosis	Cross sectional study:	- Self-collected data - Workers' case records	Of all patients with job change, 74% reported a reduced income;

(Continued)

Continued.

Author, country	Study population	Study design	Data sources	Results (direct / indirect / total costs)
	based on medical history and other confirmatory investigation	- Self-administrated questionnaire one year after diagnosis with information about respiratory symptoms, employment state, and current financial situation (including compensation) - Diagnostic data, respiratory function, and causative agent were obtained from the workers' case records		Of all patients who remained exposed, 44% reported a reduction of income - Median perceived annual loss= €7,763 (removed from exposure), €5,058 (remained exposed) - Median perceived loss as a percentage of annual income was 54% (unexposed), 35% (remained exposed) 47% had attempted to claim statutory compensation for OA; 27 (52%) had settled the claim, 17 (33%) had claims outstanding, and 8 (15%) had had the claim rejected - Median amount of compensation per year=€2,995

Abbreviations: OA = occupational asthma

Appendix C: Studies on loss of income/compensation payments due to occupational skin diseases

Author, country	Study population	Study design	Data sources	Results (direct / indirect / total costs)
Lyons et al. (2013), Victoria, Australia	N = 156 hairdressers / apprentices with a confirmed diagnosis of OCD	- Retrospective analysis of workers' compensation claims for OCD in hairdressers at a tertiary referral occupational dermatology clinic in Victoria (Australia) from 1993 to 2009 - Identification of incident OCD cases in the Occupational Dermatology Clinic Database (n = 156) and the Compensation Research Database (n = 46)	- Occupational Dermatology Clinic database - Compensation Research Database - Australian Bureau of Statistics	- Total time away from work across all claims = 2,648 days; Median time away from work per claim = 20 days (maximum = 642 days) - Less than one third (n = 46) of OCD cases claimed compensation - Total recorded cost of all workers' compensations claims for hairdressers with OCD (between 1993 and 2009) = €261,774 - Median cost per claim = €870.99 - Highest individual claim = €42,032
McCall et al. (2005), Oregon, US	N = 611 workers with OD and accepted claims identified in workers' compensation claims database	- Retrospective analysis of workers' compensation claims for OD in Oregon from 1990 to 1997 - Workers' compensation claims were merged with US census data	- Oregon Department of Consumer and Business Information and Management Division - Department of Labor's Current Population Survey	- Mean total cost per dermatitis claim (including costs of total temporary disability, medical treatment, partial permanent disability, vocational rehabilitation) = €4,062 - Total cost of all dermatitis claims for the 8-year period = €2,481,935 - Mean annual claim costs (over 8 year period) = €310,243 - Total temporary disability indemnification duration per claim = 23.9 days

Abbreviations: OD = occupational dermatitis; OCD = occupational contact dermatitis