Lung/skin connections in occupational lung disease
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Purpose of review
Exposure to occupational and environmental agents can cause a spectrum of lung diseases that are predominantly immune-mediated. Research and prevention have focused primarily on the respiratory tract. Recent studies, however, suggest that the skin may also be an important route of exposure and site of sensitization. This article highlights key findings, focusing on isocyanate asthma and chronic beryllium disease.

Recent findings
Occupational lung diseases such as isocyanate asthma and chronic beryllium disease continue to occur despite reduced airborne exposures. Although challenging to quantify, recent studies have documented isocyanate and beryllium skin exposure, even with the use of personal protective clothing. Factors that impair skin barrier function, such as trauma, may promote sensitization to such agents. Animal studies demonstrate that skin exposure to isocyanates and protein allergens is highly effective at inducing sensitization, with subsequent inhalation challenge eliciting asthmatic responses. Limited clinical studies suggest a similar role for human skin exposure to certain sensitizing agents.

Summary
Recent findings support a greater focus on the role of skin exposure in the development of certain occupational and environmental lung diseases. Although further research is needed, it is prudent to reduce both skin and inhalation exposures.

Keywords
chronic beryllium disease, epidermal barrier dysfunction, isocyanate asthma, sensitization, skin exposure

Introduction
Exposure to occupational and environmental agents can cause a spectrum of airway and interstitial lung diseases that likely involve immune mechanisms, such as occupational asthma, hypersensitivity pneumonitis and chronic granulomatous lung diseases. With generally reduced occupational exposures to the traditional inorganic dusts such as asbestos, silica and coal dust, and the expanding use of new metal and chemical-based products, predominantly immune-mediated lung diseases have become the major reported occupational lung diseases in most developed countries. Isocyanate asthma and chronic beryllium disease, two of the more commonly diagnosed occupational lung diseases, share several features that have hampered recognition and prevention. Only a fraction of exposed workers develop disease, and exposure–response relationships remain poorly defined; both diseases can occur at very low levels of exposure, below current regulatory limits [1,2,3]. It has been presumed that the respiratory tract is the key route of exposure and site for initiation of the immune responses, with research, regulation and prevention to-date focused almost exclusively on airborne exposures. Despite reductions in workplace respiratory exposures, however, isocyanate asthma and chronic beryllium disease continue to occur, prompting a focus on skin as a route of exposure [1,3,4].

This review will highlight recent findings from a diverse literature that, taken together, support the hypothesis that skin may be an important site of exposure and initial sensitization for certain occupational and environmental agents.

Challenges to investigating skin exposures
Exposure to isocyanates and to beryllium, rather than occurring as single agents at constant levels, typically occur as mixed or variable exposures, complicating exposure assessment. Use of both continues to rise, with novel applications and processes creating new opportunities for exposure. Isocyanates, a diverse group of reactive chemicals with the functional group NCO, are used extensively to produce a wide array of polyurethane coatings, foams and others products. The major commercial isocyanates are methylene diphenyl diisocyanate (MDI), toluene diisocyanate (TDI) and hexamethylene diisocyanate (HDI) and numerous polymeric forms and prepolymers

[5]. They typically are used as complex mixtures of isocyanates and other chemicals, with highly variable volatility, mass, solubility and isocyanate content [5]. Exposures can occur as vapors, aerosols, liquids, and also possibly from polyurethane products that are not yet fully cured [1••,6•]. Use has shifted to less volatile forms (MDI and polymeric forms) reducing risk of respiratory exposure, but not necessarily skin exposure [1••].

Beryllium, a lightweight strong metal with valuable physiochemical properties, is used in a growing number of industries, including aerospace, defense, electronics, and telecommunications and, like isocyanates, exposures can be variable [3••]. Beryllium can occur as metal particles, oxides, salts and alloys with copper and other metals. Beryllium compounds can have variable physiochemical properties, particle size, surface area, solubility and bioavailability, and different work processes (e.g. primary production, machining) can generate varied exposures.

Opportunities for isocyanate and beryllium skin exposure can occur in many work settings, including direct contact of unprotected skin with contaminated equipment or surfaces, deposition of airborne exposures, or failure of skin protective equipment. Opportunities for skin exposure may persist after airborne exposure is gone, for example from residual dust particles (beryllium) or polyurethane that is not fully cured and contains residual free NCO [6•,7•]. Current beryllium and isocyanate workplace exposures tend to be low, below irritating thresholds, thus workers have few 'warning signs', and may lack adequate skin protective clothing such as gloves. Exposure levels that are low, but sufficient to induce sensitization or elicit responses upon subsequent challenge, can be technically challenging to quantify, and may require highly sensitive methodologies [5,8].

Skin exposure assessment methodology is not nearly as well developed as for inhalational exposures, and is further complicated by factors such as the frequently variable and sporadic nature of skin exposure, and uncertain ties regarding skin uptake, and recovery from sampled skin or wipes, and effectiveness of protective clothing. With very limited exposure data available and few dermal exposure models, skin exposure has rarely been incorporated into epidemiologic studies to assess its potential contribution to the risk of lung disease [9,10]. Thus to-date support for the hypothesis that human skin exposures play a role in the development of systemic sensitization and subsequent lung disease is largely indirect.

Animal studies using skin sensitization
Several different animal models have used isocyanate skin exposure to induce systemic Th2-like sensitization that, when followed by inhalation challenge, induces asthma-like responses in the lung [11–13]. Murine studies have demonstrated that dose, route and timing of isocyanate exposure are key determinants of sensitization and asthma. In general, relatively modest skin exposure doses (frequency and concentration) are highly effective at inducing Th2-like sensitization, and lower skin doses may paradoxically result in greater lung inflammation following airway challenge [11,14]. Transgenic mouse models have demonstrated that isocyanates can induce mixed Th1/Th2 responses, and that the immune response is also dependent on the mouse strain [13,15].

Unlike isocyanate asthma, chronic beryllium disease has been difficult to replicate in animal models, the great majority of which have used inhalation exposures and lead to acute changes, but not the chronic granulomatous disease. Beryllium sensitization (but not lung disease) has been produced in mice following skin exposure to beryllium oxide particles [16].

Isocyanate asthma and skin exposure
Isocyanate asthma remains one of the most common causes of occupational asthma worldwide [1••]. The clinical and pathophysiological presentation of isocyanate asthma is similar to environmental atopic asthma, including Th2-like airway inflammation and hyperreactivity [17]. Isocyanate asthma is reported typically in end-use settings such as spray, foam and adhesive applications, where there can be numerous opportunities for skin exposure [1••,18•]. Concern that skin exposure may increase risk for isocyanate sensitization and asthma stems in large part from case reports and limited cross-sectional studies reporting isocyanate asthma in settings with opportunities for skin exposure (sometimes accidental exposures) and minimal airborne levels [19,20], and also the animal literature [1••].

Methodologies to assess skin exposure to isocyanates have been particularly challenging due to several factors, including isocyanate chemical reactivity and numerous different isocyanate formulations. Since all sampling methods depend on the presence of free unreacted NCO, the timing of sampling is also critical. Isocyanate skin exposure has recently been documented using newly developed qualitative and quantitative methodologies in auto body shop workers and painters that apply polyurethane products, despite the use of standard personal protective equipment such as gloves, and also in settings where airborne exposures are minimal [18•,21•,22]. An on-going epidemiological study of auto body shop workers has demonstrated HDI-specific IgG antibodies in over 20% of the workers, which was strongly associated with inhalation exposure, but skin exposure also contributed independently [23]. Together these recent human and animal studies confirm isocyanate skin exposure in the

workplace and support the concept that such exposure may lead to sensitization and the subsequent development of isocyanate asthma upon airway challenge.

Chronic beryllium disease and skin exposure

Exposure to beryllium particles (metal, oxides, alloys) can lead to Th1-type sensitization and chronic beryllium disease, an immune-mediated systemic granulomatous disease involving predominantly the lungs, and mediated by CD4+ Th1 responses to beryllium. Similar to isocyanate asthma, new cases of beryllium sensitization (detected by proliferation of beryllium-specific CD4+ T cells), and chronic beryllium disease have occurred despite large reductions in respiratory exposures, including below current regulatory standards ($2 \mu g/m^3$ in the United States) [3••,7•]. Historically, allergic contact dermatitis and acute pneumonitis were seen following skin and respiratory exposure to soluble beryllium salts (now uncommon). Beryllium sensitization and chronic beryllium disease is seen following inhalation to less soluble beryllium particles [3••].

It has been hypothesized that, in addition to respiratory exposure, skin exposure to beryllium particles may induce sensitization, which can progress to chronic beryllium disease following inhalation exposure [4••,16]. Limited studies suggest that beryllium particles may be able to penetrate human skin [16], and increased risk of chronic beryllium disease has been reported in workers with skin lesions, possibly related to increased exposure and uptake of beryllium [24]. Additional indirect data suggesting that skin exposure may contribute to beryllium sensitization come from a recent study in a beryllium ceramics facility that implemented an enhanced preventive program that targeted air and skin exposure. Beryllium sensitization was reduced in new workers hired after implementation of the program (1%), compared with workers hired previously (8.7%), during which time airborne beryllium levels, already low, and respirator use, changed little [25•]. The authors suggested that reduced skin exposure may have contributed to reduced risk of sensitization [25•], but skin exposure was not evaluated.

Documentation of beryllium skin exposure in workers has been limited, despite awareness that it likely is common, similar to isocyanates. Frequent beryllium contamination of work surfaces and skin exposure was recently documented at a copper–beryllium alloy facility, despite extensive control measures, using beryllium analysis of skin wipes and gloves [7•]. Incorporation of beryllium and isocyanate skin exposure into epidemiologic studies is needed to address skin exposure–disease relationships.

Loss of skin barrier and development of allergy and asthma

Recent studies in the dermatology, allergy and immunology literature also support the hypothesis that skin exposure to occupational and environmental agents may contribute to the development of lung disease. The skin is an active immunologic organ. Repeated skin exposure to numerous substances, primarily metals and certain chemicals are well known to induce contact dermatitis, a delayed-type hypersensitivity reaction in the skin, typically mediated by Th1 CD4+ and CD8+ T cells. Much less is known about skin immune responses to substances that typically induce primarily Th2 sensitization and lung rather than skin disease, such as protein allergens or asthmagenic chemicals.

Several recent studies have suggested that skin exposure to environmental allergens, facilitated by impaired skin barrier function, may promote the development of atopy, atopic dermatitis and eventually atopic asthma, supporting the 'atopic march' hypothesis [26,27]. Mutations in the gene encoding filaggrin, a protein that helps maintain the epithelial barrier, have been shown to impair epithelial barrier function [27]. Several recent genetic studies have found that these filaggrin mutations are associated with an increase risk for atopy, atopic dermatitis and asthma [26,28•]. The highest risk of asthma was in those with atopic dermatitis [28•], supporting the concept that environmental allergens can cross the epidermis barrier and induce Th2-like sensitisation [29]. These findings are consistent with murine models of atopic asthma in which epicutaneous allergen exposure is highly effective at inducing Th2-like sensitization and subsequent lung asthmatic responses following airway challenge [30].

Limited studies on food allergens have also recently focused on the role of skin exposure. Epicutaneous exposure to peanut protein in mice can induce potent Th2-type immune responses and prevent the normal induction of oral tolerance to peanuts [31]. Peanut allergy was associated with the use of skin creams containing peanut oil in an epidemiological study of preschool children [32].

Together these diverse studies support the hypothesis that skin may be an important site for systemic sensitization to certain environmental agents, and that factors that disrupt epidermal barrier function may increase skin exposure, promoting sensitization, asthma and food allergies [33•]. Similarly, in the workplace, host factors such as eczema, as well as co-exposures (e.g. solvents, other chemicals, trauma, hand washing) may enhance trans-epidermal skin uptake of allergens such as isocyanates or beryllium, leading to sensitization and the subsequent development of lung disease following inhalation exposure [29,34].

Conclusion

Recent developments collectively support a greater focus on the role of skin exposure in promoting sensitization and the development of asthma and other primarily immune-mediated lung diseases caused by occupational and environmental exposures. If such exposures contribute to disease, workplace exposure monitoring practices that focus exclusively on airborne exposures may falsely indicate 'safe' exposure levels, and may lead to misdiagnosis or ongoing exposure to the causative agent. Further research is needed to define risks of skin exposure and dose–response relationships, define mechanistic pathways, and develop more effective strategies for prevention. There are sufficient data, however, to conclude that it is prudent to attempt to minimize both skin and inhalation workplace exposures.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest
Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 189–190).

1 Bello D, Herrick CA, Smith TJ, et al. Skin exposure to isocyanates: reasons for
•• concern. Environ Health Perspect 2007; 115:328–335.
This article provides a detailed review of the clinical and animal literature related to isocyanate skin exposure and its potential role in the development of isocyanate asthma.

2 Redlich CA, Karol MH. Diisocyanate asthma: clinical aspects and immunopathogenesis. Int Immunopharmacol 2002; 2:213–224.

3 Kreiss K, Day GA, Schuler CR. Beryllium: a modern industrial hazard. Annu
•• Rev Public Health 2007; 28:259–277.
This article provides a comprehensive review of beryllium exposures, sensitization and chronic beryllium disease.

4 Day GA, Stefaniak AB, Weston A, et al. Beryllium exposure: dermal and
•• immunological considerations. Int Arch Occup Environ Health 2006; 79:161–164.
This article reviews the relevant literature regarding beryllium skin exposure, highlighting the potential importance of beryllium skin exposure in contributing to sensitization.

5 Bello D, Woskie SR, Streicher RP, et al. Polyisocyanates in occupational environments: a critical review of exposure limits and metrics. Am J Ind Med 2004; 46:480–491.

6 Bello D, Sparer J, Redlich CA, et al. Slow curing of aliphatic polyisocyanate
• paints in automotive refinishing: a potential source for skin exposure. J Occup Environ Hyg 2007; 4:406–411.
This study demonstrates that recently dried paints may not be fully cured, and could be a potential source of skin exposure.

7 Day GA, Dufresne A, Stefaniak AB, et al. Exposure pathway assessment at a
• copper-beryllium alloy facility. Ann Occup Hyg 2007; 51:67–80.
This study demonstrates widespread beryllium skin exposure in a beryllium facility despite exposure control measures.

8 Brisson MJ, Ashley K, Stefaniak AB, et al. Trace-level beryllium analysis in the laboratory and in the field: state of the art, challenges and opportunities. J Environ Monit 2006; 8:605–611.

9 Vermeulen R, Stewart P, Kromhout H. Dermal exposure assessment in occupational epidemiologic research. Scand J Work Environ Health 2002; 28:371–385.

10 Warren ND, Marquart H, Christopher Y, et al. Task-based dermal exposure models for regulatory risk assessment. Ann Occup Hyg 2006; 50:491–503.

11 Ban M, Morel G, Langonne I, et al. TDI can induce respiratory allergy with Th2-dominated response in mice. Toxicology 2006; 218:39–47.

12 Vanoirbeek JA, Tarkowski M, Ceuppens JL, et al. Respiratory response to toluene diisocyanate depends on prior frequency and concentration of dermal sensitization in mice. Toxicol Sci 2004; 80:310–321.

13 Herrick CA, Das J, Xu L, et al. Differential roles for CD4 and CD8 T cells after diisocyanate sensitization: genetic control of TH2-induced lung inflammation. J Allergy Clin Immunol 2003; 111:1087–1094.

14 Herrick CA, Xu L, Wisnewski AV, et al. A novel mouse model of diisocyanate-induced asthma showing allergic-type inflammation in the lung after inhaled antigen challenge. J Allergy Clin Immunol 2002; 109:873–878.

15 Tarkowski M, Vanoirbeek JA, Vanhooren HM, et al. Immunological determinants of ventilatory changes induced in mice by dermal sensitization and respiratory challenge with toluene diisocyanate. Am J Physiol Lung Cell Mol Physiol 2007; 292:L207–214.

16 Tinkle SS, Antonini JM, Rich BA, et al. Skin as a route of exposure and sensitization in chronic beryllium disease. Environ Health Perspect 2003; 111:1202–1208.

17 Wisnewski AV. Developments in laboratory diagnostics for isocyanate asthma. Curr Opin Allergy Clin Immunol 2007; 7:138–145.

18 Bello D, Redlich CA, Stowe MH, et al. Skin exposure to aliphatic polyisocya-
• nates in the auto body repair and refinishing industry: II. a quantitative assessment. Ann Occup Hyg 2008; 21 Jan [Epub ahead of print].
This study demonstrated widespread skin exposure to isocyanates in auto body shop workers, even with the use of appropriate protective equipment.

19 Donnelly R, Buick JB, Macmahon J. Occupational asthma after exposure to plaster casts containing methylene diphenyl diisocyanate. Occup Med (Lond) 2004; 54:432–434.

20 Petsonk EL, Wang ML, Lewis DM, et al. Asthma-like symptoms in wood product plant workers exposed to methylene diphenyl diisocyanate. Chest 2000; 118:1183–1193.

21 Pronk A, Yu F, Vlaanderen J, et al. Dermal, inhalation, and internal exposure to
• 1,6-HDI and its oligomers in car body repair shop workers and industrial spray painters. Occup Environ Med 2006; 63:624–631.
This study documented widespread isocyanate exposure under protective gloves worn by spray painters.

22 Fent KW, Jayaraj K, Gold A, et al. Tape-strip sampling for measuring dermal exposure to 1,6-hexamethylene diisocyanate. Scand J Work Environ Health 2006; 32:225–240.

23 Stowe MH, Liu Y, Wisnewski AV, et al. Cross-sectional study of auto body workers exposed to diisocyanates: Does dermal exposure contribute to sensitization? Proc Am Thor Soc 2006; 3:A250.

24 Schuler CR, Kent MS, Deubner DC, et al. Process-related risk of beryllium sensitization and disease in a copper-beryllium alloy facility. Am J Ind Med 2005; 47:195–205.

25 Cummings KJ, Deubner DC, Day GA, et al. Enhanced preventive programme
• at a beryllium oxide ceramics facility reduces beryllium sensitisation among new workers. Occup Environ Med 2007; 64:134–140.
This study demonstrated reduced beryllium sensitization in workers hired after a comprehensive preventive program that included skin exposure.

26 Marenholz I, Nickel R, Ruschendorf F, et al. Filaggrin loss-of-function mutations predispose to phenotypes involved in the atopic march. J Allergy Clin Immunol 2006; 118:866–871.

27 Bonness S, Bieber T. Molecular basis of atopic dermatitis. Curr Opin Allergy Clin Immunol 2007; 7:382–386.

28 Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function
• variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet 2006; 38:441–446.
This study showed an association of filaggrin mutations with atopic dermatitis and asthma, supporting the concept that skin barrier dysfunction increases risk of sensitization to allergens.

29 Proksch E, Folster-Holst R, Jensen JM. Skin barrier function, epidermal proliferation and differentiation in eczema. J Dermatol Sci 2006; 43:159–169.

30 Herrick CA, Xu L, McKenzie AN, et al. IL-13 is necessary, not simply sufficient, for epicutaneously induced Th2 responses to soluble protein antigen. J Immunol 2003; 170:2488–2495.

31 Strid J, Hourihane J, Kimber I, et al. Epicutaneous exposure to peanut protein prevents oral tolerance and enhances allergic sensitization. Clin Exp Allergy 2005; 35:757–766.

32 Lack G, Fox D, Northstone K, et al. Factors associated with the development of peanut allergy in childhood. N Engl J Med 2003; 348:977–985.

33 Callard RE, Harper JI. The skin barrier, atopic dermatitis and allergy: a role for
• Langerhans cells? Trends Immunol 2007; 28:294–298.
This review supports the hypothesis that factors that increase skin barrier dysfunc-
tion, such as frequent skin washing or genetic changes, increase risk of atopic
dermatitis and asthma.

34 Huss-Marp J, Eberlein-Konig B, Breuer K, et al. Influence of short-term
exposure to airborne Der p 1 and volatile organic compounds on skin barrier
function and dermal blood flow in patients with atopic eczema and healthy
individuals. Clin Exp Allergy 2006; 36:338–345.