

State of the Art

Skin Exposure and Asthma Is There a Connection?

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Numerous occupational and environmental exposures that increase asthma risk have been identified. Research and prevention have focused primarily on the respiratory tract. However, recent studies suggest that the skin may also be an important route of exposure and site of sensitization that contributes to asthma development. Factors that impair skin barrier function, such as filaggrin gene mutations or skin trauma, may facilitate allergen entry and promote Th2-like sensitization and subsequent asthma. Animal studies demonstrate that skin exposure to chemical and protein allergens is highly effective at inducing sensitization, with subsequent inhalation challenge eliciting asthmatic responses. A similar role for human skin exposure to certain sensitizing agents, such as isocyanates, is likely. Skin exposure methodologies are being developed to incorporate skin exposure assessment into epidemiology studies investigating asthma risk factors.

Keywords: skin exposure; asthma; isocyanates; epidermal barrier function; sensitization

Environmental and occupational asthma research and practice have focused primarily on the respiratory tract as the key route of exposure and pathogenesis. However, several lines of research support an important role for skin exposure in initiating and driving Th2-like immune responses and asthma. Human and animal studies of atopic dermatitis have identified skin epithelial barrier dysfunction, which may facilitate allergen entry, as a key factor in the development of atopic asthma and sensitization. This article highlights recent findings from a diverse literature that support the concept that skin may be an important site of exposure for certain occupational and environmental allergens.

ISOCYANATES

Isocyanates, a diverse group of reactive chemicals with the functional group NCO, remain one of the most common causes of occupational asthma worldwide. The major commercial isocyanates, methylene diphenyl diisocyanate (MDI), toluene diisocyanate (TDI), and hexamethylene diisocyanate (HDI), and various polymeric forms and prepolymers, are used extensively to produce a wide array of polyurethane coatings, foams, adhesives, and other products (1). MDI, which is less volatile than TDI and HDI, has become the dominant isocyanate produced. End-user settings, such as spray application of uncured polyurethane foams and coatings, likely pose the greatest risk (1). Once “sensitized,”

workers can develop asthmatic responses after inhalation of very low levels, below regulatory standards and detectable levels. Current isocyanate exposures tend to be nonirritating and give few warning signs, and workers may lack adequate skin-protective clothing, such as gloves. The continued occurrence of isocyanate asthma, frequently in settings with minimal airborne levels and opportunities for skin exposure, has raised concerns that isocyanate skin exposure may be an effective route of sensitization and lead to subsequent asthma (2).

SKIN AS AN IMPORTANT ROUTE OF EXPOSURE AND IMMUNE ORGAN

A basic understanding of skin structure and function is needed to appreciate the role skin may play both as an important route of exposure and an immunological organ that can contribute to pulmonary immune diseases. The skin, the largest organ of the human body, serves as an important protective barrier against exogenous exposures and also plays a critical role in the development of allergic diseases, such as atopic dermatitis. The skin is composed of the outer epidermis and the dermis. A cornified layer of lipids and proteins, such as keratins and filaggrin in the epidermis, form the major protective barrier that prevents loss of water and protects against foreign substances. The epidermis also contains keratinocytes and Langerhans cells, a major dendritic cell of the skin that can acquire antigen, migrate to draining lymph nodes, and initiate immune responses (3). The dermis layer of the skin contains the hair follicles, lymphatic and blood vessels, nerve fibers, and connective tissue.

Various factors can affect the extent of absorption of exogenous substances, including lipid solubility, size, concentration, coexposures, skin integrity, hair follicles, and clothing (4). More lipophilic lower molecular weight chemicals, including various vapors, gases, liquids, and aerosols, can be absorbed through the skin and lead to systemic toxicity. Small molecular weight haptens and allergens, such as nickel and urushiol (in poison ivy), can penetrate through the stratum corneum and cause allergic contact dermatitis, a predominantly Th1 T-cell-mediated delayed-type hypersensitivity reaction. The majority of small molecular weight environmental haptens that cause allergic contact dermatitis do not also induce Th2 sensitization and asthma, which typically is triggered by exposure to larger molecular weight protein allergens and certain asthmagenic chemicals, such as isocyanates. Whether human skin exposure to these allergens and chemicals can induce Th2-type sensitization and contribute to the development of asthma is a key question that remains largely unanswered in humans.

LOSS OF SKIN BARRIER FUNCTION AND DEVELOPMENT OF ATOPIC DERMATITIS AND ASTHMA

Human and animal studies over the past few years have implicated impaired skin barrier function as a critical event in the development of atopic dermatitis. One of the best examples

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involves the skin protein filaggrin, which facilitates the terminal differentiation of keratinocytes and formation of the epidermal barrier (5, 6). Genetic studies in several populations have shown that loss-of-function mutations in the filaggrin gene, presumably leading to impaired barrier function, increase the risk for atopic dermatitis, allergen sensitization, and the development of asthma associated with eczema (6, 7). In animal models, filaggrin-deficient mice are more susceptible to epicutaneous sensitization with protein allergen and the development of atopic dermatitis-like skin lesions that exhibited Th-17–dominated skin inflammation (8).

Another epithelial skin protein associated with increased susceptibility to atopic dermatitis-like lesions and asthma is thymic stromal lymphopoietin, which is known to activate dendritic cells and promote Th2-type inflammation (9). In mice with skin barrier defects caused by the ablation of Notch signaling, skin keratinocytes overexpress thymic stromal lymphopoietin and develop atopic dermatitis-like skin inflammation and greater susceptibility to developing asthma after airway allergen challenge (9). The findings suggest that both release of inflammatory mediators by damaged skin and greater allergen exposure contributed to asthma.

Together these animal and human studies have identified key genes involved in epithelial skin barrier function and highlight the importance of skin barrier function in atopic diseases. Filaggrin mutations, although explaining a genetic basis and mechanism for the development of atopic dermatitis and progression to asthma, alone do not explain the marked increase in atopic diseases over the past 2 decades, most likely attributable to a spectrum of interacting environmental factors. The concept that loss of skin barrier function and allergen sensitization via the skin may be critical steps in the development of asthma could provide novel opportunities to prevent asthma. Factors such as frequent use of soaps and cleaners, other skin irritants, physical trauma, heat and low humidity, and glove use (occluded skin) can impair the skin barrier and facilitate allergen entry, sensitization, and asthma (4, 10). It is possible that interventions to improve skin barrier function, such as appropriate skin creams, can reduce asthma risk.

ANIMAL MODELS OF CHEMICAL AND PROTEIN ALLERGEN SKIN EXPOSURE AND ASTHMA

Animal models that have evaluated skin as a site of initial chemical or protein allergen exposure that leads to asthma have focused largely on isocyanates and ovalbumin. Studies in mice, rats, and rabbits with the three major isocyanates (TDI, MDI, HDI) have demonstrated that isocyanate skin exposure can induce systemic Th2-like sensitization and subsequent airway inflammation when followed by inhalation challenge (11–15). These studies have demonstrated that dose, route, and timing of the sensitizing dose are key determinants of sensitization and subsequent asthma. In general, relatively modest and infrequent skin-sensitizing exposure doses, such as single or two-time with 1% isocyanate, are highly effective at inducing Th2-like sensitization (11, 14, 16), and can be more effective than sensitization by inhalation (11, 14, 17). Such exposures are likely comparable to skin exposures that can occur in the workplace. Of note, lower skin sensitizing exposure doses can lead to greater lung inflammation after airway challenge than higher skin doses (11, 16). Transgenic mouse models have also demonstrated that isocyanates can induce mixed Th1/Th2 responses, and that the immune response is also dependent on the mouse strain (13, 15). Similar asthma models involving skin sensitization followed by inhalation challenge have been developed with other chemicals, such as trimellitic anhydride (18).

A recent study evaluated potential “epigenetic-like” effects of maternal skin exposure to TDI (19). The offspring of the female mice who received topical application of TDI were more susceptible to asthma and Th2-like lung inflammation after ovalbumin sensitization and challenge than untreated mice, indicating that isocyanate skin exposure resulted in transmission of greater asthma risk to the mice offspring. Although the mechanisms involved are unclear, these findings might be relevant to the increasing prevalence of asthma (19).

Models of atopic asthma have likewise shown that epicutaneous allergen exposure with ovalbumin is highly effective at inducing Th2-like sensitization and subsequent lung asthmatic responses after ovalbumin airway challenge (20). IL-13 was the major inducer of Th2 responses, being required independent of IL-4 (20). More recent studies have demonstrated that epicutaneous ovalbumin antigen exposure also induces IL-17, which drives the airway inflammation, even in the absence of IL-4 and IL-13 (21). As noted above, mice with impaired skin barrier function are more susceptible to sensitization, atopic dermatitis, and Th2-like lung inflammation after ovalbumin exposure (8, 9).

HUMAN STUDIES LINKING ISOCYANATE SKIN EXPOSURE AND ASTHMA

Clinical and epidemiological studies evaluating the impact of skin exposure to isocyanates (or other allergens) on Th2-type sensitization and subsequent asthma are very limited, despite the observations that isocyanate skin exposure can occur commonly in certain work settings, and may precede the onset of asthmatic symptoms (22–24). Cases of isocyanate asthma and/or sensitization in settings with low airborne isocyanate levels and reported or suspected skin exposure have been reported (22–24). In a study of 214 newly employed MDI-resin workers, new-onset asthmalike respiratory symptoms were associated with liquid MDI skin exposure, determined by questionnaire (24). In an investigation of about 500 coal miners who injected MDI for rock consolidation, about half reported MDI skin exposure (25). The authors concluded that isocyanate skin exposure likely contributed to MDI-IgE and isocyanate asthma in the few workers with findings (25). Studies among other groups of workers are also very limited. A cross-sectional study of 641 tannery workers found that asthma was associated with not wearing gloves (26).

Numerous obstacles make it difficult for epidemiologic studies to more rigorously assess whether skin exposure contributes to asthma risk. Most importantly, methods to sample and quantitate skin exposures generally are not well developed or widely available, unlike airborne exposure methods. Skin exposure assessment is further complicated by factors such as the frequently sporadic nature of skin exposure, uncertain skin uptake, and unknown effectiveness of protective clothing. Thus it is difficult to incorporate skin exposure data into epidemiologic studies to assess whether such exposures contribute to asthma risk (2, 27). Other obstacles include access to exposed workers and the challenge of separating the risks of skin versus inhalational exposures.

For isocyanates, skin exposure has been particularly challenging to document and measure. Isocyanate products, typically complex mixtures of isocyanates with other chemicals, such as solvents, can have highly variable volatility, lipid solubility, and isocyanate content. Exposures can occur as vapors, aerosols, or liquids (2, 28). Use has shifted to less-volatile forms, such as MDI, which reduce risk of respiratory exposure but not necessarily skin exposure (2). Timing of isocyanate sampling is particularly critical as all isocyanate

quantitative methodologies depend on the presence of free unreacted NCO, which also react with water and skin proteins. Uptake and absorption of isocyanate across the epidermal barrier further complicates exposure assessment of isocyanate chemicals that get deposited on a worker's skin.

Despite these challenges, several investigators have recently quantified isocyanate skin exposures in auto body shop workers, spray painters, and foundry workers using several novel sampling and analytical approaches, including skin surface wipe sampling, skin tape tripping, and sampling of inner gloves (29–32). Analysis of consecutive skin tape strips has documented dermal penetration of MDI, and correlations between skin exposure and urinary metabolites support skin uptake (30, 31). These studies have demonstrated frequent skin exposure in several different settings despite the use of standard personal protective equipment, such as gloves (29–32), and that in some work settings skin and respiratory exposures can be independently modeled, potentially enabling the differentiation of skin and respiratory health effects (33). A recent study of auto body shop workers that used this skin exposure model has demonstrated that HDI-specific IgG antibodies were independently associated with both inhalation and skin exposure, suggesting that skin exposure can contribute to isocyanate-specific IgG formation (34). The skin exposure methodologies being developed should greatly facilitate future clinical and epidemiological studies that evaluate the risks of skin exposure, and also the effectiveness of industrial hygiene controls, including protective clothing, in reducing exposures.

CONCLUSIONS

Recent animal and human data collectively support a central role for skin barrier function and skin exposure in the development of Th2-like sensitization and the subsequent development of asthma. The contribution of skin exposure to asthma risk likely varies greatly with different exposures and settings. Improved skin exposure methodologies should facilitate the incorporation of skin exposure assessment into epidemiology studies of asthma to better define exposure risk factors. Further research is needed to define the risks of skin exposure and mechanistic pathways, and to develop more effective strategies for prevention.

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References

- Bello D, Woskie SR, Streicher RP, Liu Y, Stowe MH, Eisen EA, Ellenbecker MJ, Sparer J, Youngs F, Cullen MR, et al. Polyisocyanates in occupational environments: a critical review of exposure limits and metrics. *Am J Ind Med* 2004;46:480–491.
- Bello D, Herrick CA, Smith TJ, Woskie SR, Streicher RP, Cullen MR, Liu Y, Redlich CA. Skin exposure to isocyanates: reasons for concern. *Environ Health Perspect* 2007;115:328–335.
- Callard RE, Harper JI. The skin barrier, atopic dermatitis and allergy: a role for Langerhans cells? *Trends Immunol* 2007;28:294–298.
- Smith Pease CK, White IR, Basketter DA. Skin as a route of exposure to protein allergens. *Clin Exp Dermatol* 2002;27:296–300.
- Leung DY. Our evolving understanding of the functional role of filaggrin in atopic dermatitis. *J Allergy Clin Immunol* 2009;124:494–495.
- O'Regan GM, Sandilands A, McLean WH, Irvine AD. Filaggrin in atopic dermatitis. *J Allergy Clin Immunol* 2008;122:689–693.
- Palmer CN, Ismail T, Lee SP, Terron-Kwiatkowski A, Zhao Y, Liao H, Smith FJ, McLean WH, Mukhopadhyay S. Filaggrin null mutations are associated with increased asthma severity in children and young adults. *J Allergy Clin Immunol* 2007;120:64–68.
- Oyoshi, M. K., G. F. Murphy, and R. S. Geha. Filaggrin-deficient mice exhibit TH17-dominated skin inflammation and permissiveness to epicutaneous sensitization with protein antigen. *J Allergy Clin Immunol* 2009;124:485–493.
- Demehri S, Morimoto M, Holtzman MJ, Kopan R. Skin-derived TSLP triggers progression from epidermal-barrier defects to asthma. *PLoS Biol* 2009;7:e1000067.
- Proksch E, Folster-Holst R, Jensen JM. Skin barrier function, epidermal proliferation and differentiation in eczema. *J Dermatol Sci* 2006;43:159–169.
- Ban M, Morel G, Langonne I, Huguet N, Pepin E, Binet S. TDI can induce respiratory allergy with Th2-dominated response in mice. *Toxicology* 2006;218:39–47.
- Vanoirbeek JA, Tarkowski M, Ceuppens JL, Verbeken EK, Nemery B, Hoet PH. Respiratory response to toluene diisocyanate depends on prior frequency and concentration of TH2-induced lung inflammation. *Toxicol Sci* 2004;80:310–321.
- Herrick CA, Das J, Xu L, Wisniewski AV, Redlich CA, Bottomly K. 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.
- Pauluhn J. Brown Norway rat asthma model of diphenylmethane-4,4'-diisocyanate (MDI): analysis of the elicitation dose–response relationship. *Toxicol Sci* 2008;104:320–331.
- Tarkowski M, Vanoirbeek JA, Vanhooren HM, De Vooght V, Mercier CM, Ceuppens J, Nemery B, Hoet PH. 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–L214.
- Herrick CA, Xu L, Wisniewski AV, Das J, Redlich CA, Bottomly K. 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.
- Rattray NJ, Botham PA, Hext PM, Woodcock DR, Fielding I, Dearman RJ, Kimber I. Induction of respiratory hypersensitivity to diphenylmethane-4,4'-diisocyanate (MDI) in guinea pigs. Influence of route of exposure. *Toxicology* 1994;88:15–30.
- Vanoirbeek JA, Tarkowski M, Vanhooren HM, De Vooght V, Nemery B, Hoet PH. Validation of a mouse model of chemical-induced asthma using trimellitic anhydride, a respiratory sensitizer, and dinitrochlorobenzene, a dermal sensitizer. *J Allergy Clin Immunol* 2006;117:1090–1097.
- Lim RH, Arredouani MS, Fedulov A, Kobzik L, Hubeau C. Maternal allergic contact dermatitis causes increased asthma risk in offspring. *Respir Res* 2007;8:56.
- Herrick CA, Xu L, McKenzie AN, Tigelaar RE, Bottomly K. IL-13 is necessary, not simply sufficient, for epicutaneously induced Th2 responses to soluble protein antigen. *J Immunol* 2003;170:2488–2495.
- He R, Kim HY, Yoon J, Oyoshi MK, MacGinnitie A, Goya S, Freyschmidt EJ, Bryce P, McKenzie AN, Umetsu DT, et al. Exaggerated IL-17 response to epicutaneous sensitization mediates airway inflammation in the absence of IL-4 and IL-13. *J Allergy Clin Immunol* 2009;124:761–770.e1.
- Bernstein DI, Korbee L, Stauder T, Bernstein JA, Scinto J, Herd ZL, Bernstein IL. The low prevalence of occupational asthma and antibody-dependent sensitization to diphenylmethane diisocyanate in a plant engineered for minimal exposure to diisocyanates. *J Allergy Clin Immunol* 1993;92:387–396.
- Donnelly R, Buick JB, Macmahon J. Occupational asthma after exposure to plaster casts containing methylene diphenyl diisocyanate. *Occup Med (Lond)* 2004;54:432–434.
- Petsonk EL, Wang ML, Lewis DM, Siegel PD, Husberg BJ. Asthma-like symptoms in wood product plant workers exposed to methylene diphenyl diisocyanate. *Chest* 2000;118:1183–1193.
- Lenaerts-Langanke H. Isocyanate-induced respiratory disease in coal miners. *Zentralbl Arbeitsmed* 1992;42:2–25.
- Shahzad K, Akhtar S, Mahmud S. Prevalence and determinants of asthma in adult male leather tannery workers in Karachi, Pakistan: a cross sectional study. *BMC Public Health* 2006;6:292.
- Vermeulen R, Stewart P, Kromhout H. Dermal exposure assessment in occupational epidemiologic research. *Scand J Work Environ Health* 2002;28:371–385.

28. Bello D, Sparer J, Redlich CA, Ibrahim K, Stowe MH, Liu Y. Slow curing of aliphatic polyisocyanate paints in automotive refinishing: a potential source for skin exposure. *J Occup Environ Hyg* 2007;4:406–411.
29. Bello D, Redlich CA, Stowe MH, Sparer J, Woskie SR, Streicher RP, Hosgood HD, Liu Y. Skin exposure to aliphatic polyisocyanates in the auto body repair and refinishing industry: II. A quantitative assessment. *Ann Occup Hyg* 2008;52:117–124.
30. Fent KW, Trelles Gaines LG, Thomasen JM, Flack SL, Ding K, Herring AH, Whittaker SG, Nylander-French LA. Quantification and statistical modeling—part II: dermal concentrations of monomeric and polymeric 1,6-hexamethylene diisocyanate. *Ann Occup Hyg* 2009;53:691–702.
31. Liljelind I, Norberg C, Egelrud L, Westberg H, Eriksson K, Nylander-French LA. Dermal and inhalation exposure to methylene bisphenyl isocyanate (MDI) in iron foundry workers. *Ann Occup Hyg* 2010;54:31–40.
32. Pronk A, Yu F, Vlaanderen J, Tielemans E, Preller L, Bobeldijk I, Deddens JA, Latza U, Baur X, Heederik D. 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.
33. Liu Y, Stowe MH, Bello D, Sparer J, Gore RJ, Cullen MR, Redlich CA, Woskie SR. Skin exposure to aliphatic polyisocyanates in the auto body repair and refinishing industry: III. A personal exposure algorithm. *Ann Occup Hyg* 2009;53: 33–40.
34. Redlich CA, Stowe MH, Wang J, Liu J, Gore RJ, Liu Y, Woskie SR, Wisnewski AV. IgG responses to isocyanate in auto body shop workers: associations with skin and respiratory exposures. *Am J Respir Crit Care Med* 2009;179:A3670.