

SKIN EXPOSURE, SYMPTOMS AND ASTHMA IN OCCUPATIONAL SETTINGS – IS THERE A LINK?

Vânia Chongo-Faruk | MD

Division of Occupational Medicine and Centre for Environmental and Occupational Health Research (CEOHR), School of Public Health and Family Medicine, University of Cape Town

Email | vanialarice@yahoo.com.br

ABSTRACT

Occupational contact with allergens through the dermatological and respiratory route can lead to various health effects, including allergic contact dermatitis, urticaria, rhinitis and asthma, which may result in a substantial disease burden in occupational settings. Inhalation is an obvious route for sensitisation and its pathophysiological mechanisms are relatively better defined. Recent studies have suggested that skin exposure may also play an important role in the sensitisation and development of respiratory outcomes in exposed workers. The review found that the evidence for such an association was limited and the immune mechanisms were not well understood. A better understanding of this association is required, more so for agents with a high molecular weight (protein), so as to identify important risk factors that may contribute to existing preventive efforts in reducing the incidence of allergy and asthma in occupational settings.

INTRODUCTION

Diverse immune responses have been associated with various environmental allergen exposures to the skin and these have resulted in the activation of the adaptive immune response.¹ In barrier-disrupted skin, type-2 lymphoid cells, mast cells and basophils are known to trigger pathogenic Th2 responses in murine models.² However, even when the skin barrier is intact; it still has properties that may allow, to some extent, permeability to some allergens. The ‘brick-and-mortar’ model – a schematic explanation of the permeability of the stratum corneum, in which corneocytes are the bricks and lipids are the mortar – presents the stratum corneum as a metabolically active structure with adaptive functions. This could be behind the mechanism in which some allergens could be absorbed by a healthy skin.³

Some epidemiological studies and animal experiments have demonstrated positive associations between skin and respiratory symptoms and positive exposure–response relationships, whereas others have not been able to replicate this.^{4–9}

One of the main issues highlighted by these observations has been the challenges in investigating skin exposure.¹⁰ Methodologies for assessing skin exposure are not as well advanced as for inhalational assessment and exposure

data are limited.^{11,12} In addition, airborne exposure to skin is variable and sporadic and there is uncertainty regarding the extent of skin uptake.¹⁰ Furthermore, most workers are exposed to mixtures of occupational agents, making it difficult to identify the specific exposure responsible for the health outcome of interest. For example, exposure to beryllium and isocyanates typically occurs in mixed exposure settings and these agents may be present in various physical or chemical forms, namely, metal particles, oxides, salts and alloys with copper and other metals.¹⁰

The aim of this literature review is to assess the nature and extent of the associations between skin and respiratory symptoms following skin exposure to sensitisers with a high or a low molecular weight. The review includes all the relevant English publications that were retrieved from PubMed/Medline and Google Scholar. The key search terms that were employed in this review were terms used in other reviews; they included ‘skin’, ‘asthma’ or ‘dermal’, ‘high molecular weight’ or ‘low molecular weight’ and ‘sensitisation’ or ‘dose-response’ or ‘link’. Other terms subsequently added included: ‘allergen’, ‘allergy’, ‘atopy’, ‘occupational’, ‘work-related’, ‘respiratory’, ‘dermatological’ and ‘dermatitis’. Furthermore, some articles were retrieved using the functions ‘similar articles search’ in PubMed and ‘related articles’ in Google Scholar as well relevant articles that were cited in the references of these articles.



Figure 1: Bakery work handling various food proteins (high molecular weight agents)

EPIDEMIOLOGICAL STUDIES

CO-EXISTING OR SEQUENTIAL DEVELOPMENT OF DERMAL AND RESPIRATORY OUTCOMES

Workers in various occupations report both skin and respiratory symptoms. Table I illustrates case study reports in which both dermal and respiratory outcomes (diagnosed using patch tests and inhalation challenge tests respectively) were observed in occupational settings with diverse exposures. These allergens can cause both occupational asthma and allergic contact dermatitis.¹³ To ascertain which health outcome precedes the other can be a challenge because of the nature of the study design used and the lack of a comparison group in such studies.

Arrandale⁴ conducted an analysis of four cross-sectional pooled studies from a soda ash plant, a softwood planing mill, embalming and cabinet-making in which workers were exposed to ammonia, softwood dust, formaldehyde and/or glutaraldehyde and hardwood dust, respectively. Altogether, both skin and respiratory symptoms were reported by 11% (26/236). The highest prevalence of both dermal and respiratory symptoms was seen among embalmers, with no statistical significance.¹³ Although this study does not show temporality, it reinforces evidence of the co-occurrence of both respiratory and dermal symptoms

in occupational settings.¹⁴ Similarly, previous studies among sewage-treatment and isocyanate workers reported a concomitant occurrence of dermal and respiratory symptoms in exposed workers.^{15,16} However, no correlation was found between occupational hand dermatitis and flexural dermatitis, respiratory atopy (allergic rhinitis (AR) and bronchial asthma), serum IgE $\pm$ 100 IU/mL or metal sensitisation in the study of bakers by Bauer et al.¹⁴

Aside from the need to identify temporality, the co-existence of dermal and respiratory symptoms does not necessarily indicate that the same exposure is the trigger for both outcomes, unless the exposure assessment specifically characterised the nature and route of the exposures in affected workers.¹³

ASSOCIATION BETWEEN SKIN EXPOSURE, ALLERGY-SPECIFIC SENSITISATION AND SUBSEQUENT DEVELOPMENT OF RESPIRATORY DISEASE

Table II summarises the few key epidemiological studies that have investigated the role of skin exposure and symptoms and the subsequent development of respiratory symptoms, including asthma, in these workers.

Brisman et al^{17,18} have alluded to the association between bakers' asthma and eczema, without indicating whether sensitisation to wheat flour was due to inhalation or due to contact with allergens through the skin (or both).

In a study of bakers exposed to wheat and autobody-shop workers (ABSWs) exposed to isocyanates, Arrandale et al⁵ demonstrated an association between skin and respiratory symptoms. Work-related itchy skin was associated with wheeze, asthma-like symptoms and work-related asthma symptoms in ABSWs but not in bakers. The authors did, however, indicate that the autobody-shop workers had adhered to much stricter use of personal protective equipment, while such use of personal protective equipment had not been observed by the bakers.⁵ A previous study by Arrandale et al⁴ also found that eczema increases the odds

TABLE I: CO-OCCURRING OCCUPATIONAL ASTHMA (OA) AND OCCUPATIONAL CONTACT DERMATITIS (OCD) – DIAGNOSED USING SPECIFIC INHALATION CHALLENGE AND PATCH TESTING – CASE REPORTS REPORTED

EXPOSURE	OCCUPATION	AUTHOR, YEAR
2-hydroxyethyl methacrylate (HEMA)	Beautician	Moulin et al, 2009
Diglycidyl Ether of Bisphenol A (DGEBA)	Resin applier	Moulin et al, 2009
Diphenylmethane-4,4'-diisocyanate (MDI)	Manufacturing (automotive industry)	Valks et al, 2003
Potassium dichromate	Cement floorer	De Raeve et al, 1998
Aziridine hardener	Painter and varnisher	Kanerva et al, 1995
Onion	Homemaker	Valdivieso et al, 1994
Nickel	Manual grinding of metal castings	Estlander et al, 1993
Spiramycin	Poultry breeder	Paggiaro et al, 1979

Reproduced from Arrandale 2012¹³

TABLE II: STUDIES OF WORKING POPULATIONS INVESTIGATING THE ASSOCIATION BETWEEN SKIN EXPOSURE/SYMPTOMS AND RESPIRATORY SYMPTOMS/ASTHMA

AUTHORS, YEAR	ARRANDALE ET AL, 2013 ⁵	ARRANDALE ET AL, 2012 ⁴	LYNDE ET AL, 2009 ¹⁹	PETSONK ET AL, 2000 ²⁴
Aim of study	To investigate associations between skin and respiratory symptoms in bakery and ABSW	To identify predictors of reporting concurrent skin and respiratory symptoms in a clinical population	To compare the prevalence of occupational cutaneous symptoms among professional indoor cleaners to other building workers (OBW) and their association with exposures and respiratory symptoms	To evaluate the respiratory health of workers exposed to methylene diphenyl diisocyanate (MDI)
Study design	Cross-sectional	Cross-sectional	Cross-sectional	Cohort
Population	723 bakers 473 ABSW	204 patients from the occupational health clinic	549 professional cleaners 593 OBW	214 wood product plant employees (144 completed initial, follow-up and occupational questionnaires)
Agent	Isocyanate and wheat	Multiple agents (animal dander, cement, isocyanates, pesticides, wet work, dust, fumes, paint)	Cleaning agents	MDI
Assessment tool(s)	Questionnaire, IgE for common inhalants, specific challenge tests and personal airborne exposure measurements	Questionnaire	Questionnaire	Questionnaire, serial peak flow, spirometry, methacholine challenge, specific IgE
Skin symptoms prevalence (%)	Work-related itchy skin: ABSW – 9%; Bakers – 17%	Possible work-related skin disease: 82%	Current rash: cleaners - 10%, OBW 6% Rash in the past 12 months: cleaners – 19%, OBW 16% (96)	Not reported
Respiratory symptom prevalence (%)	Work-related asthma symptoms (WRAS): ABSW – 4%; Bakers – 2%	Possible work-related respiratory disease: 18%	In males with rash: • physician-diagnosed asthma – 19% • new onset asthma 14% • ≥3 respiratory symptoms: 77% • ≥2 WRAS: 63% • ≥3 WRAS: 40%	Among the 178 (who participated in at least one follow-up survey): • initial asthma-like symptoms – 11% • follow-up asthma-like symptoms – 20% • new-onset asthma-like symptoms – 12%
Association between skin exposure/symptoms and respiratory symptoms/asthma	Association between work-related itchy skin and respiratory symptoms in: ABSW: • wheeze OR = 2.50 (95% CI 1.7–3.6) • asthma-like symptoms OR = 2.12 (95% CI 1.5–3.0) • WR asthma symptoms OR = 3.61 (95% CI 1.4–9.4) • Bakers: • wheeze OR = 1.60 (95% CI 1.1–2.3) • asthma-like symptoms OR = 1.54 (95% CI 1.2–2.0) • WR asthma symptoms OR = 2.15 (95% CI 0.7–6.3) Exposure-response relationship in ABSW: • itchy/dry skin PR = 1.55, 95 % CI: 1.2–2.0 • work-related itchy skin PR = 1.97 (95 % CI 1.2–3.3)	Eczema increases odds of concurrent work-related skin and respiratory symptoms: OR = 3.68 (95% CI: 1.7–7.8)	Rash in the past 12 months associated with: • physician-diagnosed asthma OR = 2.3 (95% CI: 1.1–4.5) • new-onset asthma OR = 3.0 (95% CI: 1.2–7.6) • ≥3 respiratory symptoms OR = 2.6 (95% CI: 1.6–4.3) • ≥2 WRAS OR = 3.2 (95% CI: 1.9–5.3) • ≥3 WRAS OR = 4.0 (95% CI: 0.2–7.2)	52% of workers who reported MDI skin stains reported asthma-like symptoms
Study limitations	- Poor correlation between airborne and skin exposure for particulates - Lack of information on other, potentially causal, exposures in the workplace - Potential role of Type IV allergy or irritant mechanisms in symptom development not modelled - Healthy worker effect owing to fewer symptomatic subjects at higher exposure levels	- Cross-sectional study – temporality cannot be ascertained - Not generalisable to all workers because of the selective clinical population	- Low response rate - Outcomes (rashes) were self-reported and not clinically confirmed	- Loss to follow-up - Lack of environmental exposure measurements

of concurrent work-related skin and respiratory symptoms. It needs to be borne in mind, though, that this does not necessarily indicate that skin exposure is always predictive of respiratory outcomes.

Lynde et al¹⁹ investigated a group of predominantly male (84%) professional cleaners, 9.3% of them having a rash currently and 18.6% reporting having had a rash in the past 12 months. The study found that cleaners with a current rash and those reporting a rash in the past 12 months were at significantly increased risk of reporting work-related respiratory symptoms compared to those without a rash. This suggested an association between the presence of work-related asthma symptoms and dermatitis among professional cleaners.¹⁹ However, atopy was considered as a possible underlying mechanism for this association, and a lack of personal protective equipment (PPE) use could have also been another factor influencing this association.¹⁹

Isocyanates, used in spray-painting and polyurethane foam products, have received considerable attention in relation to skin exposure and the resulting effects of asthma.^{5,7,10,20,21} A key link for suggesting an association between allergic sensitisation via transcutaneous route for isocyanates and asthma has been the improvement in occupational health standards in workplaces due to the use of respirators to prevent isocyanate inhalation. However, the incidence of isocyanate-induced asthma remains persistently high, particularly in settings where skin contact with isocyanates has not been well controlled.²⁰ A laboratory study by Karol et al²² demonstrated that isocyanate exposure to the skin, particularly TDI, could induce pulmonary hypersensitivity in guinea pigs. Subsequent studies have shown that similar patterns of sensitisation exist in humans.^{1,5,7,23}

PATHOPHYSIOLOGICAL CORRELATES

Several studies in children have suggested that skin exposure and sensitisation precede the response in the airways. Dohi et al²⁵ compared eight atopic dermatitis (AD) patients without a previous report of asthma symptoms and eight mite-allergic asthmatic patients. These two groups were subjected to bronchial inhalation challenges (non-specific with methacholine and specific with house-dust mite (HDM)). Results demonstrated that both IgE and anti-mite IgE antibody were higher in AD patients than mite-allergic asthmatic patients. The response for methacholine in AD patients was from normal to asthmatic range. In a study by Lack et al,²⁶ peanut allergy did not show dependent association with intake of soy milk and soy formula. Peanut allergy was, however, associated with skin rash over the joints and flexures, crusted skin rash, and intake of soy milk and soy formula. In addition, the use of peanut-containing oils on the skin was associated with peanut allergy, suggesting that skin exposure could lead to generalised sensitisation. In more severe form, local skin

contact with certain foods, medications, latex, metals and occupational allergens may result in generalised urticaria or systemic symptoms (angioedema, wheezing).²⁷

It has also been suggested that beryllium sensitisation in those suffering from chronic beryllium lung disease (CBD) may also have percutaneous origins. Tinkle et al²⁸ observed that decreasing inhalational exposure had no effect on the incidence of the disease, suggesting that inhalation was not the only cause for the disease. The investigators suggested that following skin exposure to beryllium, the inhalational exposure to beryllium necessary to elicit an immune response and the formation of a CBD-related granuloma was significantly reduced. In further support of this hypothesis, the topical application of beryllium ointment to C3H/HeJ Heston mice showed an increase in beryllium sensitivity in the mice as determined through beryllium lymphocyte proliferation tests of lymph node and peripheral blood.²⁸ Furthermore, it has been shown that the stratum corneum (SC), the external layer of the skin, which although mechanically strong and resilient to stress and physical strain, may be penetrated by fine and ultra-fine beryllium particles.²⁸

The most refined models demonstrating the link between allergic sensitisation and asthma from skin exposure have been from murine experimental studies. Spergel et al²⁹ applied the high-molecular weight molecule ovalbumin (OVA) via occlusive patch tests to tape-stripped mice skin. This experiment showed an OVA epicutaneous sensitisation and local allergic dermatitis. Later, when the sensitised mice were exposed to intravenous methacholine, the response was eosinophilia in the bronchoalveolar lavage fluid and airway hyper-responsiveness.²⁹

In murine models, it has also been demonstrated that the dermal infiltration of eosinophils in response to dust-mite allergens in skin that has been sensitised by barrier disruption is greater than sensitisation through intact skin.^{29–32} This suggests that there is a higher induction of Th2-dominant immunological responses to environmental allergens through skin that has the skin barrier disrupted, as is experienced in patients with AD,³³ and particularly following rubbing or scratching of skin, compared to intact skin. There is common agreement about Th2 response that allergen exposure requires both the involvement of barrier disruption and an adaptive immune recognition in order to induce an allergic response.^{1,34}

PREDISPOSING FACTORS FOR ALLERGIC RESPIRATORY SYMPTOMS FOLLOWING SKIN EXPOSURE

Several predisposing risk factors could result in sensitisation and to the subsequent development of allergic respiratory symptoms following skin exposure to occupational and environmental allergens.

HOST RISK FACTORS

A. Pre-existing skin diseases

Atopic dermatitis (AD)

The integrity of the skin barrier is intrinsic to an individual's ability to respond to dermal allergen exposure.³⁵ In AD both cellular immune abnormalities and skin-barrier defects are known to be behind its pathophysiological mechanism.³⁶ Various non-invasive biomarkers of epidermal permeability are used to identify increased risk for allergic sensitisation through the skin. Trans-epidermal water loss (TEWL) has been directly, but not exclusively, associated with AD and the associated risk of respiratory allergy.³⁷ Kelleher et al³⁸ found that newborns with raised TEWL were at increased risk of developing AD at one year of age, and also at higher risk of IgE-associated food allergies, despite the absence of early-onset AD. Loo et al³⁹ also demonstrated that children with eczema before 18 months exposed to inhalant allergen (HDM) were more likely to present with positive skin-prick tests (SPT) at 18 months.

Irritant dermatitis

A damaged skin barrier, as is present in irritant dermatitis as a result of either physical, chemical or biological processes, is a potential route of entry for allergens.¹³ Nielsen⁴⁰ demonstrated that skin treated with higher concentrations of sodium laurel sulfate (SLS), a known skin irritant, had greater overall penetration and a greater rate of penetration of chemical substances (pesticides with a wide range of solubility) compared to undamaged skin.

Ichthyosis vulgaris

Bremmer et al³⁵ demonstrated in a study of 491 patients with AD and ichthyosis vulgaris (IV) that those with higher severity of IV were more likely to report asthma, even after adjusting for AD severity, age, sex and season of the occurrence of symptoms. Bremmer suggested that the presence of severe IV could be used as a marker for patients who have a greater likelihood of developing allergic respiratory disease.

Trauma

Skin trauma is another risk factor for facilitating the entry of contact allergens into the body. This may increase a person's risk of sensitisation, as has been observed, for instance, in seafood-processing workers and animal-handling workers (rats), resulting in the development of allergic respiratory symptoms.^{7,10,41}

B. Filaggrin gene mutations

One of the first-line factors associated with skin-barrier deficiencies is Filaggrin (FLG) defects,⁴² which typically occur as a result of inherent FLG gene mutations.⁴³ FLG is an important protein responsible for the strength and integrity of the SC, regulating the permeability of the skin to water and antigens, involved with the packing of keratin filaments in the epidermis, and maintaining the skin's normal acid pH.¹ Studies in the general population

evaluating allergen exposure via skin, sensitisation and respiratory outcomes have been reported.^{43–45} Brough et al⁴⁶ found a positive association between FLG defects and peanut allergy. Filaggrin defects have also been identified in AD patients, and there appears to be a correlation between the extent of FLG defects, the extent of allergen exposure through the skin and the severity of AD.⁴⁶ Loss-of-function mutations in the gene encoding FLG are present in up to 50% of patients with moderate-to-severe AD (in European and Asian populations) and have been shown to increase the risk of inhalant allergic sensitisation, allergic rhinitis (AR), asthma and peanut allergy. In African American populations this defect is rare.^{46,47}

ENVIRONMENTAL RISK FACTORS

Various high molecular weight (generally proteins) and low molecular weight (generally chemicals) allergens are capable of stimulating the induction of IgE antibodies and resulting in sensitisation and the development of allergic respiratory symptoms.⁷ The extent to which they are able to do so will depend on the agent's physical properties, exposure intensity and duration.

A. Agent

Physical properties

Theoretically, liquid and solid allergens will facilitate skin contact and entry in contrast to aerosolised substances. Petsonk et al²⁴ found that after two years of working in a wood-manufacturing plant, subjects who worked with liquid methylene diphenyl diisocyanate (MDI) had a relatively higher risk of reporting asthma-like symptoms than those who did not work with liquid MDI. In addition, those who reported observing MDI skin stains at least once (suggesting skin exposure) also had a higher risk of reporting asthma-like symptoms compared to those who had never observed such stains. However, the prevalence of asthma-like symptoms was more prevalent among workers who reported brief removal of respiratory PPE while performing their routine tasks, which included liquid MDI handling. The investigators concluded that although inhalation was an important route of exposure for the



Figure 2: Spray-painting work with isocyanates (low molecular weight chemicals)

development of the respiratory symptoms, skin exposure may have also played a role.²⁴

Chemical properties (molecular structure)

Transcutaneous chemical penetration also depends on the chemical characteristics of agents. Haptens must be structurally able to bind with a protein as a prerequisite for being recognised by the immune system. While lipophilic properties facilitate skin permeability for allergens,⁴⁰ hydrophilic properties are also needed to allow for movement of the chemical from the SC into the dermis. Therefore an efficient allergen should be amphiphilic (both lipophilic and hydrophilic).⁴⁸ Low molecular weight particles and molecules, such as nickel and poison ivy (urushiol), are known contact allergens that cause skin sensitisation by their action of binding to host proteins in the skin.⁷ As a result of their chemical reactivity with host proteins, these particles cause otherwise innocuous compounds to be converted into hapten–protein complexes that stimulate the adaptive immune response.¹ High molecular weight protein allergens such as peanut, dust mite or water-soluble cat allergens, which range in size from 5 000 Da to 100 000 Da, are generally unable to pass through the skin's cutaneous permeability barrier owing to their size.⁴⁹ In such instances, it is generally understood that sensitivity to such high molecular weight compounds is possible only when the integrity of the skin is to some extent compromised.¹

B. Exposure intensity and duration (dose–response relationships)

Apart from all other conditions that interfere with the skin integrity, the concentration of the agent on the skin surface and the duration of this contact may influence the body's response to an allergen. Some studies involving animal models have investigated trimellitic anhydride (TMA), phthalic anhydride (PA) and MDI and found that increasing the sensitising intradermal doses did not increase a respiratory response. However, Arakawa et al⁵⁰ found a dose-dependent response in guinea pigs for *Dermatophagoides farinae* (DF mite) and a dose–response relationship with increasing doses of intradermally administered TMA eliciting asthma-like symptoms.

Devos et al⁵¹ investigated the asthmagenic capacity of methylisothiazolinone (MI) – a known cause of allergic contact dermatitis commonly used in cosmetics, household products and in different industries – in animal models. Fifteen days after the dermal administration of MI, the subjects did not show a significant respiratory response (either airway hyperreactivity or inflammation). The study concluded that whereas MI was a dermal sensitiser and irritant, it was unable to elicit an asthma-like response.⁵¹

Pauluhn et al⁹ also investigated the dose–response relationship of MDI exposure in animal models and the lung response after primary skin exposure. Surface area or dose-to-body weight did not show specific associations. On

the contrary, the magnitude of the respiratory response was dependent on the frequency of inhalation challenge doses administered instead of the previous cutaneous doses.⁹

CONCLUSION

Skin is an important route of exposure to allergens leading to sensitisation and the potential to cause allergic skin symptoms that could co-exist or precede respiratory symptoms and other systemic health outcomes. However, much still needs to be investigated to enable us to understand better the modes of entry and sensitisation in occupational settings. Particularly among workers exposed to high molecular weight protein allergens, there is a need to ascertain the pathophysiological mechanisms involved in skin exposure that result in respiratory disease and other systemic effects. By addressing these issues, better interventions aimed at preventing occupational exposure to these allergens can be made possible.

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DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict of interest.

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