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Do chronic workplace irritant exposures cause asthma?

Orianne Dumas[1,2] and Nicole Le Moual[1,2]

[1]INSERM, U1168, VIMA: Aging and chronic diseases, Epidemiological and public health approaches, F-94807 Villejuif, France

[2] Univ Versailles St-Quentin-en-Yvelines, UMR-S 1168, F78180 Montigny le Bretonneux, France

Author of correspondence:

Nicole Le Moual
Inserm UMR-S 1168
Aging and chronic diseases. Epidemiological and public health approaches (VIMA)
Bâtiment Leriche
16, avenue Paul Vaillant Couturier
94807 Villejuif Cedex, France
e-mail: nicole.lemoual@inserm.fr
Tel: + 33 1 45 59 50 70
Fax: + 33 1 45 59 51 69

ABSTRACT (190words)

Purpose of review

The present review summarizes the recent literature on the relation between chronic workplace irritant exposures and asthma, focussing on exposures of low to moderate levels. We discuss results from epidemiological surveys, potential biological mechanisms and needs for further research. These aspects are largely illustrated by studies on exposure to cleaning products.

Recent findings

Recent results from nine population-based and workplace-based epidemiological studies, mostly cross-sectional, found an increased risk of both new-onset and work-exacerbated asthma among participants exposed to moderate level of irritants and/or cleaning products.

Summary

Evidence of a causal effect of chronic workplace irritant exposure in new-onset asthma remains limited, mainly because of a lack of longitudinal studies and the difficulty to evaluate irritant exposures. However, recent epidemiological studies strengthen the evidence of an effect of chronic exposure to irritants in work-related asthma. The underlying mechanism remains unknown but may be related to oxidative stress, neurogenic inflammation and dual irritant and adjuvant effects. However, disentangling chronic irritant effects from either acute irritant-induced asthma or immunological LMW agent-induced asthma is difficult for some agents. Further research is needed to improve assessment of irritant exposures and identify biomarkers.

Keywords: irritant-induced asthma, workplace exposures, cleaning agents, disinfectants
(3-5 keywords)

Abbreviations:

COPD: Chronic obstructive pulmonary disease

EGEA: Epidemiological case-control study on the Genetics and Environment of Asthma

ECRHS: European Community Respiratory Health Survey

ETS: Environmental tobacco smoke

FeNO: exhaled nitric oxide fraction

HMW: high molecular weight

HR: hazard ratio

IgE: immunoglobulin E

IIA: irritant-induced asthma

LMW: low molecular weight

OA: occupational asthma

OR: odds ratio

QAC: quaternary ammonium compounds

RADS: reactive airways dysfunction syndrome

RHINE: Respiratory Health In Northern Europe, participants from Northern part of ECRHS

SIC: specific inhalation challenge

SPT: skin prick test

THM: trihalomethanes TRP: transient receptor potential

WEA: work-exacerbated asthma

Text of review: 3107 words

Introduction

Work-related asthma is the most common occupational respiratory disease in industrial countries and the risk of adult-onset asthma attributable to occupation is approximately 15%[1]. Work-related asthma is commonly classified as occupational asthma (OA), induced by exposure to agents at work, or work-exacerbated asthma (WEA), i.e. pre-existing asthma worsened by workplace conditions[2]. The number of identified occupational asthmagens (hazards known to induce asthma) increased regularly from approximately 150 before 2000[3] to probably almost 500 nowadays[4-6].

Occupational asthma may be induced by allergic (sensitizer-induced) and non-allergic (irritant-induced) mechanisms. The prevalence of irritant-induced asthma (IIA) has been scarcely evaluated but might represent 10% to 20% of OA with a trend toward an increase over the past decades[7,8]. For instance, while a decrease in OA incidence has been suggested for well-known causative agents (latex, isocyanates), an increase was observed for cleaning products[9], mostly recognized as irritants[10,11].

Asthma is increasingly considered as a disorder of the airway epithelium, rather than being purely linked to allergic pathways[12]. Less than 50% of asthma is attributable to allergic mechanisms based on atopy or eosinophilic inflammation[13]. Non-allergic asthma, mostly characterized by neutrophilic than eosinophilic inflammation, may be more frequent in persistent adult-onset asthma, but remains less well understood[2,14]. In the context of OA, which is considered a good model to study asthma in general, there is a long-lasting debate regarding whether chronic irritant exposures at a low to moderate level may induce asthma[7,15-17].

The present paper reviews recent advances regarding the role of chronic occupational exposures to irritants in asthma. First, we discuss the current classifications of work-related asthma and the place of possible asthma caused by chronic workplace exposures to irritants. Second, we review epidemiological evidence for the existence of this type of IIA. Then, biological plausibility and challenging aspects regarding identification of respiratory irritants and exposure assessment are discussed.

Irritant-induced asthma among current classifications of work-related asthma

Sensitizer-induced (immunological/allergic) and irritant-induced (non-immunological/non-allergic) asthma are the two physiopathology mechanisms classically proposed for OA (Figure 1). Sensitizer-induced asthma, induced after a latency period (a few weeks to several years), may be classified in two categories: High Molecular Weight agents (HMW) agent-induced asthma and Low Molecular Weight chemicals (LMW) agent-induced asthma (Figures 1 and 2)[1,2,18,19]. HMW agents, most often animal and vegetal sensitizing proteins, are a major cause of allergic asthma in the workplace[20]. They may induce allergic airway inflammation through well-described IgE-dependant immunological mechanisms (Figure 2)[1,6,20], similar to non-work-related asthma caused by common allergens[1,2,18]. In contrast, the underlying mechanism for asthma induced by LMW chemicals, in most cases non-IgE-mediated, is more complex and remains unknown for many agents[1,2,6].

There is no consensus definition for irritant in the context of inhalation injury[15]. Respiratory irritants are noncorrosive substances that may induce airways inflammation, often considered reversible. However, if the level of exposure is high or chronic, the inflammatory processes in the airways tend to become chronic[15]. IIA was, still recently, considered to be induced by a single exposure to a high level of LMW irritants but the mechanism is unknown. A recent review[15] classified IIA in 3 categories (Figure 1): (i) definite, characterized by a rapid onset of asthma within few hours after a single-high occupational exposure to irritants. (ii) probable, induced by multiple high-level exposures to irritants ; (iii) possible, occurring with a latency period after chronic low-to-moderate level exposures. IIA with latency (low to moderate exposure level) cannot be reliably diagnosed in individual workers[21] and may be clinically indistinguishable from immunological OA and WEA[2,16,22].

It is often difficult to classify LMW agents as either sensitizer or irritant[18], as some irritants have sensitizing properties and *vice versa*. Some LMW agents, especially those with highly reactive side chains, may induce immune sensitization after a latency period, whereas others may cause IIA particularly after a high-level exposure[18] (Figure 1). It has been suggested, for some chemicals, that sensitizer and irritant properties might depend on the level/intensity of exposure, with potentially

interlinked mechanisms. For example, diisocyanates, anhydrides, formaldehyde or some disinfectants might act as an irritant and induce an oxidative stress after a high-level exposure and as a sensitizer after a low-level exposure[1,15,23,24].

Epidemiological studies

Vandenplas et al[15] and other authors recently underlined that for IIA with latency ("possible IIA"), causality cannot be ascertained at an individual level but only be inferred from excess risk of asthma observed in epidemiological studies[1,22]. This part will thus summarize results from recent epidemiological studies on irritant exposures, especially cleaning agents and work environments identified at higher risk for possible IIA including metal (aluminium and welders), wood and agricultural workers[15].

Non-specific irritant exposures

In two recent studies, we found associations between exposure to low to moderate levels of irritants, evaluated by the Asthma-specific Job-Exposure Matrix (JEM)[25], and asthma. Irritant exposures included chemicals, combustion particles/fumes, irritant gases/fumes, and/or environmental tobacco smoke. In a French case-control study on asthma (EGEA), an analysis using longitudinal data showed significant associations between chronic exposure to irritants and asthma attacks[26]. In a cross-sectional study among Estonian participants (n=34,015), a significant increased risk of current physician-diagnosed asthma was observed among workers with lifetime exposure to low level of irritants[27]. Interestingly, in both studies, the associations observed for irritant exposures were of similar magnitude, or even stronger than those observed for known HMW or LMW asthmagens.

Cleaning agents

Cleaning agents and disinfectants are among the most common irritants associated with asthma[2,10], with particularly high level and frequent exposures among health-care workers and cleaners[28-30]. They contain numerous chemicals, which may be irritants (e.g., bleach, ammonia) or sensitizers (e.g.,

perfumes)[15,30]. Evidence of their adverse effect in asthma largely comes from workplace studies, but consistent findings were observed in studies on domestic cleaning exposure[30].

We identified seven studies of particular interest on the role of chronic workplace exposures to cleaning products in asthma published in the past two years (2013-2015), mostly cross-sectional: three population-based and four workplace-based studies (Table 1). In population-based surveys[11,31,32], exposure to cleaning agents or disinfectants was evaluated through the Asthma-specific JEM[25]. In the European Community Respiratory Health Survey (ECRHS), the role of exposures to cleaning agents and disinfectants has been studied in both longitudinal and cross-sectional manner[31,32]. Among ECRHS participants in northern Europe (RHINE), an increased risk of new-onset asthma was observed among non-atopic men and women exposed to cleaning products[31]. In ECRHSII, exposure to highly reactive cleaning agents was significantly related to uncontrolled asthma, with stronger associations for long-term compared to recent exposure[32]. In EGEA, lifetime exposure to cleaning products was associated with severe and non-allergic asthma[11]. In the four identified workplace-based studies among healthcare workers and cleaners[33-36], exposure to cleaning agents or disinfectants was based on self-report, except in one survey in which exposure estimates were enhanced by an evaluation of products compounds[33]. In a French study of hospital workers, a higher risk of asthma was observed among nurses compared to administrative staff, especially for those exposed to quaternary ammonium compounds[33]. In a Polish study, almost 60% of the cleaners had work-related allergic symptoms, although skin prick tests and specific IgE antibodies to disinfectants were negative for all subjects[34]. In a U.S. survey, self-reported work-related symptoms were associated with exposure to multi-purpose cleaning products[35]. Finally, results from a two-week panel study among cleaners in Spain, suggested that short-term exposure to irritant cleaning products may exacerbate asthma, especially among non-atopic cleaners[36].

Overall, results from large European studies as well as workplace-based studies support the role of chronic exposure to cleaning products in work-related asthma[27,32,33,35,36]. Although it is difficult to disentangle chronic from high peak exposure effects, in most of these studies, workers were likely to experience chronic, low to moderate exposure to irritants. Results[11,31,34] are also generally consistent with a predominant role of irritant exposures and the hypothesis of non-allergic mechanisms for

workplace exposure to cleaning products, as previously suggested[37,38]. However, very few studies were longitudinal, preventing strong conclusions regarding the role of irritant cleaning products in asthma induction vs. work-exacerbated asthma.

Other work environments with high likelihood of irritant exposures

IIA is also likely to occur among workers in the metal industry. While there is substantial evidence of a higher risk of occupational asthma associated with work in the aluminium production, and in particular with fluorides and dust exposure, no specific immunologic mechanism has been shown[39]. An effect of chronic, moderate level exposures is suggested especially because episodes of accidental peak exposure are unlikely in the aluminium industry[39]. In a longitudinal study of Norwegian smelters, Soyseth et al. found associations between dust exposure, mostly composed of nonspecific airway irritants, and the incidence of work-related asthma symptoms as well as an increased decline in pulmonary function[40,41]. However, it remains difficult to distinguish occupational asthma from work exacerbated asthma symptoms or occupational COPD among smelters[39,41]. In a recent longitudinal study in Northern Europe (RHINE), incidence of asthma and rhinitis were associated with welding[42]. Welding fumes also contain irritants, and non-specific irritating mechanisms may partly explain associations with asthma or rhinitis.

Workers in the furniture and wood manufacturing industry are exposed to a variety of potentially asthmagenic agents, including several types of wood dust, plicatic acid, terpenes, endotoxins, as well as formaldehyde[43]. A recent review reports a clear evidence for an association between work in wood industry and an increased risk of asthma and respiratory symptoms, in particular cough[43]. However, this association is not related to IgE sensitization in most cases. Both irritating effects and non-IgE mechanism for sensitization have been suggested, though they remain unclear.

Similarly, agricultural workers are exposed to many agents at risk for asthma. Although most of them are known allergens (e.g. animal protein, plant, insects, mites), there is a lack of studies on the effect of irritant gases and chemicals (eg, disinfectants, ammonia) exposures, likely to be substantial for instance among dairy workers[44]. In addition, although pesticide exposures have been associated primarily with allergic asthma[45], most pesticides have weak immunogenicity properties but are

irritants[46]. Mechanistic hypotheses regarding the effect of pesticides involve direct airway damage and sustained neurogenic inflammation, possibly interacting with allergen exposure and increasing the risk of developing allergic asthma[46].

Biological plausibility of IIA caused by chronic exposure to irritants

Mechanisms of irritant-induced asthma are poorly known, and hypotheses have been formulated mainly in the context of acute-onset IIA[1,15,17] (Figure 2). We review these hypotheses and their relevance or plausibility in the context of possible IIA due to chronic, moderate exposure.

Injury of the airway epithelium and oxidative stress are likely to play a central role in the pathogenesis of IIA[1]. Mechanism of IIA may be related to a persistent imbalance between antioxidants and pro-oxidants resulting in oxidative stress[1]. Results from murine models of airway injury induced by chlorine, a well-known airway irritant, found increase in markers of oxidative stress after chlorine exposure and an attenuation of the adverse effects of chlorine on airway function by antioxidant treatment[47-49]. These studies also suggested that the oxidative injury was not limited to the acute, direct oxidant effects of chlorine, but was related to a persistent oxidative stress and airway damage, with ongoing production of oxidant species after exposure caused by inflammatory response[47,50]. A predominant role of neutrophilic airway inflammation in this process was recently suggested[50]. Very few studies examined a potential role of oxidative stress in IIA in human. In a study of 92 Spanish cleaning workers, levels of exhaled breath condensate 8-isoprostanes, a specific marker of lipid peroxidation, were not associated with occupational exposures to cleaning products[51]. In contrast, in a study of 723 adults without asthma, we recently showed that occupational exposures to asthmagenic chemicals and irritants, in particular cleaning products, were associated with higher levels of plasma fluorescent oxidation products, a global marker of damage due to oxidative stress, although this association was significant in men only[52]. Of note, in both studies, occupational exposure to irritant was likely to be of low to moderate levels, but repeated or chronic. Mechanisms of airway inflammation promoted by oxidative stress are also actively investigated to elucidate the long term effects of irritants in air pollution[53,54].

Sensory neurons innervating the airways have the ability to sense and react to potentially hazardous substance entering the airways and trigger an immediate protective response, involving respiratory symptoms (cough) and neurogenic inflammation. Beyond this acute response, it has been proposed that chronic stimulation of the nerve endings can lead to long-lasting neurogenic inflammation, which may contribute to asthma[55,56]. Several transient receptor potential (TRP) channels, expressed in neurons but also in different cells of the lung, play a key role in activation of the protective response and mediating inflammation. TRPA1 is of special interest for IIA, as it is activated by numerous irritants, such as air pollution (ozone), exhaust fumes, cigarette smoke or chlorine. Interestingly, several members TRP family, including TRPA1, are also the target of oxidative stress byproducts. In a gene-environment interaction study, the modulating effect of variants in candidate TRP genes on the association between occupational exposure to irritants and cough were investigated[57]. Results suggested that TRPV1 SNPs may enhance susceptibility to cough in subjects with a history of occupational exposure to vapors, gases, dusts, and/or fumes.

Some chemicals are likely to have complex interaction with the respiratory system, with the co-existence of irritant and adjuvant roles[2,58,59]. This dual effect has been demonstrated in a rat model for formaldehyde[59]. The adjuvant effect was evidenced by increased airway responsiveness and a prominent Th-2 type inflammatory response after exposure to increasing dose of formaldehyde in rats immunized to ovalbumin, a common experimental allergen. Increased airway responsiveness, and a prominent Th-1 type reaction, was observed in rats exposed to formaldehyde only, suggesting an irritant effect. The adjuvant role of formaldehyde was also suggested in humans. In a study of mite-sensitized asthmatic patients, exposure to low levels of formaldehyde significantly enhanced bronchial responsiveness to mite allergen[60]. Although the effect of chronic exposure to chemicals cannot be investigated experimentally, it is interesting to note that at least the adjuvant effect of formaldehyde was observed at low concentrations[59,60]. A similar, dual role with both adjuvant and irritant effects could be hypothesized for other asthmagenic chemicals (eg, ortho-phthalaldehyde or quaternary ammonium compounds) for which specific-IgE response has not been evidenced or is rarely observed, but an adjuvant role has been suggested[33,58,61-64]. Hypotheses regarding the mechanisms underlying the

adjuvant effect involve injury of the airway epithelium and increased permeability, facilitating the crossing of the epithelial barrier by allergens[46,60,65]. In a study of Belgian adolescents, attendance of chlorinated swimming pools, a marker of chlorination products exposure, was associated with asthma only among atopic individuals, suggesting an adjuvant effect of chlorine[66]. Attendance of chlorinated swimming pools in childhood was further associated with a decrease in markers of epithelial integrity and permeability[65]. On the other hand, results from a murine model of formaldehyde-induced asthma suggested a key role of TRPA1, TRPV1 and neuropeptides (substance P and calcitonin gene-related peptide) in the adjuvant effect of formaldehyde[67]. The hypothesis of a dual irritant and adjuvant effect is of particular interest for possible asthma due to chronic exposure to irritant as it has been noted that from a clinical point of view, acute-IIA resembles a toxic mechanism, while OA likely due to chronic irritant exposure is similar to sensitizer-induced OA[2,22].

Improvement of evaluation of irritants at risk for asthma in epidemiological surveys

Overall, few epidemiological studies have investigated the role of chronic exposures to irritants at workplace in asthma, partly because assessment of irritant exposures is challenging[61]. In most studies, exposure assessment to specific agents is based on self-report and may induce non-differential or differential misclassification bias[38]. Some studies have evaluated occupational exposures through JEMs but few included case-by-case expert-assessment[29,33,68]. To improve exposure assessment in epidemiological surveys, more precise and objective tools, especially exposure evaluation at task level (e.g. task-exposure matrices, expert-assessment) or quantitative measurements should be developed[37,61]. The use of bar codes of products, linked to their composition, has been recently suggested in the context of domestic exposures, and may also provide a better assesment[69,70]. To evaluate consumer products ingredients, an exposure assessment approach based on exposure scenario (e.g, concentration, frequency, duration, specific exposed rooms), has been recently proposed and illustrated for acetic acid[71]. Other helpful tools, based on quantitative assessments or web based listing of specific known respiratory irritant and sensitizer products, have been described, for instance to

identify asthmagens and compounds of cleaning products[72-74]. The use of large administrative databases such as products bought in industries or hospitals might be also of great interest but have never been used.

For sensitizer-induced asthma, several diagnosis tools are available such as SPT and immunological sensitization test to specific IgE[6], in addition to specific inhalation challenge (SIC) tests[20,75], considered as the gold standard[2,6] but not usable in population-based epidemiological surveys. In addition, the fraction of exhaled nitric oxide (FeNO)[2,75], considered as a non-invasive indirect marker of airway inflammation, have been suggested for allergic-induced diseases[20,76,77]. In two studies, exposure to domestic cleaning products in spray form, potentially including sensitizers (perfumes), was associated with an increase in FeNO level among both adults[76] and children[78] (passive exposure), whereas no association was observed for bleach, a well-known irritant. In contrast, there is no diagnosis tool for possible IIA with latency[15,21]. However, biomarkers of oxidative stress (e.g. isoprostane, fluorescent oxidation products)[52,79] and neurogenic inflammation (e.g. Substance P)[80] might be useful to study IIA with latency.

Identifying specific biomarkers for irritants could be especially helpful. Some biomarkers, mostly urinary ones, have been suggested to evaluate exposure to chlorine-based disinfectants or exposure to drinking water disinfection by-products (e.g. trihalomethanes (THM), haloacetic acids)[81-83]. Such biomarkers, especially THM, might also be relevant to evaluate exposure to cleaning agents as THM exposures during household cleaning tasks were shown to strongly influence urinary THM levels, both in adults and children (passive exposure)[82,84]. However, limitations of some urine biomarkers have been underlined and include rapid metabolic turnover (THM), the choice of urinary collection (24-hours, timed, spot urine samples) and the poor reproducibility of the measured urinary concentrations[81,83-85]. Further research is thus needed to determine relevant biomarkers, for chlorinated as well as non-chlorinated cleaning products.

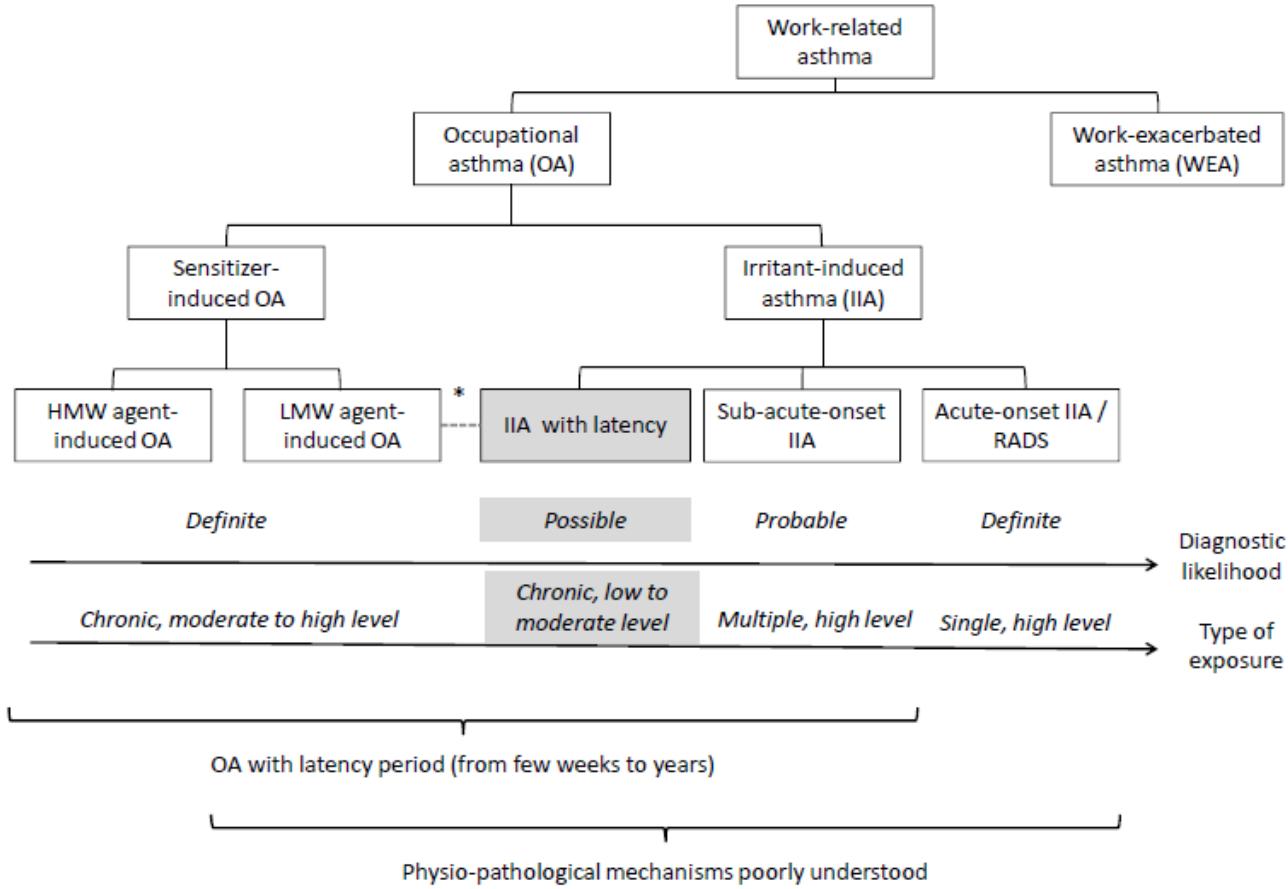
More generally, assessment methods to evaluate occupational exposure especially to irritants need improvement in order to strengthen the evidence regarding the potential role of specific chemicals in

asthma.

Conclusion

Although recent epidemiological studies consistently report an effect of chronic exposure to irritants in work-related asthma, evidence of a causal effect in new-onset asthma remains limited. Our current understanding of possible IIA with latency is limited by the lack of longitudinal studies and the difficulty to disentangle chronic from acute high level irritant exposures. Potential biological mechanisms for IIA with latency include oxidative stress, neurogenic inflammation and an adjuvant effect of some irritants. However, distinguishing IIA with latency from LMW-sensitizer induced OA is difficult for many chemicals. While improvement of irritant exposure assessment is crucial in future research, studies integrating biomarkers and/or investigating biological asthma phenotypes may provide insight into mechanisms of IIA and causality.

Figure 1.Description of various forms of work-related Asthma.

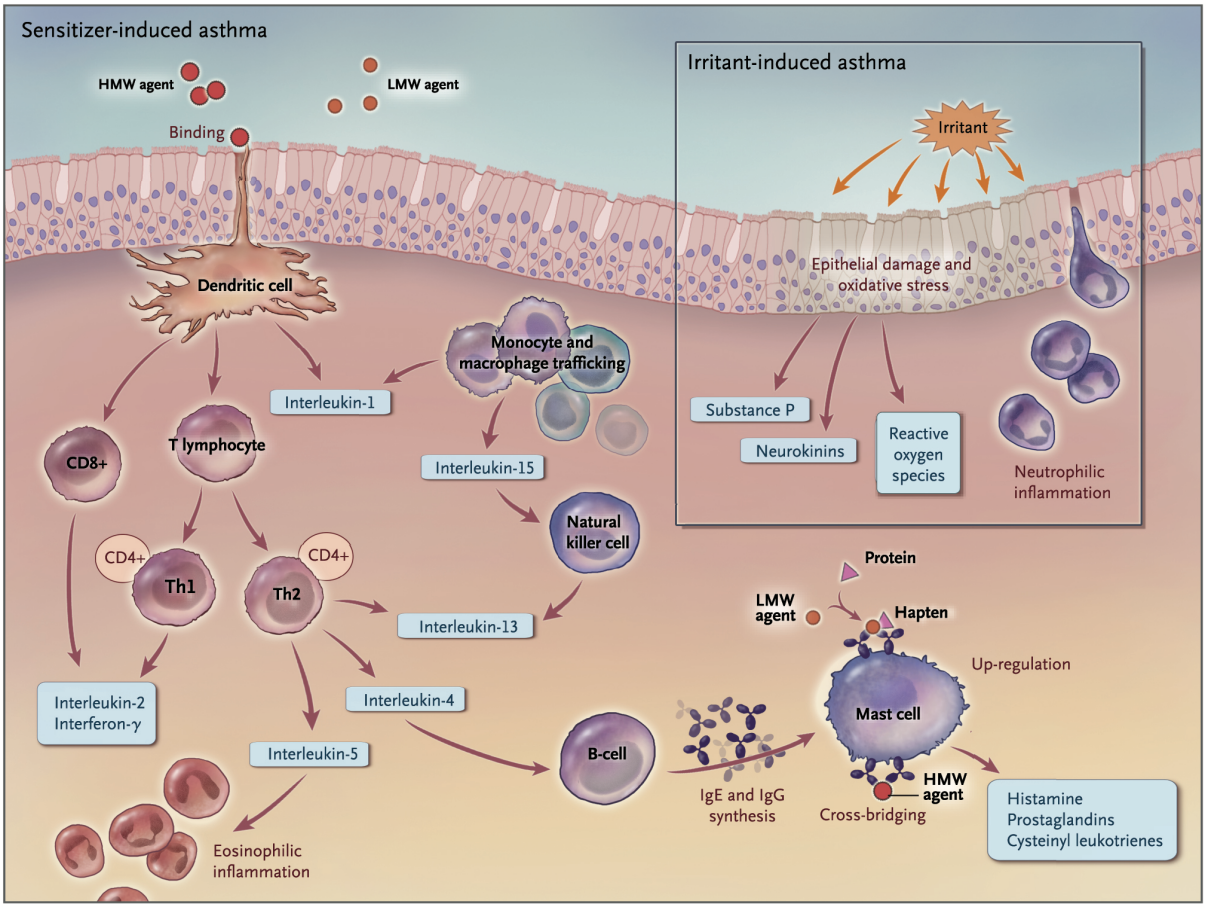


* For many agents (chemicals), it is difficult to distinguish possible IIA with latency from LMW agent-induced asthma

IIA: Irritant Induced Asthma; HMW: High Molecular Weight; LMW: Low Molecular Weight; OA: Occupational Asthma; WEA: Work-Exacerbated Asthma; RADS: reactive airways dysfunction syndrome

Source: adapted from Tarlo SM, et al.[19] (Diagnosis and management of work-related asthma: American College Of Chest Physicians Consensus Statement. Chest 2008; 134:1S-41S) and Vandenplas O, et al.[15] (EAACI position paper: irritant-induced asthma. Allergy 2014; 69:1141-53)

Figure 2: Mechanisms Involved in Sensitizer-Induced Asthma and Irritant-Induced Asthma.



Reproduced from Tarlo SM, Lemiere C. N Engl J Med 2014;370:640-649.

High-molecular-weight (HMW) agents act as complete antigens and induce the production of specific IgE antibodies, whereas the low-molecular-weight (LMW) agents to which workers are exposed that induce specific IgE antibodies probably act as haptens and bind with proteins to form functional antigens. Histamine, prostaglandins, and cysteinyl leukotrienes are released by mast cells after IgE cross-bridging by the antigen. After antigen presentation by dendritic cells, T lymphocytes can differentiate into several subtypes of effector cells. Antigen-activated CD4+ cells can differentiate into cells with distinct functional properties conferred by the pattern of cytokines they secrete. Type 1 helper T (Th1) cells produce interferon-γ and interleukin-2. Type 2 helper T (Th2) cells release cytokines such as interleukin-4, -5, and -13; activate B cells; and promote IgE synthesis, recruitment of mast cells, and eosinophilia. CD8+ cells also release interleukin-2 and interferon-γ and correlate with increased disease severity and eosinophilic inflammation. Innate natural killer cells may also release interleukin-13 in response to products of cell damage. There is evidence that some LMW agents, such as diisocyanates, can stimulate human innate immune responses by up-regulating the immune pattern-recognition receptor of monocytes and increasing chemokines that regulate monocyte and macrophage trafficking (e.g., macrophage migration inhibitory factor and monocyte chemoattractant protein 1). Further interleukin release includes interleukin-1 and -15. Injury to the airway epithelium is likely to play a central role in the pathogenesis of irritant-induced asthma. Oxidative stress is likely to be one of the mechanisms causing the epithelial damage. Inhalation of irritants is likely to induce the release of reactive oxygen species by the epithelium. Furthermore, there may be an increased release of neuropeptides from the neuronal terminals, leading to neurogenic inflammation with release of substance P and neurokinins.

Source : Reproduced with permission from Tarlo SM and Lemiere C[1].

Table 1: Main findings on associations between irritant cleaning-related exposures and asthma or asthma-like symptoms from recent studies (2013-2015)

Reference	Study population	Disease	Exposure assessment	Agents	Main findings
Population-based studies					
Lillienberg L et al, 2013[31]	Longitudinal study, n=13284, women: 53%, RHINE: ECRHS Northern Europe	New onset-asthma	N-JEM (Job Exposure Matrix) : adapted from the Asthma-specific JEM[25]	LMW agents: reactive chemicals, acrylates, epoxy compounds, diisocyantes.; Irritating agents: cleaning products, wood/paper dusts, inorganic dust, metal working fluids, vehicle exhaust, ETS; Accidental irritants peak	Increased risk of new onset-asthma in both men and women exposed to cleaning products (HR: 2.0 [1.2-3.0]) or cleaners, mostly among non-atopics (HR: 2.6 [1.4-5.0]). Increased risks were observed among non-atopic men exposed to acrylates, epoxy compounds, diisocyanates, irritant peaks and among non-atopic women exposed to reactive chemicals. No association was observed among atopic participants.
Dumas O et al, 2014[11]	Cross-sectional study, EGEA2, n=391 women, 48 years in average, France	Adult-onset asthma	Asthma-specific JEM[25]	Lifetime occupational exposure to industrial cleaning and disinfecting products (n=44 exposed *versus* never exposed to 21 agents of the JEM).	Occupational exposure to highly reactive cleaning/disinfecting agents was significantly associated with more symptomatic (OR: 2.8 [1.2-6.4]) and severe asthma. Associations were observed for asthma without positive skin prick test (OR: 3.0 [1.1-8.3]), with a low IgE level, and low blood eosinophil count. Results are consistent with the hypothesis of non-allergic mechanisms for exposure to cleaning products.
Le Moual N et al, 2014[32]	Cross-sectional study, ECRHSII, n=7077 adults, women:52%, 43 years in average, Europe	Current adult-onset asthma, asthma control	Asthma-specific JEM[25]	12-month and 10-years occupational exposure to industrial cleaning and disinfecting products, HMW, LMW agents	Current occupational exposure to highly reactive cleaning agents (OR: 2.0 [1.1-3.6]) and LMW agents were significantly associated with uncontrolled asthma, with stronger associations for long-term exposure (OR: 2.3 [1.4-3.6]). These associations were mainly explained by the exacerbation domain of asthma control.
Workplace-based studies					
Gonzales M et al, 2014[33]	Cross-sectional study, Healthcare workers (cleaners, nurses, administrative), n=543 women: 89%, France	Reported physician-diagnosed asthma and nasal symptoms at work	Self-reported exposure ($\geq$1 per month), products material safety data sheets and workplace observations	Quaternary ammonium compounds (QACs; 75% exposed), Bleach (>50%), Glutaraldehyde (19%) and disinfection tasks	Registered (OR: 5.5 [1.3-23.7]) and auxiliary nurses presented a higher risk of asthma compared to administrative staff, especially those exposed to QACs (OR: 7.6 [1.8-31.0]). Dilution of disinfection products by manual mixing (OR: 4.0 [1.3-12.0]) was the task associated with the highest risk for asthma, suggesting possible repeated peak exposures to irritants.
Lipinska-Ojrzanowska A et al, 2014[34]	Cross-sectional study, n=142 health center cleaners, women : 96%, Poland	Self-reported work-related symptoms	Self-reported by detailed questionnaire	Disinfection tasks, Chloramine T, Chlorexidine, formaldehyde, glutaraldehyde, benzalconium chloride,	Among cleaners 59% had work-related allergic symptoms, 19% positive skin prick tests and 16% Total IgE > 100 IU/ml. Skin prick tests and specific IgE antibodies to disinfectants were negative for all subjects.

Lee SJ et al, AJIM 2015[35]	Cross-sectional study, 183 cleaners in an university medical center, women : 96%, Northern California	Self-reported work-related symptoms associated to monthly use of chemicals to perform cleaning tasks	Self-reported exposures by detailed questionnaire	Work task and specific cleaning products (bleach, solvents, sprays …)	Work-related symptoms were significantly associated to exposure to sprays, solvents, carpet (OR: 3.0 [1.3-6.9]) and multi-purpose (OR: 2.6 [1.1-6.9]) cleaning products.
Vizcaya D et al, 2015[36]	2-week panel study, 21 female asthmatic cleaners with current symptoms; 45 years in average, Barcelona, Spain	Acute upper (URTS) and lower (LRTS) respiratory tract symptoms	Self-reported occupational exposure by a daily detailed questionnaire	Specific cleaning products (bleach, solvents, sprays …); 312 person-days information	Participants reported to use 2.4 cleaning products per day on average, with exposure to at least one strong irritant (eg, ammonia, bleach, hydrochloric acid) on 56% of person-days. Among non-atopics, LRTS were associated with the use of hydrochloric acid (OR: 2.5 [1.0-6.5]) and detergents (OR: 3.4 [1.4-7.5]), which suggest that short-term exposure, to such irritating cleaning products, may exacerbate asthma.

HR: Hazard Ratio; OR: Odds Ratio; JEM: Job Exposure Matrix; HMW: High Molecular Weight; LMW: Low Molecular Weight; URTS: Upper respiratory tract symptoms; LRTS: Lower respiratory tract symptoms.

Key points:
(3-5 key points/sentences that summarize your article)

- Irritant-induced asthma is a poorly understood form of work-related asthma
- Recent epidemiological studies, especially those studying cleaning products, strengthened the evidence of a role of chronic moderate workplace exposures to irritant in work-related asthma
- Distinguishing chronic irritant effects from non-IgE immunological mechanisms is difficult for many chemicals
- Research is needed to improve exposure assessment and to investigate biological asthma phenotypes associated with irritant exposure

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Conflicts of interest
The authors have no conflicts of interest.

Figure legends:
(Attach figures and tables separately)
Fig 1.
Heading: Description of various forms of work-related asthma.

Legend:
* For many agents (chemicals), it is difficult to distinguish possible IIA with latency from LMW agent-induced asthma
IIA: Irritant Induced Asthma; HMW: High Molecular Weight; LMW: Low Molecular Weight; OA: Occupational Asthma; WEA: Work-Exacerbated Asthma; RADS: reactive airways dysfunction syndrome

Source (when reusing previously published figures please ensure they are the same as the original and not adapted): adapted from Tarlo SM, et al.[19]. (Diagnosis and management of work-related asthma: American College Of Chest Physicians Consensus Statement. Chest 2008; 134:1S-41S) and Vandenplas O, et al.[15] (EAACI position paper: irritant-induced asthma. Allergy 2014; 69:1141-53)

Fig 2.
Heading: Mechanisms Involved in Sensitizer-Induced Asthma and Irritant-Induced Asthma.

Legend:
High-molecular-weight (HMW) agents act as complete antigens and induce the production of specific IgE antibodies, whereas the low-molecular-weight (LMW) agents to which workers are exposed that induce specific IgE antibodies probably act as haptens and bind with proteins to form functional antigens. Histamine, prostaglandins, and cysteinyl leukotrienes are released by mast cells after IgE cross-bridging by the antigen. After antigen presentation by dendritic cells, T lymphocytes can differentiate into several subtypes of effector cells. Antigen-activated CD4+ cells can differentiate into cells with distinct functional properties conferred by the pattern of cytokines they secrete. Type 1 helper T (Th1) cells produce interferon-γ and interleukin-2. Type 2 helper T (Th2) cells release cytokines such as interleukin-4, -5, and -13; activate B cells; and promote IgE synthesis, recruitment of mast cells, and eosinophilia. CD8+ cells also release interleukin-2 and interferon-γ and correlate with increased disease severity and eosinophilic inflammation. Innate natural killer cells may also release interleukin-13 in response to products of cell damage. There is evidence that some LMW agents, such as diisocyanates, can stimulate human innate immune responses by up-regulating the immune pattern-recognition receptor of monocytes and increasing chemokines that regulate monocyte and macrophage trafficking (e.g., macrophage migration inhibitory factor and monocyte chemoattractant protein 1). Further interleukin release includes interleukin-1 and -15. Injury to the airway epithelium is likely to play a central role in the pathogenesis of irritant-induced asthma. Oxidative stress is likely to be one of the mechanisms causing the epithelial damage. Inhalation of irritants is likely to induce the release of reactive oxygen species by the epithelium. Furthermore, there may be an increased release of neuropeptides from the neuronal terminals, leading to neurogenic inflammation with release of substance P and neurokinins.

Source (when reusing previously published figures please ensure they are the same as the original and not adapted): Reproduced from Tarlo SM, Lemiere C[1]. (N Engl J Med 2014;370:640-649.)

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Recommended reading:
Papers of particular interest, published within the annual period of review, (18 months/ 2014-2015) have been highlighted as:
• of special interest
•• of outstanding interest
(1) Author, A, Author, B, Author, C et al; Title of reference; Publication name; Year; Volume; Issue; Page numbers
••*an interesting insight into...*
(2)
(3) ...

(1) Tarlo SM, Lemiere C. Occupational asthma. N. Engl. J. Med. 2014;370(7):640-649.

** This review described, with a detailed figure, the complex pathophysiological mechanisms involved in different forms of occupational asthma.*

(2) Vandenplas O, Wiszniewska M, Raulf M, et al. EAACI position paper: irritant-induced asthma. Allergy. 2014;69(9):1141-1153.

*** This review classified irritant-induced asthma in three categories as definite (RADS, an accidental high-level exposure to irritants), probable (induce by multiple high-level exposures to irritants) and possible (chronic low to moderate level exposures to irritants).*

(3) Heederik D. Cleaning agents and disinfectants: moving from recognition to action and prevention. Clin. Exp. Allergy. 2014;44(4):472-474.

** This editorial illustrated the complex mechanism in cleaning-induced asthma and underlined the crucial issue of exposure assessment in epidemiological survey.*

(4) Gonzalez M, Jegu J, Kopferschmitt MC, et al. Asthma among workers in healthcare settings: role of disinfection with quaternary ammonium compounds. Clin. Exp. Allergy. 2014;44(3):393-406.

*** This paper illustrated the role of cleaning products and disinfectant in work-related asthma and underlined ongoing difficulties to disentangle sensitizer and irritant properties of such products.*

(5) Dumas O, Laurent E, Bousquet J, et al. Occupational irritants and asthma: an Estonian cross-sectional study of 34,000 adults. *Eur Respir J.* 2014;44:647-656.

*** This paper provided evidence for the role of chronic workplace irritant exposures at low to moderate level in physician-diagnosed asthma.*

(6) Zholos AV. TRP Channels in Respiratory Pathophysiology: the Role of Oxidative, Chemical Irritant and Temperature Stimuli. *Curr Neuropharmacol.* 2015;13(2):279-291.

** This review summarizes current knowledge on TRP channels in the airways, which have a role in activating response to oxidative and chemical irritant stimuli, and contribute to respiratory diseases. Mechanisms described in this review are of specific interest for a better understanding of IIA pathogenesis.*