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REVIEW

Comparison of high- and low-molecular-weight sensitizing agents causing occupational asthma: an evidence-based insight

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ABSTRACT

Introduction: The many substances used at the workplace that can cause sensitizer-induced occupational asthma are conventionally categorized into high-molecular-weight (HMW) agents and low-molecular-weight (LMW) agents, implying implicitly that these two categories of agents are associated with distinct phenotypic profiles and pathophysiological mechanisms.

Areas covered: The authors conducted an evidence-based review of available data in order to identify the similarities and differences between HMW and LMW sensitizing agents.

Expert opinion: Compared with LMW agents, HMW agents are associated with a few distinct clinical features (i.e. concomitant work-related rhinitis, incidence of immediate asthmatic reactions and increase in fractional exhaled nitric oxide upon exposure) and risk factors (i.e. atopy and smoking). However, some LMW agents may exhibit 'HMW-like' phenotypic characteristics, indicating that LMW agents are a heterogeneous group of agents and that pooling them into a single group may be misleading. Regardless of the presence of detectable specific IgE antibodies, both HMW and LMW agents are associated with a mixed Th1/Th2 immune response and a predominantly eosinophilic pattern of airway inflammation. Large-scale multicenter studies are needed that use objective diagnostic criteria and assessment of airway inflammatory biomarkers to identify the pathobiological pathways involved in OA caused by the various non-protein agents.

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KEYWORDS
Occupational asthma; high molecular weight agents; low molecular weight agents; sputum cells; phenotype

1. Introduction

Work-related asthma represents a significant public health concern because of its high prevalence with an estimated population attributable fraction of 16% in adult asthma [1] and its substantial health and socio-economic impact [2]. Sensitizer-induced occupational asthma (OA) is a distinguishable subset of work-related asthma that is defined as the *de novo* inception of asthma or the recurrence of previously quiescent asthma induced by (identified or presumed) immunological sensitization to a specific substance at the workplace [3,4].

The large number (>400) of substances in the work environment that can cause OA has been conventionally categorized into high-molecular-weight (HMW) and low-molecular-weight (LMW) sensitizers. HMW agents are (glyco)proteins of vegetal, animal, and microbiological origin whereas LMW agents include reactive chemicals, transition metals, drugs and wood dust. This historical classification means implicitly that these two categories of agents are associated with distinct clinical phenotypes and pathophysiological mechanisms [5]. Nevertheless, both HMW and LMW agents induce a form of asthma characterized by the clinical features of allergic hypersensitivity, including: 1) onset of work-related symptoms after an initial asymptomatic 'latent' period of exposure during which immune sensitization is thought to develop; 2) recurrence of asthmatic reactions upon exposure to the sensitizing agent at concentrations not affecting other similarly exposed workers; and 3) development of the disease in only a minority of those exposed to the agent [6].

The aim of this review was to use an evidence-based approach, to compile and critically address the available information to identify similarities and differences between HMW and LMW sensitizing agents in terms of the phenotypic, pathophysiological, and epidemiological characteristics of associated OA. The ultimate goal is to determine whether the existing distinction between these two broad categories of agents is scientifically grounded and relevant for clinical practice and research in the field of OA.

2. Methods

We conducted a comprehensive review of original publications that were relevant to the comparison of OA caused by HMW agents and LMW agents with respect to clinical manifestations, pathophysiology, and epidemiology, as well as environmental and individual risk factors. A PubMed search was performed using the keywords 'occupational asthma' and 'molecular weight.' This literature search identified 433 articles published up to August 2023, of which 32 involved a direct comparison between HMW and LMW agents, although these publications pertained only to the comparison of clinical and functional characteristics and inflammatory biomarkers. For the other predefined domains relevant to this comparison

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Article highlights

- This review provides strong evidence that high-molecular-weight (HMW) agents causing occupational asthma are associated with a few distinct phenotypic characteristics compared with low-molecular-weight (LMW) agents. However, LMW agents may exhibit some of these 'HMW-like features,' indicating that LMW compounds represent a heterogeneous group.
- Evidence is convincing that atopy, baseline nonspecific bronchial hyperresponsiveness, and smoking are significant risk factors for the inception of IgE-mediated sensitization and occupational asthma caused by HMW agents, but atopy and smoking are also associated with an increased risk of IgE-mediated sensitization to some LMW agents (i.e. platinum salts and acid anhydrides).
- Regardless of the presence of detectable specific IgE antibodies, both HMW and LMW agents are associated with a mixed Th1/Th2 immune response and a predominantly eosinophilic pattern of airway inflammation upon exposure to the causal agent.
- The conventional classification of the sensitizing agents causing occupational asthma into HMW and LMW agents is arbitrary and the threshold molecular weight differentiating these two groups of agents has never been substantiated; labeling these two categories of agents as 'protein agents' vs. 'non-protein agents' seems more meaningful in terms of the chemical nature of the sensitizing agents.

(i.e. pathophysiology, epidemiology, and risk factors), we conducted additional searches in the authors' personal digital bibliographic libraries using specific keywords. The publications cited in the reference lists of the retrieved studies as well as review articles were carefully scrutinized in order to identify other potentially relevant reports.

Whenever feasible, the level of evidence for each outcome of interest was graded according to the Royal College of General Practitioners modified three-star system which was adapted to the field of OA [7] (Table 1). The quality of available studies was categorized by consensus among the authors as 'high quality' or 'lower quality' using criteria based on study design, tools used to identify OA, quantitative assessment of exposure, and control for potential covariates in the analysis of results. For the context of this review, we considered as 'high quality' studies meta-analyses or systematic reviews and any study design that fulfilled at least one of the following criteria: 1) appropriate control for potential confounding covariates in the data analysis; 2) quantitative assessment of exposure to occupational agents; or 3) objective evidence supporting the diagnosis of OA (i.e. assessment of IgE-mediated sensitization in the case of HMW and some LMW agents and/or functional assessment through the measurement of nonspecific bronchial hyperresponsiveness (NSBH) and/or the monitoring of peak expiratory flow rates (PEF) at work and away from work and/or specific inhalation challenges (SIC) in the laboratory). Studies were considered as 'concordant' when consistent findings were derived from independent cohorts of participants. Consensus was reached through an informal iterative process among authors.

3. Historical perspective

HMW proteinaceous agents were the first to be described as causes of OA [8]. In 1928, Figley and Elrod described an endemic onset of asthma in the population of Toledo, Ohio, that was exposed to dust 'blown out into the air' by a mill producing castor oil from castor beans [9]. Thirty individuals with new-onset asthma living in the vicinity of the oil mill exhibited cutaneous reactions to scratch testing with a castor bean dust extract, providing evidence supporting an underlying hypersensitivity mechanism. In the 1930s and 1940s, vegetable gums (i.e. acacia [gum arabic], karaya and tragacanth) [10,11] and insects [12] were identified as causing OA, with the underlying mechanism substantiated by positive skin-prick test (SPT), passive transfer experiments and later by the presence of specific IgE antibodies (sIgE). In the late 1960s and 1970s, an epidemic of OA due to sensitization to enzymes among workers manufacturing detergent powders was documented [13,14].

Although OA was initially associated with exposure to proteinaceous materials acting through an IgE-mediated allergic mechanism, as described above, LMW agents also became increasingly identified as a common cause of OA. Chromium and platinum salts were the first LMW agents to be documented as causing OA in the 1930s [15] and 1940s [16]. In a study by Joules et al. intradermal injection of potassium bichromate resulted in a local skin allergic reaction and an asthmatic reaction, suggesting a 'specific allergic asthma due to chrome sensitization' [15]. The role of platinum salts in the development of OA was later supported by Pepys and coworkers who elicited positive SPT reactions to low concentrations of ammonium hexachloroplatinate and tetrachloroplatinate in eight out of ten workers who developed an asthmatic reaction during occupational-type inhalation challenge with platinum salts in powder form [17]. In 1939, Kern published an account of a chemist worker exposed to phthalic anhydride who developed OA [18]. This worker had a positive skin response to scratch skin testing with this occupational agent and his serum contained 'reagins' as shown by passive transfer. Phthalic anhydride was therefore the first reactive chemical identified as causing OA, followed by

Table 1. Grading of evidence.

Strength of evidence	British occupational health foundation grading scheme for occupational asthma*	Criteria used in this review
+++ (strong evidence)	At least 2 independent high-quality studies or a good systematic review	1 systematic review/meta-analysis or ≥2 concordant high-quality studies
++ (moderate evidence)	1 high-quality study and at least 2 studies with medium quality	1 high quality study
+ (limited evidence)	At least two studies with medium quality	≥2 concordant lower quality studies
- (very weak evidence)	No studies that meet criteria for quality or contradictory	1 lower quality study
C (contradictory)	No conclusions can be drawn when there are studies of the same quality whose finding contradict one another	Discordant lower quality studies

Note: *Reference [7].

diisocyanates, which remain a common cause of OA, although the mechanism of sensitization is uncertain [19]. OA due to Western red cedar wood dust was highlighted in 1969 [20], and the LMW agent plicatic acid was identified in 1973 as the causal agent by demonstrating that SIC with plicatic acid could induce asthmatic reactions in subjects with red cedar asthma [21].

Davies and coworkers [22] and Butcher [23] were the first to use the term 'LMW chemical agents' as a distinction from protein allergens and highlighted the importance of these compounds as a cause of OA in the context of increasingly complex industrial processes. In a state-of-the-art review on OA published in 1986 by Chan-Yeung and coworkers [24], the term 'HMW compounds' referred to 'organic compounds, such as proteins, polysaccharides, glycoproteins, and peptides' that can induce 'allergic bronchoconstriction' by producing sIgE antibodies which can be demonstrated by SPT and serum sIgE antibodies assays. The authors also referred to LMW compounds (i.e. isocyanates, acid anhydrides, wood dusts, metal salts, soldering fluxes, and drugs) under the mechanism of 'allergic bronchoconstriction.' Regarding HMW agents, Bush [11] stated that 'this arbitrary classification designates sensitizing agents that most often are proteins or glycoproteins with molecular weights > 20 kDa.' Other authors proposed threshold molecular weights differentiating HMW from LMW agents that ranged from 1 kDa [24,25] to 10 kDa [3,26], whereas some authors failed to propose a precise threshold value [5,22,23,27,28]. It could be speculated that this threshold molecular weight should refer to the minimal molecular mass required for cross-linking two sIgE molecules bound to the surface of mast cells, basophils, and other immune cells, but the distinction between HMW and LMW agents was initially made at a time when few HMW protein allergens had been characterized [29]. Among currently characterized allergens that are potentially involved in OA, as reviewed by Raulf and coworkers [30], the lowest molecular weight (*World Health Organization and International Union of Immunological Societies Allergen Nomenclature Sub-committee*, available at *www.allergen.org*) is 6 kDa for hevein from natural rubber latex (*Hev b 6.02*). Accordingly, a threshold value of 5 kDa would probably be the most appropriate for distinguishing HMW from LMW agents. Nevertheless, the authors of this review would favor labeling the two types of agents as 'protein agents' vs. 'non-protein agents' because this categorization is more meaningful in terms of the chemical nature of the sensitizing agents.

Currently, more than 400 substances used at work have been documented as inducing OA (updated list of causal agents and occupations available at *https://reptox.cnesst.gouv.qc.ca/en/occupational-asthma/Pages/occupational-asthma.aspx*). Recognition of potential respiratory sensitizers, both HMW and LMW, has been steadily growing, e.g. among workers exposed to cleaning materials containing biocides [31,32], epoxy compounds [33], pharmaceutical and cosmetic products [34,35], edible insects [36], and greenhouse cultivation [37,38]. Nevertheless, data derived from the European network for the PHenotyping of OCcupational ASthma (E-PHOCAS) cohort for the period 2006–2016 [39] as well as older data derived from voluntary notification programs and compensation statistics of OA in various countries [40], show that cereal flour and isocyanates account for approximately half of reported cases.

The distribution of causal agents may vary across geographical areas, however, depending on the pattern of industrial activities. For instance, the development of aquaculture and seafood harvesting and processing has led to increasing seafood-induced OA in developing countries [41]. Variations in the burden of causal agents over time also have been documented mostly because of the implementation of preventive strategies aimed at reducing the incidence of OA attributable to enzymes in the detergent industry [42], isocyanates [43], and natural rubber latex [44].

4. Clinical characteristics

The clinical and functional characteristics of OA caused by HMW and LMW agents are compared in Table 2 [39,45–65], and the differences in the pattern of the bronchial responses elicited by the two categories of agents are presented in Table 3 [39,49,54–56,59–61,66–70]. Available data provide strong evidence that, compared with LMW agents pooled together, HMW agents are associated with a higher prevalence of concomitant work-related rhinitis/conjunctivitis and immediate asthmatic reactions upon exposure to the causal agent compared to LMW agents. LMW agents, in turn, more frequently induce late and atypical asthmatic reactions. However, the investigation of subsets of the E-PHOCAS cohort demonstrated that OA caused by LMW acrylate compounds and platinum salts also was associated with a high rate of work-related rhinitis compared with other LMW agents [51,52].

Findings pertaining to the impact of the type of agent on asthma severity at the time of diagnosis have been inconsistent, probably because investigators have used varying indices for grading the severity of asthma, including symptoms, medication, spirometry, and the level of NSBH (Table 2) [71]. None of the included studies assessed the level of asthma control using validated instruments and only one study compared the rate of severe exacerbations in OA caused by the two categories of agents [57]. A substantial body of data, however, indicates that the type of causal agents affects the outcome of OA after avoidance of exposure (Table 2). A meta-analysis of follow-up studies published up to 2004 (28 studies, 695 patients) showed that the pooled estimate of persistent NSBH at follow-up assessment was higher among subjects with OA due to HMW agents, but the type of causal agent did not affect the pooled prevalence of symptomatic recovery [63]. The authors of a systematic review published in 2012 also concluded that there is 'moderate evidence' that subjects with OA caused by HMW agents are more likely to have persistent NSBH compared with OA caused by LMW agents [64].

5. Pathophysiological mechanisms

It is widely acknowledged that HMW agents act through a documented IgE-mediated mechanism, whereas the immunological mechanisms involved with LMW agents remain largely uncertain [5]. The similarities and differences in sensitization potential, immune response, and pattern of airway inflammation between the broad categories of HMW and LMW agents are discussed in this section. A separate section (section 8 and

Table 2. Clinical and functional characteristics of occupational asthma due to high- vs. low-molecular weight agents.

Characteristics	High-molecular-weight agents	Low-molecular-weight agents	Level of evidence
Associated work-related disorders:			
Rhinoconjunctivitis	• Higher prevalence [45]* [46]* [47]* [48]* [49]* [39]* • More intense symptoms [50]* [47]* • More often precedes the onset of asthma [50]* [47]* [48]*	• Higher prevalence compared to other LMW agents: acrylates [51]*, platinum salts [52]*	+++
Urticaria	• More frequent but not significant in multivariate regressions [39]		-
Contact dermatitis		• More frequent [53]* • No difference between HMW and LMW agents [39]*	C
Asthma-related outcomes:			
Latency period before onset of symptoms		• Median/mean latency period: - Shorter for WRC compared to HMW agents and isocyanates [54]* - Longer for LMW agents [55]* - No difference between HMW and LMW agents [56]* [49]* [39]*	C
Asthma symptoms		• More often chest tightness at work [39]*	++
		• More frequent daily sputum at work [39]*	++
Asthma severity	• Daily dose of inhaled corticosteroids: No difference between HMW and LMW agents [56]* [39]* • Severe asthma (ERS/ATS definition) ‡: No difference between HMW and LMW agents [57]*	• Moderate-severe asthma (i.e. FEV_1 <70% predicted or PD_{20} methacholine ≤300 µg): No difference between HMW and LMW agents [58]* • Moderate-severe persistent asthma (GINA classification): Higher risk with LMW agents [49]*	C
Asthma control		• Exacerbations: More frequent with LMW agents [39]*§ [57]*§	+
Baseline airway obstruction	• More marked [39]* • No difference between HMW and LMW agents [59]* [56]* [49]* [57]*		C
Baseline NSBH	• Lower degree of NSBH [60]* [61]* • No difference between HMW and LMW agents [59]* [56]* [49]* [57]*		C
Outcome of asthma after avoidance of exposure	• More frequent persistence of NSBH after cessation of exposure [62]* [63]† [64]† but no difference in the rate of symptom recovery [63]† • No effect on time trend in NSBH recovery [65]*		+++

Notes: *C*, contradictory findings; *FEV_1*, forced expiratory volume in one-second; *GINA*, global inititiative for asthma; *HMW*, high-molecular-weight; *LMW*, low-molecular-weight; *NSBH*, nonspecific bronchial hyperresponsiveness; *PD_{20}*, provocative dose of methacholine causing a 20% fall in forced expiratory volume in one-second; *SIC*, specific inhalation challenge; *WRC*, Western red cedar.
*High quality studies (see methods).
†Meta-analysis.
‡Definition of severe asthma adapted from the European Respiratory Society/American Thoracic Society criteria [225] requiring a high-level treatment (i.e. GINA treatment step 4–5) together with any one of the following criteria indicating uncontrolled asthma: (1) poor symptom control; (2) 2 or more severe exacerbations in the previous year; or (3) airflow obstruction.
§Two subsets of the same cohort.

Table 8) highlights the clinical and pathophysiological characteristics of some 'atypical' LMW agents.

5.1. Sensitization potential and immune responses

HMW sensitizing agents are (glyco)proteins that can elicit a sIgE-mediated Type I hypersensitivity reaction similar to that induced by ubiquitous inhalant allergens causing allergic asthma in the general population [83]. In clinical practice, however, sIgE-mediated sensitization to HMW agents is not always documented through SPT or serum sIgE assay because of the lack of standardized and validated extracts or reagents for most HMW occupational agents [84,85]. Systematic reviews feature pooled sensitivity estimates of 73% for SPT [86] and 74–81% [72,86] for sIgE to various HMW agents.

Although many HMW occupational allergens have been characterized at the molecular level [30], uncertainty persists with regard to the structural, functional, and biochemical features that explain how an innocuous protein becomes an allergen. Growing evidence from *in vitro* and animal model experiments indicates that nonoccupational allergens with proteolytic or lipid-binding properties can interact directly with epithelial cells facilitating allergen delivery to antigen-presenting cells and with Toll-like receptors (TLR)4 and the innate immune system, thereby promoting Th2 immune responses and airway eosinophilia [87,88]. With regard to HMW occupational allergens, serine protease activity was shown to be key to the induction of Th2 cytokine release and airway eosinophilia in a mouse model of allergic airway disease caused by subtilisin, an enzyme causing OA in the detergent industry [89]. Emerging evidence indicates that

Table 3. Pattern of bronchial response to high- vs. low-molecular weight agents during specific inhalation challenges.

Characteristics	High-molecular-weight agents	Low-molecular-weight agents	Level of evidence
Duration of exposure required to elicit an asthmatic reaction		• Longer for LMW agents [60]* [66]* [49]* [67]*	+++
		• No difference between HMW and LMW agents for immediate reactions [68]*	++
Pattern of asthmatic reactions	• More often immediate reactions [54]* [59]* [55]* [56]* [61]* [49]* [67]* [39]*	• More often late reactions [54]* [59]* [55]* [56]* [61]* [49]* [67]* [39]*	+++
		• More often atypical reactions: isocyanates [60]*; various LMW agents [59]* [61]*	+++
Time course of immediate reactions	• Maximum fall in FEV_1: Earlier (10 min) for HMW agents than for LMW agents (20 min) [68]* • Median timing of FEV_1 recovery: Shorter for HMW (60 min) than for LMW agents (90 min) [68]*	• More often followed by a late asthmatic reaction for LMW agents (37%) than for HMW agents (26%) [68]*	++
Magnitude of asthmatic reactions		• Requiring pharmacological treatment: Higher risk with LMW agents [69]* • Greater maximum FEV_1 fall with isocyanates compared to HMW agents and WRC [60]* • No difference between HMW and LMW agents [59]* [67]*	C
Increase in NSBH after a positive SIC		• Significant increase in NSBH more frequent after reactions to LMW agents: [59] * [68]* [61]* Meca, 2016 #8873}* • No difference between HMW and LMW agents [60]* [56]* [39]*	C†
Fever after a positive SIC		• More frequent compared to HMW agents [70]*	++

Notes: *FEV_1*, forced expiratory volume in one-second; *HMW*, high-molecular-weight; *LMW*, low-molecular-weight; *NSBH*, nonspecific bronchial hyperresponsiveness; *SIC*, specific inhalation challenge.
*Finding further supported by controlling for potential confounding factors.
†Postchallenge changes in NSBH are associated with the temporal type of asthmatic reactions and not the type of agent.

during airway sensitization to parvalbumins from cod other than allergenic proteins, such as non-protein components with a molecular weight < 3 kDa present in the fish-derived organic matter may act as adjuvants [90]. Resistance to degradation by physical or chemical treatments during industrial or manufacturing processes also may be important in sIgE-mediated sensitization to substances used at work. This is best illustrated by the persistence of allergenic epitopes derived from the *Hevea braziliensis* tree in natural rubber latex despite treatment with ammonia and vulcanization at high temperature [30].

In contrast to protein allergens, LMW agents are incomplete antigens (i.e. haptens) that must bind to carrier macromolecules to become immunogenic [83]. Mechanistic chemistry studies have identified 'structural alerts' in organic chemicals that are related to covalent protein binding and a high risk of respiratory sensitization, particularly when multiple functional groups are present within the same molecule [91]. These multiple reactive groups can react simultaneously with different amino acids present on the native human proteins, leading to intra-molecular cross-linking, conformational changes, and the production of neo-epitopes within the protein molecules [92]. Quantitative structure-activity relationship models have been generated from statistical comparisons of the molecular features of organic chemicals with and without documented potential for inducing OA [92]. These models allow for prediction of the asthmagenic potential of chemicals with an estimated sensitivity of 90% and a specificity of 96% [92]. LMW sensitizing agents also include salts of transition metals, such as platinum and cobalt, whose asthmagenic mechanism is thought to involve coordination bonding with human proteins [93].

Specific IgE antibodies have been detected in a minority of subjects with OA attributable to the most prevalent LMW agents, such as isocyanates and persulfate salts. Nevertheless, some LMW agents (i.e. platinum salts, acid anhydrides, reactive dyes, chloramine-T, and some wood species) are associated with positive SPT or sIgE antibodies in most affected subjects (see section 8 and Table 8). Systematic reviews have yielded pooled sensitivity estimates around 30% for sIgE against various LMW agents, but importantly, the specificity of these sIgE antibodies was high (~90%) compared with the SIC, supporting their role in at least a fraction of affected subjects [72,86]. The role of sIgE-mediated immune responses in the development of OA caused by LMW agents remains an important but controversial topic. However, the absence of detectable sIgE antibodies against most of the LMW compounds may result from technical limitations for their identification [94]. Most immunologic studies have so far focused on diisocyanate conjugated to human serum albumin (HSA) as a carrier protein. However, such conjugates can differ substantially depending on the methods used for their production [94,95]. In addition, other proteins, such as keratins, have also been identified as diisocyanate-conjugates in human endobronchial biopsy samples following *in vivo* inhalation of diisocyanates [94]. Accordingly, labeling OA due to LMW agents as 'IgE-independent' asthma may be an oversimplification.

Knowledge of the pathophysiological mechanisms of LMW-induced OA is limited and mainly based on isocyanate-induced asthma studies. Maestrelli and coworkers [96] found increased numbers of cells expressing interleukin (IL)-4 and IL-5 in bronchial biopsies performed 48 h after challenge exposure to isocyanates, supporting a Th2-type of response,

whereas expression only of IL-5 was increased when the subjects were not exposed. Exposure to diisocyanate also can induce transient activation of a subset of $CD8^+$ lymphocytes in bronchial mucosa producing interferon-gamma and IL-5 [97]. A mouse model of isocyanate-induced OA confirmed that both Th1 and Th2 type immune responses are involved by showing that intranasal challenge of sensitized mice resulted in airway eosinophilia, mucus hypersecretion, and production of Th1-type (interferon-gamma) and Th2-type (IL-4, IL-5, and IL-13) cytokines by lung inflammatory cells [98]. Remarkably, Mamessier and coworkers [99] found that SIC with both HMW and LMW agents induced a mixed Th2/Th1 response in blood and sputum samples of subjects with OA.

The lack of detectable sIgE in most cases of OA arising from exposure to LMW agents, however, has led to investigate the role of alternative, non IgE-mediated, cellular immune mechanisms. In vitro studies have demonstrated that stimulation of human monocytes by isocyanate-HSA conjugates results in the production of the pro-inflammatory chemokines monocyte chemoattractant protein-1 and macrophage migration inhibitory factors associated with increased IL-8 and interferon-gamma [100], and pattern-recognition receptors that bind chitin [101]. These findings suggest a role for direct activation of innate immune cells in clinical responses to LMW chemicals. Bernstein and coworkers [102] further demonstrated that enhanced secretion of monocyte chemoattractant protein-1 by peripheral blood mononuclear cells after coincubation with diisocyanate-HSA conjugates was associated with clinical responses to SIC with isocyanates. More recently, immunohistochemistry of bronchial biopsies from subjects with isocyanate-induced OA and a murine model of isocyanate-induced OA indicated that IL-33 and innate lymphoid cells type 2 could be involved in OA induced by LMW chemicals [103]. There is also some suggestion that LMW agents, such as isocyanates [104,105] and persulfate salts [106] may activate mast cells and release mediators that contribute to eosinophil recruitment.

A number of non-immunological mechanisms have been suggested to be involved in the pathogenesis of OA induced by LMW agents, including oxidative stress, neurogenic inflammation, and airway remodeling, although evidence of a direct participation in the pathogenesis of LMW-induced OA in humans is still lacking [83]. Neutrophils can be involved in isocyanate-induced asthma as shown by an increase in myeloperoxidase and IL-8 in sputum samples after SIC with toluene diisocyanate [107], but similar changes have also been documented after SIC with grain dust [108]. Of note, the mechanisms underlying OA caused by occupational LMW haptens has not been addressed in the updated nomenclature of allergic diseases and hypersensitivity reactions recently issued by the European Academy of Allergy and Clinical Immunology [109].

5.2. Airway inflammation

Bronchial biopsy studies of subjects with OA due to isocyanates and Western red cedar wood dust have shown inflammatory changes that are indistinguishable from those observed in allergic asthma, including eosinophilic infiltration, activated T cells, presence of mast cells in the lamina propria, and thickening of the basement membrane [104,110,111]. In addition, Boulet and coworkers found similar pathologic features in bronchial biopsies obtained from subjects with OA caused by HMW and LMW agents [112].

Studies using the noninvasive technique of induced sputum demonstrated that challenge exposure to LMW agents, such as isocyanates [113,114] and persulfate salts [115], are predominantly associated with airway eosinophilic inflammation, regardless of the pattern of asthmatic reactions. Studies involving limited numbers of patients hint that LMW agents could be associated with a neutrophilic pattern of airway inflammation [116–119]. However, an analysis of the changes in sputum inflammatory cells elicited by positive SIC in a larger series of subjects ($n = 82$) showed that the type of agent was not predictive of the inflammatory response to challenge exposure [56]. This finding was further supported by data from 296 subjects with both baseline and post-SIC sputum samples in the E-PHOCAS cohort [120]. These data demonstrated that post-challenge sputum eosinophilic and neutrophilic patterns were associated with distinct clinical and asthma-related characteristics but not with the molecular-weight category of causal agents. Multivariate regression models showed a significant association of post-challenge sputum eosinophilia with HMW agents only when work-related rhinitis was present, which is consistent with previous observations of enhanced eosinophil recruitment into the lower airways after nasal exposure to nonoccupational inhalant allergens in subjects with allergic rhinitis [121,122]. In addition, HMW and LMW agents are associated with a similar rate of post-challenge neutrophilic pattern (13% and 16%, respectively) [120]. Sputum neutrophilia was observed after challenge exposure to HMW protein agents, mainly flour, even though IgE-mediated sensitization to these HMW agents was documented in the vast majority (83.3%) of the subjects. Interestingly, an analysis of subsets of the E-PHOCAS cohort documented a more marked eosinophilic response to challenge exposure for some LMW agents, such as acrylates [51] and quaternary ammonium compounds contained in cleaning and disinfecting products [32] compared with the other LMW agents.

An analysis of subjects with available fractional exhaled nitric oxide (FeNO) data ($n = 356$) among the E-PHOCAS cohort demonstrated that asthmatic reactions elicited by HMW agents were associated with a greater increase in FeNO [39]. These findings corroborate the results of a previous cluster analysis of 98 subjects with a positive SIC showing that exposure to HMW agents was the only factor associated with a significant (i.e. >17.5 ppb) increase in FeNO [123]. In subjects with OA due to acrylates [51] and platinum salts [52] from the E-PHOCAS cohort, however, the post-challenge increase in FeNO was greater than that observed with other LMW agents and similar to that induced by HMW agents.

6. Epidemiology

6.1. Prevalence

A number of cross-sectional surveys have provided estimates of the prevalence of OA of workforces exposed to various HMW and LMW agents. Besides various pitfalls related to this

type of epidemiological design, these estimates are likely to have been affected by the means used for identify OA cases [124]. These tools predominantly included questionnaires on work-related respiratory symptoms (WRS) and documentation of IgE-mediated sensitization to the causal agent through SPT or determination of sIgE antibodies. Epidemiological studies have used immunological tests predominantly for identifying IgE-mediated sensitization to HMW agents and a few LMW agents (i.e. platinum salts and acid anhydrides). Only a few epidemiological studies have involved the measurement of spirometry or NSBH to confirm asthma. Even less often, studies have relied on assessment of the changes in functional indices related to workplace exposure (i.e. NSBH or PEF) and SIC with the suspected occupational agent to ascertain OA in a stepwise identification process. Adding such objective tests to questionnaires and immunological tests strengthens case identification and most often yields a lower, yet more conservative, estimate of the prevalence of OA [125]. SPT or sIgE assays are either unavailable or not validated for most LMW agents. For this reason, we restricted the comparison of prevalence estimates between HMW and LMW agents to the studies that relied on the stepwise performance of functional assessments to ascertain a diagnosis of OA, including measurement of NSBH and/or monitoring of PEF at work and away from work, and/or SIC (Table 4) [126–138]. When these studies are compared, the estimated prevalence of OA is generally lower (<5%) for HMW than for LMW (≥5%) agents. These figures could be related to real differences in prevalence rates between HMW and LMW agents, but also to the fact that using both functional and immunological (SPT and/or specific IgE) tools in the case of HMW agents strengthens the identification of cases, whereas prevalences are only based on functional tests for LMW agents.

6.2. Incidence

Epidemiological studies investigating the incidence of OA are far less common than studies assessing its prevalence. The difference can be explained by the inherent difficulties of conducting prospective studies in which the participation in follow-up assessments is important for a satisfactory interpretation of findings. Table 5 [139–148] details selected prospective studies, including some in apprentices newly exposed to agents causing OA and in whom the incidence of OA was assessed with a satisfactory participation at the end of the surveillance program. These epidemiological studies were selected because objective means (i.e. assessment of IgE-mediated sensitization, change in NSBH, or SIC) were used in addition to results obtained from questionnaires. However, some studies should be interpreted with caution because the number of participants was relatively small. The duration of the follow-up, for at least 2 years, is particularly relevant in the case of HMW agents because the highest rates of sensitization and development of symptoms occur within the first 2 years after starting exposure [141,142]. Gautrin and coworkers [145] further confirmed this time frame in a prospective cohort study of 408 students entering training programs that involved exposure to a HMW agent (latex, flour, or laboratory animals), who were reassessed not only during and at the end of their training but also for up to 8 years after entering the workplace. In that study, the incidence of sensitization, NSBH and WRS was assessed for students in the same type of work and for students no longer exposed to the relevant agent. In their assessment of onset and remission of these outcomes, the authors found that the incidence of probable OA defined by sensitization and an increase in NSBH was higher (8.3%, approximately 4.4 per 100 person-years) during the training period compared with the period at work in the same environment (3%, approximately 0.4 per 100 person-years). Overall, incidence rates varied from 0.4 to 4.4 per 100 person-years and these figures did not differ by HMW versus LMW agents, although the limited number of studies and differences in diagnostic tools between these two categories of agents precluded adequate comparison.

7. Risk factors

OA results from complex interactions between environmental factors and individual susceptibility. The current evidence on the role of environmental and host factors in the initiation of OA caused by HMW and LMW agents is summarized in Tables 6 and 7, respectively.

7.1. Environmental risk factors

7.1.1. Level of airborne exposure at work

Available data provide strong evidence supporting a dose-response relationship between the level of workplace exposure to HMW agents and the development of IgE-mediated sensitization, work-related asthma symptoms and probable OA (Table 6). Such exposure-response relationships also have been documented in high-quality studies for IgE-mediated sensitization to platinum salts [168,169], acid anhydrides [170,171], and isocyanates [172] as well as through mixed-quality studies for probable OA among workers exposed to isocyanates [177–179] and healthcare workers exposed to cleaning agents containing chloramine [180].

7.1.2. Mode of exposure

The evidence that skin exposure to workplace agents can increase the risk of respiratory sensitization comes primarily from animal experiments. These studies showed that dermal exposure to both HMW allergens and LMW chemicals can initiate IgE-mediated respiratory sensitization with a predominant Th2-like immune response as well as the development of airway inflammation and airway responsiveness to these agents [199,200]. Information is scarce regarding the potential impact of skin exposure on the development of OA in humans because the effects of dermal contact cannot be easily differentiated from those of inhalation exposure and both routes of exposure most often occur simultaneously [201]. However, available evidence suggests that even when exposure to isocyanates by inhalation is below occupational limits, skin exposure can be substantial [202]. Exposure-response relationships have been reported for work-related skin symptoms among bakers [155,203] and auto body shop workers exposed to isocyanates [203], and associations between work-related skin and respiratory symptoms have been documented in bakers [203] and workers exposed to isocyanates [203,204].

Table 4. Prevalence of occupational asthma due to high- and low-molecular-weight agents among exposed workforces.

Agent (occupation/industry)	Number of subjects	Means for assessing OA	Estimated prevalence of OA (%)	Reference
High-molecular-weight agents:				
Snow-crab (seafood processing)	303	WRS	21	[126]
		SPT	22	
		NSBH + WRS	20	
		SIC, PEF	16	
Psyllium (pharmaceutical workers)	130	WRS	30	[127]
		SPT	19	
		sIgE	26	
		NSBH	54 (in subjects with WRS)	
		SIC	4	
Psyllium (chronic health care workers)	193	WRS	10	[128]
		SPT	3	
		sIgE	12	
		NSBH + SIC	4	
Guar gum (carpet industry)	162	WRS	23	[129]
		SPT	5	
		sIgE	8	
		SIC	2	
Latex (hospital workers)	289	WRS	2	[130]
		SPT	5	
		WRS + SPT	2	
		NSBH + SIC	2	
Flour (bakery workers)	297	WRS + low FEV_1	28	[131]
		NSBH	34 (in subjects with WRS and low FEV_1)	
		NSBH	7 (all subjects)	
		SIC	2	
Flour (bakery workers)	392	WRS	14	[132]
		SPT	12	
		sIgE	7	
		SIC	2	
Low-molecular-weight agents				
Isocyanates (secondary industry)	51	WRS	20	[133]
		NSBH + SIC	12	
Spiramycin (pharmaceutical workers)	51	WRS	12–19*	[134]
		NSBH	19–14*	
		SIC	8	
Reactive dyes (dye industry workers)	309	WRS	25	[135]
		WRS + NSBH	12	
		SPT	15	
		sIgE	17	
		SIC	4	
Plicatic acid (Eastern white cedar)	42	WRS	58	[136]
		NSBH	42	
		SIC	7	
Methylene diphenyl diisocyanate (car upholstery factory)	58	WRS	22	[137]
		sIgG	21	
		sIgE	9	
		SIC	9	
Chromium and cobalt (metal manufacturing)	62	WRS	66	[138]
		PEF, SIC	10	

Legend: *FEV1*, forced expiratory volume in one second; *NSBH*, bronchial hyperresponsiveness to histamine/methacholine; *OA*, occupational asthma; *PEF*, monitoring of peak expiratory flow rates at work and away from work; *SIC*, specific inhalation challenge; *sIgE*, specific IgE antibodies against an occupation agent; SPT, skin-prick testing with the causal agent, *WRS*, work-related lower respiratory symptoms.
Studies were selected based on the stepwise use of immunological (SPT, sIgE) and functional assessments to ascertain the diagnosis of OA, including measurement of NSBH and/or monitoring of PEF at work and away from work and/or SIC.
*Two assessments, first, away from the production period and the second, during production.

7.1.3. Co-exposure to cigarette smoke

There is strong evidence that exposure to tobacco smoke is a significant risk factor for the development of IgE-mediated sensitization to HMW agents as well as the LMW platinum salts and acid anhydrides (Table 6). A number of studies also indicated that smoking is associated with an increased risk of probable OA among workers exposed to HMW agents, including snow crab [126,176], fish [182], and laboratory animals [173], while such an increased risk of probable OA has not been documented for LMW agents.

7.2. Host risk factors

7.2.1. Atopy

There is strong evidence that atopy, usually defined as a positive SPT or the presence of sIgE to at least one ubiquitous inhalant allergen, is a major risk factor for the development of IgE-mediated sensitization to HMW agents as well as WRS and probable OA among exposed workers (Table 7). Interestingly, pre-exposure sensitization to common allergens that are structurally related to workplace allergens, such as pets among laboratory animal workers could be a stronger predictor of sensitization to workplace allergens than atopy [142,193]. There is also convincing evidence

Table 5. Incidence of occupational asthma due to high- and low-molecular weight agents among exposed workforces.

Agent/job	Population	Duration of follow-up	Outcome	Incidence rate (per 100 p-y)	Reference
High-molecular-weight agents:					
Latex					
Dental hygiene apprentices	122	up to 32 mo	Probable OA: Development of positive SPT and increase in NSBH (3.2-fold decrease in PC_{20})	1.8	[139]
Laboratory animals					
Laboratory technician students	38	Median: 8 mo (range: 5–33)	Probable OA: WRS and positive SPT/sIgE and significant increase in NSBH at follow-up	2.6‡	[140]
Laboratory workers	342	up to 84 mo	WRS and positive SPT (rat urine extract)	1.9	[141]
Animal health apprentices	417	up to 44 mo	Probable OA: development of positive SPT and increase in NSBH (3.2-fold decrease in PC_{20})	2.7	[142]
Bakers and pastry makers					
Newly exposed workers	300	Median: 40 mo (range: 1–91)	WRS and positive SPT (flour or alpha-amylase)	1.0‡	[143]
Apprentices	287	up to 24 mo	Positive specific inhalation challenge	3.0	[144]
Bakers, pastry makers, laboratory workers and dental hygiene	408	During apprenticeship: 8–44 mo, median: 26 mo	Probable OA: positive SPT/sIgE and significant increase in NSBH at follow-up	4.4	[145]
		During work: 4–12 yrs, mean: 7.6 yrs	Probable OA: positive SPT/sIgE and significant increase in NSBH at follow-up	0.4	
Low-molecular-weight agents:					
Metalworking fluids					
Apprentices machinists	82	up to 24 mo	Probable OA: WRS and increase in NSBH (≥ 2-fold decrease in PC_{20})	3.7	[146]
Metal fumes					
Welders apprentices	286	up to 18 mo	Probable OA: Onset of WRS and increase in NSBH (2 or 3.2-fold decrease in PC_{20})	2.1*	[147]
Isocyanates					
Car-painters apprentices	385	up to 18 mo	Probable OA: Onset of WRS and increase in NSBH (3.2-fold decrease in PC_{20})	0.4*	[148]

Legend: *OA*, occupational asthma; *NSBH*, nonspecific bronchial hyperresponsiveness; *PC_{20}*, concentration of pharmacological agent inducing a 20% fall in forced expiratory volume in 1 second; *p-y*, person-year; *sIgE*, specific IgE antibodies; *SPT*, skin-prick tests; *WRS*, work-related respiratory symptoms.
*Incidence expressed in person-years as derived from the original data.
‡Assuming that each study participant was assessed at the time corresponding to the median duration of follow-up of the cohort.

that atopy is associated with an increased risk of sensitization to some LMW agents that are admittedly acting through an IgE-mediated mechanism, including acid anhydrides [171,192] and platinum salts [169], although no scientific evidence has associated atopy with ascertained OA caused by LMW agents.

7.2.2. Nonspecific bronchial hyperresponsiveness

Only one prospective cohort study has assessed NSBH of apprentices before entering exposure to HMW agents (i.e. laboratory animals, flour, and latex). This study provided formal evidence that baseline NSBH was associated with an increased risk of acquiring IgE-mediated sensitization to work-related allergens and probable OA during the apprenticeship period [142] and later in participants working in a related job [145]. By contrast, the role of NSBH as a risk factor for the development of OA related to LMW agents has not currently been convincingly substantiated. In a prospective cohort study of car painter apprentices exposed to isocyanates, the presence of NSBH at baseline was associated with an increased incidence of WRS but not with a significant increase in the level of NSBH (i.e. probable OA) during the training program [148]. In a cohort of metal refinery workers, Brooks and coworkers described an association between baseline NSBH and the conversion to a positive SPT to platinum salts over a one-year follow-up period [195].

7.2.3. Rhinitis

There is compelling evidence that allergic and non-allergic rhinitis is a risk factor for the development of non-occupational asthma [205]. A Finnish population-based study demonstrated through register linkage that occupational rhinitis, predominantly caused by HMW agents, is also associated with an increased risk for the subsequent development of both OA and non-occupational asthma [206]. Moderate evidence from longitudinal studies of workers exposed to laboratory animals indicates that work-related rhinitis is associated with an increased likelihood of developing WRS [196] and probable OA [197] (Table 7). In addition, a long-term prospective cohort study of apprentices exposed to HMW agents provided evidence that the presence of allergic rhinitis prior to work exposure is an independent risk factor for developing IgE-mediated sensitization work-related allergens and probable OA [145,207]. Information regarding the interaction between rhinitis and the development of OA due to LMW agents is currently lacking.

7.2.4. Gender

The impact of gender on the development of OA remains controversial. Some studies that controlled for other covariates provided evidence that female workers are at higher risk of probable OA from snow crab allergens [176], laboratory animals [196] and cleaning products containing chloramine [180], whereas a higher risk of probable OA has been documented among male fish processing workers [182]. However, disparities in the prevalence of OA may result from gender-related differences in job and exposure distribution [198].

Table 6. Environmental risk factors for the development of occupational asthma caused by high- and low-molecular-weight agents.

Risk factor	High-molecular-weight agents	Strength of evidence	Low-molecular-weight agents	Strength of evidence
Level of airborne exposure	IgE-mediated sensitization • Flour: [149]* [150]* [151]* [143]* [152]* [153]* [154]* [155,156]* [157]* [158]*; among atopic workers [159]* • Alpha-amylase: [150]* [151]* [160]* [143]* [155] • Laboratory animals workers: [161] * [141]* [162]* [163]*; in non-atopic workers [164]* • Latex: [165] • Garlic: [166]* • Chicken: [167]*	+++	IgE-mediated sensitization • Platinum salts: [168]* [169]* • Acid anhydrides: [170]* [171]* • Isocyanate [172]*	+++
	Work-related respiratory symptoms • Flour: [149]* [150]* [162]* [151]* [152]* [143]* [155] atopic workers [159]* • Laboratory animal workers: among sensitied workers [173]* • Garlic: [166]* • Various enzymes: "enzyme-related allergy" [174]	+++	Work-related respiratory symptoms • Isocyanate: [172]* [175]*	+++
	Probable OA† • Flour: [152]* [157]* • Snow crab: [176]*	+++	Probable OA • Isocyanate: OA claims [177]; WRS and PEF [178]*; WRS and NSBH [179]* • Cleaning agents (chloramine): WRS and onset of physician-based asthma during exposure [180]*	+++
Co-exposure to cigarette smoke	IgE-mediated sensitization • Flour: atopic workers [181] • Laboratory animals: [161]* • Various enzymes: [174]* • Fish: [182]* • Salmon: [183] • Prawn: [184] • Psyllium: [185] • Green coffee and castor bean [185]:	+++	IgE-mediated sensitization: • Acid anhydrides: [170]* • Platinum salts: [168,186]* [187]* [188]*	+++
	Work-related respiratory symptoms • Laboratory animals: [161]* • Various enzymes: "enzyme-related allergy" [174]*	+++	No data	
	Probable OA† • Snow crab: [126]* [176]* • Fish: [182]* • Laboratory animals: [173]*	+++	No data	

Legend: *HMW*, high-molecular-weight; *LMW*, low-molecular-weight; *NSBH*, nonspecific bronchial hyperresponsiveness; *OA*, occupational asthma; *SIC*, specific inhalation challenge; *WRS*, work-related respiratory symptoms.
*High quality studies (see methods).
†Probable OA defined as: 1) WRS and sensitization to occupational allergens [152,173]*; 2) WRS, NSBH and sensitization to occupational allergens [157,182]; 3) WRS and sensitization to occupational agent ± changes in peak expiratory flow rates at work [176]; or 4) a combination of positive SIC and changes in peak expiratory flows or NSBH at work [126].

7.2.5. Genetic susceptibility

The respective role of genetic factors in the development of OA attributable to HMW and LMW agents remains elusive because most studies have focused on OA due to LMW agents and predominantly on isocyanates [83]. These studies reported that certain human leukocyte antigen class II molecules which are involved in the presentation of processed antigens to T-lymphocytes, could confer either susceptibility or protection against OA caused by isocyanates and red cedar as well as IgE-mediated sensitization to acid anhydrides and platinum salts. Evidence also indicates that genes involved in immune response, response to oxidative stress, neurogenic inflammation, cellular metabolism, cell adhesion, and beta$_2$-adrenergic receptor activity could play a role in the development of OA due to isocyanates. However, a major limitation of studies on the genetics of OA is that the findings were most often not replicated. A recent meta-analysis compared 23 genetic markers in subjects with isocyanate-induced OA compared with those of control subjects. The most consistent evidence of an association with isocyanate-induced OA was for a protective effect of human leukocyte antigen DR1 and an increased risk for catenin alpha 3 single nucleotide polymorphisms involved in E-cadherin-mediated cell-cell adhesion [208]. In contrast, very few studies have investigated the role of genetic factors in OA attributable to HMW occupational agents. Jeal and coworkers reported a strong association between human leukocyte antigen DR7 and WRS in subjects sensitized to rat allergens, although the risk was lower than that conferred by atopy and high-level

Table 7. Host risk factors for the development of occupational asthma caused by high- and low-molecular-weight agents.

Risk factor	High-molecular-weight agents	Strength of evidence	Low-molecular-weight agents	Strength of evidence
Atopy	IgE-mediated sensitization:	+++	IgE-mediated sensitization:	+++
	• Flour: [149]* [150]* [151]* [143]* [152]* [144]* [154]* [181]* [132,159]* [157]* [155]* • Laboratory animals: [161]* [141,164], * [173]* [158]* [189]* • Alpha-amylase: [190]* [155]* • Latex: [130,139,165,191]* • Garlic: [166]* • Fish: [182]*		• Acid anhydrides: [171,192]* • Platinum salts: [169]*	
	WRS • Flour: [149,151]* [193]* [152]* [144]* [159]* • Laboratory animals: [141]* [163]* [158]*; among sensitized workers [173]* • Fish: [182]	+++	No data	
	Probable OA†	+++	No data	
	• Flour: [157]* • Laboratory animals: skin reactivity to pets [142]* • Latex: [139]* • Snow crab: [176]* • Psyllium [127]: • Spider mites (*Tetranychus urticae*) [194]: • Various HMW agents: [39]* [145]*‡			
Pre-existing NSBH	Incidence of IgE-mediated sensitization	+++	Incidence of IgE-mediated sensitization	-
	• Laboratory animals [142]* • HMW allergens‡ [145]*		Platinum salts [195]	
	Incidence of WRS	++	Incidence of WRS	++
	• HMW allergens‡ [145]*		• Isocyanates [148]*	
	Incidence of probable OA† -Laboratory animals [142]*	++	No data	
Work-related rhinitis	Incidence of WRS	++	No data	
	• Laboratory animals [196]*			
	Incidence of probable OA†			
	• Laboratory animals [197]*			
Gender	Higher risk in females		Higher risk in females	
	• Snow crab processors (probable OA†) [198]* [176]* • Laboratory animals (probable OA†) [196]*		• Cleaning (chloramine) (probable OA†) [180]	
	Higher risk in males		No data	
	• Fish processing workers (probable OA†) [182]*			

Legend: *HMW*, high-molecular-weight; *NSBH*, nonspecific bronchial hyperresponsiveness; *OA*, occupational asthma; *SIC*, specific inhalation challenge; *sIgE*, specific IgE antibodies; *WRS*, work-related respiratory symptoms.
*High quality studies (see methods).
†Probable OA defined as: 1) WRS and onset of asthma (physician-based) during workplace exposure [180]; 2) WRS and IgE sensitization to occupational allergens [152,194,196,209]; 3) WRS, NSBH, and sensitization to occupational allergens [157,182]; 4) sensitization to an occupational allergen and increase in NSBH over the follow-up period [139,142]; 5) WRS, sensitization to occupational agent and changes in peak expiratory flow rates at work [176]; or 6) positive SIC [39,127].
‡Exposure to laboratory animals, flour, or latex after the end of apprenticeship [145].

exposure [209]. Interestingly, there is some suggestion that Toll-like receptor 4 variants may affect IgE-mediated sensitization to HMW allergens (i.e. laboratory animals and flour) and WRS in exposed workers [210,211]. Toll-like receptor 4 alleles have not been investigated in OA due to LMW agents.

8. "Atypical" LMW agents

There is accumulating evidence that OA due to some LMW agents shares phenotypic characteristics with OA caused by HMW agents; these agents are referred to here as 'atypical' compared with other LMW agents, the archetypes being isocyanates and plicatic acid. The presence of sIgE antibodies has been documented in most subjects with OA caused by platinum salts, acid anhydrides, reactive dyes, and chloramine-T (N-chloro-4-methylbenzenesulfonamide) (Table 8) [51,52,72–82]. In addition, platinum salts and acrylate compounds are associated with a higher rate of work-related rhinitis and a greater post-exposure increase in FeNO compared with other LMW agents, characteristics that previously have been linked to HMW agents [39,123].

The mechanisms underlying OA caused by wood dusts remain largely uncertain. Occupational asthma due to Western red cedar has been the most extensively investigated form of OA related to wood dusts. It has been demonstrated through SIC that plicatic

Table 8. Phenotypic characteristics of subjects with 'atypical' low-molecular-weight agents compared to the other LMW agents.

Agent	Positive SPT	Positive sIgE	High rate of work-related rhinitis	Greater post-exposure increase in FeNO	Greater post-exposure eosinophilic response	Reference
Acid anhydrides	~69% (*n*=16) *	81% (95% CI: 46–95)†	Frequent but NI	NI	NI	[72–74]†
Acrylates	-	NI	65% vs. 38% with isocyanates, $p<0.001$	OR: 6 (95% CI: 2–18)	+88% vs 48% with other LMW agents, $p=0.060$	[51]
Chloramine-T	~92% (*n*=13)	~100% (*n*=13)	Frequent (11/13)	NI	NI‡	[75–79]
Platinum salts	~81% (*n*=23)	(+)	+86% vs. 53% with other LMW agents, $p=0.018$	OR: 10 (95% CI: 3–40)	NI	[52,80,81]
Reactive dyes	76% (*n*=42)	54% (*n*=42)	Frequent but NI	NI	NI	[82]
Wood dusts	58%§ (*n*=107)	58%§ (*n*=66)	83%§ (*n*=100)	NI	NI	Case reports review§

Legendg: *FeNO*: fractional exhaled nitric oxide; *NI*, not formally investigated or compared with other LMW agents; *OR*, odds ratio; *95% CI*, 95% confidence interval; *sIgE*, specific IgE antibodies against the causal agent; *SPT*, skin-prick testing with the causal agent.
*SPT performed with LMW agent conjugated to human serum albumin.
†Systematic review.
§Findings of a PubMed search on wood-induced OA (see section on "atypical LMW agents).
‡Palczynski and coworkers documented a significant increase in the percentage of eosinophils and the level of eosinophil cationic protein in nasal lavage fluid after challenge exposure to chloramine-T [78].

acid, a LMW organic chemical, is the causal sensitizing agent in cedar asthma. However, sIgE antibodies directed against plicatic acid conjugated to HSA have been detected in less than 40% of affected subjects. On the other hand, IgE-mediated sensitization to wood dust has been supported by positive SPT and/or the detection of sIgE against a number of wood species [212]. A PubMed search identified 48 case reports or small case series describing a total of 155 subjects with OA caused by 34 wood species, ascertained by a positive SIC. Associated work-related rhinitis was reported by 83 of 100 subjects with available information. SPT with wood extracts and the determination of sIgE antibodies showed positive results in 58% of the subjects with available information (Table 8), most consistently in those with OA caused by obeche wood dust (*Triplochiton scleroxylon*). In addition, IgE-binding proteins with molecular weights ranging between 19 and 78 kDa have been identified through immunoblotting techniques in extracts of some wood species [213–218]. One allergen of obeche, an endochitinase (*Tri s 1*), has been fully characterized and sIgE against this protein has been detected in 85% of subjects with OA caused by obeche wood dust [215]. A significant increase in sputum eosinophils has been documented after inhalation challenges with plicatic acid in subjects with red cedar asthma [219] and in five of six subjects with OA due to various wood species who were investigated through the induced sputum technique [220–223].

These data indicate that the LMW category of sensitizers is a heterogeneous group of agents with different phenotypic and immunological characteristics and pooling all LMW agents into a single group does not reflect the complexity of underlying pathobiological pathways.

9. Expert opinion

This comprehensive and evidence-based review further confirms that OA caused by HMW agents exhibits a few distinct clinical characteristics compared with OA linked to the broad category of LMW agents: higher rates of work-related rhinitis and isolated immediate asthmatic reactions, a greater increase in FeNO upon exposure to the causal agent, and a more frequent persistence of NSBH after removal from exposure. In contrast LMW agents are characterized by higher rates of late and atypical asthmatic reactions compared to HMW agents. The identification of clinical features, especially the association of HMW-induced OA with work-related rhinitis and a marked increase in FeNO, is relevant to the diagnosis of OA and may contribute to the development of diagnostic algorithms [45,123,224].

The review also provides strong evidence that atopy, NSBH, and smoking are significant risk factors for the development of IgE-mediated sensitization and OA caused by HMW agents. Atopy and smoking are also associated with a higher risk of IgE-mediated sensitization to some LMW agents (i.e. platinum salts and acid anhydrides). These risk factors, especially exposure to cigarette smoke, may have implications for implementing preventive policies.

It is widely acknowledged that HMW agents induce asthma through a Type I, sIgE-mediated hypersensitivity mechanism, whereas the immune responses underlying sensitization to most of the LMW agents are still speculative. Nevertheless, both categories of agents are associated with a mixed Th1/Th2 airway immune response and a predominantly eosinophilic pattern of airway inflammation. Only a small subset of subjects with OA show a neutrophilic pattern of airway response – either isolated or in combination with eosinophilia – regardless of the molecular-weight catgory of the causal agent.

The findings of this review challenge the conventional concept of pooling a variety of LMW agents into a single category, presuming implicitly that they act through similar pathophysiological mechanisms. OA resulting from 'atypical' LMW agents exhibits some 'HMW-like' phenotypic characteristics, including the presence of sIgE, a high rate of work-related rhinitis, and a marked increase in FeNO upon exposure. Accordingly, LMW agents should be regarded as a heterogeneous group of agents that may induce OA through different underlying pathobiological pathways that have yet to be characterized.

The conventional classification of the agents causing sensitizer-induced OA into HMW and LMW categories is arbitrary and the threshold molecular weight differentiating these two

groups of agents has not been precisely ascertained. Labeling the HMW and LMW categories of agents as 'protein agents' versus 'non-protein agents' seems more meaningful in terms of the chemical nature of the sensitizing agents. All the more so, the findings of this review suggest that the clinical characteristics (i.e. associated work-related rhinitis and marked increase in FeNO) and risk factors (i.e. atopy and smoking) usually related to HMW agents are more closely associated with the presence of sIgE antibodies than with the molecular-weight category or the protein nature of the sensitizing agent, with the exception of acrylate compounds for which sIgE antibodies have not yet been investigated.

Several factors can explain the difficulty in identifying the phenotypic, pathophysiological, epidemiological, and outcome features of OA, especially OA caused by LMW agents. The major limitations are the small number of subjects with OA caused by the diverse types of LMW agents and the currently scarce use of airway inflammation biomarkers such as FeNO and induced sputum cytology in the evaluation of subjects with WRS. In addition, the identification of OA is not sufficiently often confirmed by objective (immunological and functional) tests, with the questionnaire remaining the only means of ascertaining cases in many studies. This pitfall particularly limits satisfactory assessment of frequency (prevalence and incidence) and risk factors. A model for assessing frequency in epidemiological studies should rely on a stepwise procedure that progressively identifies cases with objective tests (assessment of NSBH, skin prick tests and sIgE assessments in the case of protein agents, and SIC). Immune responses to LMW agents remain poorly understood, in large part because of uncertainty regarding the antigenic form these agents take *in vivo* when combining with human proteins. There is a paucity of immunological studies focused on the mechanisms of OA due to non-protein agents in recent years, as the principal research interest in OA has switched from humoral to cellular factors.

Multicenter prospective studies should be implemented in order to collect information on a large number of participants with ascertained OA caused by various LMW agents. These studies should use standardized and validated instruments in order to capture the full spectrum of asthma-related outcomes. Underlying pathobiological pathways should be further characterized using proteomic and transcriptomic techniques on sputum samples and bronchial biopsies in order to identify biomarkers and hopefully therapeutic targets with the ultimate objectives of improving the diagnosis and enhancing precision medicine.

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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