

New Eliciting Agents of Occupational Asthma

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Opinion statement

Occupational asthma is a type of asthma that arises from exposures in the workplace. There are more than 400 known causes of occupational asthma and the list is growing. New causes of allergic occupational asthma involving high and low molecular weight agents are continuously being reported. Their knowledge is important for physicians and occupational health and safety professionals to maintain a high level of suspicion in exposed workers to these substances. The majority of new causes of allergic occupational asthma between 2011 and mid-2016 were seen with high-molecular-weight agents. Most new cases are observed in food and agro-alimentary industry, but also in the cosmetic industry, and frequently are associated with other IgE-mediated manifestations, especially allergic rhinoconjunctivitis and contact urticaria. Among the low-molecular weight agents, new acrylate and aldehyde compounds have been identified as eliciting agents of occupational asthma, as well as drugs, biocides, and other chemicals recently introduced in industry.

Introduction

Occupational asthma (OA) is defined as a type of asthma caused by exposures in the workplace [1]. Two types of OA are distinguished [2]: allergic OA, which is induced by sensitizers and appears after a latency period of sensitization to the causal agent, and, on the other hand, irritant-induced OA, which is due to acute high-level exposure to respiratory irritants or to persistent exposure to moderate-high level exposure to respiratory irritants.

This last subgroup of OA includes the reactive airways dysfunction syndrome (RADS) [3]. Substances causing allergic OA are classified into low-molecular-weight (LMW) compounds (often chemicals) or high-molecular-weight (HMW) agents (primarily proteins with molecular mass higher than 10 kDa). HMW agents usually induce an immediate or a dual asthmatic reaction, similar to the airway inflammation found after

common allergen inhalation challenges through an Immunoglobulin (Ig) E-mediated mechanism. LMW agents often induced delayed asthmatic reactions, and their underlying mechanism of action is still being debated, with the exception of few cases in which an IgE-mediated mechanism has been demonstrated in OA induced by isocyanates or red cedar dust [4]. Recent data suggest that patients with OA caused by LMW agents had a significantly higher risk of severity according to the GINA classification [5]. There are more than 400 known causes of OA and the list is continuously

growing. New cases involving high and low MW agents are constantly reported [6••]. Their knowledge is important for physicians to stay alert and suspect OA in exposed workers to these substances. Interestingly, the Association of Occupational and Environmental Clinics has developed a readily available Web-based listing of agents associated with new onset work-related asthma [7••], which is updated twice a year. This review focuses on recent eliciting agents recognized as a cause of allergic OA from 2011 to 2016, updating current knowledge.

New HMW Agents

The majority of new causes of allergic OA between 2011 and mid-2016 were seen with HMW agents. Most cases are associated with other IgE-mediated manifestations, especially allergic rhinoconjunctivitis and contact urticaria.

Food and Agro-Alimentary Industry

Royal jelly is a secretion of the mandible of worker honeybees and several mild to severe reactions have been reported after eating royal jelly food supplements. Gomez-Torrijos et al. [8] have reported two cases of OA induced by royal jelly in two workers from a pharmacy laboratory, tolerating the intake of honey. Skin prick tests (SPT) were positive with a homemade royal jelly extract and with natural honey. Immunoblot assays showed concordant results with previous studies that have reported the presence of IgE binding proteins of 40 to 55 kD that have been recognized as the major allergens of royal jelly. Finally, specific inhalation (SIC) showed a dual response after the exposure to royal jelly powder in one patient but one did not give his informed consent for the SIC.

Known causes of OA are seafood, including fish, mostly in fish processing workers, and egg and birds proteins in bakers or professional cooks. Wiszniewska et al. [9] described the first case of OA, rhinoconjunctivitis, and contact urticaria to a type of squid (*Loligo vulgaris*) in a seafood production worker who was exposed to squids while preparing them for further processing as well as through cleaning machines after usage. After 1 year of working, he developed respiratory and skin symptoms. Prick-by-prick with squid showed an intensive positive reaction, being negative in two control subjects. A SIC by simulating the workplace conditions elicited an immediate asthmatic reaction, a severe conjunctival reaction and a significant increase of eosinophils in tears, as well as in the nasal lavage fluid. Boulet et al. [10] reported for the first time the case of an IgE-mediated induced OA to sole fish in a restaurant worker. Diagnosis was confirmed with a positive SPT for sole fish extract and an intense and immediate positive reaction in the SIC with sole fish extract (1/126 dilution). Gomez-Torrijos et al. [11•] described the case of a daycare cook with occupational respiratory allergy and eosinophil esophagitis due to chicken serum albumin (*Gal d 5*) in relation with the ingestion of poultry and subsequently inhalation of egg proteins when handling egg. Rodriguez del Río et al.

[12] described a new workplace setting for dust mites-induced OA, in a dry-ham delivery man exposed in his van to *Tyrophagus putrescentiae*, in extensive contaminated hams with that specie of mites.

Pests and Insect Allergens

Ceratitis capitata is one of the most crop-damaging pests in the Mediterranean area. A control strategy involves the infertile mating of sterile males with wild females to reduce pest population. De las Marinas et al. [13] described two cases of OA induced by this Mediterranean fruit fly in two workers at the company where these sterile males are produced. One patient was working where the sterile fly pupae were raised while the other carried out her activity mainly in the room where the adult flies were housed. SPT with medfly extract and serum specific IgE were positive. OA diagnosis was confirmed by demonstrating increased diurnal variability of PEF at work and by a positive SIC to medfly extract that elicited an isolated early asthmatic response in both patients. However, there were important differences in IgE-binding patterns that might be explained considering the distinct activities carried out by each of the patients in the factory.

Bobolea et al. [14] described an arginine kinase from *Holocnemus pluchei*, a common spider, as a new OA-causing allergen in a farmer who handled cereal inside the warehouse. He noted the presence of many spiders in the warehouse. Although the patient was sensitized to the extracts of the bodies of two different spiders, the diagnosis was confirmed by a SIC, obtaining a positive result with the extract of cellar spider whereas it was negative with the domestic house spider. A 17-kDa protein from *H. pluchei*, identified as an arginine kinase, was considered the causative allergen after a positive specific SIC with this allergen.

Nematodes are increasingly used in horticulture instead of chemical pesticides. The final product is diluted in water and sprayed onto plants, causing the nematode solution to be potentially respirable. Although sensitization to *Steinernema feltiae* had been reported previously, Feary et al. [15] described for the first time its implication in OA confirmed with a positive SIC, in a worker who filtered an aqueous suspension of nematodes and added preservatives and inert bulking agents to produce the final product.

Enzymes used in industry are capable to induce allergic responses. Termamyl® is a thermostable endo-alpha-amylase originated from *Bacillus stercorophilus* that is used in alcohol processing and for the production of dishwashing detergents. Baur et al. [16] described an IgE-mediated sensitization (measured by serum-specific IgE) in a patient employed in the production and packaging of detergents. Unfortunately, a SIC was not performed because his lung function values were considered as a contraindication. Lipinska-Ojrzanowska et al. [17] reported a case of OA to savinase, a high-alkaline protease belonging to subtilase family enzymes, in a worker of a dishwashing tablet factory, who had been packaging ready-made tablets into foil wrappers. A positive SIC was obtained with a dual response and a significant increase of eosinophil count in induced sputum after the SIC. De Palma et al. [18] reported a case of OA caused by transglutaminase, in a worker from a company that commercialized ingredients for the food industry. Transglutaminases are obtained from *Streptomyces mobaraensis* and confer texturization and resistance to proteolytic degradation, improve flavor, and increase shelf-life. Diagnosis was

made by demonstrating a positive SPT to a diluted solution (1 U/mL in water) of microbial transglutaminase, specific IgE, and IgE-immunoblotting inhibition.

Cereal and Vegetal-Derived Allergens

Although wheat has been often described inducing baker's OA, there are still some questions that have to be answered. Knowledge of the relevant allergen components might help to improve diagnostics. Sander et al. [19••] evaluated wheat allergen components as sensitizers for bakers with work-related complaints, with consideration of cross-reactivity to grass pollen. A combination of IgE tests to 5 components, *Tri a* 27, *Tri a* 28, tetrameric α -amylase inhibitor CM2 (*Tri a* 29.02), serine protease inhibitor-like allergen (*Tri a* 39), and 1-cys-peroxiredoxin (*Tri a* 32), helped to distinguish between sensitization caused by occupational flour exposure and wheat seropositivity based on cross-reactivity to grass pollen. However, for routine diagnosis of baker's allergy, specific IgE tests with whole wheat and rye flour extracts remain mandatory because of superior diagnostic sensitivity. Moreover, most of the patients with baker's asthma almost invariably tolerate cereal products without any ill effect [20]. Gliadins represent another family of inhalable allergens in baker's asthma [21]. Moreover, Gomez-Torrijos et al. [22] recently reported the first case of occupational eosinophilic esophagitis due to wheat flour gliadin triggered by inhalation, associated with rhinoconjunctivitis and asthma on a 31-year-old woman who worked in her family bakery. Asthma was confirmed by a positive SIC to wheat flour, demonstrating a 12% fall in FEV₁ at 20 min and a 26% drop in PEF at 9 h after exposure to wheat flour. The patient's serum specifically recognized omega-5-gliadin and the gliadin fraction, and no IgE reactivity was observed to other wheat allergens.

Finally, there is evidence to suggest that bakers can develop sensitization to 'improver' enzymes other than fungal α -amylase, such as cellulase, glucoamylase, hemicellulase, and xylanase. Jones et al. [23] have recently explored the prevalence of sensitization to 'improver' enzymes in supermarket bakers and it ranged from 5 to 15%. Sensitization was far more likely if the baker was sensitized also to either flour or α -amylase. The clinical significance of these findings needs further investigation, but sensitization to enzymes in symptomatic bakers should be more often considered.

Paris et al. [24] reported three cases of OA to argan powder during a systematic investigation among all the workers exposed to argan products in a cosmetic factory. *Argania spinosa* is an endemic tree growing in arid areas of Morocco, and it is used worldwide in cosmetic products as oil and as argan powder, containing proteins from residuals after heating and pressing the fruits. Nine patients were exposed, but only three of them had a positive SIC to argan powder. Seven protein bands between 10 and 46 kDa were identified in argan powder by SDS-PAGE and a total of 15 IgE-reactive bands were detected, assessing the presence of argan-specific IgE in the serum of exposed subjects. The three proteins most commonly bound by IgE had molecular weights of 32 kDa (8/9 patients), 51 kDa (7/9 patients), and 28 kDa (5/9 patients). Identification of proteins, cross-reactions to nuts, and ELISA-inhibition tests suggested that some argan allergens could cross-react in vitro with hazelnut allergens, including 11S globulin and vicilin.

Also pertaining to the cosmetic industry, the first case of asthma induced by *Moringa oleifera* seed powder has been reported by Poussel et al. [25] in a factory worker regularly exposed while he packaged samples of the active ingredient. This herbal plant has been used as human food and as an alternative for medicinal purposes in many cultures around the world. Due to antioxidant properties, the cosmetic industry has incorporated *Moringa* as a compound in various products as moisturizers or skin ointment. They confirmed the causal relationship with the powder by a positive SIC, obtaining a strong early asthmatic reaction. Moreover, an immunoblot of the *Moringa* seed extract with patient's serum revealed the presence of IgE reactive proteins greater than 10 kDa, most of them between 24 and 56 kDa.

Decorative flowers cause OA in the floral industry. *Limonium sinuatum*, commonly known as wavy leaf sea-lavender, belongs to the *Plumbaginaceae* family, and it is commonly grown in the Mediterranean regions. Wiszniewska et al. [26] described the case of a gardener who had been working with different kind of flowers for 30 years and who had developed rhinitis and asthma over the last 10 years. SPT was positive to *L. sinuatum* and a SIC was performed. An isolated early asthmatic reaction was observed, along with a significant increase in the number of eosinophils in the nasal lavage fluid, confirming that *L. sinuatum* was the eliciting agent of OA and rhinitis.

Lipid transfer proteins (LTP) can cause OA [20]. Gomez-Torrijos et al. [27•] described the first case of OA and rhinoconjunctivitis probably caused by an LTP in the leaves and flowers of the melon plant and the rind of the melon fruit. A 27-year-old agricultural worker experienced respiratory symptoms while working in the melon harvest as well as contact urticaria to melon rind on her arms, but she tolerated melon intake. Prick-by-prick test showed positive results to melon leaves, petal, pollen, and rind. A SIC with melon flower extract (1:10 dilution) was performed, and an early positive reaction was induced, with negative reactions in two control subjects. They also demonstrated sensitization to a 10–12 kDa allergen, which seemed to correspond to a LTP present in different parts of the plant, with no cross-reactivity with *Pru p 3*, the specific peach LTP.

De las Marinas et al. [28] described a case OA in a farmer who experienced respiratory symptoms and contact urticaria while working in an orange grove with trees blooming and being almost asymptomatic at work the rest of the year. Prick-prick test was positive for the orange tree branch, leaf and blossom, and to orange pulp and peel, being negative in 5 controls. Diagnosis was based on PEF monitoring that showed clearly decreased rates during the blooming season while he was pruning and grafting, but especially when the patient was rolling. Immunoblot assays confirmed the existence of an orange aeroallergen, probably a member of the LTP family, with a molecular mass of <14 kDa, that may correspond to *Cit s 3*.

Jiang et al. [29] described another allergen from pollen of the *Rosaceae* family as a cause of OA. An orchard worker, a peach breeder whose main job was to facilitate artificial pollination showed predominant IgE-binding to a 20 kDa protein among different pollens from five species in the *Rosaceae* family. It appeared to be a cross-reactive allergen identified as a homologous to glutathione s-transferase-16 from *Arabidopsis thaliana* (*Alt a 13*). This kind of proteins represents a multifunctional enzyme superfamily, present in virtually all organisms from bacteria to humans, with demonstrated presence in mites (*Der p 8*), cockroaches (*Bla g 5*), fungi, birch pollen, and wheat.

Woods

Wittczaket al. [30] described the case of a worker in a family sawmill who developed asthma after working for 2 years. These symptoms tended to appear after the exposure to spruce wood dust. A significant increase in the symptom score and use of medication was observed during the periods at work. Diagnosis was based on daily PEF monitoring, with significant variability while at work, the presence of serum specific IgE to spruce wood and a raised eosinophil count in the induced sputum after 2 weeks of daily exposure to spruce wood.

Western red cedar (*Thuja plicata*) is a well-known cause of OA. However, Barranco et al. [31] described a new workplace setting in the manufacture of guitars. Besides the usual diagnostic process, including a positive SIC with the wood extract, they also obtained a positive basophil activation test (BAT) in a guitar maker with OA due to this wood. Recently, De las Marinas et al. [32] reported the first documented case of OA caused by iroko wood (*Chlorophora excelsa*) with a positive BAT result with this wood, and Aranda et al. [33] described the utility of BAT in OA induced by obeche wood (*Triplochiton scleroxylon*), indicating that BAT could be a useful diagnostic tool in OA.

To resume, Table 1 includes a summary of new eliciting HMW.

New LMW Occupational Agents and/or Settings

New Agents

Reactive dyes are used in textile industry and are capable to act as haptens and induce OA in exposed workers. Jin et al. [34] described the first report of OA caused by the red dye synozol red-K 3BS (Red-K), and an IgE-mediated response was suggested. A 38-year-old male non-smoker with no history of allergic disease had worked in the textile industry for 15 years and had used reactive dyes, such as synozol black B 150 (Black B) and red-K. Nine years after starting his job, he experienced rhinorrhea and 4 years later progressed to a cough and dyspnea aggravated at work. SPT was positive to Red-K (10 mg/ml), negative to Black B. Serum specific IgE to Red-K was demonstrated. SICs with both reactive dyes were performed, obtaining a positive early asthmatic response to Red-K while it was negative to Black B [34].

Whereas allergic reactions to carboplatin and cisplatin are common in patients treated with these agents, occupational allergic diseases are limited to a case of a health worker with contact urticaria. Thanasias et al. [35] have reported the first case of OA caused by potassium tetrachloroplatinate (K_2PtCl_4) in a pharmaceutical plant worker in production of cytotoxic drugs. A 22-year-old atopic subject developed work-related nasal and lower respiratory symptoms 1 year after he had started to be exposed to K_2PtCl_4 , employed in production of cisplatin, but not to further halogenated platinum salts. Specific testing was performed with K_2PtCl_4 (SPT and SIC) and sodium hexachloroplatinate Na_2PtCl_6 . The results of SPT could not be interpreted due to dermatographism. SIC was positive (early response), and serial methacholine tests did not show increased bronchial hyperresponsiveness. SIC elicited an increase in FeNO from 32 to 156 ppb 24 h after SIC. Although no specific challenge testing was performed for rhinitis, the subject's symptoms suggested also occupational allergic rhinitis.

Table 1. New high molecular weight eliciting agents of occupational asthma

Agent	Source	N	Type of job	Diagnosis	Allergen	
<i>Royal jelly</i>	Secretion of worker honeybees	2	A worker in a Pharmacy laboratory	Symptoms, SPT Positive SIC with royal jelly powder in one worker	40–55 kDa	Gomez-Torrijos et al. (2016) [8]
<i>Loligo vulgaris</i>	Squid from the cephalopods	1	Seafood production worker	Symptoms, SPT SIC in simulation of work-place conditions		Wisniewska et al. (2013) [9]
<i>Ceratitis capitata</i>	Fruit fly	2	Production of sterile males for control of pest population	Symptoms, SPT, serum specific IgE SIC with medfly extract	Different IgE-binding patterns	De las Marinas et al. (2014) [13]
<i>Holocnemus pluchei</i>	Spider	1	A farmer who handle cereal inside the warehouse	Symptoms, SPT Positive SIC	17 kDa protein identified as an arginine kinase	Bobolea et al. (2011) [14]
<i>Steinernema feltiae</i>	Nematodes used in horticulture instead of chemical pesticides	1	A worker who filtered an aqueous suspension of nematodes and added preservatives and inert bulking agents to produce the final product	Positive SIC		Feary et al. (2015) [15]
<i>Termamyl®</i>	Thermostable endo-alpha-amylase originated from <i>Bacillus stearothermophilus</i>	1	An employee in the production and packaging of detergents	Serum specific IgE		Baur et al. (2015) [16]
<i>Savinase</i>	High-alkaline protease belonging to subtilase family enzymes	1	A worker of a dishwashing tablets factory	Symptom Positive SIC and increased eosinophil count in induced sputum		Lipinska-Ojrzanowska et al. (2015) [17]
<i>Transglutaminase</i>	<i>Streptomyces mobaraensis</i>	1	A worker in a food industry	SPT Serum specific IgE and IgE immunoblot inhibition		De Palma et al. (2014) [18]
<i>Argan powder</i>	<i>Argania spinanose</i> , a tree growing in Morocco	3	A worker using Argan oil and Argan poder in a cosmetic factory	Positive SIC	3 different patterns of proteins (including 11S globulin and vicilin)	Paris et al. (2016) [23]
<i>Moringa oleifera seed powder</i>	Used in cosmetic industry	1	A worker who packaged samples of the active ingredient in a factory	Positive SIC Ig-Immunoblot	IgE reactive proteins greater than 10 kDa (24–56 kDa)	Poussel et al. (2015) [25]
<i>Limonium sinuatum</i>	Decorative flowers from the <i>Plumbaginaceae</i> family	1	A gardener	SPT Positive SIC Increased eosinophils in nasal lavage		Wisniewska et al. (2011) [26]
<i>Melon Lipid Transfer Protein (LTP)</i>	Leaves and flowers of the melon plant and the rind of the melon fruit	1	An agricultural worker in the melon harvest	SPT Positive SIC	10–12 kDa corresponding to an LTP with no cross-reactivity with Pru p3	Gomez Torrijos et al. (2015) [27]

Table 1. (Continued)

Agent	Source	N	Type of job	Diagnosis	Allergen	
Orange Lipid Transfer Protein (LTP)	Orange trees	1	A farmer with symptoms while working in the field when orange trees bloom.	SPT PEF monitoring IgE-immunoblot	A less than 14 kDa protein that could be Cis s3	De las Marinas et al. (2015) [28]
Alt a13	Homologous to glutathione s-transferase-16 from <i>Arabidopsis thaliana</i>	1	An orchard worker, a peach breeder	Symptoms IgE-Immunoblot	A 20 kDa protein	Jiang et al. (2015) [29]
Spruce Wood Dust	Spruce wood	1	A worker in a family sawmill	Daily PEF monitoring Raised eosinophil in the sputum after of two weeks of exposure		Wittczak et al. (2012) [30]

SPT skin prick test, SIC specific inhalation test, PEF peak spiratory flow, Ig immunoglobulin, kDa kilodalton

Walters et al. [36] described the first case of OA due to the biocide additive 4,4-methylene-bismorpholine present in clean metalworking fluid. A 54-year-old male, atopic, presented with a 2-year history of work-related rhinitis, wheeze, dry cough, and chest tightness. SPT were positive to some common allergens and to 4,4-methylene-bis-morpholine, with borderline reactions to cobalt chloride and clean metalworking fluid. SIC with clean metalworking fluid elicited a dual asthmatic response. Subsequent SIC to 4,4-methylene-bismorpholine resulted in immediate rhinitis symptoms and a late fall in FEV₁. He had negative SICs to the solvent, stabilizer, and cobalt chloride. A more than four-fold increase in bronchial hyperresponsiveness to methacholine, but no clinically significant change in FeNO, was observed. These results support the diagnosis of OA from sensitization due to 4,4-methylene-bismorpholine, without conclusive evidence of an IgE-mediated mechanism. 4,4-methylene-bismorpholine has a high asthma hazard index (maximum 1.0) using the Manchester Occupational Asthma Hazard Program [37]. The QSAR model has been validated using an arbitrary cut-point HI of 0.5, such that compounds with HI > 0.5 are considered likely to be asthmagenic, whereas those with an index = 0.5 are unlikely to have asthmagenic potential.

Tafenoquine is a novel 8-aminoquinoline drug currently under development as a potential treatment for the radical cure (relapse prevention) of *Plasmodium vivax* malaria. Cannon et al. [38] have reported the first case of OA caused by tafenoquine in a 38-year-old pharmacist who had been involved in the development of a drug product formulation of tafenoquine in a pharmaceutical industry. He developed rhinitis, wheezing, and breathlessness after airborne exposure to powdered tafenoquine during tablet manufacture. SPT was not attempted; an in-house assay for serum-specific IgE antibodies to tafenoquine was negative. SIC was performed using a dust tipping method in a sealed chamber, to 1% tafenoquine in lactose, and a dual asthmatic response was observed, accompanied by severe nasal symptoms. These results showed evidence that respiratory sensitization is a potential hazard during tafenoquine manufacture. Nevertheless, using the QSAR model [37], the hazard index (HI) was zero.

Ranitidine, a histamine₂-receptor antagonist that inhibits stomach acid production, is widely used. Only a few allergic reactions after intake of the drug have been reported. Henriquez-Santana et al. [39•] described the first case of a patient with OA caused by exposure to ranitidine in a pharmaceutical laboratory worker. SPT, intradermal tests, and oral challenge tests with ranitidine were negative. A SIC with ranitidine was performed and elicited a late asthmatic response.

Ortho-phthalaldehyde (OPA) is an aromatic dialdehyde that has largely replaced glutaraldehyde as a new high-level disinfectant for heat-sensitive medical devices, including endoscopes. Reports of immunological reactions have been reported in workers exposed to OPA-disinfected cystoscopes [40]. Fujita et al. [41] described the first case of OA and contact dermatitis thought to be caused by OPA exposure in a health care worker employed in an endoscopy unit. Symptoms occurred after introduction of OPA solution in the hospital. No pulmonary function test was reported, and the patient was clinically diagnosed with OA. A SIC with OPA was not performed, so the diagnosis of OA due to OPA should be considered likely, but not definitive.

Robitaille et al. [42] reported the first case of OA induced by exposure to OPA in a healthcare worker, proven with a SIC. A 55-year-old woman who consulted at the emergency department with an asthma exacerbation. She had been promoted to the endoscopic sterilization service 2 months earlier, where OPA (Cidex®) was used for disinfection of endoscopes. Symptoms developed after 3 weeks of exposure. A SIC with OPA was performed and she developed conjunctival redness and cough, as well as a late asthmatic response.

New Workplace Settings

Uriarte et al. [43] reported a rare case of OA due to polyvinyl chloride (PVC) and methyl methacrylate. A professional plumber had experienced progressive dyspnea and dry cough at work during the last 3 years. A SIC with the adhesive Tangit® PVC-U, which contained PVC powder, tetrahydrofuran, butanone, cyclohexanone, and traces of methyl methacrylate, elicited a late asthmatic response. Subsequently, the patient was exposed to PVC particles in the challenge chamber and the patient had a dual asthmatic response. Two weeks later, a SIC with methyl methacrylate elicited a dual asthmatic response. There are previous reports of OA due to the degradation PVC products or in workers handling bottle caps and packaging, but this is first case report of OA due to PVC powder contained in an adhesive.

Carmin (E-120), a natural red pigment extracted from dried female *Dactylopius coccus* (cochineal), is a well-known cause of OA. Notwithstanding, Cox et al. [44] reported the first description of carmine red allergy in a screen-printing (serigraphy) 48-year-old worker. Woman complained of increasing work-related symptoms of rhinoconjunctivitis and asthma. She had been working for years as a screen printer when she experienced respiratory symptoms, probably related to exposure to carmine red and/or cyan blue powder. Carmine-specific IgE was positive, and SPT with carmine red was positive whereas it was negative with cyan blue. A SIC with carmine red provoked nasal obstruction and a 20% decrease in FEV₁.

Vaccaro et al. [45] described a 38-year-old woman who had been working as a nail-art operator for 2 years when she developed facial dermatitis and multiple episodes of asthma at her workplace. Self-measurements of PEF showed lower values at the workplace than at home. A methacholine challenge test was positive (PC₂₀ 2 mg/ml). Skin patch tests were positive to acrylates. Although the patient refused a SIC with acrylates, she was diagnosed with airborne allergic contact dermatitis and OA caused by acrylates.

Cyanoacrylate glues have caused OA in industrial settings. In recent years, eyelash extensions have become increasingly popular worldwide. Lash extensions are attached to the customers' lashes with cyanoacrylate-based instant glues. Lindstrom et al. [46] reported a case of OA attributable to lash extension glue in a worker who developed respiratory symptoms in the workers breathing zone. SIC with lash extension glue led to a prolonged late asthmatic reaction, with an increase in FeNO levels. The volatile organic compound level (VOC) was assessed during SIC and remained below the irritant level. Beauty professionals' glues were analyzed, and (meth)acrylate and ethyl cyanoacrylate were found to be their major component. Chemical analysis of the glues also revealed small amounts of methylmethacrylate and/or butylacrylate that, unlike ethyl-cyanoacrylate, evaporate quite easily. Among beauty professionals,

acrylates appear to be a growing cause of OA, as exposure of these products continues to increase.

Quirce et al. [47] reported the first two cases of OA induced by acrylates contained in eyeglass lenses in optical laboratory technicians with work-related rhinitis and asthma symptoms. A 54-year-old nonsmoking woman had worked as an optical laboratory technician for 23 years. Her job involved grinding and polishing eyeglasses made of polycarbonate and polymethyl-methacrylate (PMM). During the last 2 years, she experienced nasal and respiratory symptoms related to exposure to the dust generated by grinding the lenses. A SIC was performed with PMM powder and a late asthmatic reaction was observed. Methacholine challenge remained negative and FeNO did not change. The second case report was a 50-year-old non-atopic, working for 34 years in the production of glass lenses. Organic lenses made of PMM were introduced 15 years ago. She had experienced nasal and asthma symptoms that had worsened over the last year, and she had had a severe asthma attack. Methacholine challenge test was positive (PC₂₀ 0.7 mg/mL). A SIC performed with PMM powder elicited rhinitis symptoms and a dual asthmatic reaction.

OA induced by sodium metabisulphite has been reported in the fish-processing industry and in radiographers. Uriarte et al. [48••] reported the first case in seafood industry. A double sensitization to sodium metabisulphite and seafood allergens was demonstrated. The patient had experienced work-related asthma symptoms for the last 3 years. Her duties consisted of handling squid, octopus, shrimp, cod, and catfish while wearing nitrile gloves. Prick-by-prick tests with shrimp, octopus, squid, hake, cod, and trout were positive. A SIC with sodium metabisulphite elicited a late asthmatic reaction. Another SIC was performed simulating the patient's working conditions, handling and cleaning a raw squid, without sodium metabisulfite, and it elicited a late asthmatic response.

Hansen et al. [49] described the first documented case of OA caused by the organic acid anhydride maleic anhydride (MA) in the production of insecticides. A 60-year-old man developed work-related respiratory symptoms after 8 years of intermittent exposure to MA. PEF measurements showed greater variance on workdays than on days off. Both, a BAT and determination of the MA-specific IgE level in serum, showed sensitization to MA.

Colophony is a common cause of OA and occupational contact dermatitis. OA is usually caused by inhalation of fumes from heated colophony. However, OA caused by unheated colophony dust is very rare. String instrument players use the unheated colophony on their bows to enhance the sound by increasing friction between the bow and the strings. Hanon et al. [50•] described the first case of OA caused by colophony in a musician. A first-violin player in a famous orchestra was diagnosed with allergic asthma. A wrist fracture forced her to stop playing the violin temporarily, and a prompt improvement in asthma symptoms was seen, which raised the suspicion of OA. A realistic SIC test with colophony was performed. The patient rosined the bow and played the violin for several consecutive periods of increasing duration. A dramatic decrease in FEV₁ (30%) was observed after a cumulative exposure time of 61 min. The patient quits violin playing, without the asthma recurring. O'Connor et al. [51] reported the case of a 61-year-old electronics lecturer who presented recurring cough and dyspnea at work. He was regularly exposed to colophony-based fluxes. A diagnosis of colophony-induced OA was assessed when PEF fell by

Table 2. New low molecular weight eliciting agents and new workplace settings of occupational asthma

Agent	Source	N	Type of job	Diagnosis	Allergen	
Red-K	Reactive dye	1	Textile industry	Symptoms. SPT Positive SIC. Serum specific IgE	Synozol Red-K 3BS	Jin et al. Allergy Asthma Immunol Res. (2011) [34]
Potassium tetrachloroplatinate	Platinum salts	1	Pharmaceutical plant worker	Symptoms, Positive SIC. SIC increased FENO	Potassium tetrachloroplatinate	Thanasias Adv Exp Med Biol. (2013) [35]
4,4-methylene- bismorpholine	Metalworking fluid	1	Industrial metalworking	Symptoms, Borderline SPT. Positive SIC with metal fluid and 4,4-methylene- bismorpholine. SIC increased BHRM	4,4-methylene- bismorpholine	Walters et al. (2013) [36]
Tafenoquine	Drug product formulation of tafenoquine	1	Pharmaceutical laboratory pharmacist	Symptoms, Positive SIC	Tafenoquine	Cannon et al. (2015) [38]
Ranitidine	Blister of ranitidine	1	Pharmaceutical laboratory worker	Symptoms. Positive SIC	Ranitidine	Henriquez-Santana et al. (2016) [39]
Ortho-phthalaldehyde	Endoscopes high-level disinfectant Cidex OPA®	1	Endoscope unit	Symptoms. Positive SIC	Ortho-phthalaldehyde	Robitaille et al. (2015) [42]
Polyvinyl Chloride and methyl methacrylate	PVC powder content in an adhesive	1	Professional plumber	Symptoms. Positive SIC with Polyvinyl Chloride and methyl methacrylate	Polyvinyl Chloride and methyl methacrylate	Uriarte et al. (2013) [43]
Carmine red (E-120)	Carmine red powder	1	Screen-printing (serigraphy) worker	Symptoms, Positive SPT Positive SIC		Cox et al. B-ENT. (2012) [44]
Acrylates	Lily Angel®	1	Nail art operator	Symptoms. Serial PEF, BHRM	?	Vaccaro et al. (2014) [45]
Ethylcyanoacrylate	Lash extension glue	1	Beauty professional	Symptoms, Positive SIC with glue	Methylmethacrylate and/or butylacrylate?	Lindstrom et al. (2013) [46]
Polymethyl methacrylate	Organic eyeglasses	2	Optical laboratory technicians	Positive SIC with polymethyl methacrylate powder	Polymethyl methacrylate	Quirce et al. (2015) [47]
Sodium metabisulphite	Seafood	1	Seafood packing assistant	Symptoms. Positive SIC with sodium metabisulphite and handling raw squid	Sodium metabisulphite. Seafood (?)	Uriarte et al. (2015) [48]

Table 2. (Continued)

Agent	Source	N	Type of job	Diagnosis	Allergen	
Maleic anhydride	Insecticide	1	Insecticides industry	Symptoms. Serial PEF measurement. Basophilic activation test +, Maleic anhydride specific IgE +	Maleic anhydride	Hansen et al. (2014) [49]
Unheated colophony	Violin bows	1	Violin player	Symptoms Realistic SIC	Colophony	Hanon et al. (2014) [50]
Abietic acid, Boswellic acid	Colophony, incense	1	Electronics lecturer	Serial PEF. Positive SIC	Abietic acid, Boswellic acid	O'Connor et al. (2014) [51]

17% after exposure to solder fumes at work for 1 h. At review, the patient reported cough, dyspnea, and wheeze that occurred acutely when exposed to the fumes from burning incense (Greek and Vatican), during Easter services at his church. SIC with those two blends of incense led to a significant reduction in FEV₁ 15 min after exposure (Greek incense 15% reduction, Vatican incense 20% reduction). Abietic acid is the most important sensitizing agent in colophony-associated asthma, and boswellic acid is a main active component of incense, being chemically similar in structure to abietic acid. The combination of colophony-induced asthma and asthma due to chemically related incense had not previously been reported.

To resume, Table 2 includes a summary of new eliciting LMW agents and new work-place settings of LMW OA.

Conclusions

A variety of novel high and LMW agents have been shown to induce occupational asthma. Apart from the identification of the allergenic sources implicated, molecular diagnosis and detailed characterization of the culprit allergens, as well as elucidation of the patterns of airway inflammation involved, contribute to increase our knowledge into the pathogenic mechanisms of this disorder. These advances may help to develop better preventive and therapeutic strategies.

Compliance with Ethical Standards

Conflict of Interest

Dr. Javier Dominguez-Ortega, Dr. Ignacio Pérez-Camo, Dr. Santiago Quirce declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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