Old and New Causes of Occupational Asthma

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KEYWORDS

• Occupational asthma • Low molecular weight
• High molecular weight • Asthmagens

The earliest account of an occupational asthma (OA) cause was attributed to Hippocrates (460–370 BCE), who described panting, a literal translation of asthma, in metal workers, fullers, tailors, horsemen, farmhands, and fishermen. His perceptive observations have been confirmed in the modern era in that OA has been well characterized in all of these occupations. OA and other respiratory disorders became more widely accepted in the medical community after Bernardino Ramazzini wrote his treatise, "De morbis artificum diatriba" in 1713, which described asthma in bakers; grain handlers; and silk, hemp, and flax workers. OA rapidly accelerated in the twentieth century with the advent of new technologies introducing a spectrum of new agents into the workplace. In the latter half of the twentieth century, the low-molecular-weight (LMW) chemical agents were first recognized as potential respiratory sensitizers that could cause OA. Presently, occupational asthmagens are categorized as LMW (<1000 kd) and high-molecular-weight (HMW, $\geq$1000 kd) agents. HMW agents are further subclassified as plant or animal derived.

International reviews suggest that the median proportion of adult cases of asthma attributable to occupational exposure is between 10% and 15%.[1] Therefore, it is essential that clinicians have a broad knowledge of the various causes associated with this condition. The purpose of this article is to review the most common representative causes of OA over the past 70 years, with specific emphasis on newer causes that have been reported over the past 5 years.

OLD CAUSES OF OCCUPATIONAL ASTHMA

Traditionally, causes of OA are divided into HMW and LMW agents. These causes have been widely reviewed and most extensively in the text, *Asthma in the Workplace*,

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published in 1993 and updated in subsequent editions. This text was the first to extensively review the most prevalent causes of OA. The HMW agents that were considered most relevant were flour dusts, enzymes (both plant and animal derived), gums, foods and tobacco, rubber-derived proteins, animal- and insect-derived allergens, and fish/seafood-derived allergens (**Table 1**). The LMW agents considered most relevant were polyisocyanates and their polymers, acid anhydrides, metals, a spectrum of chemical substances (ie, azobisformamide, amines, colophony and fluxes, formaldehyde, persulfate, diazonium salts and reactive dyes, pharmaceuticals, polyvinylchloride and adhesives and acrylates), and western red cedar (see **Table 1**). Irritant-induced asthma, including the reactive airways dysfunction syndrome, is considered a form of OA caused by nonspecific exposure to high levels of irritating vapors, fumes, or smoke and is discussed elsewhere in this monograph. Occupational respiratory disorders, including airway obstruction caused by cotton dusts and organic dust toxic syndrome, are asthmalike conditions but do not fall within the definition of OA. In reviewing the causes of OA over the past 50 to 70 years, it is important to note that many of the reported case series lack confirmatory evidence of OA, including skin testing or specific bronchoprovocation testing (see **Table 1**).

High-Molecular-Weight Agents

In the workplace, HMW protein allergens are natural sensitizers. Baker's asthma, described initially by Thiel and Ulmer[2] in 1980, is a classic example. Subsequently, several studies have reported sensitizing cereal and noncereal grain antigens contained in wheat, triticale, rye, barley, oats, rice, and corn in the workplace.[3] Other relevant allergens associated with baker's asthma include fungal antigens (*Aspergillus* and *Alternaria*); enzymes derived from the *Aspergillus* species, such as α-amylase and hemicellulase; plant-derived enzymes, such as papain/chymopapain; as well as mite antigens.[4–8]

Enzymes are proteins used as biocatalysts to reduce or replace the use of chemicals in a variety of processes.[9] As catalysts, enzymes are used in a variety of industries, including cleaning, food processing, animal feed, fuel alcohol, textile, paper, and pharmaceuticals. The first enzyme commercially introduced in the United States and England was Alcalase in 1967, which was derived from *Bacillus subtilis* for use in soap detergents.[10] Within 3 years, 80% of all soap detergents sold in the United States contained enzymes. Subsequently, Flindt and Pepys[10,11] reported the first cases of respiratory symptoms in detergent workers after inhalation exposure to the *Bacillus subtilis*–derived powdered enzymes, Alcalase and Maxatase. Eighty percent of workers with respiratory symptoms elicited a positive wheal and flare skin test response to skin test reagents prepared from the enzymatic material and *Bacillus subtilis* spore extracts.[10] These index cases demonstrated that enzymes were highly allergenic and that susceptible workers exposed to these agents were at an increased risk for becoming sensitized and developing asthma.

In general, enzymes are plant or microbial derived. Examples of plant-derived enzymes known to cause occupational sensitization and asthma include papain widely used in cosmetic, food, and pharmaceutical consumer products; chymopapain (a proteolytic enzyme, structurally related to papain), once used for intradiscal dissolution of herniated lumbar disks; pepsin used as an additive in the production of liquors, cheeses, and cereals; and bromelain, which is used in the pharmaceutical industry.[9]

Microbial-derived enzymes are typically produced by bacterial microorganisms belonging to *Bacillus* sp and *Pseudomonas sp* and fungal organisms, such as *Aspergillus sp, Streptomyces sp*, and *Trichoderma sp*, and are most commonly used to

Table 1
Representative older causes of occupational asthma induced by high-molecular-weight agents

Agents	Occupation	N	Skin Test (%)	Specific IgE	Bronchoprovocation	References
High-Molecular-Weight Agents						
Laboratory animal	Laboratory workers	296	13	34	ND	Venables,[15] 1988
Cow dander	Agricultural workers	49	100	ND	ND	Mantyjarvi, 1992
Egg protein	Egg producers	188	34	29	ND	Smith, 1990
Crab	Snow-crab processors	303	22	ND	72% of 42+	Cartier, 1984
Prawn	Prawn processors	50	26	16	2/2+	Gaddie,[20] 1980
Hoya	Oyster farm	1413	82% of 511+	89% of 180+	ND	Jyo,[25] 1980
Cuttlefish	Deep-sea fishers	66	ND	ND	ND	Tamaszumas, 1988
Salmon	Processing plant	291	ND	25	ND	Douglas,[24] 1995
Red soft coral	Fishers	74	2/2+	ND	ND	Onizuka,[26] 1990
Grain mite	Farmers	290	21	19% of 219+	ND	Cuthbert, 1984
Grain mite	Grain-store workers	133	25	23% of 128+	1/1+	Blainey, 1989
Amblyseius cucumeris (bell pepper pollen)	Horticulturists	472	23	Some	ND	Groenewoud, 2002
Locust	Laboratory workers	118	32% of 113+	Done	ND	Burge, 1980
Screw worm fly	Flight crews	182	91% of 11+	ND	ND	Gibbons, 1965
Insect larvae	Fish-bait handlers	76	32	19	ND	Siracusa, 2003
Fruit fly	Laboratory workers	22	27	27	ND	Spieksma, 1986
Mealworm larvae	Fish-bait handlers	5	4/5	3/5	ND	Bernstein, 1983
Larva of silkworm	Sericulture	5519	100% of 9+	1/1+	100% of 9+	Armentia, 1998
Grain dust	Grain elevators	610	9	ND	ND	Chan-Yeung, 1985
Wheat, rye, and soya flour	Bakers, millers	279	9	ND	ND	Musk et al,[6] 1989
Coffee bean	Food processor	372	24	12	ND	Jones, 1982
Rose	Culture of roses	290	ND	19.5	ND	Demir, 2002

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Table 1
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Agents	Occupation	N	Skin Test (%)	Specific IgE	Bronchoprovocation	References
Chrysanthemum	Greenhouse workers	104	20.2	+ in some	ND	Groenewoud, 2002
Helianthus annuus	Processing workers	102	23	ND	ND	Atis, 2002
Biologic enzymes *(Bacillus subtilis)*	Detergent industry	1642	4.5%–75.5%	ND	ND	Juniper, 1977
Papain	Pharmaceutical	29	34	34	89% of 9+	Baur, 1982
Fungal amylase	Bakers	118	100% of 10+	ND	ND	Baur et al,[4] 1986
Fungal amyloglucosidase and hemicellulase	Bakers	140	ND	5%–24%	ND	Baur et al,[8] 1988
Esperase	Detergent industry	667	ND	5%	ND	Zachariae, 1981
Lactase	Pharmaceutical	207	31	ND	ND	Muir, 1997
Guar	Carpet manufacturer	162	8	ND	ND	Malo, 1990
Latex	Glove manufacturing	81	11	ND	ND	Tarlo et al,[30] 1990
Low-Molecular-Weight Agents						
Toluene diisocyanates	Polyurethane, plastics, varnish	112	3	0	45% of 11+	Butcher et al,[35] 1976
Toluene diisocyanates	Polyurethane, plastics, varnish	162	ND	ND	57	Mapp et al,[36] 1988
Diphenylmethane diisocyanate	Foundry	11	ND	27	54.5	Zammit-Tabona et al,[37] 1983
Hexamethylene diisocyanate	Spray painters	20	ND	ND	10+	Vandenplas, 1993
Phthalic anhydride	Plastics	118	18% of 11+	ND	ND	Wenfors, 1986
Trimellitic anhydride	Epoxy resins, plastics	4	100	75	100% of 1+	Zeiss et al,[41] 1977
Aliphatic amines	Chemical factory	12	NA	ND	ND	Ng, 1995
Ethanolamines	Beauty culture	10	ND	ND	100% +	Gelfand, 1963
Quaternary amines	Cleaning product	1	+	ND	+	Bernstein, 1994

Colophony	Electronics workers	34	ND	ND	100%+	Burge, 1980
Western red cedar	Furniture making	1320	19	ND	ND	Ishizaki et al,[44] 1973
Platinum	Platinum refinery	136	17	26	ND	Brooks et al,[48] 1990
Psyllium	Pharmaceutical	130	19% of 120+	26% of 118+	27% of 18+	Bardy et al,[49] 1987
Spiramycin	Pharmaceutical	51	100	ND	25% of 12+	Malo et al,[27] 1988
Reactive dyes	Reactive dyes manufacturer	309	15	34	65% of 20+	Alanko, 1978
Chloramine T	Chemical manufacturing	6	100	ND	ND	Feinberg, 1945
Polyvinyl chloride	Meat wrapper	96	ND	ND	27% of 11+	Andrasch, 1976
Persulfate salts and henna	Hairdressing	23	4	ND	100%	Blainey, 1986
Diazonium salt	Manufacturing of fluorine polymer precursor	45	ND	20	100% of 2	Luczynska, 1990
Azobisformamide	Plastics, rubber	151	ND	ND	ND	Slovak, 1981
Formaldehyde	Hospital staff	28	ND	ND	50% of 4+	Hendrick, 1975
Methyl-methacrylate	Adhesive	7	ND	ND	86%+	Lozewicz et al,[103] 1985

Abbreviations: N, number of workers; ND, not done.

Modified from Malo JL, Chan-Yeung M. Agents causing occupational asthma with key references. In: Bernstein IL, Malo JL, Chan-Yeung M, et al, editors. Asthma in the workplace. 3rd edition. New York: Taylor and Francis; 2006. p. 825–66; with permission.

manufacture soap detergents.[9] These serine protease enzymes derived from *Bacillus* organisms (also called subtilisins or subtilopeptidases) are also useful in household cleaning agents because of their potent enzymatic activity and stability over wide ranges of pH and temperature.[12]

OA induced by cellulose and β-d-galactoside derived from the *Aspergillus niger and oryzae* species, respectively, have been well documented in the pharmaceutical industry.[9] A cross-sectional survey performed on 94 pharmaceutical workers exposed to *Aspergillus oryzae*–derived β-d-galactoside galactohydrolase revealed that 29% of exposed workers had lactase sensitization and lactase-sensitized workers were 9 times more likely to experience upper- or lower-respiratory symptoms compared with skin test negative subjects.[13] Atopic workers were 4 times more likely to develop lactase sensitization compared with nonatopic workers. Reduction of lactase exposure and restricting atopic workers from working with lactase successfully prevented lactase-induced occupational symptoms.[13] Other examples of microbial-derived enzymes causing sensitization and OA include workers exposed to pectinases in the food industry, phytase and β-gluconase in the animal feed industry, and porcine pancreatic amylase in a laboratory.[9]

Egg-processing workers are at an increased risk for OA after becoming sensitized to egg proteins, such as ovalbumin, ovomucoid, and conalbumin, as well as egg lysozyme.[13,14] OA in laboratory animal handlers has been well documented.[15] Atopy is a risk factor for animal handler's OA. Exposed workers typically become sensitized within the first year and the most common cause is rats, followed by mice and rabbits.[16]

Fish and seafood–derived allergens are common causes of OA.[17–26] Many of these workers are fishers or processors that have frequent dermal and inhalational exposure to these allergens.[17–26] Specific immunoglobulin (Ig) E antibody responses have been demonstrated for cuttlefish, trout, shrimp, prawn, crab, and oyster processors and in many instances confirmed by specific bronchoprovocation.[17–27]

OA caused by natural rubber latex sensitization (NRL) was first reported in 1987.[28] Since that time, numerous cross-sectional studies have reported that NRL protein allergens from the rubber tree *Hevea brasiliensis* caused OA in health care workers using high-protein powdered latex gloves, glove manufacturers, and several other occupations.[28–31] Latex-induced OA is an excellent example illustrating the effectiveness of modifying exposure in the workplace in preventing symptoms in workers with established NRL sensitization or OA and in preventing new cases. Since latex-safe environments have been instituted in hospitals by switching to low-protein latex and nonlatex gloves, the prevalence of latex sensitization and reported new cases of OA have dramatically decreased.[32]

Low Molecular Weights

Diisocyanates are LMW chemicals widely used to produce polyurethane foam insulation and spray paints that have wide applications in the automobile and building industries. These chemicals may at times act as haptens and conjugate to endogenous proteins to form complete allergens. Soon after toluene diisocyanate (TDI) was introduced commercially, reports of asthma in exposed workers were reported.[33] Since that time, diisocyantes have become recognized as one of the most common causes of OA in the world. The structural differences between the aromatic compounds, TDI and methylene diphenyl diisocyanate (MDI), and the aliphatic compound, hexamethylene diisocyanate (HDI), confer different chemical properties leading to different exposure risks for workers.[34] For example, TDI is highly volatile at room temperature and is now used less than MDI, which requires heating before vapors are emitted.[34] Many

specific bronchoprovocation studies have confirmed that isocyanates are respiratory sensitizers causing OA but specific IgE-mediated sensitization can be demonstrated in only a minority of workers with OA caused by MDI, TDI, or HDI.[31,35–37]

Trimellitic anhydride (TMA) is an acid anhydride widely used as a curing or hardening agent in epoxy resins, in the production of plasticizers for polyvinyl chloride, and in polyester and alkyd resins.[38] The National Institute of Occupational Safety and Health estimates that 20,000 workers in the United States have developed TMA-induced occupational illness in various work processes.[39] TMA can cause irritant-induced asthma after a single large exposure as well as a spectrum of occupational respiratory conditions, asthma being the most common. TMA is a unique LMW chemical because it binds to endogenous protein to form a complete antigen capable of eliciting IgE sensitization that can be demonstrated by skin prick testing or serologically.[40,41] Studies have reported workers becoming sensitized to TMA and have confirmed OA by specific bronchoprovocation.[40,41]

Milne[42,43] first described western red cedar asthma in the timber industry in 1969. Since that time, numerous cases of OA have been described in furniture factory workers, sawmill workers, and other woodworker occupations.[44,45] The constituent thought to induce respiratory sensitization and asthma is plicatic acid.[45]

The most well-described cause of OA induced by metals has been in the platinum refinery industry.[46–48] Exposed workers have been reported to develop positive IgE-specific skin and serologic tests to platinum salts.[46–48] The persistence of sensitization and asthma can be quite prolonged after workers are removed from the workplace, especially if there is a significant delay in removing these workers from further exposure after recognizing the development of sensitization.[48]

Finally, numerous cases of OA have been reported among workers in the pharmaceutical manufacturing industry. Psyllium, which is manufactured as a laxative, has been found to induce IgE sensitization and asthma in susceptible exposed workers.[49] Bardy and colleagues[49] evaluated 130 pharmaceutical workers exposed to psyllium and found that 39 had symptoms suggestive of OA; 23 of 120 workers were skin test positive to psyllium and 31 of 118 workers had specific IgE antibodies to psyllium. Five of 18 workers able to undergo specific bronchoprovocation testing to psyllium were positive.[49]

NEW CAUSES OF OCCUPATIONAL ASTHMA

The high-risk occupations and industries associated with the development of OA vary depending on the predominant industrial sectors in a particular country.[50,51] The list of causative agents of immunologically mediated OA is continuously growing, and new agents and professions are described each year (**Table 2**). A variety of novel HMW and LMW agents have been shown to induce OA. Recent data indicate that LMW chemicals account for more new cases of OA caused by sensitization than HMW agents.[52,53]

HIGH-MOLECULAR-WEIGHT AGENTS

Food and Baking Industry

There are many foods, food additives, and contaminants that have been associated with OA.[54] Exposure to food allergens occurs primarily through inhalation of dust, powder, vapors, and aerosolized proteins generated during cutting, cleaning, cooking or boiling, and drying activities. In the last few years, novel wheat allergens have been implicated in the pathogenesis of baker's asthma. Constantin and colleagues[55] identified in 2008 a serine proteinase inhibitor as a novel allergen in baker's asthma by

Table 2
New causes of occupational asthma

HMW Agents	Occupation	Confirmed By	IgE Pos (+ or -) and to Which Specific Allergens	Reference
Brassica oleracea pollen (cauliflower and broccoli)	Plant breeders	Clinical history	SPT+ IgE+	Hermanides et al,[112] 2006
Korean ginseng & sanyak	Herbal-products trader	SIC+	SPT+ to both IgE+ to sanyak IgE- to ginseng	Lee et al,[113] 2006
Yarrow (*Achillea millefolium*) and Safflower (*Carthamus tinctorious*)	Florist	SIC+	SPT+ IgE+	Compes et al,[114] 2006
Cedrorana (*Cedrelinga catenaeformis* Ducke) wood dust	Carpenter	SIC+	SPT+ IgE+	Eire et al,[72] 2006
Roe deer (*Capreolus capreolus*)	Animal-rehabilitation workers	CPT+	SPT+ IgE+	Carballada et al,[76] 2006
Mushroom (*Pleurotus ostreatus*)	Grocer	SIC+	SPT+ IgE+	Vereda et al,[115] 2007
Arabidopsis thaliana	Laboratory plant worker	SIC+ PEF monitoring	SPT+	Yates et al,[116] 2008
Chamomile (*Matricaria chamomilla*)	Tea-packing-plant worker	SIC+	SPT+ IgE+	Vandenplas et al,[117] 2008
Ivy (*Hedera helix*)	Florist	SIC+ PEF monitoring	SPT-	Hannu et al,[95] 2008
Linseed oilcake (*Linum usitatissimum*)	Chemist	SIC+	SPT+ IgE+	Vandenplas et al,[118] 2008
Tomato (*Lycopersicum esculentum*)	Greenhouse worker	SIC+	SPT+ IgE+	Vandenplas et al,[119] 2008

Tampico fiber (*Agave lechuguilla*)	Brush maker	SIC+	SPT+ IgE+	Quirce et al,[75] 2008
Olive fruit (*Olea europaea*)	Olive oil mill worker	NPT+	SPT+ IgE+ Thaumatinlike protein	Palomares et al,[59] 2008
Octopus (*Octopus vulgaris*)	Seafood processor	SIC+	SPT+ IgE+	Rosado et al,[68] 2009
Bovine serum albumin (Bos d 6)	Laboratory researcher	SIC+	IgE+	Choi et al,[78] 2009
Malt	Machine operator at a malt company	SIC+	SPT+	Miedinger et al,[61] 2009
Chengal wood (*Neobalano-carpus hemeii*)	Carpenter	SIC+ PEF monitoring	ND	Lee and Tan,[73] 2009
Sausage mold (*Penicillium nalgiovensis*)	Semi-industrial pork butchers	Clinical history	SPT+	Talleu et al,[82] 2009
Marigold flour (*Tagetes erecta*)	Animal fodder factory employee	NPT+	SPT+ IgE+	Lluch-Pérez et al,[64] 2009
Cabreuva wood (*Myrocarpus frondosus*)	Parquet floor layer	SIC+	SPT- IgE+ BAT+	Pala et al,[74] 2010
Rice (*Oryza sativa*)	Rice mill workers and handlers	SIC+	SPT+ IgE+	Kim et al,[62] 2010
Turbot (*Scophthalmus maximus*)	Fish-farm workers	PEF monitoring	SPT+ IgE+	Pérez Carral et al,[67] 2010
Gerbil (*Meriones unguiculatus*)	Biologist	SIC+	SPT+ IgE+ 23-kDa lipocalin	de las Heras et al,[77] 2010
Cellar spider (*Holocnemus pluchei*)	Farmer	SIC+	SPT+ IgE+ Arginine kinase	Bobolea et al,[85] 2010
LMW agents				

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Table 2
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HMW Agents	Occupation	Confirmed By	IgE Pos (+ or -) and to Which Specific Allergens	Reference
Escin	Pharmaceutical worker	SIC+	SPT- IgE-	Munoz et al,[86] 2006
Sevoflurane and isoflurane	Anesthetic staff	SIC+ PEF monitoring	ND	Vellore et al,[87] 2006
Ortho-phthalaldehyde	Nurse	Clinical history	ND	Fujita et al,[88] 2006
Lasamide	Pharmaceutical workers	SIC+	ND	Klusackova et al,[89] 2007
Alendronate	Pharmaceutical worker	SIC+ (occupational rhinitis)	SPT+	Pala et al,[90] 2008
Eugenol	Hairdresser	SIC+	SPT-	Quirce et al,[94] 2008
Turpentine	Art painter	SIC+	SPT-	Dudek et al,[96] 2009
Metal arc welding of iron	Welder	SIC+	ND	Muñoz et al,[97] 2009
Vancomycin	Pharmaceutical worker	PEF monitoring	SPT-, IDT+ IgE- BAT+	Choi et al,[91] 2009
Trimethylolpropane triacrylate	Thermal printer	SIC+	ND	Sánchez-García et al,[111] 2009
Dodecanedioic acid	Electronics instructor	SIC+ PEF monitoring	ND	Moore et al,[98] 2009
Rhodium salts	Operator of an electroplating plant	SIC+	SPT+ IgE-	Merget et al,[99] 2010
5-ASA	Pharmaceutical worker	SIC+	SPT-	Sastre et al,[92] 2010
Colistin	Pharmaceutical worker	SIC+	IgE-	Gómez-Ollés et al,[93] 2010
Polymethyl methacrylate (from eyeglasses)	Optical laboratory technicians	SIC+ PEF monitoring	ND	Quirce et al,[110] 2011

Abbreviations: BAT, basophil activation test; CPT, conjunctival provocation test; IDT, intradermal test; ND, not done; NPT, nasal provocation test; PEF, peak expiratory flow; Pos, positive; SIC, specific inhalation challenge; SPT, skin prick test.

screening of a cDNA library from wheat seeds with serum IgE from patients with asthma. The allergen is a 9.9 kDa protein, which represents a new member of the potato inhibitor I family. It is probably involved in plant defense and belongs to the pathogenesis-related protein-6 family. Palacin and colleagues[56] have characterized wheat Tri a 14 as a major allergen associated with baker's asthma. Specific IgE to this wheat flour was detected in 60% of sera from 40 Spanish patients with baker's asthma, and positive skin prick tests (SPT) were found in 15 (62%) of 24 of these patients. Furthermore, recombinant Tri a 14 has been produced in *Pichia pastoris*; its physicochemical properties, heat and proteolytic resistance, and IgE-binding capacity were shown to be almost equivalent to those of its natural counterpart.[57] Thaumatinlike proteins (TLPs) are the latest salt-soluble protein family from wheat flour that has been associated with baker's respiratory allergy by Lehto and colleagues[58] in 2010. Most TLPs have molecular masses ranging from 21 to 26 kDa. Moreover, OA caused by a TLP from olive fruit has been described.[59] An SPT with purified TLP at 1 μg/ml was positive, as was the nasal challenge test with TLP (0.1 μg/ml).

Constantin and colleagues[60] analyzed the IgE reactivity profiles of patients suffering from baker's asthma, wheat-induced food allergy and grass pollen allergy to microarrayed recombinant wheat flour allergens and grass pollen allergens. They identified recombinant wheat flour allergens, which are specifically recognized by patients suffering from baker's asthma. Profilin was identified as a cross-reactive allergen recognized by patients suffering from baker's asthma and food and pollen allergies.

Miedinger and colleagues[61] reported for the first time a case of IgE-mediated OA to malt in a machine operator for a malt manufacturing company.

Kim and colleagues[62] reported 3 cases of OA caused by exposure to rice powder in the work environment. All 3 patients showed positive SPT and IgE determinations to rice extract, and specific inhalation challenge (SIC) induced immediate and late asthmatic responses.

Pirson and colleagues[63] described the case of a patient working in a factory producing inulin from chicory who developed rhinoconjunctivitis and asthma from the dust of dry chicory roots. An SIC with dry chicory elicited acute rhinoconjunctivitis and an early asthmatic response. SPT results were positive to birch pollen and fresh/dry chicory and negative for inulin. Specific IgE to rBet v 1 was strongly positive. IgE immunoblotting with chicory extract showed a 17 kDa IgE-binding band, which was inhibited with purified Bet v 1.

Marigold flour, prepared from the flowers of *Tagetes erecta* or the flowers of *Calendula officinalis*, has been extensively used by the food additive industry as poultry feed colorant. Lluch-Pérez and colleagues[64] reported the first case of IgE-mediated occupational rhinitis and asthma caused by marigold flour. It was demonstrated by SPT, nasal challenge test, and specific IgE determination. A 60 kDa IgE-binding band was observed by immunoblotting, and cross-reactivity between extracts from marigold flour and *Helianthus annuus* pollen was demonstrated.

Bernstein and colleagues[65] described a case of respiratory sensitization to konjac flour (glucomannan) occurring in a food manufacturing worker. The worker presented with 3 episodes of hives, shortness of breath, chest tightness, wheezing, and hoarseness after exposure to a variety of powdered food ingredients. The evaluation included spirometry, methacholine challenge, and allergy testing to standard allergens and extracts made from food ingredients from the workplace. Serum-specific IgG and IgE enzyme-linked immunosorbent assay (ELISA), ELISA inhibition assays, and specific provocation to relevant food ingredients were also performed. SPT was significantly positive to konjac glucomannan (KGM) and guar gum F glactomannan. Sensitization was confirmed by SIC using a sifting technique. After sifting KGM for 5

minutes, the patient developed upper- and lower-respiratory symptoms associated with a significant decrease in peak expiratory flow rate requiring emergency treatment. Subsequent avoidance of KGM in the workplace resulted in the resolution of all symptoms. This case demonstrates the potentially sensitizing nature of polysaccharide-based food additives that can lead to severe allergic reactions.[65]

Lucas and colleagues[66] have reviewed OA in the commercial fishing industry, indicating that it more commonly occurs because of crustaceans, but mollusks and finfish are also implicated. Pérez Carral and colleagues[67] reported 3 workers at a fish farm who experienced rhinoconjunctivitis and asthma caused by sensitization to turbot. The allergens were parvalbumin in 1 case and a different allergen in the remaining 2 patients.

Rosado and colleagues[68] described the first case of OA from aerosolized octopus allergens in a seafood-processing worker. Immunoblotting revealed IgE-binding bands of 43 and 32 kDa that could correspond to tropomyosin.

OA caused by exposure to the fish and nematode parasite, *Anisakis simplex*, through an IgE-mediated mechanism has also been reported among fish processors.[69]

Wood and Vegetal Fiber

Wood-dust exposure may cause IgE-mediated allergic diseases. Schlünssen and colleagues[70] reported that the prevalence of pine and beech sensitization among current Danish woodworkers was 1.7% and 3.1%, respectively. No differences in sensitization rates were found between woodworkers and references, but the prevalence of wood-dust sensitization was dose-dependently associated to the current level of wood-dust exposure. They suggested that the importance of beech and pine-wood sensitization may be of clinical significance for a few workers if the IgE epitopes are proteinaceous.

Campo and colleagues[71] evaluated the frequency of work-related specific sensitization and respiratory symptoms in carpentry apprentices with exposure to wood dust and diisocyanates. SPTs to a panel of 14 different woods were performed in 101 apprentices. Sensitization to wood was detected in 9% of the participants, all of whom were atopic with a history of rhinitis; 2 of them had asthma. Seven apprentices showed a positive SPT reaction to olive tree wood, 1 to obeche wood, and 1 to pine tree wood.

Eire and colleagues[72] described a carpenter who developed occupational rhinitis and asthma caused by cedrorana (*Cedrelinga catenaeformis Ducke*) wood dust. SPT and specific IgE to this wood were positive. Both nasal provocation and SIC to cedrorana wood elicited early responses.[72]

Chengal is a resistant rainforest hardwood that is commonly used in Southeast Asia. Exposure to chengal wood dust can lead to OA and rhinitis of an uncertain mechanism.[73]

Pala and colleagues[74] reported the case of an atopic man employed as a parquet floor layer who developed occupational rhinitis and asthma caused by cabreuva wood (*Myrocarpus frondosus*). SPT with cabreuva wood dust was negative, and SIC elicited rhinitis and a dual asthmatic response. IgE reactivity toward a 75-kDa protein and a positive basophil activation test strongly suggested a role of IgE in cabreuva wood–induced respiratory allergy.

Two brush-making workers who developed asthma and rhinitis symptoms following occupational exposure to Tampico fiber were described.[75] Tampico fiber, which is extracted from the leaves of *Agave lechuguilla*, is used extensively for making yard brooms, deck brushes, and bath brushes. SPTs and IgE-immunoblotting to Tampico

extract were positive. The results of SIC and induced sputum supported an effect of Tampico fiber exposure in causing OA on a nonirritating basis.[75]

Animal and Arthropod Allergens

Occupational rhinitis and asthma caused by roe deer-derived allergens has been described in two workers at an animal rehabilitation center.[76] De las Heras and colleagues[77] have described a biologist who developed rhinitis and OA when she worked with gerbils (*Meriones unguiculatus*). A new gerbil allergen of 23 kDa was identified in the gerbil urine, epithelium, hair, and airborne samples. Partial characterization of this allergen suggested that it was possibly a lipocalin.

Bos d 6, bovine serum albumin (BSA), is a major allergen in beef and a minor allergen in milk. It is also commonly used in research laboratories. Choi and colleagues[78] reported a case of OA and rhinitis in a laboratory worker caused by the inhalation of BSA powder in which an IgE-mediated response was demonstrated.

OA caused by the mold *Chrysonilia sitophila* (asexual state of *Neurospora sitophila*), which was previously reported in the lodging industry, has been recently shown to also affect workers in the coffee industry. OA has been demonstrated by SPT, serial peak expiratory flow (PEF) measurements, and IgE analyses.[79–81]

A case of chronic cough related to OA with sensitivity to dry sausage mold (*Penicillium nalgiovensis*) has been reported in a semi-industrial pork butcher worker.[82] The diagnosis was based on positive SPT, spirometry, and a favorable outcome after avoidance of the allergen.

Miedinger and colleagues[83] have described the case of an engineer who worked for an electric power company who developed OA caused by caddis flies (Phryganeiae) confirmed by a SIC using an extract of these insects.

Amblyseius californicus has been recently added to the list of predatory mites that induced IgE sensitization and OA among greenhouse workers.[84]

Bobolea and colleagues[85] have recently reported a case of OA in a farmer caused by the cellar spider (*Holocnemus pluchei*) and confirmed by SIC. Immunoblotting displayed different bands in the spider extract, in a range of 20 to 70 kDa. All were hemocyanins, except for a 17-kDa protein identified as an arginine kinase.

LOW-MOLECULAR-WEIGHT AGENTS

Escin

A 57-year-old man employed in the pharmaceutical industry developed asthma while working with *Plantago ovata* and escin, an active ingredient derived from horse chestnut with antiinflammatory and venotonic properties. An SIC with escin was positive, whereas SIC with *P ovata* was negative. The mechanism by which escin can produce asthma is unknown, but possibly non-IgE mediated.[86]

Sevoflurane and Isoflurane

Three cases of OA, work-related angioedema or dermatitis to isoflurane (1-chloro-2,2,2-trifluoroethyl difluoromethyl ether) and sevoflurane (fluoromethyl 2,2,2-trifluoro-1-[trifluoromethyl] ethyl ether), were described in anesthetic assistants or nurses in the same hospital. All presented a positive SIC. In 2 patients, a late asthmatic response was elicited after SIC (one with isoflurane and sevoflurane and another with sevoflurane). In another patient, exposure to isoflurane was followed by an itchy rash.[87]

Ortho-phthalaldehyde

A nurse employed in the endoscopic unit developed asthma and contact dermatitis a few months after starting to work with ortho-phthalaldehyde for the disinfection of endoscopes.[88]

Lasamide

Lasamide (2,4-dichloro-5-sulfamoylbenzoic acid) is used in the manufacture of the diuretic furosemide (4-chloro-*N*-furfuryl-5-sulfamoylanthranilic acid). Three patients from a lasamide production line were diagnosed with OA. All 3 patients had positive SIC. Two patients were diagnosed with occupational rhinitis.[89]

Alendronate

Sodium alendronate (SA) is an LMW compound inhibiting bone resorption that is used to treat osteoporosis. A woman employed in a pharmaceutical company started to complain of nasal itching, rhinorrhea, and dry cough 1 month after being moved exclusively to the SA line. SPT and patch tests with SA in saline were positive. An SIC with exposure for 60 minutes to SA 10 mg dissolved in lactose provoked a significant increase in the nasal symptoms score and a significant decrease in peak nasal inspiratory flow but no change in FEV_1. After SA exposure, bronchial hyperresponsiveness to methacholine and induced sputum eosinophils increased.[90]

Vancomycin

A 33-year-old man, employed in the pharmaceutical industry, developed rhinorrhea, cough, dyspnea, and chest discomfort at work, which consisted of purifying vancomycin to manufacture into its powder form. The diagnosis of vancomycin-induced OA was based on clinical history, work-related symptoms, and increased PEF variability at the workplace.[91]

5-Aminosalicylic Acid

A 56-year-old man complained of cough, dyspnea, and wheezing 1 month after beginning work in manufacturing a drug containing 5-aminosalicylic acid (5-ASA), despite taking measures to protect the skin and respiratory system. SPT to 5-ASA (10 mg/mL) was negative. PC_{20} methacholine was greater than 16 mg/mL, fractionated exhaled nitric oxide (FENO) level was 32 ppb, and induced sputum showed no eosinophils. During an SIC, the patient was exposed to 5-ASA (5% in lactose) in the chamber at a mean concentration of 2.65 mg/m^3 for a total of 30 minutes. A late response was observed 9 hours after the challenge; 24 hours later, methacholine PC_{20} was 10 mg/mL, with a FENO value of 53 ppb and induced sputum showed 65% eosinophils.[92]

Colistin

An atopic 24-year-old man working in a pharmaceutical company transporting and storing raw material developed occupational rhinitis and asthma to colistin. Three months after starting his current job, he developed rhinitis, which improved over the weekends. Nine months after the onset of rhinitis, exposure to colistin caused him to suffer sudden cough, wheeze, and dyspnea. The SIC confirmed the diagnosis of OA and rhinitis to colistin. Specific IgE was not detected.[93]

Eugenol

A hairdresser developed occupational rhinitis and asthma caused by eugenol, confirmed with an SIC test (late asthmatic reaction). SPT with common aeroallergens, latex and eugenol 2% weight per volume, were negative, as well as a patch test with

eugenol.[94] An increase in sputum eosinophils and lymphocytes was observed 24 hours after eugenol SIC, and a methacholine inhalation test became positive. Proliferation tests of peripheral blood mononuclear cells from the patient showed a strikingly (15 times higher) different eugenol-induced proliferation as compared with the control subject.[94]

Ivy

A 40-year-old woman who had worked in her own flower shop for the past 11 years developed cough and dyspnea when she handled ivy. SPT with different plants, including *Hedera helix* (leaf), were negative. An SIC during which the patient cut and tore the flowers, stalks, and leaves of the plants for 30 minutes elicited an immediate asthmatic reaction.[95]

Turpentine

Turpentine, a fluid obtained by distillation of wood resins containing a mixture of terpenes, is a known inducer of contact dermatitis. A 27-year-old art painter using turpentine as a thinner for oil-based paints developed asthmatic reactions after 5 years of working with turpentine. An SIC showed a late asthmatic reaction and an increase of eosinophils in sputum 24 hours after the challenge.[96]

Iron Welding Fumes

Muñoz and colleagues[97] described 3 patients with OA secondary to exposure to welding fumes generated during metal arc welding of iron. The exposure time ranged from 7 to 43 years and the time of the onset of symptoms following the start of exposure was 2 to 12 years. Patients were diagnosed by SIC.

Dodecanedioic Acid

Moore and colleagues[98] reported the first case of OA caused by electronic colophony-free gel flux predominantly containing dodecanedioic acid. The patient worked as an electronics instructor, and OA was demonstrated by serial PEF measurements and by a positive SIC with dodecanedioic acid fluxes, whereas the SIC was negative to the colophony wire and wire containing predominantly palmitic acid.

Rhodium Salts

A 27-year-old atopic operator of an electroplating plant developed work-related shortness of breath and runny nose with sneezing after exposure to rhodium salts. The patient showed positive SPT reactions and positive bronchial immediate-type reactions with rhodium and platinum salts.[99]

Triglycidyl Isocyanate

Triglycidyl isocyanate (TGIC) is a hardening agent used in powder paints. TGIC has been reported to cause allergic contact dermatitis, OA, and hypersensitivity pneumonitis in powder paint sprayers.[100] A 28-year-old woman developed work-related asthma symptoms when aluminum frames were treated with an electrostatic powder paint containing 2.5% to 10.0% TGIC.[101] OA was confirmed by serial PEF measurements and a methacholine test. An SIC with TGIC (4% in lactose) at a mean concentration of 3.61 mg/m^3 for 15 minutes induced an isolated early asthmatic response. No IgE to TGIC was detected by ELISA testing and no IgE-binding bands were found by immunoblot analysis. Anees and colleagues[102] reported 6 workers at a factory that made domestic gas appliances that had a powder coat containing 10% TGIC applied to them electrostatically to provide a protective and decorative finish. These workers,

who were exposed as bystanders to heated TGIC, developed OA confirmed by serial PEF measurements. SIC testing resulted in late or dual asthmatic reactions to heated TGIC in 4 of the 4 tested and was negative in 3 control subjects with asthma. One worker tested only with unheated TGIC had a negative SIC test. Thus, heated TGIC can cause OA from bystander exposure.

Acrylates

Acrylates are well-known causative agents of occupational rhinitis and asthma.[103,104] The widest series of OA caused by acrylates were reported by Savonius and colleagues and Piirilä and colleagues.[105,106] Jaakkola and colleagues[107] reported that the risk of adult-onset asthma, nasal symptoms, and other respiratory symptoms significantly increases with the daily use of methacrylates in dental assistants' work. Sauni and colleagues[108] recently described the first 2 cases of OA caused by sculptured nails containing methacrylates. Both patients had a dual type of asthmatic reaction after a work simulation test, and 1 of them also had allergic contact dermatitis from exposure to methacrylates. Similarly, Jurado-Palomo and colleagues[109] reported a case of OA caused by cyanoacrylates contained in sculptured fingernails, confirmed by means of SIC, significant changes in airway hyperresponsiveness to methacholine, and an increase in FENO. Quirce and colleagues[110] have recently reported 2 cases of optical laboratory technicians with work-related rhinitis and asthma. Acrylates contained in eyeglass lenses have not been previously reported as an etiological agent of OA. Her job consisted of cutting and polishing eyeglasses made of polycarbonate and polymethyl methacrylate. Sánchez-García and colleagues[111] described a nonatopic, nonsmoking 62-year-old woman who had been working for 20 years selling lottery tickets inside a 4-m^3 kiosk. Over the last 3 years, she had been using a point-of-sale (POS) terminal to print lottery coupons. POS are devices used worldwide to pay with credit cards or to print lottery/bet coupons. She had a 2.5-year history of rhinoconjunctivitis, facial edema, cough, shortness of breath, and wheezing within 30 to 60 minutes after arriving at her workplace, which improved during holidays. SIC in a 7-m^3 chamber in a worker performing painting on a cardboard with the tint provided by the lotto company (containing trimethylolpropane-triacrylate) elicited an early asthmatic reaction. Twenty-four hours after the challenge, methacholine PC_{20} was 1.68 mg/mL (baseline methacholine PC_{20} was 6.18 mg/mL) and FeNO 22 ppb (baseline 14 ppb). Induced sputum cell count showed a 100% increase in eosinophils in comparison with baseline counts. One week later, an occupational-type challenge was performed simulating her work environment using the patient's own POS and printing coupons for 90 seconds, and again an early asthmatic reaction was observed.

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