

Agents causing occupational asthma

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The workplace is a significant contributor to the burden of asthma. Although the majority of cases probably represent what is labeled *work-exacerbated asthma*, in a significant number of subjects, asthma is actually caused by 1 or more agents present in the workplace; this is occupational asthma. Two types of occupational asthma are distinguished, according to whether the asthma appears after a latency period. This article discusses (1) two types of agents causing asthma with a latency period and acting through an apparently immunologic mechanism (high-molecular-weight agents and low-molecular-weight agents) and (2) agents causing asthma without a latency period. (J Allergy Clin Immunol 2009;123:545-50.)

Key words: Asthma in the workplace, occupational asthma, irritant-induced asthma

The workplace is a significant contributor to the burden of asthma, with approximately 1 in every 10 patients with asthma in population-based studies reporting that their symptoms are worse at work.^{1,2} Although the majority of cases probably represent what is labeled *work-exacerbated asthma*,³ in a significant number of subjects, asthma is actually caused by the workplace—that is, occupational asthma (OA; Fig 1). OA has been defined as follows:

[A] disease characterized by variable airflow limitation and/or hyperresponsiveness and/or inflammation due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace. Two types of occupational asthma are distinguished by whether they appear after a latency period: 1. After a latency period (allergic): this category is characterized by work-related asthma appearing after a latency period and encompasses: (a) occupational asthma caused by most high- and certain low-molecular-weight agents for which an allergic (IgE mediated) mechanism has been proven; and (b) occupational asthma induced by specific occupational agents (e.g. Western red cedar) but the allergic mechanisms responsible have not yet been fully characterized. 2. Without a latency period (non-allergic).

Abbreviation used

OA: Occupational asthma

This category includes irritant-induced asthma or reactive airways dysfunction syndrome (RADS), which may occur after a single or multiple exposures to non-specific irritants at high concentrations.⁴

AGENTS CAUSING ASTHMA WITH A LATENCY PERIOD AND ACTING THROUGH AN APPARENTLY IMMUNOLOGIC MECHANISM

Agents that cause OA can be divided into 2 groups according to their molecular weight: agents of high-molecular and low-molecular weights. Some characteristics of these 2 types of agents are shown in Table I.

High-molecular-weight agents

Virtually all proteins of animal or plant origin are capable of causing IgE-dependent sensitization, rhinoconjunctivitis, and asthma. There is a huge list of agents, and many new agents are reported each year (see www.asthme.csst.qc.ca). In this summary article, only the most frequent causes are covered.

Cereals and flours. Cereals and flour are the oldest causes reported⁵ and remain, with isocyanates, the most common causes (Table II). Dockworkers are exposed to various cereals that can cause, apart from OA, different syndromes as a result of exposure to organic dust, including allergen-induced airway obstruction and a febrile alveolitis-like condition.⁶ Wheat is the most commonly incriminated cereal, probably because it is the most frequently encountered, but soya is highly allergenic, responsible for cases of allergy and asthma in population living in the vicinity of harbors, as in the Barcelona epidemics.⁷ Bakers are at risk of developing sensitization not only to various cereal flours they handle at work but also to storage mites, various other added protein products, and enzymes (α -amylase is the most common) that are added to offer better control of processing. During the 1990s, several immunoassays became available to determine the allergenic content of material obtained from personal sampling.⁸ Bakeries, along with small animal facilities, were the first workplace for which a dose-response curve between exposure and risk of sensitization was clearly established,⁹ with atopic individuals at risk even at lower exposure, although nonatopic subjects can develop sensitization at higher concentrations. A relatively low exposure of 0.2 $\mu\text{g}/\text{m}^3$ has been observed to reduce risk for sensitization significantly, leading to that threshold being specifically recommended in Europe. Diagnosis should not be based on

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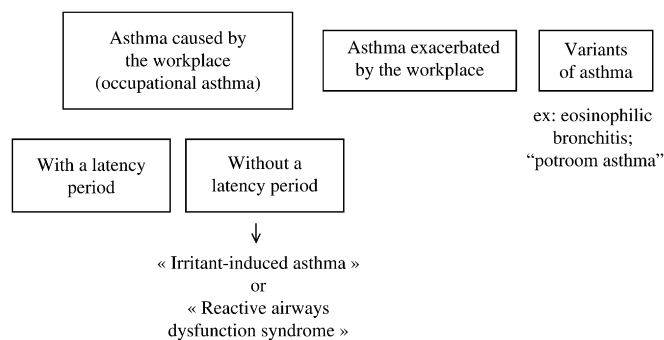


FIG 1. Asthma in the workplace.

symptomatology alone, however. Although 1 study showed an incidence of 16% of work-related rhinoconjunctivitis symptoms in apprentices in a bakery program, only a minority of the symptomatic subjects (10%) also developed IgE-mediated sensitization.¹⁰ Therefore, objective confirmation that combines assessment of IgE-mediated immunity and functional assessment (peak expiratory flow monitoring, specific inhalation challenges) is mandatory.

Laboratory animals and shellfish allergy. Small animals represent a frequent cause of OA in laboratory technicians and veterinarians. Of all proteins present in the workplace, whatever their nature, proteins excreted in urine are probably the most potent source of sensitization, especially proteins produced by male rats.¹¹ An incidence of 8.9 per 100 person-years has been found in approximately 400 apprentices examined before and after starting exposure,¹² with this figure dropping to 1.3 per 100 person-years once employed and seen on average 8 years afterward,¹³ showing that onset of sensitization and symptoms is more common soon after exposure starts, with the latency period here relatively short. Atopy is a risk factor of relatively low impact, with the main personal risk factor baseline sensitization to the usual pets, dogs and cats.¹² As for antigens in bakeries, quantification of airborne antigens is feasible with reasonable precision. Animal facilities represent a workplace where control of exposure should represent a priority because this is feasible using individually ventilated cages.¹¹ Animal handlers are exposed not only to animal-derived allergens but also to endotoxin. Endotoxin exposure was found in 1 study to be responsible for the presence of symptoms in individuals who showed no evidence of IgE-mediated sensitization.

Exposure to larger animals such as cows is also a common cause of OA. This is the leading cause of OA in Finland.¹⁴

Various fishes¹⁵ and shellfishes can cause OA, especially crab, for unknown reasons, much more so than lobster. Both species are intensively harvested in waters off most parts of the northeastern coast of North America.^{16,17} The responsible allergens are present in cooking water and meat.

Latex. Latex allergy became a real epidemic of allergies and OA in the 1980s. Allergic sensitization causing life-threatening anaphylactic reactions has been documented in patients as well. Health professionals are affected by skin and anaphylactoid reactions as well as asthma. The prevalence of OA was 2.5% in 1 meticulous study.¹⁸ Diagnosis was initially hampered by the lack of satisfactory and safe extracts for skin testing. Adequate reduction of this allergen in workplaces, along with the case of enzymes (see “Enzymes” below), provided proof that environmental control (for

example, use of low-latex content gloves, low-powdered gloves, or no latex gloves) can considerably reduce the number of cases. This has been the case in health care workers who are nowadays much less frequently affected. Subjects who are allergic to latex often experience cross-allergic reactions to foods such as banana, kiwi, avocado, and chestnut.

Enzymes. If latex allergy was a major cause of OA in the 1980s, enzymes presented a major threat of allergic sensitization, especially in the soap industry, in the 1970s.¹⁹ The prevalence of sensitization to enzymes derived from *Bacillus subtilis*, alcalase and maxatase, reached levels of 20% to 60% at the time. Although adequate control of the environment through encapsulation has greatly reduced the risk of sensitization, cases continue to be reported. Enzymes were the first occupational agent for which control of the environment was convincingly shown to reduce the risk greatly. A multitude of plant-derived and microbe-derived enzymes are used in the workplace, and many have been reported to cause sensitization and asthma.

Various occupational allergens of plant and flower origins, beans and gums, can cause OA. Greenhouse workers, who represent a high-risk group, have been the focus of epidemiologic surveys because they represent a large population and the environment can well be characterized.²⁰

Many ubiquitous allergens can, at times, be considered as occupational allergens. This is the case of grass pollens for municipal workers cutting lawns or mites for hotel employees making beds. These workers are exposed to higher doses of antigens, which can cause asthmatic reactions that would not occur in the context of ubiquitous exposure. For some jurisdictions, a diagnosis of occupational asthma can be accepted in these instances.

Low-molecular-weight agents. There are at present approximately 100,000 individual chemical entities on the European Inventory of Existing Commercial Substances, and new low-molecular-weight chemicals are frequently introduced into the market. It is possible to predict potential sensitizing properties of these agents.²¹

Many low-molecular weight agents are capable of inducing OA. Some of these agents, such as acid anhydrides, and some metals, such as platinum salts, induce asthma through an IgE mechanism, but for a large number of agents of this class, the mechanisms of induction of asthma remain unknown. Inhalation challenge testing with the responsible agent can induce different types of asthmatic reactions, most often isolated late and atypical reactions. The following discussion is confined to the more common causes of occupational asthma caused by low-molecular-weight agents.

Anhydrides. Acid anhydrides are used in making alkyd and epoxy resins. Epoxy resins are widely used in adhesives, casting, coating, and sealants, whereas alkyd resins form the base for paints, varnishes, and plastics.

Phthalate anhydride has long been known to cause OA and rhinitis. Trimellitic anhydride exposure is associated with a spectrum of lung diseases: asthma, rhinitis, late respiratory systemic syndrome, and pulmonary disease–anemia syndrome.²² As many as 2.5% of workers exposed to trimellitic anhydride and 8.8% of workers exposed to various anhydrides may show work-related respiratory symptoms. A significant association has been found between HLA antigens DR3 and specific IgE antibodies to trimellitic anhydride.

Exposure to tetrachlorophthalate anhydride has been associated with asthma. Specific IgE antibodies have been reported in 12% of atopic subjects and 6% of nonatopic subjects exposed to

TABLE I. Characteristics of high-molecular-weight and low-molecular-weight agents as causes of occupational asthma

	High-molecular-weight agents	Low-molecular-weight agents
Structure	Proteins, polysaccharides	Chemicals, metals
Duration of the latency period before getting "sensitization"	Generally longer (ex: flour)	Generally shorter (ex: isocyanates)
Oculonasal symptoms	+++	+
Accompanying dermatitis	Rare	Possible
Immunologic mechanism	IgE-dependent	Generally not IgE-dependent IgG, MCP-1 (isocyanates)
Cellular component	Eosinophils	Eosinophils and neutrophils
Feasibility of skin testing to elicit immediate reactions	Yes	No
Type of asthmatic reaction after challenge	Immediate, dual	Isolated late or atypical
Frequency of referral	One third	Two thirds
Diagnostic means	Numerous	More limited

tetrachlorophthalate anhydride.²³ Smokers who are atopic have the highest prevalence of increased specific IgE antibodies.

Metals. Metals in the first series of the periodic table are more potent sensitizers compared with the rest, but cases of OA caused by metals mostly come from platinum and aluminum exposure.

Platinum salts, particularly the halides, are more potent in inducing sensitization and asthma than any other metallic salts.²⁴ In some chemical plants, the cumulative risks for sensitization can be as high as 51% within 5 years. Smoking is a strong risk factor for a positive skin prick test, but not atopy or bronchial hyperresponsiveness. The HLA-DR3 phenotype has been associated with a significant increased risk of skin sensitization to platinum salts.

The prevalence of sensitization correlates closely with OA. Skin prick testing has a high sensitivity and specificity for detecting patients with platinum salt-induced OA. A maximum concentration of 1 g/L sodium hexachloroplatinate has been recommended for skin testing and for bronchial challenge testing, because this concentration does not induce false-positive reactions.

The threshold limit value for exposure platinum salts is 2 $\mu\text{g}/\text{m}^3$, but it is not known whether this level prevents sensitization. Secondary prevention by medical surveillance programs using skin prick testing with platinum salt and a questionnaire has been recommended.²⁵

A variant of OA has been reported among potroom workers in aluminum smelters who report respiratory symptoms, including wheezing, during a shift at work. The cause of potroom asthma is not known. There is a large variation in the prevalence/incidence of potroom asthma in the aluminum industry, from 0.06% to 4% of exposed workers, with a low prevalence in North American studies compared with Scandinavian studies.²⁶ A typical asthmatic reaction with changes in FEV₁ beyond 20% on a work shift has rarely been demonstrated.

Di-isocyanates. In many parts of the world, di-isocyanates are the most common cause of OA. The commonly used di-isocyanates in industries are shown in Table II. All these chemicals have N=C=O groups that are highly reactive and explain their sensitizing properties. The prevalence of di-isocyanate-induced OA is from 5% to 10%. In recent years, lowering the permissible concentration from 20 ppb to 5 ppb may have reduced cases.²⁷ Dermal exposure is postulated as a reason for sensitization.

As for most low-molecular-weight agents, atopy is not a predisposing factor. However, predisposition conferred by certain HLA class II antigens has been reported in some studies, whereas the presence of GSTP1 Val/Val genotype was found to confer protection.²⁸

Although the mechanism of OA caused by di-isocyanates has been explored in a vast number of studies, there is still considerable controversy regarding its pathogenesis, more specifically whether the disease is a result of a non-IgE-dependent mechanism. Specific IgE antibodies to toluene di-isocyanate (TDI) have been reported in only a minority of workers with (TDI-induced OA (0% to 50%, depending on the study). Bronchial biopsies of patients with di-isocyanate-induced OA show the absence of bronchial IL-4 RNA message, irrespective of response to inhalation challenge, suggesting that this is a non-IgE-mediated disease. Specific IgG and monocyte chemoattractant protein 1 have also been incriminated. The characteristics of the inflammatory process in di-isocyanates-induced OA are similar to those of common asthma. Both neutrophils and eosinophils are found in induced sputum and lavage.

Cleaning agents. In many population-based studies, exposure to cleaning agents at work has steadily been shown to be associated with increased risks of asthma after adjusting for confounders.²⁹ Many cleaning and sterilizing agents can cause OA (Table II). The most notable example is glutaraldehyde, which is used extensively for disinfecting heat-sensitive equipment such as fiber-optic endoscopes and also for developing radiographs. Health care workers are known to be at risk for exposure to a number of sensitizers other than cleaning agents at work (Table II).

Much less is known about the risk factors, exposure levels, clinical features, and pathogenetic mechanisms of asthma related to cleaning agents. Professional cleaners are exposed not to 1 agent but to many such as bleach, ammonia, and hydrochloric acid. Most of these agents are low-molecular-weight compounds, and it is not clear whether they induce the production of specific IgE antibodies. Many are irritants and may interact with sensitizers to induce asthma.

Wood dusts. Many different species of wood have been identified as being associated with OA; some are listed in Table II. Most cases of OA caused by wood dusts were published as case reports, with the exception of OA caused by Western red cedar (*Thuja plicata*), which has been studied extensively.³⁰ The prevalence of work-related asthma in Western red cedar sawmills ranges from 1.6% to 13.5% and is directly related to the level of exposure. The permissible concentration of Western red cedar dust has currently been reduced from 10 mg/m^3 to 1 mg/m^3 . The agent responsible for asthma has been identified as plicatic acid, which is a low-molecular-weight compound of 440 d. The clinical picture and outcome have been well described, and the pathology is similar to di-isocyanate-induced OA. As for OA caused by di-isocyanates, the mechanisms responsible for red cedar asthma are

TABLE II. Agents causing occupational asthma with a latency period

Classes	Agent	Industry/exposure
Low-molecular-weight agents		
Anhydrides	Phthalate anhydride, trimellitic anhydride, maleic anhydride, tetrachlorophthalate anhydride	Plastics, epoxy resin, dye
Metals	First series of transitional metals: vanadium, chromium, cobalt, nickel, zinc	Electroplating, refineries, metal alloys for welding
	Second series of transitional metals: palladium, ruthenium, rhodium, and cadmium	Refineries
	Third series of transitional metals: iridium and platinum	Refineries
	Group III metals: aluminum	Smelters
Diisocyanates	Indeterminate metals	
	Toluene diisocyanate, methylene diphenyl diisocyanate I, hexamethylene diisocyanate, prepolymers of TDI and hexamethylene di-isocyanate	Polyurethanes, plastics, foundries, spray paints
Cleaning agents	Biocides: hexachlorophene, chlorhexidine, glutaraldehyde, hypochlorite, quaternary ammonium compounds, chloramines T	Health care professionals, professional or domestic cleaners
	Preservatives: benzalkonium chloride, isothiazolinones, formaldehyde	
	Corrosion inhibitors: ethanolamines	
	Surface care: acryl polymers, polyethylene	
	Perfumes or scents: D-limonene, terpenes	
Wood dusts	Western red cedar, <i>Thuja plicata</i> ; Eastern white cedar, <i>Thuja occidentalis</i> ; California red wood, <i>Sequoia sempervirens</i> ; iroko, <i>Chlorophora excelsa</i> ; Cedar of Lebanon, <i>Cedrus libani</i> ; oak, <i>Quercus robur</i> ; Mahogany-Shereal sp; and others	Sawmill workers, carpenters, woodcarvers, cabinet- or furniture-makers
Soldering fluxes	Colophony	Electronics industry
Pesticides	Organophosphates	Farming
Pharmaceutical	Psyllium, ipecacuanha, pancreatic, and glandular extracts	Health care professionals
	Antibiotics: penicillin, amoxicillin, ampicillin, penicillamine, cephalosporins, spiramycin	
Reactive dyes	Black henna, brilliant yellow E36, carmine, FD&C blue dye #2	Hairdressers, textile workers, food industry workers
High-molecular-weight agents		
Enzymes	Alcalase, maxatase, amylase, various	Soaps, baking products, food industry workers
Cereals and flour	Cereals, enzymes	Baking and pastry-making, harbor workers
Animals	Rat and mouse urine, various small animals, cows, shellfish (crab)	Laboratory technicians, veterinarians, farmers, shellfish processors
Latex	Latex	Health care professionals

still unclear but are likely a combination of immunologic and non-immunologic factors. Atopy is not a predisposing factor, but certain HLA class II antigens are associated with predisposition and others with protection.

Much less is known about OA caused by other wood dusts shown in Table II because epidemiologic studies have not been as systematically carried out as for Western red cedar. Specific IgE antibodies have been found in some workers, but in most instances, this is not the case.

Colophony and fluxes. Colophony is widely used as a flux in electronic industry. In the United Kingdom, colophony-induced asthma was responsible for 9% of all cases of OA in 1998. Colophony is obtained from pine trees containing abietic

acid. The prevalence of work-related respiratory symptoms among electronic workers was 22%. The prevalence of symptoms was related to the degree of exposure. Half of the workers with colophony-induced asthma continued to have symptoms 4 years after cessation of exposure.³¹

Exposure to multiple agents

In many industries or occupations, workers are exposed to a number of high-molecular-weight agents, low-molecular-weight sensitizers, and irritants, some of which are listed in Table III. Health care workers are the most obvious group, accounting for 16% of work-related asthma in the United States. Health

TABLE III. Workplaces associated with exposure to more than 1 agent

Industry	Agents
Health care	Cleaning agents
	Sterilizing agents
	Pharmaceuticals: psyllium, antibiotics,
	Metals in dental alloys
	Methacrylates
	Aerosolized medications: ribavirin, pentamidine
Hairdressing	Spills of chemicals, such as acetic acid
	Latex
	Persulfate salts, reactive dyes, henna
	Bleaching agents
	Secondary, tertiary and quarternary amines, either aliphatic, heterocyclic or aromatic
	Latex
Farming	Herbicides, insecticides, fungicides
	Endotoxin
Baking	Animal derived allergens, arthropods, plants, molds
	Cereals
Auto body repair	Enzymes
	Isocyanates
	Acrylates
	Amines

professionals involved with instrument cleaning, exposed to powdered latex gloves, and administering aerosolized medications are at increased risk of asthma.

Hairdressers are also exposed to multiple respiratory sensitizers. The prevalence/incidence of OA in hairdressers ranges from 0.20 to 0.26 per 1000 in Norway to 3.9 per 1000 in Sweden. In France, from 1996 to 1999, 6.8% of all reported cases of OA were hairdressers. Although persulfate salts are the most likely cause of asthma in most hairdressers, the mechanism is unknown.

Farmers and other agricultural workers are exposed to a large variety of protein-derived and animal-derived allergen products as well as to chemicals and endotoxins at work (Table III). Exposure to organophosphate pesticides is known to be associated with airway hyperresponsiveness and asthma. Pesticides may also modulate inflammatory responses to endotoxin and allergens, because they are associated with atopic but not nonatopic asthma.

AGENTS CAUSING ASTHMA WITHOUT A LATENCY PERIOD

Irritant gases used in World War I, accidental spills from trains in residential urban areas, and events of immense public concern such as the Bhopal and World Trade Center catastrophes are examples of what is referred to as irritant-induced asthma or reactive airways dysfunction syndrome, a label given to this condition by Brooks et al in 1985.³²

After an accidental inhalation event, exposed individuals start in the next few minutes and hours to present a sensation of burning in the nose and throat, followed by symptoms that mimic asthma. Coughing is more of a concern than wheezing.³³ Many agents have been incriminated, with vapors and aerosols more harmful than dry particles. Chlorine and ammonia are the most frequently reported agents. Workers often visit first-aid and emergency units, at which time they are mainly administered bronchodilators and oxygen, whereas they should instead be treated rapidly with

oral and inhaled steroids that have a beneficial effect in irritant-induced asthma. Moreover, rather than discharging these patients, follow-up should be organized to ensure that workers are not left with permanent airway obstruction and hyperresponsiveness.

In conclusion, although some agents are less often reported as causing OA with a latency period (such as detergent enzymes and latex), others (such as flour and isocyanates) still represent a significant threat. Many chemicals are introduced in the occupational environment without sufficient information on their potential sensitizing properties. Finally, all agents that exist as vapors or aerosols can cause irritant-induced asthma if generated at high concentrations. All workers are at risk of such inhalational accidents.

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