

Occupational Asthma in the Food Industry

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Opinion statement

Inhalation of food-derived allergens during food processing at the workplace represents a risk for developing occupational asthma (OA) in exposed workers. Cereal flours and seafood are the causal agents most frequently involved. The management of food-derived OA includes timely pharmacologic therapy and environmental interventions aimed to avoid or reduce exposure to the offending agent to increase the probability of recovery. Cessation of exposure is the best option, but when the causative agent cannot be completely avoided reduction of exposure, through modification of food processing, improving ventilation, mechanization, etc. can be considered as an alternative. Quantification of real exposure levels is crucial, and new accurate immunologic and chemical assays able to detect low levels of aerosolized flour and seafood allergens have recently been developed. Recent papers have described intervention strategies effective in reducing airborne allergen exposure in flour and seafood industry, but the long-term health impact of this intervention has still to be defined. Specific allergen immunotherapy (SIT) might be another management option in individuals with IgE-mediated food-induced OA. Both a short- and a long-lasting beneficial effect of SIT with wheat flour in reducing symptoms whilst keeping the patient at work has been shown in bakers' asthma, but at present, SIT is not for routine use for bakers' asthma due to the lack of commercial standardized extracts. A better identification on a molecular basis of allergens involved in flour and in other IgE-mediated food-derived OA might help in preparing new extracts suitable for immunotherapy. In selected cases of bakers' asthma, the monoclonal antibody omalizumab has been effective in reducing symptoms. SIT and omalizumab might represent further management options in IgE-mediated OA in food industry.

Introduction

Work-related asthma (WRA) represents between 3 and 20% of all asthma cases and is the most common form of occupational lung disease [1]. WRA comprises two major entities, i.e., occupational asthma (OA), defined as a type of asthma “caused” by the workplace, and work-exacerbated asthma (WEA), i.e., personal asthma exacerbated at the workplace by various work-related factors, and variants like eosinophilic bronchitis (Fig. 1). OA is the most common type and may be allergic and non-allergic [1, 2]. OA is frequently associated and preceded by occupational rhinitis (OR) and the two conditions share the same mechanisms and agents [3]. The majority of cases of OA and OR are allergic, caused by animal and vegetal high-molecular-weight proteins. A proportion of them derives from aerosolized foods during food processing at the workplace, and represents an occupational risk factor in food industries. Exposure occurs through inhalation of dust, steam, vapours, and aerosolized proteins generated during cutting, scrubbing or cleaning, cooking or boiling, or drying activities. The spectrum of diseases includes asthma, rhinitis, conjunctivitis [4–6], and anaphylaxis [7, 8]. Most reactions are allergic IgE-mediated, others can be due to non-IgE allergic mechanism, or may even be non-allergic. Food additives used as preservatives and antioxidants [9], enzymes contained in bread improvers like fungal or bacterial alpha-amylase [10], or contaminants like mites or cereal pests [11–13] may also induce asthma in food industry. Moreover, the inappropriate use of latex gloves during food processing in some occupational settings, like kitchens, can also lead to the development of latex allergy and asthma. [14]. Usually, workers

that have developed sensitization to a food allergen at the workplace can tolerate the responsible food by ingestion, and only few cases of adverse reactions by ingestion in sensitized workers are reported in the literature [15, 16].

An extensive list of main occupations and agents responsible for OA in food industry is available [6]. More recently, some new agents have been described [17–26] (Table 1). A yearly updated list of occupational respiratory sensitizers is available in http://www.eaaci.org/images/pdf.files/Occupational_Allergens_1-16.pdf.

Some agents like flours or seafood [15] have an epidemiological relevance, for others small populations or single cases are reported. Cereal flour is one of the leading causes of OA and OR all around the world [10, 27]. Bakers employed in small enterprises or in supermarket bakeries [28] are not only the workers most frequently affected but also other workers handling bakery allergens such as confectioners, or flour millers, can develop the disease [6]. Bakers’ asthma is a classical IgE-mediated OA. Wheat and rye flour proteins and the enzyme alpha-amylase are the most frequently involved allergens [10, 27•, 29], but other enzymes used as improvers [25•, 30•], or proteins derived from others cereals [20], or storage mites [17], may be involved.

The management of OA in food industry includes environmental interventions aimed to avoid or reduce exposure to the offending agent, and appropriate therapy. Besides, assessment of impairment and compensation is mandatory [31, 32].

The present paper will review the most recent available data on management of OA in food industry.

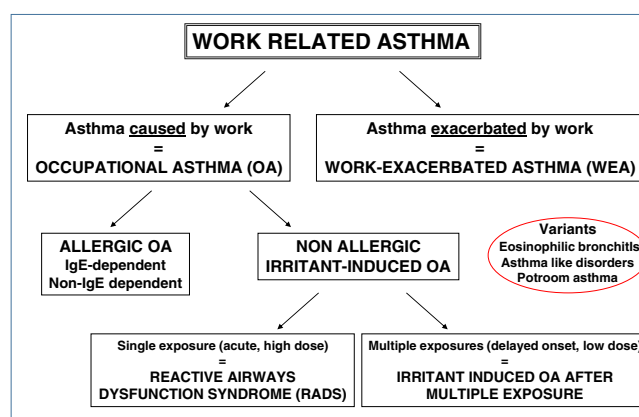


Fig. 1. Classification of work-related asthma (from Ref. [1]).

Table 1. New agents recently described as responsible for occupational asthma in food industry. A comprehensive list is available in Ref no. [6]

Agent	Occupation	Associated occupational diseases	Study design	Ref.
Storage mites	Baker	None	Case report	Pala G et al. 2010 [17]
Gum arabic	Candy factory worker	Contact urticaria and rhinitis	Cross-sectional	Viinanen A et al. 2011 [18]
Lima bean (<i>Phaseolus lunatus</i>)	Food processing factory (cake dough production)	None	Case report	Tonini S et al. 2012 [19]
Rice	Baker	None	Case report	Villalta D et al. 2012 [20]
Goat cheese (casein)	Cheese factory worker	Rhinitis	Case report	Sastre I et al. 2013 [21]
Squid (<i>Loligo vulgaris</i>)	Seafood production worker	Conjunctivitis, rhinitis, and contact dermatitis	Case report	Wiszniewska M et al. 2013 [22]
Sole fish (yellowfin sole)	Restaurant's kitchen worker	None	Case report	Boulet LP et al. 2014 [23]
Ham storage mites	Ham worker	Rhinitis	Cross-sectional, case-control	Tafuro F et al. 2015 [24]
Bakery adjuvants (xylanolytic enzymes)	Baker	Conjunctivitis and contact dermatitis	Case report	Lipinska et al. 2016 [25]
Mushroom spores (<i>Pleurotus ostreatus</i>)	Vegetable vendor	None	Case report	Baldassarre A et al. 2016 [26]

Treatment

Pharmacologic therapy

The concept of “control-based management” of asthma in the food industry should result in the early pharmacological treatment set-up according to the initial severity of the disease, and in non-pharmacological treatment (early cessation or reduction of exposure from the sensitizing agent) to increase the probability of recovery, continuously reviewed and adjusted according to symptom control [33]. Pharmacologic therapy does not differ from that of non-OA [33]. The treatment of concomitant rhinitis should always be considered. There is currently insufficient evidence that treatment with inhaled corticosteroids and long-acting β_2 -agonists is able to prevent the long-term deterioration of asthma in subjects who remain exposed to the agent causing OA, and anti-asthma medications should not be regarded as a reasonable alternative to environmental interventions [34].

Allergen-specific immunotherapy

In the proportion of cases of OA and OR caused by sensitizers acting through an allergic, IgE-mediated mechanism, the possibility of allergen-specific immunotherapy (SIT) might be evaluated [28, 35••, 36, 37••]. SIT consists of the administration by subcutaneous (SCIT) or sublingual (SLIT) route of gradually increasing doses of allergen extracts aimed to induce the tolerance of the immunologic system of the individual to that allergen [38]. In non-occupational field, both SCIT and SLIT with inhalant extracts have been demonstrated to be effective in reducing rhinitis and asthma symptoms and in modifying the natural history of respiratory allergy, preventing the onset of asthma in patients with allergic rhinitis [38, 39]. Less data is available for SIT with food allergens.

In occupational setting, the use of SIT is greatly limited by the poor quality and lack of standardized allergen extracts, and in food industry, only a few experiences in bakers' asthma have been reported.

In a double-blind placebo-controlled study [40], 20 bakers with OA treated with an aqueous wheat flour extract up to 20 months showed symptom improvement, and a significant decrease in skin sensitivity, in serum-specific IgE to flour and in bronchial hyperreactivity to methacholine. No change was observed in ten subjects treated with placebo.

In an observational, cross-sectional, retrospective study conducted in Italy [41], 41 bakers sensitized to flour, with work-related rhinitis and/or asthma, mostly working in small enterprises, underwent SCIT with wheat flour extract for 4 or more years. Respiratory symptoms improved and the subjects could continue their work activity. At two follow-up investigations by a questionnaire after 5 and 10 years, 34 of the 41 subjects were still at work with an acceptable quality of life and a normal working efficiency, demonstrating a long-lasting beneficial effect of SCIT with wheat flour, and its efficacy in protecting from symptoms of rhinitis and/or asthma while continuing occupational exposure to flours.

Other promising data on the efficacy of SIT in bakers' asthma were derived from single case reports [42].

Overall, the available data seem to demonstrate that in bakers' asthma, SIT may help in reducing symptoms and keeping the patient at work, but the lack of standardized commercial extracts greatly limits its use in the routine practice.

The lack of available standardized allergen flour extracts reflects the difficulties in identifying the major allergens in wheat flour-induced OA [28••, 30•]. As a matter of fact, a total of 70 different IgE-binding protein spots in wheat flour have been identified, and sera of most sensitized bakers show IgE reactions with many of these proteins, but each baker shows an individual IgE-binding profile with great interindividual variation. Therefore, no wheat allergen can be classified as the major allergen [30•]. Possibly, a better identification of proteins involved in the disease at a molecular level may help in preparing new standardized extracts suitable for immunotherapy [28••].

Despite the paucity of data on the effectiveness of SIT in OA, the ACCP guidelines concluded that SIT may be an effective management option in individuals with sensitizer-induced OA due to selected high-molecular-weight agents when a commercial extract is available, and the causative agent cannot be completely avoided for economic, professional, or other reasons [43].

Omalizumab

The monoclonal anti-IgE antibody omalizumab has been shown to have clinical benefit in two subjects with uncontrolled severe bakers' asthma.

Olivieri et al. [44] described a case of a 53-year-old baker who had been suffering for several years from asthma when exposed to flour dust at the workplace. Skin prick test was positive to wheat flour and alpha-amylase. Despite the daily administration of high-dose inhaled combined fluticasone/salmeterol (2000/200 µg) and montelukast tablet (10 mg), the patient had continuous respiratory symptoms at the workplace. Treatment with omalizumab 375 mg twice a month was prescribed. After 1 month, montelukast could be discontinued and combined fluticasone/salmeterol was gradually reduced every 4 weeks. During the treatment, the asthma control test (ACT) [45] score gradually increased from an initial value of 11 up to 25 at the fourth month and persisted without variations, and the Juniper asthma quality of life (QoL) questionnaire [46] showed a remarkable improvement of all individual domains' score. The patient continued his work free of asthmatic symptoms.

Perez-Piemento et al. [47] described a case of a 35-year-old baker, with a 13-year history of perennial rhinitis and asthma. He had been working in a bakery since the age of 20 years. During the last year before observation, the patient referred four asthmatic exacerbations requiring emergency medical visits and multiple doses of oral prednisone. After diagnosis of OA due to flour, SCIT with wheat flour was initiated, but immediately after administration of a dose, the patient experienced a systemic reaction. SCIT was discontinued and omalizumab (375 mg every 2 weeks) was prescribed. During treatment, the patient's clinical condition improved considerably, as demonstrated by improved QoL scores, by a reduction in the need for systemic corticosteroids, and fewer emergency visits. The patient could continue his work.

Interventional procedures

Environmental interventions

The avoidance or reduction of exposure to the offending allergen is a cornerstone in the management of OA. Interventions should be carried out as early as possible after onset of symptoms to prevent permanent asthma; therefore, an early diagnosis is mandatory for a favourable outcome of the disease [43].

In allergic OA, complete cessation of exposure to the workplace sensitizer is the most desirable intervention, since it is associated with the highest probability of improvement, although it may not lead to a complete recovery from asthma [34, 48]. When elimination of the agent from the workplace is not possible, relocation of the worker in an area without exposure to the causal agent, or changing job, may be proposed but are associated with the worst socioeconomic consequences (loss of income, unemployment, financial disruption, etc.) [31, 49, 50]. Therefore, alternatives to reduce exposure while maintaining the subject at work could be considered [32, 34, 43, 48].

Strategies to reduce exposure to the causal agent are specific to each occupation, and in food industry may vary from modification of food processing, to improving ventilation, mechanization or automation, use of modified materials, better organization of work, improvement of workplace conditions, and use of protective devices [6].

Keeping the worker at work wearing protective devices may help in the short term resulting in an improvement—but not a complete suppression—of respiratory symptoms and airway obstruction [34]. Recently, Casper et al. [51] have described two cases of OA, in one case associated to rhinitis, due to airborne fungal and pancreatic-based enzyme powders used in cheese production to soften and flavour cheese in which respiratory symptoms improved after taking appropriate respiratory protection measures during powder exposure. However, the use of devices may still lead to deterioration of asthma and should not be regarded as a safe approach, especially in the long term and in patients with severe asthma [34].

The characterization of real work exposure is a key point in management and prevention of allergic OA, and effectiveness of interventions to reduce levels of aerosolized allergens can only be evaluated if appropriate allergen measurements are included. Unfortunately, air monitoring of food allergens is currently very limited [52••], and a time-weighted average (TWA) threshold limit value based on no observed adverse effect levels (NOAEL) has only been proposed for flour dust (0.5 mg/m^3) by ACGIH [53]. However, the value of this threshold is discussed [54] and based on re-analysis of national epidemiological data, the Dutch Expert Committee on Occupational Standards (DECOS) [55] concluded that since the risk increases with increasing exposure, no NOAEL can be defined, and no threshold is observable [54].

In a dusty workplace, such as bakeries, the flour allergen levels show a high correlation with dust concentrations [56]. Recently, Baatjies et al. [57••] have described the effectiveness of a specially designed intervention strategy aimed to reduce airborne flour dust exposure in supermarket bakeries using a randomized design. A total of 30 bakeries of a large supermarket chain store were randomly assigned to two intervention groups, and a control group of 15 bakeries was also investigated. Personal samples were used to characterize exposure to flour dust and wheat and rye allergen levels pre- and post-intervention. The intervention strategy included a series of specific flour dust control measures (e.g., redesigned lid for mixer tub) and training of workers to improve awareness on the health risks associated with exposure to flour dust, and on work practices able to reduce the risk. The intervention effect revealed a 50% decrease in mean flour dust, wheat, and rye allergen exposure, and the greatest reduction (80%) was observed when using a combination of all control measures. Further studies are requested to evaluate the long-term impact of the intervention on reducing the disease burden among that group of bakers [58].

In another paper, based on the observation that a consistent proportion of bakers' asthma is due to IgE-mediated allergy to fungal amylase contained in bread improvers, Smith et al. [59] described a strategy to limit bread improver exposures to $<1 \text{ mg/m}^3$ (8 TWA threshold limit value whilst exposures to all other ingredients, including flour, were limited to $<10 \text{ mg/m}^3$ (8-h TWA). Over a 10-year period of surveillance, there was an overall reduction in the incidence of new cases of symptomatic sensitization, from 2085 per million employees per year in the first 5 years of the surveillance programme, to 405 per million employees per year in the subsequent 5 years.

Seafood processing plants are at high risk for allergic OA and OR [15]. The prevalence of OA in seafood workers is between 2 and 36% [60••]. The prevalence of OR associated with fish and seafood proteins is between 5 and 24%, although this is likely to be an underestimate [3, 60••]. OA is more

commonly associated with shellfish (4–36%), which comprise crustaceans and molluscs, than with bony fish (2–8%) [60••]. Several allergenic proteins have been identified in seafood, but few have been characterized at a molecular level [60••]. Parvalbumin appears to be the major fish allergen, while tropomyosin the major crustacean allergen. Other seafood-associated biological (*Anisakis simplex*) and chemical agents (protease enzymes, toxins, and preservatives) have also been implicated in OA in seafood plants.

Several work processes can generate excessive bioaerosols, but activities generating dry aerosol particulates through using compressed air, as in prawn blowing operations and fishmeal loading/bagging, seem to produce higher levels of particulate than wet processes [60••]. These wet or dry aerosolized particles are inhaled by workers and, due to their small dimensions, most of them are capable to reach the small airways. Although of great interest both for medical surveillance of exposed workers, and for management of WRA and rhinitis, monitoring of airborne seafood-derived allergen exposure is not readily available for routine use, and there are currently no regulatory exposure standards for seafood allergens since there is no standardized assays for quantifying these allergens [15]. Promising new immunological and chemical assays able to detect various aerosolized seafood allergens at levels as low as 10 ng/m have recently been developed [60••, 61–66]. In cross-sectional studies aimed to characterize the bioaerosol exposure of workers of various seafood processing plants in which high frequency of respiratory symptoms had been observed, these assays proved sensitive to detect the aerosolized Atlantic salmon (*Salmo salar*) parvalbumin Sal s 1 antigen [64], the airborne herring (*Clupea harengus*) antigen [65], and several airborne crab-derived proteins [66]. Identifying departments and activities with high-aerosol exposure such as filleting in salmon [64] and herring [65] processing plants, or raw crab processing [66], might lead to the introduction of improved local exhaust ventilation systems, change in machine and in food processing (e.g., cleaning and brushing raw crab before it is cooked [62] and using wet instead of compressed air jet processing) which may help in reducing exposures.

Follow-up

The optimal management of OA should include a follow-up programme, with periodic assessment of symptoms and lung function, and close collaboration between health care providers and patients, to provide education and skills on the disease [43]. Workers with OA should be informed not only about the strong evidence that removal from any further exposure is relevant in the management of the disease but also about the economic and legal implications of the diagnosis [33]. Proper education of workers on work practices able to reduce exposure (e.g., right way of wearing respiratory protections and proper use of gloves) and on therapy may help for a favourable outcome and should be implemented in high-risk industries.

Conclusions

Several food processing plants are at increased risk for OA and OR, nevertheless, overall few papers have specifically focused on the treatment of OA in food industry. The management of food-derived OA includes hygiene interventions

aimed to avoid of reducing culprit exposure, pharmacologic therapy, and SIT where appropriate. Although most cases of food-derived OA are IgE-mediated, studies on SIT have been performed only in bakers' asthma, and demonstrated the effectiveness of SIT in reducing symptoms even when the patient is continuing to work. Despite these promising results, at present, SIT is not for routine use in bakers' asthma due to the lack of commercial standardized extracts. A better identification of the responsible allergenic proteins at a molecular level could be of relevance to prepare validated extracts suitable for SIT not only for bakers' asthma but also for other food-derived OA. Interesting reports in selected cases of bakers' asthma demonstrate the effectiveness of omalizumab in controlling symptoms keeping the patient at work. New sensitive immunologic assays to detect airborne allergen levels have been developed and successfully applied for air monitoring in cross-sectional studies aimed to characterize the allergen exposure in seafood plants. Effective intervention strategies aimed to reduce airborne allergens have been described in flour industry.

Compliance with Ethical Standards

Conflict of interest

Gianna Moscato declares that she has no conflict of interest.

Gianni Pala declares that he has no conflict 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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