



Food processing and occupational respiratory allergy- An EAACI position paper

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Abstract

Occupational exposure to foods is responsible for up to 25% of cases of occupational asthma and rhinitis. Animal and vegetable high-molecular-weight proteins present in aerosolized foods during food processing, additives, preservatives, antioxidants, and food contaminants are the main inhalant allergen sources. Most agents typically cause IgE-mediated allergic reactions, causing a distinct form of food allergy (*Class 3 food allergy*). The allergenicity of a food protein, allergen exposure levels, and atopy are important risk factors. Diagnosis relies on a thorough medical and occupational history, functional assessment, assessment of sensitization, including component-resolved diagnostics where appropriate, and in selected cases specific inhalation tests. Exposure assessment, including allergen determination, is a cornerstone for establishing preventive measures. Management includes allergen exposure avoidance or reduction (second best option), pharmacological treatment, assessment of impairment, and worker's compensation. Further studies are needed to identify and characterize major food allergens and define occupational exposure limits, evaluate the relative contribution of respiratory versus cutaneous sensitization to food antigens, evaluate the role of raw versus cooked food in influencing risk, and define the absolute or relative contraindication of patients with ingestion-related food allergy,

pollinosis, or oral allergy syndrome continuing to work with exposure to aerosolized food allergens.

KEYWORDS

food processing, occupational food allergy, work-related asthma, work-related rhinitis

1 | INTRODUCTION

The burden of occupational respiratory diseases is a global health problem. It is estimated that up to 25% of all asthma cases are related to work¹ and occupational asthma (OA) is the most common occupational lung disease in industrialized countries.² Occupational rhinitis (OR) is 2-4 times more frequent than OA, with which it is frequently associated.³ Between 10% to 25% of OA and OR is caused by inhalation of food-derived materials during food handling and processing activities in the workplace.⁴

A broad spectrum of workers is at increased risk for OA and OR associated with food handling and processing, with no EAACI document providing specific guidance. The aims of the FORA (Food processing and Occupational Respiratory Allergy) Task Force were to:

- Develop an up-to-date consensus document through an expert panel of allergologists, pneumologists, and occupational medicine physicians from various European countries and beyond.
- Summarize the current scientific evidence on the risks associated with food handling and processing with specific reference to OA and OR, including the epidemiology, risk factors, and specific agents causing these adverse respiratory outcomes.
- Outline key messages in this position statement based on consensus reached by the expert panel members.
- Propose consensus-based guidance for the assessment, management, and prevention of food-induced OA and OR in clinical practice.

2 | METHODS

This document was prepared by the EAACI FORA Task Force expert panel of allergologists, pneumologists, and occupational medicine physicians. A literature search was conducted by individual panel members. One meeting was held to review the findings and reach informal consensus. Further consensus was obtained through an informal iterative process soliciting input on earlier drafts from all panel members. Due to the heterogeneous quality of published studies, evidence-based recommendations could not be developed. This final article is the result of expert consensus opinion following a thorough review of the available literature. The expert recommendations have been summarized through "key messages" (see Key Messages Box 1) and "suggestions".

2.1 | Data sources, search strategy, and study selection

Published studies in English were identified from PubMed and MEDLINE from 1965 to March 2017. The following keywords were used in the search strategy: (work-related* OR occupational*) AND (asthma OR rhinitis OR respiratory) AND (food processing OR food industry OR food manufacturing). References published within the 1965-2017 timeframe that had not been otherwise identified in the initial search were added where relevant.

3 | EPIDEMIOLOGY (INCLUDING CAUSATIVE AGENTS AND RISK FACTORS)

It is estimated that more than four million workers in Europe⁵ are employed in the food industry. The largest food-handling working population is in the agriculture, food manufacturing, and processing industry. While comprehensive epidemiological data on OA and OR associated with food are not available, published data suggest that these do not vary significantly. OA occurs in 3%-10% of green coffee bean workers, 4%-13% of bakers, 2%-8% of bony fish processors, and 4%-36% of shellfish processors.^{6,7} Ocular-nasal symptoms and allergic rhinitis are commonly encountered.^{6,7} The prevalence of OR is twofold higher, and it may precede or coincide with the onset of OA.⁹

Tables 1 and 2 outline common food sources (cereals, plants/vegetables/fruits/spices, seeds, herbal teas, mushrooms, seafood, and farm products), additives (colorants, thickening agents, sulfites, and enzymes), and food contaminants (mites, insects, fungi, and parasites) found in food processing, preparation, and storage facilities. These agents commonly contain proteins (>10 kDa) derived from food sources, which act as respiratory sensitizers through inducing IgE-mediated reactions.⁹⁻¹¹

Various work processes produce wet aerosols or dust particulates that can be inhaled and cause allergic sensitization and/or irritant reactions.¹² Other food processing activities such as storage, thermal denaturation, acidification, and fermentation may destroy allergens, cause conformational changes, or result in new sensitizing epitopes, all of which may increase the allergenicity of the food proteins.^{13,14}

The most important occupational risk factors (Table 3) include the allergenic potential of the food, the nature of the work

Box 1 Key messages

- Food and food products are responsible for up to 25% of occupational rhinitis and/or occupational asthma
- Raw and processed animal and plant products, additives and preservatives, microbes, and insect and mite contaminants are the main allergen sources
- Food processing activities produce dust particulate or aerosols that are readily inhaled and can act as primary sensitizers in the airways, causing a distinct form of respiratory food allergy, usually without any symptoms upon ingestion (*Class 3 food allergy*)
- The allergenicity of a food protein, nature of work process, and allergen exposure levels are important occupational risk factors
- While most food agents typically cause IgE-mediated allergic reactions, other mixed IgE- and non-IgE-mediated reactions can occur
- Atopy, rhinitis, and ingestion-related allergy are important host risk factors
- Exposure assessment, including allergen determination, is a cornerstone for establishing improved preventive measures
- Diagnosis relies on a thorough medical and occupational history, functional assessment, assessment of sensitization, including component-resolved diagnostics where appropriate, and in selected cases specific inhalation tests
- Management includes allergen exposure avoidance or reduction (second best option), pharmacological treatment, assessment of impairment, optimizing rehabilitation, and worker's compensation
- Individuals with co-existent ingestion-related food allergy should institute dietary and environmental avoidance of the offending food

process, and the level of exposure to the causative agent.⁹ Some foods such as crustaceans (eg, crab) and cereal flours (eg, wheat, rye) are more potent sensitizers than others from their phylogenetic group. There is increasing evidence that the risk of occupational sensitization and OA/OR is increased with higher exposures to food aerosols of flour (wheat and rye), fungal α -amylase, green coffee, castor bean, and seafood (crab, prawn, salmon, pilchard, and anchovy fish).^{8,9,15,16}

Atopy is an important host risk factor for allergic sensitization and OA/OR (Table 3). Atopy is associated with an increased risk of sensitization in workers exposed to crabs, prawns, cuttlefish, pilchard, anchovy, green coffee beans, flour, and enzymes.^{8,9,15} The association between atopy and OA has been reported in workers exposed to flour (bakers), enzymes, and crabs, but not in other settings (eg, salmon).^{15,17} Some studies also show that nonatopic workers exposed to flour dust can also have an increased risk of sensitization.¹⁶ Genetic risk factors, Toll-like receptor 4 (TLR4), and β 2-adrenergic receptors (ADRB2) gene polymorphisms have also been suggested in bakers.^{18,19} Rhinitis has been associated with an increased risk of developing OA due to food proteins.¹⁵ The role of gender is inconsistent in various studies. While both men and women bakers demonstrate an increased risk for asthma, in table grape farmers, male gender was a risk factor for asthma and rhinitis while female gender was associated with an increased risk for work-related asthma symptoms and OA due to fish and snow crab (Table 3). This can partly be explained by the gendered distribution of work.²⁰ Smoking has been associated with an increased risk of sensitization to some foods such as prawns, crab, fish (pilchard, anchovy, and salmon), green coffee beans, and flour.^{9,15,17} Finally, epidemiological studies of workers with asthma symptoms due to flour or spice dust appear to be more likely to report ingestion-related allergy due to grain products or spices, respectively,²⁰ as are isolated case reports of workers with seafood allergy.²¹

4 | EXPOSURE ASSESSMENT

Exposure to food allergens occurs primarily through inhalation of dust, steam, vapors, and aerosolized proteins generated during cutting, scrubbing or cleaning, cooking or boiling, and drying activities.¹¹ Work processes and tasks that generate excessive dust and bioaerosols contribute to the increased exposure in these settings. Environmental sampling is commonly conducted in exposure assessment of workplaces in the food industry using commonly accepted approaches as is the processing of dust samples, allergen analysis, and quantification techniques.²² Exposure assessment studies for OA/OR commonly collect the inhalable dust fraction.

Various immunological techniques have been developed to determine food allergen concentrations in dust particulate.²² Several immunoassays have been reported for various allergens, which have enabled quantification of allergen concentrations of sufficient sensitivity and specificity to detect allergen concentrations in the $\mu\text{g}/\text{m}^3$ to pg/m^3 range (Table 4). Assays using monoclonal antibodies can detect a specific epitope, but are often not very sensitive. Immunoassays based on polyclonal antibodies are often used to enhance sensitivity. However, the lack of standardized methods to quantify different allergens remains a challenge resulting in the inability to compare exposures from settings that use different assays.

Exposure assessment studies in key food handling and processing sectors reveal a wide range of allergen exposures, some more closely correlated with particulate dust than others such as in the baking industry.²³ However, this has not been observed in the seafood processing industry since exposure is characterized by mainly wet aerosols.²⁴ There are a few internationally recognized occupational exposure limits for food allergens as opposed to chemical agents (eg, ACGIH TLVs) to protect against the development of sensitization or OA/OR, leading to variation in exposure limit between countries (Table 5).

TABLE 1 Foods as causative agents for occupational allergy and asthma

Agent	Occupational exposure
Cereals	
Corn	Making stock feed (Park 1997)
Gluten	Baker (Lachance 1988)
Grain	Millers, grain elevators (Chan-Yeung 1980, Cockcroft 1983, Park 1998)
Malt	Machine operator (Miedinger 2009)
Rice	Rice miller (Lim 1984, Kim 2010)
Wheat, rye, barley	Baker, pastry maker, supermarket bakers (Brisman 2002, Ehrlich 2005, Brant 2007, Baatjes 2013)
Plants, vegetables, fruits, and spices	
Sunflower (pollen)	Sunflower workers (Bousquet 1985)
Artichokes	Warehouse (packaging artichokes) (Miralles 2003)
Asparagus	Harvesting asparagus (Lopez-Rubio 1988, Tabar 2004)
Bell peppers	Greenhouse worker (Groenewoud 2002, Vermeulen 2003)
Broccoli, cauliflower, cabbage	Plant breeder, restaurant worker, and supervisor (Quirce 2005, Hermanides 2006,)
Carrots	Cook (handling and cutting raw carrots) (Moreno-Ancillo 2005)
Courgettes (zucchini)	Warehouse (packaging courgette) (Miralles 2000)
Leek	Cook (Armentia 2005)
Spinach	Fieldworkers, Baker (handling spinach) (Ausin 2002, Schuller 2005)
Sugar beet (pollen)	Sugar beet workers (Dulton 1938)
Tomatoes (flower)	Greenhouse grower (Vandenplas 2008)
Grape (pollen)	Grape growers (Tsukioka 1984)
Melon plant	Agricultural worker (Gomez Torrijos 2015)
Oranges (pollen, leaves, and zest/flavido)	Farmer, orange peeling (De las Marinas 2013, Felix 2013)
Peaches (leaves and fruit)	Farmer, factory worker handling peaches (Carrasquer 2002, Garcia 2004)
Raspberries	Chewing gum coating (Sherson 2003)
Cacao	Confectionery (Perfetti 1997, Zuskin 1998)
Chicory	Factory producing inulin from chicory roots, chicory grower (Pirson 2009)
Coffee beans (raw and roasted)	Handling raw coffee beans, roasting green coffee beans (Kaye 1961, Lehrer 1978, Karr 1979, Zuskin 1981, Jones 1982, Osterman 1988, Zuskin 1989, Lemiere 1996)
Devil's tongue root (maiko)	Food processor (Kobayashi 1974)
Green beans	Homemaker (Igea 1994)
Hops	Baker (Brisman 2002), brewery chemist (Newmark 1978)
Lima bean (<i>Phaseolus lunatus</i>)	Food processing factory (Tonini, 2012)
Linseed oilcake	Laboratory worker (Vandenplas 2008)
Okra (<i>Hibiscus esculentus</i> Linn)	Picking and packing (Ueda 1993)
Olive oil	Olive mill worker (Palomares 2008)
Soybeans	Dairy food product company, baker, animal food preparation (Bush 1977, Lavaud 1994)
Almonds	Almond-processing plant (Foti 2008)
Anise	Anise liqueur factory (Gonzalez-Gutierrez 2000)
Aniseed	Meat industry (handling spices) (Fraj 1996)
Aromatic herbs (rosemary, thyme, bay leaf, garlic)	Butcher (handling spices) (Lemiere 1996)
Cinnamon	Worker processing cinnamon (Uragoda 1984)
Garlic, onion, chili pepper	Sausage makers, garlic harvesters, spice factory, packing, and handling garlic (Falleroni 1981, Lybarger 1982, Couturier 1982, Navarro 1995, Anibarro 1997, van der Walt 2010)
Ginseng	Cook (Lee 2006)

(Continues)

TABLE 1 (Continued)

Agent	Occupational exposure
Paprika, coriander, mace	Butcher (Sastre 1996), greenhouse worker (van Toorenenbergen 1984), factory worker (van Toorenenbergen 1985, Zuskin 1988)
Saffron (pollen)	Saffron worker (Feo 1997)
Seeds	
Buckwheat flour	Health food products, noodle maker, cook (Gohte 1988, Valdivieso 1989, Choudat 1997)
Fennel seeds	Sausage-manufacturing plant (Schwartz 1997)
Lupine seeds	Agricultural research worker (Crespo 2001)
Red onion (<i>Allium cepa</i>) seeds	Seed-packing factory worker (Navarro 1995)
Sesame seeds	Miller (grounding waste bread for animal food), baker (Alday 1996)
Tea (including herbal teas)	
Chamomile	Tea-packing plant worker (Vandenplas 2008)
Liquorice root	Herbalist (Cartier 2002)
Sarsaparilla root	Herbal tea worker (Vandenplas 1996)
Tea	Green tea factory, tea packer (Uragoda 1970, MacKay 1975, Uragoda 1980, Castellan 1981, Zuskin 1984, Blanc 1986, Roberts 1988, Cartier 1990, Shirai 1994, Shirai 2003)
Mushrooms	
<i>Boletus edulis</i> (porcini or king bolete)	Pasta factory (Foti, 2008)
<i>Pleurotus cornucopiae</i>	Mushroom grower (Michils 1991)
<i>Saccharomyces cerevisiae</i>	Mixing baker's yeast (Belchi-Hernandez 1996)
Mushroom powder	Food manufacturer (Symington 1981)
Seafood (shellfish and fish)	
Crustaceans	
Snow crabs, Alaskan king crabs, dungeness crabs, tanner crabs, rock crabs	Crab processing worker (Jeebhay 2010)
Prawns, shrimp/shrimp meal, clams	Prawn processor, food processor (lyophilized powder), fishmonger, seafood delivery (Jeebhay 2010)
Lobster	Cook, fishmonger (Jeebhay 2010)
Mollusks	
Abalone	Fisherman (Jeebhay 2010)
Cuttlefish	Deep sea fisherman (Jeebhay 2010)
King and queen scallops	Processor (Jeebhay 2010)
Mussels	Mussel opener, cook (Jeebhay 2010)
Octopi and squid	Processor (Jeebhay 2010, Rosado 2009, Wiszniewska 2013)
Fish	
Salmon, pilchard, anchovy, plaice, hake, tuna, trout, turbot, cod, swordfish, sole, Nile perch, pomfret, yellowfin, herring, fishmeal flour	Fish processor, fishmonger (Jeebhay 2010), cook (Tomm 2013), fish farmers (Pérez Carral 2010)
Farm products	
Bees, honey, pollens	Beekeeper, honey processor, cereal producer (Yunginger 1978, Reisman 1983, Bousquet 1985, Ostrom 1986, Johnson 1999)
Beef (raw)	Cook (Blaumeiser 1996, San-Juan 2005, Tonnel 2009)
Cows	Dairy farmer (Rautalahti 1987, Terho 1985, Virtanen 1988)
Eggs	Confectionery worker (Blanco 1992, Leser 2001, Escudero 2003), bakery, egg processing plant (Edwards 1983, Bernstein 1987, Smith 1987, Smit 1990, Bernstein 1993, Boeniger 2001)
Hogs	Pig farmer (Harries 1982, Matson 1983, Zuskin 1991, Donnay 2006)
Lamb (raw)	Cutting raw lamb meat (Tonnel 2009)

(Continues)

TABLE 1 (Continued)

Agent	Occupational exposure
Pork (raw)	Meat-processing plant (Labrecque, 2004), meat packer (Hilger 2010)
Pheasants, quails, doves	Breeder (Hoffman 1988)
Poultry (turkey and chicken)	Food processing plant, poultry slaughterhouse (Bar-Sela 1984, Perfetti 1997)
Milk derivatives	
α-lactalbumin	Candy maker (Bernaola 1994), baker (Toskala, 2004)
Bovine serum albumin powder	Laboratory worker (Choi 2009)
Casein	Delicatessen factory, milking sheep, candy maker (Vargiu 1994, Bernaola 1994)
Lactoserum	Cheese maker (Moneret-Vautrin 1984)
Rennet	Cheese maker (Jensen 2006)

(Adapted and updated from reference 6,9,10,11)

5 | MECHANISMS AND CLINICAL ASPECTS

Although allergic reactions to foods occur typically after ingestion, inhalation of aerosolized food particles can also give rise to allergic manifestations, commonly respiratory symptoms such as rhinitis, coughing, wheezing, and dyspnea, and less frequently, urticaria and anaphylaxis. Workplace exposure to inhaled food allergens, enzymes, contaminants, and pests present in foods cause allergic sensitization and OA/OR Inhalant allergic reactions to foods encompass both IgE- and non-IgE-mediated mechanisms.¹¹ High-molecular-weight (HMW) agents, such as wheat flour allergens, typically induce IgE-mediated reactions, while some low-molecular-weight (LMW) agents (eg, epigallocatechin gallate from green tea) may do the same.²⁵ Other LMW agents used as antioxidants or preservatives elicit OA through pharmacologic or not well-characterized mechanisms (eg, metabisulfite).²⁶

Moreover, inhalation of vegetable dust (ie, grains, seeds) containing endotoxins can induce inflammatory responses resulting in organic dust toxic syndrome (ODTS), typically presenting with asthma-like symptoms, which should be differentiated from OA.²⁷ While the mechanism for OR/OA to seafood proteins is commonly IgE-mediated,²⁸ in vitro models have also demonstrated that digestive enzymes such as trypsin (from salmon, pilchard, and king crab) can activate protease-activated receptor-2 on airway epithelial cells causing airway inflammation through IL-8 expression.²⁹

Two forms of food allergy have traditionally been described depending on the clinical manifestations, profile of allergens involved, and the underlying immunological mechanism.³⁰ *Class 1 food allergy*, which commonly occurs in children but can also develop in adults, refers to sensitization to allergens usually through the gastrointestinal tract that are resistant to gastric digestion, but can also arise from skin contact.³¹ In addition, workers with prior ingestion-related food allergy could experience allergic reactions as a result of inhaling aerosolized food products in the workplace. Among fish processing workers, this is estimated to affect 7% of workers.¹²

Class 2 food allergy is more commonly observed in adults and develops following allergic sensitization to aeroallergens. The immunological mechanism involved in this form of food allergy is usually due to IgE cross-reactivity with allergens present in common inhalant

sources, but can also be observed in the occupational setting with primary sensitization to work-related allergens. Examples of this type of food allergy include the latex-fruit syndrome, where subjects sensitized to latex report allergic symptoms with fruits or nuts (ie, banana, kiwifruit, chestnut). Another is the house dust mite-shellfish syndrome³² due to sensitization to tropomyosin and other shared allergens, such as ubiquitin as well as sarcoplasmic protein, hemocyanin, and enolase.³³ Workers with pollinosis and oral allergy syndrome (OAS) due to cross-reacting allergens present in pollens and food³⁴ can also experience symptoms when occupationally exposed to related aerosolized food such as spices.

However, many food allergens eliciting OA appear to act as primary sensitizers through inhalation, with no evidence of cross-reactivity to other common inhalant allergen sources.¹⁰ Once allergic sensitization has developed, allergic symptoms can also occur after ingestion of the incriminated food. However, this is uncommon in the occupational setting, since most affected workers tolerate the ingested foods, with relatively few cases reporting symptoms after ingestion.^{17,21} This form of primary sensitization to foods through inhalation (or occasionally through a disrupted skin barrier) in adults, usually without associated symptoms after ingestion, should be considered a distinct form of food allergy, for which the term *Class 3 food allergy* is proposed (Table 6).

Finally, beside IgE-mediated food allergy, other mixed IgE- and non-IgE-mediated food allergy reactions can occur. Two cases of OA and eosinophilic esophagitis have been described: one induced by egg, coinciding with the “egg-bird syndrome,” and another in a baker.^{35,36} In both cases, avoidance of the inhalable offending agent (feathers and flour) resolved the asthma and the esophagitis.

6 | SPECIFIC CAUSES OF OCCUPATIONAL RESPIRATORY ALLERGY IN THE FOOD INDUSTRY

6.1 | Seafood

Fishery capture, aquaculture production, and land-based processing for food preparation have been increasing globally, especially

TABLE 2 Food additives and contaminants as causative agents for occupational allergy and asthma

Agent	Occupational exposure
Food additives	
<i>Bacterial enzymes</i>	
Transglutaminase (<i>Bacillus subtilis</i>)	Production superintendent in ingredient commercialization (De Palma 2014)
<i>Colorants</i>	
Carmine	Butcher (production of sausages) (Ferrer 2005)
Chinese red rice (derived from <i>Monascus ruber</i>)	Delicatessen manufacturing plant (Vandenplas 2000)
Marigold flour (derived from <i>Tagetes erecta</i>)	Porter in animal fodder factory (Lluch-Perez 2009)
<i>Fungal enzymes</i>	
α -amylase, cellulase, xylanase	Baker (Flindt 1979, Blanco Carmona 1991, Baur 1998, Brisman 2002, Brant 2007)
Glucoamylase	Baker (Quirce 2002)
Pectinase, glucanase	Fruit salad processing (Sen 1998)
<i>Papain, bromelain</i>	Meat tenderizer (Baur 1979, Lemiere 1999, Galleguillos 1978, Milne 1975, Baur 1982, Flindt 1978)
<i>Thickening agents</i>	
Acacia gum (Gum Arabic), Tragacanth gum	Food manufacturing (Aleman 1999, Danoff 1978)
Carob bean flour	Jam factory (Van der Brempt 1992), ice cream maker (Scoditti 1996)
Konjac glucomannan	Food-manufacturing plant (Bernstein 2007)
Pectin	Candy maker, preparation of jam (Cohen 1993, Kraut 1992)
<i>Others</i>	
Castor beans	Factory and dock workers (Panzanni 1986, Patussi 1990)
Gluten	Biscuit maker (Lachance 1988)
Sodium metabisulfite	Spraying potatoes (Malo 1995), prawn processing (Steiner 2008), seafood packing (Uriarte 2015)
Vitamins (thiamine)	Manufacturing-enriched breakfast cereals (Drought 2005)
Food contaminants	
<i>Mites</i>	
Grain storage mites (<i>Glycyphagus destructor</i>)	Grain worker (Cuthbert 1979, Cuthbert 1984, Ingram 1979, Alvarez 1999)
Poultry mites (<i>Ornithonyssus sylviarum</i>)	Poultry worker (Lutsky 1982, Lutsky 1984)

(Continues)

TABLE 2 (Continued)

Agent	Occupational exposure
Spider mites (<i>Tetranychus urticae</i> , <i>Panonychus ulmi</i> , <i>Panonychus citri</i>)	Table grape (Jeebhay 2007), apple (Kim 1999), citrus farmers (Burches 1996)
Storage mites with ham (<i>Tyrophagus putrescentiae</i> , <i>Acarus siro</i> , <i>Lepidoglyphus destructor</i>)	Van driver for dry cured ham (Rodriguez 2012), ham production workers (Tafuro 2015)
<i>Insects</i>	
Champignon flies	Champignon cultivator (Cimarra 1999)
Cockroaches (<i>Blattella spp</i>)	Baker (Brisman 2002)
Flour moth (<i>Ephestia kuehniella</i>)	Cereal stocker (Pala 2010), baker (Brisman 2002)
Granary weevils (<i>Sitophilus granarius</i>)	Baker (Brisman 2002)
Rice flour beetles (<i>Tribolium confusum</i>)	Baker (Schultze-Werninghaus 1991)
<i>Fungi</i>	
<i>Aspergillus</i> , <i>Alternaria spp</i>	Baker (Klaustermeyer 1977)
<i>Aspergillus niger</i>	Brewer (contaminated malt) (Heaney 1997)
<i>Chrysionilia (Neurospora) sitophila</i>	Service operator of coffee dispenser (Heffler 2009, Monzon 2009)
<i>Penicillium nalgiovensis</i>	Semi-industrial pork butcher (Talleu 2009), dry sausage packer (Merget 2008)
<i>Verticillium alboatrum</i>	Greenhouse tomato grower (Davies 1988)
<i>Parasites</i>	
<i>Anisakis simplex</i>	Fish processing workers, frozen fish factory (Jeebhay 2010)
<i>Plants</i>	
Hoya (sea squirts)	Oysters handlers (Jeebhay 2010)
<i>Others</i>	
Soft red coral	Spiny lobster fisherman (Jeebhay 2010)

(Adapted and updated from reference 6,9,10,11)

in developing countries.¹⁷ During processing, seafood is separated into major allergen sources: muscle, visceral contents, skin slime/mucin, or collagen.¹² These processes produce steam, organic dust particulate, and bioaerosols (eg, air blowing and water jets) having a wide range of concentrations, reaching levels as high as 11 mg/m³ for total inhalable particulates, 6 mg/m³ for protein, and 75 µg/m³ for allergens.^{12,17} Some of the highest levels are detected in fishmeal operations and crab processing aboard sea vessels.

All three major groups (phyla) of marine organisms, Arthropods, Molluscs, and Pisces (sub-phylum Chordata), can cause occupational allergy and asthma (Table 7).¹² The prevalence of OR associated with

TABLE 3 Risk factors for work-related asthma, rhinitis, and symptoms in food processing workers: selected epidemiological studies

Author/Country	Study design	Subjects (n)	Participation rate (%)	Age (yrs.) mean (range)	Workplace	Diagnostic methods for defining rhinitis	Diagnostic methods for defining asthma	Atopy assessment	Risk factors (host and occupational)	Predictors of WRS/rhinitis symptoms/asthma symptoms/OA: OR (95% CI) (unless otherwise stated)
Bakers										
Brisman & Järholm, Sweden, 1995 & 1999	Retrospective cohort study (1959-1989)	1258	75	Males 31 Females 26	Bakeries	Q	Q	Q	Male sex male bakers only: atopy	RR for male bakers: • rhinitis 2.8 (2.3-3.4) • asthma 1.8 (1.3-2.6) RR for female bakers: • rhinitis 2.0 (1.6-2.7) • asthma 1.1 (0.5-2.3)
Year Houba et al, The Netherlands, 1996	Cross-sectional	178	88	34 (20-61)	Bakeries	Q	Q	SPT	α -amylase sensitization: α -amylase exp. & atopy WRS: positive SPT to α -amylase	Bakers with WRS and + SPT to α -amylase: • rhinitis PR: 4.8 (2.0-11.2) • chest tightness PR: 11.9 (3.2-44.5)
Houba et al, The Netherlands, 1998	Cross-sectional	393	75	34 (17-61)	Bakeries	Q	Not defined	Total and specific serum IgE to common aeroallergens	Atopy	WRS in wheat flour-sensitized workers: • high wheat exp. 3.5 (1.6-7.5) • medium wheat exp. 2.6 (0.9-2.9)
Cullinan et al, UK, 2001	Cohort study (1990-1993)	300	≈ 80	(27-31)	Bakeries	Q	Q	SPT	WRS or positive SPT to flour: level of total dust or flour aeroallergen	High flour aeroallergen exp.: • chest sx 7.7 (1.8-33.0) • eye/nose sx 9.6 (3.7-25.0) High total dust exposure:. • chest sx 5.2 (1.3-21.0) • eye/nose sx 4.5 (2.0-10.0)
Brisman et al, Sweden, 2003	Case-control	26 asthmatics, 21 rhinitis, 44 referents	86	(31-33)	Cases and referents selected from bakers	Q	Q	SPT	Bakers' asthma only: sensitization to wheat flour or α -amylase	WR asthmatics: sensitization to flour or α -amylase OR 5.8 (1.1-32.0) Work-related rhinitis: sensitization to flour or α -amylase OR 2.6 (0.4-16.0)
Droste et al, Belgium, 2003	Cross-sectional	246	36 (bakeries) 90-100 (bakers)	33	Industrial and small traditional bakeries	Q	Q	SPT	WRS: Atopy and sensitization to wheat flour or α -amylase	Atopy OR 2.7 (1.3-5.7) Sensitization to baker's allergens OR 4.9 (2.0-12.0)
Baatjes et al, South Africa, 2009	Cross-sectional	517	≈ 90	32	Supermarket bakeries	Q and positive SPT	BHR and positive SPT/serum IgE	Phadiatop	Probable OA: atopy, work-related ocular-nasal symptoms, current job status, previous peak exposure incidents, ingestion-related food allergy	Probable OA: atopy 4.2 (2.3-7.5) work-related ocular-nasal symptoms 3.1 (1.8-5.5) baker 1.6 (0.7-3.7) confectioner 1.1 (0.3-4.6) supervisor/manager 4.01 (1.3-12.6) previous peak exposures causing asthma sx 2.7 (1.1-6.8) ingestion related food allergy 6.4 (2.0-19.8)
Seafood workers										
Glass et al, New Zealand, 1998	Cross-sectional	223	99.6	33	Mussel processing plants	Not done	Q	Not stated	WRS: duration of mussel opening (years)	WRS: duration 2.0-6.9 y 2.3 (1.1-4.9) ≥7.0 y 3.7 (1.5-9.1)

(Continues)

TABLE 3 (Continued)

Author/Country	Study design	Subjects (n)	Participation rate (%)	Age (yrs.) mean (range)	Workplace	Diagnostic methods for defining rhinitis	Diagnostic methods for defining asthma	Atopy assessment	Risk factors (host and occupational)	Predictors of WRS/rhinitis symptoms/asthma symptoms/OA: OR (95% CI) (unless otherwise stated)
Jeebhay et al, South Africa, 2008	Cross-sectional	594	≈ 90	36	Pilchard canning and fishmeal processing plant	Q and positive SPT/serum IgE	Q and positive SPT/serum IgE	SPT to common aeroallergens/Phadiatop	Fish sensitization: age, male, current smoking, atopy WR asthma symptoms: atopy, female gender Occupational asthma due to fish: age	WR asthma symptoms: atopic subjects 2.2 (1.4-3.4) female gender 1.9 (1.2-3.2) occupational asthma sx due to fish: age 1.07 (1.01-1.14)
Gautrin et al, Canada, 2010	Cross-sectional	215	43	40	Snow crab processing plants	Q	Q and positive SPT/serum IgE to crab allergens	SPT	Occupational asthma: female gender, atopy, smoking, job held when sx started (cleaning, packing, freezing), cumulative exposure to crab	Occupational asthma: female gender 10.7 (3.6-32.1) atopy 2.8 (1.2-6.8) smoking 3.1 (1.3-7.4) crab job 3.7 (1.6-8.7) highest vs lowest cumulative exposure index 14.0 (3.0-65.8)
Other										
Laresse et al, Italy, 1998	Cross-sectional	112	63	34	Coffee manufacturing plant	Q	Q	SPT to common aeroallergens	WRS, common allergic symptoms and atopy: sensitization to green coffee beans	WRS: sensitization to green coffee beans ($P < 0.01$) Common allergic symptoms: sensitization to green coffee beans ($P < 0.05$) Atopy: sensitization to green coffee beans ($P < 0.01$)
Jeebhay et al, South Africa, 2007	Cross-sectional	207	Not reported	36	Table grape farms	Q and positive SPT/serum IgE	Q and positive SPT/serum IgE	SPT to common aeroallergens/Phadiatop	Work-related wheeze/probable asthma: sensitization to spider mite, atopy age WR rhino-conjunctivitis symptoms: sensitization to spider mite, atopy, male gender, pesticide crop sprayer	WR wheeze: age 1.0 (1.0-1.1) WR rhino-conjunctivitis symptoms: male gender 1.9 (1.0-3.7) pesticide crop sprayer 4.9 (1.6-14.7) WR rhino-conjunctivitis in workers sensitized to spider mite: atopy 4.7 (1.4-15.5) low cholinesterase 4.5 (1.1-18.7) Probable work-related asthma in spider mite sensitized: atopy 9.3 (2.3-36.6)
Van der Walt et al, South Africa, 2013	Cross-sectional	150	≈ 95	33	Spice mill (garlic, chili pepper)	Q and positive serum IgE	Q and positive serum IgE	Phadiatop	WRS: Garlic allergen exposure and sensitization, ingestion-related food allergy	Work-related rhino-conjunctivitis symptoms: high garlic allergen exposure 2.4 (1.1-5.3) WR asthma-like symptoms: high garlic allergen exposure 4.1 (1.1-15.7) ingestion-related food allergy 15.4 (2.8 to 84.7)

Q, questionnaire; exp, exposure; sx, symptoms; WR, work-related; WRS; work-related respiratory symptoms; BHR, bronchial hyperresponsiveness; RR, relative risk; SPT, skin prick tests; PR, prevalence ratio; OA, occupational asthma.

TABLE 4 List of available allergen tests suitable for allergen monitoring in the food processing industry

Detected allergens	Standard test antigen	Type of assay	Antibodies	Detection limit	Company/Institute	Author, year
Plants						
Wheat flour	Wheat flour protein mix	Inhibition-ELISA	human IgG4 or rabbit IgG	20 ng/mL	IRAS, The Netherlands	Bogdanovic 2006
Wheat flour	Wheat flour protein mix	Sandwich-ELISA	pAb	0.2 ng/mL	IRAS, The Netherlands	Bogdanovic 2006
Wheat α -amylase inhibitor Tri a 15	Wheat α -amylase inhibitor	Sandwich-ELISA	mAb	0.1 ng/mL	Health and Safety Laboratory, UK	Wiley 1997
Rye flour	Rye flour protein mix	Sandwich-ELISA	pAb	0.2 ng/mL	IPA, Germany	van Kampen 2009, Baatjes 2010
Soy hull	Soy hull protein mix	Sandwich-ELISA	pAb	0.04 ng/mL	Laboratorios Clinicos-Barcelona (IRAS), Spain	Gómez-Ollés 2006
Molds/Enzymes						
<i>Aspergillus oryzae</i> α -amylase Asp o 21	Asp o 21 (Fungamyl 1600S)	Lateral flow immunoassay	pAb/mab	1 ng/mL	IRAS, The Netherlands/ IPA, Germany	Bogdanovic 2006
<i>Aspergillus oryzae</i> α -amylase Asp o 21	Asp o 21 α -amylase (Megazym)	Sandwich-ELISA	mAb	0.2 ng/mL	Health and Safety Laboratory, UK	Elms 2001
<i>Aspergillus oryzae</i> α -amylase Asp o 21	Asp o 21 (Fungamyl 1600S)	Sandwich-ELISA	pAb	0.02 ng/mL	IRAS, The Netherlands	Sander 2007
<i>Aspergillus oryzae</i> α -amylase Asp o 21	Asp o 21 (Fungamyl 800L)	Sandwich-ELISA	mAb	0.08 ng/mL	IPA, Germany/ Karolinska Institutet, Sweden	
Animals						
Tropomyosin	Recombinant tropomyosin (based on RNA from black tiger prawn; <i>Penaeus monodon</i>)	Sandwich-ELISA	pAb	60 pg/m ³	James Cook University, Australia	Kamath 2014
Atlantic salmon parvalbumin	<i>Salmo salar</i> Sal s 1 (Atlantic salmon parvalbumin)	Sandwich-ELISA	pAb	50 pg/mL	University of Bergen, Norway	Dahlman-Höglund 2012
Herring parvalbumin	Herring (<i>Clupea harengus</i>) Parvalbumin	Sandwich-ELISA	pAb	100 pg/mL	University of Bergen, Norway	Dahlman-Höglund 2013
Fish (pilchard and anchovy)	Fish protein mix	Inhibition-ELISA	pAb	500 ng/mL 105 ng/m ³	IDM, University of Cape Town, South Africa	Lopata 2005
Fish (pilchard and anchovy)	Fish protein mix	Inhibition-ELISA	pAb	10-69 ng/m ³	University of Cape Town, South Africa	Jeebhay 2008
Fish (whiff and hake)	Fish protein mix	Inhibition-ELISA	human IgE pool	200 μ g/mL	Mayo Clinic and Graduate School in Rochester, MN, USA	Taylor 2000
Crab	Crab cooking water	Inhibition-IgE-test	human IgE pool	100 ng/filter	University of Washington, USA	Beaudet 2002
Crab	Crab protein mix	Inhibition-IgE-test	human IgE pool	5-50 ng/m ³	Mayo Clinic and Graduate School in Rochester, MN, USA	Howse 2006

IRAS, Institute for Risk Assessment Sciences, Utrecht University, The Netherlands; IPA, Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Ruhr-University Bochum, Germany; JCU, James Cook University, Townsville, QLD, Australia; IDM, Institute for Infectious Diseases and Molecular Medicine, University of Cape Town, South Africa. (Modified and updated from reference 22,38,43)

TABLE 5 List of occupational exposure limits (OELs) for allergens in the food processing industry

Food substance	OEL (8-h time-weighted average, total fraction, unless otherwise specified)	Country
Grain dust	1 mg/m ³	Japan ^a
	4 mg/m ³	Austria ^b , Belgium, Canada (Ontario), Canada (Quebec), Japan, China ^b , Singapore, South Korea, Spain, USA (NIOSH, ACGIH)
	5 mg/m ³	Austria
	10 mg/m ³	Ireland, USA (CAL OSHA), UK, South Africa
	Short term:	
	10 mg/m ³	Austria ^c
Flour dust	0.5 mg/m ³	Belgium, Israel ^c , South Korea ^c , USA (ACGIH, CAL OSHA)
	1 mg/m ³	Ireland, EU (SCOEL)
	2 mg/m ³	Finland
	3 mg/m ³	Canada (Ontario) ^c , Sweden, Norway ^c
	4 mg/m ³	Austria, Spain ^c
	6 mg/m ³	Latvia
	10 mg/m ³	UK
	Short term:	
	8 mg/m ³	Austria ^c
	30 mg/m ³	UK ^d
Penicillium	0.1 mg/m ³	Sweden ^c
Tea dust	2 mg/m ³	China ^c
	3 mg/m ³	Latvia
Poultry dust	10 mg/m ³	Canada (Ontario)
Proteolytic enzymes (suatilisins, 100% pure crystalline)	15 ng/m ³	China
	40 ng/m ³	UK
	60 ng/m ³	Belgium, Denmark, Ireland, USA (NIOSH) ^d
	1 glycine unit/m ³	Sweden ^e
	Short term:	
	30 ng/m ³	China ^d
	60 ng/m ³	Australia ^f , Canada (Ontario) ^f , Canada (Quebec) ^f , Denmark ^f , Ireland ^d , New Zealand ^f , Singapore ^d , Spain ^d , Switzerland ^d , USA (ACGIH) ^f , USA (NIOSH) ^g , Norway ^f
	3 glycine unit/m ³	Sweden ^{d,e}

Sources: National Institute for Occupational Safety and Health (NIOSH): Recommended Exposure Limit (REL), <https://www.cdc.gov/niosh/npg/default.html>; American Conference of Governmental Industrial Hygienists (ACGIH): Threshold Limit Value (TLV), ISBN 978-1-607260-90-5; Occupational Safety and Health Administration, California (CAL/OSHA): legal Permissible Exposure Limit (PEL), http://www.dir.ca.gov/title8/5155table_ac1.html#_blank; European Union (EU): European Commission Scientific Committee on Occupational Exposure Limits (SCOEL): <http://ec.europa.eu/social/main.jsp?catId=148&intPagId=684&langId=en>; Norwegian Ministry of Labour and Social Affairs. <https://lovdata.no/dokument/SF/forskrift/2011-12-06-1358>; National Institute for Public Health and the Environment The Netherlands. RIVM Letter report 2014-0151. © RIVM 2014; Health and Safety Executive (HSE). 2nd edition. ISBN 978 0 7176 6446 7; OSHA 2017. <https://www.osha.gov/dsg/annotated-pels/tablez-1.html>. Annotations: ^aRespirable fraction, ^bInhalable fraction, ^c30-min average, ^d15-min average, ^eOne glycine unit is approximately equivalent to 30 ng of pure subtilisin, ^fCeiling limit value, ^g60-min average

seafood in epidemiological studies is estimated to be 5%-24%.³ OA is more commonly associated with shellfish (4%-36%) than bony fish (2%-8%).^{12,17} Their allergenic potential is dependent on the phyla, crustaceans being most allergenic.¹² Other by-products such as protease enzymes from the gut, chitin from shellfish, and endotoxins in high concentrations also promote airway inflammation and asthma.²⁹ Nonseafood contaminants such as parasites (*Anisakis*

simplex), as well as chemical preservatives and spices, may also trigger allergic and respiratory symptoms.^{12,17,37}

Tropomyosin, a 34–39 kDa protein, is the major crustacean allergen identified in crab processing environments (Table 7).^{28,38} Considerable cross-reactivity exists between crustaceans due to highly conserved amino acid sequences with up to 98% homology between species.^{9,28} Cross-reactivity also extends to other

TABLE 6 Proposed classification of food allergy

	Primary route of sensitization	Population affected	Symptoms with food ingestion	Symptoms with food inhalation
Class 1	Gastrointestinal tract, transcutaneous (with disrupted skin barrier)	Commonly children but can also occur in adults	Always	Occasional
Class 2	Cross-reactive allergens present in inhaled sources	Commonly adults but can also occur in children/adolescents	Always	Seldom
Class 3	Respiratory tract, transcutaneous (with disrupted skin barrier)	Commonly adults in the workplace, but can also occur in the domestic setting with food preparation	Seldom	Always

(modified from ref. 30)

arthropods such as insects, mites, and the fish parasite *Anisakis*. A minor allergen in crab legs, *arginine kinase* (40 kDa),²⁸ has also been identified.³⁹ Studies suggest that cooked crab may be more allergenic than the raw form^{17,40} and is associated with higher tropomyosin levels.⁴¹ While tropomyosin has also been identified in mollusks, several other proteins (4.4–97 kDa) have yet to be identified. A conserved epitope sequence in crustaceans and mollusks could be responsible for their cross-reactivity despite relatively low overall homology of 60%.⁴²

Parvalbumin (10–12 kDa), the major fish allergen, has also been isolated in fish processing workplaces (Table 7).^{28,43,44} The allergenicity of fish species correlates with parvalbumin content, which varies between species and the amino acid sequence (55%–95%) in the IgE antibody binding epitope regions.⁴⁵ Cross-reactivity between fish species is common. While ingestion-related food allergic patients mainly recognize parvalbumin monomer, sensitized workers appear to recognize higher molecular weight isoforms.²⁸ Fish glyceraldehyde 3-phosphate dehydrogenase (36 kDa)²⁸ and several other proteins (29–61 kDa), including *phosphoglucosyltransferase*, *muscle actin*, *apolipoprotein AI* in Nile perch^{28,46,47} as well as two muscle enzymes *enolase* (50 kDa) and *aldolase* (40 kDa),⁴⁸ have also been isolated. Unlike parvalbumin, these enzymes are heat-sensitive, resulting in increased risk of sensitization to these enzymes while handling raw rather than cooked fish.^{17,49}

6.2 | Cereal flour

Cereal flour is an essential ingredient of basic commodities in many products of the food industry. Flour dust contains various agents that can cause occupational respiratory allergy⁵⁰ (Table 7). The most common source of flour is wheat, followed by rye, barley, oats, and corn; however, noncereal sources such as buckwheat, soya, or lupin should not be overlooked.^{51,52} Wheat flour is composed of starch and four groups of proteins, namely glutenins, gliadins, globulins, and water-/salt-soluble albumins. Globulins and albumins show the highest allergic potency in bakers.^{51,52} However, over 100 different allergen spots have been extracted from the salt-/water-soluble wheat flour fraction.⁵³ No major allergen has yet been identified for baker's asthma, but α -amylase inhibitors (eg, Tri a 28) and Tri a 27 (thiol reductase) are most frequent.⁵⁴ Flour dust may also contain

several other allergenic components such as enzymes (eg, α -amylase, cellulase, hemicellulose, xylanase, glucoamylase, malt enzymes), additives (eg, baker's yeasts, flavorings, spices, sugar, egg and milk powder, preservatives, food pigments), and microorganisms (eg, fungi, bacteria, mites).⁵²

Farming, milling, bread baking, pastry making, cereal handling or grain cleaning, and packing have been identified as high-risk occupational activities. Bakers continue to be the most common high-risk occupational group for respiratory allergy,⁵⁵ commonly sensitized to wheat or rye flour allergens (Table 7).⁵³ Individual variation in the specific IgE binding patterns has been observed to both these allergen sources, which may be due to either variation in individual host risk factors or single allergen exposure levels.^{53,56} Recently published studies revealed that 44.5% of bakers with work-related respiratory symptoms were diagnosed with OA⁵⁷ and an increased incidence of asthma in supermarket bakery workers.⁵⁸

IgE-mediated mechanisms are most well-known means of sensitization to flour allergens⁵⁹; however, the nature of interactions between cells and flour dust depends on the size of bioaerosol particles and site of deposition.⁵² Their aerodynamic diameter ranges up to 30 μ m, those >10 μ m are trapped in the upper respiratory tract and cause local irritant or allergic reactions, whereas smaller particles (5–10 μ m) may evoke asthmatic reactions.⁵²

Atopy and increasing level of exposure are the most important risk factors for respiratory allergy to cereal flours.⁶⁰ Furthermore, cereal allergens “taken home” from the workplace are also potential sensitizers for family members.⁶¹

6.3 | Additives and enzymes

Additives and enzymes are widely used as preservatives, antioxidants, and antibrowning agents that are added to improve the quality of food. Enzymes are potent sensitizers eliciting specific IgE-mediated reactions resulting in OA and/or OR among exposed workers (Table 7).⁶² In addition, in vitro studies have demonstrated that seafood proteases also stimulate airway inflammation by IgE-independent mechanisms.²⁹

The association between food enzyme exposures (eg, amylase, glucoamylase, cellulase, protease, phytase, bromelain, pectinase, papain) and OA has been well documented.^{63,64} In bakery workers,

TABLE 7 Allergens associated with occupational allergy and asthma in food processing work environments

Seafood					
Phylum	Class	Family species (common name)	Allergen name (source)	Molecular Weight (kDa)	Potential cross-reactivity
Arthropoda	Crustacea	Crab	Chi o 1 (tropomyosin - meat)	33 kDa	Crustacean species, insects, mites and <i>Anisakis (fish parasite)</i>
			Chi o 2 (arginine kinase - meat)	40 kDa	
		Scampi, lobster	Unidentified (meat, crab water)	4.4, 18.5, 25 kDa	
			Nep n DF9, Nep n 1 (tropomyosin - meat, wastewater)	30.2, 97 kDa	
	Shrimp, shrimp meal		Unidentified (dried whole body)	80 kDa	
			Unidentified (raw, shrimp water)	35-39 kDa	
			Unidentified (cysts)	97 kDa	
	Prawn		-	-	
			-	-	
			Unidentified (meat, viscera)	19-42 kDa	
Mollusca	Gastropoda	Abalone	-	-	Gastropods and Arthropods
		Scallop	-	-	Molluscs and Arthropods
	Bivalvia	Clam, oyster, mussel	-	-	Cephalopods and Arthropods
		Octopus, squid	Unidentified (meat)	32, 43 kDa	
		Cuttlefish	-	-	
	Cephalopoda		Sar sa1, Sal s1 (parvalbumin - whole body, meat)	12, 36, 48, 60 kDa (monomers/oligomers)	Fish species of the bony fish and cartilaginous fish group
			Glyceraldehyde-phosphate-dehydrogenase (whole body)	36 kDa	
			Unidentified (meat)	38, 58 kDa	
			Phosphoglucosylase, muscle actin, apolipoprotein AI (meat)	61, 42, 29 kDa	
			-	-	
Pisces (sub-phylum Chordata)	Osteichthyes (bony fish)	Pilchard, anchovy	-	-	Fish species of the bony fish and cartilaginous fish group
			-	-	
			-	-	
			-	-	
			-	-	
	Chondrichthyes (cartilaginous fish)	Shark (cartilage)*	-	-	Fish species of the bony fish and cartilaginous fish group
			-	-	
			-	-	
			-	-	
			-	-	
Other agents		Hoya (Sea squirt), <i>Anisakis</i> , Red soft coral, Daphnia, Marine sponge, Algae	-	-	Crustacean species, insects, mites and <i>Anisakis (fish parasite)</i>
			-	-	

(Continues)

TABLE 7 (Continued)

Type	Species name	Group of allergens	Allergen name (source)	Molecular Weight (kDa)	Potential cross-reactivity
Cereal flours					
Wheat	<i>Triticum sp</i>	Profilin	Tri a 12 (seed, pollen)	14 kDa	Rice, barley, oats, maize, rye, natural rubber latex, common grass pollen, peach
		α -amylase inhibitor	Tri a 15, Tri a 28, Tri a 29, Tri a 30, Tri a 40 (all in seed)	10-20 kDa	
		Thioredoxin	Tri a 25	13.4 kDa	
		Nonspecific lipid transfer protein (ns LTP)	Tri a 14 (seed)	9 kDa	
		Thiol reductase homologue	Tri a 27 (seed)	27 kDa	
		Triosephosphate isomerase	Tri a 31 (seed)	27 kDa	
		Peroxioredoxin	Tri a 32 (seed)	23.9 kDa	
		Serpin	Tri a 33 (seed)	36, 5 kDa	
		Glyceraldehyde 3-phosphate dehydrogenase	Tri a 34 (seed)	36, 5 kDa	
		Dehydrin	Tri a 35 (seed)	12, 4 kDa	
		Serine protease inhibitor-like protein	Tri a 39 (seed)	12, 4 kDa	
		Secalins:	Sec c 1 (Sec c 38) (pollen), Sec c 5 (pollen)	13.5 kDa	
		α -amylase/trypsin inhibitor			
Rye	<i>Secale cereale</i>				Barley, oats, wheat, maize, rice
Barley	<i>Hordeum sp</i>	Hordeins:			Rye, wild rye grass, wheat, couch grass, lyme grass, oats, rice, maize
		α -amylase/trypsin inhibitor	Hor v 1 (Hor v 15)	14-16 kDa	
		α -amylase	Hor v 16 (pollen)		
		β -amylase	Hor v 17		
Oats	<i>Avena sativa</i>	Avenins	Unidentified		Rye, wheat, triticale, barley, maize, rice, Johnson grass, sorghum, canary grass
Sorghum	<i>Panicum miliaceum</i>	Hydrolase	Sor h 13	54-55 kDa	Barley, oats, rice, wheat
		Expansin	Sor h 1 (pollen), Sor h 2 (pollen)	30-35 kDa, 12 kDa	
Rice (Wild rice)	<i>Oryza sativa</i>	Expansin	Ory s 1 (pollen)	28-35 kDa	Corn, buckwheat, wheat, barley
Corn (Maize)	<i>Zea mays</i>	Expansin	Zea m 1 (pollen)	25-35 kDa	Rice, soybean, peanut, sunflower seed, wheat, barley, rye, oat
		Profilin	Zea m 12 (pollen, seed),	14 kDa	
		Lipid transfer protein	Zea m 14 (pollen, seed)	9 kDa	
		Thioredoxin	Zea m 25 (seed)		

(Continues)

TABLE 7 (Continued)

Type	Species name	Group of allergens	Allergen name (source)	Molecular Weight (kDa)	Potential cross-reactivity
Noncereal flours					
Soy	<i>Glycine hispida</i> (<i>Glycine max</i>)	Glycinins	Gly m 1 (seed)	7-8 kDa	Pea and other legumes, birch pollen
			Gly m 2 (seed)	8 kDa	
			Gly m 4 (seed)	17 kDa	
			Gly m 5 (seed)		
			Gly m 6 (seed)		
Buckwheat	<i>Fagopyrum esculentum</i>	Unidentified proteins	-	8-67 kDa	Tartary buckwheat, wheat, rice, natural rubber latex
Peas	<i>Pisum sativum</i>	Unidentified proteins	Pis s	9.5-66 kDa	Soybean, birch pollen
Fungal enzymes					
α -amylase	<i>Aspergillus oryzae</i>	Hydrolase	Asp o 21	14-47 kDa	-
β -xylosidase	<i>Aspergillus niger</i>	Hydrolase	Asp n 14	105 kDa	-
Glucoamylase	<i>Aspergillus niger</i>	Hydrolase	-	61-71 kDa	-
Cellulase	<i>Aspergillus niger</i>	Hydrolase	-	63 kDa	Xylanase
Xylanase	<i>Aspergillus niger</i>	Hydrolase	-	29 kDa	Cellulase
Pectinase	<i>Aspergillus niger</i>	Protease	-	66 kDa	-
Phytase	<i>Aspergillus niger</i>	Protease	-	100 kDa	-
Plant-derived enzymes					
Papain	<i>Carica papaya</i>	Protease	-	10-35 kDa	-
Bromelain	<i>Ananas comosus</i>	Protease	Ana c 2	28 kDa	-
Ficin	<i>Ficus insipida</i>	Protease	-	23.8 kDa	-
Animal-derived enzymes					
Lysozyme	Hen's egg white	Protease	-	14 kDa	-
Pepsin	Gastric/pancreatic from hog/beef stomach	Hydrolase	-	36 kDa	-

Reference sources: WHO/IUIS Allergen Nomenclature Sub-Committee (www.allergen.org/), Allergome (www.allergome.org/), Jeebhay and Cartier 2010, Lopata and Jeebhay 2013) and additional references (Pérez Carra 2010, Torm 2013). For cereal flour additional references (Karpinski 2003, Quirce 2013, Stobnicka 2015, Sander 2001, Sander 2015, Varjonen 1994).

*Anaphylactic reaction

a clear relationship between exposure to α -amylase, derived from *Aspergillus oryzae*, and IgE production has been reported.⁶⁵ The prevalence of sensitization to α -amylase and glucoamylase ranged between 5% and 24% among symptomatic workers without sensitization to cereal flour.^{66,67} In the modern baking industry, sensitization to glucoamylase (28%) and cellulase (16%) appears to be most common.⁶⁸ Furthermore, xylanolytic enzymes can also cause OA and OR in bakers.⁶⁹ The major determinant of sensitization to enzymes is the level of exposure⁷⁰ and its ability to become airborne.⁷¹

OA associated with allergy to pectinase and gluconase has been reported in fruit processing activities and in wine production, while hen's egg derived lysozyme causing OA in the egg processing industry and in bakers (Table 2). Furthermore, sulfites and other preservatives can also cause OA or OR in seafood processing and wine production. The underlying mechanism for OA is not well understood, but it does not appear to be IgE-mediated.^{21,72,73}

7 | DIAGNOSIS

The investigative approach for suspected occupational respiratory allergy in food processing workers is similar to that due to other causes.^{2,3,9} Its purpose is to confirm the presence of respiratory disease and demonstrate work-relatedness through both nonspecific tests and specific immunological tests to demonstrate sensitization to the suspected food.

7.1 | In vivo tests

The first step is a thorough clinical and occupational history followed by objective tests. Confirmation of the presence of respiratory disease should follow the current international guidelines.^{74,75} Together with a suggestive clinical history, the work-relatedness of bronchial symptoms can be demonstrated using serial peak expiratory flow (PEF) and/or nonspecific bronchial responsiveness (NSBH) monitoring during and away from work.^{2,3} With regard to rhinitis, functional specific tools (ie, rhinomanometry, acoustic rhinometry, and peak nasal inspiratory flow) have limited applicability in clinical practice and are generally limited to specialized centers or for research purposes.³ Both upper and lower airway inflammation can also be evaluated by noninvasive methods (assessment of cells and mediators in induced sputum and/or nasal lavage, nasal, and exhaled nitric oxide)⁷⁶ as a complementary tool, and for excluding the presence of other specific occupational respiratory diseases (eg, nonasthmatic eosinophilic bronchitis).⁷⁷

Sensitization to a suspected food allergen is assessed using skin prick tests (SPT) and/or serum-specific IgE (sIgE) determination. The lack of standardized and validated extracts for several food allergens affects the test performance since fresh natural raw extracts are often used.⁷⁸ Recombinant proteins may, in selected cases, allow for better identification of sensitization to the responsible allergenic proteins.^{54,79} The positive and negative predictive value of immunological tests for OA/OR varies depending on the allergen involved.

Overall, a negative SPT test does not exclude the diagnosis of OA/OR, whereas a positive test supports the diagnosis but is not definitive in making the diagnosis.^{2,11,78}

The specific inhalation challenge (SIC) is considered the reference standard for the diagnosis of OR/OA. However, its use is limited to expert clinicians in specialized centers as it is a complex and time-consuming procedure, requiring proper facilities.^{2,3,80}

7.2 | Component-resolved diagnosis (CRD)

A growing number of food allergens have been identified and characterized using CRD.⁸¹ These allergenic molecules, purified from allergen source or produced in recombinant form, are increasingly being used as single components in non-occupational food allergy diagnosis, whereas in food-induced occupational allergy its use has been limited to wheat and seafood.⁸¹ In baker's asthma, CRD has contributed toward improved diagnosis and enabled better discrimination between sensitization to wheat from occupational inhalation of flour, ingestion of wheat containing food products, and grass pollen allergy.⁵⁴ However, specific IgE measurements using whole wheat flour extracts are still important for reliable in vitro diagnosis of baker's asthma, due to their higher diagnostic sensitivity.⁵⁴

Sensitive detection of single allergen components also provides for better exposure assessment evaluation in food processing activities.^{22,28} The specific sensitization profile established through CRD enables better identification of the putative allergen to institute allergen-preventive measures. In seafood processing workplaces, the major shellfish allergen, tropomyosin, could be quantified as low as 60 pg/m³ (Table 4).^{38,82}

7.3 | Other in vitro tests

While other in vitro tests, such as the basophil activation test (BAT)⁸³ or inhibition test,⁸⁴ may be useful, they are not used for routine testing. The BAT is a functional assay that measures the response of basophils to allergen-mediated cross-linking of IgE antibodies. In comparison with the sole determination of specific serum IgE levels, the BAT resembles more closely the clinical phenotype of patients.⁸⁵

8 | GENERAL APPROACH TO MANAGEMENT AND PREVENTION

The management of food-induced OA/OR includes environmental interventions aimed at avoiding or reducing exposure to the offending agent, timely pharmacological treatment, and assessment of impairment, and optimizing rehabilitation and compensation.^{3,86,87} An early diagnosis is essential for a favorable outcome of the asthma.^{86,88} Removal from exposure is the intervention of choice; however, should this not be possible, exposure reduction is an alternative.⁸⁹

In individuals with IgE-mediated OA, specific allergen immunotherapy [SIT] may be a useful option when validated extracts

are available.⁸⁶ A short- and a long-term beneficial effect of SIT with wheat flour in baker's asthma while the patient remained at work have been shown.^{51,90} However, SIT has not been approved for routine management in bakers' asthma due to the lack of commercially validated extracts. In selected cases, the monoclonal antibody omalizumab has proven to be effective in reducing symptoms of bakers' asthma.⁹¹

Patients with co-existent ingestion-related food allergy and food-induced OA and/or OR should practice both dietary and environmental avoidance. Subjects with a previous ingestion-related food anaphylactic reaction should undergo a strict environmental control and surveillance, and should be provided with a written emergency management plan, an adrenaline auto-injector and educated on its use.^{92,93}

The optimal management of OA should include follow-up program medical evaluation that includes periodic assessment of symptoms, lung function, and allergen-specific IgE levels where appropriate. Education of workers on improved work practices to reduce exposure and therapy compliance may contribute toward a favorable outcome.

OA/OR due to inhaled food allergens is preventable. Primary prevention through elimination of exposure to known sensitizing agents is most effective.⁹⁴ Due to the lack of exposure standards, keeping exposure as low as possible by using appropriate risk management and exposure control strategies is advocated as best practice. Strategies for reducing exposure to the causal agent/s are specific to the industry and may include modification of food processing, use of modified materials, encapsulation or dissolved enzyme formulation, mechanization or automation, improving ventilation, use of personal protective devices (eg, respirators), working techniques avoiding dust production, better organization of work, and improvement of workplace conditions.^{11,17,51} Information campaigns at schools aimed at guiding the professional choice of adolescents at risk, pre-apprentice information on at-risk professions, and rigorous medical surveillance of apprentices is recommended.⁹⁶ Atopic workers should not be excluded from occupations at risk due to the low positive predictive value of atopy for the development of OR/OA.¹⁵ Medical surveillance, especially of workers exposed to HMW agents such as food allergens, should be prioritized in the first 2-3 years of exposure since OR/OA occur more frequently during this period.⁹⁷

9 | CONCLUSION AND RECOMMENDATIONS

Food processing activities produce dust particulate or aerosols that are readily inhaled and can act as primary sensitizers in the airways, causing a distinct form of IgE-mediated respiratory food allergy, usually without any symptoms upon ingestion (*Class 3 food allergy*). Exposure assessment and primary prevention measures to minimize exposure to offending agents are therefore key to reducing the risk of occupational allergy and asthma among workers in food processing industry. Medical surveillance and regular follow-up of exposed

workers can ensure an early diagnosis, which is mandatory for a favorable outcome. Furthermore, prompt environmental interventions aimed at avoiding or minimizing exposure to the offending agent increase the probability of recovery in workers with food-induced OA/OR. For workers with co-existent ingestion-related food allergy and food-induced OA/OR, both dietary and environmental avoidance are essential. Finally, workers with a history of an ingestion-related food anaphylactic reaction in the past should be subjected to strict environmental control measures and medical surveillance, and be provided with a written emergency management plan and trained as to its use.

10 | RESEARCH NEEDS

Future research that would enable a better understanding of occupational allergy and asthma in food processing environments should focus on:

- The relative contribution of respiratory versus cutaneous sensitization to food antigens in relation to different phenotypic manifestations
- Characterization of different phenotypes of occupational inhalant food allergy and asthma through sentinel group surveillance/exposure cohorts
- Development of commonly accepted high-quality sampling methods, analytical assays, and quantification techniques for allergens and other components in complex mixtures
- Detailed exposure-response studies using standardized food allergen immunoassays to establish the utility of exposure threshold limits for food allergens
- The adjuvant effects associated with the presence of associated agents in the food matrix such as pro-inflammatory agents (eg, toxins, enzymes)
- The relevance of the food matrix physical state (eg, raw versus cooked seafood) in influencing the risk of inhalant food allergy and asthma
- the mechanisms through which patients with food-induced occupational asthma and/or occupational rhinitis tolerate the ingestion of the same food
- Identifying and characterizing major food allergens (eg, seafood and cereals) and their clinical relevance in causing inhalant allergy and asthma
- Evaluating the effectiveness of intervention packages (exposure control/best practice) for common high-risk food sensitizers
- Absolute or relative contraindication of patients with ingestion-related food allergy, pollinosis, or oral allergy syndrome continuing to work with exposure to aerosolized food allergens

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

This Position Paper is the result of the collaboration of a panel of experts who contributed to the document according to their different experiences and competences with the taskforce being coordinated by Gianna Moscato (chair) and Mohamed Jeebhay (secretary).

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