

POSITION PAPER

Occupational anaphylaxis – an EAACI task force consensus statement

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Abstract

Anaphylaxis is a systemic allergic reaction, potentially life-threatening that can be due to nonoccupational or, less commonly, to occupational triggers. Occupational anaphylaxis (OcAn) could be defined as anaphylaxis arising out of triggers and conditions attributable to a particular work environment. *Hymenoptera* stings and natural rubber latex are the commonest triggers of OcAn. Other triggers include food, medications, insect/mammal/snake bites, and chemicals. The underlying mechanisms of anaphylactic reactions due to occupational exposure are usually IgE-mediated and less frequently non-IgE-mediated allergy or nonallergic. Some aspects of work-related allergen exposure, such as route and frequency of exposure, type of allergens, and cofactors may explain the variability of symptoms in contrast to the nonoccupational setting. When assessing OcAn, both confirmation of the diagnosis of anaphylactic reaction and identification of the trigger are required. Prevention of further episodes is important and is based on removal from further exposure. Workers with a history of OcAn should immediately be provided with a written emergency management plan and an adrenaline auto-injector and educated to its use. Immunotherapy is recommended only for OcAn due to *Hymenoptera* stings.

Anaphylaxis is a severe allergic reaction characterized by rapid onset of potentially life-threatening symptoms (1, 2). Main elicitors of anaphylaxis are food, medications, insect stings/bites, and natural rubber latex (NRL) (3); these have also been reported to cause occupational anaphylaxis (OcAn) (4). Occupational exposures may differ from non-occupational exposures with regard to the intensity and route of exposure. *Hymenoptera* stings are common occupational triggers and can induce anaphylaxis in beekeepers and forestry workers (5, 6). Exposure to other triggers of OcAn, such as NRL in healthcare workers (HCW), is declining in industrialized countries. Reduction of exposure can prevent or reduce sensitization rates and

therefore risk of anaphylactic reactions (7). Removal from exposure is mandatory to prevent further episodes. A European Consensus document on the management and prevention of OcAn is needed as a benchmark for future policies.

The aim of this document was to

- summarize current scientific evidence linking exposure to occupational triggers and the risk of anaphylaxis and suggest possible preventive measures and
- develop a European Consensus on policy suggestions for management and prevention addressed to general practitioners, allergologists, dermatologists, and occupational physicians.

Key Messages Box

- Occupational anaphylaxis (OcAn) can be defined as anaphylaxis arising out of causes and conditions attributable to a particular work environment.
- *Hymenoptera* stings and natural rubber latex are the most common triggers of OcAn.
- Other triggers of OcAn less frequently reported are food, medications, animal/insect bites, and chemicals.
- Underlying mechanisms of anaphylactic reactions due to occupational exposure are usually allergic—IgE-mediated and sometimes allergic—non-IgE-mediated or nonallergic.
- Some aspects of work-related allergen exposure, such as route and frequency of exposure, type of allergens, and cofactors may explain the variability of symptoms in contrast to the nonoccupational setting.
- The diagnosis of OcAn requires the confirmation of the diagnosis of anaphylactic reaction and identification of the occupational anaphylactic trigger.
- For higher-risk workers, for example, with cardiovascular or respiratory disease and allergic symptoms such as urticaria with a potential elicitor of anaphylaxis, consideration should be given to avoidance of further exposure to prevent a potentially life-threatening response.
- Prevention of further episodes of anaphylactic reactions is based on removal from exposure.
- Workers with a history of OcAn should immediately be provided with a written emergency management plan and an adrenaline auto-injector and education on its use.
- Immunotherapy is recommended only for OcAn due to *Hymenoptera* stings.

Methods

This consensus document was prepared by an EAACI Task Force consisting of an expert panel of allergologists, dermatologists, occupational physicians, and epidemiologists. A literature search was conducted by panel members using PubMed Medline. In the selection of papers, the current definition of anaphylaxis was used (1, 2). Two meetings were held to review the findings and reach informal consensus. Further consensus was obtained by 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 article is the result from an expert opinion consensus after a thorough review of the available literature. The expert recommendations have been summarized in 'key messages' (see Key Messages Box) and 'suggestions'.

Data sources, search strategy, and study selection

Published studies in English were identified from PubMed from 1965 to August 6, 2013. The following key words were

used in the search strategy: (work* OR occupation*) AND (anaphylaxis OR anaphylactic OR anaphylactoid OR 'venom allergy' OR 'latex allergy' OR 'systemic reaction*'). References published within the 1965–2013 timeframe that had not been otherwise identified in the initial search were added where relevant.

Anaphylaxis: current definition and main elicitors

The recent EAACI and WAO Guidelines defines anaphylaxis as a severe, potentially life-threatening systemic hypersensitivity reaction, characterized by a rapid onset of airway, breathing, circulatory, or gastrointestinal problems, which is usually associated with skin and mucosal changes (Table 1) (1, 2).

There is no universal agreement upon the definition of OcAn. It could be defined as anaphylaxis arising from elicitors and triggering factors attributable to a particular work environment. The elicitor could be a known or previously unidentified allergen introduced into the body following inhalation, dermal contact (only in a person with preexisting skin disease; e.g., dermatitis, skin trauma), accidental inoculation, insect sting, or following hand to mouth transmission in workplaces with poor industrial hygiene practices (4). The main categories of workplace elicitors include food, medications, insect stings/bites, mammal/snake bites, NRL, and chemicals (Table 2).

If anaphylaxis occurs in the workplace, it is likely that is induced by workplace exposures. However, anaphylactic

Table 1 Clinical criteria for diagnosing anaphylaxis in adults

Anaphylaxis is likely when any one of the three criteria is fulfilled:

- (1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips/tongue/uvula)
And at least one of the following
 - a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
- (2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips/tongue/uvula)
 - b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
- (3) Reduced BP after exposure to a known allergen for that patient (minutes to several hours):
Systolic BP of <90 mm Hg or >30% decrease from that person's baseline

PEF, peak expiratory flow; BP, blood pressure.

Reproduced from Muraro et al. (2).

Table 2 Examples of elicitors of occupational anaphylaxis

Elicitor	Industry
Food proteins: buckwheat (28), tamarillo (25), coriander (26), paprika (27), chicory leaves (21)	Food processing
Medication: immunotherapy extract (42), cefotiam (15, 37, 38), piperacillin (7), penicillin (32), psyllium (39), cephaloridine (35)	Pharmaceutical manufacturing plants, healthcare institutions (preparation of medication)
Insect bites/stings: <i>Hymenoptera</i> (43, 45, 46), tick (49, 50), tsetse fly (56)	Beekeepers (honey making), agriculture, parks and forestry, and gardening and landscaping
Mammal and snake bites: mouse (58), rat (58, 59), rabbit-related (62), snake (63, 65)	Laboratory animal workers
Natural rubber latex (NRL) (17, 66, 67, 69, 71, 72)	Healthcare and manufacturing plants with NRL in the production process
Chemicals: iridium salts (77), chlorothalonil (80), reactive dyes (84), cobalt (78), HBTU (89), perfume (88), ammonium persulfate (83), chromium (76)	Various industries depending on chemicals used, for example, agriculture (chlorothalonil), hair dressing (persulfates), welding (chrome)

Adapted from Knight and Jeebhay (4).

reactions arising from nonworkplace exposures may manifest at work, so reactions require additional evidence before being labeled as 'occupational'. Workers may also initially be sensitized from workplace allergen exposures but only manifest anaphylactic reactions in nonworkplace contexts. For example, this may occur for HCW with latex allergy undergoing either surgical/medical/dental procedures or workers ingesting food or medication after developing sensitization and minor symptoms (e.g., rhinitis, urticaria, and asthma) at work.

Mechanisms of occupational anaphylaxis

Underlying mechanisms of anaphylactic reactions due to occupational exposure are usually IgE-mediated; however, they can be potentially due to nonallergic mechanisms. The investigations and advice are the same for both mechanisms. Potential mechanisms of anaphylaxis are described in detail elsewhere (1, 8).

Some aspects of work-related allergen exposure may explain the variability of the clinical pattern of symptoms in contrast to the nonoccupational setting:

- Route of exposure. In the work place, foods and drugs causing OcAn are usually not orally ingested. Allergen exposure takes place by inhalation, skin contact, animal sting/bites, or accidental inoculation (e.g., needle injuries) that usually will be associated with a lower allergen dose.
- Frequency of exposure. Work exposure may be more frequent and trigger earlier sensitization or progressive reactions in allergic subjects. Alternatively, very frequent and intense exposures may contribute to clinical tolerance. In a retrospective study, all beekeepers who received >200 stings per year tolerated bee stings, whereas systemic allergic reactions were more frequent in subjects who were stung <25 times per year (9).
- Type of allergen. For some elicitors, different allergens are involved in OcAn compared to the nonoccupational setting. HCW and patients undergoing multiple medical procedures may become sensitized to NRL allergens by exposure to medical gloves. However, patients and HCW

typically exhibit different patterns of IgE antibodies to compounds within NRL (10). The exposure to the inner vs outer side of the glove or the site of exposure may modify the sensitization pattern.

- Cofactors. Physical activity during work may be a sufficient trigger to induce exercise-induced anaphylaxis, either as a sole factor or as a cofactor/aggravating factor following ingestion of a non-work-related food (8).

Diagnosis

The diagnosis of OcAn is made if characteristic symptoms occur (Table 1) and the causative role of a specific workplace agent can be demonstrated (Table 2) (1, 2). An effort should be made to identify the causative agent as this has major implications for secondary and tertiary prevention including removal from exposure and relocation. The following approach should be followed (11).

Confirm the diagnosis

- Detailed history of the episode focusing on the antecedent clinical symptoms and signs and obtaining information from co-workers.
- Review of relevant medical records from the ambulance, emergency department, occupational health clinic, etc.
- Review of laboratory tests (e.g., serum tryptase) performed during the episode.
- Consider the differential diagnosis, which commonly includes hives, asthma, anxiety/panic attack, fainting, choking.

Identify the anaphylaxis trigger

There are several issues to consider when the worker has recovered from the acute episode. It is vital that all testing is carried out in a controlled environment by an allergist/immunologist or pulmonologist with the necessary precautionary measurements and resuscitation facilities readily available:

- Carefully review the history of the episode and enquire about potential inhalational and ingestion-related triggers. Review the production process and job tasks and identify potential exposure agents. Review the Chemical Safety Data Sheets (SDS) of all products the worker may have used.
- Investigate for concomitant diagnoses such as asthma and cardiovascular diseases as well as concurrent medications such as β -blockers and ACE inhibitors.
- Perform relevant skin tests—skin prick tests (SPTs) for foods or other agents (e.g., latex) and intradermal tests for insect venoms or β -lactam antibiotics (2). These tests should be carried out under controlled conditions 3–4 weeks after the incident because skin tests performed shortly after the acute episode may be falsely negative. However, for many occupational allergens, there are no commercially available test allergens. Skin testing with raw materials should be carried out carefully using non-toxic dilutions only from the original materials. The interpretation of positive skin tests to nonstandardized substances for which controls in nonallergic subjects are not available has to be carried out with utmost caution.
- Perform allergen serum-specific IgE quantitative measurements using standardized test systems (ELISA) if available (2). For many potential work-related allergens, standardized tests are not available or are often of poor quality due to poor sensitivity/specificity. Cellular tests may help to prove allergen-specific sensitization (2). Identification of cross-reactive allergens may be necessary (e.g., latex cross-reactive fruit allergens such as banana, kiwi, pear, and avocado; pollen cross-reactive spice/food allergens).
- Challenge tests such as specific inhalation challenge using the suspected product may confirm clinical relevance of a sensitization to an allergen and are the only method to verify hypersensitivity to nonallergic elicitors. As they are potentially dangerous, they should be undertaken only if their outcome is required to clarify a clinically important question (11). All precautions to minimize the patient's risk should be taken, and challenge tests should only be performed by clinicians with this expertise (12).
- Other assessments such as workplace industrial hygiene review may prove useful in certain contexts.

The specificity and sensitivity of each test and its correlation with health effects are quite variable. Discussion with the allergologist and laboratory technologist can assist the practitioner in choosing the most appropriate tests taking the clinical context and potential workplace exposures into account. After proper investigation, only a few cases will be labeled as 'idiopathic' OcAn.

General approach to management, early detection, and prevention addressed to general practitioners, allergologists, and occupational physicians

Emergency management of anaphylactic responses occurring from either occupational or nonoccupational exposures

should follow current and WAO guidelines (2, 13, 14). In a worker without a previous diagnosis of anaphylaxis, adrenaline may not be available, but emergency services should be called. Meanwhile, available emergency measures to maintain the airway and provide cardiopulmonary resuscitation should be delivered. If adrenaline is available, this should be administered while awaiting emergency services.

Following emergency management and unless further avoidance to the elicitor can be guaranteed, patients for whom the cause is unclear or those at continuing risk should be advised to carry 2 preloaded adrenaline delivery systems with appropriate instructions for use and a MedicAlert bracelet stating 'anaphylaxis, carries EpiPen' (or equivalent) (13, 14). Workers with suspected OcAn should be removed from possible causative exposures at work until fully investigated and managed to ensure they are not exposed to further risk at work. Protective gloves, masks, or clothes may be effective in some cases. However, despite these measures, there have been reports of anaphylaxis, for example, in HCW with drug allergy (15). The cause may already be known, if there have been previous allergic responses (e.g., to stinging insects or NRL), but if not previously identified, the worker should undergo specialist assessment, as detailed above, to identify the trigger and receive advice as to future avoidance measures.

The worker should subsequently avoid further exposure to the cause of his/her anaphylaxis, both in and out of the workplace, as even low exposures could potentially cause a life-threatening response. The exception is that some workers who have successfully received immunotherapy, such as for venom allergy, may be able to safely continue work.

Early detection

Workers who have had allergic responses that are not anaphylactic can be at increased risk of an anaphylactic response, especially from some allergens. Anaphylactic responses are more likely with allergens that are ingested (e.g., psyllium) or injected, or that permeate the skin or mucosal barrier (e.g., NRL allergen from gloves in a worker with hand dermatitis, or rat allergen exposure from scratches or bites). Anaphylaxis has seldom been reported from inhaled exposures without concurrent breach of the skin barrier, although it can occur. Workers with an anaphylactic response should have a thorough allergy assessment with a specialist to provide objective diagnosis and identify risk. The possibility of anaphylaxis at work and outside work from cross-reacting allergens should also be considered, for example, food allergens in NRL-allergic workers, pollen allergic workers in food processing environments (16).

General prevention measures

Prevention in relation to the natural history and prognosis of occupational allergy is a cornerstone of dealing with OcAn as it is a potentially life-threatening reaction.

Primary prevention comprises reducing/avoiding exposure to causative or sensitizing agents and considering host-related

factors (poorly controlled asthma, cardiovascular disease) among workers exposed to workplace agents that can cause anaphylaxis (17). As for other occupational diseases, exposure principles in order of priority include substitution with a safer product at work (e.g., nitrile gloves in place of NRL gloves), reduction of exposure (e.g., psyllium granules in place of powder), containment (e.g., use of robotics), use of protective equipment, and improved ventilation.

Secondary preventive measures comprise focused medical surveillance of high-risk working populations (using questionnaires and immunological testing) health and safety education and training of workers to read product labels to identify allergenic constituents and be aware of their risks should be enforced. Recognition of early warning signs of an allergic response can be a useful adjunct to other workplace interventions as it may reduce the incidence of fatal allergic reactions (4, 18).

Tertiary prevention comprises early recognition and diagnosis followed by appropriate removal from further exposure and the management strategies detailed above.

Specific causes of occupational anaphylaxis

Occupational anaphylaxis due to foods

Although anaphylaxis is the most serious consequence of food allergy, occupational exposure to foods more often leads to contact dermatitis, urticaria, and respiratory symptoms.

Food processing in general appears to be a major cause of contact urticaria (19). In workers handling seafood, the prevalence of occupational asthma and contact dermatitis ranges from 7% to 36% and 3% to 11%, respectively (20). In contrast, OcAn has been described in a few case reports only.

Sensitization to chicory caused chronic contact dermatitis and episodes of generalized pruritus, facial erythema, and dyspnea at work in a male cook (21). Sensitization to fish and crustaceans at work elicited symptoms progressing from initial contact urticaria to generalized urticaria at work, non-occupational anaphylaxis and finally occupational asthma in a truck driver in charge of seafood deliveries (19). Although not genuine cases of anaphylaxis, bakers asthma with a fatal outcome (22) and fatal asthma due to exposure to shark cartilage dust (23) has been reported.

Anaphylaxis to food caused by work-related sensitization

Occupational sensitization to a food allergen can lead to systemic and anaphylactic reactions in a nonoccupational environment after consumption of the relevant food allergen. Generalized pruritus and erythema has been described after ingestion of baby squid in a fishmonger (24). Sensitization to obeche wood resulted in anaphylaxis in a carpenter consuming the biologically related tamarillo (25). Anaphylaxis after ingestion of coriander has been described in a sensitized subject working at a spice factory (26). Anaphylaxis after intake of paprika has been seen in a spices and condiment seller (27), and buckwheat-induced anaphylaxis in a worker sensitized to buckwheat has been reported in one case study (28).

There is a striking discrepancy between reported prevalence of work-related skin and respiratory disorders and the sparse data on OcAn to food allergens. For instance, the incidence of occupational sensitization to lupin, an allergen able to induce anaphylaxis, is up to 29% (29). In contrast, OcAn to lupin has not been reported. This may be because lupin exposures by inhalation and direct skin contact may not lead to anaphylaxis as easily as ingestion does. However, work-associated food-induced anaphylaxis in a nonoccupational setting might represent an under-recognized problem.

Occupational anaphylaxis due to medications

Sensitization to drugs can take place in the work place either through topical contact with spilled drugs or by inhalation of powder or foam. Occupations at increased risk include nurses, pharmacists, and people employed in the manufacturing process.

The rates of sensitization vary according to the drug. Some drugs, such as psyllium, appear to have high risk of sensitization with some studies suggesting that up to 40% of exposed nurses become sensitized (30). The risk of sensitization was increased in atopic individuals. β -lactam antibiotics also have a propensity for sensitization. In a recent study, 2.6% of nurses were sensitized to β -lactam antibiotics; this rate increased to 6.9% when there was a history of skin allergy (31). An earlier study reported sensitization rates of 12% to penicillin in nonallergic nurses (32). This effect is also seen with cephalosporins with 17.4% of 161 Korean HCW having specific IgE to cefotiam, ceftriaxone, or ceftizoxime (33). The risk was higher in those with atopic dermatitis. In this cohort, the *FcεRI*β-109T>C polymorphism was significantly associated with IgE sensitization to cephalosporins, suggesting a genetic basis for sensitization (34).

When subjects develop symptoms in the occupational setting, these commonly include exacerbations of asthma, upper airway symptoms, and contact dermatitis. While anaphylaxis is less frequent, there is often a history of milder self-limiting reactions prior to its development. Anaphylaxis can take place in the workplace; however, it is also common for it to happen when the sensitized worker receives the implicated medication as a patient.

The commonest class of drugs associated with OcAn are the β -lactam antibiotics (Table 3). The earliest report relates to nonoccupational cephaloridine anaphylaxis in a nurse with no history of past personal exposure (35). Three cases of OcAn to penicillin were reported by Rudzki and Rebandel (36); all cases were nurses who had their reaction while preparing medication at work. Tadokoro et al. (15) describe eight nurses who suffered anaphylactic/systemic reactions to cefotiam at work. Interestingly, five of these nurses had a history of hand dermatitis. Further cases have been reported in the literature to cefotiam (37, 38). There have been cases of anaphylaxis to other β -lactam antibiotics. Kim et al. (7) reported a case of a nurse with atopic dermatitis who had an anaphylactic reaction to piperacillin following many years of occupational exposure.

Table 3 Case reports of occupational anaphylaxis due to medications

References	Subjects (n)	Occupation/activity	Agent	Previous atopic diseases	Acute onset (min to several h) after exposure to occupational agent	Involvement of skin/mucosal tissue	Respiratory compromise	Systolic blood pressure (mm Hg)	Persistent gastrointestinal symptoms	Specific SPT/serum IgE	OcAn/Sensitization at work, anaphylaxis outside work place
Rudzki and Rebandel (36)	1	Nurse	Penicillin	No	Yes	Yes	No	Yes	No	Yes	OcAn
Sussman and Dorian (39)	1	Nurse	Psyllium	Yes	Yes	Yes	No	No	No	Yes	Sensitized at work; reaction off work
Sussman and Dorian (39)	1	Nurse	Psyllium	Yes	Yes	Yes	No	Yes	No	No	Sensitized at work; reaction off work
Khalili et al. (40)	1	Nurse	Psyllium	Yes	Yes	Yes	Yes	Yes	No	Yes	Sensitized at work; reaction off work
Tadokoro et al. (15)	1	Nurse	Cefotiam	Yes	Yes	Yes	Yes	Yes	Yes	Yes	OcAn
Tadokoro et al. (15)	1	Nurse	Cefotiam	Yes	Yes	Yes	No	Yes	Yes	Yes	OcAn
Mizutani et al. (38)	1	Nurse	Cefotiam	Yes	Yes	Yes	Yes	Yes	Yes	Yes	OcAn
Mizutani et al. (38)	1	Nurse	Cefotiam	No	Yes	Yes	Yes	No	No	No	Sensitized at work; reaction off work
Kim et al. (37)	1	Nurse	Cefotiam	Yes	Yes	Yes	Yes	No	No	Yes	OcAn
Kim et al. (37)	1	Nurse	Piperacillin	Yes	Yes	Yes	Yes	Yes	Yes	Yes	OcAn
Newman and Goel (41)	1	Doctor	Succinylcholine	Yes	Yes	Yes	Yes	Yes	No	Yes	OcAn
Bandino and Tankersley (42)	1	Technician	Timothy grass extract	Yes	Yes	Yes	Yes	Yes	No	Yes	OcAn

SPT, skin prick test; OcAn, occupational anaphylaxis.

Other classes of drugs have also been identified as causing OcAn. Psyllium was frequently reported as a cause of occupational allergy until the powdered form was changed to granules and while it is unusual, there are case reports of OcAn (39, 40). Sussman and Dorian (39) reported anaphylaxis to ingested psyllium in two nurses with a prior history of rhinitis to occupational exposure. There have been single case reports of OcAn in an anesthetist to neuromuscular blocking drugs (41) and a nurse to immunotherapy extracts (42).

Occupational anaphylaxis due to animals (insects, mammals, and snakes)

Hymenoptera stings

Beekeepers (43), gardeners (44), farmers, truck drivers, and masons (45) are the professionals most frequently involved in occupational venom allergy. In 444 Turkish beekeepers, the prevalence of OcAn after bee stings in the last 12 months was 2%, and in 323 Japanese forestry workers, the frequency of loss of consciousness after a sting of paper wasps, yellow jackets, and other *Hymenoptera* was 3.4% (5, 6). This frequency exceeds that expected among the general population.

The type of insect causing allergic reactions in outdoor workers may also differ from those in the nonoccupational setting. Some representatives of *Vespula* species, mainly *V. vulgaris* and *V. germanica*, play a major role as nonoccupational elicitors of wasp sting anaphylaxis. Insects belonging to genera *Bombus* (e.g., bumblebees), *Dolichovespula*, *Polistes*, or *Vespa* usually do not collect food at anthropogenic sources. The latter insects are generally less aggressive and stings by these insects occur very rarely in the general population. In some occupations, however, there is an intense exposure to the habitat of these insects and sting reactions may occur at an increased frequency. In greenhouses, bumblebees are used for the pollination of plants. Therefore, greenhouse workers are at risk for bumblebee venom allergy (46).

Host and exposure risk factors may play a role in insect venom allergy: for example, for having allergic reactions to *Hymenoptera* stings or for the severity of anaphylaxis. Repeated (one or more) preceding stings were found to increase the risk for subsequent severe anaphylactic sting reactions (47). The male preponderance for severe anaphylactic reactions probably reflects in part a gender-specific occupational exposure being higher in males than in females (47).

Currently, 12 allergens of honeybee venom and five *Vespula* venom allergens have been sequenced. Some allergens of *Vespula* venom and bee venom share minor to moderate sequence identity and correspondingly cross-reactivity. However, the closer the taxonomic relationship of the insects, the more in common are the structures of molecular venom allergens.

In the primary and secondary prevention of hypersensitivity reactions to insect stings, reduction of exposure is recommended. Education of employees, how to prevent stings, should be part of the safety provisions for outdoor workers. For highly exposed employees, protective clothing with nets should be routine, at least during hazardous activities, for example, for beekeepers who work in or clo-

sely to beehives and for gardeners who work near wasp nests. Workers with insect venom anaphylaxis should not work with the relevant stinging insects or outdoors in areas where they are more likely to be stung and particularly should not work on ladders or at heights due to the increased risk of loss of consciousness associated with a sting. If an intensely exposed patient presents with a history of insect venom anaphylaxis, efficacy of venom immunotherapy should be demonstrated before allowing this patient to return to his/her occupation. Patients with bee venom allergy and an intense exposure should be treated with an increased maintenance dose of 200 µg venom (48). Venom immunotherapy should be continued for the duration of the hazardous occupation.

Other insects

Anaphylactic reactions after tick bites have been reported, especially during occupational or recreational exposure. Specific IgE antibodies have been demonstrated to *Ixodes holocyclus*, *I. ricinus*, *I. pacificus*, *Rhipicephalus* sp (49), and *Argas reflexus* (50) (Table 4). Anaphylactic reactions caused by bites of the European tick *A. reflexus*, a parasite of wild pigeons colonizing urban buildings and houses, are common among building maintenance workers. The major allergen of *A. reflexus*, Arg r 1, a lipocalin, has been used as a diagnostic tool in a series of anaphylactic reactions caused by pigeon tick bites (51). Recently, anaphylaxis due to IgE against a mammalian oligosaccharide epitope, galactose- α -1,3-galactose (α -gal), associated with delayed-onset anaphylaxis 3–6 h after ingestion of mammalian food products, was described (52). Tick bites were associated with IgE responses to α -gal and red meat allergy (53). The α -gal epitope is present in the gastrointestinal tract of ticks (*I. ricinus*) and also in the monoclonal antibody cetuximab (53).

The pine processionary caterpillar *Thaumetopoea pityocampa* is a frequent cause of contact urticaria and angioedema. Although this insect may cause skin lesions by nonallergic (mechanical, irritant) mechanisms, an allergic IgE-mediated mechanism is usually involved in contact urticaria in adults (54). Anaphylactic reactions were reported in 40% of 30 workers with occupational allergic urticaria caused by *T. pityocampa*. Pinecone or resin collectors, woodcutters, farmers, and stockbreeders were the most frequently and severely affected workers.

Other insect-derived allergens implicated in anaphylactic reactions are *Chironomidae* larvae used by aquarists as fish food, whose hemoglobins can cause IgE-mediated allergic diseases (55), mosquito, and tsetse fly bites (56). Carmine (E-120), a natural red dye widely used as a food coloring agent and for cosmetic manufacture, is extracted from the dried females of the insect *Dactylopius coccus* var. Costa (cochineal). Inhalation of carmine powder may give rise to respiratory allergy and anaphylaxis following its ingestion (57).

Mammals

Workers exposed to laboratory animals are at risk of developing allergic respiratory symptoms and contact urticaria. Less commonly, they may experience systemic symptoms

Table 4 Selected reports of occupational anaphylaxis to animals (insects, mammals, and snakes)

References	Animal	Occupation or site	Exposure	Comments
Acero et al. (49)	<i>Rhipicephalus</i> sp.	Goatherd	Hard tick bite	Cross-reactivity among the hard tick allergens
Kleine-Tebbe et al. (50)	<i>Argas reflexus</i>	Pigeon breeding facilities and <i>Argas</i> -infested buildings	Soft tick bite	12 of 148 (8%) subjects had SR after tick bites
Vega et al. (54)	<i>Thaumetopoea pityocampa</i>	Pinecone/resin collectors, woodcutters, farmers	Pine processionary caterpillar skin contact	12 of 30 (40%) workers had anaphylaxis
Stevens et al. (56)	<i>Glossina morsitans</i>	Laboratory worker	Tsetse fly bites	
Acero et al. (57)	<i>Dactylopius coccus</i> var. Costa	Spice warehouse worker	Carmine (E-120) ingestion	Associated occupational asthma due to carmine
Teasdale et al. (58)	Rodents	Laboratory animal handlers	Rat and mice bites	
Hesford et al. (59)	Rat	Laboratory research director	Rat bite	Life-threatening anaphylaxis
Rankin et al. (60)	Rat	Laboratory technician	Rat bite	No previous rat allergy
Torres et al. (61)	<i>Phodopus sungorus</i>	Laboratory animal handler	Siberian hamster bite	Lack of cross-reactivity with other rodents
Watt and McSharry (62)	Rabbit	Research physician	Needle injury after use on rabbit tissue	Previous rhinitis due to rabbits
de Medeiros et al. (63)	<i>Bothrops</i> spp.	Herpetologist	Snake bite	First snakebite, had worked 13 years
Nishioka et al. (65)	<i>Bothrops moojeni</i>	Viper farm worker	Viper bite	Anaphylaxis after 3rd bite and given antivenom for the 2nd time

SR, systemic reactions (urticaria, angioedema, dyspnea, cardiovascular dysregulation, unconsciousness).

and anaphylaxis, especially after rodent bites. Case reports of anaphylactic reactions among laboratory animal handlers, technicians, and researchers after rat (58–60), mice (58), or dwarf hamster bites (61) have been reported (Table 4). Exposure to rabbit tissue allergens has been reported to elicit anaphylaxis after a needle injury in a research physician (62).

Snakes

Herpetologists and snake farm workers are at risk of anaphylaxis due to handling of venom and snakebites (63) (Table 4). Indeed, anaphylactic reactions to snake venom might be an underestimated factor contributing to fatal snakebites, independently from the toxicity of the venom itself.

Among workers exposed to *Bothrops jararaca* venom, the prevalence of IgE sensitization was 10.4%. Venom sensitization was associated with length of employment, high levels of total IgE, atopy, and handling of dried venom (64). Aerosolized snake venom has also been considered a potential source of allergens that may result in anaphylaxis on subsequent exposure. Anaphylaxis and serum sickness to antivenom are a risk particularly to those working with vipers (*Bothrops moojeni*) who were bitten more than once (65).

Occupational anaphylaxis due to natural rubber latex

NRL allergy was reported as an anaphylactic reaction in 1989 (66) and occupational latex allergy continues (67). Following its recognition, the number of cases reported initially rose markedly, apparently in parallel with the increase in use of powdered latex gloves, especially among HCW, in response to universal precautions for protection against diseases transmitted by body fluids (68). Increased demand and production per-

haps increased the allergenic protein content of the gloves. When powder latex gloves were donned or removed, the consequent airborne powder contained NRL proteins.

The range of the allergic responses to NRL includes contact urticaria, angioedema, rhinitis, conjunctivitis, asthma, and anaphylaxis. In addition, there can be cross-reacting responses to several foods including banana, kiwi, avocado, mango, and chestnut. Allergic responses occur with both occupational and nonoccupational exposures, including 'hidden' exposures to NRL allergens in food. HCW have been the most commonly affected, likely from their greater exposure, but others include those using NRL gloves in other jobs, such as hairdressers, cleaners, and food handlers and those making NRL products (e.g., in glove, condom and doll manufacturing). Those sensitized at work may also have increased risk in a nonoccupational setting, during medical/surgical procedures when others wear NRL gloves or use catheters, etc. Anaphylaxis has occurred in both the occupational setting (e.g., in an operating room nurse) (66) and following occupational sensitization to NRL, during health care (e.g., a radiologist during a personal barium enema procedure (69) and a laboratory technician during Caesarian section (70)). Sensitized workers have also had responses, including anaphylaxis to cross-reacting fruits (71).

Risk factors, management, and prevention

Risk factors include host factors (e.g., atopy) and environmental factors (occupational or health-related high exposure to NRL as in regular use of powdered NRL gloves or frequent surgical procedures). Glove characteristics also increase risk: the use of highly powdered, high-protein gloves carries the highest risk, while nonpowdered or low-protein NRL gloves carry reduced risk (72).

Management of workers allergic to NRL consists of avoidance, by personal use of non-NRL gloves and other products; use of only powder-free, low-protein gloves by co-workers; a latex-free environment for personal healthcare procedures, and avoidance of relevant cross-reacting foods.

Elicitor-specific primary prevention measures include avoidance of unnecessary use of NRL gloves and, when these are needed, using low-protein, low-powder NRL gloves (17, 68).

Occupational anaphylaxis due to chemicals

Chlorhexidine/povidone: Chlorhexidine is widely used as an antiseptic and disinfectant. It may act as an occupational sensitizer that can cause different delayed and immediate-type allergic reactions including anaphylaxis (73). Chlorhexidine has been widely reported to cause IgE-mediated allergic reactions (from urticaria and angioedema to anaphylaxis) among patients and HCW (74). Iodinated povidone has also been reported to induce IgE-mediated anaphylaxis (75).

Metals: Several metals, such as chromium (76), iridium (77), and cobalt (78) have been shown to cause occupational contact urticaria, asthma, and anaphylaxis of uncertain mechanism. Positive SPTs have been observed to iridium, and the involvement of cell-mediated mechanisms to chromium has been suggested.

Insecticides and fungicides: Insecticides, for example, pyrethroids (79) and fungicides, for example, chlorothalonil (80) can also induce contact urticaria, asthma, and anaphylaxis.

Dyes and bleach: Paraphenylenediamine (PPD) is a strongly sensitizing aromatic amine, which is used in hair and leather dying, and it is also included in temporary henna tattoos. Severe skin and respiratory symptoms and anaphylaxis to PPD (81) and other hair dyes (82) as well as to ammonium persulfate present in hair bleaches (83) have been reported.

Reactive textile dyes are a common cause of IgE-mediated occupational asthma and exceptionally may give rise to anaphylaxis after inhalation (84).

Other chemicals: Miscellaneous agents may induce systemic symptoms and/or anaphylaxis by unknown mechanisms. Causative agents include diphenylmethane diisocyanate (85), methylmethacrylate (86), benzonitrile (87), fragrances (88), and HBTU (89).

Research needs box

- Epidemiologic data on occupational anaphylaxis (OcAn) and the proportion of anaphylactic episodes that relate to work.
- Relevance of sensitization through different routes of exposure or to various occupational allergens and subsequent development of anaphylaxis in nonoccupational settings.
- A register for (new) cases of OcAn.
- Current relative importance/frequency of the various causes of OcAn.
- Registry for skin testing (procedure and results) with material from the workplace.

- Studies on management strategies, such as potential role for immunomodulation to further reduce risks for workers who have had occupational anaphylactic reactions.
- The role of immunotherapy or omalizumab for those with OcAn.

Conclusions

A number of case reports and a few epidemiological studies have shown that anaphylactic reactions may be due to an occupational trigger. *Hymenoptera* stings, such as bee stings in beekeepers, bumblebee stings in greenhouse workers, *Vespula* and *Polistes* stings in gardeners, farmers, truck drivers, and masons are the most frequent triggers involved in OcAn. In a number of cases, NRL causes anaphylactic reactions in HCW, although recently they are less frequent. Moreover, workers exposed to foods, medications, insect/stings/contact, mammals/snake bites, or various chemicals at the workplace may sporadically show an occupational anaphylactic reaction. For workers with a previous episode of OcAn, measures of prevention, including removal from exposure to the dangerous substance and relocation of the workers, should be taken, and for *Hymenoptera* allergic workers, venom immunotherapy treatment, which is highly effective, should be started. A written emergency management plan, health and safety education and training and surveillance should be enforced in occupations at greater risk.

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Author contribution

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, coordinated by Andrea Siracusa.

Conflicts of interest

See ICMJE Forms for Disclosure of Potential Conflict of Interests.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Allergens of honeybee and *Vespula* venoms.

Table S2. Characterized latex allergens.

Table S3. Selected reports of occupational anaphylaxis to NRL.

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Table S1 Sequenced allergens of honeybee and *Vespula* venoms
(IUIS Allergen Nomenclature Sub-Committee, www.allergen.org)

Honey bee venom allergens			
Allergen	Name / Function	Molecular weight (kDa)	% of dry weight
Api m 1	Phospholipase A2*	16	12
Api m 2	Hyaluronidase*	39	2
Api m 3	Acid phosphatase	43	1-2
Api m 4	Melittin*	3	50
Api m 5	Dipeptidylpeptidase IV	100	<1
Api m 6		8	1-2
Api m 7	CUB serine protease	39	?
Api m 8	Carboxylesterase	70	?
Api m 9	Serine carboxypeptidase	60	?
Api m 10	Icarapin variant 2, carbohydrate-rich protein	50-55	<1
Api m 11	Major royal gellee protein	50 (deglycosylated form)	?
Api m 12	Vitellogenin	200	?
Vespula venom allergens			
Allergen	Name / Function	Molecular weight (kDa)	% of dry weight
Ves v 1	Phospholipase A1*	34	6-14
Ves v 2	Hyaluronidase*	28	1-3
Ves v 3	Dipeptidylpeptidase IV	100	?
Ves v 5	Antigen 5*	23	5-10
Ves v 6	Vitellogenin	200	?

*Major allergens. ?, unknown.

Table S2 Immunological and clinical properties of characterized latex allergens of the rubber tree *Hevea brasiliensis*

Latex allergen*	Molecular weight (kDa)	Protein name, biological function or physiological role	Significance as allergen
Hev b 1	14	Rubber Elongation Factor (REF)	Major allergen for SB
Hev b 2	34	β -1,3-Glucanase	(Major) allergen
Hev b 3	24	Small rubber particle proteins	Major allergen for SB
Hev b 4	53-55	Lecithinase homolog	Minor allergen
Hev b 5	16	Acidic structural protein	Major allergen for SB as well as for HCW
Hev b 6.01	20	Prohevein (hevein precursor)	Major allergen (the dominant IgE-binding epitope is Hev b 6.02)
Hev b 6.02	4.7	Hevein	
Hev b 6.03	14	C-domain of prohevein	Minor allergen
Hev b 7	44	Patatin-like protein (esterase) from latex-B- and C-serum	Minor allergen
Hev b 8	14	Profilin (actin-binding protein)	Minor allergen
Hev b 9	51	Enolase	Minor allergen
Hev b 10	26	Manganese superoxide dismutase (MnSOD)	Minor allergen
Hev b 11	30	Class I chitinase	Minor allergen
Hev b 12	9	Non-specific Lipid Transfer Protein	Minor allergen
Hev b 13	42	Esterase	(Major) allergen
Hev b 14	30	Hevamine	Minor allergen

*IUIS Nomenclature. SB, *spina bifida*; HCW, health care workers.

Allergens

Up to now about 250 different NRL polypeptides have been identified, about 60 are capable of binding human IgE (1) and currently 17 allergens have been included in the latest nomenclature list of the International Nomenclature Committee of Allergens (IUIS) and assigned official numbers (<http://www.allergen.org>). There is good evidence that various risk groups are sensitised by different NRL allergens (the most important latex allergens for HCW are Hev b 6.01/Hev b 6.02 and Hev b 5 and for *spina bifida* patients Hev b 1, Hev b 3 and Hev b 5 (2)). It is obvious that the path of contact with the allergenic proteins is of enormous importance for the development of sensitisation.

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Table S3 Selected reports of occupational anaphylaxis to NRL*

Reference	# subjects	Occupation	Site of anaphylaxis	Exposure	Comments
Spaner et al. 1989 (1)	1	OR nurse	OR, during work	NRL gloves	She also had hand eczema with NRL gloves
Leynader et al. 1989 (2)	5	3 worked in hospitals	OR as patients	NRL gloves	All had known urticarial with NRL and 3 had fruit reactions
Pecquet et al. 1990 (3)	17 (12 with anaphylaxis)	10 of 17 had occupational use of NRL gloves, unknown how many of these had anaphylaxis	OR as patients	NRL gloves	
Sussman et al. 1991 (4)	11 with occupational NRL allergy, including 5 with anaphylaxis	1) Radiologist x2 2) ICU nurse 3) Dental assistant 4) OR nurse	4 in hospital, 1 in dental office	1) During barium enema, as a patient (2 cases) 2) during C. Section as patient 3) wearing NRL gloves at work 4) with NRL gloves at work	
Chen et al. 1992 (5)	1	Obs and gynae physician	Work	NRL surgical gloves	
Bonnekoh and Merk 1993 (6)	1	Dental assistant	Dental office at work	NRL gloves	
Fernandez de Corres et al. 1993 (7)	8 with NRL allergy, 3 workers with anaphylaxis	1 used rubber gloves in industrial work, and 1 in electronics work. 1 worked with refrigerator assembly 2 with anaphylaxis at work and all 3 then had anaphylaxis with chestnut and/or with	Outside of work	NRL in 4, and cross-reacting fruit in 4 (chestnut and/or banana)	All NRL allergic

		banana				
Karathanasis et al. 1993 (8)	1	Former ICU nurse	Home	Attributed to contact with NRL allergens via skin of her husband, a gynaecologist.		
Kelly et al. 1993 (9)	Among 15 HCW with sx of latex allergy, 3 developed anaphylaxis with skin testing	HCW	Clinic as patients	Skin testing with unstandardized glove extract		
Rosen et al. 1993 (10)	5 NRL-allergic HCW, 3 with anaphylaxis	HCW (1 physician, 1 ICU nurse, 1 physical therapist)	2 at work, 1 not stated	2 latex gloves, 1 not stated		
Sanmartin Jimenez et al. 1993 (11)	15 cases, 5 with anaphylaxis	7 HCW, 4 homemakers	2 at work, 2 at clinic as patients, 1 at home	NRL gloves	Two cases of anaphylactic shock occurred during gynecological exam	
Blanco et al. 1994 (12)	25 with NRL allergy, 9 had anaphylaxis with NRL	Total group included 9 greenhouse workers, 6 hospital workers. Among the 9 with anaphylaxis were 3 nurses, 2 agricultural workers, 1 cleaner, 1 administrator, 2 housewives.	Details of anaphylactic responses to NRL not given	Focus of paper was on food cross-reactions	52% had fruit allergy. 42 food allergies identified, 23 with anaphylaxis: avocado, chestnut, banana, kiwi, papaya	
Moreno Ancillo et al. 1994 (13)	28 cases, 9 with anaphylaxis				In anaphylaxis, increased risk from work as HCW	
Tarlo et al. 1994 (14)	1	Hospital lab worker HCWs	C. Section	NRL gloves		
Masood et al. 1995 (15)	2 with anaphylaxis		Both had episodes at work and 1	NRL gloves self-use in one subject. Co-worker NRL use in		

			also outside work	the other, + feeding baby with NRL nipple, and dental work with NRL	
Taylor et al. 1996 (16)	44 with NRL allergy, 7 with anaphylaxis,	38 occupational exposure, (36 dental or HCW, 1 dairy farmer, 1 beautician). 4 (all HCW) had anaphylaxis. 5 of 41 reported subsequent anaphylaxis on follow-up questionnaire 0-7 years after first seen (details not given)	At initial assessment 3 of those with occupational sensitization had a history of anaphylaxis with work, 1 outside work	3 with NRL gloves, 1 with condom use	
Palczynski et al. 1997 (17)	3 health care workers with anaphylaxis	HCW	Not at work	1 blowing balloon, 1 during challenge, 1 during gynae exam as a patient	
Shingai et al. 2003 (18)	1	HCW	Not at work	during gynae exam as a patient	
Bernstein et al. 2003 (19)	67 NRL allergy	All HCW, 4 with anaphylaxis	Work-related	NRL glove exposure	90% remained well after switch to non-NRL gloves. 3 of the 4 with anaphylaxis moved to latex-free environments and 1 remained but avoided personal NRL use
Buyukozturk et al. 2010 (20)	6 NRL allergy	HCW	Anaphylaxis during treatment	6 treated with NRL SLIT, causing anaphylaxis in 2	
Stirapongsasuti et al. 2010 (21)	1	nurse	Food induced anaphylaxis to cooked phuk-waan-ban	Daily exposure to NRL gloves and well-known occupational urticaria; anaphylactic shock 30 min after eating cooked phuk-waan-	Phuk-waan-ban (Thai name), is in the same botanical family as the rubber tree; (English name: katuk or spinach tree)

				ban	
Risenga et al. 2013 (22)	South Africa, 8.3% of 144 nurses (12 nurses) had latex allergy, of these 8.3% (1 worker) had anaphylaxis	HCW	Work- related – not indicated	not indicated	Case with anaphylaxis required mechanical ventilation

*Includes only publications with an abstract in English

NRL, natural rubber latex; OR, operating room; ICU, intensive care unit; obs, obstetric; gynae, gynaecologist; sx, symptoms; HCW, health care workers.

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