



The Need of Integrated Tools for the Study of Occupational Exposure to Allergens

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Received: November 30, 2021

Published: January 17, 2022

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Abstract

The workplaces represent an important source of exposure to a variety of biological, chemical and physical agents. The aim of this paper is to investigate the topic of allergens in occupational settings, promoting the practice of human biomonitoring, which is now mostly used for environmental exposure to chemical agents in the management of occupational allergies.

We conducted a search on the websites of international institutions and/or associations focusing on allergens potentially relevant in workplaces. Allergy-related biomonitoring and biomarkers were included, and data on work-related allergic diseases available on the Italian Workers' Compensation Authority (INAIL) data bank were collected in cumulative years 2014-2019.

Both biological- and chemical-derived allergens found in industry and services, as well as in agriculture, may induce respiratory and cutaneous effects, resulting in work-related diseases.

The number of cases confirmed in cumulative years 2014-2019, included 97 cases of allergic rhinitis unspecified, 409 cases of predominantly allergic asthma diseases, 916 cases of allergic contact dermatitis and 10 cases of allergic urticaria.

The number of cases of allergic rhinitis unspecified was the same in both industry and services and agriculture, while the majority of cases of predominantly allergic asthma were found in industry and services (276) with respect to agriculture (129).

The survey and/or notification of work-related allergy cases, jointly with data from environmental monitoring, human biomonitoring, specific biomarkers, individual sensitization and health surveillance practice play a key role in the building of a network aimed at improving preventive measures in the field of occupational allergies.

Keywords: Human Biomonitoring; Occupational Allergies; Workplaces; Environmental Exposure; Health Surveillance; Occupational Allergens; Exposome

Introduction

Over time, occupational exposure to biological, chemical and physical agents was studied with regard to offices, healthcare fa-

cilities, industrial settings, agriculture, livestock breeding, urban and extra-urban green areas [1-3]. This allowed the exploration of occupational allergies increasingly in terms of causal agents and

in relation to different occupational sectors. Dermatitis, urticaria, rhinitis and allergic asthma may develop in workers sensitized to various allergens [4-8].

Moreover, sensitization to specific allergens may contribute to clinical features characterizing the sick building syndrome and building-related illnesses [9-12]. Workplaces represent an important source of exposure to a variety of allergens, giving a significant contribution to the total burden of allergic diseases [7,13]. In the past, the study of occupational allergies focused on indoor pollutants, but a growing body of data on allergic diseases in the general population and some other new evidence has addressed the research to the study of outdoor exposures, paying attention to the health effects from allergen exposure as well as from multiple exposures. This adds complexity to a topic complex by itself [14-16] as an increased exposure from different sources occurs. Multiple exposures are intrinsic to the exposome concept that, as stated by Wild in 2005: “encompasses life-course environmental exposures (including lifestyle factors), from the prenatal period onwards” [17], including: “nongenetic drivers of health and disease and, with the genome, it defines the phenome of an individual” [18]. The concept of exposome was recently applied to respiratory and skin allergy [19]. To remark the importance of occupational exposures in the occurrence of diseases the term worksome was suggested, which may be regarded as a subset of the exposome, i.e. the occupational exposome [20]. The health effects of different occupational exposures may also be investigated in human biological matrices in order to identify biomarkers of exposure, effects and susceptibility [21]. The approach of occupational exposome discloses new perspectives, including the creation of databases allowing the targeted analysis for single and multiple diseases [22] using -omics approaches, such as proteomics, genomics, transcriptomics, and metabolomics [8,23,24]. At the same time, largely consolidated (and often mandatory) systems of recording and notification of diseases allow the search of occupational origin in particular disease cases. Thus, the system of notification of work-related diseases is a precious tool to study causes and temporal trends of occupational diseases.

Another important tool to assess the exposure resulting from all pathways and sources as well as its outcomes is human biomonitoring, which makes use of different procedures to detect and measure substances or biological markers in human biological ma-

trices [25]. In occupational settings, including several outdoor and indoor workplaces, a significant exposure to biological and chemical allergens was observed and antibodies, interleukins, leukotrienes, and prostaglandins were referred as biomarkers of exposure in blood and urine samples [26-28].

Human biomonitoring data related to allergic diseases contribute to build exposome also using -omics methodologies [29,30], in order to set a multidisciplinary and integrated procedure aimed at improving occupational risk assessment [31,32].

The aim of our study was to investigate the topic of allergens in occupational settings, promoting the use of an interdisciplinary approach including human biomonitoring - this latter generally applied to assess the occupational exposure to chemicals - as a valid tool to improve the study of health effects following exposure to allergens. To this regard, we conducted a search on the websites of international institutions and/or associations concerning allergens potentially present in workplaces as well as on scientific literature database to search papers regarding biomonitoring and/or biomarkers in occupational allergic diseases. Moreover, we analysed data on allergic diseases, both respiratory and cutaneous, occurred in Italy for the period 2014-2019, using the Italian Workers' Compensation Authority (INAIL) data bank based on the Italian regulation, which states the notification of all work-related diseases to the competent authority.

Materials and Methods

Occupational allergens search on websites of Institutions and/or Associations

A preliminary search focused on allergic diseases in general and working population was performed on the following websites: World Health Organization (WHO <https://www.who.int>), World Allergy Organization (WAO <https://www.worldallergy.org>), Commission des normes, de l'équité, de la santé et de la sécurité du travail (CNESST <https://www.csst.qc.ca>), European Academy of Allergy and Clinical Immunology (EAACI <https://www.eaaci.org>), National Institute of Environmental Health Sciences (NIEHS <https://www.niehs.nih.gov>), European Agency for Safety and Health at Work (EU-OSHA <https://osha.europa.eu/en>), National Institute for Occupational and Safety Health (NIOSH <https://www.cdc.gov/niosh/index.htm>), Health and Safety Executive (HSE <https://www.hse.gov.uk>). In our opinion these websites show more complete lists.

Occupational allergies and biomonitoring search on PubMed and Scopus

We performed the search of scientific papers using the following free terms on PubMed and Scopus: workers and allergy and Italy, workers and biomonitoring and allergy. The search was restricted to articles published in the period of 2010-2020. Out of the retrieved papers, we only selected the ones regarding workers exposure, through a complete reading of the documents. We considered all type of documents (i.e. research articles, reviews, proceedings of congress), only including papers written in English and Italian language.

Data on work-related diseases search on National data bank

Italian Workers' Compensation Authority (INAIL) data bank (<https://www.inail.it/cs/internet/attivita/dati-e-statistiche/banca--dati-statistica.html>) was screened (accessed: 13 February 2020) in order to extract the data on work-related diseases in three occupational settings for the time period 2014-2019. We matched data regarding respiratory and cutaneous diseases such as unspecified allergic rhinitis, predominantly allergic asthma, allergic contact dermatitis and allergic urticaria with data classified on International Statistical Classification of Diseases and Related Health Problems (ICD-10). In particular for the period 2014-2019 the search on the INAIL data bank of work-related diseases was conducted regarding:

- Cases of respiratory diseases, distinguishing between high respiratory airways (e.g. rhinitis) and low respiratory airways (e.g. asthma); industry and services, agriculture and public administration were considered;
- Cases of skin and subcutaneous tissue diseases, such as dermatitis and urticaria; industry and services, agriculture and public administration were considered.

In the case of allergic contact dermatitis, data related to the source of exposure in industry and services, agriculture and public administration were considered.

All selected disease cases for the time period 2014-2019 were entered into a Microsoft Excel database and were processed for a descriptive statistical analysis using the same software.

Results and Discussion

Occupational allergens search on websites of Institutions and/or Associations

The preliminary search allowed us to select two links reporting useful information about lists of occupational allergens: WAO (World Allergy Organization), which published a list of Occupational Allergens - Sensitizing Agents Inducers of Occupational Asthma, Hypersensitivity Pneumonitis and Eosinophilic Bronchitis on July 2016 with a total of 475 agents [WAO, accessed 24 October 2019] that were grouped into classes and by chemical and biological origin, and CNESST (Commission des normes, de l'équité, de la santé et de la sécurité du travail) reporting occupational allergens Causing Occupational Asthma, grouped in high- and low molecular weight agents [CNESST, accessed 24 October 2019] as shown in table 1 and table 2 based on the allergens reported in WAO and CNESST links.

As shown in table 1, industry and services seemed the occupational settings with higher exposure to chemical and biological allergens, while the biologically-derived allergens seemed to be mainly present in agriculture. High-molecular weight allergens of biological origin were present in industry and services (13) as well as in agriculture (10), while low-molecular weight allergens of chemical origin were more common in industry and services (26) and less in agriculture (5).

The allergens with high molecular weight, grouped in table 2, were represented in industry and services as well as in agriculture, while the allergens with low molecular weight were mainly represented in industry and services.

Occupational allergies, biomonitoring and biomarkers search on PubMed and Scopus

In the online supplementary **table S**, selected papers from PubMed and Scopus were reported, distinguishing between biologically-derived allergens and chemically-derived allergens, reporting information and remarks for each article.

Regarding the workers and allergy and Italy search, we retrieved 36 articles from the two databases. Out of these articles, 6 were excluded because they were not about workers' exposure, thus 30 papers were selected. Six of the included papers were in

Occupational allergen of chemical origin	Number of agents	Occupational setting
Isocyanates	11	Industry and services
Anhydrides	11	Industry and services
Amines	15	Industry and services
Epoxy resins	0	
Metals	23	Industry and services
Drugs	43	Industry and services
Plastics (including their monomers)	15	Industry and services Public administration
Dyes	9	Industry and services
Other chemicals	39	Industry and services Agriculture
Occupational allergen of biological origin	Number of agents	Occupational setting
Arthropods	36	Industry and services Agriculture
Shellfish	5	Industry and services
Fish	6	Industry and services
Animal products	22	Industry and services Agriculture
Plants	~ 90	Industry and services Agriculture
Vegetable gums	6	Industry and services
Flours	12	Industry and services Agriculture
Woods	45	Industry and services
Microorganisms	32	Industry and services Agriculture
Enzymes	25	Industry and services Agriculture
Agents related to irritant induced occupational asthma	Number of agents: 15	Occupational setting: Industry and services Agriculture
Occupational eosinophilic bronchitis	Number of agents: 15	Occupational setting: Industry and services

Table 1: Classes of 475 occupational allergens causing occupational Allergic and/or Irritant-Induced Occupational Asthma (IIOA) based on the description reported by World Allergy Organization (<https://www.worldallergy.org/education-and-programs/education/allergic-disease-resource-center/professionals/sensitizing-agents-inducers-of-occupational-asthma>).

Etiological Agents	Occupational setting
High-molecular weight	
Animal-derived antigens, animal epithelia, hairs, secretions	Industry and services Agriculture
Arthropods	Industry and services Agriculture
Crustacea, seafoods, fish, food-borne proteins	Industry and services
Acarians, Mites, Insects	Industry and services Agriculture
Molds	Industry and services Agriculture
Mushrooms	Industry and services Agriculture
Algae	Industry and services
Flours, cereals	Industry and services Agriculture
Pollens	Industry and services Agriculture
Plants	Industry and services Agriculture
Plant-derived natural products, Latex proteins	Industry and services Agriculture
Biologic Enzymes, Enzymes	Industry and services Agriculture
Vegetable Gums	Industry and services
Low-molecular weight	
Diisocyanates	Industry and services
Isocyanates	Industry and services
Combination of diisocyanates	Industry and services
Other hardeners	Industry and services
Anhydrides, Acid anhydrides	Industry and services
Aliphatic amines (ethyleamines)	Industry and services
Aliphatic amines (ethanolamines)	Industry and services

Aliphatic amines (others)	Industry and services
Heterocyclic amines	Industry and services
Aromatic amines	Industry and services
Quaternary amines	Industry and services
Mixture of amines	Industry and services
Acrylates (methacrylate, cyanocrylate)	Industry and services
Aldehydes (e.g. glutaraldehyde)	Industry and services
Fluxes, soldering flux (colophony)	Industry and services
Wood dust (red cedar, iroko, obeche, etc) or bark	Industry and services
Metals (e.g. platinum, nickel sulfate)	Industry and services
Persulfate salts	Industry and services
Drugs	Industry and services Agriculture
Reactive dyes	Industry and services
Biocides	Industry and services Agriculture
Fungicides	Industry and services Agriculture
Chemicals	Industry and services Agriculture
Healthcare	Industry and services
Synthetic Material	Industry and services Agriculture
Unidentified	Industry and services

Table 2: List of agents and related occupational setting associated to Occupational Asthma. Based on agents reported by Commission des normes, de l'équité, de la santé et de la sécurité du travail (CNESST) (https://reptox.cnesst.gouv.qc.ca/en/occupational-asthma/Pages/bernsteinang.aspx#N2_4) and Classes of 475 occupational allergens causing occupational Allergic and/or Irritant-Induced Occupational Asthma (IIOA) reported by World Allergy Organization (<https://www.worldallergy.org/education-and-programs/education/allergic-disease-resource-center/professionals/sensitizing-agents-inducers-of-occupational-asthma>).

Italian. Regarding the workers and biomonitoring and allergy search, we retrieved 4 papers from the two databases, keeping all of them, since they all met the criteria. The total number of papers we selected from the two searches was 34, we included all of them in table S.

In the last years the main animal allergens were from rats and mice, hymenoptera and house dust mites, whereas the vegetable ones were from *Parietaria* pollen, colophonium, green coffee, latex, natural and synthetic rubbers, and flour dust. Exposure to these allergens caused IgE response, eye rhinitis, allergic bronchial asthma, allergic contact dermatitis and contact urticarial. Regarding chemically-derived allergens, nickel, methylchloroisothiazolinone/methylisothiazolinone, epoxy resins, chlorhexidine, acrylates and methacrylates, polyurethane, formaldehyde, carbapenems, cobalt, chromium, cleaning products and detergents were the mainly reported ones, causing in most cases allergic contact dermatitis and eczema, although asthma and rhinitis were also described (supplementary table S).

The research focused on human biomonitoring and biomarkers related to allergic diseases allowed the study of the interactions

with multiple environmental exposures, using -omics methodologies in addition to the conventional ones [29,30] in order to improve the study of occupational risk [31,32].

Biomarkers of exposure included either stressors themselves (e.g. the parent compounds) or their metabolites (reaction products), detected in a variety of human biological matrices such as blood, urine [33]. Moreover, specific IgEs driving airway hyperresponsiveness; IL-4, IL-5, IL-13 in serum, ORMDL3 (as epithelium-associated biomarker), macrophage activation markers such as CD14, CD16, CD18, TNF- α in exhaled breath condensate, microRNAs and lipid mediators as well as urinary leukotriene E4 were all suggested as biomarkers of exposure, effect and susceptibility in allergic asthma [26-41].

Allergies and occupational settings search on INAIL (Italian Workers' Compensation Authority, Italy) data bank

A descriptive analysis of the cases of allergic occupational diseases was reported over the period 2014-2019 in table 3.

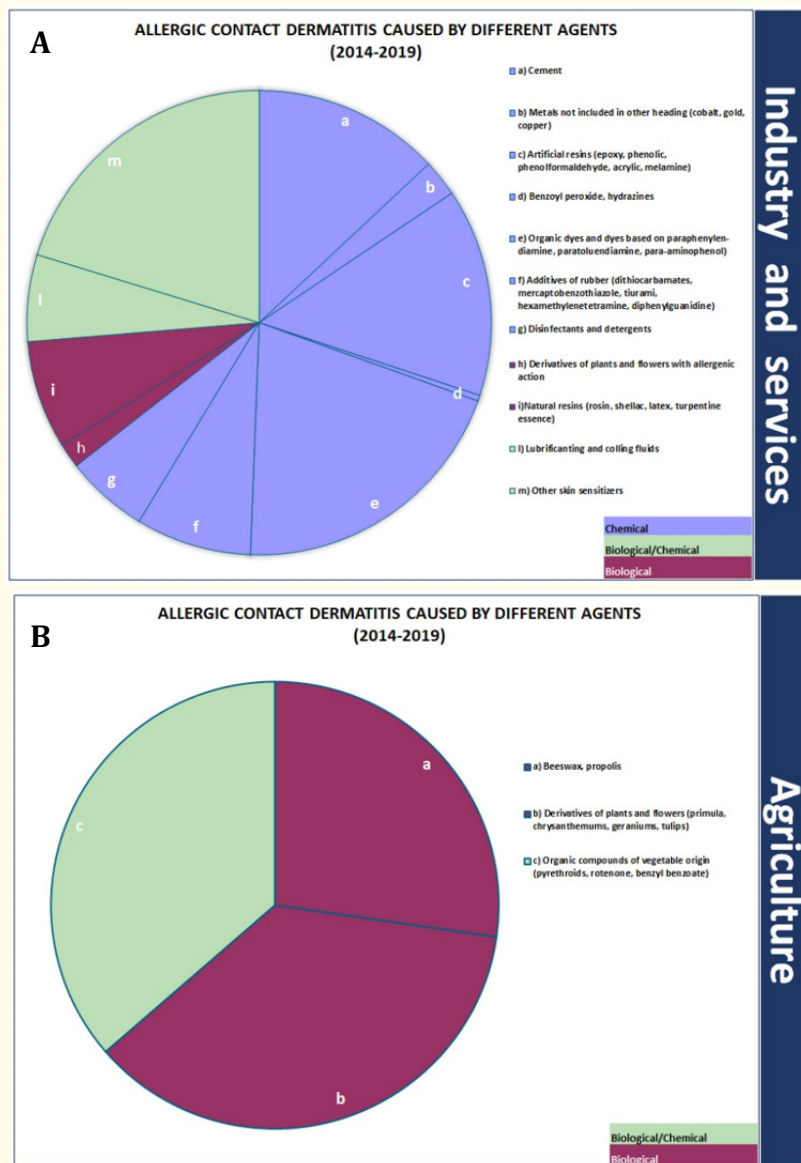
Total occupational settings							
Work-related diseases	2014	2015	2016	2017	2018	2019	2014-2019
Allergic rhinitis unspecified	15	12	24	20	17	9	97
Predominantly allergic asthma	95	79	69	52	61	53	409
Allergic contact dermatitis	177	176	166	144	132	121	916
Allergic urticaria	6	2	1	1	0	n.d.*	10
Industry and services							
	2014	2015	2016	2017	2018	2019	2014-2019
Allergic rhinitis unspecified	7	5	9	11	12	8	52
Predominantly allergic asthma	63	52	51	29	40	41	276
Allergic contact dermatitis	175	169	162	142	131	120	899
Allergic urticaria	5	1	1	1	0	n.d.	8
Agriculture							
	2014	2015	2016	2017	2018	2019	2014-2019
Allergic rhinitis unspecified	8	6	15	9	5	1	44
Predominantly allergic asthma	32	27	17	21	21	11	129
Allergic contact dermatitis	2	6	3	2	1	1	15
Allergic urticaria	1	1	n.d.	n.d.	n.d.	n.d.	2
Public administration							
	2014	2015	2016	2017	2018	2019	2014-2019
Allergic rhinitis unspecified	0	1	0	0	0	0	1
Predominantly allergic asthma	0	n.d.	1	2	0	1	4
Allergic contact dermatitis	0	1	1	n.d.	n.d.	n.d.	2
Allergic urticaria	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

Table 3: Cases of work-related respiratory airways and cutaneous diseases referred in cumulative years 2014-2019 for all occupational settings and classified in industry and services, agriculture and public administration.

* n.d.= non determined. Source: INAIL (Accessed: 13-02-2020 and 24-05-2021).

The cumulative number of cases confirmed by INAIL included 97 cases of allergic rhinitis unspecified, 409 cases of predominantly allergic asthma diseases, 916 cases of allergic contact dermatitis and 10 cases of allergic urticaria. With regard to occupational settings, the number of cases of allergic rhinitis unspecified was 52 in industry and services and 44 in agriculture, also the majority of cases of predominantly allergic asthma were found in industry and services (276) with respect to agriculture (129). Moreover,

899 and 15 cases of allergic contact dermatitis were observed, respectively, for industry and services and agriculture. A total of 8 cases of allergic urticaria were reported in industry and services and only 2 cases in agriculture. A very low number of cases was recorded in the public administration for all diseases. With regard to allergic contact dermatitis, a relative quantification of the class of causal agents involved (Figure 1) was possible for all occupational settings concerned.



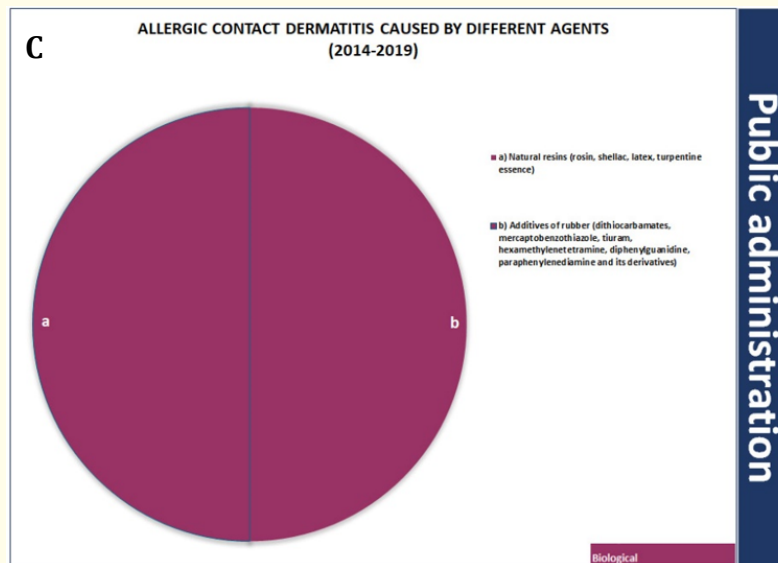


Figure 1: Causal agents of allergic contact dermatitis in industry and services (A), agriculture (B) and public administration (C) for the time period 2014-2019. Source: INAIL.

Discussion

In this paper, we collected data on allergy in Italy, occupational allergens, biomonitoring and biomarkers related to allergies, national cases of work-related allergic diseases referred to respiratory and cutaneous ones. Multiple sources may contribute to the occurrence of allergic diseases in occupational settings, as biologically-, chemically- and physically-derived allergens may be found in different workplaces. A fundamental tool to assess allergen exposure from all pathways and sources and its consequences is human biomonitoring, which makes use of different procedures to detect and quantify compounds or biological markers in human biological samples [25].

Data obtained from Institutions such as WAO show that industry and services are the occupational settings with the highest exposure to chemical and biological allergens. To this regards, it should be important to further investigate which working activities, categories of workers are mainly involved. It should be stressed that sources of allergens are continuously increasing, in particular the high molecular weight ones, which may be usefully sub grouped into plant- and animal-derived agents [42].

Data obtained by INAIL on confirmed work-related diseases indicate industry and services and agriculture as occupational settings that are more important for exposure to biological agents and for asthma and dermatitis occurrence. To this regard, the first case of IgE-mediated occupational asthma was documented in a worker in a malt manufacturing company [43] and the development of occupational asthma in industrial settings changes as a function of specific activities [34,44,45]. With reference to allergic contact dermatitis, a large number of cases are observed in workers employed in the wood industry, such as machinists, or in agriculture, and the main allergen sources are wood-derived materials, followed by glues and metalworking fluids. Moreover, among biologically-derived agents colophonium is included, which is used in several activities [46].

These data evidenced that a variety of occupational stressors do exist and, although some agents are measurable in biological samples by human biomonitoring, for other stressors new analytical methods need to be developed and standardized. In this context, different tools to study the worksome (the occupational part of the exposome) should be fully developed in order to measure biomarkers of exposure, effects and susceptibility. Specifically,

a biomonitoring program of the exposed workers should include specific antibodies, interleukins, cellular markers and other compounds found both in serum and urine samples [25-28], especially with reference to work-related airway diseases [47]. This approach is useful to complete the health surveillance protocols, thus contributing to prevention of occupational allergies.

We considered to extend the research activity on occupational allergies to different categories of workers including migrants of relevant importance. The latter represent a very useful population on which to explore this topic in relation to changed lifestyles and environmental exposures. At this regard, migrants are likely to increase and additional studies are recommended, including those aimed to detect novel biomarkers of allergen exposure. To summarize, the allergies are complex diseases and an interdisciplinary approach should be promoted in order to identify new biomarkers. In occupational sector the knowledge of more detailed aspects regarding different environments of exposure can help to optimize the management of preventive and control measures.

Conclusion

Respiratory and skin allergic diseases are important issues in occupational medicine as different groups of workers employed in both outdoor and indoor activities may be involved.

There is an increasing need for studies in order to detect and quantify in biological samples novel biomarkers of exposure, effect and susceptibility for environmental stressors in relation to allergic diseases in different occupational sectors. The improvement of survey of work-related diseases is equally important, especially for the most vulnerable workers.

Finally, it's important that new tools such as biological monitoring are being used increasingly in health surveillance practice in order to take into account multiple sources of exposure, disclose novel risks in relation to specific working activities, define individual profiles of susceptibility, provide more targeted preventive and protective measures, give a contribution to the exposome. All these aspects should be integrated in order to improve the management, control and prevention of occupational allergies.

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