The Director General

Maisons-Alfort, 10 January 2014

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on the state of knowledge on the health impact associated with exposure of the general population to pollen found in ambient air

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ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its Opinions are made public.
This Opinion is a translation of the original French version. In the event of any discrepancy or amibuity, the French language text dated 14 January 2014 shall prevail.

On 10 June 2011, ANSES received a formal request from the Directorate General for Health, the Directorate General for Risk Prevention and the Directorate General for Energy and Climate to conduct the following expert appraisal: state of knowledge on the health impact associated with exposure of the general population to pollen found in ambient air.

1. BACKGROUND AND PURPOSE OF THE REQUEST

According to estimates regularly put forward, the prevalence of allergic respiratory diseases such as seasonal rhinitis and asthma has nearly doubled in industrialised countries in the past 20 years. The estimates usually reported indicate that in France, 20 to 25% of the general population have an allergic disease, with respiratory allergies being the leading chronic childhood illness. More than 10% of the French population may be affected by pollen allergies, and allergic rhinitis in particular. However, questions are asked about the robustness of these estimates because the sources used to establish them are rarely mentioned.
Moreover, allergic rhinitis is an important risk factor for asthma, and relationships between pollen allergies and food allergies have been described.
Lastly, the studies published in recent years have shown that climate change may influence the production of pollen, mainly by extending the pollen season and changing

spatial distribution and air pollution. This may therefore interfere with pollen and pollinoses.

The aim of the request was to obtain an update on the state of knowledge on the health impact associated with exposure of the general population to pollen found in ambient air. Following a consultation with the Ministries making the request, it was agreed that ANSES would focus its expert appraisal work on the following priority objectives :

- update the state of knowledge on pollen and its effects on health, on the role of different pollens in the aetiology of respiratory allergies, and on the existence of an allergenicity threshold and/or "dose-response" relationship;
- review the interactions between pollen and atmospheric pollutants;
- update the state of knowledge on the factors governing development of allergenic plants, pollen emission and its environmental dispersion, as well as on the factors influencing the presence of allergens;
- describe and analyse the metrological monitoring schemes in place in France and abroad, and engage in a debate on the prospects for appropriate management: on what scale, for which priority pollen species, and with which monitoring tools.

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in compliance with Standard NF X 50-110 "Quality in expertise activities – general requirements of competence for an expertise activity (May 2003)".

The appraisal fell within the competence of the Expert Committees (CES) on Assessment of the risks related to air environments and Biological risks for plant health. The CES on Assessment of the risks related to air environments oversaw the expert appraisal while the CES on Biological risks for plant health conducted a critical review of the parts relating to the state of knowledge on the factors governing plant development, and emission and environmental dispersion of pollen grains. ANSES entrusted the expert appraisal to the working group on Pollen. The methodological and scientific aspects of the work were presented to both CESs: on 8 September and 1 December 2011, 25 October and 13 December 2012, and 14 May, 25 June, 5 September and 8 October 2013 to the CES on Assessment of the risks related to air environments, and on 17 October and 11 December 2012, and 9 April 2013 to the CES on Biological risks for plant health. On 7 November 2013, the work was adopted by the CES on Assessment of the risks related to air environments, after having been submitted to the CES on Biological risks for plant health on 4 June 2013.

ANSES analyses the links of interest declared by the experts prior to their appointment and throughout the work, in order to avoid potential conflicts of interest with regard to the matters dealt with as part of the expert appraisal.
The experts' declarations of interests are made public via the ANSES website (www.anses.fr).

Since the objective was to update the state of knowledge, the working method was primarily based on an analysis of the available bibliographic data.
Two hearings with stakeholders provided information on the expectations of patients and healthcare professionals (from the *Asthme et Allergies* association), and on the point of view of the operator of the main metrological monitoring scheme for pollen in France, the RNSA[1].

[1] French Aerobiology Network (http://www.pollens.fr/en/network/allergy.php)

With regard to the question of cross allergies between pollen and food, an expert rapporteur was appointed to draft a concise bibliographical note outlining current knowledge and future prospects in this field.

3. ANALYSIS AND CONCLUSIONS OF THE CES

The pollen grain is the male gametophyte and therefore plays a critical role in the reproduction of most plants. Depending on the species, pollen is distributed either by insects (for entomophilous plants) or by wind (anemophilous plants). Allergenic anemophilous pollens are responsible for the majority of pollinoses, because they are emitted into the atmosphere in larger quantities and naturally come into contact with respiratory and ocular mucosa due to their smaller size.

Pollen allergens are located inside the grain, mainly in the cytoplasm. Pollen grains also contain compounds with pro-inflammatory or adjuvant effects to the allergic reaction, that may increase the inflammation of the airways induced by the pollen. Pollen grains can release their contents following various events such as contact with water or mucosa.

Pollen: health effects and role in the aetiology of respiratory allergies

Pollen is responsible for allergic reactions known as pollinoses in the respiratory and ocular mucosa, manifested mainly by rhinitis and rhinoconjunctivitis, and more rarely by asthma. Allergic rhinitis due to pollen is seasonal and is often called “hay fever”, even though this name more specifically refers to an allergy to grass pollen.

A genetic predisposition to the development of an allergy, or atopy, is an important risk factor in the development of pollinoses. Atopic subjects are often polysensitised and an allergy to pollen usually develops in adolescence or young adulthood. However, an allergic disease can also occur independently of any genetic predisposition. Indeed, for certain pollens, especially those of Cupressaceae (such as cypress or juniper) and ragweed, the allergy has been seen to develop at a more advanced age, in subjects who are often monosensitised without any atopic disposition. An allergy to these specific pollens can therefore affect any individual, provided that there has been sufficiently intense and prolonged exposure.

The allergenicity and biological mechanisms involved are irregularly documented according to the pollen species. The contribution of different pollens responsible for allergic diseases depends on the geographic location. For instance, the most problematic pollens in France are those of Cupressaceae in the southeast, grasses throughout the country, Betulaceae in the north-eastern quarter, and common ragweed in the Rhone Valley.

Update on the existence of allergenicity thresholds and/or dose-response relationships

At the population level, there seems to be a sigmoid type dose-response relationship between the concentration of allergens and allergic disease. However, it is currently difficult to determine a threshold for the onset of the effect for the different pollen species, firstly because the existing studies are based on the concentration of pollen grains (whereas allergens are not just found in the whole grain), and secondly because many other factors influence the dose-response relationship. These factors include :

- the allergenicity of the pollen,
- individual sensitivity,
- the interval between exposure and manifestation of symptoms (ranging between one and seven days),
- the clinical phenomenon of priming, i.e., repeated exposure to pollen at low doses over several consecutive days, which can lead to the occurrence of major clinical manifestations,
- pollen polysensitisation, which will trigger a greater response to a given pollen in subjects previously exposed to one or more other pollen species to which they are sensitised.

Cross allergies

Some pollen species may be implicated in cross allergies with food allergens belonging to the same major protein families found in plants and therefore present throughout the plant kingdom. A patient can therefore seem polysensitised whereas in fact they are only sensitised to a single family of homologous proteins. This is the case for example with the Bet v 1 protein, the major allergen in birch pollen which has homologous proteins found in particular in apples, or the Pru p 3 protein found in peaches, whose homologues are found especially in Parietaria and Artemisia pollen. The allergic reaction to the ingestion of these proteins depends on the family: that of birch pollen (PR10[2]) is generally limited to an oral syndrome unlike that of Parietaria pollen (LTP[3]) which can be serious in 20 to 30% of cases. Most of the time, pollinosis precedes a food allergy, but not all patients sensitised to these pollens manifest clinical symptoms of cross allergy with food.

Prevalence of pollen allergy

It is difficult to estimate the current prevalence of pollen allergy in France. The available epidemiological studies primarily assess the prevalence of allergic rhinitis. However, most of these studies date back 10 to 15 years and are based mainly on questionnaires. It has been shown that questionnaire surveys lead to an overestimation bias. Moreover, the methods differ from one survey to another because of the questionnaire used and/or the population targeted. Lastly, allergic rhinitis and non-allergic rhinitis have similar symptoms, making it difficult to differentiate between them from a simple questionnaire: without allergy, skin or serum tests being associated with these questionnaires, it is not easy either to confirm whether the rhinitis is indeed allergic, or to identify the allergen responsible. It therefore seems difficult to compare the results of these studies. Thus, in all the surveys that included only one questionnaire, the prevalence rate of allergic rhinitis, for all allergens combined, shows a significant overestimation of the order of 100 to 300%. The intensity of the pollen season is another source of variation in one-off studies. When the pollen season is particularly intense in the year of the study or in the previous few years, the symptoms of pollen allergy are also intense, leading to greater awareness of the disease which may lead to a corresponding increase in the reported prevalence rate.

Given the available data and the major limitations mentioned above, only an upper estimate of prevalence is possible. In epidemiological surveys conducted in France from 1994 to 2006, the prevalence was estimated to be **at most**:

- 7% in children aged 6-7 years,
- 20% in children aged 9 to 11 years, with nearly 27% of children sensitised to at least one aeroallergen,

[2] PR10: pathogenesis-related protein no.10, or family of Bet v 1 homologues
[3] LTP: lipid transfer proteins

- 18% in adolescents aged 13-14 years,
- 31 to 34% in adults.

From a purely qualitative perspective, prevalence is higher among young adults than in children and the elderly, and it varies from one region to another. This inter-regional variation was observed in all the studies, and is related to differences in vegetation between regions, as well as to the intensity of different pollen seasons.

Concerning the change in prevalence of pollen allergy, Phase III of the ISAAC study[4] concluded that allergic rhinitis prevalence rates were stabilising in developed countries, whereas they were continuing to grow in developing countries.

Development factors and factors governing pollen dispersion: impact on the presence of allergens

The production and emission of pollen are controlled by several factors including the photoperiod and climate characteristics such as temperature. The number of days needed to reach peak flowering and the amount of pollen emitted may therefore vary from one year to the next. Once emitted, anemophilous pollen grains are carried by the wind to varying distances. Pollen concentrations decrease very rapidly the further away they are from the source: at 300-400 metres, they stabilise and reflect the average atmospheric pollen concentration. Anemophilous pollen grains can however be transported hundreds or even thousands of kilometres from the emission source during favourable climate conditions.

There are three main periods in France: winter/spring pollination of trees and shrubs, from mid-January to May depending on the area; pollination of herbaceous plants including most grasses, plantain and sorrel, from mid-spring to summer; and finally pollination of species of the genus Ambrosia (ragweed) from mid-August to late September. The pollination period extends even into October-November in the Mediterranean region, with prickly (or cade) juniper.

In recent decades, pollination of many plant species has tended to start earlier, by a few days to more than a fortnight, which has the effect of extending the duration of pollination by a fortnight on average. This phenomenon could be attributed to climate change. This early start seems more pronounced for early flowering plants from January to April, usually trees, whereas for herbaceous plants and grasses in particular, no significant changes in pollination have been observed. Moreover, pollination of the latter could also be limited in time by an increase in heat waves and droughts.

Experimental studies have shown that the rise in atmospheric temperatures and CO_2 concentration makes some pollens more allergenic. For instance, it was observed that the quantity of allergens in pollen grains from birch and ragweed increased with the temperature.

Climate change could also influence the geographical distribution of plants, with a shift from south to north for certain species (olive, ash). However, this shift is due more to humans taking advantage of climate change to introduce these species into new areas. Models linking temperature increases and vegetation maps in 50 or 100 years predict a generalised northward shift in species.

[4] ISAAC: International Study of Asthma and Allergies in Childhood: This study compared the international and regional prevalence of asthma and allergies in children aged 6 to 7 years and adolescents aged 13 to 14 years. It took place in three phases; phase III, conducted from 1999 to 2004, and mainly between 2002 and 2003, was a repeat of phase I (conducted from 1992 to 1998, and mainly between 1994-1995). Phase II took place between 1998 and 2000 with the aim of studying the risk factors associated with childhood allergic and respiratory diseases.

Interactions between pollen, atmospheric pollutants and allergic reactions

Some chemical pollutants may modulate the allergic reaction by acting directly on sensitised subjects, or by acting on pollen grains, especially their wall and protein content.

In sensitised subjects, atmospheric pollutants can promote an allergic reaction by lowering the threshold of bronchial responsiveness and/or by intensifying the irritation of nasal or ocular mucosa. For example, ozone affects the respiratory mucosa and increases its permeability, causing an allergic reaction at lower pollen concentrations.

Regarding the pollen grains themselves, one of the most documented types of interactions with atmospheric chemical pollutants is the deformation or rupture of the grain wall. Fragments of pollen grain and cytoplasmic granules are of a size that enables them to penetrate the respiratory system much more deeply than whole pollen grains: 0.5 to 4.5 µm compared with 20-40 µm on average for most allergenic pollen grains. Chemical pollutants can also modify the protein content of pollen grains, thus altering their allergenic potential. But at present, while it can be said that atmospheric pollution increases the allergenic potential of pollen grains in some cases, the opposite effect has also been observed.

Lastly, it has been shown experimentally that pollen allergens may adsorb to particles, especially soot characteristic of road traffic, but the extent of this phenomenon needs to be clarified under real conditions.

Metrological monitoring schemes and associated management tools

Pollen exposure is quantified by measuring the concentrations of different pollens found in air. This involves first collecting the airborne pollen grains. The two types of sensors used in France are the Hirst pollen trap and the Cour pollen trap. The Hirst trap is today one of the most commonly used instruments in the world, particularly in Europe. It sucks in a known volume of air and collects the pollen grains on an adhesive strip. It has a time resolution of 2 hours. The Cour trap faces into the wind and catches windborne pollen grains in two vertical gauze filters coated with silicone. Its time resolution depends on the frequency of human intervention, usually weekly.
It is then necessary to identify and count the pollen grains; these two steps require time-consuming and complex manual work. There are automated systems that can identify pollen from purified samples fairly well, but as yet none of these has clearly demonstrated its ability to identify different pollen species from samples taken from ambient air as precisely and reliably as humans.

In France, the RNSA operates the main system for monitoring pollen. It covers the entire mainland territory using Hirst pollen traps. In 2013, the RNSA had 82 sites, with 75 sensors for all pollens and seven sensors dedicated to monitoring ragweed. Since October 2009, the RNSA has also been monitoring pollen and spores in Saint-Denis (Reunion Island). A second site was installed on the same island, in Saint-Paul, in January 2011.
There are other stations for allergy studies based in France, funded mostly by associations. In 2002, there were 13 stations using the Cour volumetric method (five in the Rhone Valley, three around the Mediterranean and five in the French overseas territories). The four stations belonging to the French Association for the Study of Ragweed (AFEDA) are still active. The pollen series from the Montpellier (1973-2004) and Lyon stations (from 1982 to the present) obtained with the Cour method form part of the two longest continuous French pollen series, with a frequency of one dataset per week.

The research undertaken by the Working Group failed to identify any countries with legislation relating specifically to pollen monitoring. In several countries, the weather agencies (this is the case in Switzerland and the United Kingdom), or the environmental

agencies (Italy and the Czech Republic) are responsible for the pollen measurement network.

Counting pollen grains provides an approximate calculation of the presence of allergens in the air. But the specific measurement of allergens is still confronted with technical and cost problems. Nevertheless, it would be extremely useful to begin taking measurements of allergens over the long term at several points across the country. Such measurements, when compared with pollen grain counts, would enable correlations to be studied and would also help verify changes in the amounts of allergens in the air, particularly related to atmospheric pollution and global warming.

Preventing the development of allergenic plants: discussion points

Managing allergenic plants, especially in urban areas, would reduce population exposure to pollen. This could target the eradication of these plants, the control of their dispersion, the management of their size or their monitoring. These different management methods depend on the types of plants and the environment in which they will grow.
Therefore, the eradication of plants with allergenic pollen can only be considered for plants that are not native to France and for invasive plants. Against a general background of conservation of biodiversity, it is hardly conceivable to undertake the destruction of plants growing in their area of natural origin. The same is true for agricultural species. In the case of ornamental plants, it is important that managers of public facilities, whether they are decision makers within a local authority or industry professionals (landscape architects or gardeners, etc.), in addition to individuals, are informed of the allergic potential of such species, when this is high, in order to limit their introduction.

At the intersection of many sometimes conflicting issues, the management of allergenic plants in the context of the fight against pollinoses should take place in consultation with the various stakeholders, by means of cost/benefit and risk/benefit approaches.

Recommendations of the collective expert appraisal

The evidence reported in the context of this expert work indicates that population exposure to pollen is a public health issue. Given this information, the CES is making the following recommendations:

Concerning knowledge about the epidemiology of pollen allergy, the CES considers it essential to have regularly updated knowledge about the prevalence (in both time and space) of allergies to the different pollens, and to assess the effectiveness of public policies designed to fight against this disease. The CES therefore recommends conducting a periodic national cross-sectional study that includes, in particular, specific measurements of IgE.

Concerning the plants emitting allergenic pollens, the CES recommends improving management of their development, especially in urban areas, by:

- promoting diversification of plants, to reduce local concentrations of a particular pollen;
- limiting the use of these plants for ornamental purposes. With this in mind, local authorities should be informed of the risks associated with allergenic pollens, and professionals in the preparation and maintenance of green spaces should be made aware of this problem, for example, through the dissemination of guides

such as *"Végétation en Ville"* ("Vegetation in Towns") published by the RNSA. For private gardeners, labelling of the most allergenic species could be introduced;

- adopting specific pruning protocols, mainly at the bud stage, that limit pollen emissions;
- conducting eradication campaigns for invasive species such as ragweed;
- monitoring the introduction into France and dispersion of species whose allergenic potential has already been shown in other countries;
- using cost/benefit and risk/benefit studies.

Concerning pollen monitoring, the CES recommends:

- strengthening and sustaining a monitoring system whose purpose is to inform the population and health professionals about atmospheric concentrations of pollen, allowing them to anticipate when to take medication or postpone an activity;
- standardising pollen grain measurement methods;
- gradually introducing automated measurement devices, able to provide real-time information, despite them still being only at the development or validation stage, without however abandoning the historical sensors that enable the changes over time to be studied;
- developing modelling tools that can predict pollen grain emissions and dispersion;
- developing ways of measuring airborne allergens that provide complementary information to pollen counts: development of methods, standardisation and increase in the number of allergens detected by these measurements;
- monitoring not only the pollen found in France, whose health impact has already been established, but also pollen that would pose a threat to human health in the event of introduction into the territory. Establishing a precise list of pollen types to be monitored would require a multidisciplinary expert assessment on prioritisation, which remains to be done.

Concerning the improvement of allergic disease management, the CES recommends:

- informing people about the symptoms of pollen allergy to encourage them to seek consultation, screening and treatment;
- strengthening and diversifying the means of providing information on pollen concentrations;
- assessing the impact of existing information systems on the behaviour of allergic individuals;
- developing a university hospital specialty in environmental medicine, that would include, among others, the management of allergic diseases.

Concerning the interactions with atmospheric pollution and climate change, the CES recommends improving knowledge on:

- the action of atmospheric pollutants (including ozone, nitrogen dioxide and particulate matter) on plants and pollen;
- co-exposure of a person allergic to pollen and to atmospheric chemical pollution;

- climate factors influencing the quantity of pollen grains produced and emitted as well as the production of allergens in pollen (kinetics, quantity, temperature, stress, humidity, etc.) and possible links to climate change.

The CES on Assessment of the risks related to air environments adopted the work of the expert group and its conclusions and recommendations at its meeting of 7 November 2013 and informed the ANSES General Directorate accordingly. At its meeting of 4 June 2013, the CES on Biological risks for plant health had previously found that the information presented in the expert report on the factors governing plant development, pollen emission and its environmental dispersion, were sufficient to answer the questions posed.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety endorses the conclusions and recommendations of the CES on Assessment of the risks related to air environments presented above.

This expert appraisal highlights the importance of pollen among the different causes of respiratory allergies. It is necessary to continue work aiming to identify the other environmental sources of allergies, whether proven or suspected, such as certain chemical pollutants, mould, etc., and to characterise exposure whenever possible in order to guide risk management actions more effectively.

In this regard, in 2014 the Agency will continue its work on agents in indoor and outdoor environments that may be responsible for allergic manifestations, such as mould in particular.

The Director General

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KEY WORDS

Pollen, pollen allergy, seasonal allergic rhinitis, pollinosis, rhinoconjunctivitis, general population, pollen allergy prevalence, pollen metrological monitoring schemes modelling, aerobiology environmental health.