Science of the Total Environment 926 (2024) 171575

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Method to develop a regional guide for the allergenic potential of tree pollen

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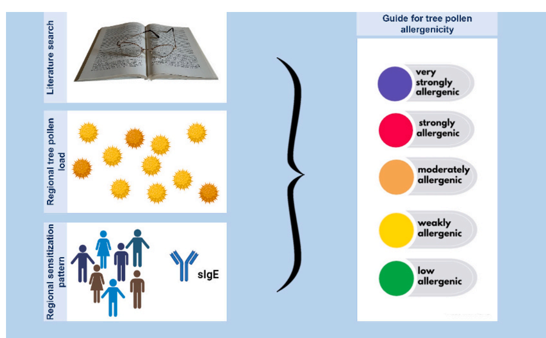
HIGHLIGHTS

- A method to classify the regional allergenic potential of tree pollen is developed.
- The method combines scientific studies, pollen abundancy and sensitization data.
- 8 tree genera are classified as very strong to moderate allergenic pollen producers.
- 14 tree species are considered weakly allergenic under the current circumstances.

GRAPHICAL ABSTRACT



ARTICLE INFO

Editor: Philip Hopke

Keywords:
Allergic rhinitis
Pollen
Tree species
Urban planning

ABSTRACT

Allergic rhinitis, caused by airborne pollen, is a common disease with a great impact on the quality of life for patients and high costs for society. Prevention of high pollen concentrations in the air is relevant for creating a safe environment for allergic patients. Due to climate change, the heat in cities during the summer is a recurring problem. The local climate can be improved by using the cooling properties of trees, providing shade and cooling by evapotranspiration. When deciding which tree species will be planted, it is important to take into account the allergenicity of the pollen that the tree produces. Available guides, used all over the world, on the allergenicity of pollen are very divers in content and interpretation and not applicable for the Netherlands. In this study a

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https://doi.org/10.1016/j.scitotenv.2024.171575
Received 23 November 2023; Received in revised form 6 March 2024; Accepted 6 March 2024
Available online 9 March 2024

method is described to develop a guide for the allergenic potential of tree pollen in a region, in this case the Netherlands.

For the most common tree species in the Netherlands the scientific knowledge on the allergenicity of the pollen was collected, followed by an inventory on regional pollen abundance. Subsequently, the sensitization pattern in a patient group with possible inhalation allergy was analyzed. Based on these data allergenicity of the tree pollen was classified into five classes. Eight tree species/genera of the 61 most planted tree species in the Netherlands are considered to have a very strong to moderate allergenic potential. We propose to use this methodology to develop regional-specific guides classifying the allergenic potential of tree pollen.

1. Introduction

Plants that rely on wind pollination for their reproduction emit numerous pollen grains into the air, contributing to the bioaerosols that are present in the atmosphere (Fröhlich-Nowoisky et al., 2016). These pollen grains are relevant triggers of allergic rhinitis (Meltzer, 2016). Although the symptoms of allergic rhinitis are often considered to be trivial, patients can be severely inhibited in their work, social activities and sleep. Furthermore, due to the high prevalence of the disease and the often underestimated indirect costs (absenteeism, presenteeism), the total costs of the disease to society are high (Zuberbier et al., 2014).

One of the possibilities to prevent the development of symptoms in allergic patients is to avoid contact with the allergen. Obviously, this is very difficult for pollen sensitized patients, since during the flowering season the pollen will be present in the outside air they breathe and even indoors (Menzel et al., 2017). Thus, prevention of high pollen concentrations in the air plays a key role in creating a safe environment for allergic patients. In urban environments preventing the planting of allergenic pollen producing tree species could be an option to lower the pollen concentration.

One of the results of climate change is the rise in temperature in urban areas (heat island effect) causing an increase in mortality rates (Tan et al., 2007; Garssen et al., 2005). Trees reduce temperatures by providing shade and by releasing water vapour through transpiration (Bowler et al., 2010). Furthermore, trees have other health related ecosystem-services like absorbing air pollutants, noise and promoting well-being all together (Grote et al., 2016). However, trees are not only beneficial; they also produce pollen which cause pollen-related allergies and asthma. Surprisingly for many (common) tree species the allergenic potential is hardly studied and the guides available in the world, classifying tree species in terms of the allergenicity of the pollen they produce, differ from each other (Sousa-Silva et al., 2021; Sousa-Silva et al., 2020; Bergmann et al., 2012; Cariñanos and Marinangeli, 2021; Ogren, 2000; Ortolani et al., 2015). Those guides are mostly expert-based and frequently, they lack support from scientific evidence, or from regional parameters like the pollen abundancy or sensitization patterns of the population. So the reasons for these differences in allergenicity classification among the different guides can be multiple: 1. the scientific basis of the classification of the allergenicity of the tree pollen is not always clear; 2. the pollen numbers that tree species produce can vary enormously around the world, due to differences in climate and number of plants present; 3. the sensitivity of the individuals of the regional population for pollen can differ.

Since decades three species from the Betulaceae family, *Betula, Alnus* and *Corylus* are considered to be the most relevant allergenic tree pollen species in the Netherlands (D'Amato et al., 1998), where *Betula* was the most relevant species, directly followed by *Alnus* and *Corylus*. Other tree species were considered less/not allergenically relevant. However, in this period the amount of pollen produced by the different tree species and the sensitization patterns of the patients may have changed. A contemporary scientific inventory on the allergenicity of the pollen produced by the common tree species in the Netherlands is essential. Especially since in the coming years many trees will be planted in the cities to reduce the heat island effect. The aim of the present study is to develop a national guide in which the pollen types produced by the most common trees in the Netherlands are classified according to their allergenic potential. We aim to classify the allergenicity according to well- described criteria in contrast to former studies (Lorenzoni-Chiesura et al., 2000; Ogren, 2000) which are mainly expert-based. Such a guide should provide everyone (authorities, professionals and the public) who decides to plant a tree, with the right information on the allergenic properties of the pollen of the tree species.

First, what is known in literature about the allergenicity of the pollen of each of these tree species will be studied, as is recommended by Sousa-Silva et al., 2021. Many allergenic proteins in pollen have been identified and biochemically characterized in the past decades. After careful review by a committee of experts, the allergens can be included in the database of the WHO-IUIS, the World Health Organization (WHO) and International Union of Immunological Societies (IUIS) (Goodman and Breiteneder, 2019). Most tree pollen allergens in this WHO-IUS database are present within the families Betulaceae, Fagaceae, Cupressaceae, Oleaceae and Platanaceae (Asam et al., 2015). Besides the well-characterized allergenic proteins, many other tree pollen have been described to trigger allergic symptoms in different regions in the world (Asam et al., 2015; Lin et al., 2002; Quiralte et al., 2007; Ribeiro et al., 2009). Furthermore, the pollen abundancy and the susceptibility of the population may differ between different parts of the world (Somoza et al., 2022). Therefore, we developed a method to classify the tree pollen-allergenicity within a region, in this case the Netherlands. We compiled an inventory of prevalent tree species in the Netherlands and collected the following data and information about the allergenicity of pollen: (i) scientific knowledge on the allergenicity of the pollen; (ii) the seasonal pollen load (seasonal pollen index) produced in the Netherlands (iii) the sensitization to that pollen within patients with a possible inhalation allergy in the Netherlands.

2. Material and methods

2.1. Allergenicity of pollen of most common tree species

Tree experts (authors HHJMK, WWB) composed a list of the most common tree species planted by municipalities in the Netherlands. For each of these species we consulted six published classification guides (Bergmann et al., 2012; Cariñanos and Marinangeli, 2021; Lorenzoni-Chiesura et al., 2000; Ogren, 2000; Ortolani et al., 2015; RNSA, 2022) that classified the allergenicity of tree pollen for different regions. Subsequently, a literature research was performed on all tree species in our Dutch list. Peer reviewed studies were collected using the search terms <pollen> < tree species name in latin> and < allerg* > in two search engines (PubMed and Google Scholar). In many studies the allergenicity of the pollen is studied on genus level (e.g. *Betula, Quercus*) and in those cases the genus name is used. During our search we mainly focused on clinical papers studying sensitization patterns in the population/patients. All the information from literature was combined into a table to make an inventory of the allergenic potential of the pollen described all over the world. The regions where allergenicity was described were noted in a separate column.

2.2. Seasonal pollen index

Airborne pollen were collected by Hirst Type 7-day volumetric pore traps (Burkard Manufacturing Co., Ltd., UK) placed at 20–25 m above ground level and analyzed microscopically at the two pollen monitoring stations (de Weger et al., 2021) in the Netherlands: in Leiden (Leiden University Medical Center, LUMC; longitude: 4.47; latitude: 52.17) and Helmond (Elkerliek Hospital; longitude: 5.63; latitude: 51.48), the Netherlands. Pollen monitoring at roof top level gives an indication of the pollen abundancy in a circle of around 30–40 km around the pollen sampler and these pollen counts are related to the chance that people come into contact with the pollen and can have an allergic reaction. For the two pollen monitoring stations, the daily values for all identified tree pollen species were summed per species per year to obtain seasonal pollen totals, i.e. Seasonal Pollen Indices (SPIs) (Galán et al., 2017). The SPIs were averaged over the past 10 years (2013−2022) and further analyzed using STATA 17.

2.3. Sensitization to tree allergens

In 2021 and 2022, the sera of 467 patients of the Delft Allergy Center (Reinier de Graaf Gasthuis) were tested in a multiplex allergy array test, ALEX® (=Allergy Explorer; Micro Array Diagnostics) (Buzzulini et al., 2019; Heffler et al., 2018). Patients ranged in age from 1 to 85 years, with three-quarters of patients being under 39 years of age. The patients had been referred to the outpatient clinic under suspicion of "inhalation allergy". In this multiplex assay, the serum was tested for the presence of specific IgE (sIgE) against various inhalation, food and latex allergens in the presence of a CCD (Carbohydrate Cross-Reactive Determinants) inhibitor. In the test, extracts and molecular components (allergens) are used as a substrate. In this study, only results of the sIgE reactions to tree pollen allergens present in the ALEX test were used (Fig. 1). The different tree pollen allergens tested available in the ALEX test are shown in Table 2. A serum result with a sIgE concentration higher than 0.35 kU/L was considered positive. Data were analyzed using Excel and STATA 17.

2.4. Criteria for allergenic potential

Based on the allergenicity of pollen found in literature, the amount of airborne pollen and the sensibilization by pollen found in patients we determined the allergenic potential of the most important tree species. Throughout the research, criteria were developed for a classification of the allergenic potential of the tree pollen into five classes (Table 1).

3. Results and discussion

3.1. Allergenicity of tree pollen

Sixty-one tree species/genera were selected as the most common tree species in the Netherlands (Table 3). The classification of their allergenicity (Table S1, Supplement 1) was often not consistent in the six classification guides used (Bergmann et al., 2012; Cariñanos and Marinangeli, 2021; Lorenzoni-Chiesura et al., 2000; Ogren, 2000; Ortolani et al., 2015; RNSA, 2022). During the subsequent literature search on the individual tree species we noticed that on 17 species/genera no reports were available (see Table S1, Supplement 1), which might indicate that these species have not (yet) been recognized as allergenic pollen species.

Table 1
Allergenic potential of tree pollen classification as low, weak, moderate, strong or very strong based on classification of allergenicity in literature, the Seasonal Pollen Index in the Netherlands and the sensitization rates in Dutch Patients.

Classification	Literature	Seasonal Pollen Index	Sensitization
Very strong	Very strong to strong	Very high	Very high
Strong	Very strong to strong	Very high to high	High
Moderate	Strong to moderate	Moderate to low	High to moderate
Weak	Strong to moderate allergenicity described in other regions	Moderate to low	Low
Low	Low or not available	Moderate to low	Low

Pollen of birch and other related tree species of the families Betulaceae and Fagaceae are the most numerous airborne pollen species in Northern and Central Europe. They are considered a major cause of allergic rhinitis (Biedermann et al., 2019). Birch pollen is regarded as the most significant sensitizer for allergic reactions. (Egger et al., 2008), while the sIgE reactivity to pollen of the Fagaceae family (e.g. oak and beech) is considered to be mainly due to cross reactivity with birch pollen. Other relevant allergenic pollen species in Europe, recognized by the WHO-IUIS (Asam et al., 2015), are present in the families (i) Oleaceae (Liccardi et al., 1996), with *Fraxinus* as the most relevant representative in the Netherlands; (ii) Platanaceae (Nuñez-Borque et al., 2022), with *Platanus* described mainly in the Mediterranean countries as a relevant allergenic pollen species; (iii) Cupressaceae (Charpin et al., 2019) which include many different species of which several are common in the Netherlands too. However, the allergenicity of the pollen of these species have mainly been described in Mediterranean (Ariano et al., 2002) or Asian countries (Osada and Okano, 2021). Furthermore, genera *Populus* and *Salix* of the Salicaceae family are widely spread in the Netherlands. Sensitizations to genera *Populus* and *Salix* have been described in Mediterranean countries (e.g. Spain, (Cosmes Martín et al., 2005) or Turkey (Erkara et al., 2009)), but the clinical relevance is variable in different studies (Costache et al., 2021). *Acer* spp. have been described as a relevant allergen in the US and some Mediterranean countries (Weber, 2002; Ribeiro et al., 2009), but for instance in Germany it has been classified as low risk for allergies and thus suitable species for planting (Ribeiro et al., 2009). The detailed results of the literature search for all species are shown in (Table S1, Supplement 1).

3.2. Seasonal pollen index

The results of the mean Seasonal Pollen Index (SPI) observed at the two different stations in the Netherlands (Helmond and Leiden) for different species over a ten year period (2013–2022) are shown in Fig. 2. Pollen species of the Fagaceae/Betulaceae family, i.e. *Betula, Quercus* and *Alnus*, and the Cupressaceae family have the highest SPI, followed by the Pinaceae family, *Fraxinus, Salix* and *Populus* and in lower quantities *Platanus, Castanea, Carpinus, Corylus, Fagus* and *Ulmus*. The mean SPI was lower than 60 pollen for *Juglans, Tilia, Sambucus, Aesculus, Acer, Ilex* and *Ligustrum*. The sparseness of pollen of these species in the air is further illustrated by their daily values which are usually below 10

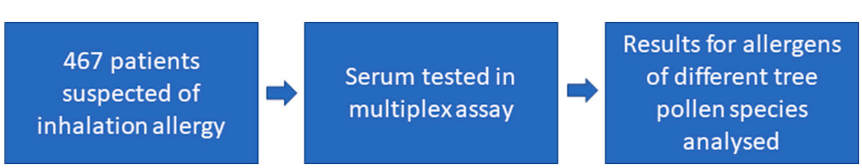

Fig. 1. Scheme of determination of the sensitization to tree pollen species in the patient group.

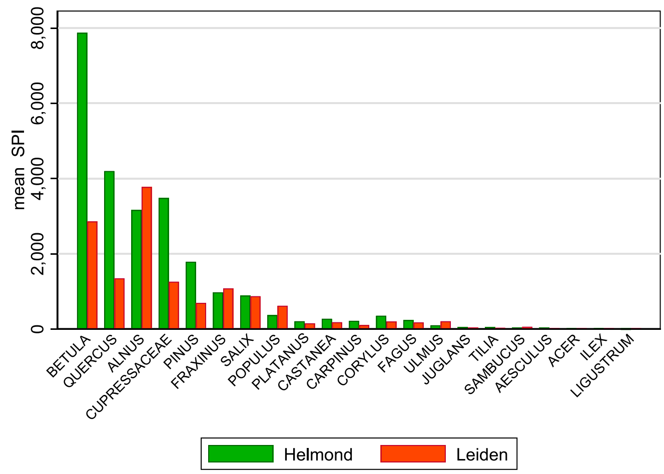

Fig. 2. The 10-year-mean of the Seasonal Pollen Index (SPI) of the tree pollen species observed in the air by two pollen monitoring stations in the Netherlands (Helmond and Leiden).

pollen*day/m^3 and their peak values that only exceptionally reach values up to 20 pollen*day/m^3. Therefore the allergenic potential of these species in the Netherlands is considered to be of minor relevance.

3.3. Sensibilization patterns

In a group of 467 successive patients suspected of an inhalation allergy the sIgE serum responses to tree pollen were analyzed. Almost 50 % of the patients showed a positive IgE response to *Betula* (Bet v1) followed by 41–46 % of the patients responding to *Fagus, Corylus* and *Alnus* (Table 2). A quarter of the patients showed positive IgE responses to allergens of the Oleaceae family (*Fraxinus and Olea*). For *Juglans* 9 % of the patients responded positively in the IgE test, while for species *Populus* and *Platanus* and the Cupressaceae family (*Cupressus* and *Cryptomeria*) 4–5 % of the patients responded positively.

Subsequently the level of sIgE in the sera of the patients responding positively in the IgE tests was further analyzed. The sIgE levels in the positive sIgE tests showed large variations in concentration of specific IgE (Fig. 3). This analysis showed that for the species of the Betulaceae, Fagaceae and Oleaceae family the sIgE concentrations were relatively high (> 20 kU/l), while for *Populus, Platanus, Juglans, Cryptomeria* and *Cupressus* the sIgE concentrations in the sera were low in most patients (<10 kU/L).

3.4. Tree guide for allergenic pollen

The ranking of the different species within each of the three criteria mentioned in Table 1 is provided in Table S2 (Supplement 2) and the resulting guide is presented in Table 3. There is only one species with a very strong allergenic potential: *Betula. Betula* is considered the most relevant allergenic tree species in Northern Europe (Biedermann et al., 2019). Furthermore, it has the highest SPI and the highest sensitization among Dutch patients and therefore it is placed in the highest class: very strong allergenic. We classified two other *Betulaceae* species, *Alnus* and *Corylus*, as species with a strong allergenic potential. *Alnus* pollen is the most abundant pollen collected at the pollen monitoring station in Leiden and among allergic patients there is a high sensitization rate. Also for *Corylus* a high percentage of the allergic patients are sensitized, however relatively low numbers of *Corylus* pollen are collected by the samplers in the Netherlands (Fig. 2). These low numbers are in conflict with the criteria for a strong allergenic species. However since *Corylus* has been considered in the past decades as a major allergen in the Netherlands and the fact that half of the patients respond to the *Corylus* antigens, the classification of this species as strongly allergenic is maintained in this guide.

Table 2
Percentage of patients with a positive serum response in the specific IgE multiplex assay (% sIgE pos) to different tree species allergens. Colors range from red (high percentage of sIgE positive patients) to green (low percentage (low percentage sIgE positive patients). The table indicates whether a molecular allergen or an extract is used in the test (column 'molecule/extract') isolated from the different tree species (column 'Tree species').

Allergen	Tree species	Molecule/extract	% sIgE pos
Bet v 1	*Betula verrucosa*	PR-10	49,9
Fag s 1	*Fagus sylvatica*	PR-10	45,8
Cor a 1.0103	*Corylus avellana*	PR-10	45,4
Cor a 1.0401	*Corylus avellana*	PR-10	41,5
Cor a_pollen	*Corylus avellana*	extract	41,5
Aln g 1	*Alnus glutinosa*	PR-10	40,5
Fra e	*Fraxinus excelsior*	extract	26,3
Fra e 1	*Fraxinus excelsior*	pectinestrase	24,4
Ole e 1	*Olea europaea*	pectinestrase	23,8
Jug r_pollen	*Juglans regia*	extract	9,4
Bet v 2	*Betula verrucosa*	profiline	9,2
Bet v 6	*Betula verrucosa*	iso-flavonreductase	7,3
Pop n	*Populus nigra*	extract	5,4
Pla a 2	*Platanus acerifolia*	polygalacturonase	5,1
Cup a 1	*Cupressus arizonica*	pectaatlyase	4,7
Cry j 1	*Cryptomeria japonica*	pectaatlyase	4,5
Pla a 3	*Platanus acerifolia*	nsLTP	1,7
Aln g 4	*Alnus glutinosa*	polcalcine	1,3
Pla a 1	*Platanus acerifolia*	plant invertase	1,3
Ail a	*Ailanthus altissima*	extract	0,9
Cup s	*Cupressus sempervirens*	extract	0,4
Jun a	*Juniperus ashei*	extract	0,4
Bro pa	*Broussonetia papyrifera*	extract	0,2
Ole e 9	*Olea europaea*	1,3βGlucanase	0,0

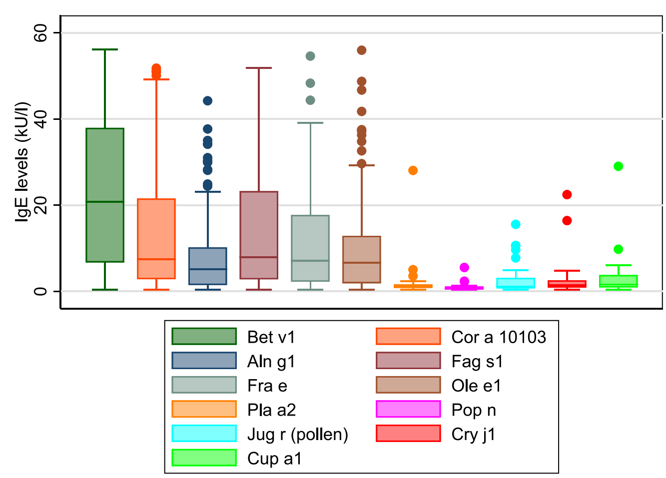

Fig. 3. *Boxplots of the specific IgE (sIgE) concentrations in the sera of patients that respond positively in the multiplex allergen test. The boxes show the distribution of the results with the mean indicated by a dark line. The plot also shows the outliers (dots). The tree species from which the allergens are isolated are listed in* Table 2.

Five species are classified with a moderate allergenic potential. They include one species of the Betulaceae family (*Carpinus*), two species of the Fagaceae family (*Fagus* and *Quercus*) and two species of the Oleaceae family (*Fraxinus* and *Olea*).

For *Carpinus* the number of pollen produced during the flowering

Table 3
Guide for allergenicity of tree pollen. The table shows a column for the Latin name of the tree species (species/ genus) as well as a column for the common name. The allergenicity in the Netherlands is given in five classes (Allergenicity in NL) and indicated by a color; purple = very strong; red = strong; orange = moderate; yellow = weak; green = low. The fourth column indicates regions where allergenicity has been described in literature. The fifth column indicates the availability of exclusive female species.

Species/Genus	Common name	Allergenicity in NL	Region where allergenicity has been described	female species
Betula spp	Birch	very strong	North, Central Europe	
Alnus spp	Alder	strong	North, Central Europe,Asia	
Corylus spp	Hazel	strong	Europe, Asia	
Carpinus spp.	Hornbeam	moderate	Spain Italy	
Fagus spp	Beech	moderate	Mediter., Germany	
Fraxinus spp	Ash	moderate	Switzerland	
Olea europea	Olive	moderate	Mediter.	
Quercus spp	Oak	moderate	Mediter, Germany, Asia	
Acer spp	Maple	weak	USA	
Elaeagnus angustifolia	Russian olive	weak	Spain	
Juglans spp	Walnut	weak	China	
Juniperus communis	Common juniper	weak	Italy	
Ligustrum spp	Wild privet	weak	Mediter.	
Morus spp	Mulberry	weak	Turkey, Spain	
Platanus spp	Plane tree	weak	Mediter.	
Populus spp	Pople	weak	Mediter., Turkye, Asia	
Robinia pseudoacacia	Black locust	weak	Mediter.	
Salix spp	Willow	weak	MiddleEast, USA, Asia	
Taxodium distichum	Swamp cypress	weak	USA	
Thuja	Northern white-cedar	weak	USA	
Tilia spp	Lime trees	weak	Mediter.	
Ulmus spp	Elm	weak	USA, Asia	
Abies spp	Silver fir	low		
Aesculus spp	Horse chestnut	low		
Amelanchier spp	Currant treee	low		
Castanea spp.	Chestnut	low		
Catalpa bignonioides	Trumpet tree	low		
Cedrus atlantica = C. libani	Cedar	low		
Celtis australis	European nettle tree	low		
Cercidiphyllum japonicum	Katsura	low		
Cercis siliquastrum	Judas tree	low		
Chamaecyparis lawsoniana	Lawson Cypress	low		
Cornus alba	Siberian dogwood	low		
Crataegus	Hawthorn	low		
Cupressocyparis leylandii	Leylandii	low		
Ginkgo biloba	Maidenhair tree	low		
Gleditsia triacanthos	Honey Locust	low		
Gymnocladus dioicus	Kentucky coffeetree	low		
Hamamelis mollis	Chinese witch hazel	low		
Ilex aquifolium	Holly	low		
Koelreuteria paniculata	Chinese varnish tree	low		
Laburnum x watereri 'Vossii'	Golden Chain Tree	low		
Larix decidua	European larch	low		
Liquidambar styraciflua	American sweetgum	low		
Liriodendron tulipifera	Tulip tree	low		
Magnolia spp.	Magnolia	low		
Malus spp	Apple	low		
Metasequoia glyptostroboides	Dawn redwood	low		
Parrotia persica	Persian ironwood	low		
Paulownia tomentosa	Empress tree	low		
Picea spp	Spruce	low		
Pinus spp	Pine	low		
Prunus spp	Prunus	low		
Pterocarya fraxinifolia	Caucasian walnut	low		
Pyrus spp	Pear	low		
Sambucus nigra	Elder	low		
Sophora japonica (Styphnolobium jap.)	Japanese pagoda tree	low		
Sorbus spp	Whitebeam	low		
Tamarix gallica	Salt Cedar	low		
Taxus baccata	English yew	low		
Zelkova serrata	Japanese elm	low		

season is low, but allergenicity has been described in literature (Gumowski et al., 2000). *Fagus* showed a surprisingly high percentage of patients with high levels of sIgE in their serum (Table 2 and Fig. 3). Surprisingly as, so far, *Fagus* has never been considered as a relevant species to cause allergic rhinitis in the Netherlands. Possibly, the number of symptoms is low as the SPI of *Fagus* is low. Due to the low SPI and the low to moderate allergenicity described in literature on one hand, and the high sensitization patterns on the other hand, we decided to classify Fagus as a moderate allergenic species. Contrary to the close relative of *Fagus*, *Quercus* has a high SPI and is known to cause allergic reactions in the Mediterranean and Germany. However, neither *Quercus* has been considered a relevant allergenic species in the Netherlands and also in literature it is considered less allergenically relevant than for instance *Betula* (Egger et al., 2008). Therefore, *Quercus* is added to the moderate category.

Also, the two species of the Oleaceae family (*Fraxinus* and *Olea*) were classified as moderate allergens since a quarter of the patients (23.8–26.3 %) showed a positive IgE response to the allergens of these species with relatively high IgE levels. Currently, *Olea* pollen are hardly counted but as the tree is popular in garden centers since a few years, it is warranted to classify this species as moderately allergenic.

The fourth category is classified as weakly allergenic. The species in this category are not (yet) known as relevant allergenic species in the Netherlands but are described to have allergenic potential in other regions in the world with different climatic conditions. However, this may change when the intensity of pollen production of these species might increase due to climate change or when the species will be planted in large numbers leading to more regional airborne pollen. This may lead to more exposure of the public to the pollen and thereby development of new allergies. The region where allergenicity has been described is mentioned in Table 3 in the column "Region where allergenicity For the Salicaceae species, Populus and Salix, considerable pollen levels have been monitored in the Netherlands (Fig. 2) and allergenicity has been described in other regions of the world (Costache et al., 2021; Ince et al., 2004). However, since in this study the percentage of patients responding to Populus allergens (Salix was not tested) was low as well as the sIgE concentration in their sera (Table 2, Fig. 3), these species are considered as having a weak allergenic potential.

In Mediterranean countries *Platanus* is known as a relevant cause of allergy (Thibaudon et al., 2017; Varela et al., 1997). A previous study found a sensitization rate of 4.7 % in the Netherlands (Heinzerling et al., 2009) which is comparable to our findings for Pla a2 (Table 3). Also, in this Dutch patient group the prevalence of a positive IgE response to the specific recombinant antigen *Platanus* Pla a2 was higher than to Pla a1, as was also found in a Spanish patient group (Nuñez-Borque et al., 2022). Due to the low percentage of sensitized patients, the relatively low specific IgE Levels (Fig. 3) and the relatively low plane tree pollen numbers, *Platanus* was classified as a weak allergenic species.

Species from the Cupressaceae family, *Cupressus and Cryptomeria* are tested in the ALEX° assay and reveal a low percentage positively responding patients (Table 2) with low specific IgE levels (Fig. 3). However, these species are not included in the tree guide, since they are not considered as common tree species in the Netherlands. For *Juniperus communis* allergenicity has been described in Tuscany, Italy and therefore this species is classified as weakly allergenic. For the other Cupressaceae species present in the guide (*Chamaecyparis lawsoniana, Cupressocyparis leylandii*) no literature was found and therefore considered as lowly allergenic. Other tree species for which currently (low) airborne pollen can be detected in the Netherlands (e.g. *Acer*, *Juglans*) and/or for which moderate to low allergenic properties have been described in other climatic regions, are classified as weak allergenic species. Finally, the tree species for which no literature is available or for which low allergenic properties have been described are classified as having a low allergenic potential. The pollen of most of these species are currently not detected in the air in the Netherlands.

The final addition to the guide is a column to indicate whether exclusive female members are available for the species. Within the dioecious species (Ogren, 2000), the trees can either be a male, having only male reproductive organs (stamens) or a female member, having only female reproductive parts (pistils). The female members will not produce pollen and are therefore 'allergenically safe'.

This approach's strengths lie in its integration of information from international literature and consideration of regional factors, such as pollen abundance and the sensitization patterns to the pollen allergens of various tree species in a regional group of patients. This is particularly valuable because patients are typically tested with a comprehensive mix of tree pollen allergens, without specific differentiation. Unfortunately, not all tree pollen allergens from our list of tree species were available in the allergen test, so for these species the classification is only based on the knowledge from literature combined with the regional pollen abundance. Furthermore, sensitization patterns do not indicate the real burden of the disease the pollen will cause. It is also important to recognize that certain tree species lack documented studies about their allergenic properties in literature. This could be attributed to the fact that these particular species haven't been considered or suspected of causing allergies, for instance tree species that have their flowering period at the same time as other known allergenic tree species. The allergenicity of these species may be underestimated in this classification.

In contrast to previous studies on allergenicity guides for pollen (Ogren, 2000; Lorenzoni-Chiesura et al., 2000), we have outlined the criteria for classifying the allergenicity of pollen to elucidate the classification process, as detailed in Table 1. The criteria provided are descriptive and do not establish specific hard thresholds or ranges of values as -for instance- pollen numbers (SPIs) may vary significantly from one region to another. Determining the allergenicity class for certain species, such as Fagus and Corylus, may still pose challenges. In such instances, expert opinion may remain necessary to reach a conclusive decision.

The relevance of regional allergenicity guides for pollen has been nicely presented by Sousa-Silva (Sousa-Silva et al., 2021). It also touches on an intriguing discussion about the classification of pollen allergenicity: when there would have been only limited presence of birch trees in the Netherlands it would not have been classified as the 'most strong allergenic tree'. However the pollen from this tree species does not undergo a change in allergenicity.

4. Conclusions

Through the combination of knowledge derived from systematically collected scientific studies on the allergenicity of tree pollen species, along with the recorded pollen concentrations at two reference stations in the Netherlands spanning from 2013 to 2022, and data on the allergic sensitization of 467 Dutch patients from 2021 to 2022, we were able to make a Dutch guide with information on the allergenic potential of tree species. Of the sixty-one most planted tree species/genera only one species is considered to have a very strong allergenic potential (*Betula*). Two species/genera (*Alnus* and *Corylus*) have a strong allergenic potential while five species/genera (*Carpinus*, *Fagus*, *Fraxinus*, *Olea europea* and *Quercus*) have a moderate allergenic potential. Fourteen species/genera are classified as having a weak allergenic potential. These species are known to cause allergic reactions in other more warmer climates. With the expected increase in temperature due to climate change, it is possible that the allergenic potential of these tree species in the Netherlands might increase in the future. We suggest to be also restrictive in planting these species in large densities in both urban as less-urbanized areas. The final 39 species are classified as having a low allergenic potential.

This national guide gives stakeholders, like tree specialists, arborists, landscape architects, municipal officials and the public, the option to include the allergenic potential of the tree pollen in their decision on which tree species to plant. The method described in this paper can be followed to develop allergenicity guides for tree pollen in other regions. These regional-specific guides are strongly recommended since they provide persons deciding on the planting of trees with information which is relevant for their own region. Use of these allergenicity guides by stakeholders should lead to more awareness on this negative health effect of some tree species and subsequently to a better environment.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2024.171575.

CRediT authorship contribution statement

Letty A. De Weger: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Liesbeth E. Bakker-Jonges:** Writing – review & editing, Methodology, Data curation. **Hans De Groot:** Writing – review & editing, Methodology. **Henry H.J.M. Kuppen:** Writing – review & editing, Data curation. **Wendy W. Batenburg:** Writing – review & editing, Data curation. **Anna Van Leeuwen:** Writing – review & editing, Methodology. **Mieke Koenders:** Writing – review & editing, Data curation. **Arnold J.H. Van Vliet:** Writing – review & editing, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Pollen data will be made available upon request. The patient data that have been used is confidential.

Acknowledgements

This study was supported by ZonMw (grant number 10240012010002). We thank Lisbeth Hall (National Institute for Public Health and the Environment) for helpful advice.

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