

**ALLERGIC HYPERSENSITIVITY TO DIFFERENT WASPS IN SPAIN**

Angel San Miguel\*<sup>1</sup>, Maria San Miguel Rodríguez<sup>2</sup>, María Isabel Hormiga<sup>3</sup>, María Vega<sup>3</sup>, Jose María Vega<sup>3</sup> and Alicia Armentia<sup>3</sup>

<sup>1</sup>Department of Clinical Analysis. Río Hortega University Hospital. Valladolid. Professor International University of Rioja (UNIR). Spain.

<sup>2</sup>Research Unit. Río Hortega University Hospital (HURH). University of Valladolid. Spain.

<sup>3</sup>Allergy Service. Río Hortega University Hospital (HURH). University of Valladolid. Spain.

\*Corresponding Author: Angel San Miguel

Department of Clinical Analysis. Río Hortega University Hospital. Valladolid. Professor International University of Rioja (UNIR). Spain.

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**ABSTRACT**

Hymenoptera is a large order that includes insects such as bees, wasps and ants. Within this, are the Suborder Apocryta and the Infraorder Aculeata, to which belongs the Family Vespidae that includes the genus *Polistes* and *Vespula* spp, wasps protagonists of this study. The hymenopterans that produce the most cases of allergy in our country are bees and *Polistes wasps. dominates* (in the south) and *Vespula germanic* (in the north). Hypersensitivity reactions occur with a prevalence of 2.8% to 28.7%, occurring systemically in 0.3%-7.5%, and can lead to anaphylactic shock. Immunotherapy is a highly effective method to prevent these reactions, thus protecting allergic people against the serious consequences that these insect bites can cause. A descriptive observational study is carried out analyzing the results of the specific IgE tests performed on patients with suspected allergy to Hymenoptera in Valladolid at the Río Hortega Hospital in the years 2010 and 2019 in order to check if there are changes in the prevalence of allergy. to Hymenoptera based on the hypothesis that in recent years there has been an increase in hypersensitivity to the genus *Polistes* with respect to the others. Obtaining statistically significant results for *P. dominula* ( $p < 0.005$ ), climate change is analyzed as a causative agent and the way in which it influences this species. Concluding that *P. dominula* It has modified its thermal characteristics in order to better survive changes in the environment, thus gradually expanding to other territories and increasing exposure to its bite and, therefore, to allergic reactions.

**KEYWORDS:** Hymenoptera. hypersensitivity Poison. *Polistes dominates*. *Vespula germanic*. Climate change.

**INTRODUCTION**

In recent years, a change in the distribution of different insects has been observed that has been related, among other factors, to climate change. This may also involve Hymenoptera and have repercussions on human health, given the seriousness of the hypersensitivity reactions caused by these arthropods.

**Justification**

- I. Check if there are differences in the distribution of sensitization to Hymenoptera venoms.
  - II. The severity of hypersensitivity reactions caused by Hymenoptera.
  - III. Climate change is a topical issue and we can observe one of many aspects in which it affects health.
  - IV. Raise awareness of the impact of climate change.
- The interest of this study is in:

**Objectives**

Through this work we intend to study the evolution of the distribution of hymenoptera venom hypersensitivity

with the data obtained from specific IgE in 2010 and 2019.

In addition, based on this information, draw conclusions about the potential causes of this increase, assessing the possible implication of climate change and the way in which this factor influences.

**Hypothesis**

Climate change, in addition to other factors, is leading to an increase in cases of hypersensitivity to the genus *Polistes* with respect to *Vespula spp*, since rising temperatures favor the former.

**Generalities of the Hymenoptera**

Within the Order Hymenoptera, whose main characteristic is the presence of two pairs of membranous wings (the first ones larger than the second ones) and the mouth apparatus, which is of the shredder type, or shredder-licker, with a strong and well-developed jaw, species such as bees, wasps and ants are found. These

show a homogeneous morphology but a wide variety of lifestyles, including phytophagy, parasitoidism, predation, pollen feeding, and eusociality. They include agricultural pests, ecosystem invaders, biological control agents, and pollinators. They are essentially earth-shakers: they either dig their nests in the earth or use it to create them. They usually live alone or in colonies. The geographic distribution of nests is mainly dominated by temperature. They seek warmth above all else.<sup>[1,2,3]</sup>

A characteristic fact is that sex determination generally follows a haplo-diploid system. Unfertilized eggs are haploid, leaving males, and, on the other hand, those that are fertilized are diploid and give rise to females.<sup>[4]</sup>

There are two Suborders within the Order *Hymenoptera*, Symphyta and Apocrita, which differ according to the presence or not of a strangulation that separates the thorax from the abdomen, being present in the second case. Regarding this feature, we can differentiate *Vespula* from *Polistes* by the shape of the abdomen, inferior to the strangulation, since in *Vespula* it becomes wide immediately and in *Polistes* more progressively. Within the Suborder *Apocrita* is the Infraorder *Aculeata* to which the Family *Vespidae* belongs. The underorder *Aculeata* is characterized by the fact that a stinger is found in the place where the ovipositor organ is usually found, which is the one used by females to lay eggs.<sup>[4,5]</sup>

In view of the theme of this work, we are going to focus on introducing wasps in a general way, more specifically the *Vespidae* Family, to which the *Polistes* and *Vespula* genus, protagonists of the study, belong.

*Vespidae* is a moderately large Family that is widespread but especially numerous in temperate climates. Important

morphological characters include long, slender antennae, curved but not curled. They are medium in size (9-25 mm), dark, but marked with yellow, white, or red. The wings are usually folded longitudinally when the insect is at rest. It is divided into the Subfamilies *Vespinae* (yellow jackets and hornets) and *Polistinae* (wasps).<sup>[6,7]</sup> The Subfamily *Vespinae* is divided into three genus: *Vespula* (yellow jackets), *Dolichovespula*, and *Vespa* (hornets). Common names in general use can be misleading: in Europe, the term "wasps" generally refers to any of the social wasps and not just the *Polistes* species.<sup>[8]</sup>

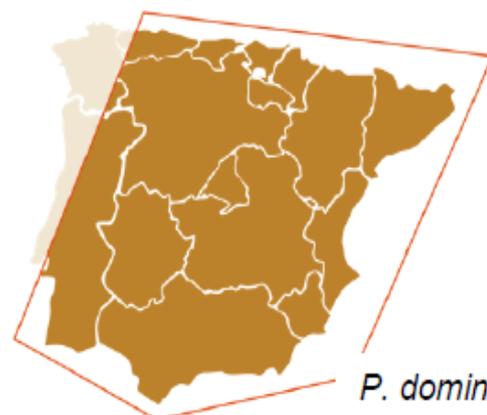
*Vespula* (yellow jacket wasp) nests are most often found below ground, but also under roofs or in shutters.<sup>[8]</sup> They nest mainly in rural areas, agricultural areas, forests, gardens, but also in buildings and urban structures.<sup>[6]</sup>

Common paper wasps (*Polistes*) build honeycomb nests in bushes or under house ledges by mixing plant fibers with their saliva. They generally have a single layer of open cells with minimal outer covering. The important species of *Polistes* in Europe are *P. dominula* and *P. gallicus* (8). Their area of origin is Mediterranean Europe and in this case, they are usually found more frequently in cosmopolitan areas, although they can also be seen in rural areas (6) (Figures 1 and 2).

In the following maps we can see the current distribution of the main wasp species in Spain. Although the distribution of both wasps is throughout Spain, a greater abundance of *Polistes* in the Mediterranean area and of *Vespula* in the Northwest has been accepted due to vaccination data.



*V. germanica*



*P. dominula*

Figures 1 and 2: Distribution of the main wasp species in Spain. Source: Treatise on Allergology. Introduction, epidemiology and clinic.<sup>[6]</sup>

### Epidemiology and generalities of allergic reactions to Hymenoptera

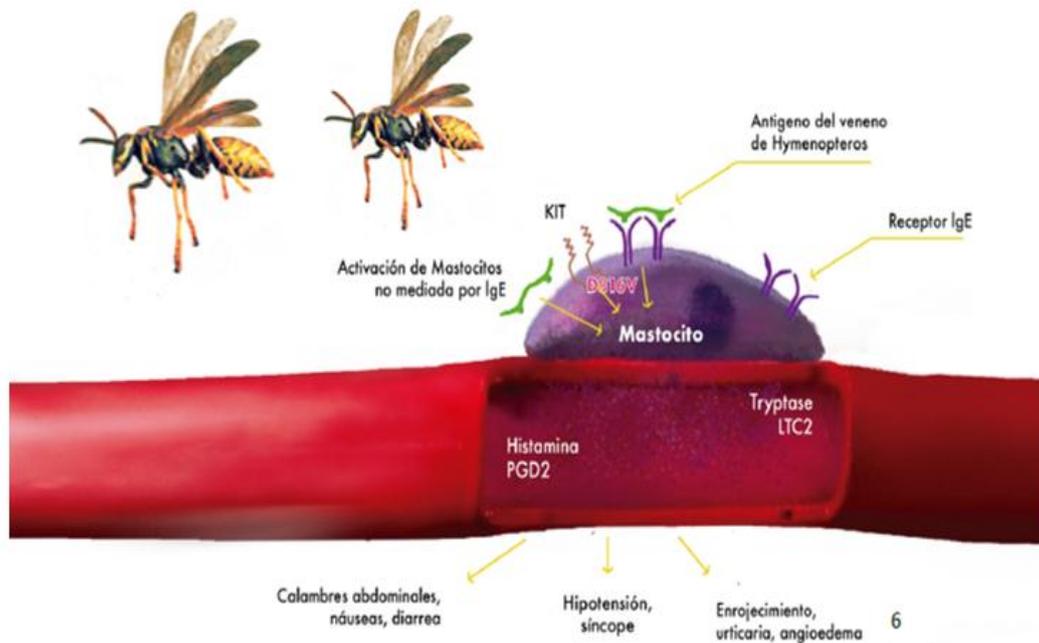
An allergic reaction occurs when the immune system overreacts to a substance that is normally harmless and should not be detected as foreign.<sup>[9]</sup> Hymenoptera venom allergy is a type I hypersensitivity reaction, being

mediated by IgE, which binds to mast cells releasing inflammatory mediators.<sup>[10]</sup> (Figure 3).

Allergic reactions to Hymenoptera are produced by the inoculation of the poison of these insects through their bite. The prevalence of these reactions is 2.8% to

28.7%.<sup>[12]</sup> Being that of local reactions from 2.4% to 26.4% and that of systemic reactions 0.3% to 7.5%.<sup>[13]</sup> Its venom is one of the most common causes of

anaphylaxis. In addition, it is estimated that more than half of the population (57% to 95%) will be stung by a hymenopteran at least once in their lives.<sup>[14]</sup>



**Figure 4: Allergic reaction mechanism.** Source: *Anaphylaxis After Hymenoptera Sting: Is It Venom Allergy, a Clonal Disorder, or Both?*<sup>[15]</sup>

International mortality is between 0.03 and 0.48 per 1,000,000 habitants/year. There are risk factors such as age over 40 years, male sex, comorbidities, bites in areas such as the head and neck, and the type of insect.<sup>[14]</sup>

These range from mild reactions such as hives, itching, etc., to other serious systemic reactions that can compromise the lives of the people who suffer from them.<sup>[16]</sup> Through the Müller classification we can differentiate 4 degrees of reactions as shown in Table 1.<sup>[13]</sup>

There is a wide variety of clinical manifestations that can be produced by a hymenopteran sting in allergic patients.

**Table 1: Classification into groups of severity of systemic reactions to hymenopteran stings** Source: *Anaphylaxis due to hymenopteran sting: study of 113 cases.*<sup>[13]</sup>

Degree	MÜLLER	Manifestations
Mild	I	Generalized urticaria, pruritus, malaise, anxiety
	II	Any of the above associated with 2 or more of the following: angioedema, chest tightness, nausea, vomiting, diarrhea, abdominal pain, vertigo. Isolated angioedema.
Severe	III	Any of the above associated with 2 or more of the following: dyspnea, wheezing, or isolated stridor.
	IV	Any of the above associated with 2 or more of the following: hypotension, collapse, loss of consciousness, sphincter relaxation, cyanosis.

Although not all the allergens that make up hymenopteran venom are yet known, it has been

observed that most contain hyaluronidases, dipeptidylpeptidases and vitellogenins, so these are

considered part of the cause of the cross-reactions that occur between venoms.<sup>[17]</sup>

The following tables (2, 3 and 4) show the allergens that make up the poisons of the different Hymenoptera. Data obtained from ALLERGEN NOMENCLATURE. WHO/IUIS Allergens Nomenclature Sub-Committee.<sup>[18]</sup>

Tables 2, 3 and 4: Allergens that make up the poisons of the different Hymenoptera.

Species	Table 2	Poison Allergens
 <i>Apis mellifera</i>	Api m 1	Fosfolipasa A2
	Api m 2	Hialuronidasa
	Api m 3	Fosfatasa ácida
	Api m 4	Melitina
	Api m 5	Dipeptidilpeptidasa IV
	Api m 6	Inhibidor de proteasa
	Api m 7	CUB serin proteasa
	Api m 8	Carboxilesterasa
	Api m 9	Serin carboxipeptidasa
	Api m 10	Icarapina variante 2, proteína rica en carbohidratos
	Api m 11	Proteína principal de la jalea real
	Api m 12	Vitelogenina

Species	Table 3	Poison Allergen
 <i>Polistes dominula</i>	Pol d 1	Fosfolipasa A1
	Pol d 2	Hialuronidasa
	Pol d 3	Dipeptidilpeptidasa IV
	Pol d 4	Serin proteasa
	Api m 12	Antígeno 5

Species	Table 4	Poison Allergen
 <i>Vespula germanica</i>	Ves g 5	Antígeno 5

There are cross-reactions between allergens of the three species. For example, between *Polistes* antigen 5 *dominates* and *Vespula's germanic* and, on the other hand, also between hyaluronidases and dipeptidylpeptidases IV from *Apis mellifera* and *Polistes dominates*.<sup>[16]</sup>

The diagnosis of this pathology is based on an exhaustive clinical history, where it is necessary to ask for information about the circumstances of the bite, such as the date, the symptoms that occurred and when. In

addition, skin tests and quantification of specific IgE antibodies are available.<sup>[19]</sup>

Skin tests are very sensitive, simple and cheap. To carry out these, standardized preparations of venom or dialyzed complete venoms are used.<sup>[19]</sup> Within this type of test are the intradermal and prick tests in which different concentrations of the allergen are used, requiring more concentration in the prick (20). It is advisable to start with a skin prick because intradermal testing carries a higher risk of anaphylaxis. Skin tests

should be performed a few weeks after the bite, otherwise false negatives may be obtained.<sup>[19]</sup>

The determination of specific IgE is the method initially used for diagnosis, and has been used to obtain the data for this work. It will be briefly explained later.

Given the seriousness of the reactions, immunotherapy is used to generate tolerance to the poison and prevent them, with very high efficacy. This is used in patients with severe systemic reactions where IgE-mediated sensitization has been demonstrated. It is performed by subcutaneous injection of the allergen extract in ascending doses for a few weeks or months until reaching the maintenance dose, also reaching protection at this time. It is the only curative treatment for this pathology in addition to avoiding the bite, which is not always possible. The effectiveness is between 77%-84% for the bee and between 91%-96% for the wasp, and can sometimes fail and not produce immunological tolerance, which is a risk for these patients who are exposed to dangerous reactions (twenty).<sup>[10]</sup>

## MATERIALS AND METHODS

### Type of study

Descriptive observational study has been carried out analyzing the evolution of allergic sensitization to the

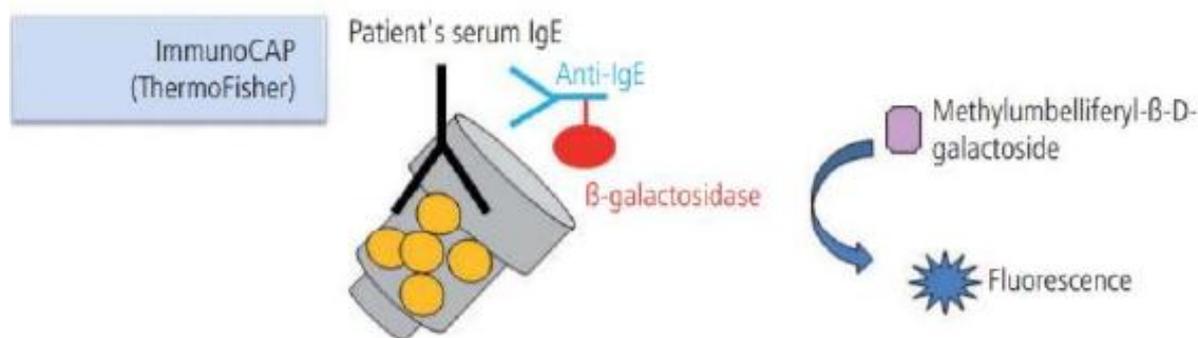
venom of hymenopterans that cause more cases of allergy (bee and wasps of the genus *Polistes* and *Vespula*) in patients who attended the Allergy Unit of the Hospital. Universitario Rfo Hortega de Valladolid due to reactions after being stung in 2010 and 2019.

### Determination of specific IgE

The technique used to quantify the levels of specific IgE was ImmunoCAP (Thermo Fisher Scientific ®), with high sensitivity and specificity.

This technique consists of exposing the patient's serum to the allergen and subsequently adding Anti-IgE antibodies linked to  $\beta$ -Galactosidase. The union of this Anti-IgE to the patient's IgE will cause that when adding Methylumbelliferyl  $\beta$ -D-galactosidase, it is transformed by  $\beta$ -Galactosidase into a fluorescent compound called 4-methylumbelliferone. The more IgE bound to the allergen, the more intense the fluorescence will be.<sup>[21]</sup>

The value from which the positive test is considered is 0.35, considering values lower than this as negative. In addition, the intensity of the sensitization can be analyzed, since values greater than 3.5 imply a very high sensitization.



**Figure 5: Technique specific IgE was ImmunoCAP (Thermo Fisher Scientific ®). Source: Recommendations for the Use of In Vitro Methods to Detect Specific Immunoglobulin E: Are They Comparable? (20).**

### Statistic analysis

In the first place, the data obtained for each species and year have been grouped, with respect to two cut-off points. The two options chosen are: on the one hand, dividing the samples taking into account the value from which they are considered positive (0.35), thus obtaining a group of negatives (<0.35) and another group of positives (>0.35). And, on the other hand, separating them according to whether it is a high sensitization (<3.5) or a very high sensitization (>3.5), starting from the value that indicates the intensity of the sensitization (3.5).

The use of these two cut-off points will help us to verify if there is an increase in the number of cases and, in turn, if the awareness is more intense. For this, it is necessary to check the statistical significance of the differences

between the two years for each species, by performing a hypothesis test, thus studying whether or not these inequalities are due to chance.

Carrying out the contrast of hypotheses for each species (bee, *Vespula* and *Polistes*), we will be able to compare if there is a significant increase in the prevalence of allergy to *Polistes dominates* with respect to the other Hymenoptera that most frequently cause hypersensitivity reactions in our country.

This contrast of hypotheses is done through a Chi Square test. With it, quantitative or nominal samples can be studied, as in this case in which we analyze proportions. Through Chi Square it is possible to know if some samples are related or independent. In our study, we observed whether there is a relationship by contrasting

the observed samples with those expected for the allergy data for each Hymenoptera.

Depending on the results of the p-value, we can accept or reject the null hypothesis, H0 (allergic sensitization has not increased), depending on whether or not there are statistically significant differences between the expected and observed frequencies. Assuming, if any, that the alternative hypothesis, H1 (allergic sensitization has increased) is true. Accepting an error of 0.05. Statistical calculations carried out using the SPSS program.

**RESULTS**

A total of 432 samples were collected, of which 131 belong to patients with suspected allergy to bees (72 in

2010 and 59 in 2019), 150 to those with suspected allergy to *Polistes spp* (82 in 2010 and 65 in 2019) and 154 to *Vespula spp* (88 in 2010 and 66 in 2019). An increase in the prevalence of allergy to *Polistes* is observed *spp*, which in his case has evolved from 25.6% of positives, of all specific IgE tests carried out in 2010, to 47.7% in 2019.

The results of specific IgE against hymenoptera venom are shown in Table 5.

**Table 5: Results of specific IgE against hymenoptera venom.**

 <p><b>Bee</b></p>	2010	55	17	72
	2019	44	15	59
 <p><b>Polistes dominula</b></p>	2010	61	21	82
	2019	34	31	65
 <p><b>Vespula germanica</b></p>	2010	52	36	88
	2019	37	29	66

Considering the data presented in the table, we realize that, despite having carried out *Polistes* - specific IgE tests on fewer people in 2019, the proportion of positive results is higher than in 2010. On the contrary, in the case of the bee and *Vespula spp* the proportions are practically similar in the two years.

Based on our hypothesis, in which we assume that climate change and the increase in temperatures that this implies favors the genus *Polistes*, causing its distribution area to expand nationwide, being increasingly frequent in northern areas and that.

As a consequence of this, there is an increase in allergy cases, we would expect to find statistically significant differences when comparing the proportion of positive results for *Polistes* in both years. Hoping, furthermore, not to find this difference for the *Bee* and *Vespula spp*, which are not affected by this change in temperatures.

As for the bee, of the 72 samples studied in 2010, 17 were positive, which represents 23.6%. While, in 2019, of the 59 samples studied, 15 were positive, assuming 25.42%. Therefore, there is a 1.82% more positives in 2019 compared to 2010. After the statistical analysis we can conclude with a  $p > 0.8$  (see results in Table 6) that there is no statistically significant difference, therefore, it

cannot be consider that there has been an increase in the prevalence of allergy.

Regarding **Polistes**, as we mentioned before, 21 positive results were obtained from 85 samples studied in 2010 (25.6%) and 31 positive results from 65 samples studied in 2019 (47.7%). In this case, the difference between the two years is 22.1% more positives in 2019, with a statistically significant increase in prevalence for this gender with  $p < 0.005$  (see results in Table 7).

Finally, in relation to **Vespula** 41% of positives were observed in 2010, 36 of 88 samples analyzed, and 44% in 2019, 29 of 66 samples studied. This represents an increase in positives of 3%, with a  $p > 0.7$  (see Table 8), not being able to consider that there is an increase in prevalence since there are no significant differences.

These results confirm our hypothesis. Yes, there is an increase in the prevalence of allergy to *Polistes* with respect to the other two most allergenic Hymenoptera in Spain. Likewise, the data were analyzed using the cut-off point 3.5, which shows the intensity of sensitization, but no significant results were obtained with respect to any of the three Hymenoptera, concluding that, although the number of cases of allergy to *Polistes*, allergic sensitization is not more intense for any of them.

Table 6: Statistical analysis result, Bee. Df: Degrees of freedom.

significance	Value	df	Asymptotic significance	Exact significance	Exact
			(bilateral)	(bilateral)	(unilateral)
Chi-cuadrado de Pearson	,058 <sup>a</sup>	1	,810		
Corrección de continuidad <sup>b</sup>	,001	1	,971		
Razón de verosimilitud	,058	1	,810		
Prueba exacta de Fisher				,840	,484
Asociación lineal por lineal	,057	1	,811		
N de casos válidos	131				

Table 7: Statistical analysis result, Polistes dominates. Df: Degrees of freedom.

significance	Value	df	Asymptotic significance	Exact significance	Exact
			(bilateral)	(bilateral)	(unilateral)
Chi-cuadrado de Pearson	7,734 <sup>a</sup>	1	,005		
Corrección de continuidad <sup>b</sup>	6,798	1	,009		
Razón de verosimilitud	7,745	1	,005		
Prueba exacta de Fisher				,009	,005
Asociación lineal por lineal	7,682	1	,006		
N de casos válidos	147				

Table 8: Statistical analysis result, Vespula germanic. Df: Degrees of freedom.

significance	Value	df	Asymptotic significance	Exact significance	Exact
			(bilateral)	(bilateral)	(unilateral)
Chi-cuadrado de Pearson	,142 <sup>a</sup>	1	,706		
Corrección de continuidad <sup>b</sup>	,045	1	,832		
Razón de verosimilitud	,142	1	,706		
Prueba exacta de Fisher				,743	,416
Asociación lineal por lineal	,141	1	,707		
N de casos válidos	154				

## DISCUSSION

Having obtained these results, we must consider the causes of this increase in the prevalence of the *Polistes* genus with respect to the others. One of the options that has gained more weight in recent years is that of increased temperatures in relation to climate change, which is capable of causing changes in the distribution of insects, including hymenoptera, causing serious consequences no longer only at an allergological level, also at an economic and ecological level.

### Role of climate change

Temperature is an important factor in the life of animals, influencing many biological processes.<sup>[22]</sup> In the case of insects, this is even more remarkable because, being ectothermic organisms, they regulate their body temperature depending on the temperature of the environment.<sup>[23]</sup> Climate change influences the distribution of insects causing adaptations in them to be able to face environmental alterations.<sup>[22]</sup>

In a study by *Helmut Kovac et al.*<sup>[22]</sup> in 2017 on the thermal characteristics of *Polistes dominates* and *Polistes gallicus*, which are the most frequent paper wasps in Europe, “differences were observed, such as the lower critical thermal limit than in *P. dominula* was -1.4 °C and in *P. gallicus* -0.4°C.

This difference is attributed to the need for *P. dominula* to adapt to the colder temperatures of Central Europe in order to expand successfully. On the other hand, there are no significant differences in terms of the maximum temperature limit, being for *P. dominula* of 47.1 °C and for *P. gallicus* of 47.6°C. In addition, it was also observed that *P. dominula* has a greater capacity to withstand greater differences between the minimum and maximum temperatures of a place, being able, in high temperatures, to keep its thorax a few degrees below the ambient air. Another feature is that *P. dominates* it cools its nests with an evaporative mechanism and through the

choice of the place where they nest, preferring sites isolated from the outside”.

The survival of the nests and the queens after the hibernation period is one of the main factors that influence the maintenance of the populations of these insects.<sup>[24]</sup> The adaptations mentioned above are the reason why, in the case of *Polistes*, they have a higher survival rate, thus being able to increase their population.

According to the information prepared by the *State Meteorological Agency*.<sup>[25]</sup> in 2010 the average temperature in Spain was 14.98 °C (0.35 °C above the normal value). Observing the map we can see that in most of the territory the temperatures are in normal or warm ranges. The year 2010 had the lowest average temperature since 1996.

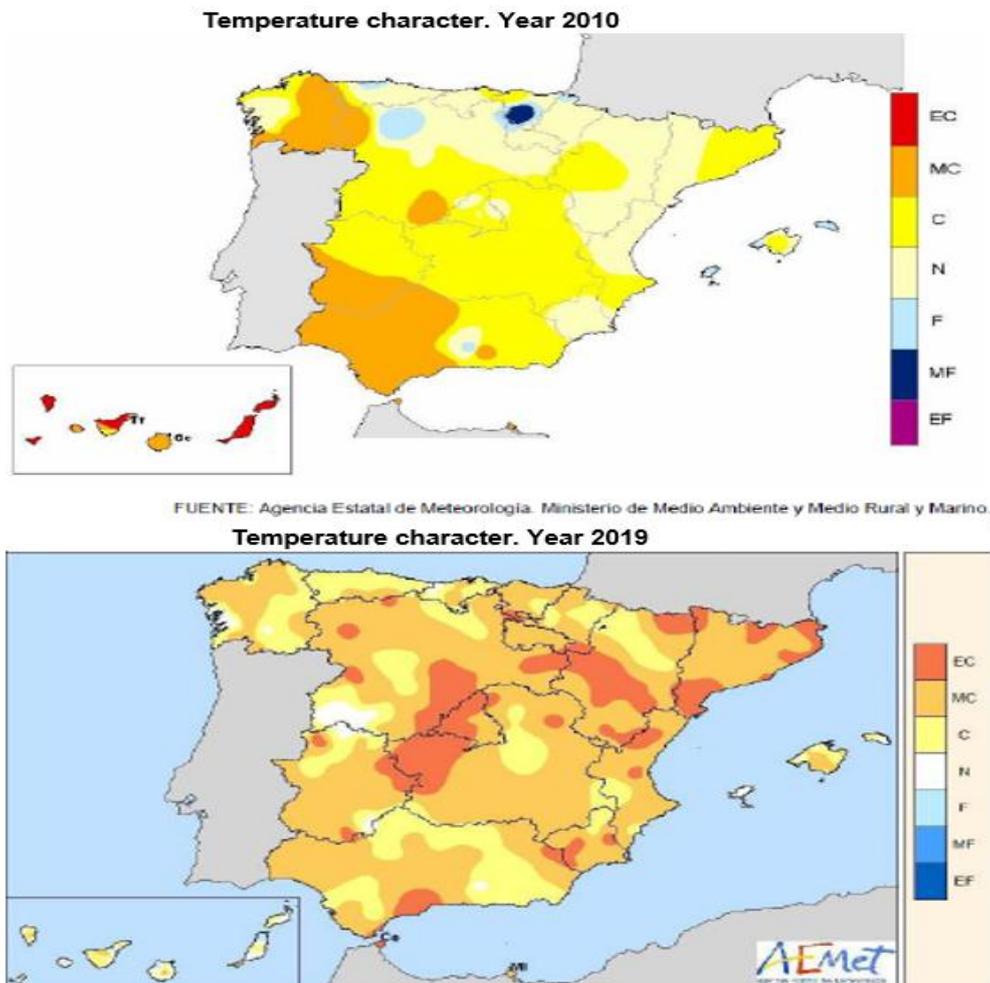
However, as for 2019, there was an average temperature of 15.9 °C , 0.8°C above the annual average value using the time period between 1981 and 2010 as a reference. Being the sixth warmest year of the 21st century. In addition, in terms of maximum temperatures, they have been 1.2 °C higher than the normal value. As you can see on the following map, the temperatures are mostly in the range that belongs to very hot and extremely hot.

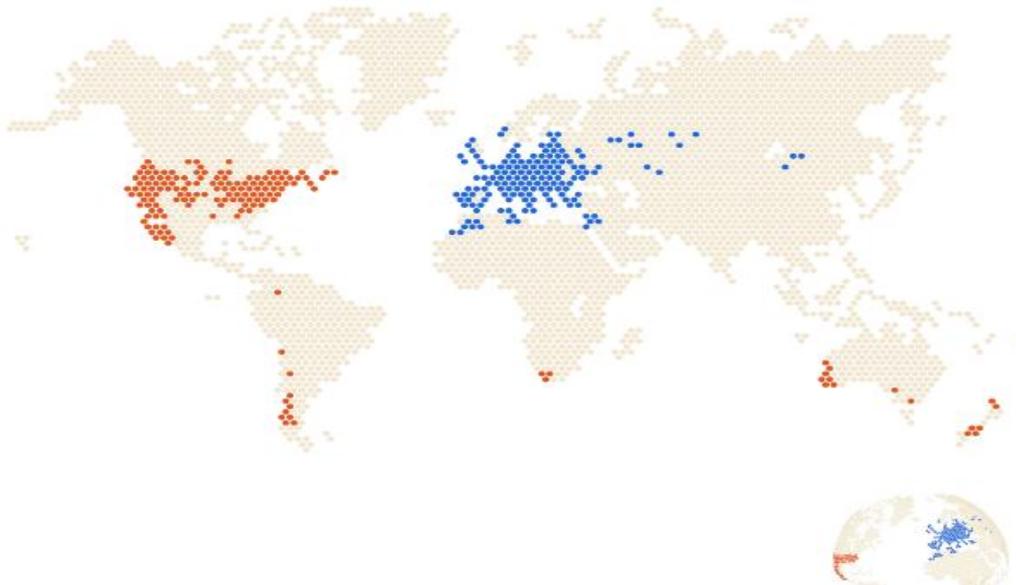
Therefore, the evolution of the temperature has gone from being normal or warm to very warm or extremely warm. Comparing the average temperature of 2019 with that of 2010 we can see an increase of almost 1°C.

**Other consequences of expansion**

The adaptability of *Polistes dominates* not only has it allowed its expansion in areas of northern Europe, but it has also been imported into countries such as the United States, Australia and some South American countries, being an invasive species in these, managing to spread rapidly, with what that this entails. Apart from allergic reactions, it also causes damage to the ecosystem, being a predator of other species such as butterflies, feeding on their larvae. On the other hand, there are the economic consequences, since it damages crops.<sup>[26,27]</sup>

According to *Miller GL. et. Al.*<sup>[28]</sup> in the United States it has managed to displace *P. fuscatus* , the native species. In the following map we can see in red the areas where *P. dominates* it is an invasive species and in blue what corresponds to its current normal area of distribution.<sup>[27]</sup> (Figure 6).





**Figure 6: Source: Bioclimatic Modeling Identifies Suitable Habitat for the Establishment of the Invasive European Paper Wasp (Hymenoptera: Vespidae) across the Southern Hemisphere.<sup>[27]</sup>**

## CONCLUSIONS

We observe that there has been a significant increase in cases of allergy to *Polistes dominula* in the last ten years.

In addition, the causes of this increase, according to verified sources, are that, unlike other species, *P. dominula* has managed to successfully adapt to the alterations caused by climate change, changing its characteristics, thus being able to expand fast and efficient. In addition to the fact that the increase in temperatures and its tendency to warmer areas favors this extension. From this information we can see how climate change harms some species, a factor that also affects humans, but, on the other hand, as in the case of *Polistes*, the fact that some species are favored is also a problem.

This expansion has meant that this species has increased its distribution area leaving the Mediterranean area, which corresponds to its original place, its presence being more and more common in northern areas and countries such as Germany, which are colder, invading on the other hand other continents like America. Its greater presence entails a greater exposure of the population to its bite, hence the prevalence of hypersensitivity has increased. This can have serious consequences because the venom of these insects is capable of producing serious reactions in people with hypersensitivity and the only method we have to prevent them is immunotherapy.

Climate change is a challenge that we have faced in recent decades. The way of life of the human being has managed to modify the climatic conditions with actions such as the emission of greenhouse gases and the high consumption of resources. This entails catastrophic consequences such as an increase in temperature, a rise in sea level due to melting ice, etc. In turn, these factors cause changes in different areas that have an impact on

our lives and our health. That is why we must raise awareness about this issue and take the necessary measures to stop it, since if we continue the same we can be seriously harmed.

## Conflict of interests

All authors declare no conflict of interest.

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