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ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

Νανογαλακτώματα φυτικών ελαίων με ενυδατικές και εντομοαπωθητικές ιδιότητες

ΕΠΙΒΛΕΠΩΝ ΚΑΘΗΓΗΤΗΣ: ΕΡΕΥΝΗΤΗΣ Α', ΖΩΓΡΑΦΟΣ ΣΠΥΡΟΣ

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IN BIOENTREPRENEURSHIP

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Nanoemulsions of essential oils with moisturizing and insect repellent properties

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Summary

This study indicates the growing interest of consumers in insect repellents because of the concerns about the increase in diseases transmitted through mosquitoes. Also it mentions the development of the insect repellent world market as well as the efforts made to introduce new products based on growth formulations of plant / synthetic substances. However, some drawbacks of the commercially available repellents continue to exist, thus giving room to novel products. These factors, which will be analyzed extensively in the following chapters, have become bases for the development of QFytoTera project.

This project refers to the development of an innovative natural repellent product derived from essential oils of Greek flora with hydrating properties and long-lasting action against mosquitoes. It analyzes the profile of the product, the steps of its development, its innovation, indicative cost and its foreseeable rise in the coming years.

Keywords

Natural repellent, control release system, nanoemulsion, reverse chemical ecology

Objective

The purpose of the project is to provide the reader with the necessary information on insect repellents, their drawbacks and their trends today. The current study gives information on their market, competition, distribution channels, in Greece and worldwide and finally the European regulations applicable to this type of products. Furthermore, the current study includes the indicative proportion of ingredients and estimated price of the final product as well as its potential for distribution in Greece and abroad, taking into account the problems and what is on the market today. All this information is useful for the reader to understand the idea of QFytoTera project and how it was developed,

analyzing as much as possible all stages of its growth, with the final aim of presenting the competitive advantage of the product and its superiority to competing products.

1. Mechanism of human-host recognition

Insects locate their human and/or plant-hosts by sensing certain volatile compounds emitted by them. Hematophagous mosquitoes use human volatiles to find their blood-host and receive blood meals that are rich in nutrients that mosquitoes cannot synthesize such us cholesterol an B vitamins (Gupta et al., 2007).

If we could succeed to disrupt this procedure, then disease vectors would lose their ability to orient themselves towards their human hosts, obtain a blood meal and transmit infectious parasites in the process.

Mosquitoes are attracted by carbon dioxide, which is released in large quantities when humans exhale and by the skin and lactic acid which is released in sweat. They are also attracted by skin temperature, moisture, dark clothing, floral and fruity fragrances. Mosquitoes prefer the increase in temperature, humidity and carbon dioxide. If their levels are reduced, then mosquitoes leave the area (Gupta et al., 2007).

The perception of odors by mosquitoes occurs through chemoreceptors present in their antennae (Patel et al., 2012). It is considered that insect repellents act through inhibition of the olfactory receptors (Gupta et al., 2007). Therefore, to prevent human target from mosquitoes, repellents are aimed at blocking receptor sites in mosquito sensory hairs (Gupta et al., 2007).

1.1. Vector-borne diseases

Mosquitoes are the primary vectors of multiple parasites and viruses that cause serious diseases to humans, such as Zika, malaria, dengue fever and West Nile encephalitis.

According to World Health Organization

• Vector-borne diseases account for more than 17% of all infectious diseases, causing more than 700 000 deaths annually.

• More than 3.9 billion people in over 128 countries are at risk of contracting dengue, with 96 million cases estimated per year.

• Malaria causes more than 400 000 deaths every year globally, most of them children under 5 years of age.

• Other diseases such as Chagas disease, leishmaniasis and schistosomiasis affect hundreds of millions of people worldwide.

• Many of these diseases are preventable through informed protective measures.

The globalization of travel, trade and migration as well as climate change have resulted in the introduction of exotic mosquito species in new areas and the emergence of new communicable diseases as well as the appearance of diseases in areas that had been previously eliminated (WHO, 2017).

The main mosquito vectors and the diseases transmitted by them are listed in Table 1 (WHO, 2017)

Table 1: Mosquito vectors and the diseases transmitted by them

Mosquitoes	*Diseases*
Aedes	*Chikungunya, Dengue fever, Lymphatic filariasis, Rift Valley fever, Yellow fever, Zika*
Anopheles	*Malaria, Lymphatic filariasis*
Culex	*Japanese encephalitis, Lymphatic filariasis, West Nile fever*

1.2. Repellents

Natural and synthetic insect repellents are hydrophobic volatile substances, slightly diluted in water, that in a certain concentration repel mosquitoes effectively. The majority of insect repellents, are active in a concentration above 10%. They have an odor unpleasant for mosquitoes and form a protective layer over the skin, thus reducing landing and biting of mosquitoes (Islam and Tavares et al., 2017, 2018). Therefore, the use of insect repellents is expected to reduce the infectious diseases that are caused by mosquito biting (Ribas and Carreño, 2010).

The ideal characteristics of an insect repellent are its ability to repel the largest number of species simultaneously, to be effective for eight hours, nontoxic, non-irritating for the skin and eyes, odorless to humans and unbearable to mosquitoes, water and abrasion resistant and of low cost. In addition, it should not affect clothing by staining it, bleaching it or puncturing it, nor leave oily residue on the skin, permeate the skin, and enter the bloodstream. Finally, it has to be environmentally friendly (Katz et al., 2008).

Finally, the presence of a contact repellent should be limited in the stratum corneum, which is the most superficial layer of epidermis (Pinto et al., 2017). Suitable formulation is able to make a repellent safer by preventing active skin permeation and systematic absorption.

1.3. Trends in repellents

Consumers have a particular preference for products that are safe, have cosmetic properties as easy application and reduced oily feeling to the skin, and are environmentally sustainable (Maia et al., 2011). Their demand for natural insect repellent products has increased over the last few years as they are considered to be safer than synthetic ones. For this reason, researches have been directed towards new insect repellents of natural origin. However, it must be noted that natural insect repellents must be subjected to safety evaluation tests similar to the synthetic insect repellents (Maia et al., 2011).

Although natural insect repellents are considered pure, healthy and environmentally friendly, they have a great disadvantage, namely high volatility after skin application, which leads to reduced protection time (Tavares et al., 2018).

Several studies have been carried out to reduce the volatility of essential oils present in natural insect repellents. These studies concern new formulations which encapsulate both essential oils and synthetic substances, based on controlled release systems (CRSs). In contrast, the conventional repellents contain free molecules having the danger of penetrating the skin and being absorbed by the bloodstream. Also they have large amount of alcohol and propylene glycol causing irritation to the skin and rapid evaporation. The new formulations are composed of materials which are able to protect and release the active substances by prolonging their action time (Tavares et al., 2018).

Polymer microcapsules (MCs) comprise natural and synthetic polymers, whose formulations resemble a cavity able to encapsulate volatile substances such as insect repellents. The formulations containing CRSs can gradually release the active substances increasing the duration of action, when applied to the skin. At the same time, the active substances are preserved in the skin surface, i.e. the cornea stratum where they act, in this way the dermal absorption is reduced. Finally, the MCs, can protect the active from environmental conditions as excessive heat, humidity, oxygen and light (Tavares et al., 2018).

In contrast to other lipid-carrier systems, the solid lipid micro and nano particles are formed by a solid lipid matrix. The advantages of these systems are include very good cutaneous biocompatibility, easy production of biocompatible lipids and controlled release of actives in the skin. These systems store enough repellent on the skin, capable of being released slowly, thus increasing the duration of insect repellent activity and reducing skin permeation (Tavares et al., 2018).

The liposome systems are structured by a lipophilic phospholipids bilayer and a hydrophilic aqueous core. It's ideal to use them as vehicles to transfer hydrophilic, lipophilic drugs and repellents to the skin, because they are biocompatible and they are capable of having a large supply of active on the skin extending its slow release. The benefits of encapsulated repellents by liposomes are the extended release, the prolongation of the action time, the reduction of skin permeation, toxicity and volatilization rate (Tavares et al., 2018).

The hydrogels based on Pluronic F127, polymer surfactant, are nanostructured micellar gels and are used as repellent vehicles. The Pluronic F127 it's able to structure micellar gel for assimilating lipophilic active substances such as repellents. The latter form a film in the skin that reduces active evaporation, thus increases the duration time

of the repellent action. Dermal absorption is reduced and the repellent release is extended (Tavares et al., 2018).

Cyclodextrins are cyclic oligosaccharides D-glucopyranose containing a hydrophilic surface and a hydrophobic cavity. There are several types of cyclodextrins depending on the number of D-glycopyranose units. Insect repellents are small hydrophobic molecules thus are suitable for complexation with cyclodextrins; the complexing is done with several techniques (Tavares et al., 2018).

As mentioned in the characteristics of the repellents in section 1.2, it is understood that acceptable dermal delivery vehicles are needed. For this reason nanoemulsions are used as vehicles for dermal administration because they have a good dispersion of lipophilic substances (such as insect repellents) in water in the form of nanometric droplets and are more stable than classic emulsions. These systems are able to be used as vehicles for skin administration as they exhibit high stability, low viscosity, easy spread in the skin, without leaving spots and their making is easy by high and low energy consumption methods. (Tavares et al., 2018).

Finally, all encapsulation techniques reported above have the effect of increasing the persistence of the active substance in the skin. As a result, besides increasing the insect repellent effect they improve the cosmetic appeal of the products (Gupta et al., 2007). The importance of the cosmetic properties in the products will be analyzed in next sections.

Annex 1 Table 2 presents the encapsulation and new formulations attempts of insect repellents.

1.4. OBP Proteins as molecular targets

Insect olfaction is a legitimate biotechnological target in the effort to reduce the spread of insect-transmitted infectious diseases. For this reason, research is being made to discover new insect repellent compounds which have a chemical affinity with key proteins involved in insect olfaction.

Odorant-Binding Proteins (OBPs) that mediate the first step in the olfactory signal transduction cascade of insects have been shown to play a central role in olfactory

recognition, thus becoming the target of choice for discovering new allelochemicals (Drakou et al, 2017; Thireou et al, 2018; Tsitsanou et al, 2013; Tsitsanou et al, 2012; Zographos et al, 2018). Figure 1 illustrates the route followed by the mosquito's olfactory molecules in sensillar lymph space.

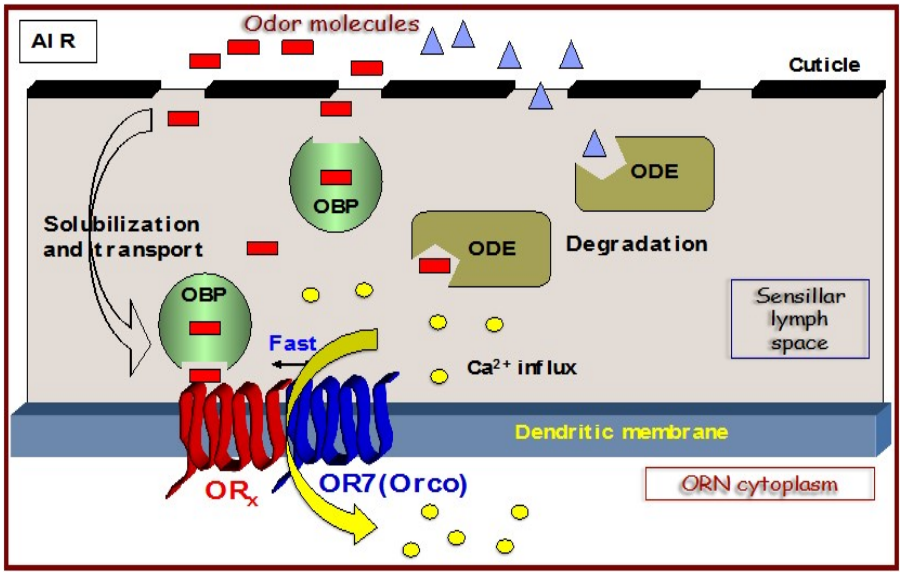


***Figure 1**. Current understanding of the perireceptor events that take place in the lymph cavity: Specific interactions between small molecules and proteins must take place for depolarization of the ORN membrane to occur. The hydrophobic odor molecules that would stimulate this particular sensillum (red bars) entering the sensillar lymph cavity from the outside air via cuticular pores, are immediately captured by OBPs with binding specificity for these odorants. The binding of the odors by OBPs increases their effective solubility and facilitates their transport through the hydrophilic environment of the sensillar cavity before delivery to the ORs located on the dendritic membrane of the ORNs. ORs detect odorant compounds and transduce olfactory signals to the brain to mediate insect behaviors. ODEs are thought to degrade odorants that are not bound by OBPs (blue triangles) or released after stimulation of olfactory receptors.*

OBPs play a major role in the olfactory system as they are selectively linked to the candidate ligands. The odors that mosquitoes can detect are higher in number than the OBPs; the latter recognize specific classes of odors and can distinguish semio-chemicals of different chemical structures. ORs have a large spectrum and their specificity vary from narrow to broad tuning. The perception of a specific odor is likely to occur by interplay between OBPs and ORs as none of them are extremely specific. Has been proposed that OBPs-ORs system may function as a two-level filter with few common ligands. Therefore, OBP-structure-based design can be used to propose novel

leads with improved binding affinity and specificity that will interact with Ors to trigger a behavioral response.

On the one hand, among insect repellents of similar volatility those that have increased chemical affinity for OBPs could be used at lower concentration and be detected over longer distances. On the other hand, insect repellents with lower volatility could provide a longer-lasting protection than conventional plant derived products. These repellents can be used as a holistic product for protection against mosquito-borne diseases (Tsitsanou et al., 2012).

The first crystal structure of an olfactory macromolecule with a repellent was protein 1 from *Anopheles gambiae* (AgamOBP1) with DEET (Tsitsanou et al., 2012), Today, the only available studies on 3D-crystal structures between an olfactory protein and a repellent are those of odorant binding protein 1 from *Anopheles gambiae* (AgamOBP1) with DEET (Tsitsanou et al., 2012), 6-methyl-5-hepten-2-one (6-MH) (Murphy et al., 2013) and icaridin (Drakou et al., 2017).

1.5. Methods for the discovery of new active substances

There are various methods for the development of new active substances in the chemical, pharmaceutical and cosmetic fields. Some of them are

- ***In vitro* Screening:** The study of biological effect of a number of compounds at one or more molecular targets to select the most active of them.
- **Virtual Screening:** The evaluation of very large libraries of compounds using appropriate software. Virtual screening can be ligand-based or target-based or both.
- **Rational design:** Based on the knowledge of the pathophysiology of the disease, the macromolecules and small molecules that involved and their function.
- **Structure-based drug design (SBDD):** The design based on the structure of the target protein and of the ligand in the binding site. This technique

involves knowledge of the 3D structure of the receptor (target protein) ligand complex and synthesis of appropriate ligand derivatives with enhanced affinity and specificity.

- **Ligand-based drug design (LBDD):** Exploits chemical and structural information on known bioactive ligands for selected molecular targets.
- **Fragment-based drug design (FBDD):** It is based on the use of specialized biophysical methods for the detection of low molecular weight compounds (structural fragments, fragments) that are about half the size of a typical pharmacomorph and interact weakly with the pharmaceutical target.
- **Drug-likeness**: The physicochemical properties of drugs are limited to a narrow range called a physicochemical space of similarity (Dimopoulos, et al., 2015).

The methods mentioned above may also be applied in various other ways such as by combining each other or by applying variants.

1.6. OBP-based Reverse Chemical Ecology for discovery novel mosquito repellents

A similar approach as that described in section 1.5 for drugs can be applied to insect repellents. In this case, the macromolecular targets are OBPs and the small molecules are volatile compounds. This approach is called OBP-based Reverse Chemical Ecology. This section will analyze this approach, which was used to discover novel repellent substances.

Reverse chemical ecology combines modern methods of Computational chemistry, Protein Crystallography and macromolecule NMR. In this approach, OBPs which are expressed in the female mosquito and whose concentration changes after blood meals, serve as the molecular targets. Odorant molecules of plant origin with repellent activity are used as parental compounds for ligand-based studies. The aim is the discovery of

novel natural mosquito repellents of unexploded Greek flora with lower volatility and increased protection time.

An approach that was successfully applied by combination of ligand and structure-based techniques was described by Thireou et al., 2018, for the discovery of new bioinspired synthetic mosquito repellents with increased time protection and lower volatility compared to plant insect repellents.

The screening protocol comprises two filter steps.

The first filter is based on eleven (11) known plant insect repellents. These compounds are used as reference molecules for *in silico* screening of a chemical library composed of 42,755 synthetic molecules available from Key Organics Ltd.

The program OMEGA 2.5.1.4 (OpenEye SWcientific, Santa Fe, NM, USA) was used to generate 3,725,390 and 300 molecular conformations of the target and parental compounds respectively. The program ROCS (OpenEye SWcientific, Santa Fe, NM, USA) was used to calculate the Tanimoto_Combo score (ROCS Combo) to identify molecules from the library showing high shape and chemical similarity with the 11 parental compounds. For each of the eleven parental compounds, the top ten hits, those with the highest score, were selected resulting in a set of 110 compounds. The compounds predicted to be toxic were removed, using the program FILTER which resulted to 48 compounds, of which 33 were unique.

The second filter is based on the ligand's binding mode to the *Anopheles gambiae* odorant binding protein (AgamOBP1) relative to that of DEET and icaridin. The 33 compounds were docked on AgamOBP1 crystal structures using AutoDock (Morris et al., 2009). 16 compounds with high binding mode similarity and docking scores were selected for further *in vitro* binding studies.

As a result of this research the compound KO9, a derivative of cuminic acid, exhibits higher affinity than DEET and icaridin for *AgamOBP1* and ten times lower volatility compared to common insect repellents including the natural parental compound cuminic acid (3.8x10-3 mmHg).

1.7. Nanoemulsions

As mentioned in section 1.3, there is an increased interest of consumers in plant repellents. However, natural insect repellents have increased volatility and sensitivity. Therefore, formulations have been developed to increase their duration of action against insects. The plant- based repellent products indented to be developed in this project will use the nanoemulsion formulation. For this reason this section will analyze nanoemulsion technology.

Nanoemulsions are emulsions having droplet size at the nanoscale. They are colloidal dispersions composed of two immiscible liquids (water and oil) and surfactants in which one liquid is dispersed as droplets in another liquid. The dispersed nanodroplets are spherical and their diameter typically ranges from 20 to 200 nm. (Bouchemal et al., 2004, Mason et al., 2006). They have low viscosity and can be prepared either by high-energy emulsification methods (high-pressure homogenizers, microfludizers and ultrasound generators) or by low energy methods (spontaneous emulsification, phase inversion temperature) (de campos et al., 2012). Depending on the size of the dispersed droplets, nanoemulsions are transparent, translucent or milky (Solans et al., 2005). Depending on proportion and chemical nature of the components, nanoemulsions can be classified into two types, namely water-in-oil (w/o) and oil-in-water (o/w). Their uniqueness is due to the fact that they can be either kinetically or long-term physically stable (Bouchemal et al., 2004). The stability of nanoemulsions can be regulated and sustained for a lifetime of months to years (Gupta et al., 2016).

During the past few years there has been an increasing interest in the utilization of nanoscale liquid-in-liquid dispersions in a variety of technological applications including drug delivery systems, functional food formulations and nanoparticles formation. Due to their long-term stability over storage and an improved high bioavailability, nanoemulsions have attained particular interest as delivery systems for the encapsulation and protection of bioactive compounds. In addition, oil-in-water (o/w) nanoemulsions can be diluted with water without changing their droplet size, as opposed to micro emulsions (Gutiérrez et al., 2008, Fermamdez et al., 2004). In general, o/w nanoemulsions offer a good potential in food, drug and cosmetic applications especially for the encapsulation of lipophilic compounds. Nanoemulsions are ideal for cosmetics and food because they are less sensitive towards dilution, temperature and pH changes as compared to other colloidal dispersions (Gupta et al., 2016).

1.8. Application of nanoemulsions in cosmetics

The product to be developed will be an insect repellent, which, as known, are not cosmetic products. However, the term ‘’cosmetic properties’’ is often used in these products, wishing to describe the properties of the product formulation. The performance of the final product can be affected by the composition and the properties of the formulation. However, the subjective perception of the product is sometimes different (e.g., fragrance, oiliness, color). The new formulations of insect repellents, as mentioned in section 1.3, could increase the persistence of the active ingredient on the skin and also improve the cosmetic appearance of repellent products. For example, they can reduce the odor, the greasy textures in the skin and also provide a better resistance to water and friction. (Gupta et al., 2007). As has been stated in the previous chapter, the encapsulation technology used in the final product of this work is based on nanoemulsification. This section will mention the application and suitability of nanoemulsions in cosmetic products. Although the final product will not be a cosmetic but a repellent with cosmetic properties, it is important to note that these systems are effective carriers of compounds with cosmetic properties, as well.

Oil-in-water (o/w) nanoemulsions are suitable for the efficient delivery of lipophilic active ingredients through the skin. The advantages of nanoemulsions that make them ideal in the application of cosmetic and personal care products is the use of lower concentration of surfactants and the higher stability as compared to other types of emulsions. Also, they possess the features of low viscosity, lack of irritant and toxicity, transparent appearance and versatility of formulation as foams, creams, liquids and sprays (Ribeiro et al., 2015). Oil-in-water nanoemulsions are fluid and offer a pleasant sensation to the skin as they have low concentration of oils (Pereira et al., 2016). Finally, they can also deliver alcohol free fragrances, essential oils and a variety of other compounds used in the production of cosmetics (Bouchemal et al., 2004).

However, the very small size of their droplets, favors penetration through the ‘’rough’’ skin surface and this could enhance penetration of actives. The large surface area of the whole emulsion system, its low surface tension and the low interfacial tension of the oil droplets are possible to favour penetration of actives agents. To avoid this possibility, in the case of insect repellents a suitable choice of surfactants and active

substances will be taken into consideration as well as the high molecular weight and high lipophilicity of a substance which impede rapid transdermal absorption.

Nanoemulsions are colloidal dispersions with a wide range of possibilities for innovative applications in the cosmetic and dermatological fields (Yukuyama et al., 2016). Cosmetic industry due to the features mentioned above, has an increased interest in nanoemulsions which have been tested for easy application and skin hydration (Gupta and Pereira et al., 2016).

In general, cosmetics based on either o/w or w/o emulsions have two basic functions to offer, a) skin hydration and b) formation of an oil barrier on the skin surface suitable for dry skin protection. As it is well known, cosmetics contain amounts of both oily and water-soluble ingredients; emulsions can combine them in one homogeneous formulation and are effectively used in a variety of cosmetic products such as lotions, crystal-clear gels, and transparent milks. Depending on what the desired product requirements and the type of skin to be applied to, the appropriate rheological properties and the type of emulsions (w/o, o/w) are applied. The overall performance and the easy application of the product on the skin mainly depends on the rheological properties of the final emulsions (Magdassi et al., 1997).

Exposure to sunlight and other atmospheric conditions, cause adverse effects on the skin; botanical extracts exhibit a variety of beneficial properties in cosmetic products, photoprotection, antimicrobial, antioxidant, and moisturizing activity. As a result, acting on skin areas creates softening, healing, rejuvenating and protective effects (Chanchal et al., 2008). As mentioned in section 1.3, essential oils are sensitive and have high volatility. Also herbal extracts and phytochemicals have difficulty in being absorbed and dissolved. As a result, the formulation of cosmetic products has to provide them with protection and at the same time must enhance their effective cosmetic properties to the skin. Conventional formulations of cosmetics do not possess these functions as they usually display low efficiency to the skin. For this reason, innovative approaches have been made to improve the efficiency, performance and effectiveness of administration of bioactive substances and extend the action of cosmetic products for skin application. (Chanchal et al., 2008).

An approach of formulation that provides the above qualities for cosmetic products is based on the application of nanoemulsions. They can be used for both lipophilic and hydrophilic substances increasing their bioavailability, improving the absorption and

dissolution of herbal extracts and phytochemical deficiencies and also have good aesthetic properties, e.g. transparent visual aspect and low viscosity (Chanchal et al., 2008). In cosmetic products more studies have been conducted with o/w than w/o nanoemulsion types.

High and low energy emulsification methods have been applied for the fabrication of nanoemulsions to be used in cosmetic products. The high-energy methods using either high pressure homogenization or ultrasonication result in stable colloidal dispersions. In the low-energy methods, the nanoemulsion is formed using gentle mixing or low energy. This method contains spontaneous and phase inversion methods. As a process it is desirable because it can save energy for the production of large-scale nanoemulsions and it is a mild process ideal for sensitive molecules. The method to be used depends on the physicochemical properties of the surfactants. (Yukuyama et al., 2016).

A relevant example of a successful application of nanoemulsions in cosmetics is the following.

A type of dermal formulation, which consists of the positively charged o/w nanoemulsion cream containing phytosphingosine incorporating ceramides and SC lipids (PNSC cream), was developed. The results of this formulation are that the stratum corneum lipids and the phytosphingosine inducing the positive charge of nanoemulsions play a decisive role to upgrade the skin elasticity and humidity. These positively charged o/w nanoemulsions are promising carriers for dermal applications (Yilmaz et al., 2006).

1.9. Applications of nanoemulsions in repellents

As analyzed in sections 1.3, 1.7 and 1.8, nanoemulsions are ideal encapsulation vehicles for many bioactive substances including proteins, antioxidants, vitamins, drugs and also insect repellents that are of interest in this study. Some successful attempts made to encapsulate essential oils with repellent action through nanoemulsions will be mentioned below (Tavares et al., 2018).

A nanoemulsion with essential oils aiming to repel *Aedes aegypti* was developed by Sakulku et al 2009. This was prepared with the high-pressure homogenization

method and contains citronella oil, hairy basil oil and vetiver oil. The formulation was assessed for its stability, droplet size, release of the active substance and its effective action. The results have shown that this is a promising formulation for the repulsion of the *Aedes aegypti* (Tavares et al., 2018).

Another approach was developed using the hydrodynamic cavitation process to fabricate nanoemulsions consisting of Tween 80 and Span 80 as surfactants and citronella oil repelling mosquitoes as the oil phase (Agrawal et al 2017). The formulation was evaluated and the result was that stable and efficient nanoemulsions were produced (Tavares et al., 2018).

The nanoemulsion that was developed by Milhomem-Paixão et al 2017 contains Kolliphor ELP surfactant, using the phase inversion temperature emulsification PIT method. Also, it contains andiroba oil for repellent activity. Although the biological tests are at an early stage, it is considered that the oil in nanostructured form is a promising formulation in cosmetic and pharmaceutical products (Tavares et al., 2018).

1.10. Citridiol

The insect repellent product to be developed and described in subsequent sections will have a plant-derived active insect repellent, Citridiol. This section will provide important information about this active.

The leaves of the lemon eucalyptus tree (Eucalyptus citriodora or Corymbia citriodora) with the accelerating ageing process produce lemon eucalyptus oil with the trade name ''Citridiol®''. The active repellent ingredient of this oil is the para-menthane 3, 8 diol (PMD) (Maia and Moore et al., 20011). Citridiol contains 26%-30% PMD as active ingredient[1] (Gupta et al., 20017).

Citridiol offers very high repellent protection for a wide various of insect vectors, its action lasts for several hours in contrast with other essential oils whose repellent action last for about one hour. Also, it has lower vapour pressure than other plant oils which contain volatile monoterpines. Citridiol is proven safe for human health, it's able to

[1] ''Citridiol and PMD actually refer to the same active substance. Hereinafter the term Citridiol will be used for both PMD and Citridiol to avoid confusion for the readers''

protect them from Malaria and West Nile and is recommended by CDC (Centres for Disease Control) to be used in endemic areas. (Maia and Moore et al., 2011).

1.11. Encapsulation of Citridiol

Citridiol is a substance widespread for its efficacy against mosquitoes, used in many repellent formulations. For example, Drapeau and colleagues produced microemulsions containing 25% citridiol (Drapeau et al., 2009). The repellent microemulsion with a droplet size of 17 nm was produced using the ternary phase diagram method. These systems according to the EPA protocol were tested in the mosquito *Aedes aegypti*, to determine the duration of action time and it was estimated at 385 minutes of protection against *Aedes aegypti*. With the related investigations it has been realized that these alternative formulations used in essential oils can effectively protect against mosquitoes (Tavares et al., 2018)

2. Repellent Market

2.1. Top factors impacting world mosquito repellent market

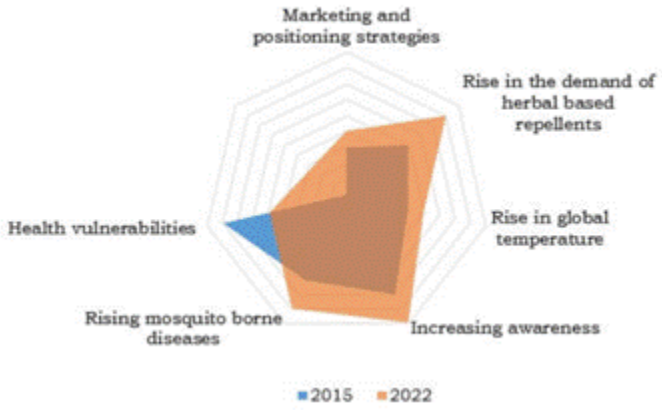
- Over the recent years, the global mosquito repellent industry has been growing rapidly. The recent outbreak of mosquito-based Zika virus, as well as the Chikungunya, Yellow Fever and Malaria, has resulted in an increase in the global mosquito repellent market.
- Raising awareness and knowledge of people on vector-borne diseases has increased the demand for insect repellents
- Climate change like planet's overheating will increase the population of mosquitoes, hence the market for insect repellents.
- Developed countries show preference to herb based creams, oils and sprays. This trend is likely to increase in the coming years.

- Marketing and positioning strategies will continue to propel the demand of mosquito repellents in the future.

(Source Allied market research, 2016).

Figure 2 illustrates the factors affecting the global mosquito repellent market.

Figure 2: Top factors impacting world mosquito repellent market, (Source AMR analysis 2016, and accessed 25/2/2018)



2.2. Global market

The global market and its size are analyzed in the following charts. Chart 1 represents the expected increase in the global mosquito repellent market in CAGR %[2], (Sources: Technavio market research Company 2016, Zion market research 2017, Allied market research 2016, Orbis research 2017, ReportsnrReports 2017, Ibisword 2017, Research and markets 2016, Knowledge based value research 2017, Newsient mosquito repellent market 2018, Abnewswire insect repellent market 2017)

Chart 2 represents the expected increase in the global mosquito repellent market in USD billion, (Sources: Zion market research 2017, Allied market research 2016, Orbis research 2017, ReportsnrReports 2017, Ibisword 2017, Knowledge based value research 2017, Newsient mosquito repellent market 2018).

[2] CAGR%: Compound Annual Growth Rate

In addition to the predicted worldwide increase in the insect repellent market, it is also important to take into account the expected growth in the European repellent market. In Chart 3 the European repellent market in CAGR%, for the forecast period 2017-2023 and 2015-2023 is illustrated (Sources: Knowledge Based Value Research 2017 and Transparency Market Research 2016).

Chart 1: Predicted increase in the word mosquito repellent market (CAGR%).

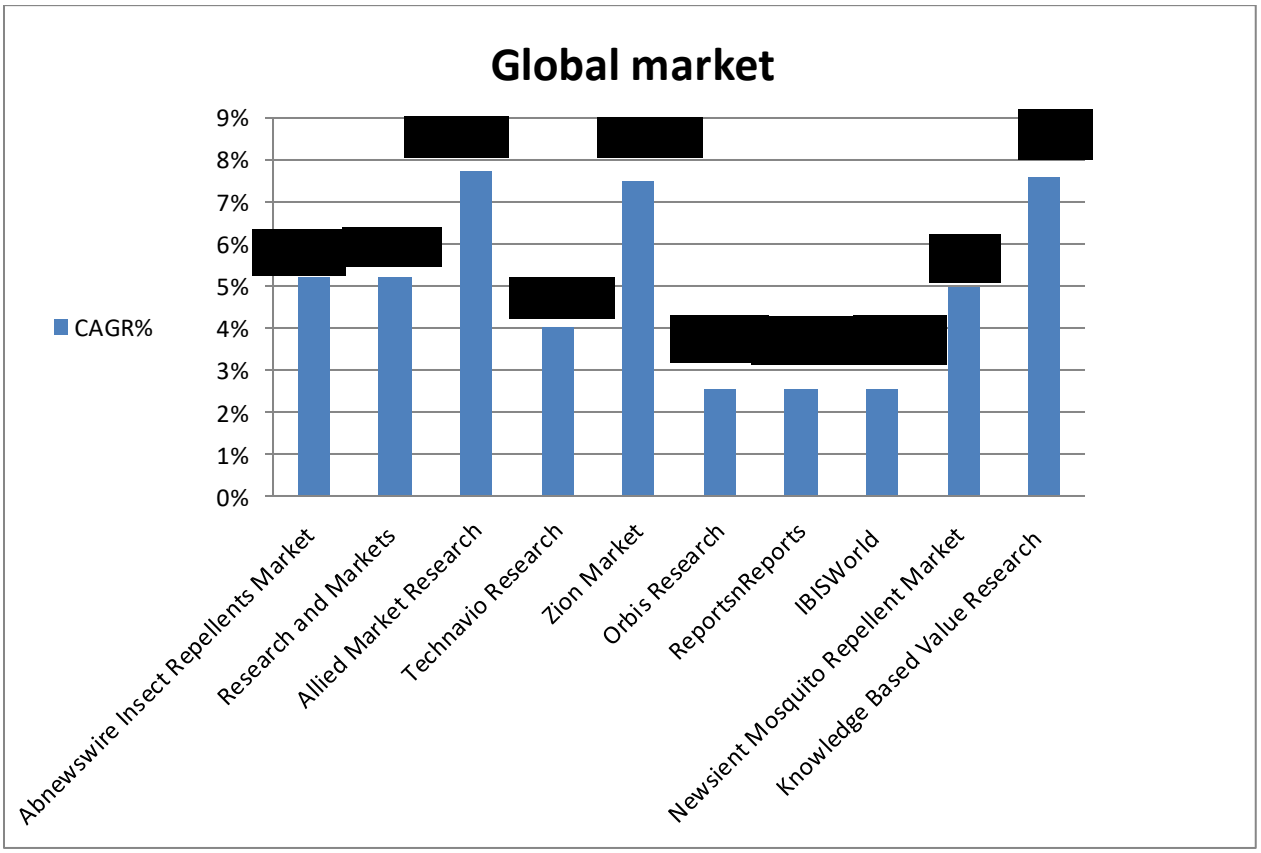


Chart 2: Predicted increase in the word mosquito repellent market (USD billion)

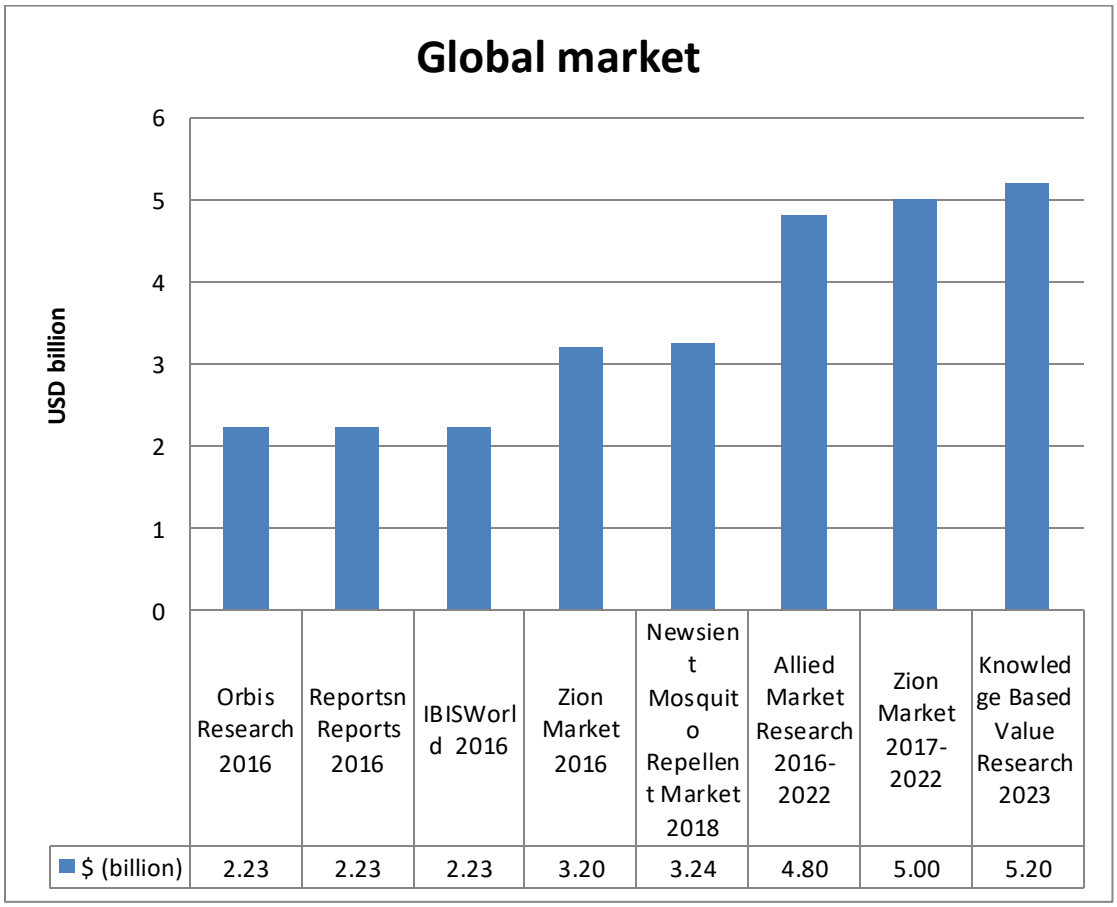
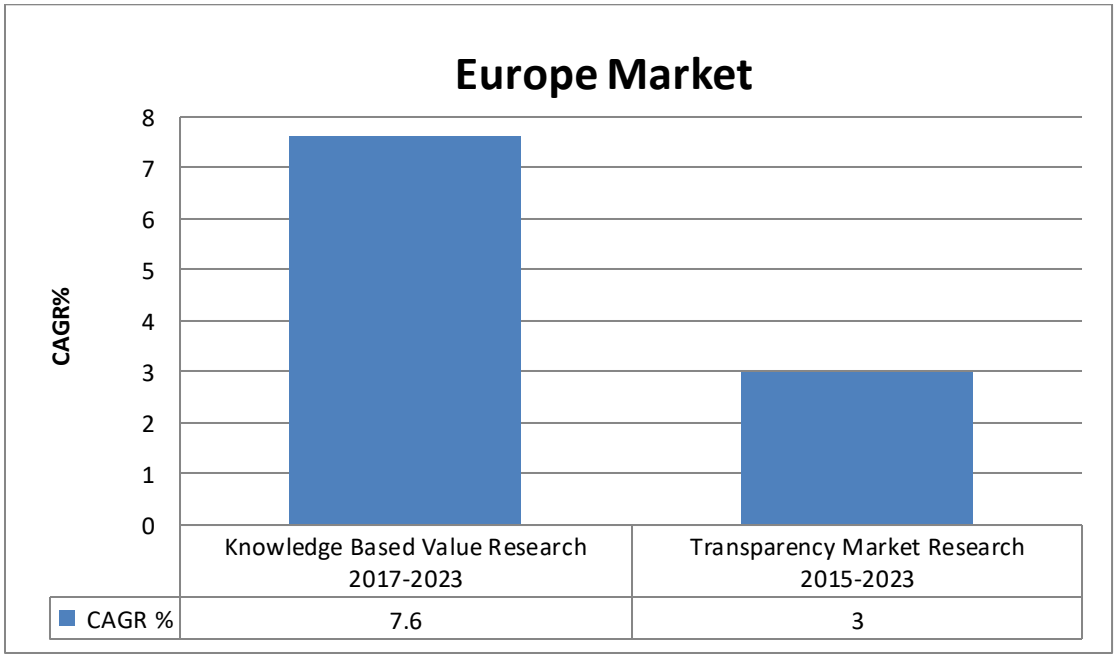


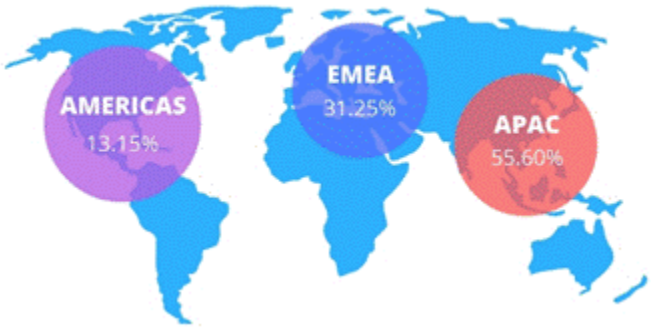
Chart 3: Predicted increase of the mosquito repellent market (CAGR %) in Europe.



2.3. Geography market segments

Figure 3 shows the distribution of the world market regions.

Figure 3: Global mosquito repellent market by geography segmentation (% share) in 2016, (Source Business Wire 2017, accessed 20/1/2018)

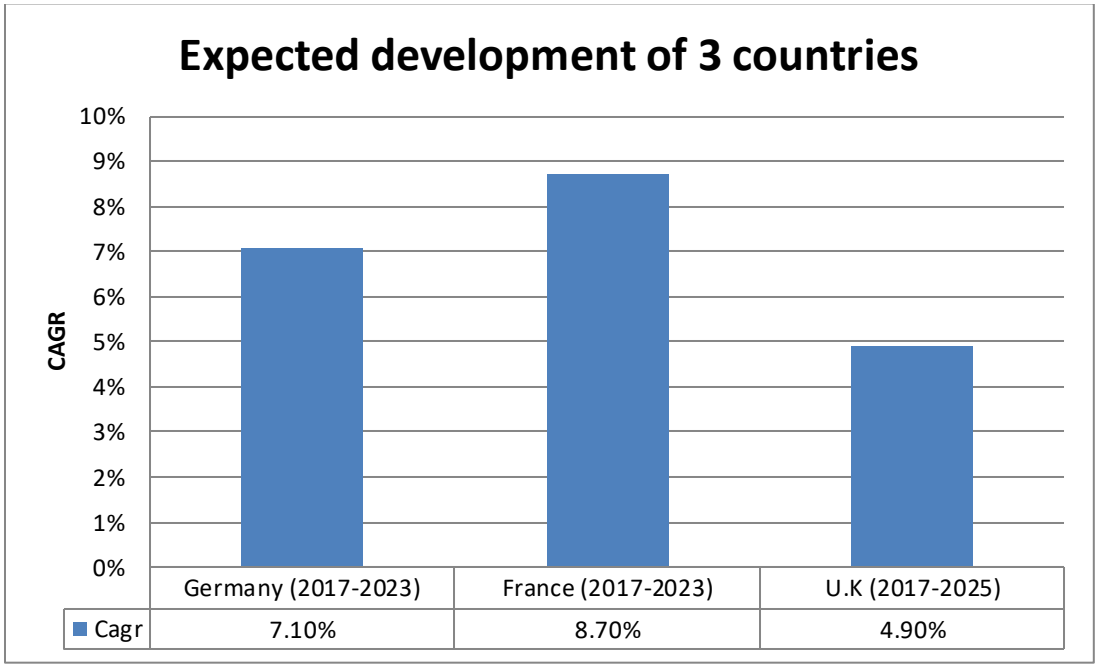


- APAC includes the countries China, Japan, India, Malaysia, Singapore, Australia and Rest of Asia Pacific. It has the largest share of the world market for insect repellents in excess of 55% in 2016 and is expected to grow at a CAGR of 5.49% by 2021. India and China have the greatest demand in this region and the products that are most in demand in developing countries are coils and then mats (Source Business Wire 2017 and Zion market research 2017). In China insect repellents are the most demanded product, the household insecticide market witnessed a growth rate of 6.2% in 2015. That's why China has the largest market share within APAC.
- Americas include the countries, North America (US, Canada, Mexico and Rest of North America) and Latin America. This market is expanding, with many vendors to enter the market with new innovative products especially in Latin American regions. For example, MosquitNo with active substance Saltidin® (Icaridin) has been growing rapidly in Latin America and its company also offers other insect repellent products (Source Business Wire 2017). In the US, new innovative products attracting customers continuously. With a share of round 70% the US was the largest market in

the Americas in 2015. For example, Spectrum Brands with novel product AccuShot, push-button spray with refills, brought revenue to the market and thus increased the entry of new products into the market (Source Kbv research 2017). Brazil following the US, because of frequent incidences of dengue, has a high market of insect repellents. The top players are two namely S. C. Johnson & Son with its flagship brands Baygon and Raid and Reckitt Benckiser Group with its flagship brand Mortein (Source Kbv research 2017). The North America market is expected to witness a CAGR of 8.1% during 2017-2023 (Source Knowledge Based Value Research 2017).

- EMEA includes the countries, Germany, UK, France, Russia, Spain, Italy and Rest of Europe. Due to rising malaria incidents, chikungunya, and West Nile fever in Europe, consumer awareness is increasing, driving the growth of the repellent market. The market in Europe was valued at 1.40 billionn US$ in 2014 and is expected to reach S$1.82 billion by 2023, increasing at a CAGR of 3.0% from 2015 to 2023 (Source Transparency Market Research 2016). France has the highest consumption of insect repellents in the region. Their weather favors the growth of mosquitoes, so the need for insect repellents is increased. S. C. Johnson & Son, holding over 65% of the market in 2015. France market is expected to witness a CAGR of 8.7% during 2017 – 2023 (Source Kbv research 2017). Germany, due to climatic conditions, has an increased number of mosquitoes and as a result it has the highest demand for insect repellent after France (Source Business Wire 2017). A CAGR of 7.1% during 2017 – 2023 is expected to be witnessed (Source Kbv research 2017). The U.K. market for insect repellents, which stood at US$ 66.4 million in 2016, will expand the opportunity in this market to US$100.0 million by the end of 2024 (Source Transparency Market Research 2017). Chart 4 illustrates the expected growth in the three countries with the largest insect repellent market in Europe (Sources Kbv research 2017 and Transparency Market Research 2017).

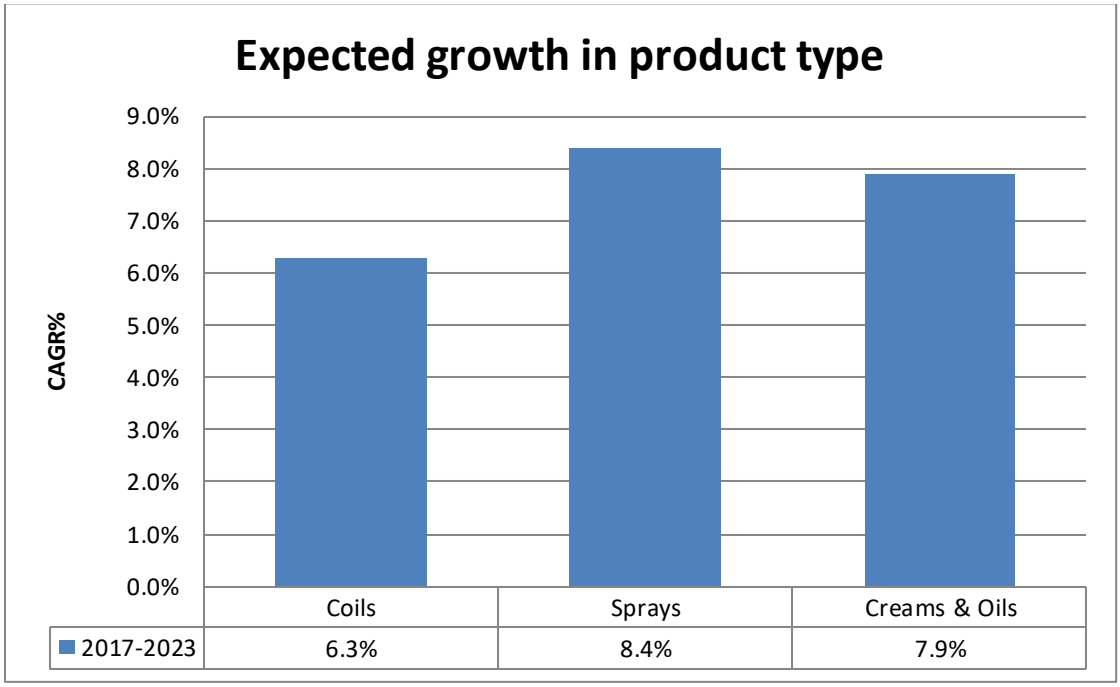
Chart 4: The expected growth of the three countries in the insect repellent market, (Sources Kbv research 2017 and Transparency Market Research 2017)



2.4. Segmentation by product type

The segmentation of product type of mosquito repellents are, colis, mats, sprays, vaporizers and creams. Middle and lower income groups prefer coils due to lower cost. For this reason the coil market dominated the Global Mosquito Repellent Market in 2016; Chart 5 depicts the intended development, CAGR%, in a product type (Source Knowledge Based Value Research 2017). Moreover, oils and creams have a large segment because they are economical, easy to use, and remain effective for several hours (Source Market Research Report Search Engine 2018). China and India have a high demand for mosquito repellent products such as sprays, creams and oil (Source Abnewswire 2017).

Chart 5: Expected growth (CAGR %) in product type (Source Knowledge Based Value Research, accessed 6/3/2018)



2.5. Segmentation by channels of distribution

The channels of distribution are large retail stores, small retail stores, specialty stores and online stores. The online distribution channel will be highly developed due to the increasing use of the internet in the daily lives of developing countries (Source Allied market research 2016). People are now dependent on the online platforms and it has been observed that people today are easily influenced by anything displayed on websites (Source Business Wire 2017). However, the retail stores are currently dominating the market (Source Allied market research 2016).

In the period until 2023 the small retail stores are expected to reach $1,116.5 million and CAGR of 7.6%, the online store is expected to increase 7.7-7.8% and the large retail store market will dominate the global mosquito repellent market in sales at the same period (Source Knowledge Based Value Research 2017).

2.6. Segmentation by body worn and non- body worn products

Insect repellents are divided into two major categories, non-body worn and body worn.

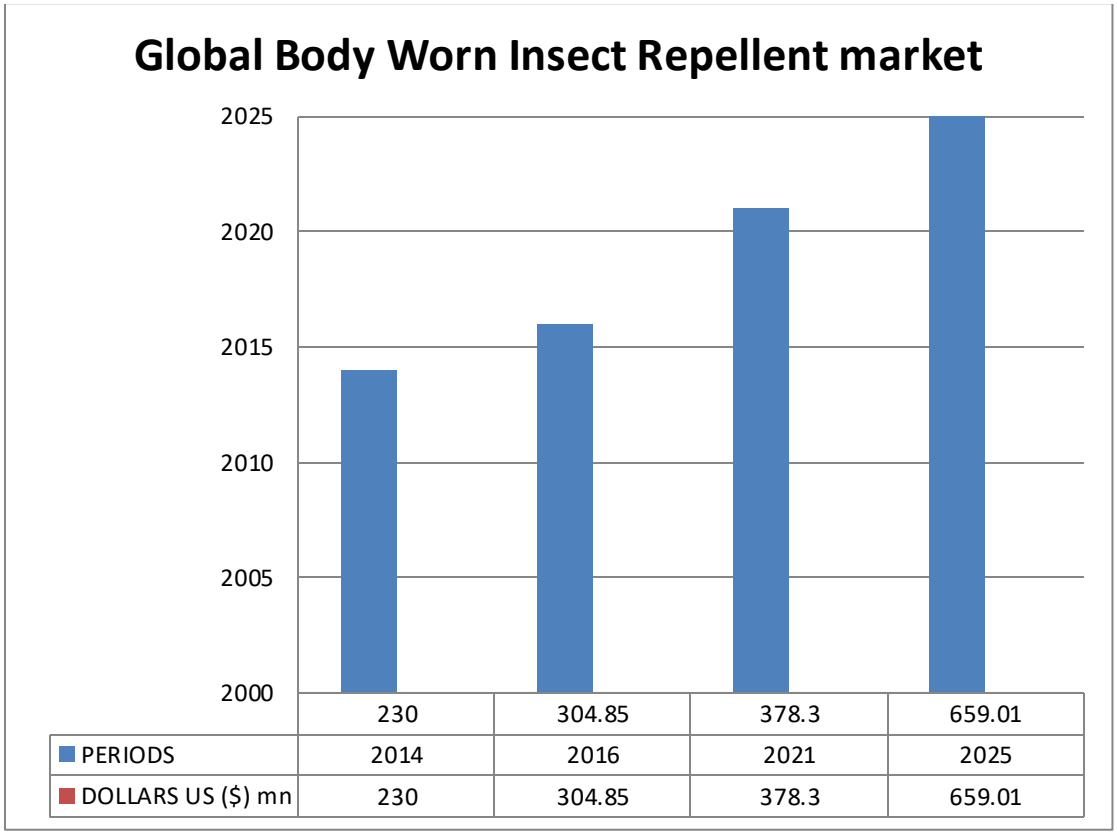
Non-body worn products include coils, mats, sheets, electric/liquid vaporizers, and aerosol sprays. Among them sprays are those that have the biggest demand. The active ingredients of non-body worn are malathion, carbaryl and pyrethrin among others. Pyrethrin held the majority market share in 2016 (Source Market Research Report Search Engine 2018). Products of this category have low prices and are easy to dispose in online shops, retailers and supermarkets. That's why they are being developed more (Source Transparency market research 2016).

Body worn insect repellents include many substances such as deet, icaridin, IR 3535, citronella oil, citridiol, plant oil and others. Citridiol, which occupies the largest market share in natural insect repellents for 2016, has antibacterial properties, invigorating immune system response and other benefits (Source Market Research Report Search Engine 2018). The global body worn insect repellent market depicted in Chart 6 is expected to surge at a CAGR of 9.29% (Sources Transparency market research 2017 and The statistics Portal, 2018).

Plant-based substances are commonplace body-worn insect repellents, sold as oils & creams. The environmental consciousness of consumers has increased their preference for natural products. For this reason they are expected to grow globally at a CAGR of 10.29% during 2017-2025. (Source Transparency market research 2017).

North America owned the maximum market share in this market in 2014 and it is expected to be 34.1% in 2021, followed by Asia Pacific, which is expected to have 30.3% share of the global market in 2021. The increasing awareness of consumers' leads to the growth of the body-worn insect repellent market in North America (Source PR Newswire 2016).

Chart 6: Global body-worn insect repellent market. During 2016-2025, (Source Transparency market research 2017, accessed 6/3/2018), (Source The statistics Portal 2018, accessed 10/3/2018)



2.7. Segmentation by leader vendors

According to Technavio market research the leading vendors in the mosquito repellent market are Godrej Consumer Products, Reckitt Benckiser, S. C. Johnson & Son and Spectrum Brands. Other vendors, Coghlan's, Dabur, Enesis Group, GLOBE-Janakantha, Goodluck Syndicate, Herbal Strategi, Hovex, Jyothy Laboratories, KAPI, Kincho, Kittrich, Murphy's Naturals, PIC, PT Mega Artha Perkasa, Quantum Health, TAINWALA, Thermacell, Vardhaman Remedies, Vijay International, Vin Corporation, Woodstream, and Zhongshan LANJU Daily Chemical Industrial (Source Tecnhnavio market research company 2016).

The insect repellent manufacturing industry has high barriers to surpass to enter the market. One of the largest potential barriers is the high degree of market share concentration. The top three major industry operators are estimated to account for

62.6% of total industry revenue, with the top two (Spectrum Brands and SC Johnson & Sons Inc) accounting for over 50.0% combined. These companies operate on a global scale and have a large amount of capital and resources at their disposal to research and create new, more effective products. In addition, capital intensity in the industry is high because of the financial burden associated with research and innovation. New operators must also establish a relationship with retailers and wholesalers to get their product on the shelves (Source IBISWorld 2017).

2.8. Leader vendors in Europe

In Europe 14 countries play the main role in the insect repellent market and these are, Germany, the U.K. France, Italy, Spain, Belgium, Switzerland, the Netherlands, Denmark, Norway, Sweden, Finland, Iceland, and the rest of Europe. The U.K is estimated to have the largest market share over the next few years.

Leading players in Europe are Avon Products Inc., S.C. Johnson & Son, Inc., 3M Corporation, E.I. DuPont de Nemours and Company, BASF S.E and Omega Pharma (Source Transparency Market Research 2016).

2.9. Innovative mosquito repellents

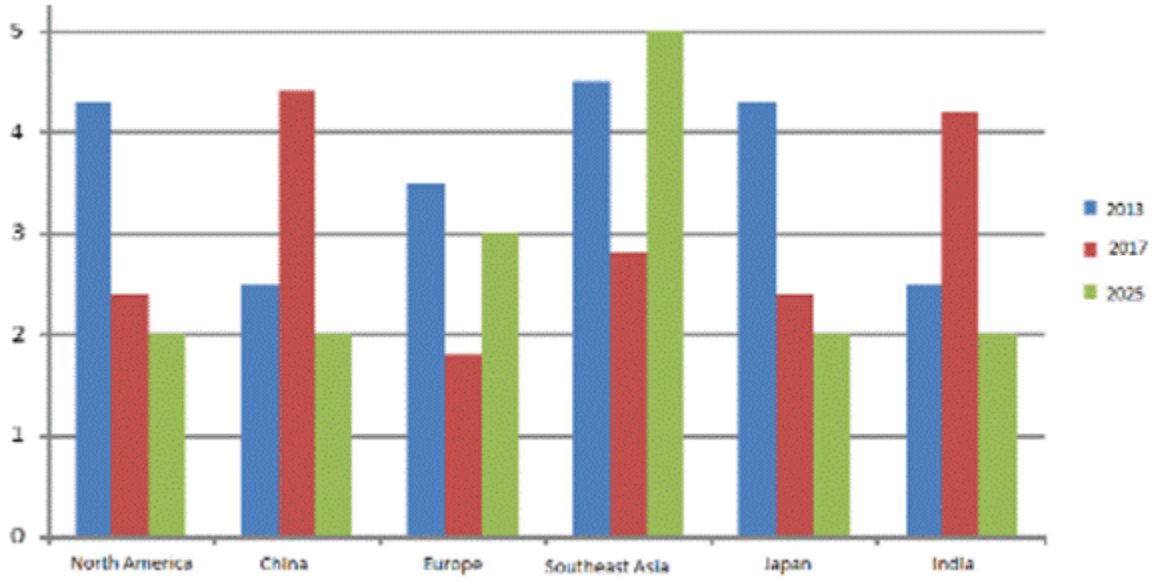
One of the latest developments is organic insect repellent, which is constantly increasing in demand. For example, Godrej Consumer Products launched its new range of mosquito repellents that are specifically meant for kids and are pediatrically certified (Source Business Wire 2017).

2.10. Citridiol in market share

The active substance which will be used in our product is citridiol. For this reason some information about its market and which companies use it in their products will be provided.

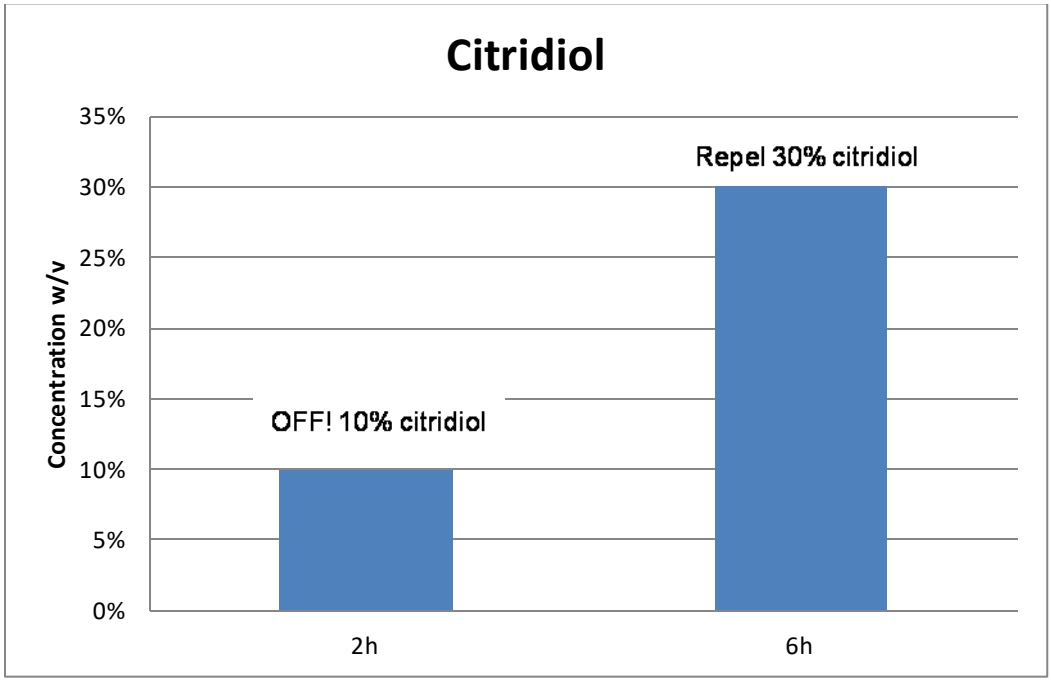
In Chart 7 the citridiol market segmented by regions 2013-2025 is depicted. Its market is predicted to grow at CAGR 10-15% in forecast period 2018-2023 (Source Reid W., 2018).

Chart 7: Citridiol Market Segmented by Regions 2013-2025, (Source Reid W., 2018, accessed: 10/5/2018)



Spectrum Brands have the most insect repellent products with citridiol in the market, which are sold under the brand names Repel and Cutter. Some studies claim that concentrations of 20-26 % citridiol may perform as well as 15-20 % DEET against mosquitoes (Wade et al., 2017). In Chart 8 compared commercial repellents, OFF! Botanicals Insect Repellent with 10% citridiol to products that contain 30% citridiol such Repel Essential Insect Repellent against mosquitoes and their data are depicted. (Wade et al., 2017).

Chart 8: Compared two commercial repellents for their duration action time against mosquitoes (Wade et al., 2017)



2.11. Top vendors

The following companies are the top vendors in the global citridiol market Spectrum Brands, Edens Garden, Sun Organic, Plant Therapy, Eucalyptus, REPEL, Now (Daily News KS 2017).

3. Greek Market

The charts and tables that are illustrated in Annex I were based on and formed according to the list of Greek Republic Ministry of Rural Development and Food, with insect repellent / attractive (PT19). In Annex I, Tables 3 and 4 depict the approved products (PT19) on the Greek market. The percentage of synthetic vs. natural repellent products in Greek market are presented in Annex I, Chart 9. The individual fragmentation of the two categories is illustrated in Annex I, Charts 10 and 11, while the

fragmentation of these two groups per product type is depicted in Annex I, Charts 12, 13, 14.

In Greece insect repellents are shrinking in value (4.8%) and in sales (1.7%) in branded products. Private labels also drop by 10.7% in value and 11.4% in sales. All items moved down, in value and sales, except for liquid repellents that rose up in sales 1.2%. Part of the reduction is due to consumers' tendency for alternative ways of protection such as screen door. But because of climate change such as more humid climate in Greece and the outbreaks of mosquito transmitted diseases such as West Nile fever, contributing to the growing concern of the people, it is estimated that insect repellent sales in the coming years will increase. Sales figures of 2017 confirm that businesses wanting to increase their market share apply pricing strategies such as offers and low prices. These strategies as well as the constant consumer preference for branded products lead to a shrinking share of private label products (''σελφ σερβις'' self service, 2018).

3.1. Online shops

Consumers are beginning to get acquainted with online insect repellent markets, as they offer significant discounts, up to 58%. The more on-line markets grow, the more their distribution share increases. The range of insect repellent products available, either online or from pharmacies, from companies e.g. frezyderm, chicco, korres, powerhealth, etc, grows as well. There are many on-line pharmacies with competitive product prices causing physical stores to design competitive solutions (''σελφ σερβις'' self service, 2018).

Online pharmacies reached market value of 112 million € in 2016, a 52% increase in profit since 2015, according to the Convert Group survey (''σελφ σερβις'' self service, 2018).

3.2. Demographic characteristics of consumers

Women account for 78% of on-line purchases in pharmacies, 64% of those aged 25-34 and 30% of age 35-44 (‘’σελφ σερβις’’ self service, 2018).

3.3. Promotional actions

Companies invest in promotional activities and in the development of the subcategory for the treatment of bugs and flying insects which are called "double-efficiency" products ("2 in 1"). Moreover they prefer to present products with low content of chemicals and friendly to the environment. Consumers prefer the well-known brand name products but with affordable solutions and they buy these products in the periods of great promotional activity. Shoppers favor the innovative insect repellent products that protect effectively against the growing transmitted diseases (‘’σελφ σερβις’’ self service, 2018).

3.4. New products of 2018

- Eureka launched for the first time the new Aroxol Natural 4 series with four natural essential oils, citronella, eucalyptus, lavender and lemon. The series includes liquid set, liquid refill, mat refill and spiral. The series is also include the new Aroxol Mec Trigger with eucalyptus flavor
- SC Johnson launches Autan renewed with new labels
- Sarantis managed to reach the second place in sales and third place in value, introducing ‘’Sam Loves Betty’’ series in roll-on form, it also have it in lotion and launched the new Pyroxol series of insect repellent spirals
- Kostas Papaellinas S.A. renews the packaging of all Spira products

(‘’σελφ σερβις’’ self service, 2018)

4. Regulation and cost of product type PT-19 (repellents/attractants)

An insect repellent to be marketed as insect repellent must meet certain specifications laid down by the regulations of the European Chemical Agency. Only then will it be able to enter the list with the approved products of the Hellenic Republic Ministry of Rural Development and Food in the category of ''Repellents and Attractants PT-19''. Biocidal products are regulated by the European Regulation 528/2012 for their placing on market and use. The systematic examination of all existing active substances contained in biocidal products is regulated by the European regulation 1062/2014.

The European regulations to be followed by the candidate products and approval procedures for an insect repellent product are described in the following sections.

4.1. Procedure and cost for approval of new bioactive molecule or natural mixture as type PT 19 product by the European Chemical Agency (ECHA).

The Member State, or the company, which is interested in introducing a new bioactive substance, or natural mixture, must deposit a request for authorization of the bioactive substance by submitting a dossier to ECHA. The interested Member State must pay a fee whose estimated cost is 100.000€.

The dossier for the active substance to be submitted for evaluation to ECHA includes the studies based on chapter II of the European regulation 528/2012. This chapter requires studies for efficacy, toxicological, ecotoxicological, bioaccumulation and physicochemical properties. The estimated cost for the creation of the dossier is 10.000.000€. After validation check by ECHA, the evaluating competent authority performs a complete check and evaluation. Evaluation includes assessment of compliance (CCH) and testing (TPE) which takes about 12 months. The result of the evaluation is forwarded to the ECHA's Committee for Biocidal Products, which issues an opinion. The opinion and the monograph of the active substance serves as the basis for commentary between Member States to decide that the substance fulfills the conditions laid down in Regulation. This process needs 9 months to complete. The final step is

voting by the Member states an addition of the new bioactive substance in the PT-19 product lists of the European Union.

4.2. Procedure and cost approval of new formulation as type PT-19 product by the European Chemical Agency (ECHA).

The Member State, or the company which is interested in introducing a new formulation, must submit a dossier of the formulation based on chapter III of the European regulation 528/2012. Dossier consists of studies similar to chapter II (see above), with estimated cost of creation 1.000.000€. The submition is 20.000€ or 40.000€ for a family of products e.g. series of different concentrations

The dossier for the formulation must be submitted together with the dossier of the bioactive substance/natural mixture to be used.

A. If the bioactive substance to be used is already approved, then the dossier could be purchased from the owner. Alternatively, an agreement can be made with the owner to provide the Dossier free of charge under a commercial agreement for exclusive supply of the bioactive substance. The supplier should be a company included in the Greek Republic Ministry of Rural Development and Food's list of approved suppliers for the bioactive and the type of product.

B. If the bioactive substance to be used in the new formulation is under review, then the Article 89 of European regulation 528/2012 states that a new formulation can be approved, following national measures, which are simpler for a PT-19 product. In this case the registration, fee estimated to 200€. However, the formulation/product can only be available in the market of the requesting country e.g. Greece until the approval of the active substance and for an additional period of two years after the approval date. During this two years time, the dossier for the formulation (fees 20.000-40.000€) must be deposited, followed by the commercial agreement with approved supplier, owner of dossier, for the bioactive molecule/natural mixture.

4.3. Procedure for approval of final product

Having taken into consideration the information in sections 4, 4.1, 4.2, it was decided that the final product will follow the approval procedure accordance described in section 4.2.B, i.e. the national measures and the procedures they define, for new formulation of an active substance under review. The product will contain the natural bioactive substance Citridiol (Citrepel 75) as active repellent-substance, which is under review according to the list of active substances by ECHA (2017), (Annex I; Table 5). Finally, the novel natural ingredients which have been resulted by the OBP-based Reverse Chemical Ecology approach (described in section 5.1.1) will be included in the final product as co-formulants.

5. QFytoTera Project

QFytoTera is a collaborative project among three research organizations, National Hellenic Research Foundation, Benaki Phytopathological Institute, University of Patras and Qualia Pharma for the development of innovative plant insect repellents. The project was inspired by the following facts.

In recent years, more and more consumers have shown their interest in insect repellents because of their concerns over mosquito transmitted diseases. There is also a great concern of consumers about the insect repellent they intend to buy (Tavares et al., 2018).

Synthetic insect repellents are widely accepted by the market. The most common are DEET, IR3535 (Ethyl Butylacetylaminopropionate) (EB), Icaridin (Picaridin). Several studies have expressed concern about possible toxicity of synthetic insect repellents. The potential toxicity may be due to cutaneous absorption because of their low molecular weight (Tavares et al., 2018).

For the above reasons, natural products are constantly gaining ground in the insect repellent market because they are considered to exhibit low toxicity, thus burden as little as possible the human health and are environmentally friendly.

Many synthetic and plant-derived insect repellents are on the market. However, a problem that continues to exist in both product groups is their short duration of action; consumers need to reuse the product several times during the day / night to avoid mosquito bites. The problem becomes more pronounced in products based on essential oils of plant origin, as they are more volatile and their duration is in effect from a few minutes to 2h.

This fact has lead the companies of the field of repellents to try to replace the existing insect repellents with new safer, long-lasting products, more effective in smaller doses and active against broad spectrum species. The new products should have a nice fragrance and texture acceptable to consumers. Section ''1.3 Trends in repellent'' and Table 2 report several attempts of encapsulation that have been made to cope with volatility of essential oils.

Solving this problem is a research challenge to which this project responds with the introduction of plant origin ingredients with significantly increased insect repellent action. Also, the active ingredient will be encapsulated in natural nanoemulsions with improved safety, efficacy, durability and cosmetic properties.

5.1. Project implementation

5.1.1. Discovering new plant actives by the AXO method

The National Hellenic Research Foundation team has developed an innovative *in silico* and *in vitro* "Reverse Chemical Ecology" (AXO) method, for the discovery of novel insect repellents based on affinity and primarily the specificity of volatile compounds for characterized mosquito-binding olfactory molecules (OBPs) (Tsitsanou et al., 2012-;2013 and Drakou et al., 2017). AXO methodology includes modern methods of computational chemistry (*in silico* AXO) (Zografos et al., 2018, Thireou et al., 2018), in combination with advanced experimental techniques such as protein crystallography and macromolecular NMR. An innovative HT-ligand fishing technique has been developed to identify active ingredients from plant extracts or essential oils based on OBPs 1, 4, 5 and 48. Selection is performed by the equilibrium micro-dialysis technique, while identification is accomplished by LC-MS and GC-MS techniques. The methodology has already been successfully applied to extracts of Greek aromatic plants resulting in new

active ingredients with a Minimum Effective Dose of 100-20 μg / cm^2 up to ten times less than that of the most commonly used and effective synthetic DEET (MED = 200 μg / cm2) or natural Citridiol ™ with MED = 250 μg / cm^2.

In this study, these new active ingredients from Greek plants extracts will be mentioned as AXO essential oils whose main role is to enhance the repellent activity, the aroma and other benefits for the skin as co-formulants to the final product.

5.1.2. Insect repellent efficacy testing

Assessment of the efficacy of AXO essential oils against *Ae. albopictus* (tiger mosquito), has taken place at the Benaki Phytopathological Institute according to a prototype experimental protocol based on the number of landings of mosquitoes on human skin, (Giatropoulos, Papachristos and Michaelakis,. et al 2012) depicted in Figure 4. This protocol will be used for the evaluation of new ligands as well as for comparison between free and nanoparticulate bioactive compounds.

Figure 4: Bioassays based on the number of mosquito landings in human skin, according to the original experimental protocol in Benaki Phytopathological Institute

5.1.3. Encapsulation of insect repellents in oil-in-water (o/w) nanoemulsions

Oil-in-water (o/w) nanoemulsions based on biocompatible and safe surfactants and oils which are already used in pharmaceutical formulations for dermatological applications will be fabricated. The procedure includes the following steps: Initially, the hydrophobic insect repellent will be solubilized in the oil phase, mainly from oils of plant origin or fatty acid esters. Then it will be followed by the dispersion of this phase in the

aqueous phase through surfactant. Plant glycerol will be also used as a co-solvent to stabilize the system and regulate the rate of release of the insect repellent (Kalaitzaki and Papadimitriou et al., 2015, Nuchuchua & Sakulku et al., 2009). For the preparation of insect repellent nanoemulsions homogenization using a high pressure homogenizer will be applied (DanielssonI and Lindman,. 1981; Solans et al., 2005; Gupta, Eral, Hatton, & Doyle et al., 2016 and McClements et al., 2012). The physicochemical characterization and stability study of nanoemulsions versus time and temperature, in the absence and presence of the insect repellent will be accomplished using, Dynamic Light Scattering (DLS), Viscometry, and Electron Paramagnetic Resonance Spectroscopy (EPR).

5.1.4. Safety studies

Once the new plant insect repellent-AXO essential oils have been discovered and evaluated for their effectiveness, the next step is to test them for their safe use. For the bioactives *in vitro* perform cytotoxicity studies in human keratinocytes and fibroblast cultures as well as epidermal and ocular irritation will be carried out. Studies for eye irritation with *in vitro* test- EpiOcular™ (Stern, M., et al. 1998) and also for skin irritation with *in vitro* test-EpiDerm™ (Schafer-Korting, M., et al. 2008) will be performed, the toxicity will be assessed spectrophotometrically and possible lesions will be detected by histological evaluation of the epidermis (Furio, L., et al., A., Sotiropoulou, G., and Hovnanian, A. 2015). Furtermore, Human Repeat Insult Patch Tests (HRIPT), Mutagenicity testing of chemicals, Genotoxicity testing of chemicals and Photoxicity testing will be carried out.

5.1.5. Study of epidermal permeability and skin hydration

The emulsions which have been prepared will then be studied in terms of epidermal permeability of the encapsulated bioactive substance. The EpiDerm™ system will be performed, adapted for *in vitro* permeation in combination with GC-MS for the determination of active substances that permeate the skin layer. Skin hydration capacity will be determined by electrical impedance studies of EpiDerm FT (FT: full thickness), which contains the differentiated keratinocytes on a fibroblast layer (chori).

5.1.6. Final product safety study and total cost

For the final product, all the tests required i.e. safety assessment, challenge test, patch test and stability test will be carried out to ensure the required quality. Table 6 presents all the studies that will be conducted in the final product.

The cost of final product studies is estimated at about 30.000€

Table 6: Safety tests to be carried out on the new raw materials and studies of the final cosmetic product dossier

Safety Tests of Novel Raw Material for Cosmetic Use
Cytotoxicity assay for acute oral toxicity testing - *3T3 Balb/c Neutral Red Uptake Test*
In Vitro Skin Irritation Test - *EpiDerm™ (EPI-200-SIT) under GLP*
In Vitro Eye Irritation Test - *EpiOcular™ under GLP*
HRIPT - *200 volunteers*
Mutagenicity testing of chemicals - *reverse mutation test using bacteria (Ames Test)*
Genotoxicity testing of chemicals - *in vitro chromosome aberration test*
Phototoxicity testing - *3T3 Balb/c Neutral Red Uptake Photoxicity Test (OECD TG 432 : In Vitro 3T3 NRU Phototoxicity Test)*
Dossier of Finished Cosmetic Product
Product Information File according to 1223/2009 - *Including Safety Assessment, Challenge Test, Patch Test and Stability Test* *Safety Data Sheet complying with Regulation 1907/2006/EC Article 31 (REACH Regulation, 453/2010/EC and Regulation No 1272/2008/EC (CLP) - English language*
Physical and chemical properties, TDS – (*appearance, color, odor, density, refractive index, viscosity, dry matter, allergens)*

5.2. Product description

The final product will be in the form of spray and will be an innovative insect repellent, 100% natural, non toxic, with mosquito repellent and moisturizing cosmetic properties. The product will provide a holistic approach addressing both hydrating skin care and protection against mosquito-transmitted diseases. It will be completely safe and more efficient than existing products. Its competitive advantage will be the slow release of the active ingredients, resulting in a longer duration of its repellent action, as well as in reduced dermal absorption. This product aspires to be a plant insect repellent with the longest duration compared to the competition. Finally, it will have longer repellent reapplication intervals.

5.2.1 Ingredients and proportion of the final product

The product has not yet been completed, for this reason its ingredients and their proportionality to the final product are mentioned indicatively and are depicted in Table 7.

The proposed ingredients are the following.

Oils

Isopropyl myristate (4% w/w) or medium chain triglycerides (caprylic/capric triglycerides) (4% w/w) or sunflower oil (4% w/w)

Repellent compound

Citrepel 75 (2%)

Water

Ultra pure water (82%)

Surfactants

Span 80 (8% w/w) or Tween 40 (8% w/w) or Tween 60 (8%w/w) or Tween 80 (8%w/w), Soy bean Lecithin (2%w/w)

Co-formulants

AXO essential oils (1%) and glycerol (1%).

The oil phase consists of oils which are commonly used in nanoemulsion formulations, and of the active natural repellent substance Citrepel 75, containing 75% PMD. This herbal substance provides invigorating and antibacterial properties except for its insect repellent action. The final concentration of the oil phase in the nanoemulsion is 6% w/w

The aqueous phase is also important in the physicochemical properties and characteristics of the final nanoemulsion. The proposed concentration is 82% w/w

Various surfactants or their mixtures will be applied (Table 7). All these surfactants are known for their safety and are applied in several food or cosmetic formulations. Surfactants consist of two regions of different polarity, a hydrophilic and a hydrophobic. Their main role is to reduce the interfacial tension between oil and water to achieve the dispersion and stabilization of one phase in the other. Lecithin helps to emulsify and entrap bioactive compounds. In addition it acts as a stabilizing carrier, hydration agent, reduces viscosity and helps to homogenize the components of the mixture.

Co-formulants include glycerol which is actually co-solvent i.e. it is mixed with the aqueous phase and facilitates the emulsification. Furthermore, they include AXO essential oils which enhance the repellent active of the final product. At the same time they are also beneficial to the skin as they are aromatic, refreshing, soothing, have mildly disinfectant properties and are anti-irritants. AXO essential oils are added in the oil phase.

Table 7: Indicative reference of ingredients and their proportion in the final product

Ingredients		*% (w/w)*	
Oil phase	*isopropyl myristate*	*4*	*6*
	medium chain triglycerides		
	sunflower oil		
	repellent compound: Citrepel 75	*2*	
Aqueous phase	*ultra pure water*		*82*
Surfactans	*Span® 80*		*10*
	Tween® 40		
	Tween® 60		
	Tween® 80		
	Soy bean Lecithin		
Co-formulants	*AXO essential oils*		*2*
	Glycerol		

5.3. Innovation

The project's innovation lies in the following points:

The first concerns the discovering of essential oils from unexploited Greek flora with mosquito repellent properties by the AXO method. The AXO essential oils as analyzed in section 5.1.1., have an effective repellent action with a minimum effective dose ten times smaller than the most commonly used and effective conventional substances. This makes them particularly important when it comes to enhancing the insect repellent effect of the final product. In addition, they offer aroma and beneficial properties as refreshment to the skin, have mildly disinfectant properties, soothe the skin and they are anti-irritants.

The second concerns the innovation in formulation, namely the encapsulation of the natural insect repellent compound Citrepel 75 and AXO essential oils in o/w nanoemulsions. This formulation will provide controlled release of the active repellent compounds thus long duration time of the repellent action. In addition, nanoemulsions will offer resistance of the repellent to sweat and water. There are also other properties to be mentioned. Ethyl alcohol won't be used, there will be a reduced sense of greasiness, hydration of the skin and it will be easily spread. It will also enhance the beneficial properties of AXO essential oils and Citrepel 75 (aroma, refreshing, soothing, disinfectant, invigorating and antibacterial properties) on the skin. In addition, it won't irritate the skin and eyes and it will easily wash out with soap.

5.4. Instruction for use

Spray the product on uncovered parts of the body that are easier to get in contact with the mosquitoes and spread evenly. Use the product on dry and clean skin. Avoid use on irritated or hurt skin. One application per day is sufficient to protect for up to 6 hours. This product is appropriate for adults and children over 3 years old.

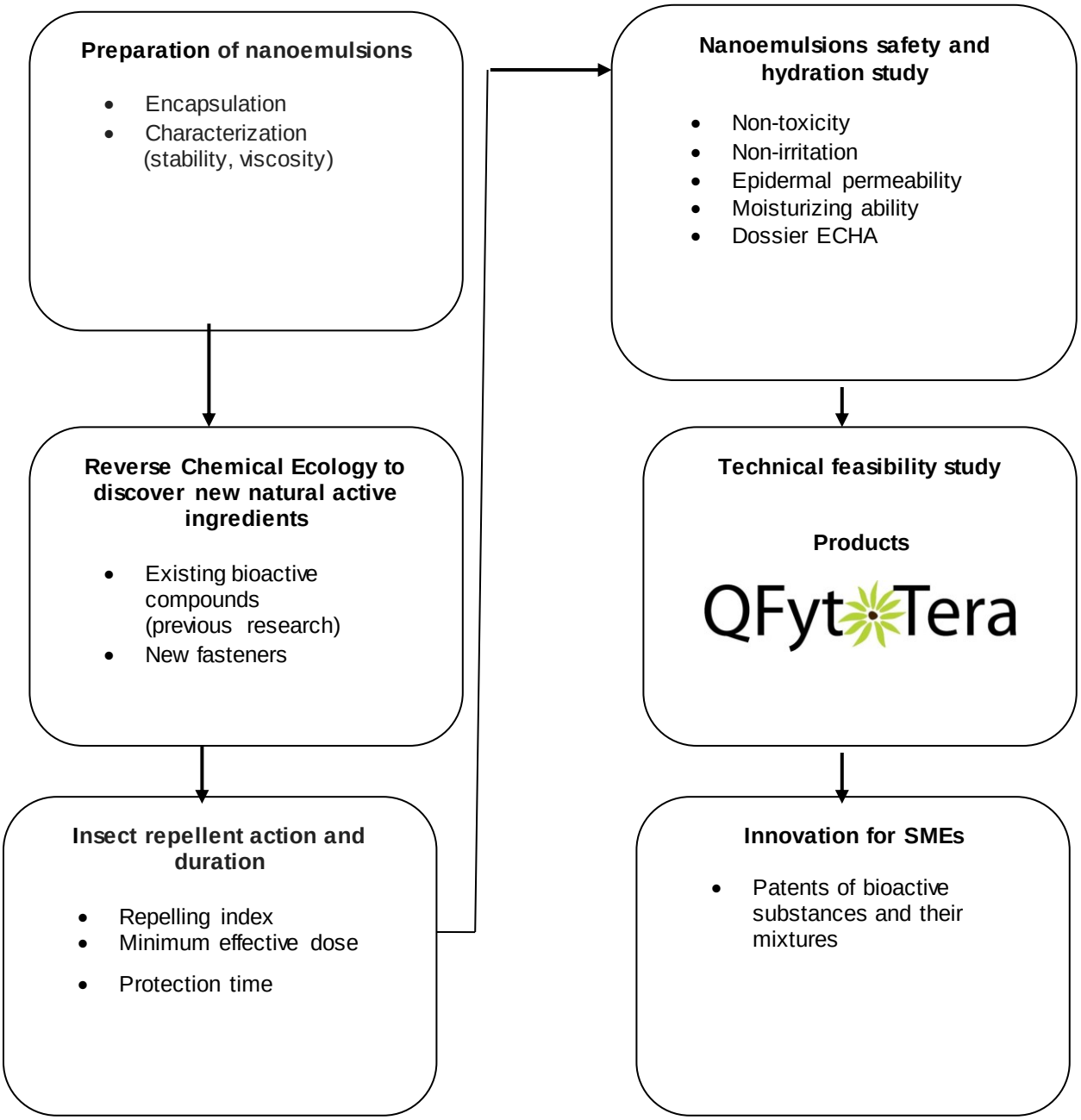
5.5. Characteristics of final product

Table 8 mentions all the features of the final product.

Table 8: A detailed description of the end-product characteristics.

Characteristics of product	
Nanoemulsions of oil with moisturizing and insect repellent properties	*Pleasant odor*
Long duration of insect repellent action (6 hours)	*Reduced sense of greasiness*
100% natural ingredients of plant origin	*Without ethyl alcohol*
Not toxic, not irritating for skin or eyes	*Resistance to water*
Reduced dermal absorption	*Form of spray*
No animal testing	*Easy removal with soap and water*

6. Workflow



7. Financial plan of the development of the new product

In order to determine whether the company that will undertake the production of the product will have a profit and if the product will be able to stand on the insect repellent market, a feasibility study, which takes place at the early stages of any business project is needed. For this purpose a market analysis, competition analysis, Gantt diagram, swot analysis and indicative pricing of final product are carried out.

This feasibility study, as it is contract manufacturing, will not provide information on the cost of equipment, packaging, operating costs, human resources, marketing, promotion, distribution channels, and also working capital that will be needed to produce the final product, as they will be taken over by the company which will produce the product namely Qualia Pharma. However, for marketing plan, promotion and distribution channels some suggested actions are mentioned below.

7.1. Competition

In section 2, the worldwide and European insect repellent market was extensively analyzed. Also the same pattern was followed in section 3 for the Greek market. In Annex I, Tables 9-12 show insect repellent products that exist in Greece which are categorized into synthetic–natural, prices and their production companies are mentioned.

7.2. Marketing plan

As the insect repellent product will be incorporated into the Qualia Pharma production unit, the marketing plan will be undertaken by it, provided that it has channels for the promotion, distribution and sale of products. However, some proposed practices that are considered as good marketing strategies for this product will be listed below.

Launching product

The launching of the product on the market, as well as the target group, has a major role in designing the marketing strategy and promoting it appropriately.

The innovative product has an increased insect repellent efficacy combined with Citriodiol and AXO essential oils which are proven for their efficacy in comparison to other insect repellents and their beneficial properties on the skin. Also, the formulation of plant origin nanoemulsion prolongs the time of action of active substances, hydrating and leaving good sensation when applied to the skin. It is obvious that it is addressed to consumers who are interested in innovative high-quality plant products with integrated repellent action. They want this action to last for several hours with just an application to the skin, leaving a pleasant fragrance and a nice feeling. This innovative product with its long-lasting action is absolutely natural and safe to use for adults and children over 3 years of age.

7.3. Product pricing

The pricing policy will be based on the differentiation of the new product in relation to the existing ones, both in terms of high-quality efficiency and components and in terms of technology. However, the retail price of the final product must have as its main priority the consumer's approach, as well as the operating and equipment costs and the profit that should be incorporated into the retail price of the final product. For this reason, an indicative profit margin 75%[3] is calculated to the total cost of the raw materials, to give the indicative retail price of the final product. Having all this in mind the final retail price is calculated to be 3,61€ per package of 100ml. This is considered to be competitive in relation to existing products of the same kind, especially for the differentiation it offers due to the nanoemulsions and the ingredients contained. Table 13 below illustrates the cost of raw materials and Table 14 shows the indicative final product retail price. As mentioned in the previous section, the product has not yet been prepared with the result that the exact proportion, the raw materials and the price of the final product are not yet known. The company will provide its own suppliers, which are

[3] Profit margin 75%: 0,9026€ (final cost of raw materials) / 25% (operating and equipment costs)= 3,61€ (retail price of the final product)

likely to be able to supply the raw materials at better prices. In addition, the company will provide information on operating costs, the cost of equipment and the loans that may be needed. Taking all this into account, the price of the final product may change.

In the aqueous phase the product will contain ultra pure water. It is estimated that 1m^3 of ultra pure water costs 1€ of tap water EYDAP and the cost of consumables and electricity for the production of ultra pure water 0,4€/m^3. This means that the cost is estimated at 1,4€/m^3 which is very low and will not be included in the following costing; most companies produce their own pure water because of low cost.

Table 13: Cost of raw material per €/g.

Ingredients	*Row material cost €*
Isopropyl myristate	*0,15€/g*
Medium chain triglycerides (caprylic/capric triglycerides)	*0,029€/g*
Sunflower oil	*0,0010€/g*
Citrepel 75	*0,04€/g*
Ultra pure water	*-*
Span® 80	*0,088€g*
Tween® 40	*0,056€/g*
Tween® 60	*0,067€/g*
Tween® 80	*0,04€/g*
Soy bean Lecithin	*1€/g*
AXO essential oils	*~ 0,1€/g*
Glycelor	*0,009€/g*

Table 14: Indicative retail price of final product

Ingredients		% (w/w)		Price €
Oil phase	isopropyl myristate	4	6	0,3376 €
	medium chain triglycerides			
	sunflower oil			
	repellent compound: Citrepel 75	2		
Aqueous phase	ultra pure water		82	0,00 €
Surfactans	Span® 80		10	0,504 €
	Tween® 40			
	Tween® 60			
	Tween® 80			
	Soy bean Lecithin			
Co-formulants	AXO essential oils		2	0,061 €
	glycerol			
Final cost of raw materials				0,9026 €
Final retail price (0,9026€ / 25% (operating and equipment costs))				3,61 €

7.4. Promotion channels

In our days there are plenty of insect repellent products (natural-synthetic), to meet all the needs of the consumer community. Therefore, it is clear that for the success of the new product promotion is crucial. Qualia Pharma, as mentioned at the beginning of this chapter, is the company which will take over the promotion of the final product as it has channels for promotion and distribution. However, some promotional actions for the final product are suggested below.

The aim of the action should be for the product to be accepted by the public. Social media, as it is known, are predominant in our days, with plenty of ads of various kinds.

For this reason the content marketing strategy is considered appropriate to apply. The company in this case should use its social media and its website to present the public with useful information. Detailed information on raw materials, the technology that has been used as well as scientific research into the effectiveness of the product will be offered. Finally, the website as well as the social media will make it easy for the company to communicate with its customers providing answers to their questions.

In addition, the promotion of the product will be strengthened with the participation of the company in pharmacy campaigns. Free samples will be available attracting consumers' interest as well as information on the effective action and the cosmetic properties that it provides. Finally, the participation of the company in conferences is another good promotion action.

7.5. Distribution channels

In order for the consumer to become familiar with the product and to create a product-to-consumer relationship, it must be readily available to the consumer. Qualia Pharma will use its distribution and sales channels which include wholesale in pharmacies. It is also proposed to be available on e-shop through the company's official website and online pharmacies in order to be easily found both in Greece and abroad.

7.6. SWOT analysis

SWOT analysis is a strategic planning tool present in Annex I Table 15 that displays the strengths and weaknesses of the final product as well as opportunities and threats presented to it when entering the repellent market. This tool will demonstrate whether the final product can stand in the insect repellent market with its potential, weaknesses and its possible risks.

7.7. GANTT diagram

The Gantt diagram provides a graphical representation of the project that helps the design, coordination and specialization of work needed. This is illustrated in Annex I Chart 15 and will check all activities for the preparation of the final product. If some activity, however, escapes its time frames, those responsible will take every necessary action.

7.8. Forecast revenue

As already mentioned in this work, the world's worries about mosquito transmitted diseases are growing, with the result for the worldwide and European market of insect repellents to be increasing as well. Section 2 analyzes in detail the growth of the insect repellent market in Europe as well as France, Germany and the U.K which are the dominant countries in the repellent market. Furthermore, with regard to the Greek market, section 3 states that there has been a reduction in the previous years, because of alternative forms of consumer treatment. But, during these years due to climate change, the humidity of the country has increased. As a result the outbreaks of mosquito transmitted diseases such as West Nile fever have made their appearance in Greece, contributing to the growing concern of the people. Thus, the insect repellent market is expected to increase in Greece.

The foreseeable revenue for the final product is based on the above facts. More specifically in section 2.3 ‘’Transparency Market Research 2017’’ is mentioned that the U.K. insect repellent market, which stood at US$ 66.4 million in 2016, will reach US$100.0 million by the end of 2024 with CAGR 4.9%. The U.K has too much humidity with outbreaks of mosquito transmitted diseases and consequently with a large insect repellent market. For these reasons, this European country is ideal to be used as the base for the forecast revenue in the Greek repellent market.

As the information of U.K is for 2016, the calculation was based on the population of the U.K. and Greece and the exchange rate US$ to euro in 2016 as depicted in the following Table 15.

Table 15: The population and the market of Greece in 2016

	U.K	Greece
Population 2016	64.928.787	10.933.457
Market[4]	72.794.320€	12.257.946€

Then, based on the 21 competitive insect repellent products that are listed in Annex I Tables 9-12, the average retail price of an insect repellent per unit of 100ml was calculated and estimated 5,9€ /unit.

The next step is to calculate the forecast revenue in the Greek repellent market and this is based on the growth rate (4,9%) and the average retail price of insect repellent packaging (5,9€ /unit). Calculated as shown in the following Table 16 and Chart 16, the market for insect repellents in € and units per year in Greece.

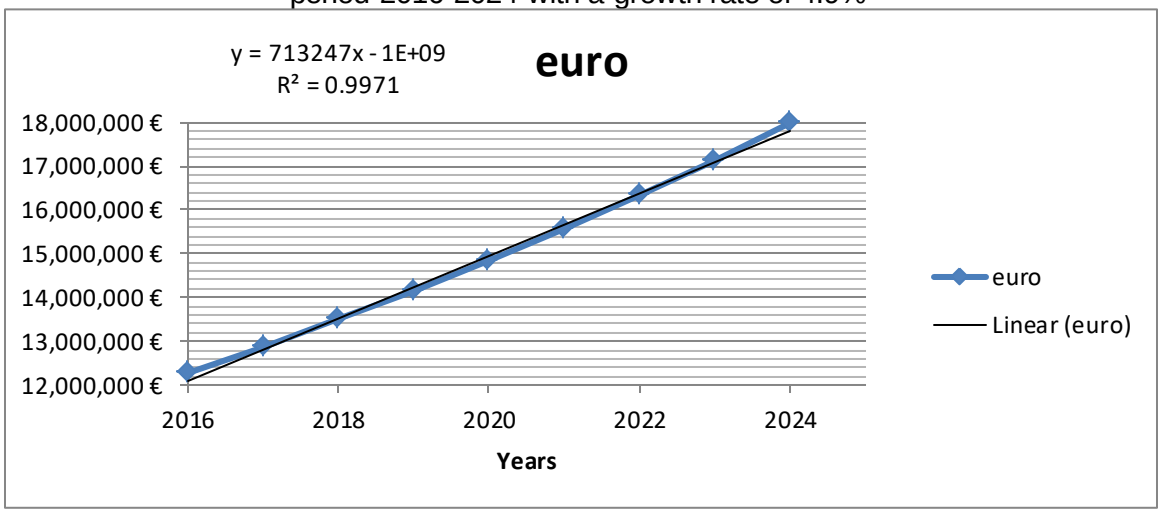
Table 16: Market of insect repellents in euro and in units in Greece with a growth rate of 4,9%

Year	Market in euro	Market in units (5,9€/unit)
2016	12.257.946 €	2.077.618
2017	12.858.585 €	2.179.421
2018	13.488.656 €	2.286.213
2019	14.149.600 €	2.398.237
2020	14.842.931 €	2.515.751
2021	15.570.234 €	2.639.023

[4] US$ 66.4 million*1.0963 (exchange rate for 2016)

2022	*16.333.176 €*	*2.768.335*
2023	*17.133.501 €*	*2.903.983*
2024	*17.973.043 €*	*3.046.278*

Chart 16: Graphic depiction of the Greek market of insect repellents in euro for the period 2016-2024 with a growth rate of 4.9%



Based on the above assumptions in Table 16, the estimated revenue for the final product was calculated.

Considering that the average retail price of the competition is 5,9€/unit while the final product is 3,61€/unit it is understood that the product is highly competitive. For this reason, it is estimated that from the first year already the market share of the product will be satisfactory. More specifically, in the first year the product is estimated to have 5% of market share, 8% in the second year, 10% in the third year, 12% in the fourth year and 15% in the fifth year of the market share. Based on these estimates, the Table 17 presents the forecast revenue in units and in euro, based on the final product with retail price 3,61€ / unit.

Table 17: It shows the estimated revenue based on the market share of the final product per year

Years	Market share%	Revenue in units	Revenue in euro
2019	5	119912	432.882 €
2020	8	201260	726.549 €
2021	10	263902	952.687 €
2022	12	332200	1.199.243 €
2023	15	435597	1.572.507 €

8. Future plans

The future plans of the company are to initially focus on Greece as a pilot test with warehouses in Greece to evaluate the consumer response. The next step is the exports to the European countries with the highest consumption of insect repellent products, namely France, Germany and the United Kingdom.

9. Conclusion-Discussion

This work was aimed at presenting the innovative QFyTotera project. This project was inspired by global consumer concerns about mosquito-borne diseases that year by year are rising due to climate changes, globalization of travel, trade and migration. For this reason, the insect repellent market is growing by introducing a wide range of insect repellent products for all requirements. A market analysis was carried out on the repellent industry and it was found to be highly developed with many prospects based on studies showing an increase in CAGR% over the coming years. Due to their wide

variety, consumers have begun to have high demands on these products. Their tendency is to prefer plant products as they are concerned about any side effects of synthetic ones. The disadvantage of repellents (plant-synthetic) is that their time of action is not long, with greater difficulty in dealing with plant repellents as the essential oils that constitute them are very volatile. For these reasons efforts have been made by companies and scientists to discover new plant repellents based on new biotechnological targets that are more effective than known active substances. Also, efforts have been made for new formulations of plant and synthetic insect repellents to increase the duration of their active ingredients.

This project was based on these facts and in the gap which exists in the repellent market. Its purpose is to develop a natural repellent product with plant active substances (Citrepel 75 and AXO essential oils as co-formulant) that will enhance the repellent effect of the product. In addition AXO co-formulant will offer beneficial properties on the skin. Encapsulation of these active compounds in (o/w) nanoemulsions based on natural ingredients will offer prolonged time of duration and improve the cosmetic properties of the final product.

Citrepel 75 is an effective plant active substance listed by the Greek Republic Ministry of Rural Development and Food as a substance under review for product type (PT-19) which can be used as insect repellent. The nanoemulsions to be prepared will provide controlled release of active substances, with the result of prolonging the duration of the repellent action. Epidermal permeability tests of the loaded nanoemulsions will be carried out. The proposed nanoemulsions will offer cosmetic properties as moisture, soothing, a nice skin feeling and easy application.

AXO essential oils will be used as co-formulants, the latter being the result of an innovative *in silico* and *in vitro* "Reverse Chemical Ecology" (AXO) method. The volatile compounds of AXO essential oils have a high affinity and specificity for mosquito-binding proteins (OBPs). Test of their repellant effect showed that AXO essential oils have a minimal effective dose (MED) up to ten times lower than common ingredients used in insect repellents. They also provide beneficial properties for the skin and perfume. Safety studies will be carried out for both AXO essential oil alone and the final product.

Due to the ingredients and the innovative technology that the product contains in its preparation, it was considered to be a fairly competitive natural product compared to

the existing ones. That is why it was necessary to assess what its prospect will be in the insect repellent market and a feasibility study was done.

As the project has not yet been materialized and Qualia Pharma will take over the production of the insect repellent, information such as operating costs, equipment costs, packaging, human resources, hasn't been included. Nevertheless, when it comes to marketing plan, distribution channels and promotion, some suggested actions have been mentioned.

The final product has an innovative formulation and contains AXO ingredients that haven't been used in a similar natural product. This constitutes a great advantage for the rapid response of the market. The retail price was calculated at 3,61 € per 100 ml of product, which is indicative since the exact concentration of final ingredients is not yet known. At the same time, its retail price is much lower than the average retail price of the competition. For these reasons, it is thought that its market share will be satisfactory enough and it may offer an extra increase of its market share the years to come.

Given the assumptions used to generate this forecast revenue, it cannot be absolutely precise and a +(-)10% deviation of the indications should be taken into account.

10. Bibliography

Abnewswire (2017). Global Mosquito Repellent Market Size, Share, Trends, Growth Analysis, Opportunities and Forecast to 2022. Available at:http://www.abnewswire.com/pressreleases/global-mosquito-repellent-market-size-share-trends-growth-analysis-opportunities-and-forecast-to-2022_134522.html [accessed 5/3/2018]

Allied market research (2016). Mosquito Repellent Market by Product Type (Spray, Coil, Cream & Oil, Mat, Vaporizer, Other products) and Channels of Distribution (Large retail stores, Small retail stores, Specialty stores, Online) - Global Opportunity Analysis and Industry Forecast, 2015 2022. Available at: https://www.alliedmarketresearch.com/mosquito-repellent-market [accessed 25/2/2018]

Bouchemal, K., Briançon, S., Perrier, E., &Fessi, H. (2004). Nano-emulsion formulation using spontaneous emulsification: solvent, oil and surfactant optimisation. International journal of pharmaceutics, 280(1-2), 241-251

Business Wire (2017). APAC Tops the Household Insecticide Market | Technavio. Available at: https://www.businesswire.com/news/home/20171104005064/en/APAC-Tops-Household-Insecticide-Market-Technavio [accessed20/1/2018]

Chanchal, D., & Swarnlata, S. (2008). Novel approaches in herbal cosmetics. Journal of cosmetic dermatology, 7(2), 89-95.

Commission Delegated Regulation. E.U. (2014). No 1062/2014 of 4 August 2014 on the work programme for the systematic examination of all existing active substances contained in biocidal products referred to in Regulation (EU) No 528/2012 of the European Parliament and of the Council. Official Journal of the European Union L,294

Daily News KS (2017). Global Lemon Eucalyptus Essential Oil Market Professional Survey by Production, Consumption, Import and Export Forecast 2017-2022. Available at: http://dailynewsks.com/2017/08/global-lemon-eucalyptus-essential-oil-market-professional-survey-production-consumption-import-export-forecast-2017-2022/ [accessed 10/5/2018]

Danielsson, I., Lindman, B. (1981). The definition of microemulsion. Colloids Surfaces 3, 391-392

Drakou, C. E., Tsitsanou, K. E., Potamitis, C., Fessas, D., Zervou, M., & Zographos, S. E. (2017). The crystal structure of the AgamOBP1• Icaridin complex reveals alternative binding modes and stereo-selective repellent recognition. Cellular and molecular life sciences, 74(2), 319-338.

Drapeau, J., Verdier, M., Touraud, D., Kröckel, U., Geier, M., Rose, A., & Kunz, W. (2009). Effective Insect Repellent Formulation in both Surfactantless and Classical Microemulsions with a Long-Lasting Protection for Human Beings. Chemistry & biodiversity, 6(6), 934-947.

de Campos, V. E., Ricci-Júnior, E., & Mansur, C. R. (2012). Nanoemulsions as delivery systems for lipophilic drugs. Journal of nanoscience and nanotechnology, 12(3), 2881-2890.

European Chemical Agency (2017), Treated articles: allowed active substances. Available at: https://www.echa.europa.eu/ Accessed on: 14/11/2018

Fermamdez, P., André, V., Rieger, J., &Kühnle, A. (2004). Nano-emulsion formation by emulsion phase inversion. Colloids and Surfaces A: Physicochemical and Engineering Aspects, 251(1-3), 53-58.

Furio, L., Pampalakis, G., Michael, I. P., Nagy, A., Sotiropoulou, G., & Hovnanian, A. (2015). KLK5 inactivation reverses cutaneous hallmarks of Netherton syndrome. PLoS genetics, 11(9), e1005389.

Giatropoulos, A., Papachristos, D. P., Kimbaris, A., Koliopoulos, G., Polissiou, M. G., Emmanouel, N., & Michaelakis, A. (2012). Evaluation of bioefficacy of three Citrus essential oils against the dengue vector Aedes albopictus (Diptera: Culicidae) in correlation to their components enantiomeric distribution. Parasitology research, 111(6), 2253-2263.

Greek Republic Ministry of Rural Development and Food. Available at: http://wwww.minagric.gr/syspest/ [accessed 20/1/2018]

Gupta, R.K., Bhattacharjee, A.K., (2007). Discovery and design of new arthropod/insect repellents by computer-aided Molecular Modeling. In: Debboun,

M.F.S., Strickman, D. (Eds.), Insect Repellents: Principles, Methods, and Uses. CRC, Boca Raton, FL, pp.275–304.

Gupta, A., Eral, H. B., Hatton, T. A., & Doyle, P. S. (2016). Nanoemulsions: formation, properties and applications. Soft matter, 12(11), 2826-2841.

Gutiérrez, J. M., González, C., Maestro, A., Solè, I. M. P. C., Pey, C. M., & Nolla, J. (2008). Nano-emulsions: New applications and optimization of their preparation. Current opinion in colloid & interface science, 13(4), 245-251.

IBISWorld (2017). Insect Repellent Manufacturing-US Market research Report. Available at:https://www.ibisworld.com/industry-trends/specialized-market-research-reports/life-sciences/otc-medicines/insect-repellent-manufacturing.html [accessed 25/2/2018]

Islam, J., Zaman, K., Duarah, S., Raju, P. S., & Chattopadhyay, P. (2017). Mosquito repellents: An insight into the chronological perspectives and novel discoveries. Actatropica, 167, 216-230.

Kalaitzaki, A., Papanikolaou, N. E., Karamaouna, F., Dourtoglou, V., Xenakis, A., & Papadimitriou, V. (2015). Biocompatible colloidal dispersions as potential formulations of natural pyrethrins: a structural and efficacy study. Langmuir, 31(21), 5722-5730.

Katz, T. M., Miller, J. H., & Hebert, A. A. (2008). Insect repellents: historical perspectives and new developments. Journal of the American Academy of Dermatology, 58(5), 865-871.

Kbv research (2017). Europe Mosquito Repellent Market is expected to register a CAGR of 7.1% during the forecast period (2017 – 2023) – KBV Research. Available at:https://kbvresearch.com/news/europe-mosquito-repellent-market/ [accessed 24/2/2018]

Knowledge Based Value Research (2017). Global Mosquito Repellent Market to reach a market size of $5.2 billion by 2023 – KBV Research. Available at: https://kbvresearch.com/news/global-mosquito-repellent-market/[accessed 6/3/2018]

Lindman, B., & Danielson, I. (1981). The definition of microemulsion. Colloid Surf, 3(391392.3).

Magdassi, S. (1997). Delivery systems in cosmetics. Colloids and Surfaces A: Physicochemical and Engineering Aspects, 123, 671-679.

Maia, M. F., & Moore, S. J. (2011). Plant-based insect repellents: a review of their efficacy, development and testing. Malaria journal, 10(1), S11.

Market Research Report Search Engine (2018). Insect Repellent Market – U.K Industry Analysis, Size, Share, Growth, Trends and Forecast 2017- 2025. Available at: https://www.scoop.it/t/chemicals-8 [accessed 5/3/2018]

Mason, T. G., Wilking, J. N., Meleson, K., Chang, C. B., & Graves, S. M. (2006). Nanoemulsions: formation, structure, and physical properties. Journal of Physics: condensed matter, 18(41), R635.

McClements, D. J. (2012). Nanoemulsions versus microemulsions: terminology, differences, and similarities. Soft matter, 8(6), 1719-1729.

Morris, G. M., Huey, R., Lindstrom, W., Sanner, M. F., Belew, R. K., Goodsell, D. S., & Olson, A. J. (2009). AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. Journal of computational chemistry, 30(16), 2785-2791.

Murphy, E. J., Booth, J. C., Davrazou, F., Port, A. M., & Jones, D. N. (2013). Interactions of Anopheles gambiae Odorant-binding Proteins with a Human-derived Repellent IMPLICATIONS FOR THE MODE OF ACTION OF N, N-DIETHYL-3-METHYLBENZAMIDE (DEET). Journal of Biological Chemistry, 288(6), 4475-4485.

Nuchuchua, O., Sakulku, U., Uawongyart, N., Puttipipatkhachorn, S., Soottitantawat, A., &Ruktanonchai, U. (2009). In vitro characterization and mosquito (saegypti) repellent activity of essential-oils-loaded nanoemulsions. AapsPharmscitech, 10(4), 1234.

Orbis Research (2017). Global Mosquito Repellent Market 2017-2022 Analysis, Size, Trends and Opportunities by Sales Channel, Country and Region. Available at:https://www.reuters.com/brandfeatures/venture-capital/article?id=18356[accessed 25/2/2018]

Patel, E. K., Gupta, A., &Oswal, R. J. (2012). A review on: mosquito repellent methods. IJPCBS, 2(3), 310-317.

Pereira, T., Guerreiro, C., Maruno, M., Ferrari, M., & Rocha-Filho, P. (2016). Exotic vegetable oils for cosmetic o/w nanoemulsions: In vivo evaluation. Molecules, 21(3), 248.

Pinto, I. C., Cerqueira-Coutinho, C. S., Santos, E. P., Carmo, F. A., & Ricci-Junior, E. (2017). Development and characterization of repellent formulations based on nanostructured hydrogels. Drug development and industrial pharmacy, 43(1), 67-73.

PR Newswire (2016). Body Worn Insect Repellent Market - Global Industry Analysis, Size, Share, Growth, Trends and Forecast 2015 – 2021. Available at: https://www.prnewswire.com/news-releases/body-worn-insect-repellent-market---global-industry-analysis-size-share-growth-trends-and-forecast-2015---2021-300211857.html [accessed: 10/5/2018]

Regulation, E. U. (2012). No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products. Official Journal of the European Union L, 167.

Reid W., (2018). Para-menthane-3, 8-diol (PMD) Market Growth Analysis and Opportunities Forecast 2018 to 2023. BELAIR DAILY. Available at: http://www.belairdaily.com/para-menthane-38-diolpmd-market-growth-analysis-and-opportunities-forecast-2018-to-2023/ [accessed: 10/5/2018]

Ribas, J., &Carreño, A. M. (2010). Evaluation of the use of repellent against mosquito bite by military personnel in the Amazon Basin. Anais brasileiros de dermatologia, 85(1), 33-38.

Ribeiro, R., Barreto, S., Ostrosky, E., Rocha-Filho, P., Veríssimo, L., & Ferrari, M. (2015). Production and characterization of cosmetic nanoemulsions containing Opuntia ficus-indica (L.) mill extract as moisturizing agent. *Molecules*, *20*(2), 2492-2509.

Sakulku, U., Nuchuchua, O., Uawongyart, N., Puttipipatkhachorn, S., Soottitantawat, A., & Ruktanonchai, U. (2009). Characterization and mosquito repellent activity of citronella oil nanoemulsion. International journal of pharmaceutics, 372(1-2), 105-111.

Schäfer-Korting, M., Bock, U., Diembeck, W., Düsing, H. J., Gamer, A., Haltner-Ukomadu, E., & Kietzmann, M. (2008). The use of reconstructed human epidermis

for skin absorption testing: Results of the validation study. Alternatives to laboratory animals: ATLA, 36(2), 161-187.

Solans, C., Esquena, J., Forgiarini, A. M., Uson, N., Morales, D., Izquierdo, P., ...& Garcia-Celma, M. J. (2003). Absorption and aggregation of surfactants in solution. Nano-emulsions: Formation, Properties and applications. Marcel Dekker, New York, 525-554.

Solans, C., Izquierdo, P., Nolla, J., Azemar, N., & Garcia-Celma, M. J. (2005). Nano-emulsions. Current opinion in colloid & interface science, 10(3-4), 102-110.

Stern, M., Klausner, M., Alvarado, R., Renskers, K., & Dickens, M. (1998). Evaluation of the EpiOcularTM tissue model as an alternative to the Draize eye irritation test. Toxicology in vitro, 12(4), 455-461.

Syed, Z., & Leal, W. S. (2008). Mosquitoes smell and avoid the insect repellent DEET. Proceedings of the National Academy of Sciences, 105(36), 13598-13603.

Tavares, M., da Silva, M. R. M., de Siqueira, L. B. D. O., Rodrigues, R. A. S., Bodjolle-d'Almeira, L., dos Santos, E. P., & Ricci-Júnior, E. (2018). Trends in insect repellent formulations: A review. International journal of pharmaceutics, 539(1), 190-209.

Tecnhnavio market research company (2016). Global Mosquito Repellent Market 2017-2021. Available at:https://www.technavio.com/report/global-general-retail-goods-and-services-global-mosquito-repellent-market-2017-2021 [accessed 20/1/2018]

Thireou, T., Kythreoti, G., Tsitsanou, K. E., Koussis, K., Drakou, C. E., Kinnersley, J., Kröber, T., Guerin, P. M., Zhou, J., Iatrou, K., Eliopoulos, E., & Zografos S. E. (2018). Identification of novel bioinspired synthetic mosquito repellents by combined ligand-based screening and OBP-structure-based molecular docking. Insect biochemistry and molecular biology, 98, 48-61.

Tsitsanou, K. E., Thireou, T., Drakou, C. E., Koussis, K., Keramioti, M. V., Leonidas, D. D., Eliopoulos E., Iatrou K., & Zographos, S. E. (2012). Anopheles gambiae odorant binding protein crystal complex with the synthetic repellent DEET: implications for structure-based design of novel mosquito repellents. Cellular and Molecular Life Sciences, 69(2), 283-297

Tsitsanou, K. E., Thireou, T., Gruber, A.V., Kythreoti, G., Azem, A., Fessas, D., Eliopoulos, E., Iatrou, K., & Zografos, S.E (2013). Crystal and Solution Studies of the "Plus-C" Odorant-binding Protein 48 from Anopheles gambiae CONTROL OF BINDING SPECIFICITY THROUGH THREE-DIMENSIONAL DOMAIN SWAPPING. J Biol Chem 288, 33427-33438

Tsitsanou, K. E., Thireou, T., Eliopoulos, E., & Zographos, S. E. (2017). OBP Structure-Aided Repellent Discovery: An Emerging Tool for Prevention of Mosquito-Borne Diseases. In Computational Design of Chemicals for the Control of Mosquitoes and Their Diseases (pp. 65-106). CRC Press.

The statistics Portal (2017).U.S. population: Which brands of insect repellent do you use most often? Available at:https://www.statista.com/statistics/275079/us-households-most-used-brands-of-insect-repellents/ [accessed 1/3/2018]

Transparency Market Research (2016). Europe Insect Repellent Market to Account For US$1.82 Bn In Revenue By 2023 Demand For Natural Products On The Rise. Availabe at: https://www.transparencymarketresearch.com/pressrelease/europe-insect-repellent-market.htm [accessed 24/3/2018]

Transparency Market Research (2017). Insect Repellent Market (Product - Non-Body Worn (Coil, Mat and Sheet, Electric/Liquid Vaporizer, and Aerosol Sprays) and Body Worn (Oils and Creams, Aerosol, Stickers and Patches, Apparels, trousers, shirts, jackets, head nets and others are the sub segment of apparels. Oils & Creams is farther split into plant-based and synthetic.); Composition - Body Worn (Deet, Picaridin, Oil of Lemon Eucalyptus/ p-Menthane-3,8-diol, IR 3535, and Plant Oil) and Non-Body Worn (Malathion, Carbaryl, and Pyrethrin) - U.K. Industry Analysis, Size, Share, Growth, Trends and Forecast 2017 – 2025. Available at: https://www.transparencymarketresearch.com/uk-insect-repellent-market.html [accessed 5/3/2018]

Transparency market research (2017). Global Body Worn Insect Repellent Market: Plant-based Body Worn Insect Repellent to be in High Demand, says TMR. Available at: https://www.transparencymarketresearch.com/pressrelease/body-worn-insect-repellent-market.h [accessed 15/3/2018]

Wade E., (2017). CDC Says Lemon Eucalyptus as Effective as DEET at Repelling Mosquitoes. Available at: http://thinkaboutnow.com/2017/06/cdc-says-lemon-eucalyptus-as-effective-as-deet-at-repelling-mosquitoes/ [accessed 8/5/2018]

World Health Organization (2017), Vector-borne diseases. Available at: http://www.who.int/mediacentre/factsheets/fs387/en/ Accessed on:13/11/2018

Yilmaz, E., & Borchert, H. H. (2006). Effect of lipid-containing, positively charged nanoemulsions on skin hydration, elasticity and erythema—an in vivo study. International journal of pharmaceutics, 307(2), 232-238.

Yukuyama, M. N., Ghisleni, D. D. M., Pinto, T. D. J. A., & Bou-Chacra, N. A. (2016). Nanoemulsion: process selection and application in cosmetics–a review. International journal of cosmetic science, 38(1), 13-24.

Zion Market Research (2017). Mosquito Repellent Market: Global Industry wills Reach USD 5.00 Billion by 2022, Zion Market Research. Available at: https://globenewswire.com/news-release/2017/10/25/1152800/0/en/Mosquito-Repellent-Market-Global-Industry-will-Reach-USD-5-00-Billion-by-2022-Zion-Market-Research.html[accessed 25/1/2018]

Δημόπουλος Β., Τσαντίλη-Κακουλίδου Α., (2015). Ανακάλυψη Ενώσεων-Οδηγών. Εκδόσεις: Κάλλιπος, Βασικές Αρχές Σχεδιασμού και Ανάπτυξης Φαρμάκων. Σύνδεσμος Ελληνικών Ακαδημαϊκών Βιβλιοθηκών σελ.42-85

Στοφόρος Κ (2018) ΕΝΤΟΜΟΚΤΟΝΑ-εντομοαπωθητικα: Σε… χαμηλές πτήσεις η αγορά. Σελφ σερβις. (Τ. 482).

Annexes

Annex I

Chart 9: Represent the segmentation of Synthetic-Natural Greek market products.

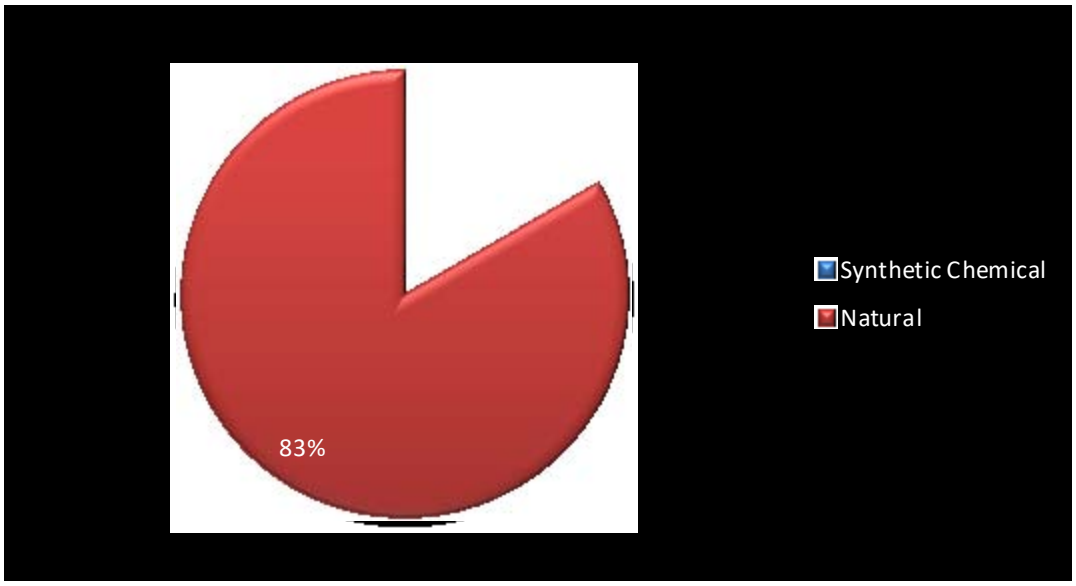


Chart 10: Represent the individual fragmentation of Synthetic-Chemical repellents.

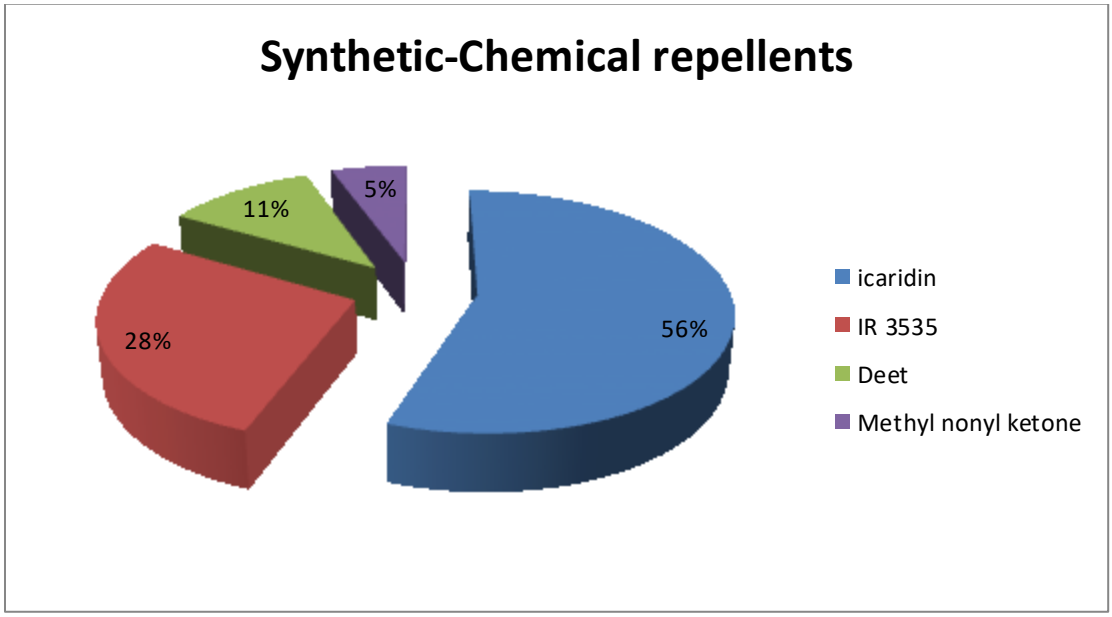


Chart 11: Represent the individual fragmentation of natural repellents.

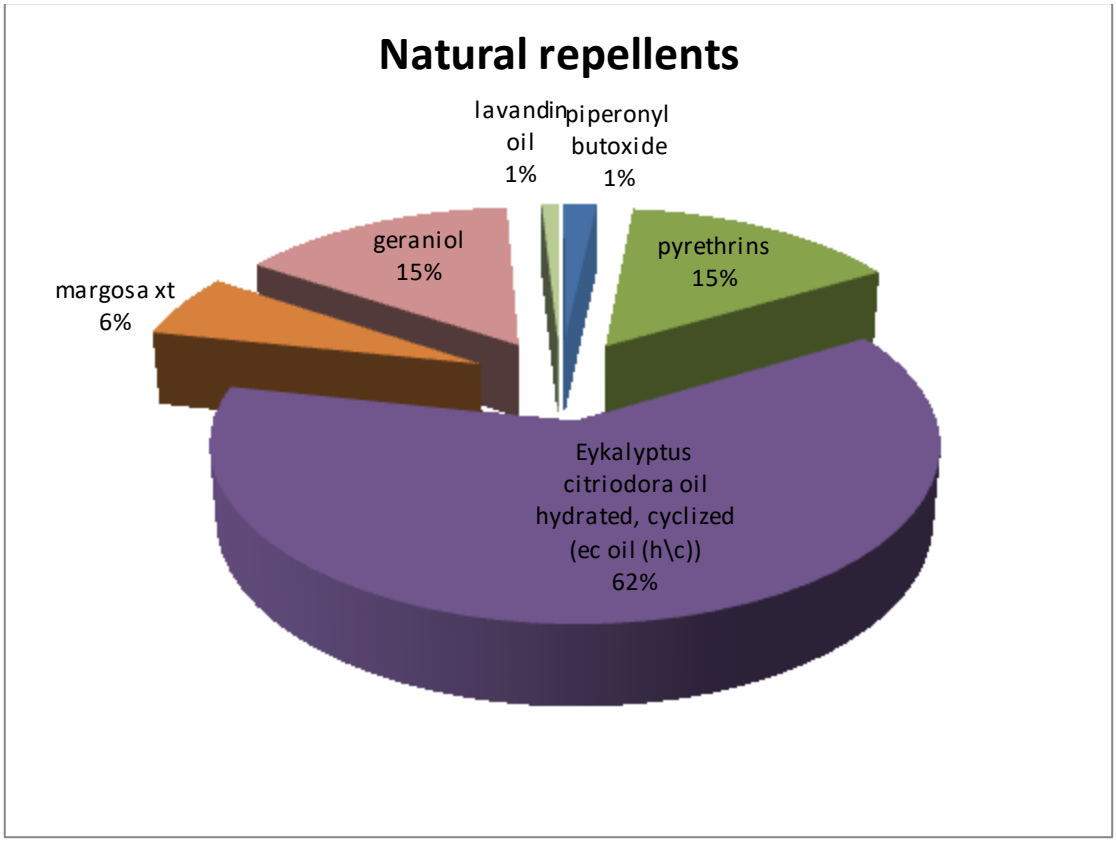


Chart 12: Represent the segmentation of synthetic-chemical Greek market by type.

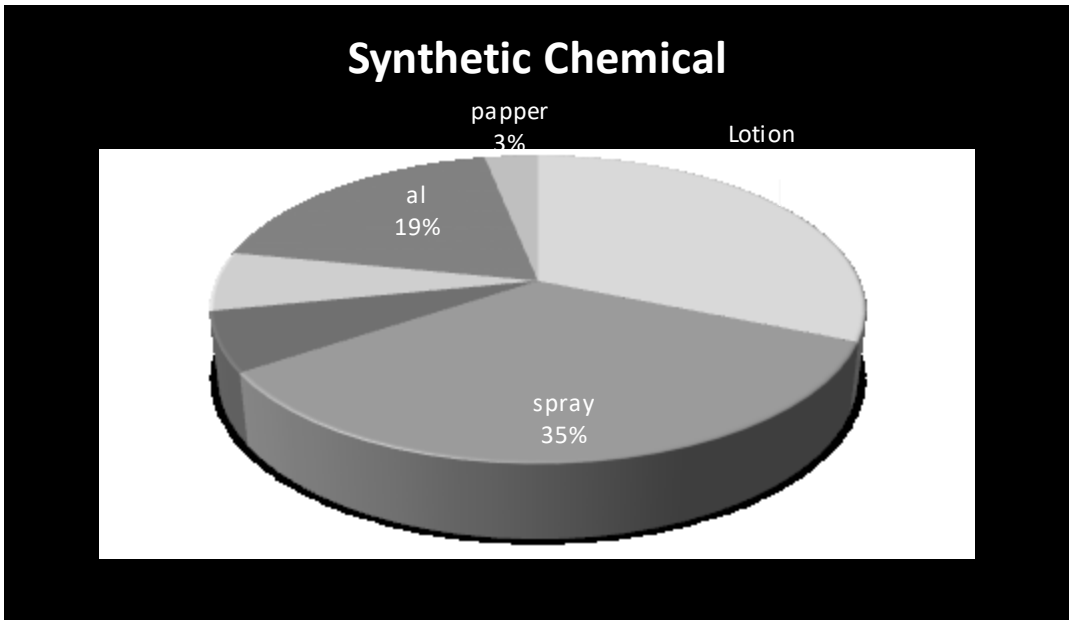


Chart 13: Represent the segmentation of natural Greek market by type

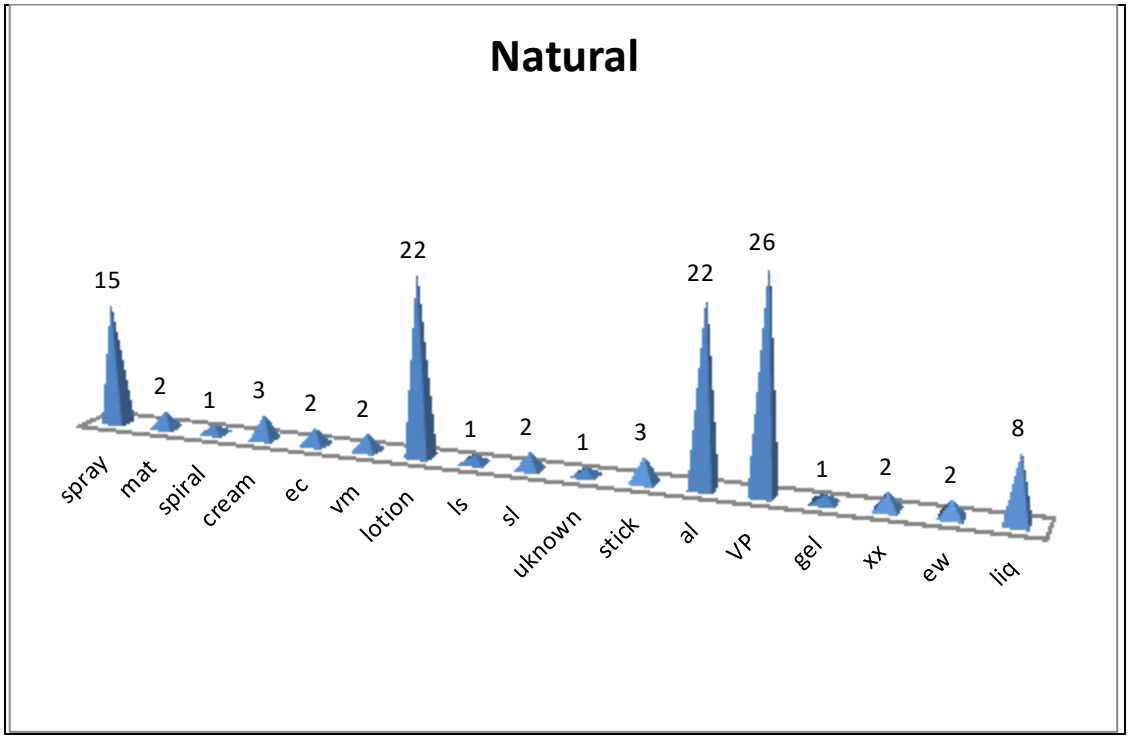


Chart 14: Represent the segmentation of total Greek market

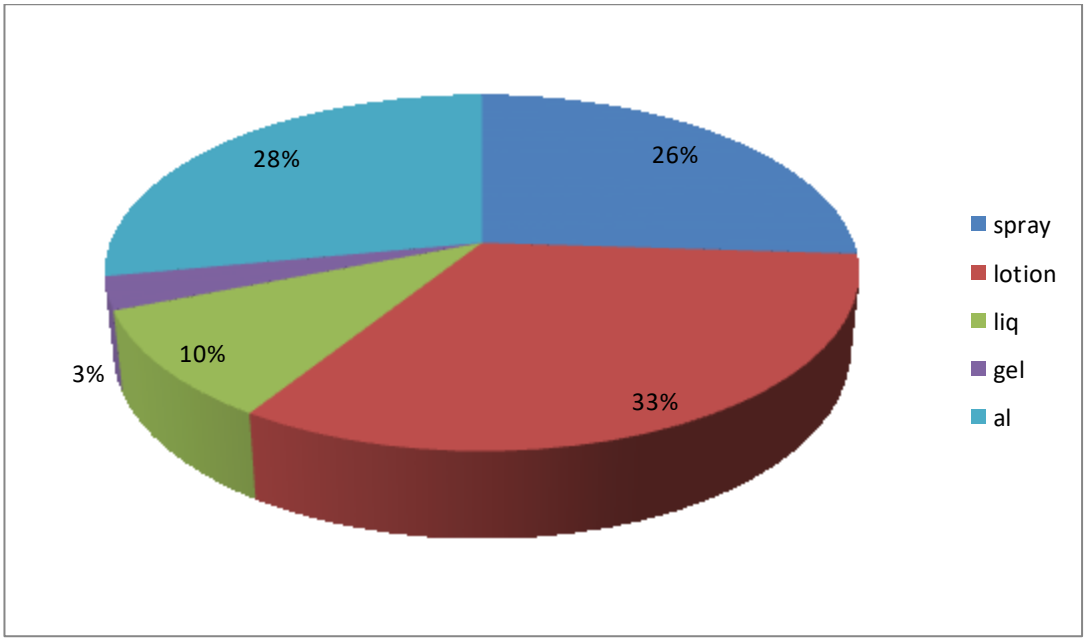


Table 2: Controlled release systems (CRS) of repellent active, encapsulating material, active repellent, production method

CRS	Encapsulating material	Repellent	Production method	References
Polymeric microcapsules and nanoparticles				
Polymeric Microcapsules	Alginate	Eucalyptu.s oil	Complex Coacervation	Chang & Dobashi (2003)
Polimeric Microcapsules	Alginate	DEPA	Emulsion technique followed by	Rakkiyappan et aL (2012)
Polymeric Microcapsules	Chitosan	Citronella essential oil	Coacervation	Hsieh et aL (2006)
Polymeric Microcapsules	Gelatine	Zanthoxylwn limonella essential oil	Coacervation	Maji & Hussain (2009)
Polymeric Microcapsules	Gelatine	Citronella essential oil	Coacervation	Solomon et aL (2012)
Polymeric Microcapsules	Alginate and Gelatine	Zanthoxylwn limonella essential oil	Double emulsion and solvent	Banerjee et aL (2013)
Polymeric Microcapsules	Chitosan	Limonene essential oil	Coacervation	Souza et aL (2014)
Polymeric Microcapsules	Polyurethane	DEET	Interfacial Polimerization	Ribeiro et aL (2016)
Polymeric Microcapsules	Polyhexamethylene biguanide	Picaridin	Complex Coacervation	Place et aL (2017)
	(BSA)			
Polymeric Microcapsules	Cetyl alcohol core/PEG 3350	DEET	Interfacial Precipitation	Misni et aL (2017)
Polymeric Microcapsules	Cetyl alcohol core/PEG 3350	Alpinia galanga essential oil	Interfacial Precipitation	Misni et aL (2017)
Polymeric Microcapsules	Cetyl alcohol core/PEG 3350	Citrus grandis essential oil	Interfacial Precipitation	Misni et aL (2017)
Polymeric Microcapsules	Cetyl alcohol core/PEG 3350	C. aurantifolia essential oil	Interfacial Precipitation	Misni et aL (2017)
Polymeric Microcapsules		Permethrin		GAT Microencapsulation (2018)
Polymeric Microcapsules		Permethrin		PermaCap CS (2018)
Nanoparticles	Sucralose, Ammonium	Permethrin	Micromulsification and Liophilization	Anjali et aL (2010)
	soybeanphosphatidylcholine			
Solid lipid				
Solid lipid Microparticles	Hydrogenated vegetable oil and	DEET	Precipitation	Domb et aL (1995)
Solid lipid Nanoparticles	Beeswax, Compritol ATO 888,	DEET	High-pressure homogenizer	Iscan et aL (2005)
	116, Imwitor 900			
Solid lipid Microparticles	Spermaceti and Polawax	DEET	Precipitation	Kasting et aL (2008)
Solid lipid Microparticles	Stearic acid	DEET	Ultrasound	Puglia et aL (2009)
Solid lipid Nanoparticles	Lanete 16NF, Citroflex A4,	DEET	Precipitation	Karr et aL (2012)
Solid lipid Nanoparticles •	Oleic acid, stearic acid and	lcaridin		Nano Vectors (2016)
(NanoIcaridin•)				
Solid lipid Nanoparticles •	Oleic acid, stearic acid and	Citronella and Rosemary essential oil		Nano Vectors (2016)
(NanoRepellent•)				
Lipid-core Nanocapsules	Polycaprolactone, sorbitan	Permethrin	Self-assembling	Forgearini et aL (2016)
	Monostearate and			
Lipospheres	Hhydrogenated vegetable oil	DEPA or DEET	Emulsification followed by cooling	Kalyanasundaram and Mathew
Nanoemulsions/microemulsions				-2006
Nanoemulsion	Montanov 82	Citronella oil	High-pressure homogenizer	Sakulku et aL (2009)
Nanoemulsion	Tween 80 e Span 80	Citronella oil	Hydrodynamic cavitation	Agrawal et aL (2017)
Nanoemulsion	Kolliphor"ELP	Andiroba oil	Phase Inversion Temperature (PIT)	Milhomem-Paixao et aL (2017)
Microemulsion	Cremophor RH40, Texapon N70,	p-Menthane-3,8-diol	Ternary Phase Diagram	Drapeau et aL, (2009)
Liposomes				
Liposomes	Phospholipids	DEET		Sawyer (2015)
Polymeric micelles				
Polymeric micelles (Nano-	PEG 400, Soya Lecithin and	DEPA	Polymerisation followed by PIT	Balaji et aL (2015)
			emulsification method	Balaji et aL (2017)
Polymeric micelles (Nano-	PEG 400, Soya Lecithin and	DEPA	Polymerisation followed by PIT	
			emulsification method	
Nanostructured hydrogels				
Micellar gel	Pluronic Fl27	DEET	High-speed Homogenizer	Barradas et aL (2013)
Micellar gel	Pluronic Fl27	Butylacetylaminopropionate (IR3535)	High-speed Homogenizer	Pinto et aL (2017)
Cyclodextrines				
Cyclodextrine	β)-ciclodextrine	Citronellol and Citronella! essential oils	Kneading	Songkro et aL (2012)
Cyclodextrine	β)-ciclodextrine	Permethrin	Complexation solid-liquid	Romi et aL (2005)

Chart 15: Gantt diagram of the operating program

Title	Month	1	2	3	4	10	12	13	18	19	20	22	23	24	27	30	33	34	35	36	start (month)	end (month)
Compounding of natural emulsions of plant insect repellents	Development and structural characterization of new biocompatible nanoparticles																				1	30
	Effects of nanoparticulation																					
	Physicochemical characteristics and stability of insect repellent emulsions. Copies of publications in journals and conferences																					
Discovering new natural ligands OBPs by Reverse Chemical Ecology	A list of plant associations with affinity and specialization for Obps-targets. Copies of publications in journals and conferences																				1	24
Determination of insect repellent activity and duration	Bioassay behavior. Copies of publications in journals and conferences																				4	33
Study of the safety of the active and moisturizing properties of the product	Report to cytotoxicity, epidermal and ocular irritation																				13	36
	Report epidermal permeability and moisturizing ability																					
	Dossier approval National Organization for Medicines of final products																					
Execution of a technical feasibility study	Contract with subcontractor																				27	36
	Technical feasibility study																					
Innovation of SMEs	Copy of a patent deposit																				27	35

Synthetic Chemical Repellents

Table 3: (Greek Republic Ministry of Rural Development and Food, 2017)

Ημ/νία Έγκρισης	Εμπορικό Όνομα	Εγγυημένη Σύνθεση	Ποσοστό %	Λήξη Εγκρισης	Λήξη Διάθεσης Αποθεμάτων	Κατηγορία	Παρασκευαστής	Χώρα	Υπεύθυνος Επικοινωνίας / Κάτοχος Έγκρισης	
30/4/2010	AUTAN FAMILY CARE lotion	icaridin	10% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	SCJ EurAFNELimited	ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	S.C. Johnson Hellas Ltd.	
18/1/2010	AUTAN FAMILY CARE stick	icaridin	10% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	SCJ EurAFNELimited	ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	S.C. Johnson Hellas Ltd.	
2/11/2009	AUTAN PROTECTION PLUS	AE	icaridin	16% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	S.C.JohnsonEuroAFNE Limited	ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	S.C. Johnson Hellas Ltd.
24/2/2010	HANSAPLAST INSECT REPELLENT spray	IR 3535	15% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	Beiersdorf AG	ΓΕΡΜΑΝΙΑΣ	BeiersdorfHellas AE	
23/6/2011	MOUSTIBLOK CL1	IR 3535	8% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΤΡΙΑ ΑΕΒΕ	ΕΛΛΑΔΑΣ	ΤΡΙΑ ΑΕΒΕ	
13/12/2011	TAN	IR 3535	15% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	VICAN Ν.ΑΝΑΓΝΩΣΤΑΚΗΣ ΚΑΙ ΣΙΑ ΕΕ	ΕΛΛΑΔΑΣ	VICAN Ν.ΑΝΑΓΝΩΣΤΑΚΗΣ ΚΑΙ ΣΙΑ ΕΕ	
16/4/2013	APAISYL εντομοαπωθητική-αντικουνουπικήλοσιόν	IR 3535	19.6% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	MERCK MEDICATION FAMILIALE	ΓΑΛΛΙΑΣ	ΠΕΤΣΙΑΒΑΣ ΑΕ	
25/11/2013	SUMMERLINE	IR 3535	8% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	MEDI SEI ΕΠΕ	ΕΛΛΑΔΑΣ	MEDI SEI ΕΠΕ	

29/4/2014	Repel By Uni-Pharma Spray	IR 3535	15% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	INTERMED, Ιουλία & Ειρήνη Τσέτη Φαρμακευτικά εργαστήρια ΑΒΕΕ	ΕΛΛΑΔΑΣ	UNI-PHARMA ΚΛΕΩΝ ΤΣΕΤΗΣ ΦΑΡΜΑΚΕΥΤΙΚΑ ΕΡΓΑΣΤΗΡΙΑ ΑΒΕΕ	
29/4/2014	Repel By Uni-Pharma gel	IR 3535	15% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	INTERMED, Ιουλία & Ειρήνη Τσέτη Φαρμακευτικά εργαστήρια ΑΒΕΕ	ΕΛΛΑΔΑΣ	UNI-PHARMA ΚΛΕΩΝ ΤΣΕΤΗΣ ΦΑΡΜΑΚΕΥΤΙΚΑ ΕΡΓΑΣΤΗΡΙΑ ΑΒΕΕ	
29/7/2014	JUNGLE FORMULA kids	IR 3535	20.4% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	JAICO RDP N.V.	ΒΕΛΓΙΟΥ	JAICO RDP N.V., ΒΕΛΓΙΟΥ	
13/10/2015	NoopieEpsilonHealth	IR 3535	20% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	JAICO RDP N.V.	ΒΕΛΓΙΟΥ	Νέστορας Βλάχος Ο.Ε.-EpsilonHealth	
30/10/2015	PHARMASEPT INSECT LOTION	IR 3535	8% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	PHARMASEPT ΕΠΕ	ΕΛΛΑΔΑΣ	PHARMASEPT ΕΠΕ	
23/7/2014	JUNGLE FORMULA STRONG ORIGINAL SPRAY	deet	19.38% β/ο	1/11/2023		ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	JAICO RDP N.V.	ΒΕΛΓΙΟΥ	ΩΜΕΓΑ ΦΑΡΜΑ ΕΛΛΑΣ Α.Ε	
18/12/2014	JUNGLE FORMULA MAXIMUM ORIGINAL SPRAY	deet	48.5% β/ο	1/8/2024		ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	JAICO RDP N.V.	ΒΕΛΓΙΟΥ	ΩΜΕΓΑ ΦΑΡΜΑ ΕΛΛΑΣ Α.Ε	
16/6/2017	AUTAN FAMILY CARE SOFT SPRAY	AE	deet	15% β/ο	20/2/2027		ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	SCJ EurAFNELimited	ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	S.C. Johnson Hellas Ltd.
16/6/2017	AUTAN PROTECTION PLUS SPRAY	AE	deet	25% β/β	20/2/2027		ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	SCJ EurAFNELimited	ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	S.C. Johnson Hellas Ltd.
7/11/2011	AUTAN JUNIOR	icaridin	10% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	S.C.JohnsonEuroAFNE Limited	ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	S.C. Johnson Hellas Ltd.	

30/4/2012	AGROGEN απωθητικό εντόμων	icaridin	16% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	PBW ACRYLMED	ΠΟΛΩΝΙΑ	Σάγκος ΑΒΕΕ - Agrogen	
23/5/2013	VAPONA skinrepellentlotion	icaridin	12% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	HENKEL HELLAS S.A.	ΕΛΛΑΔΑΣ	ΦΕΣΣΑΣ ΓΕΩΡΓΙΟΣ	
23/5/2013	VAPONA skinrepellentspray	icaridin	10% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	HENKEL HELLAS S.A.	ΕΛΛΑΔΑΣ	ΦΕΣΣΑΣ ΓΕΩΡΓΙΟΣ	
19/11/2013	VAPONA derm repellent aloe wipes	icaridin	9.88% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	GPM - HENKEL LIMITED	ΚΥΠΡΟΣ	ΦΕΣΣΑΣ ΓΕΩΡΓΙΟΣ	
19/11/2013	VAPONA derm repellent aloe lotion	icaridin	12% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	GPM - HENKEL LIMITED	ΚΥΠΡΟΣ	ΦΕΣΣΑΣ ΓΕΩΡΓΙΟΣ	
16/12/2013	ALONTAN FAMILY	icaridin	20% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	Pharmamillenniu mS.r.l.	ΙΤΑΛΙΑΣ	PharOS-Pharmaceutical Oriented Services Ltd	
29/7/2014	JUNGLE FORMULA strong soft care	icaridin	20.6% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	JAICO RDP N.V.	ΒΕΛΓΙΟΥ	JAICO RDP N.V., ΒΕΛΓΙΟΥ	
11/5/2015	Z-Z RED	icaridin	10% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ACTIVA s.r.l.	ΙΤΑΛΙΑΣ	ΦΑΡΜΑ-ΧΗΜ ΑΒΕΕ	
11/6/2015	AUTAN PROTECTION PLUS, Λοσιόν	icaridin	20% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	S.C.JohnsonEuroAFNE Limited	ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	S.C. Johnson Hellas Ltd.	
16/5/2016	INSECT OUT lotion	icaridin	10% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	fgw3 GmbH	ΓΕΡΜΑΝΙΑΣ	fgw3 GmbH, ΓΕΡΜΑΝΙΑΣ	
16/5/2016	INSECT OUT FORTE	icaridin	20% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	fgw3 GmbH	ΓΕΡΜΑΝΙΑΣ	fgw3 GmbH, ΓΕΡΜΑΝΙΑΣ	

11/10/2016	AUTAN PROTECT, Γαλάκτωμα	icaridin	20% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	SCJ EurAFNELimited	ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	SCJ EurAFNELimited, ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	
14/12/2016	APAISYL REPULSIF MOUSTIQUES	icaridin	19.4% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	MERCK MEDICATION FAMILIALE	ΓΑΛΛΙΑΣ	MERCK MEDICATION FAMILIALE, ΓΑΛΛΙΑΣ	
3/5/2017	AUTAN PROTECT	AE	icaridin	16% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	S.C.JohnsonEuroAFNE Limited	ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	S.C.JohnsonEuroAFNE Limited
25/7/2017	ANTIPIQUE LOTION	LT	icaridin	9.7% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ACTIVA s.r.l.	ΙΤΑΛΙΑΣ	ΤΑΦΑΡΜ, ΙΩΑΝΝΗΣ ΚΩΝ ΤΑΤΣΙΡΑΜΟΣ ΕΠΕ
2/11/2009	AUTAN PROTECTION PLUS	AE	icaridin	16% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	S.C.JohnsonEuroAFNE Limited	ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	S.C. Johnson Hellas Ltd.
19/3/2015	Vaponaprotectsticks	Methyl nonyl ketone	21.45% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	HENKEL HELLAS S.A.	ΕΛΛΑΔΑΣ	ΦΕΣΣΑΣ ΓΕΩΡΓΙΟΣ	
19/3/2015	Vaponaprotectsticks	Methyl nonyl ketone	21.45% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	HENKEL HELLAS S.A.	ΕΛΛΑΔΑΣ	ΦΕΣΣΑΣ ΓΕΩΡΓΙΟΣ	

Natural Repellents

Table 4: (Greek Republic Ministry of Rural Development and Food, 2017)

Ημ/νία Έγκρισης	Εμπορικό Όνομα	Εγγυημένη Σύνθεση	Ποσοστό %	Λήξη Έγκρισης	Λήξη Διάθεσης Αποθεμάτων	Κατηγορία	Παρασκευαστής	Χώρα	Υπεύθυνος Επικοινωνίας / Κάτοχος Έγκρισης	
18/10/2010	FLY OUT	piperonyl butoxide	14.1% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	OR.MA. s.a.s., di Mangogna& C	ΙΤΑΛΙΑΣ	ΤΟΥΤΟΥΤΖΙΔΑΚΗΣ ΑΝΤΩΝΗΣ & Σία Ε.Ε. AGRIBIZ	
10/11/2010	EXPEL MOSQ	pyrethrins	0.5% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΦΑΡΜΑ-ΧΗΜ ΑΒΕΕ	ΕΛΛΑΔΑΣ	ΦΑΡΜΑ-ΧΗΜ ΑΒΕΕ	

9/12/2010	FLERIANA, απωθητικό γαλάκτωμα κουνουπιών	Eykalyptus citriodora oil, hydrated, cyclized (ec oil (h\c))	10% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	PROVIPAX A.E.	ΕΛΛΑΔΑΣ	PROVIPAX A.E.	
15/3/2011	PYROX mat με φυσικές πυρεθρίνες	pyrethrins	2.3% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΣΑΡΑΝΤΗΣ ΑΒΕΕ	ΕΛΛΑΔΑΣ	ΣΑΡΑΝΤΗΣ ΑΒΕΕ	
15/3/2011	PYROX Spiral με φυσικές πυρεθρίνες	pyrethrins	0.25% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΣΑΡΑΝΤΗΣ ΑΒΕΕ	ΕΛΛΑΔΑΣ	ΣΑΡΑΝΤΗΣ ΑΒΕΕ	
12/10/2010	NATHERBA	pyrethrins	0.5% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΒΙΟΡΥΛ Α.Ε.	ΕΛΛΑΔΑΣ	ΒΙΟΡΥΛ Α.Ε.	
18/10/2010	FLY OUT	pyrethrins	1.75% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	OR.MA. s.a.s., di Mangogna& C	ΙΤΑΛΙΑΣ	ΤΟΥΤΟΥΤΖΙΔΑΚΗΣ ΑΝΤΩΝΗΣ & Σία Ε.Ε. AGRIBIZ	
29/6/2011	HEDSTOP	pyrethrins	0.4% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΒΙΟΡΥΛ Α.Ε.	ΕΛΛΑΔΑΣ	GOODAMI TRADING LTD	
	DEFON idea	pyrethrins	3.8% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	VAPALIGHT Limited	ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	DEFON Ε.Π.Ε	
21/3/2012	PIR O'SOL	pyrethrins	1.925% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ACTUS AE	ΕΛΛΑΔΑΣ	ACTUS AE	
21/6/2012	PIN FLY	pyrethrins	1.33% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	LEBO S.L.U	ΙΣΠΑΝΙΑΣ	AROMATICA	
27/6/2012	INSECTA	pyrethrins	1.8% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	Clearnet Κοινωνία κληρονόμων Παπαδημητρίου Μαρία	ΕΛΛΑΔΑΣ	Clearnet Κοινωνία κληρονόμων Παπαδημητρίου Μαρία	
12/10/2012	ROTANER fly	pyrethrins	2% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	MEGA SYSTEMS A.E.B.E.	ΕΛΛΑΔΑΣ	MEGA SYSTEMS A.E.B.E.	

16/10/2012	PIRACTOL	pyrethrins	1.3% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ACTUS AE	ΕΛΛΑΔΑΣ	ACTUS AE	
18/6/2013	QUITAMOS 1 EC	pyrethrins	1% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΒΙΟΡΥΛ Α.Ε.	ΕΛΛΑΔΑΣ	ΒΙΟΡΥΛ Α.Ε.	
1/7/2014	INTRAFLY POWER	pyrethrins	1.925% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	INTRACLEAN M.I.K.E	ΕΛΛΑΔΑΣ	INTRACLEAN M.I.K.E	
11/8/2016	ECOSOL R	pyrethrins	2% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	OR.MA S.r.l	ΙΤΑΛΙΑΣ	ΤΟΥΤΟΥΤΖΙΔΑΚΗΣ ΑΝΤΩΝΗΣ & Σία Ε.Ε. AGRIBIZ	
28/12/2011	OSKAR lotion	citriodiol	10% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	OSKAR HELLAS ΕΠΕ	ΕΛΛΑΔΑΣ	OSKAR HELLAS ΕΠΕ	
24/1/2012	MACROREPEL	eucalyptus citriodora oil, hydrated, cyclized (ec oil (h/c))	10% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	MACROVITA A & E ΒΑΣΙΛΑΚΑΚΗΟΕ	ΕΛΛΑΔΑΣ	MACROVITA A & E ΒΑΣΙΛΑΚΑΚΗΟΕ	
8/6/2012	MOSQUIT OFF	citriodiol	5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΦΑΙΝΟΜΕΝΟΝ ΕΠΕ Γενική Εμπορία Μονοπρόσωπη ΕΠΕ	ΕΛΛΑΔΑΣ	ΦΑΙΝΟΜΕΝΟΝ ΕΠΕ Γενική Εμπορία Μονοπρόσωπη ΕΠΕ	
23/6/2011	MOUSTIBLOK CL1	citriodiol	0.075% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΤΡΙΑ ΑΕΒΕ	ΕΛΛΑΔΑΣ	ΤΡΙΑ ΑΕΒΕ	
23/6/2011	MOUSTIBLOK CL2	citriodiol	7.5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΤΡΙΑ ΑΕΒΕ	ΕΛΛΑΔΑΣ	ΤΡΙΑ ΑΕΒΕ	
29/11/2011	BUG OFF	citriodiol	5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΜΑΥΡΟΓΙΑΝΝΗΣ Ε.Ε.Β.Τ.Ξ.Κ.Α.Ε. "MADIS A.E."	ΕΛΛΑΔΑΣ	ΜΑΥΡΟΓΙΑΝΝΗΣ Ε.Ε.Β.Τ.Ξ.Κ.Α.Ε. "MADIS A.E."	
8/6/2012	MOSQUIT OFF	citriodiol	5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΦΑΙΝΟΜΕΝΟΝ ΕΠΕ Γενική Εμπορία Μονοπρόσωπη ΕΠΕ	ΕΛΛΑΔΑΣ	ΦΑΙΝΟΜΕΝΟΝ ΕΠΕ Γενική Εμπορία Μονοπρόσωπη ΕΠΕ	

18/9/2012	ALGOGEL insectrepellent	citriodiol	8% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	Α. ΜΕΡΜΙΓΚΗ ΖΑΧΑΡΑΚΗ & ΣΙΑ ΕΕ	ΕΛΛΑΔΑΣ	Α. ΜΕΡΜΙΓΚΗ ΖΑΧΑΡΑΚΗ & ΣΙΑ ΕΕ	
30/10/2012	EF ROLL ON	citriodiol	30% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΣΑΡΑΝΤΗΣ ΑΒΕΕ	ΕΛΛΑΔΑΣ	ΣΑΡΑΝΤΗΣ ΑΒΕΕ	
30/10/2012	EF SPRAY	citriodiol	30% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΣΑΡΑΝΤΗΣ ΑΒΕΕ	ΕΛΛΑΔΑΣ	ΣΑΡΑΝΤΗΣ ΑΒΕΕ	
30/10/2012	EF CREAM	citriodiol	30% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΣΑΡΑΝΤΗΣ ΑΒΕΕ	ΕΛΛΑΔΑΣ	ΣΑΡΑΝΤΗΣ ΑΒΕΕ	
30/10/2012	EF STICK	citriodiol	32.09% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΣΑΡΑΝΤΗΣ ΑΒΕΕ	ΕΛΛΑΔΑΣ	ΣΑΡΑΝΤΗΣ ΑΒΕΕ	
2/1/2013	Helpic	citriodiol	10% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	AVIVA COSMETIC GMBH	ΓΕΡΜΑΝΙΑΣ	Καλλιανιώτης Δημήτριος	
8/4/2013	TOPSAFE spray	citriodiol	10% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	GOODAMI TRADING LTD	ΕΛΛΑΔΑΣ	GOODAMI TRADING LTD	
10/6/2013	NUPI lotion	citriodiol	5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΗΛΕΚΤΡΟΧΗΜΙΚΑ ΕΛΛΑΣ ΑΕΒΕ	ΕΛΛΑΔΑΣ	ΗΛΕΚΤΡΟΧΗΜΙΚΑ ΕΛΛΑΣ ΑΕΒΕ	
10/6/2013	BOSS lotion	citriodiol	5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	Πανέρας Ν. Δημήτριος	ΕΛΛΑΔΑΣ	Πανέρας Ν. Δημήτριος	
10/6/2013	ESQUITO lotion	citriodiol	10% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	GOODAMI TRADING LTD	ΕΛΛΑΔΑΣ	GOODAMI TRADING LTD	
18/6/2013	FLAMINGO εντομοαπωθητικό βραχιόλι	citriodiol	94.34% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	GOLD MAGIC CLEAN Μ.ΙΩΑΝΝΟΥ&ΣΙΑΟΕ	ΕΛΛΑΔΑΣ	GOLD MAGIC CLEAN Μ.ΙΩΑΝΝΟΥ&ΣΙΑΟΕ	

9/9/2013	MISS SANDY lotion	citriodiol	5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	MISS SANDY ABEE	ΕΛΛΑΔΑΣ	MISS SANDY ABEE	
4/10/2013	CHICCO αντικουνουπικό ROLL ON	citriodiol	7.5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ARTSANA SPA	ΙΤΑΛΙΑΣ	SustchemEngineering	
4/10/2013	CHICCO αντικουνουπικόσπρέϋ	citriodiol	7.5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ARTSANA SPA	ΙΤΑΛΙΑΣ	SustchemEngineering	
4/10/2013	CHICCO αντικουνουπικήγέλη	citriodiol	7.5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ARTSANA SPA	ΙΤΑΛΙΑΣ	CHICCO-ΣΚΑΡΜΟΥΤΣΟΣ Β. & Μ. Α.Ε.	
19/11/2013	ZANZARA BAND	citriodiol	32.8% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	VICAN Ν.ΑΝΑΓΝΩΣΤΑΚΗΣ ΚΑΙ ΣΙΑ ΕΕ	ΕΛΛΑΔΑΣ	VICAN Ν.ΑΝΑΓΝΩΣΤΑΚΗΣ ΚΑΙ ΣΙΑ ΕΕ	
24/1/2014	REPELKITO	citriodiol	6% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΒΙΟΡΥΛ Α.Ε.	ΕΛΛΑΔΑΣ	ΒΙΟΡΥΛ Α.Ε.	
11/2/2014	ZANZARA BAND bracelet	citriodiol	16.67% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	VICAN Ν.ΑΝΑΓΝΩΣΤΑΚΗΣ ΚΑΙ ΣΙΑ ΕΕ	ΕΛΛΑΔΑΣ	VICAN Ν.ΑΝΑΓΝΩΣΤΑΚΗΣ ΚΑΙ ΣΙΑ ΕΕ	
25/2/2014	NATGUARD CLIP 4VP	citriodiol	4% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΒΙΟΡΥΛ Α.Ε.	ΕΛΛΑΔΑΣ	ΒΙΟΡΥΛ Α.Ε.	
17/3/2014	M-Freelotion	citriodiol	8% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	BNeF Benefit Hellas A.E.	ΕΛΛΑΔΑΣ	BNeF Benefit Hellas A.E.	
21/3/2014	KATOL lotion	citriodiol	5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΠΑΠΑΠΕΤΡΟΠΟΥΛΟΣ ΝΙΚΟΛΑΟΣ	ΕΛΛΑΔΑΣ	ΠΑΠΑΠΕΤΡΟΠΟΥΛΟΣ ΝΙΚΟΛΑΟΣ	
21/3/2014	ZANZARA JUNIOR lotion	citriodiol	5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	VICAN Ν.ΑΝΑΓΝΩΣΤΑΚΗΣ ΚΑΙ ΣΙΑ ΕΕ	ΕΛΛΑΔΑΣ	VICAN Ν.ΑΝΑΓΝΩΣΤΑΚΗΣ ΚΑΙ ΣΙΑ ΕΕ	

2/4/2014	REPELKITO 10%	citriodiol	10% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΒΙΟΡΥΛ Α.Ε.	ΕΛΛΑΔΑΣ	ΒΙΟΡΥΛ Α.Ε.	
9/4/2014	NATGUARD SPRAY 20%	citriodiol	20% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΒΙΟΡΥΛ Α.Ε.	ΕΛΛΑΔΑΣ	ΒΙΟΡΥΛ Α.Ε.	
9/4/2014	REPELKITO PET 15%	citriodiol	15% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΒΙΟΡΥΛ Α.Ε.	ΕΛΛΑΔΑΣ	ΒΙΟΡΥΛ Α.Ε.	
9/4/2014	Mosi-guard Natural Spray Extra	citriodiol	40% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	CitrefineInternationalLtd	ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	Citrefine International Ltd, ΗΝΩΜΕΝΟΒΑΣΙΛΕΙΟ	
9/4/2014	Mosi-guardNaturalSpray	citriodiol	30% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	CitrefineInternationalLtd	ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	Citrefine International Ltd, ΗΝΩΜΕΝΟΒΑΣΙΛΕΙΟ	
9/4/2014	Mosi-guardNaturalStick	citriodiol	32% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	CitrefineInternationalLtd	ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	Citrefine International Ltd, ΗΝΩΜΕΝΟΒΑΣΙΛΕΙΟ	
9/4/2014	Mosi-guard Natural Roll On	citriodiol	30% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	CitrefineInternationalLtd	ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	ΔΑΦΝΗ Agrotrade ΕΠΕ	
16/4/2014	REPELKITO PET 5VP	citriodiol	5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΒΙΟΡΥΛ Α.Ε.	ΕΛΛΑΔΑΣ	ΒΙΟΡΥΛ Α.Ε.	
29/4/2014	ZANZARATΣΙΡΟΤΟ	citriodiol	5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	VICAN Ν.ΑΝΑΓΝΩΣΤΑΚΗΣ ΚΑΙ ΣΙΑ ΕΕ	ΕΛΛΑΔΑΣ	VICAN Ν.ΑΝΑΓΝΩΣΤΑΚΗΣ ΚΑΙ ΣΙΑ ΕΕ	
22/5/2014	PhysisRepellentLotion	citriodiol	30% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	PRIME SOLUTIONS ABEE	ΕΛΛΑΔΑΣ	PRIME SOLUTIONS ABEE	
22/5/2014	PhysisRepellentCream	citriodiol	30% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	PRIME SOLUTIONS ABEE	ΕΛΛΑΔΑΣ	PRIME SOLUTIONS ABEE	

27/5/2014	FUZI lotion	citriodiol	5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	EUROCHEMICA, ΣΤΥΛ. ΠΑΠΑΠΕΤΡΟΠΟΥΛΟΣ	ΕΛΛΑΔΑΣ	EUROCHEMICA, ΣΤΥΛ. ΠΑΠΑΠΕΤΡΟΠΟΥΛΟΣ	
27/5/2014	OSKAR repellent	citriodiol	5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	OSKAR HELLAS ΕΠΕ	ΕΛΛΑΔΑΣ	OSKAR HELLAS ΕΠΕ	
10/6/2014	REPELAN	citriodiol	6% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	Athena (Guangzhou Cosmetics Manufacturer Co. Ltd	ΚΙΝΑ	NOVAPHARM, ΒΛΑΝΤΗΣ Π. ΑΛΕΞΙΟΥ ΟΕ	
1/7/2014	M-Freecream	citriodiol	8% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	BNeF Benefit Hellas A.E.	ΕΛΛΑΔΑΣ	BNeF Benefit Hellas A.E.	
1/7/2014	M-Freeliquid	citriodiol	8% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	BNeF Benefit Hellas A.E.	ΕΛΛΑΔΑΣ	BNeF Benefit Hellas A.E.	
29/7/2014	JUNGLE FORMULA strong plants extract	citriodiol	36% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	JAICO RDP N.V.	ΒΕΛΓΙΟΥ	JAICO RDP N.V., ΒΕΛΓΙΟΥ	
19/3/2015	Vaponaprotectsticks	citriodiol	1.5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	HENKEL HELLAS S.A.	ΕΛΛΑΔΑΣ	ΦΕΣΣΑΣ ΓΕΩΡΓΙΟΣ	
11/5/2015	PERFECT CARE COLLAR	citriodiol	7% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	Χρυσόπουλος Βασίλειος & Σία ΟΕ.	ΕΛΛΑΔΑΣ	Χρυσόπουλος Βασίλειος & Σία ΟΕ.	
3/7/2015	MOSQUITO SHIELD	citriodiol	22.06% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	V.Y.T.E. ΙΚΕ	ΕΛΛΑΔΑΣ	V.Y.T.E. ΙΚΕ	
13/10/2015	PERFECT CARE SPRAY	citriodiol	0.7% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	Χρυσόπουλος Βασίλειος & Σία ΟΕ.	ΕΛΛΑΔΑΣ	Χρυσόπουλος Βασίλειος & Σία ΟΕ.	
13/10/2015	NATGUARD bracelet 3,5VP	citriodiol	3.5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΒΙΟΡΥΛ Α.Ε.	ΕΛΛΑΔΑΣ	ΒΙΟΡΥΛ Α.Ε.	

13/10/2015	NATGUARD pet 3,2 VP	citriodiol	3.2% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΒΙΟΡΥΛ Α.Ε.	ΕΛΛΑΔΑΣ	ΒΙΟΡΥΛ Α.Ε.	
30/11/2015	KORRES Ευκάλυπτος και Μύρτιλο	citriodiol	15% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	PRIME SOLUTIONS ABEE	ΕΛΛΑΔΑΣ	KORRES NATURAL PRODUCTS SA	
30/11/2015	NATGUARD fashionable 16.67VP	citriodiol	16.67% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΒΙΟΡΥΛ Α.Ε.	ΕΛΛΑΔΑΣ	ΒΙΟΡΥΛ Α.Ε.	
30/11/2015	NATGUARD SKIN WIPES 5%.	citriodiol	5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΒΙΟΡΥΛ Α.Ε.	ΕΛΛΑΔΑΣ	ΒΙΟΡΥΛ Α.Ε.	
1/3/2016	ZANZARA FLAT	citriodiol	21.28% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	VICAN Ν.ΑΝΑΓΝΩΣΤΑΚΗΣ ΚΑΙ ΣΙΑ ΕΕ	ΕΛΛΑΔΑΣ	VICAN Ν.ΑΝΑΓΝΩΣΤΑΚΗΣ ΚΑΙ ΣΙΑ ΕΕ	
4/3/2016	NATGUARD 6%	citriodiol	6% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΒΙΟΡΥΛ Α.Ε.	ΕΛΛΑΔΑΣ	ΒΙΟΡΥΛ Α.Ε.	
4/3/2016	FLERIANA ΑΝΤΙΚΟΥΝΟΥΠΙΚΟ ΜΑΝΤΗΛΑΚΙ	citriodiol	11.13% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	PROVIPAX Α.Ε.	ΕΛΛΑΔΑΣ	PROVIPAX Α.Ε.	
23/3/2016	SAM IonesBetty (Εντομοαπωθητικό γαλάκτωμα)	citriodiol	15% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	BiocidetechLimited	ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	BiocidetechLimited, ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	
23/3/2016	CER'8 MicrocapsulesPatch	citriodiol	2.74% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	VICAN Ν.ΑΝΑΓΝΩΣΤΑΚΗΣ ΚΑΙ ΣΙΑ ΕΕ	ΕΛΛΑΔΑΣ	VICAN Ν.ΑΝΑΓΝΩΣΤΑΚΗΣ ΚΑΙ ΣΙΑ ΕΕ	
1/6/2016	NOBUGS lotion	citriodiol	8% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΒΟΣΚΑΚΗΣ ΓΕΩΡΓΙΟΣ & ΣΙΑ ΟΕ	ΕΛΛΑΔΑΣ	ΒΟΣΚΑΚΗΣ ΓΕΩΡΓΙΟΣ & ΣΙΑ ΟΕ	
16/6/2016	CARE ΑΝΤΙΚΟΥΝΟΥΠΙΚΟ SPRAY ΓΑΛΑΚΤΩΜΑ ΣΩΜΑΤΟΣ	citriodiol	14% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	PROVIPAX Α.Ε.	ΕΛΛΑΔΑΣ	PROVIPAX Α.Ε.	

4/8/2016	ANTIPHLEBOTOME SPRAY	citriodiol	20% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΤΑΦΑΡΜ, ΙΩΑΝΝΗΣ ΚΩΝ ΤΑΤΣΙΡΑΜΟΣ ΕΠΕ	ΕΛΛΑΔΑΣ	ΤΑΦΑΡΜ, ΙΩΑΝΝΗΣ ΚΩΝ ΤΑΤΣΙΡΑΜΟΣ ΕΠΕ	
8/8/2016	APOTHOL SPRAY	citriodiol	20% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	Morpheussarl	ΓΑΛΛΙΑΣ	ΤΑΦΑΡΜ, ΙΩΑΝΝΗΣ ΚΩΝ ΤΑΤΣΙΡΑΜΟΣ ΕΠΕ	
14/2/2017	PHARMALEAD απωθητικό spray για κουνούπια	eucalyptus citriodora oil hydrated, cyclized	5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	VITORGAN ΜΟΝΟΠΡΟΣΩΠΗ Ε.Π.Ε.	ΕΛΛΑΔΑΣ	VITORGAN ΜΟΝΟΠΡΟΣΩΠΗ Ε.Π.Ε.	
14/2/2017	PHARMALEAD εντομοαπωθητικό αυτοκόλλητο	eucalyptus citriodora oil hydrated, cyclized	5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	VITORGAN ΜΟΝΟΠΡΟΣΩΠΗ Ε.Π.Ε.	ΕΛΛΑΔΑΣ	VITORGAN ΜΟΝΟΠΡΟΣΩΠΗ Ε.Π.Ε.	
29/3/2017	CER'8 lotion	eucalyptus citriodora oil hydrated, cyclized	6.5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	Αφοί Σ. Παπαπετρόπουλου ΟΕ, ACTIVA HELLAS	ΕΛΛΑΔΑΣ	VICAN Ν.ΑΝΑΓΝΩΣΤΑΚΗΣ ΚΑΙ ΣΙΑ ΕΕ	
29/3/2017	BUG OFF Family	eucalyptus citriodora oil hydrated, cyclized	6% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΜΑΥΡΟΓΙΑΝΝΗΣ Ε.Ε.Β.Τ.Ξ.Κ.Α.Ε. "MADIS A.E."	ΕΛΛΑΔΑΣ	ΜΑΥΡΟΓΙΑΝΝΗΣ Ε.Ε.Β.Τ.Ξ.Κ.Α.Ε. "MADIS A.E."	
25/7/2017	BLOCK MAGIC AntiMosquitos	EW	eucalyptus citriodora oil, hydrated, cyclized (ec oil (h/c))	10% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	SmellwellVertriebsGmbH	ΑΥΣΤΡΙΑΣ	Lidl Ελλάς και ΣΙΑ Ο.Ε
25/7/2017	Smellwell απωθητικό κουνουπιών	EW	eucalyptus citriodora oil, hydrated, cyclized (ec oil (h/c))	10% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	SmellwellVertriebsGmbH	ΑΥΣΤΡΙΑΣ	SmellwellVertriebsGmbH
22/5/2017	TOP STOP REPELLENT	AE	pyrethrins	2.75% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΝΤΙΛΑΞΟ ΕΛΛΑΣ Μ.Ι.Κ.Ε	ΕΛΛΑΔΑΣ	ΝΤΙΛΑΞΟ ΕΛΛΑΣ Μ.Ι.Κ.Ε
9/10/2013	VITALVET O collar	margosa ext	2% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	BEAPHAR SAS	ΓΑΛΛΙΑΣ	GOODAMI TRADING LTD	
9/10/2013	VITALVET O spoton	margosa ext	8% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	AGROBIOTHERS	ΓΑΛΛΙΑΣ	GOODAMI TRADING LTD	

11/5/2015	PERFECT CARE COLLAR	margosa ext	3% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	Χρυσόπουλος Βασίλειος & Σία ΟΕ.	ΕΛΛΑΔΑΣ	Χρυσόπουλος Βασίλειος & Σία ΟΕ.	
13/10/2015	PERFECT CARE SPRAY	margosa ext	0.3% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	Χρυσόπουλος Βασίλειος & Σία ΟΕ.	ΕΛΛΑΔΑΣ	Χρυσόπουλος Βασίλειος & Σία ΟΕ.	
16/6/2016	INFRONT solution	margosa ext	0.45% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	BEAPHAR Hellas	ΕΛΛΑΔΑΣ	ΛΥΔΙΑ ΕΠΕ	
16/6/2016	TOP SAFE NEW Collar	margosa ext	2.5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	DARYGTON MANAGEMENT LIMITED	ΕΛΛΑΔΑΣ	DARYGTON MANAGEMENT LIMITED	
3/8/2016	REPELI solution	margosa ext	0.52% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	BEAPHAR Hellas	ΕΛΛΑΔΑΣ	ΛΥΔΙΑ ΕΠΕ	
12/10/2012	ROTANER fly	piperonyl butoxide	14.2% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	MEGA SYSTEMS A.E.B.E.	ΕΛΛΑΔΑΣ	MEGA SYSTEMS A.E.B.E.	
22/11/2010	GERANIOL -AB7 Industries-2,19 VP	geraniol	2.19% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	AB7 Industries	ΓΑΛΛΙΑΣ	AB7 Hellas	
23/11/2010	GERANIOL -AB7 Industries-2,5 VP	geraniol	2.25% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	AB7 Industries	ΓΑΛΛΙΑΣ	AB7 Hellas	
24/2/2011	NATGUARD	geraniol	2.5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΒΙΟΡΥΛ Α.Ε.	ΕΛΛΑΔΑΣ	ΒΙΟΡΥΛ Α.Ε.	
29/6/2011	TOPSAFE VP	geraniol	3% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΒΙΟΡΥΛ Α.Ε.	ΕΛΛΑΔΑΣ	GOODAMI TRADING LTD	
8/4/2013	ANTIPHLEBOTOME COLLAR	geraniol	2.38% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΤΑΦΑΡΜ, Ι.ΤΑΤΣΙΡΑΜΟΣ & ΣΙΑ ΟΕ	ΕΛΛΑΔΑΣ	ΤΑΦΑΡΜ, Ι.ΤΑΤΣΙΡΑΜΟΣ & ΣΙΑ ΟΕ	

17/4/2013	FLERIANA εντομοαπωθητικό υγρό	geraniol	10% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	PROVIPAX A.E.	ΕΛΛΑΔΑΣ	PROVIPAX A.E.	
16/12/2013	APOTHOL spoton	geraniol	0.97% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	AB7 Industries	ΓΑΛΛΙΑΣ	ΤΑΦΑΡΜ, Ι.ΤΑΤΣΙΡΑΜΟΣ & ΣΙΑ ΟΕ	
16/12/2013	ANTIPHLEBOTOME spoton	geraniol	0.97% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΤΑΦΑΡΜ, Ι.ΤΑΤΣΙΡΑΜΟΣ & ΣΙΑ ΟΕ	ΕΛΛΑΔΑΣ	ΤΑΦΑΡΜ, Ι.ΤΑΤΣΙΡΑΜΟΣ & ΣΙΑ ΟΕ	
7/2/2014	NATGUARD PET 3VP	geraniol	3% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΒΙΟΡΥΛ A.E.	ΕΛΛΑΔΑΣ	ΒΙΟΡΥΛ A.E.	
15/10/2014	VaponaWristband	geraniol	10% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	HENKEL HELLAS S.A.	ΕΛΛΑΔΑΣ	ΦΕΣΣΑΣ ΓΕΩΡΓΙΟΣ	
23/3/2016	SAM loves Betty (ΥγρόΕντομοαπωθητικό)	geraniol	8% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	BiocidetechLimited	ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	BiocidetechLimited, ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	
23/3/2016	SAM lovesBetty (Εντομοαπωθητική Κάψουλα)	geraniol	21.79% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	BiocidetechLimited	ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	BiocidetechLimited, ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	
23/3/2016	SAM LovesBetty (Εντομοαπωθητικό Κερί)	geraniol	6% β/ο			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	BiocidetechLimited	ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	BiocidetechLimited, ΗΝΩΜΕΝΟ ΒΑΣΙΛΕΙΟ	
16/6/2016	INFRONT solution	geraniol	0.45% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	BEAPHAR Hellas	ΕΛΛΑΔΑΣ	ΛΥΔΙΑ ΕΠΕ	
16/6/2016	TOP SAFE NEW Collar	geraniol	2.5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	DARYGTON MANAGEMENT LIMITED	ΕΛΛΑΔΑΣ	DARYGTON MANAGEMENT LIMITED	
3/8/2016	REPELI solution	geraniol	0.38% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	BEAPHAR Hellas	ΕΛΛΑΔΑΣ	ΛΥΔΙΑ ΕΠΕ	

22/5/2017	TOP STOP REPELLENT	AE	geraniol	2.63% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	ΝΤΙΛΑΞΟ ΕΛΛΑΣ Μ.Ι.Κ.Ε	ΕΛΛΑΔΑΣ	ΝΤΙΛΑΞΟ ΕΛΛΑΣ Μ.Ι.Κ.Ε
9/10/2013	VITALVET O collar	lavandin oil	1.5% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	BEAPHAR SAS	ΓΑΛΛΙΑΣ	GOODAMI TRADING LTD	
16/5/2011	CLEAR SCORE lanterna	pyrethrins	4% β/β			ΑΠΩΘΗΤΙΚΑ ΚΑΙ ΠΡΟΣΕΛΚΥΣΤΙΚΑ (ΤΠ-19)	MEGA SYSTEMS Α.Ε.Β.Ε.	ΕΛΛΑΔΑΣ	MEGA SYSTEMS Α.Ε.Β.Ε.	

Table 5: Substances review/under review as biocides type PT-19 (ECHA, 2017)

Substance Names	EC Numbers	Cas Numbers	PT	eCA	Type of application	Status
Eucalyptus citriodora oil, hydrated, cyclized		1245629-80-4	19	UK	Existing active substance	In progress
Geraniol	203-377-1	106-24-1	19	FR	Existing active substance	In progress
Lavender, Lavandula hybrida, ext/Lavandin oil	294-470-6	91722-69-9	19	PT	Existing active substance	In progress
Margosa extract		84696-25-3	19	DE	Existing active substance	In progress
Pyrethrins and Pyrethroids	232-319-8	8003-34-7	19	ES	Existing active substance	In progress
sec-butyl 2(2-hydroxyethyl)piperidine-1-carboxylate/Icaridine(Icaridine)	423-210-8	119515-38-7	19	DK	Existing active substance	In progress
Metofluthrin		240494-71-7	19	SE	New active BPD	In progress
N,N-diethyl-meta-toluamide	205-149-7	134-62-3	19			Approved
methyl nonyl ketone		240494-71-7	19			Approved
Nonanoic acid, Pelargonic acid	203-931-2	112-05-0	19			Approved
(Z,E)-tetradeca-9,12-dienyl acetate		30507-70-1	19			Approved
cis-tricos-9-ene (Muscalure)	248-505-7	27519-02-4	19			Approved
Ethyl butylacetylaminopropionate	257-835-0	52304-36-6	19			Approved
Lauric acid	205-582-1	143-07-7	19			Approved
Decanoic acid	206-376-4	34-48-5	19		Existing active substance	Approved

Natural

Table 9: Natural insect repellents (Skroutz.gr, 2018, keyword ‘’εντομοαπωθητικά’’, entomoapothitika)

 0.059€/ml **Insect repellent action:** **Citronella**	Crilen cream herbal protective emulsion with insect repellent action by Frezyderm. Crilen Cream repels insects while moisturizing and nourishing the skin. Its action is due to the active ingredients it contains: Sitronella: Insect repellent action, Allantoin | Vitamin E, Betaine | Sodium Hyaluronate: Moisturizing action.
 0.034€/ml **Insect repellent action:** **Citridiol® / blueberry extract**	Korres Eucalyptus & Blueberry with insect repellent from the plant Eucalyptus Citriodora and blueberry extract. Insect repellent body and face emulsion protects the skin and leaves a gentle hydration sensation
 0.13€/ml **Insect repellent action:** **Citridiol®**	Mosquit.Off No More Bites Stick by 3M Insect repellent protect from mosquitoes, midges & other biting insects
 0.035€/ml **Insect repellent action**: C**itridiol®**	ErgoPharm Protection Lotion by Algogel With Aloe Vera and Allantoin

 0.012€/ml **Insect repellent action: Citridiol®**	Antimosquito Insect Repellent Family Lotion by Miss Sandy
 0.047€/ml **Insect repellent action: Citridiol® or Geraniol**	Fleriana® Natural Mosquito Repellent Emulsion Roll-On, by Power Heallth
 0.041€/ml **Insect repellent action: Citridiol® or Geraniol**	Sam loves Betty™, effective mosquito repellent emulsion for the body with active ingredients of plant origin
 0.080€/ml **Insect repellent action: Citridiol®**	Mosi-guard® Natural Insect Repellent Spray by Citrefine Int'l Ltd

 0.044€/ml **Insect repellent action: Citridiol®**	Pharmalead Insect Repellent Spray by Vitogan Combination of five essential oils of plant origin (geranium, peppermint, eucalyptus, lavender and basil) that protects and cares the skin.

Synthetic

Table 10: Synthetic insect repellents (Skroutz.gr 8/18, keyword ''εντομοαπωθητικά'', entomoapothitika)

 0.030€/ml Spray 0.052€/ml Lotion **Contains Insect repellent action: IR3535**	Hansaplast Anti-Insect Spray. Insect repellent spray that provides skin-friendly protection and mosquito protection it has a non-greasy composition and pleasant aroma.
 0.060€/ml Spray 0.072€/ml Lotion **Contains insect repellent action: DEET**	Autan® Protection Plus by Johnson&Son. Dry skin sensation. Protection against 3 species of insect, mosquitoes, stinging flies and ticks.

 0.100€/ml Stick **Contains insect repellent action: Icaridin**.	Autan® Family Care Mosquito repellent by Johnson&Son.
 0.12€/ml **Contains insect repellent action: Deet**	Jungle Formula Maximum Insect repellent action by Omega Pharma. Repels mosquitoes and biting insects.
 **Contains insect repellent action: Icaridin**	Alontan® Family Insect repellent action by Pietrasanta pharma spa.
 **0**.063€/ml **Contains insect repellent action: Icaridin**	Apaisyl Insect Repellent Lotion by Merck Medication Familiale Insect repellent body and face
 0.058€/ml **Contains insect repellent action:IR3535**	Zanzara®Tan Insect Repellent Spray by Vican

Advertised as Herbal Insect Repellents

(Without permission by Greek Republic Ministry of Rural Development and Food)

Table 11: Insect repellents advertised as herbal without permission by Greek Republic Ministry of Rural Development and Food (Skroutz.gr 8/18, keyword ‘’εντομοαπωθητικά’’, entomoapothitika)

 0.045€/ml	Garden of Panthenols. Herbal moisturizer with essential oils of basil, geranium, lavender. Ideal for countryside and summer nights.
 0.037/ml	Fytocura nights and day hydrating lotion. Moisturizing lotion contains lavender, eucalyptus, thyme and basil.
 0.063€/ml	ApivitaPropoline. Natural Body Lotion for Summer Days and Nights with Basol & Geranium.

Synthetically advertised as naturally

(Licensed by Greek Republic Ministry of Rural Development and Food)

IR3535 and icaridin are both synthetic compounds developed as alternatives to DEET. However, IR3535 is considered as a biopesticide because it is obtained from a natural amino acid, beta alanine and therefore is often advertised as natural repellent.

Table 12: Synthetic insect repellents advertised as natural (Skroutz.gr, 2018, keyword ‘’εντομοαπωθητικά’’, entomoapothitika)

 0.079€/ml Mousse 0.114€/ml Gel 0.048€/ml Spray **Contains insect repellent action: IR3535**,	Repel by UNI-PHARMA. Moisturizing and protective with insect-repellent action and hyaluronate. The active ingredient IR3535, a naturally occurring repellent
 0.069€/ml **Contains insect repellent action: IR3535**,	Insect Lotion by Pharmasept. Repellent spray for mosquitoes & mites. Its effective composition contains 8% IR3535. Contains: Citronella, Eucalyptus, Lavender, Tea Tree oil Natural essential oils distinguished for their insect repellent properties. Aloe Vera, Allantoin, Provitamin B5 Moisturizes & cleanses the skin. Protective body lotion for calm summer days & nights with natural essential oils.
 0.053€/ml **Contains insect repellent action: IR3535**	Summerline Insect Repellent Cream with Aloe Vera by Medisei Pleasant aroma based on the combination of natural citronella essential oils, eycalyptus, basilic and geranium

SWOT analysis

Table 15: SWOT analysis of final product

SWOT analysis	
Strengths	**Weaknesses**
• 100% Natural product • Natural insect repellent with cosmetic properties • Innovation product with a competitive advantage using plant origin nanoemulsions and essential oils from unexplored Greek flora to increase the repellent activity • Use of an innovative AXO method for the discovery of new essential oils (AXO essential oils) with proven repelling effect • Continuous growth of insect repellent industry • Safe and appropriate for adults and children • It will be launched under the brand name of an already existing well know company (Qualia Pharma) • Existing channels of promotion and sales of the partner company • The retail price of the final product is lower than the average retail price of the competition	• Possible risk as it is an innovative product • High cost for approval of new AXO essential oils as insect repellents PT-19 • The risk that the proposed biocompatible surfactants and oils not to lead to the formation of stable nanoparticles. • The likelihood that nanoemulsions will not have satisfactory moisturizing capacity
Opportunities	**Threats**
• Word concern for mosquito-transmitted diseases • Turning consumers towards natural products • Continuous technological progress and improvement of new technologies to produce efficient products	• Economic crisis affecting Greece • Reduce consumer in existing products • Possibility of product replication by other companies • High degree of insect repellent market share concentration