

(19) **DANMARK**

(10) **DK/EP 2416785 T3**



(12) **Oversættelse af  
europæisk patentskrift**

Patent- og  
Varemærkestyrelsen

- 
- (51) Int.Cl.: **A 61 K 31/715 (2006.01)** **A 61 K 38/14 (2006.01)**
- (45) Oversættelsen bekendtgjort den: **2016-04-11**
- (80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2016-02-10**
- (86) Europæisk ansøgning nr.: **10714402.4**
- (86) Europæisk indleveringsdag: **2010-04-06**
- (87) Den europæiske ansøgnings publiceringsdag: **2012-02-15**
- (86) International ansøgning nr.: **US2010030097**
- (87) Internationalt publikationsnr.: **WO2010118028**
- (30) Prioritet: **2009-04-06 US 167005 P**
- (84) Designerede stater: **AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO SE SI SK SM TR**
- (73) Patenthaver: **Levine, Joshua D., 106 Circadian Way, Chapel Hill, North Carolina 27516, USA**  
**Levine, Robert A., 31 Pilgrim Lane, Guilford, CT 06437, USA**
- (72) Opfinder: **Levine, Joshua D., 106 Circadian Way, Chapel Hill, North Carolina 27516, USA**  
**Levine, Robert A., 31 Pilgrim Lane, Guilford, CT 06437, USA**
- (74) Fuldmægtig i Danmark: **Budde Schou A/S, Hausergade 3, 1128 København K, Danmark**
- (54) Benævnelse: **Fremgangsmåde til behandling og forebyggelse af neuro-olfaktorisk udløste eller forværrede sygdomme eller relaterede tilstande**
- (56) Fremdragne publikationer:  
**US-B1- 6 528 081**  
**MILLQVIST E ET AL: "Provocations with perfume in the eyes induce airway symptoms in patients with sensory hyperreactivity" ALLERGY (COPENHAGEN), vol. 54, no. 5, May 1999 (1999-05), pages 495-499, XP002583772 ISSN: 0105-4538**  
**MILLQVIST E ET AL: "Placebo-controlled challenges with perfume in patients with asthma-like symptoms" ALLERGY (COPENHAGEN), vol. 51, no. 6, 1996, pages 434-439, XP002583773 ISSN: 0105-4538**  
**BELL I R: "White paper: Neuropsychiatric aspects of sensitivity to low-level chemicals: A neural sensitization model" TOXICOLOGY AND INDUSTRIAL HEALTH, PRINCETON, NJ, US, vol. 10, no. 4-5, 1 January 1994 (1994-01-01), pages 277-312, XP009133915 ISSN: 0748-2337**



# DESCRIPTION

## BACKGROUND OF THE INVENTION

### 1. Technical Field

[0001] This invention relates to the field of treating neuro-olfactory triggered or related or exacerbated conditions in general, and to temporarily and safely disabling and/or inhibiting a subject's sense of smell in particular.

### 2. Background Information

[0002] Many physical conditions are known to be triggered or caused in whole, or in part, or aggravated by a neuro-olfactory response to an odorant or irritant chemical (hereinafter referred to as an odorant or an odor), or chemicals sensed by the olfactory receptors of a subject. Such conditions (sometimes referred to as "disorders") can include one or more of multiple chemical sensitivity, somatoform disorder, chronic fatigue syndrome, fibromyalgia, panic disorder, autism, epilepsy, asthma and posttraumatic stress disorder in which afflicted individuals have may hypersensitivity to chemical odorants. For instance, panic attacks have been shown to be triggered by certain odorants in susceptible individuals. Over-eating habits that lead to obesity also have a complex, not yet completely understood, neuro-olfactory components.

[0003] Multiple Chemical Sensitivity (MCS) is one example of a disorder, or constellation of disorders, that causes certain individuals to have multi-organ symptoms in response to low-level chemical exposures that are considered safe for the general population. Individuals with MCS may experience a large catalogue of debilitating symptoms after an exposure to certain chemical substances. Examples of debilitating symptoms include the following: a) neurologic symptoms including headache, fatigue, irritability, cognitive dysfunction, decreased attention span, loss of concentration and memory, dizziness, loss of motivation, confusion, sleep disturbances, anxiety, depression, mood swings, neurasthenia, numbness, hyperactivity, shortness of breath, tingling/numbness in fingers/toes; b) cardiovascular symptoms including palpitations, irregular heartbeat, etc.; c) respiratory symptoms including dyspnea, cough, chest pain and tightness, shortness of breath, rhinorrhea, nasal and eye burning, pharyngeal irritation; d) gastrointestinal symptoms include dyspepsia, diarrhea, nausea; e) genitourinary symptoms including dysmenorrhea, urinary frequency, ovarian cysts; f) musculoskeletal symptoms including myalgia, weakness, muscle tension, arthralgia, dyskinesia; and g) dermatologic symptoms including skin irritation.

[0004] The degree of sensitivity to each odorant or irritant chemical varies with each individual with MCS, but a general, but non-comprehensive, list of problem odorants and irritant chemicals that includes: solvents, pesticides, combustion products of gas, oil, and coal, fresh paint, turpentine, mineral spirits, fertilizers, perfumes, cosmetics, nail polish, cleaning products, air fresheners, cigarette smoke, carpet, adhesives, building materials, automobile and diesel exhaust, roof and road tar, industrial air pollutants, chemical preservatives (sulfur, sweetening agents), chlorine in water, medications, synthetic textiles, copy machines, and laser printers. The prevalence of this disorder in the United States is believed to be between 0.2% and 6% of the population, with 4% being an often-cited figure. In one study, Silberschmidt reports that thirty percent (30%) of all Swedish housepainters were shown to have MCS. Approximately thirty percent (30%) of the entire population experiences some low-level, but often debilitating, response to aggravating chemicals.

[0005] While the etiology of MCS is not known, it is generally felt to be triggered by the olfactory stimulation either by odor or irritant of the olfactory receptors, and subsequent stimulation of the limbic system, and or other areas of the brain resulting in the complex and varied symptoms known to be manifestations of the MCS. Some experts believe that a psychological conditioning response to odors that previously triggered an adverse reaction in the individual plays a role in the overall causal mechanism for MCS. The condition MCS is assumed to be developed in two steps: a) an initial phase with exposure often to a high concentration of a chemical substance; and b) a trigger phase, which is the subsequent set off of a number of symptoms by exposure to low concentrations of chemicals. Researchers have shown that, in a kind of compounded Pavlovian response, when an individual is experiencing adverse affects from one chemical, other inhaled chemical odorants that are in proximity to the individual at the time, may be added to the triggering odorants. The number of chemicals that a MCS individual are sensitive to may increase exponentially in this manner.

[0006] While avoidance of exposure to all manner of neuro-olfactory triggers is typically the prescribed course of action, this

strategy is obviously difficult, if not impossible, to carry out. Perfumes, personal fragrances, paints, aerosol sprays, indoor carpets, household cleaners, pollutant from building materials and mattresses are a small sample of the routine chemicals encountered daily which may make a neuro-olfactory sensitive person (e.g., someone who suffers from MCS) seriously ill. Such illnesses often greatly limit a subject's ability to work, shop, travel, and socialize. Many subjects become homebound due to their illness. The illness can be severely disabling to the patient and costly to society.

**[0007]** Another neuro-olfactory triggered condition is the common reaction of nausea and/or disgust upon exposure to the odorants associated with rotten flesh or food, especially protein containing foods, feces, anaerobic infections and other pathophysiologic substances such as vomitus, body discharges, and infection related exudates. While the reaction to these odors is probably determined in part by evolutionary means, and is beneficial in that the subject should not eat those substances or avoid exposure to substances emanating those odors, it is sometimes not possible to avoid them as in the case of care givers, health service personnel, and first responders. In such cases, it would be desirable to provide a methodology that enables avoidance of normal physiologic response or sensation or discomfort engendered by the exposure to such odorants. For purposes of this document such conditions shall be referred to by the term "Neuro- Olfactory Triggered or Aggravated or Related Conditions".

**[0008]** Obesity is another condition or illness attributable to complex genetic, environmental and social causes where the condition is associated with an exposure to an odorant, and where the normal, usually beneficial, physiologic response may lead to an undesired outcome- obesity. People are aware of increased appetite after exposure to pleasant food odors as well as the Pavlovian increase in saliva, stomach acid and intestinal motility - all beneficial - except when a propensity to obesity exists, and the subject overeats. It is known in the prior art to use strong pharmacologic agents such as sodium and calcium ion channel blockers, vasoconstrictors, as well as anticholinergic drugs such as atropine and local anesthetics to induce temporary anosmia. AU of the aforementioned active pharmacologic agents have significant side effects, and known toxicity rendering them subject to careful medical supervision as well as regulatory supervision by the United States FDA, or other supervisory agency appropriate to the geographic location. Over dosage with these drugs may result in serious illness or even death.

**[0009]** In the previously described conditions the subject must determine the need for avoidance of stimulation by the odorant, and this determination is therefore appropriately labeled as completely subjective. This dependence upon the subjects' perceived need renders the use of potentially dangerous pharmacologic agents unwise and unsafe since the needed frequency of administration depends upon many variable factors, and may result in toxicity if the potentially toxic drugs present in the agent are applied too frequently. The factors affecting the needed frequency of administration of an agent that will induce temporary anosmia/hyposmia include, but are not limited to: a) the concentration of the odorant; b) the ability of the subject to avoid continued exposure; c) the sensitivity of the chemo sensors of the olfactory sensors to the odorants; d) the solubility of the odorant in the layer of mucus overlaying the nasal olfactory sensors; and e) the thickness and viscosity of the mucous layer overlaying the sensors (since the odorant must diffuse through that layer to reach the sensor to be perceived, and to initiate and/or trigger the undesired response.)

**[0010]** Millqvist E. et al: "Placebo-controlled challenges with perfume in patients with asthma-like symptoms" *Allergy* (Copenhagen), Vol. 51, No. 6, 1996, pages 434-439, subjected a group of 9 patients with respiratory symptoms to perfume provocation with or without a carbon filter mask to ascertain whether breathing through a filter with active carbon could prevent the symptoms. The patients breathed through the mouth during provocations, as they used a nasal clamp to prevent any smell of perfume. It was found that the patients' earlier symptoms could be verified by perfume provocation. Breathing through the carbon filter had no protective effect. Therefore, it was concluded that the symptoms may have been induced by a trigeminal reflex via the respiratory tract or by the eyes.

**[0011]** Millqvist E. et al: "Provocations with perfume in the eyes induce airways symptoms in patients with sensory hyperreactivity", *Allergy* (Copenhagen), Vol. 54, No. 5, May 1999 (1999-05), pages 495-499 exposed 11 patients with a history of hyperreactivity to chemical trigger factors, such as perfume, to a common inducing factor, perfume. The patients' airways and eyes were exposed separately. During airway exposure, the eyes were covered by a mask, and during eye exposure, a nose clip was used. It was found that asthma-like and other symptoms may be induced by exposure of both the airways and the eyes.

## **DISCLOSURE OF THE INVENTION**

**[0012]** Subject-matter of the present invention is a composition for use in a method for treating at least one of neuro-olfactory triggered illnesses and aggravated conditions and conditions relating to neuro-olfactory triggered illnesses within a subject, as claimed in claim 1, and composition for use in a method for the prevention of nauseoceptive reactions to odors within a subject,

as claimed in claim 15. Embodiments of the invention are claimed in the dependent claims.

**[0013]** An object of the present invention is to diminish and/or prevent the perception of smells by increasing one or both of the thickness and viscosity of the mucous layer overlaying the nasal olfactory sensors, and/or to decrease the rate of diffusion of an odorant in the mucous layer, thereby diminishing or preventing the amount of odorant reaching the sensors. The term "prevent" is used here to describe those instances where a subject cannot perceive an odor.

**[0014]** An additional object is to accomplish the above without any significant toxicity so that the user may apply the remedy on an as-needed-basis without limiting its dosage, as would be required if potentially dangerous drugs were employed.

**[0015]** An additional object of the present invention is to diminish or prevent the neurological-emotional-physical cascade of events that may occur after exposure to olfactory stimulation by decreasing or preventing the olfactory stimulation either prophylactically or intercurrently with the exposures. The term "prevent" is used here to describe those instances where the subject has either no olfactory stimulation at all, or if the subject does have stimulation, it is at a diminished level that does not create a resultant effect.

**[0016]** The terms "olfactory nerves" and "olfactory receptors" are used interchangeably herein to mean the olfactory receptors in the nasal cleft, and any receptors to irritants and odorants in the nasopharynx, including those innervated by the first branch of the trigeminal nerve. Stimulation from these nerves due to exposure of their receptors to odorants or irritant chemicals can result in stimulation of the limbic system of the brain. This stimulation of the midbrain limbic system affects behavior and organs via the autonomous nervous system as well as affecting the regulation of the hormonal balance of the body.

**[0017]** In this document, a method for treating neuro-olfactory triggered and/or aggravated conditions is described. The method includes the steps of: a) providing a composition that includes an agent adapted to induce a level of anosmia/hyposmia in a subject, which level of anosmia/hypo smia is sufficient to substantially decrease olfactory sensory perception within the subject and neurologic response related to the condition; and b) applying the composition to the subject's olfactory receptors. The term "anosmia/hyposmia" is used to describe the inability, or decreased ability, of a subject to smell an odor, and/or a subject's decreased sensitivity to an odor or irritant. The term mucous layer as used herein shall refer to the normal mucous layer overlying the olfactory sensors, and the mucous layer whose composition is changed by the addition of the agents described in the present invention, such as thickening agents. Odors are caused by one or more volatilized chemical compounds (referred to herein as "odorants"). The olfactory nerve and the first cranial nerve include cilia or microscopic hair like protrusions which extend from olfactory receptor cells that are present in the upper region of the nasopharynx into the mucous layer of the uppermost portion of the nasopharynx. These cilia (which are the terminal portions of the olfactory nerve) are covered by a layer of mucus whose water content permits the water soluble odorant to reach the sensors by diffusion through the mucous layer. The absence of moisture in the normally present mucous layer will result in anosmia/hyposmia by not allowing the olfaction to be captured and/or dissolved into the predominantly aqueous mucous layer and diffused to the receptor cells. If, on the other hand, the layer of mucus normally covering the cilia is increased in one or both of thickness and viscosity, the time required to diffuse through the layer of mucus to the receptor will be increased, and the odorant will be completely or partially prevented from reaching the sensor. The mucous layer is constantly being regenerated by the mucus producing cells lining the nasopharynx. The mucus containing the captured and/or dissolved odorant will be either expelled or swallowed prior to the odorant reaching the sensor thereby resulting in the desired anosmia/hyposmia. Viscosity increasing agents can, in addition to increasing the viscosity, also increase the thickness of an adherent layer to an object, especially if the layer is hygroscopic and water is available as is the case in the nasopharynx. Sufferers with the common cold will frequently have increased production of viscous mucus and will often suffer from anosmia/hyposmia, albeit with a multitude of concurrent undesirable effects of the viral infection. It should be noted, however, that the aforementioned upper respiratory infection example is not mentioned as a proposed treatment but is given as a proof that increase layer thickness of the mucous layer and/or viscosity will induce temporary anosmia/hyposmia. The present invention operates to induce a temporary condition of anosmia/hyposmia by permitting the subject to apply the agent by a nasal spray or drops of a mixture of viscous or viscous inducing agents. The agent will be optimally be used prior to exposure, but may be used concurrent with the exposures, and reapplied as often as necessary since the preferred embodiment of these agents are GRAS agents. "Generally Recognized As Safe", or "GRAS" is a United States Food and Drug Agency designation.

**[0018]** According to a preferred embodiment of the present invention, the agent is adapted to increase the viscosity of the mucous layer overlaying the olfactory receptors, which are located at the top of the nasopharynx. The increase in the viscosity of the mucous layer or replacement of the mucous layer with a synthetic viscous mucus-like material induces a level of anosmia/hyposmia in the subject that is sufficient to substantially decrease olfactory sensory perception within the subject, and consequent neurologic response. The agent increases the viscosity of the mucous layer to a level that is greater than the normal viscosity of the mucous layer.

**[0019]** Depending on the particular manner in which the agent is applied, it is typically desirable to incorporate a mildly acidic (pH 5.0 to 6.5) buffered isotonic aqueous fluid containing up to about 15 percent by weight, more typically about 2 to 10 percent by weight of a viscosity increasing agent, such as a polymer or other material. Useful materials include, without limitation thereto, sodium carboxymethyl cellulose, algin, carageenans, carbomers, galactomannans, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycols, polyvinyl alcohol, polyvinylpyrrolidone, sodium carboxymethyl chitin, sodium carboxymethyl dextran, sodium carboxymethyl starch and xanthan gum and chitosans. Mucilage (a naturally occurring plant constituent with a molecular weight of 200,000 or greater) derived from botanicals such as acacia gum or gum arabic, marshmallow, tragacanth, carrageen, guar, quince seed, psyllium, sterculia, comfrey, fenegreek, coltsfoot, Icelandic and Irish moss, flax or linseed, locust bean, coltsfoot, and slippery elm bark may also be employed. Combinations of any two or more of the foregoing may be used.

**[0020]** According to another preferred embodiment of the present invention, the agent is used to increase the thickness of the mucous layer present within the subject's nasal passages. Agents that increase the viscosity will also tend to increase the thickness of the layer, since gravity will cause the mucous layer to fall off the sensors unless the person is upside down. The increase in mucous layer thickness induces a level of anosmia/hyposmia in the subject that is sufficient to substantially decrease olfactory sensory perception within the subject, and consequent neurologic response. The agent increases the average mucous layer thickness to a level that is greater than the normal average mucous layer thickness. The composition is applied through a nasal application preferably by a nasal spray but may be applied by in the form drops, by direct application or by sniffing of a gaseous suspension of the composition. As increased perception of odorants is often accomplished by "sniffing"; i.e., shallow inspiration of air into the nose with the mouth closed with the inspired volume being naturally limited to an amount approximately sufficient to fill the nasopharynx. The average volume of a sniff in an adult is about 200 ml. This naturally occurring sniffing mechanism is a desirable method for delivering the composition (which includes a coating agent or other active agent) to the nasal sensors while avoiding, or limiting its delivery to the lower respiratory tract. Alternatively, the composition may be also applied to the nasal sensors while using a spray and holding one's breath.

**[0021]** Also described herein is the use of an oil, wherein an oil is an agent that inhibits diffusion of odorants and/or chemicals to olfactory nerves by preventing the odorant from dissolving in the aqueous layer. The use of oil is effective because odorants generally need to be water soluble to be capable of being sensed. The oil is disposed in particles sized about four microns in diameter or larger. The term "diameter" is used herein to mean the largest cross-sectional dimension of a particle. The oil can form a molecular layer on the outer surface of an aqueous mixture, or remain as an emulsion. Both forms will diminish access by diffusion of the odorants through the mucous layer to the nasal sensors. The use of volatilized oil in small amounts is safe, but must be carefully formulated and administered so that inhalation of oil does not reach the lungs where it could cause damage. Application of a composition including an oil agent by sniffing or spray while holding one's breath is a preferred means of application.

**[0022]** In summary the present invention discloses diminishing or preventing the triggering of symptoms of patients suffering from neuro-olfactory triggered illnesses or disorders (NTIs) by decreasing or preventing the neural cascade produced by deleterious neuro-olfactory stimulation. The treatments may be used as either as a prophylactic when the patient is likely to be exposed to one of the precipitators described above, or intercurrently when exposure is detected. This, in turn, interrupts or decreases the sequence of neurophysiologic and psychological events that precipitate an adverse reaction in the subject. The present invention may also be used to induce temporary anosmia/hyposmia for the desired result of suppressing appetite, and helping manage obesity, as well as avoiding unpleasant reactions to offensive odors. For example, in the case of care givers, health service personnel, and first responders, the present method can be used for treating a subject to enable the subject to avoid normal physiologic response, sensation, and/or discomfort engendered by the exposure to a normally objectionable odor; e.g., enable the first responder to work in an environment containing putrid odors, body, waste odors, etc.

#### **DETAILED DESCRIPTION**

**[0023]** Chemicals capable of stimulating olfactory receptors can access the receptors in several different ways. A chemical that is volatile enough to reach the nasopharynx can be inhaled with breathed air. An odorant chemical or combination of chemicals that is/are sufficiently water soluble can dissolve into, and pass through, the aqueous surface of the nasal mucus, provided water is present on the surface of the receptor. Chemical odorants must diffuse through the aqueous layer in the mucus overlying the sensor cells to reach the receptors. The efficiency of the diffusion, however, is dependent on factors including the thickness and viscosity of the layer that the chemical must transverse. Odorant chemicals may be sufficiently lipid-soluble to permit them to pass through the cell membrane of the sensor cells, and thereby stimulate the olfactory receptors. Of course, once such a chemical reaches the sensor cell, stimulation and the neurological response that normally results depends upon the ability of the sensor cell to send its neural signal to the brain. If the stimulating chemical does not reach the olfactory receptor, or if the receptor is

unable to send its signal, the neurological response associated with the stimulation will be avoided or reduced to the extent the stimulation is reduced. Embodiments of the present invention are operable to decrease or prevent the stimulation of the olfactory receptors, and thereby prevent or decrease the neurological response to olfactory stimulation and the resultant neuro-olfactory triggered or related or exacerbated conditions.

**[0024]** Mucin is normally present in the nasal pharynx as an important component of the mucus. Mucins are a family of high molecular weight, heavily glycosylated proteins (glycoconjugates) produced by epithelial tissues in humans and other animals. One of the key characteristics of mucin is its ability to form gels. In most gel-like secretions, mucin provides lubrication and participates in cell signaling, chemical barrier formation, etc. Mucus is a liquid secretion on the mucosal surface, which contains mucins as well as other important constituents including antibodies and electrolytes. The main component of the mucus is water. The lubricity and viscosity of mucus is a function of its mucin glycoproteins. An additional property of mucins and compounds similar to mucins, whether natural or synthetic, is their increased adherence to mucosal surfaces. The presence of mucins within mucus helps to increase the depth of the mucous layer and increase the viscosity of the layer.

**[0025]** The present invention emulates this process for the purpose of treating neuro-olfactory triggered illnesses or disorders (NTIs). A synthetic or animal or plant derived agent is provided within a composition that is applied to the subject to facilitate the production of a mucous layer (referred to herein as a "derived" mucous layer) within the subject's nasopharynx region. The term "synthetic or animal or plant derived agent" as used herein refers to an agent that is: a) synthetically derived from, for example, chemical, animal, or plant matter; and b) adapted to increase one or both of the viscosity and thickness of the mucous layer within the subject; e.g., cause the viscosity of the layer to increase to a viscosity greater than water. The increased viscosity of the mucus decreases the ability of the odorant or irritant chemical to diffuse through the mucous layer and subsequently physically or chemically access the olfactory receptors since the diffusion rate is typically inversely related to the viscosity and thickness of the mucous layer. An agent synthetically derived from chemical or plant matter is advantageous because it eliminates the possibility of the animal derived agent carrying infectious disease particles (such as prions) that may be resistant to ordinary sterilization. Alternatively, "disease free" agents could be bioengineered from recombinant DNA. A synthetically derived mucous layer has the clinical advantage of having a lower incidence of allergenicity and is a preferred embodiment of the present invention. In some preferred embodiments, a viscosity increasing agent is included within the composition, which agent is adapted to increase the viscosity of nasal mucus within a subject to about 150 Poise or greater.

**[0026]** The pharmaceutical compositions described herein are prepared in a manner known to those skilled in the art, for example, by means of conventional dissolving, lyophilizing, mixing, granulating, or confectioning processes. Methods well-known in the art for making formulations are found, for example, in Remington: The Science and Practice of Pharmacy (21st ed.), ed. A. R. Gennaro, Lippincott Williams & Wilkins, 2005, and Encyclopedia of Pharmaceutical Technology, ed. J. Swarbrick, Informa Healthcare, 2006, each of which is hereby incorporated by reference.

**[0027]** The pharmaceutical compositions described herein may contain a buffering agent. Any pharmaceutically acceptable buffering agent may be used in the composition, including, e.g., phosphate, borate, citrate, acetate, or carbonate. Preferably, the buffering agent will produce a pH that is slightly acidic, less than 7, and preferably between 5 and 6.9 since acidic conditions cause a more viscous mucus. Suitable acids (e.g., hydrochloric acid) and bases (e.g., sodium hydroxide) may be used to adjust the pH of the pharmaceutical composition. Tonicity agents may be added to adjust the tonicity of the pharmaceutical composition with respect to the tonicity at the site of administration. Hypertonicity can also be employed since the mucins will swell by adsorption of water present in the naturally secreted and present mucus. Exemplary tonicity agents include, e.g., sodium chloride, potassium chloride, dextrose, mannitol, and sorbitol. Humectants, or water-binding compounds, may be added to the compositions described herein to aid in the retention of moisture. Exemplary humectants include, e.g., glycerin, propylene glycol, and polyethylene glycol. Humectants may also be added to, e.g., surfaces to which the pharmaceutical composition is applied to keep the surface hydrated and moist. The pharmaceutical composition may include preservatives in an amount sufficient to prevent microbial growth in the composition when stored. Preservatives may include, e.g., benzylkonium chloride, chlorohexidine gluconate, polyhexamethylene biguanide, and ascorbic acid.

**[0028]** The pharmaceutical compositions according to the invention may be formulated to release the active compound immediately upon administration (e.g., targeted delivery), or at any predetermined time period after administration, using controlled or extended release formulations to decrease the duration of action.

**[0029]** A further possibility described herein is an agent that is operable to physically coat the surface of the mucous layer coating the olfactory receptors. An example of such an agent is a vegetable, mineral, or synthetic oil that would act as physical barrier for the odorant or irritant chemical by naturally forming a surface coating on the mucous layer and preventing the water soluble odorants from entering the aqueous content of the mucous layer. The oil coating of the olfactory receptors in the nose will also decrease the amount of odorants reaching the olfactory receptors by preventing odorants that are oil soluble from leaving

the coating layer. The oil layer could therefore work as both a barrier to water soluble odorants as well as affinity capture of the oil soluble odorants. The oil may therefore be described as substantially inhibiting entry of an odorant into the mucous layer overlying nasal olfactory sensors within the subject. An oil that creates an oil/odorant suspension can be combined with a synthetically derived agent, if desired, that produces an increase in the viscosity and/or thickness of the subject's mucous layer thereby delaying the diffusion through the mucous layer overlying the nasal olfactory sensors. The concentration of the oil may range from about one to one hundred milligrams of oil within ten milliliters (1 - 100 mg/10 ml) of isotonic aqueous spray, and optimally contains unscented oil such as mineral oil.

**[0030]** Further described herein are liposomes. Liposomes are another agent that can be used to decrease the ability of an odorant or irritant chemical from reaching a subject's olfactory receptors. The liposomes can perform this function in two different, but related, manners. On the one hand, liposomes can be used to increase the viscosity of a mucous layer, and thereby decrease the chance of an odorant diffusing through the mucous layer and reaching the olfactory receptors prior to the mucus being expelled or ingested. On the other hand, liposomes can also be used to absorb odorants. The absorbed odorant(s) are less likely to reach the olfactory receptors because they are disposed within the liposome structure and because the liposomes typically have limited mobility within the viscous mucus. The liposomes may therefore be described as substantially inhibiting entry of an odorant into a mucous layer and/or delaying the diffusion through the mucous layer overlying the nasal olfactory sensors within a subject.

**[0031]** The present invention employs natural or synthetic mucin or a polysaccharide.

**[0032]** In preferred embodiments of the present invention, increased viscosity of the mucus is used to block odorants from reaching the olfactory epithelium. Mucous films function as both mechanical buffers and micro-filters, and in the case of this invention, as an affinity filter by capturing and containing the odorant. The mucus containing the entrapped odorants is either expelled as it is replaced by natural mucus, or swallowed, as it is nontoxic. A patient may be directed to periodically use an intranasal spray containing an agent adapted to induce a level of anosmia/hyposmia in a subject to safeguard against exposure to chemical odorants.

**[0033]** A mucin containing aqueous solution suitable for nasal use may be derived from animals (e.g., see U.S. Pat. 4,438,100) or may be manufactured from polyethylene oxide (e.g., see U.S. Pat. 3,767,789), or manufactured from mixtures of microcrystalline cellulose and alkali metal carboxyalkylcellulose (e.g., see U.S. Patent 6,565,832) all three of which are incorporated by reference herein in their entirety. Additionally, water soluble cellulose derivatives such as methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, etc. may serve as synthetic mucus and act as mechanical buffers and affinity filters when applied to the nose. The nature and composition of these synthetic mucus-like materials is well known in the art and are employed as components of nasal sprays to increase the viscosity of the applied medication so as to prevent their dripping in to the nasopharynx. Examples of such medications containing viscosity-increasing agents in the form of synthetic mucus-like material include: Afrin No Drip™, Vancenase AQ™, and Vick's Early Defense™ nasal sprays. In all the aforementioned products, however, the viscosity agent is always administered with an active pharmacologic agent, generally a decongestant or steroid, in a manner that designed to stop the dripping of the medication from the applied medication, and increase the subject's ability to breathe. As such, these products are not administered to decrease olfactory sensation, but rather teach away from such an application, and are in all cases combined with medications. In the present invention, an agent adapted to induce a level of anosmia/hyposmia in a subject is administered to a subject in an amount and frequency that produces a level of anosmia/hyposmia that is sufficient to temporarily substantially decrease or abolish olfactory sensory perception within the subject, and therefore the subsequent neurological response related to the condition. The aforesaid products, and others like them, cannot be used in the manner described within the present invention without the toxicity or side effects created by overdosing the medication contained within the product.

**[0034]** A preferred embodiment of the present invention is one in which the only active materials within the composition are GRAS materials, and one in which the user may use it as often as needed to accomplish the goal of decreasing or abolishing olfactory sensation during extended periods of expected, or actual, exposure to the problematic odorant or irritant chemical. Within the present invention, the viscosity of the applied composition (including the agent) is preferably greater than the viscosity of water, but sufficiently low enough to allow spraying of the material for deposition in the sensory area of the nasopharynx. A non-Newtonian liquid may be optimally used so that the stationary viscosity is higher than the viscosity under shear forces induced by spraying, thereby permitting easy deposition by spraying, and adequate retention on the mucosal surface. The composition may be provided in a dosage form that is suitable for intranasal administration either in the form of a spray or drops of a suspension, emulsion, solutions, gels, and hydro gels, which gels may be referred to as being in a topical form. The composition may be sterile.

**[0035]** Agents that are useful to create a desirable applied material viscosity include mixtures of microcrystalline cellulose and an alkali metal carboxyalkylcellulose. An example of such a mixture in a commercially available form is sold by FMC Corporation, Philadelphia, Pa. U.S.A. as Avicel™ RC-591. This material contains approximately 89 weight percent microcrystalline cellulose and approximately 11 weight percent sodium carboxymethylcellulose, and is known for use as a suspending agent in preparing various pharmaceutical suspensions and emulsions. Certain compositions of the present invention may contain at least about 2.5 weight percent of the cellulose / carboxyalkylcellulose compound mixture, generally not exceeding about 10 weight percent to avoid producing high viscosities which impede spraying with the usual devices. Another mixture that can also be used (also available from FMC Corporation^ Avicel(TM) RC-581, which has the same bulk chemical composition as the RC-591. Alternatively, microcrystalline cellulose and alkali metal carboxyalkylcellulose are commercially available separately, and can be mixed in desired proportions for use in the invention, with the amount of microcrystalline cellulose preferably being between about 85 and about 95 weight percent of the mixture for both separately mixed and co- processed mixtures.

**[0036]** Depending on the intended application, it may be desirable to incorporate up to about 10 percent by weight, more typically about 0.5 to about 5 weight percent, of an additional rheology-modifying agent, such as a polymer or other material. Useful materials include, without limitation thereto, sodium carboxymethyl cellulose, algin, carageenans, carbomers, galactomannans, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycols, polyvinyl alcohol, polyvinylpyrrolidone, sodium carboxymethyl, chitin, sodium carboxymethyl dextran, sodium carboxymethyl starch and xanthan gum. Combinations of any two or more of the foregoing are also useful.

**[0037]** The more simple techniques commonly used to determine rheological properties of fluid compositions, including the Brookfield rotating kinematic viscometer which measures torque transmitted through a sample using a rotating spindle, do not yield the most meaningful information for non-Newtonian fluids such as those of this invention. Since the viscosity of the thixotropic composition varies inversely according to the magnitude of shear force being applied, and the viscosity increases over time following withdrawal of the shear force, it is more useful to measure and compare complex viscosity. A mathematical derivation of complex viscosity can be found in H. A. Barnes et al., *An Introduction to Rheology*, Elsevier, N. Y., 1989, particularly at pages 46- 48. Complex viscosity from a oscillatory applied shear is defined by these authors at page 48 as being: "the ratio of the shear stress... to the rate of shear..." Units for expressing complex viscosity (typically represented by the symbol  $\eta^*$ ) are in Pascal seconds (Pa.s.), equivalent to newton seconds/meter<sup>2</sup> in the International System of Units.

**[0038]** The above-described treatments or combinations of the treatments will enable people with odorant or irritant chemical sensitivities to lead more productive, fulfilling lives, less circumscribed by this illness. One significant advantage provided by the present invention is the temporary, reversibility of the induced anosmia/hyposmia. A subject can choose when to treat herself with the medication described in the present invention. The patient may elect when to practice the described method, and to some degree the dosage as well. As a result, the subject can tailor the practice to their specific needs and thereby have more ability to avoid debilitating symptoms. For example, the composition provided in nasal spray form may be administered once, twice, three times, four times, or five times each day, or in other quantities and frequencies as subjectively needed by the patient to prevent detrimental olfactory stimuli. The duration of therapy can be intermittent or regular depending upon the exposure to the stimuli. In cases as described in the present invention where there are no active pharmacologic agents such as local anesthetics or anticholinergics (an anticholinergic agent is a substance such as atropine that blocks the neurotransmitter acetylcholine in the central and the peripheral nervous system) there would be no significant limitation as to frequency of use, other than instructions to diminish use or avoid use if local irritation or side effects occur.

**[0039]** The invention will be further described by means of the following example and reference examples, which are not intended to limit the scope of the invention in any manner.

**[0040]** In a first example (according to the invention), a composition in the form of a nasal spray or drops that includes an agent adapted to induce a level of anosmia/hyposmia in a subject is administered to a subject. The agent is adapted to increase one or both of the viscosity and thickness of the mucus layer within the sensory area of the subjects' nasopharynx. The thickness of the normal nasal mucus ranges from 5 to 100 microns as reported in the literature. Agents described in the background material of this application that increase the viscosity will generally also increase the depth of the mucous layer. The increased viscosity and/or thickness of the mucous layer decreases the ability of the odorant or irritant chemical to pass through the mucous layer, and subsequently physically or chemically access the olfactory receptors. In most cases, the odorant or irritant chemical becomes trapped within the mucous layer, and is subsequently either expelled as nasal secretions or swallowed, and in either case, the olfactory sensation is prevented or significantly diminished. The level of anosmia/hyposmia created by the agent acting on the mucous layer is sufficient to substantially decrease the olfactory sensory perception within the subject and the neurologic response related to the condition. Since mucus production is continuous from the mucous producing cells on the mucous membrane lining the nasopharynx, the repeated application of thickening agents and/or viscosity increasing agents will serve to

prevent, and/or decrease odorants present in the surface layer of the mucus from ever reaching the olfactory sensor. The entrapped and/or dissolved odorants will be expelled from the nose and or swallowed prior to reaching the olfactory sensors thereby causing anosmia/hyposmia.

**[0041]** In a second example (reference example), the agent included in the composition includes an oil/water emulsion where the particles of oil are of sufficient size so as not to pose the risk of aspiration induced lipoid bronchitis or pneumonitis. Oil particles above about four microns (4  $\mu$ ) in size, with a particle size of about five to thirty microns (5-30  $\mu$ ) in diameter are preferred to avoid inadvertent passage into the alveoli of the lungs. The composition may be administered by the subject as previously described. This method of administration will help prevent aspiration of the particles into the bronchial tree and lungs. The gaseous volume of spray may be limited to less than 200 cc/ per spray, and proportionally less for children, and the spray administered while holding ones breath. The oil is used to temporarily occlude the nasal receptors from reacting with the odorant. Odorants are typically water soluble and of small molecular size. Oil provides a temporary barrier between the odorant and the olfactory receptors. Most, if not all, of the odorant will not make contact the olfactory receptors, thereby preventing or mitigating olfactory-triggered episodes.

**[0042]** In a third example (reference example), the agent included in the composition includes one or more liposomes. Liposomes are used for drug delivery due to their unique properties. A liposome encapsulates a region of aqueous solution inside a hydrophobic membrane. Dissolved hydrophilic solutes cannot readily pass through the lipids. Hydrophobic chemicals can be dissolved into the membrane, and in this way liposome can carry both hydrophobic molecules and hydrophilic molecules. Initially, the liposomes can operate to coat the mucous layer as well as the olfactory receptors. As the oil/lipid external layer of the liposome dissolves, the liposome can then release its internal watersoluble contents. In some embodiments, the water soluble contents can include a mildly acidic buffered solution in the pH range of less than 7 to increase the viscosity of the mucous layer since the constituents of the mucous layer are known to become more viscous with increasing acidity. The liposomes can be used as solitary agents within the composition, or in combination with other agents; e.g., agents that increase the viscosity or thickness of the mucous layer.

**[0043]** While the invention has been described with reference to exemplary embodiments, it will be understood by those skilled in the art that various changes may be made and equivalents may be substituted for elements thereof without departing from the scope of the invention. In addition, may modifications may be made to adapt a particular situation or material to the teachings of the invention without departing from the essential scope thereof. Therefore, it is intended that the invention not be limited to the particular embodiment(s) disclosed herein as the best mode contemplated for carrying out this invention.

## **REFERENCES CITED IN THE DESCRIPTION**

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

### **Patent documents cited in the description**

- [US4438100A](#) **[0033]**
- [US3767798A](#) **[0033]**
- [US6565832E](#) **[0033]**

### **Non-patent literature cited in the description**

- **MILLQVIST E. et al.** Placebo-controlled challenges with perfume in patients with asthma-like symptoms *Allergy* (Copenhagen), 1996, vol. 51, 6434-439 **[0010]**
- **MILLQVIST E. et al.** Provocations with perfume in the eyes induce airways symptoms in patients with sensory hyperreactivity *Allergy* (Copenhagen), 1999, vol. 54, 5495-499 **[0011]**

- **REMINGTON**The Science and Practice of PharmacyLippincott Williams & Wilkins20050000 [0026]
- Encyclopedia of Pharmaceutical TechnologyInforma Healthcare20060000 [0026]
- **H. A. BARNES et al.**An Introduction to RheologyElsevier1989000046-48 [0037]

**PATENTKRAV**

1. Sammensætning til anvendelse ved en fremgangsmåde til behandling af i det mindste én af neuro-olfaktorisk udløste sygdomme og forværrede tilstande og tilstande relateret  
5 til neuro-olfaktorisk udløste sygdomme i et subjekt, hvilken sammensætning omfatter ét eller flere midler indrettet til at inducere et niveau af anosmi/hyposmi i subjektet, hvilket niveau af anosmi/hyposmi er tilstrækkeligt til i det væsentlige at mindske olfaktorisk sensorisk stimulation i subjektet og en neurologisk reaktion på stimuleringen, som er én eller begge af udløsning af og forværring af sygdommen eller tilstanden, hvor i det  
10 mindste ét af midlerne er et viskositetsforøgende middel, som forøger én eller begge af viskositeten og tykkelsen af et mukøst lag, som ligger over nasale olfaktoriske sensorer i subjektet, og som omfatter en naturlig eller syntetisk mucin, eller et polymert polysaccharid; og  
hvilken fremgangsmåde omfatter trinnene med tilvejebringelse af sammensætningen og  
15 påføring af sammensætningen på et nasopharynx område på subjektet.
2. Sammensætning til anvendelsen ifølge krav 1, hvor det polymere polysaccharid vælges fra gruppen bestående af mikrokrySTALLINSK cellulose og vandopløselige cellulosederivater.  
20
3. Sammensætning til anvendelsen ifølge krav 2, hvor de vandopløselige cellulosederivater vælges fra gruppen bestående af methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose og en alkalimetall-carboxyalkylcellulose.  
25
4. Sammensætning til anvendelsen ifølge ethvert af kravene 1 til 3, hvor det viskositetsforøgende middel omfatter en blanding af mikrokrySTALLINSK cellulose og en alkalimetall-carboxyalkylcellulose, fortrinsvis natrium-carboxymethylcellulose.
- 30 5. Sammensætning til anvendelsen ifølge krav 4, hvor det viskositetsforøgende middel omfatter en blanding af 89 vægt% mikrokrySTALLINSK cellulose og 11 vægt% natrium-carboxymethylcellulose.
6. Sammensætning til anvendelsen ifølge krav 4 eller 5, hvor sammensætningen  
35 indeholder fra 2,5 vægt% til 10 vægt% af den nævnte blanding.

7. Sammensætning til anvendelsen ifølge krav 1, hvor ét eller flere af midlerne er et viskositetsforøgende middel indrettet til, individuelt eller i kombination med andre midler, at øge viskositeten af nasal mucus i subjektet til mere end 150 Poise.
- 5 8. Sammensætning til anvendelsen ifølge krav 1, hvor det ene eller flere midler, som påvirker anosmi/hyposmi, er GRAS-(Generally Recognized As Safe)-midler.
9. Sammensætning til anvendelsen ifølge krav 1, hvor trinnet med at påføre sammensætningen omfatter at subjektet sniffer sammensætningen.
- 10
10. Sammensætning til anvendelsen ifølge krav 1, hvor sammensætningen er i en næsesprayform, eller en næsedråbeform, eller i en topisk form.
11. Sammensætning til anvendelsen ifølge krav 1, hvor trinnet med påføring af sammensætningen omfatter påføring af sammensætningen til behandling af overvægt eller til behandling af multipel kemisk følsomhedssyndrom.
- 15
12. Sammensætning til anvendelsen ifølge krav 1, hvor trinnet med påføring af sammensætningen omfatter påføring af sammensætningen for behandling af én eller flere af en somatoform lidelse, kronisk træthedssyndrom, fibromyalgi, panisk lidelse, autisme, astma, epilepsi og posttraumatisk stresslidelse.
- 20
13. Sammensætning til anvendelsen ifølge krav 1, hvor trinnet med påføring af sammensætningen omfatter påføring af sammensætningen for undgåelse af normal fysiologisk reaktion eller følelse skabt ved udsættelsen for en normalt uacceptabel lugt.
- 25
14. Sammensætning til anvendelsen ifølge krav 1, hvor trinnet med påføring af sammensætningen eller trinnet med tilvejebringelse af sammensætningen ikke kræver en læges ordination.
- 30
15. Sammensætning til anvendelse ved en fremgangsmåde til forhindring af nauseocaptiv reaktion på lugte i et subjekt, hvor sammensætningen omfatter ét eller flere midler som angivet i et vilkårligt af kravene 1 til 8, indrettet til at inducere et niveau af anosmi/hyposmi i subjektet, hvilket niveau af anosmi/hyposmi er tilstrækkeligt til i det væsentlige at mindske olfaktorisk sensorisk
- 35

stimulation i subjektet, hvilken sammensætning er i en form eller påføres, som defineret i et vilkårligt af kravene 9 til 14;

og fremgangsmåden omfatter trinnene med at tilvejebringe sammensætningen og påføring af sammensætningen på subjektet periodisk i en mængde, som inducerer

5 anosmi/hyposmi.