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<p>(54) Title: METHODS AND KITS FOR REMOVING, TREATING, OR PREVENTING LICE WITH DRIABLE PEDICULOSTATIC AGENTS</p> <p>(57) Abstract</p> <p>Methods and kits for removing, treating or preventing head lice infestations in patients in need of such treatment are disclosed and include topically applying to the lice-infested area an effective amount of a driable pediculostatic agent for a time sufficient to immobilize the lice, drying the agent onto the application site and removing the dried agent, thereby removing the lice and nits.</p>		

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METHODS AND KITS FOR REMOVING,
TREATING, OR PREVENTING LICE
WITH DRIABLE PEDICULOSTATIC AGENTS

Field of the Invention

5 The present invention relates to methods and
kits for the diagnosis, treatment, removal or
prevention of pedicular parasite infestations. More
particularly, the methods and kits relate to the use of
nontoxic driable agents that rapidly immobilize head
10 lice and keep them immobilized when dried, in order to
facilitate their removal from the hair and scalp. The
methods and kits further relate to the use of driable
agents that inhibit hatching of nits, obviating nit-
picking and combing in the treatment of lice
15 infestation.

Background of the Invention

Pediculosis is a scalp infestation produced
by *Pediculus humanus capitis*. Cases of pediculosis are
quite frequent, both in their endemic and epidemic
20 forms. As the lice feed on human skin and blood, they
inject their digestive juices and fecal material into
the skin. These materials, as well as the puncture
wound itself, cause skin irritation and lesions from
the resulting scratching, and can cause a serious
25 infection with ganglionic inflammation. Lice are also

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vectors of certain diseases, such as exanthematic or epidemic typhus and recurrent fever.

The adult female louse has a life span of about one month and lays up to ten nits a day which are
5 firmly attached to hair through an excreted cement. The nits hatch to release instars in about seven to nine days, and the instars become mature adults in another week. To cure someone of head lice requires an approach that eliminates all 3 stages of the louse life cycle.

10 Many currently utilized treatment methods are based on the application of pediculicides, which are toxic pharmaceutical agents that, when internalized, poison and kill lice. Typically, such pediculicidal agents enter via the respiratory spiracles, and once
15 inside the louse, interfere with the function of a critical metabolic or physiological pathway, leading to death. Malathion, for example, inhibits acetylcholinesterase, disrupting signaling in the nervous system.

20 Examples of insecticidal agents used to treat lice are described in EP 0191236 and U.S. Patent No. 5,288,483. A significant disadvantage of using these agents is that lice can become resistant. The need for further treatment increases the exposure to these harsh
25 agents and increases the cost. Additionally, clinicians and parents are reluctant to treat children with agents that can also prove toxic to human beings. There are reports in the medical literature, for example, that children treated with lindane have
30 developed seizures.

Moreover, many of these compounds have unpleasant odors or other undesirable properties, causing noncompliance by the patient, leading to re-infestation of the individual, and spreading of the

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infestation to others. In addition, the harshness of these agents make them unsuitable for use as prophylactics.

Home remedies such as application of corn
5 oil, olive oil, eucalyptus oil, neem oil, coconut oil, mayonnaise, or petroleum jelly for a period of time sufficient to kill the lice (e.g. overnight) are not practical or completely effective.

A further disadvantage of prior methods is
10 the requirement of removing the nits from the hair in a separate treatment step. The removal of nits has typically been done by hand using special fine-tooth combs. U.S. Patent No. 4,927,813 teaches compositions containing formic acid that facilitate removal of nits
15 from the hair; however, formic acid is a known caustic agent.

Use of combing alone to treat head lice has the disadvantage that the lice can hold onto the hair shafts using their claws or escape by crawling away
20 from the area being combed. This labor intensive method requires daily combing, is painful, and is unpleasant since the lice are active, visible and crawling.

Heat has also been suggested as a means of killing head lice. However, its use has not been
25 effective, due in part to the fact that crawling lice will rapidly move away from the heat source. Moreover, the temperatures needed to kill the lice, typically 140°F or higher, can burn or scald the scalp.

The use of heat in conjunction with
30 pediculicidal compositions is discouraged. Not only are some of the solvents used in the pediculicidal compositions inflammable at the temperatures necessary to kill the lice, but the heat may additionally degrade the active pediculicidal agents as well.

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Thus, there remains a need in the art for methods and kits useful for treating and removing lice infestations that are easy to use, inexpensive, cosmetically attractive and effective against lice resistant to other treatments. Moreover, there remains a need for methods and kits that eradicate nits as well as adults and instars, and that can be used prophylactically to prevent initial infection or re-infestation. Accordingly, these are some of the objects of the present invention.

Summary of the Invention

These and other objects are furnished by the present invention, which in one aspect provides a method for the treatment or removal of lice and/or nits, particularly head lice and/or nits, in animal subjects, including humans. According to the method, an effective amount of a drier pediculostatic agent is applied to a lice-infested area of an animal subject, preferably a human subject, for a time sufficient to trigger an immersion reflex in the lice. The drier pediculostatic agent is then dried, and the lice and/or nits removed prior to or concomitantly with removal of the dried agent.

In one embodiment, the dried agent is removed, along with lice and nits, by combing the hair with a fine-toothed delousing comb, preferably prior to shampooing or wetting the hair. In another embodiment, the dried agent is removed, along with lice, by washing the hair with water, optionally with the aid of soaps, shampoos, conditioners, etc. If the dried agent is removed by washing, nits are optionally removed by combing the washed hair with a fine-toothed delousing comb.

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The driable pediculostatic agent can be dried with the application of heat or air-dried, depending upon the formulation. To avoid dilution of the pediculostatic agent, the agent is preferably applied
5 to the dry hair of the lice-infested area, typically in an amount sufficient to completely soak or saturate the hair and skin.

Regardless of the method of removing the dried agent, the efficiency of nit and/or lice removal
10 can be optionally increased by adding a combing step between applying and drying the driable pediculostatic agent. In this optional embodiment, the agent applied to the hair is allowed to remain on the hair for a period of time sufficient to trigger the immersion
15 reflex in lice. While the wet agent is still in the hair, the hair can be combed with a fine-toothed delousing comb. The wet agent removed by combing can be conveniently collected on paper towels, which can be sealed in a plastic bag, conveniently a zipper-loc
20 plastic bag. The agent remaining on the hair can then be dried onto the hair and scalp and removed as previously described. In this alternative embodiment, the wet agent collected on the paper towels can be inspected for the presence of lice and/or nits, thereby
25 providing a convenient diagnostic means for monitoring the course of the treatment and/or the severity of the infestation.

A pediculostatic agent is one that elicits the "immersion reflex" in lice, whereby the lice become
30 immobilized as a consequence of reflexes that have evolved to avoid suffocation. The lice remain immobilized while in contact with the driable pediculostatic agent in its wet form, and do not recover from the immersion reflex once the agent has

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been dried onto the lice. In a preferred embodiment of the method of the present invention, the driable pediculostatic agent induces the immersion reflex within about 2 hours, preferably within about 5 minutes and most preferably within about 6 seconds, and can be readily dried by air evaporation or by application of heat from, for example, a hair-drier or hair curlers.

In a preferred method, the dried agent is permitted to remain on the hair for a period of time sufficient to induce the immersion reflex in the substantial majority of lice, and thus is preferably at least as long, in minutes, as the Immersion Reflex Index of the pediculostatic agent being applied. Typically, the dried pediculostatic agent is permitted to remain on the hair for a time sufficient to kill at least some of the lice, prior to removal of the lice and/or dried agent by washing and/or combing, usually at least about 2 to about 8 hours, typically overnight.

The pediculostatic agents of the present invention also serve to prevent nit hatching during the period of contact with the nits.

In another aspect, therefore, the methods of the present invention are designed to obviate nit removal as an obligate component of treating lice infestation. In this aspect, driable pediculostatic agent is applied to a lice-infested area of the body, and after triggering the immersion reflex, is dried thereon. The dried pediculostatic agent is left in contact with the body for a prolonged period, at least about 8 hours, preferably at least about 24 hours, more preferably at least two days, most preferably a week, before removal of the agent and/or reapplication of the driable agent. Nit hatching is prevented for the duration of contact, and the embryos therein thus

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progressively killed, thus obviating nit removal as a requirement of cure.

Optionally, a conventional pediculicidal active ingredient can be incorporated into the
5 pediculostatic formulations described herein. The pediculicidal active ingredients can be used at levels effective to achieve their intended result, typically from about 0.25 wt% to about 2.5 wt%. Non-limiting examples of suitable pediculicidal agents include
10 natural or other pyrethrins, pyrethroids, permethrin, lindane, malathion, carbaryl, ivermectin and combinations thereof. Piperonyl butoxide can additionally be added at levels from about 1 wt% to 5 wt% to hinder the development of resistance of the lice
15 to the pediculicidal additives.

In an alternative embodiment, a driable pediculostatic agent can be applied to the infested area first, followed by application of a pediculicidal composition according to the methods of the invention,
20 or vice versa. If the pediculicidal agent is applied first, the hair of the infested area is preferably dried prior to application of the driable pediculostatic agent.

The driable pediculostatic agent is
25 optionally combined with a dye or other visible marker for temporarily marking the treated area in order to verify that the agent has been applied. The dye is preferably a fluorescent dye or other agent which is detectable when dried onto the body, chitinous nits or
30 hair.

In another aspect, the invention provides a kit for the treatment, removal or prevention of lice and/or nits. In one embodiment, the kit comprises an amount of a driable pediculostatic agent sufficient for

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at least one application packaged in association with instructions for use in methods for removing, treating or preventing lice as described herein. In another embodiment, the kit comprises an amount of a driable
5 pediculostatic agent sufficient for at least one application and a comb, optionally a fine-toothed delousing comb for removing lice and nits. Alternatively, the above-described kits can contain individual components that when mixed together, with or
10 without the addition of water or other solvents, provide an amount of a driable pediculostatic agent sufficient for at least one application. The kits can optionally contain additional components, such as shower caps or other non-absorbent coverings,
15 pediculicidal agents, dyes that can be mixed with the pediculostatic agents, etc.

Detailed Description of the Invention

The prior art teaches that topical agents to treat and cure head lice are pediculicidal: if lice are
20 temporarily inactivated and later recover from exposure, the agent is considered ineffective by those skilled in the art.

Typically, such topical agents have included toxic agents that are well known to kill lice, such as
25 natural pyrethrins, pyrethroids, permethrin, lindane, malathion, carbaryl, ivermectin and combinations thereof. These agents, once internalized, typically target and interfere with specific components of metabolic or other physiologic pathways, leading to
30 death of the organism. Given the physiologic similarities among eukaryotes, many of these agents disrupt metabolic or physiologic pathways, and thus prove toxic, in human beings as well.

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More recently, nontoxic agents not previously considered lousicidal have also been identified as having pediculicidal activity. U.S. Patent No. 5,783,202 discloses nonresidual pediculicidal mousse compositions in which the mousse foaming agent alone is said to be pediculicidal, and further is said to act synergistically with known pediculicides such as pyrethrins to kill head lice and nits. U.S. Patent No. 5,858,383 discloses compositions and methods in which a substantially air-impermeable liquid composition, left sufficiently long in contact with lice, is said to be effective as a lousicide.

None of the art teaches that compositions that stun or immobilize the lice can be used as effective treatments; in fact, the prior art teaches away from using such agents.

It has now been surprisingly discovered that drible pediculostatic agents can be used in novel methods for the treatment, removal and/or prevention of lice and/or nit infestations, overcoming the disadvantages of the prior art methods.

A pediculostatic agent is one that elicits the "immersion reflex" in lice. The immersion reflex is a self-preservation behavior that lice have evolved to protect themselves against drowning when, through actions of the host, they are immersed in water. Lice are obligate air breathers and cannot derive oxygen when underwater; the immersion reflex allows them greatly to increase the amount of time that they can survive without access to air. During submersion, the spiracles and tracheoles, through which lice breathe, become blocked by water. As the lice become anoxic, they rapidly switch into a state of profound suspended animation, decreasing their need for oxygen, thus

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prolonging their survival. They become completely immobile, unresponsive to stimuli, and even cease gut motility. If the reflex continues too long, however, the lice eventually run completely out of oxygen and
5 die from anoxia.

A pediculostatic agent is one that elicits the "immersion reflex" in lice. A driable pediculostatic agent is one that triggers the immersion reflex when wet, and that maintains the lice in the
10 immersion reflex when thereafter dried *in situ*.

In contrast to classic pediculicidal agents, which act biochemically to disrupt a vital physiologic function, pediculostatic agents (including driable pediculostatic agents) function mechanically to trigger
15 a normal endogenous behavioral reflex.

The methods and kits of the invention take advantage of driable pediculostatic agents to induce and maintain the immersion reflex to provide regimens for lice and nit removal and treatment that are safe, effective, and non-toxic. Since the methods and kits
20 do not require application of a toxic pediculicidal agent for success, they are highly unlikely to engender resistance in the lice. Moreover, since the methods and kits are non-toxic, they provide safe prophylactic
25 treatment for the entire at-risk group, thereby providing effective means of eradicating lice outbreaks and re-infestations.

In general, the method of treating or removing lice and/or nits according to the present
30 invention comprises applying a driable pediculostatic agent to a lice-infested area of the body, typically the scalp, and allowing the agent to remain in contact with the lice for a period of time sufficient to trigger the immersion reflex in the lice by oxygen

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deprivation. Depending on the composition of the
driable pediculostatic agent, the agent is then dried
by air evaporation or application of heat, typically by
blow-drying the hair. The dried pediculostatic agent
5 is then removed, along with the lice and/or nits,
typically by rinsing, shampooing or combing with a
fine-toothed delousing comb, or by a combination of the
three.

The frequency of treatment or application
10 ranges from once per day to once every 30 days, with a
preferred schedule being 1 time per week, as further
discussed below. However, the treatment can be
repeated at intervals as necessary, and as desired to
accommodate bathing, completely to remove the lice
15 and/or nits, as further described below.

The treatment can also be used as needed as a
prophylactic measure to prevent initial infestation or
repeated as needed for persons at risk of re-infection.
Because the driable pediculostatic agents of the
20 invention are non-toxic and do not engender resistance,
the treatment methods described herein can be repeated
indefinitely, if necessary.

The ability of a pediculostatic agent to
induce the immersion reflex will depend upon its
25 composition, which is further discussed *infra*, and upon
its concentration after contact with hair. As to the
latter, those of skill will appreciate that hair can
experience varying degrees of wetness - from complete
dryness, to damp, to towel-dry, to wet, to dripping -
30 and that the varying degrees of hair wetness will
effect varying degrees of dilution of an agent applied
thereto.

The degree to which the hair must be dry upon
application of the driable pediculostatic agent can

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readily be determined for any such driable
pediculostatic liquid composition by its ability, when
applied to the hair at a given degree of wetness, to
induce the immersion reflex in the lice present
5 therein, which is a critical determinant of its
efficacy. The immersion reflex can readily be
ascertained by visual inspection of the lice in the
hair using slight magnification: if the lice are
immobile and do not avoid a comb, the agent is
10 effective at the concentration achieved *in situ*; if the
lice are motile and avoid combing, the agent is
ineffective. Thus, as defined herein, "dry hair"
refers to a degree of hair dryness that does not effect
dilution of a desired pediculostatic agent applied
15 thereto beyond the point at which the agent timely
triggers the immersion reflex in lice.

Preferably, the driable pediculostatic agent
is applied full strength, *i.e.*, in substantially
undiluted form. This can be accomplished by applying
20 the agent to the dry hair of the infested area,
preferably in an amount sufficient completely to soak
or saturate the area and/or hair, and massaging the
agent in. For full-strength application, the agent can
be applied not only to hair that is completely dry, but
25 also to hair that is moist or damp, and to hair that is
substantially dry, such as is obtained by towel-drying
the hair following shampooing. The preferred aspect of
the invention is that the hair be sufficiently dry that
the driable pediculostatic agent is not substantially
30 diluted when applied to the hair. Hair of the
appropriate level of dryness can be obtained by
squeezing, toweling or otherwise drying wet hair until
water ceases dripping from the hair. In particularly
preferred embodiments of the invention, the driable

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pediculostatic agent is applied to towel dry hair, more preferably to completely dry hair. Thus, if the driable pediculostatic agent is applied following shampooing, the hair should be wrung out or towel
5 dried, preferably completely dried, prior to application.

Following application, the agent is dried. Depending upon its composition, the driable pediculostatic agent is dried either by air-drying or
10 with the aid of heat from, for example, a blow- or other hair-dryer, heat-based curlers, a curling iron, etc. Since lice will typically crawl away from heat applied by a blow-dryer or other hair implement, in embodiments utilizing heat drying it is important that
15 the driable pediculostatic agent be permitted to remain on the hair in its wet form for a time period sufficient to trigger the immersion reflex before it is dried. Since the immersion reflex immobilizes the lice, they are unable to crawl away from the heat
20 source. Moreover, it is important that the driable pediculostatic agent be composed of solvents and other ingredients that are not inflammable at the temperatures applied by the dryer. Thus, when heat-drying is used, the agent is preferably an aqueous-
25 based or aqueous composition, although nonaqueous formulations that will not ignite at the drying temperature can also be used.

The time interval between applying the driable pediculostatic agent and then drying the agent
30 depends upon the "Immersion Reflex Index" of the particular driable pediculostatic agent, which is defined as the time, in minutes, within which the immersion reflex is triggered in a louse upon being contacted with the agent. Typically, drying can be

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commenced after a period of time equal to the Immersion
Reflex Index of the particular pediculostatic agent
used. However, longer intervals between application
and drying can be used, and in some cases are even
5 preferred. Most preferably, the pediculostatic agent
remains in the hair prior to drying for a period of
time equal to about 1 to 100 times, even more
preferably about 1 to 50 times, more preferably about 5
to 30 times the Immersion Reflex Index of the
10 particular driable pediculostatic agent being used.

Whether air-drying or heat-drying the driable
pediculostatic agent, excess agent can be removed from
the hair prior to drying to reduce the amount of time
necessary for the agent to dry. The agent should be
15 permitted to remain on the hair for a time period
sufficient to trigger the immersion reflex as described
above prior to removal of excess agent.

Excess agent can be removed by a variety of
means, including but not limited to, squeezing off the
20 hair with hands and combing with a regular hair comb or
delousing comb. Preferably, excess agent is removed by
combing. Removing excess agent by toweling the hair is
not recommended, as it has been discovered that
toweling removes the agent from the lice and permits
25 them to recover from the immersion reflex, thereby
undermining the treatment regimen. If desired, the
removed agent can be placed on a towel or other
material or surface and inspected for lice and/or nits
as a means of monitoring the progression of treatment
30 regimen. When monitoring is desired, at least some of
the excess agent should be removed with a fine-toothed
delousing comb.

It should be noted that in order to remove
nits, the hair must be combed at some point with a

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fine-toothed delousing comb. This combing can be done in conjunction with removal of excess agent in its wet form (described *supra*), after the agent has been dried onto the hair (described *supra* and further described
5 *infra*), or even after the dried treatment agent has been completely removed. As it has been found that certain driable pediculostatic agents aid the removal of nits when in their wet form - that is, prior to drying - particularly the preferred CETAPHIL® Cleanser
10 driable pediculostatic agents, in a preferred embodiment of the invention nits are removed by combing the hair with a delousing comb between application of the pediculostatic agent and its drying. Removing nits at this stage provides the added benefit that the
15 removed agent can be inspected for lice and nits, permitting the infestation and effectiveness of the treatment to be monitored.

As further discussed *infra*, the time-consuming and unpleasant task of nit-removal, which is
20 obligatory in prior art methods to prevent reinfestation of the treated patient, and which is desirable in certain of the embodiments of the present invention, as just described, is obviated in those
embodiments of the present invention that prevent
25 hatching of the nits for a period of time sufficient to kill the embryos therein.

Once the agent has been dried onto the lice, hair and scalp, the lice do not recover from the
immersion reflex and remain immobilized. While not
30 intending to be bound by any theory of operation, it is believed that when the driable pediculostatic agent is dried, non-volatile compounds in the agent deposit onto the lice, thereby encasing, encapsulating, enveloping,

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enwrapping or otherwise covering the lice in a film or coating that prevents them from recovering from the immersion reflex even though they are dry.

If lice are encased in a film of dried
5 pediculostatic agent for a sufficiently long duration, they suffocate and die. Because the mechanism of death so differs from that wrought by conventional pediculicides, however - through the mechanical,
10 surface-occlusive induction of a normal endogenous reflex, rather than the biochemical disruption of a physiologic pathway - the term "pediculicide" is reserved herein for agents that act biochemically within the louse to disrupt metabolic or physiological pathways, leading to death.

15 While killing the lice is not necessary for success of the methods described herein, in preferred embodiments it is desirable to kill at least some of the lice prior to removing the dried agent. For most
20 drible pediculostatic agents, at least some of the lice can be killed by leaving the dried agent on the lice and hair for at least about 8 hours. For some drible pediculostatic agents, shorter periods might be sufficient. The amount of time necessary for a particular agent to kill a louse can be readily
25 determined using the in vitro assays described *infra*.

Heat has been implicated as one method of killing lice. Accordingly, once the agent has been dried, heat from a hair implement, such as a blow
30 dryer, can be applied to the head to facilitate killing of the lice. Since the lice remain immobile, they cannot escape the heat. However, the use of heat should be exercised with care, so as to avoid scalding or burning the head or other treatment site. Moreover, the drible pediculostatic agent preferably should not

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contain solvents or other ingredients that are inflammable at the temperatures encountered during heating.

After the dried agent has been left on the
5 hair for a sufficient period of time, typically 8 hours
or overnight, it can be removed. Having immobilized
all crawling adults, and having killed some proportion
thereof, the agent has rendered the adults readily
removable by combing. Because only adults migrate from
10 host to host, and because more than a week is required
for maturation of any newly-hatching nits, the
overnight treatment renders the patient noncontagious
for at least one week. Thus, a treatment regimen that
includes overnight treatment at least once per week
15 renders the patient completely noncontagious. If the
driable pediculostatic agent includes a marker that
signals its application (see *infra*), this could
revolutionize treatment of schoolchildren, who are
today forbidden in most jurisdictions from attending
20 school with even a single nit: evidence of treatment
within the week prior, using the methods of the present
invention, would suffice to indicate that the child is
noncontagious to classmates.

While the agent can be removed immediately
25 following an overnight treatment, a particular
advantage of the method of the invention is that the
dried agent is almost undetectable. Thus, it can be
left in the hair during the day and conveniently
removed at night. This is particularly convenient for
30 treating children, because the agent can be removed in
the evening at bath time.

Moreover, leaving the dried agent on the hair
during the day further reduces the chance of
transmitting the infestation to others.

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Rather than having to stay home from school, as presently required by most school districts, infested children could thus attend school with the dried agent in their hair. By incorporating into the drierable pediculostatic agent a visible or fluorescent dye, or other easily detectable agent, school officials could readily determine whether the child were "wearing" the treatment, and thus able to attend classes.

10 In fact, since the agents do not require toxic pediculicides for success, the dried agent can be left on the hair for a few days, or even a week, prior to removal. Thus, in an alternative treatment regimen, the dried pediculostatic agent is left on the hair for 15 a week. The first-applied agent is then removed, and the treatment repeated, or alternatively the initially applied agent is left in the hair as a second application of pediculostatic agent is undertaken. The second treatment immobilizes, kills, and permits 20 removal of any adults that had matured in the week following initial application.

It has now further been discovered that prolonged exposure -- that is, greater than 8 hour exposure -- to the dried pediculostatic agent inhibits 25 nit hatching. Because newly hatched instars must obtain a blood meal shortly after hatching, prolonged exposure to dried pediculostatic agent, with concomitant inhibition of hatching during that period, can serve to starve embryos within the nit, preventing 30 a new cycle of infestation. A single, prolonged, exposure to dried pediculostatic agent can thus serve to eradicate the infestation. Furthermore, because the nits, so treated, will not give rise to reinfestation of the treated patient, removal of nits is not required

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in these embodiments, either to effect cure or to prevent contagious transmission.

Thus, in another aspect, the dried pediculostatic agent can be left on the affected area for days, or even a week or more, even up to a month, prior to removal by combing, washing, or combination thereof. Treatment can then be repeated, with the newly-applied and newly-dried pediculostatic agent again left in contact with the hair for days, or even a week or more, prior to removal.

Optionally, the dried pediculostatic agent can be left on the hair for days, or even a week or more, and the treatment continued by further application of pediculostatic agent, optionally followed by combing, and then followed by drying, without the intervening removal of the earlier-applied pediculostatic agent.

In this way, all stages of the louse life cycle can be eradicated, curing the infestation. Of course, agents containing pediculicides should be removed according to the recommended usage instructions for the particular pediculicide. A preferred application schedule for such prolonged exposure to dried pediculostatic agent is once per week; a regimen consisting of two treatments, repeated at one week intervals, is often sufficient to effect full cure.

A further advantage of such prolonged contact with dried pediculostatic agent is that newly-laid nits appear unable to adhere to hair shafts coated with the dried pediculostatic agents of the present invention, deterring reinitiation of infestation through egg laying by adult lice acquired from other patients in the period between applications of drierable pediculostatic agent.

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Another advantage of using the driable pediculostatic agents according to the methods of the invention is that the head need not be covered during overnight treatment. Since the agent is dried onto the hair and scalp, it does not come off during sleep or soak or stain bed pillows and linens. Thus, the methods of the invention are far easier and convenient than many of the "home" remedies that require overnight application of greasy, non-driable materials such as olive oil, mayonnaise, etc.

The dried agent can be conveniently removed by washing the hair with water, optionally with the aid of soaps, shampoos or conditioners. In this embodiment, the lice simply wash away with the agent. Alternatively, the lice and/or nits can be removed by combing the hair with a fine-toothed delousing comb prior to washing out the dried agent. If combing is used, any remaining dried agent can be removed by washing the hair.

Driable pediculostatic agents useful in the methods and kits of the present invention are characterized by their ability to induce an immersion reflex in lice in their wet form and to keep the lice in the immersion reflex once dried. The following *in vitro* test can be conveniently used to determine whether any individual agent is a pediculostatic agent, and can further be used for routine screening of agents - such as those from natural products libraries and combinatorial chemical libraries - to identify those that can be used in the methods, compositions, and kits of the present invention:

1. Contact a louse with an agent suspected of being a pediculostatic agent; and

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2. Observe whether the louse becomes immobile.

Observations can readily be performed using a standard inexpensive light microscope with 10X or 40X magnification. The length of time necessary to render
5 the louse completely immobile, in minutes, is the Immersion Reflex Index of the agent tested.

Once it has been determined that an agent is a pediculostatic agent, the following *in vitro* test can be conveniently used to determine whether the agent is
10 a driable pediculostatic agent useful in the methods and kits of the invention:

1. Contact a louse with a pediculostatic agent for a period of time sufficient to immobilize the louse (i.e., for at least 1X the
15 Immersion Reflex Index of the agent);
2. Dry the agent onto the louse, either by air-drying or by application of heat, and observe whether the louse remains immobilized.

If the louse does not regain mobility for an extended
20 period of time when encased in the dried agent, (i.e., about 20 to 60 min.), the agent is a suitable driable pediculostatic agent. The period of time necessary for a particular dried agent to kill the louse can be conveniently determined by rinsing the dried agent off
25 lice as a function of time and observing whether the rinsed lice regain mobility upon drying off.

The driable pediculostatic agents of the present invention typically have an Immersion Reflex Index of no more than 120 minutes. For preferred
30 agents, the Index is 5 minutes or less. For the most

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preferred agents, the Index can be as low as 0.1 minute, or even lower.

The driable pediculostatic agents of the invention are typically compositions comprising one or
5 more non-volatile compounds that are capable of keeping lice in the immersion reflex (*i.e.*, immobile) once volatile solvents have been removed by drying. While it is convenient to envision that the non-volatile compounds encase the louse in a film or coating, the
10 invention is not intended to be bound by any theory of operation. Any non-volatile agents that do not permit lice to recover from the immersion reflex once dried onto the lice, no matter by what means, are suitable non-volatile agents for use in the driable
15 pediculostatic agents of the invention. Surfactants, lipid materials and alkanols are preferred non-volatile compounds for use in driable pediculostatic agents according to the invention, as will be described more fully below.

20 The driable pediculostatic agents of the present invention generally comprise pharmaceutically or cosmetically acceptable compositions suitable for topical application to the hair, body and scalp of animals and humans which induce an immersion reflex
25 effect in lice and which cause the lice to remain immobile when the agent dries. In a preferred embodiment, the driable pediculostatic agent is a water-soluble liquid or is incorporated into a liquid or semisolid composition which is flowable or
30 spreadable over the scalp when in its wet form. These compositions are convenient in use, and are an effective medium for coating the lice and scalp.

There are a number of acceptable formulations suitable for use in the present invention, including

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but not limited to, solutions, lotions, sprays, creams, ointments, emollients, salves, and gels. Descriptions of non-limiting examples of suitable formulations may be found in the PHYSICIAN'S DESK REFERENCE, Medical Economics Co., Pub., Oradell, N.J., PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS, 1995, Williams & Wilkins, Malvern, PA and THE NATIONAL FORMULARY, American Pharmaceutical Association, Pub., Washington, DC., each of which is incorporated herein by reference in its entirety.

The driable pediculostatic agent is preferably transparent or translucent in order to facilitate observation of the area being treated, and is preferably easily driable and easily removed once dried, such as by rinsing with water, or is readily washed out using a shampoo. In general, the driable pediculostatic agent used in the present invention is a liquid or semisolid that, upon drying, presents a barrier that prevents the transfer of oxygen to the lice.

While the driable pediculostatic agents of the invention are preferably water-soluble or aqueous-based, water by itself is not a suitable driable pediculostatic agent. While water triggers the immersion reflex, upon drying the lice recover and regain mobility.

It has been found that aqueous or organic compositions containing surfactants are effective driable pediculostatic agents. While not intending to be bound by any particular theory of operation, it is believed that the surfactant not only triggers the immersion reflex by increasing the ability of the water to effectively coat the lice, thereby blocking their breathing apparatus, but it also covers the lice with a

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film or coating of surfactant which blocks their breathing apparatus upon evaporation of the solvents from the composition. Once dried, this film encases the louse, blocking its ability to breathe until the
5 dried agent is removed, such as would typically occur by resolubilization.

Thus, in a preferred embodiment, the drible pediculostatic agent of the present invention is a composition containing one or more surfactants.

10 Typically, the surfactant is present in an amount of about 0.1 wt% to 80 wt%, preferably about 1 wt% to 50 wt%. In some instances, the surfactant can be applied neat and caused to form a film on the lice by application of heat.

15 The amount of surfactant optimal for use in a composition may depend upon such factors as the particular surfactant and the solvent system used. The optimal amount can be readily determined by routine experimentation using the above-described in vitro
20 tests. The literature contains numerous examples of specific surfactant compositions which are suitable for use in the present invention. Examples are found in U.S. Patent Nos. 5,288,483; 4,495,079; 5,034,218; 5,656,280; 5,284,833; 5,562,912; and 5,480,633, each of
25 which is incorporated herein in its entirety by reference.

Non-limiting examples of suitable classes of surfactants that can be used in the drible pediculostatic agents include wetting agents, surface
30 tension depressants, detergents, dispersing agents, emulsifiers, and quaternary ammonium antiseptics. Non-limiting examples of suitable surfactants include anionic agents, cationic agents, amphoteric agents, zwitterionic agents, and nonionic agents.

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Anionic surfactants suitable for use in the drible pediculostatic agents of the invention include, but are not limited to, those described in McCutcheon's Detergents and Emulsifiers, 1979, M.C. Publishing Co., North American Edition; Schwartz et al., 1949, Surface Active Agents, Their Chemistry and Technology; and U.S. Patent Nos. 3,929,678, 5,858,383, and 6,001,339, each of which is incorporated herein in its entirety by reference. A preferred anionic surfactant for use in the present invention is sodium lauryl sulfate, which can conveniently be used in an aqueous solution at a concentration from about 1 to 30% by weight, preferably at about 1 wt% to 20 wt%, or even in the range of 1 wt% to 10 wt% or 1 wt% to 5 wt%.

Non-limiting examples of nonionic surfactants include, but are not limited to, fatty alcohols such as lauryl alcohol, cetyl alcohol and stearyl alcohol, glyceryl esters (such as mono, di and tri glycerides), fatty acid esters of fatty alcohols and other alcohols such as polyalkylene glycols (including propylene glycol and polyethylene glycol) sorbitan, and sucrose. Examples of nonionic surfactants suitable for use in the drible pediculostatic agents of the invention include those described in U.S. Patent Nos. 5,858,383 and 6,001,339, the disclosure of each of which is incorporated herein by reference. Propylene glycol can be conveniently used in an aqueous solution at a concentration from 1 to 80% by weight. A preferred propylene glycol concentration is 10 to 50% by weight.

Cationic surfactants suitable for use in the drible pediculostatic agents of the present invention include, but are not limited to, quaternary ammonium salts, fatty amines and mixtures thereof. Suitable exemplary quaternary ammonium salts and fatty amines

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include, but are not limited to, those described in McCUTCHEON'S Detergents & Emulsifiers, 1979, M.C. Publishing Co., North American Edition; Schwartz et al., 1949, Surface Active Agents, Their Chemistry and
5 Technology, Interscience Publishers, New York, and U.S. Patent Nos. 3,155,591; 3,929,678; 3,959,461; 4,387,090; 5,288,483; 5,858,383, and 6,001,339, the disclosure of each of which is incorporated herein by reference.

Other examples of suitable surfactants are
10 Span 65 (sorbitan tristearate), Span 60 (sorbitan monostearate), Span 40 (sorbitan monopalmitate), sodium bis-(2- ethylhexyl)sulfosuccinate, butylene glycol distearate, and Tween 80 (polysorbate 80).

An antifoaming agent can be optionally
15 included in the surfactant composition, an example of which is silicone fluid, or other silicone polymers, such as those described in U.S. Patent No. 5,288,484, incorporated herein by reference in its entirety

In another embodiment, the driable
20 pediculostatic agent of the invention is a composition comprising a non-volatile lipid material, a non-volatile fatty alcohol, a non-volatile fatty ester or mixtures thereof. Suitable lipid materials, which are typically used in gel-type compositions, include, but
25 are not limited to, fatty materials consisting of acids, acid derivatives, alcohols, esters, ethers, ketones, amides and mixtures thereof, typically having carbon chain lengths of from about 12 to 22, preferably from about 16 to about 18. Additional useful lipid
30 materials are described in Bailey's Industrial Oil and Fat Products, S. Swern, ed., 3rd Ed., 1979, which is incorporated herein by reference in its entirety.

Suitable non-volatile fatty alcohols are disclosed in US 5,288,483; US 4,165,369; and US

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3,155,591; British Patent 1,532,585; Fukushima et al., 1983, *Cosmetics & Toiletries* 98:89-102 and Hunting, Encyclopedia of Conditioning Rinse Ingredients, at 204 (1987), each of which is incorporated herein by

5 reference in its entirety. Additional examples of suitable non-volatile fatty alcohols include C12-C16 alcohols, ceteryl alcohol, cetyl alcohol, isostearyl alcohol, lanolin alcohol, lauryl alcohol, olelyl alcohol, stearyl alcohol and mixtures thereof.

10 Preferred are cetyl alcohol, stearyl alcohol and mixtures thereof. A particularly preferred fatty alcohol is a mixture of cetyl alcohol and stearyl alcohol containing from about 55 wt% to about 65 wt% cetyl alcohol.

15 Suitable non-volatile fatty esters are disclosed in US 5,288,483 and US 3,341,465, which are incorporated herein by reference in their entireties. Additional examples of suitable non-volatile fatty esters include cetyl lactate, cetyl octonate, cetyl
20 palmitate, cetyl stearate, glyceryl monostearate, glyceryl laurate, glyceryl myristate, glyceryl oleate, glyceryl stearate, glyceryl monoacetate and mixtures thereof. Preferred are cetyl palmitate, glycerol monostearate and mixtures thereof.

25 Typically, the lipid material, fatty alcohol, fatty ester or mixture thereof comprises from about 0.1 wt% to about 80 wt%, usually about 0.5 wt% to about 10 wt% of the composition, preferably from about 1 wt% to about 5 wt% of the composition. Alternatively, the
30 lipid material, fatty alcohol, fatty ester or a mixture thereof can be applied neat and caused to form a film on the lice by application of heat.

Those of skill in the art will recognize that the optimal amount of lipid, fatty alcohol, fatty ester

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or mixture used will depend on, among other factors, the specific lipids, fatty alcohols and fatty esters and the composition of the solvent system. The optimal amount can be readily determined by routine
5 experimentation using the above-described in vitro tests.

As will be appreciated by those of skill in the art, since the driable pediculostatic agent must be capable of being dried, the nature of the solvents
10 comprising the agents is an important feature. While in many instances water will be used as the solvent, water is not a preferred solvent because heat must typically be used to expedite the drying of water-based agents.

15 To hasten the drying time, or to provide an agent that can be conveniently air-dried without applying heat, different solvent systems can be used. For example, the solvent can be a mixture of water and a volatile organic solvent, such as a C2-C6 alkanol,
20 phenyl C2-C6 alkanol, C2-C6 alkandiol, phenyl C2-C6 alkandiol, C1-C6 ether, C1-C6 ketone or other well-known volatile solvent. Alternatively, volatile organic solvents can be used neat to dissolve the
25 ester. The only requirement of the solvent system is that the components of the composition be soluble in it and that it be fairly easily evaporated, with or without the aid of moderate heat (such as that produced by a hair-dryer, electric curlers, etc.). In preferred
30 embodiments the solvents comprising the agents are non-toxic and of a viscosity sufficient to effectively coat the hair and lice. Selection of suitable solvent systems is well within the capabilities of those of skill in the art. When heat will be used to aid drying

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of the agent, the solvents are preferably not inflammable at the applied drying temperature.

The driable pediculostatic agents of the present invention can be used singly or in combination, and can optionally include other components such as thickeners, penetration enhancers, conditioners, osmotic adjusters, acids, bases, buffering agents, skin protectants, stabilizers, antioxidants, coloring agents, preservatives, and fragrances. Thickeners can be included in the driable pediculostatic agents of the invention for decreasing the tendency of the composition to flow away from the treated area. Non-limiting examples of thickeners include cetyl alcohol, stearyl alcohol, petrolatum, glyceryl monooleate, myristyl alcohol and isopropyl palmitate. Other hydrophillic thickeners include polysaccharide gums, an example of which is xanthan gum. Non-limiting examples of preservatives include methyl paraben, propylparaben, and butylparaben. A non-limiting example of an acid is citric acid. Non-limiting examples of coloring agents include FD&C Green No. 8, FD&C Green No. 3, D&C Violet No. 2, and D&C Red No. 3.

Additional optional ingredients that can be used in the driable pediculostatic agents of the invention can be found, for example, in Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th Ed., Ansel et al., eds., Lea & Febinger, 1995, incorporated herein by reference in its entirety

Commercially available products such as soaps, skin cleansers, lotions, moisturizers, conditioners and shampoos that are non-toxic and pharmaceutically acceptable for topical application may also be used as driable pediculostatic agents, provided that when dried they keep the lice in the immersion

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reflex. These are preferably applied in their undiluted state and without agitation in order to minimize the formation of foam. The presence of air in the foam or suds can provide oxygen to the lice and
5 therefore lessen the ability of the agent to stun the lice.

Certain compositions that are designed to foam, however, particularly those that are applied as a collapsing foam, such as hair mousse compositions, can
10 usefully be used as driable pediculostatic agents provided that, when applied, they induce the immersion reflex and that when dried, they keep the lice in the immersion reflex. Hair mousse compositions are described in U.S. Patent Nos. 5,783,202; 5,066,481;
15 6,001,339; 4,913,893; 5,681,546, incorporated herein by reference in their entireties; such compositions can readily be tested for their ability to serve as driable pediculostatic agents using the tests set forth *supra*.

In a preferred embodiment of the invention,
20 the driable pediculostatic agent is an aqueous-based composition comprising one or more surfactants and one or more alkanols. Typically, the surfactant-alkanol composition comprises about 0.1 wt% to 80 wt% surfactant and about 0.1 wt% to 80 wt% alkanol.
25 Preferably, the composition is an aqueous-based composition comprising at least about 50 wt% water.

An example of a suitable alkanol-surfactant driable pediculostatic agent is BABY MAGIC® baby
shampoo (Mennen Co., Morristown, N.J.) which contains
30 water, polysorbate 20, sodium lauryl sulfate, lauroamphoglycinate, polysorbate 80, PEG-150 distearate, fragrance, citric acid, and quaternium 15. In use, the shampoo is applied in the absence of water

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in order to avoid foaming and dried onto the hair with a blow dryer.

Another example of an alkanol-surfactant drible pediculostatic agent suitable for use in the present invention is SUAVE® Baby Care bath soap tear-free formula (Helene Curtis, Inc., Chicago, IL) which contains water, PEG-80, sorbitan laurate, sodium tridecyl sulfate, cocamidopropyl hydroxysultaine, disodium lauroamphodiacetate, PEG-150 distearate, sodium lauryl-13 carboxylate, aloe vera gel, quaternium-15, DMDM hydantoin, methylchloro isothiazolinone, methylisothiazolinone, fragrance, citric acid, D&C Violet No. 2, D&C Red No. 3.

The presently most preferred composition for use as a drible pediculostatic agent in the invention is a mixture of water, cetyl alcohol, propylene glycol, sodium lauryl sulfate, stearyl alcohol, methyl paraben, propylparaben, and butylparaben sold commercially as a nonirritating, non-greasy skin cleanser under the trademark CETAPHIL® Cleanser (Galderma Laboratories, Inc., Fort Worth, TX).

CETAPHIL® Cleanser is additionally advantageous since it aids in the removal of the nits when in its wet form. While the mechanism for this property is not fully understood, a component or components in CETAPHIL® Cleanser may dissolve or loosen the cement which holds the nits to the hair shaft, and may also make the shaft slippery, thus facilitating the removal of the nits during combing.

CETAPHIL® Cleanser has the ability rapidly to trigger the "immersion reflex" in head lice. Both in vivo and in vitro, lice coated in CETAPHIL® Cleanser became immobilized within 6 seconds. On the patients' scalp, the lice became totally immobilized, floating on

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the scalp in the Cleanser. They were easily removed by forceps without any effort to escape or to grasp the hair shaft to stay in place. Under the microscope, they were immobile, did not respond to being touched, and
5 lost their normally visible gut motility. They remained immobilized as long as they were in the Cleanser. This phenomenon was observed for periods ranging from 6 seconds to 4 hours. At any point prior to drying the cleanser, the louse could be removed from the Cleanser
10 and usually awakened and resumed crawling. When immersed overnight in CETAPHIL® Cleanser (12 hours) the lice died.

When CETAPHIL® Cleanser was dried onto lice (6 lice tested), the lice remained immobile. When the
15 dried agent was removed by redissolving it in water after 4 hours of contact, the lice recovered and regained mobility. When left on the lice for more than 8 hours before redissolving, the lice died.

While the methods of the invention are
20 effective at treating, removing and preventing crawling lice, they are also effective on nits.

A film of CETAPHIL® Cleanser dried onto nits (n=2) and left on for 8 hours prior to redissolving, killed the nits: *i.e.*, the nits did not hatch. The
25 result was replicated in an *in vivo* test, further described *infra* in Example 4. Briefly, dried pediculostatic agent was left on a patient's hair (n=1) for one week. Upon combing with a fine-toothed louse comb at one week, there was significant increase in the
30 percentage of embryo-containing nits among the removed nits. While not intending to bound by any theory of operation, it is believed that the nit is prevented from opening during the entire period of contact with

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the dried pediculostatic agent, but that the agent does not significantly interfere with growth and maturation of the embryo. Because the embryo must obtain a blood meal shortly after hatching, failure to emerge causes
5 death of the embryo and progressive accumulation of embryo-containing nits. Alternatively or in addition, it is possible that the dried pediculostatic agent starves the embryo for oxygen, which must pass into the nit from the external milieu. Whatever the mechanism
10 of action, however, it has now been discovered that prolonging exposure to the dried pediculostatic agent prevents hatching of nits and death of the embryos therein.

As a result, in those embodiments of the
15 present invention in which contact with dried pediculostatic agent is sufficiently prolonged as to kill nits, nit removal by combing is not required as part of the treatment regimen.

The invention can also incorporate a system
20 for verifying whether the dried pediculostatic agent has been applied. This is an important feature for certain populations where cross-contamination is known to occur, such as in a grade school setting. It is particularly important in embodiments of the invention
25 in which nit removal is neither required for treatment nor practiced, and thus where reliance upon nit absence - presently the critical indicium of noncontagious status - is no longer diagnostic of effective treatment.

30 The driable pediculostatic agent is optionally combined with a dye that will temporarily remain on and mark the hair and/or scalp and/or nits after drying, in order to verify that the agent has been applied. The dye is present at a concentration

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that will leave an observable mark (e.g. 0.1 to 1 wt%
in the driable pediculostatic formulation) and
preferably is non-volatile and non-toxic. The dye can
be fluorescent, and thus visible only under an
5 ultraviolet light, so that the presence can be detected
but will not alter the color of the patient's hair.
Non-limiting examples of suitable dyes include those
described in US 4,610,806 and US 5,302,371. Additional
suitable dyes can be found in the Molecular Probes
10 (Eugene OR) catalogue and the references cited therein.

Alternatively, the dye can be visible in
natural light, with the color chosen to be attractive,
either by mimicking a natural hair color different from
the patient's, or alternatively by its unnatural color,
15 the latter particularly suitable as a novelty that will
be attractive to children. Alternatively or in
addition to dyes, the composition can include glitter,
or other particles that are visibly detectably. A
nonlimiting example is described in U.S. Patent No.
20 5,853,706, the disclosure of which is incorporated
herein by reference.

Optionally, a driable pediculostatic agent
and a conventional pediculicide can be coadministered.
In one embodiment of the method of the invention, a
25 conventional pediculicidal active ingredient can be
incorporated into the driable pediculostatic
formulation described herein. The active ingredients
can be used at levels of from about 0.25% to about
2.5%. Exemplary useful pediculicidal agents include
30 natural pyrethrins, pyrethroids, permethrin, lindane,
malathion, carbaryl, ivermectin and combinations
thereof. Piperonyl butoxide can be optionally included
at levels of from about 1 wt% to 5 wt% to hinder the

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development of resistance of the pediculicidal additives.

In an alternative embodiment, a pediculicidal agent can be applied first, followed by application of a driable pediculostatic composition, or vice versa. Such compositions are well known in the art and include, but are not limited to, RID® (Pfizer Inc., New York, NY), NIX® (Warner-Lambert, Harristown, NJ), KWELL® (Reed and Carnick, Jersey City, NJ), A-200® (Hogil, Purchase, NY), PRONTO® (Del Pharmaceuticals, Uniondale, NY), LINDAINE® (Alpharma, Baltimore, MD), CLEAR® (Care Technologies, Inc., Greenwich, CT), and those described in US 5,292,504, which is incorporated herein by reference in its entirety. If the pediculicidal agent is applied first, it can be rinsed from the hair prior to application of the driable pediculostatic agent, or can be dried onto the hair along with the driable pediculostatic agent.

In another aspect, the invention provides kits for the treatment, removal or prevention of lice. One kit according to the invention includes an amount of a driable pediculostatic agent according to the invention, packaged in association with instructions for use in the methods described herein. The instructions can conveniently be affixed to a bottle or container containing the driable pediculostatic agent, and the kit can, if the instructions are so affixed directly to the container, exclude further packaging. The instructions can conveniently be abbreviated by provision of an Internet web site address (URL), at which site the user can obtain more detailed instructions, and/or provision of a telephone number, preferably a toll-free telephone number, email address, or even a radio frequency at which the user can obtain

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more detailed instructions, either directly, or via an automatic response system.

The kit can optionally including a comb for removing excess agent or a delousing comb.

5 Another kit according to the invention includes an amount of a driable pediculostatic agent suitable for at least one treatment (about 8 ounces) and a comb for removing excess agent, and optionally at least one delousing comb suitable for removing adult
10 lice and nits. Alternatively, the kits can contain ingredients in quantities suitable that when they are mixed together, either with or without the addition of water or other solvents, provide an amount of driable pediculostatic agent sufficient for at least one
15 application or treatment. Examples of suitable delousing combs are known in the art and include ACU-MED® Lice Comb (Health Enterprises, North Attleboro, MA), LICEMEISTER® Lice Comb (National Pediculosis Association), MEDI-SWEEP® Lice Comb (US 4,612,944), and
20 dog and/or cat FLEA COMB® (Classic Products, Oxnard, CA), each of which is incorporated herein by reference in its entirety. The comb is preferably constructed of rigid material such as metal or plastic. In a preferred embodiment, the comb is inexpensive and
25 designed to be disposable after a single use, in order to prevent contamination. In another embodiment the comb has a removable, and preferably disposable, piece having a plurality of teeth which attaches to a handle portion such as described in US 5,636,646, incorporated
30 herein by reference in its entirety.

Of course, other components such as pediculicidal agents, markers such as fluorescent dyes, shower caps, paper towels, etc. can also be included in the kits of the invention. Typically, the kit will

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contain a quantity of driable pediculostatic agent to completely eradicate a lice infestation, thereby providing an effective treatment for lice.

While the invention has been described in
5 terms of removal, treatment or prophylaxis of head lice, it will be appreciated that the methods and kits of the invention can be used as described for the treatment, removal or prevention of other types of lice infestations, including body and pubic lice. Moreover,
10 the methods and kits can be used to treat, remove or prevent infestations of other insects, mites, ectoparasites or other bugs or pests which evince an immersion reflex when immersed in water, and/or which suffocate when coated with a dried driable
15 pediculostatic agent, such, as for example, ticks, fleas, etc.

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration
20 of the invention and are not intended to be limiting thereof.

EXAMPLE 1

CETAPHIL® Cleanser Triggers
the Immersion Reflex in Lice
25 Within Seconds

Ten crawling lice were obtained from patients with head lice and each one placed on a separate microscope slide for observation under a microscope at 10x or 40x power. Each louse was placed in a drop of
30 CETAPHIL® Cleanser for up to 4 hours. All of them exhibited the same response. Within 6 seconds of application, they stopped all spontaneous movement. Usually within 30 seconds, and always within 60

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seconds, they would not respond to contact by a probe and ceased previously visible gastrointestinal motility. They remained in this state of suspended animation as long as they were kept in wet CETAPHIL® Cleanser. If the louse was pulled to the side of the drop, it could be seen that the CETAPHIL® Cleanser formed an adherent layer surrounding and conforming to the body and limbs. When the lice were removed from the CETAPHIL® Cleanser and allowed to dry off, they usually awoke and all prior activity. Thus, the lice were stunned but were not killed by the Cleanser. The longer the louse was coated, the longer it took to awaken after removed from the Cleanser. After five of the lice were placed in the Cleanser overnight, they were all dead following 12 hours of immersion in the Cleanser. To reliably kill head lice with the Cleanser, immersion for periods longer than 4 hours were required.

EXAMPLE 2

Dried CETAPHIL® Cleanser
Maintains the Immersion Reflex In Lice

Six crawling lice were obtained from patients with head lice and each placed in a drop of CETAPHIL® Cleanser as described in EXAMPLE 1. After 2 min., the cleanser was dried onto the lice by air drying (4 lice) or gentle warm air from a hair dryer (2 lice). The lice continued to demonstrate the immersion reflex, *i.e.*, they remained immobile the entire time they were encased in the dried cleanser, as judged by examination under a microscope.

When the dried agent was removed at fewer than four hours by re-solubilizing with water and gentle mechanical stirring, the lice recovered and

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gained mobility. Lice encased in the dried agent for at least 8 hours prior to removal by re-solubilizing died.

Two nits encased in dried CETAPHIL® Cleanser
5 prior to removal by re-solubilizing failed to hatch.

EXAMPLE 3

Clinical Use of a Driable Pediculostatic Agent in the Treatment of Head Lice

A group of 23 patients with active head lice
10 infestations were treated with CETAPHIL® Cleanser by soaking the hair and scalp with the cleanser and removing any excess by combing with a delousing comb. The cleanser was then dried onto the hair with a blow dryer and the dried cleanser allowed to remain on the
15 hair for 8 to 24 hours prior to removal by shampooing. All patients gave a history of symptoms of lice and/or recent exposure to a close family member or friend with lice. Some of the patients had previously tried one or several commercially available lice treatments; one
20 patient had tried a buzz haircut. All patients or their parents signed informed consent forms prior to entry into the study. The patients ranged in age from 3 years to 37 years, with most of the patients being around 4 to 7 years old.

25 All treatments were done at the patients' homes, usually by the parent. Treatment was done once weekly until no lice were present. All of the patient's family members were treated with at least one treatment to see if they had lice or nits in their data
30 collection. If identified as affected, then they were added to the study.

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Method of Application

All patients in the study were asked to follow the following protocol once weekly until requested to stop by the research director:

- 5
- 1) Start with dry hair;
 - 2) Use a wide-toothed comb to detangle the hair;
 - 3) Apply CETAPHIL® Cleanser thoroughly throughout the scalp to totally soak the scalp and hair (usually this requires 6 oz. for short hair and 12 oz. for long hair);
 - 4) Wait 2 minutes;
 - 15 5) Use a wide-toothed comb to detangle hair and then comb hair with a fine-toothed delousing comb to remove excess CETAPHIL® Cleanser, lice and nits;
 - 20 6) Place the removed cleanser on paper towels, seal the towels in a plastic zipper bag and return the bags to the research director for analysis;
 - 25 7) Dry the Cleanser onto the hair with a blow-dryer;
 - 8) After at least 8 hours (conveniently overnight), remove the dried cleanser by rinsing with water, shampoo and/or conditioner, as desired.
 - 30

During the course of treatment, all patients were advised to wear clean clothes after each

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treatment, to launder all dirty clothes and to put clean sheets on the bed. Patients were also requested to sanitize all combs and brushes daily by soaking for 10 minutes in rubbing alcohol and to sanitize all hair ribbons, scrunchies, etc. and hats by placing in plastic bags for 14 days. Patients were further advised not to share combs, brushes, hats or other hair items with anyone and to avoid friends or classmates showing symptoms of lice infestation.

10 Data Analysis

Each bag received from patients was opened and all lice and nits present counted and recorded on a computerized data form. The total number of nits present, the number of instars present and the number of adult lice present were recorded.

Determination of Cure

Complete lice removal was defined as meeting three criteria:

- 20 1) No lice in the data collection from the paper towels returned after treatment;
- 2) No further symptoms of lice infestation; and
- 25 3) No recurrence of lice reported by the patients within 2 months of achieving a zero lice data collection result.

The number of applications to achieve complete lice removal, or cure, is defined as the number of applications that produced lice before the zero lice collection result was achieved. For example,

if on the third application there were no lice in the towel data, then it took 2 applications to remove all the lice.

Results

5 All 23 patients achieved complete lice removal. Of the 23 patients, 20 achieved complete removal after 1 treatment and 3 achieved complete removal after 2 treatments. On average, it took 1 treatment to achieve complete removal. Some of the
 10 patients had previously tried pediculicidal treatments without success. A sufficient number of nits were removed to allow the patients to return to school, whereas with the conventional pediculicidal treatments they could not. In some instances, parents had to
 15 manually remove a small number of residual nits in order for the patient to return to school. The raw data are shown in TABLE 1, infra:

TABLE 1				
Age	Prior Treatment	No. Treatments Until Cured	Total No. Lice Removed	Total No. Nits Removed
20 7 yrs	Nix®; Rid®	1	23	188
8 yrs	Nix®; Rid®	1	10	10
12 yrs	Nix®; Nix®; Generic; Generic	1	6	942
9 yrs	Nix®; Generic; Generic; Generic	1	2	112

TABLE 1				
Age	Prior Treatment	No. Treatments Until Cured	Total No. Lice Removed	Total No. Nits Removed
10 yrs	Nix [®] ; Generic; Generic; Generic	1	17	103
4 yrs	None	1	2	7
3 yrs	Nix [®] ; Nix [®] ; Elmite	1	4	0
4 yrs	Oil: olive, tea; Nix [®] ; Clear [®]	1	7	15
5 6 yrs	Nix [®] ; Rid [®] ; Generic; Generic	1	30	333
32 yrs	Nix [®] ; Rid [®] ; Generic;	1	2	4
8 yrs	Nix [®] ; Rid [®] ; Generic; Generic	1	10	17
11 yrs	Nix [®] ; Rid [®] ; Generic; Generic	1	1	43
7 yrs	None	1	2	3
10 12 yrs	Rid [®]	1	1	4
7 yrs	Nix [®] ; Rid [®] ; Vaseline	1	1	38
33 yrs	Nix [®] ; Rid [®] ; Vaseline	1	1	0

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TABLE 1				
Age	Prior Treatment	No. Treatments Until Cured	Total No. Lice Removed	Total No. Nits Removed
37	Nix®; Rid®; Vaseline	1	1	0
34 yrs	Nix®	1	6	15
7 yrs	None	1	1	0
34 yrs	None	1	2	2
5 8 yrs	Nix®	2	30	75
6 yrs	Nix®; Haircut/ Buzz	2	2	0
5 yrs	Rid®	2	2	12

A total of 163 lice and 1923 nits were removed, yielding an average of 7.1 lice and 83.6 nits per patient. All patients and parents described the process as not unpleasant. All reported immediate relief of itching after the first application. None of the patients complained that the dried agent was unpleasant to wear.

15

EXAMPLE 4

Extended Exposure to Dried
Pediculostatic Agent Inhibits
Nit Hatching

A six year old patient with an active lice infestation that had previously been treated unsuccessfully with two different pediculocidal compositions (Nix® and Pronto®) was treated with drible pediculostatic agent as follows.

CETAPHIL® Cleanser was applied to the patient's dry hair in a quantity sufficient fully to wet the hair. After a short interval, the patient's hair was combed with a louse comb. The removed material, which included excess Cleanser, was inspected, revealing 19 first stage instars and 95 nits. The patient's hair was then dried using a blow dryer.

The patient was instructed to leave the hair totally dry for 1 week and then to return to the Research Center for further treatment. On the second day after treatment, however, the patient's hair reportedly became partly wet during bathing. The hair was allowed to air dry, and no additional driable pediculostatic agent was added at that time.

At one week, the patient returned to the Research Center, and the treatment described above was repeated: without any washing or removal of the earlier-applied driable pediculostatic agent, CETAPHIL® Cleanser was applied to the patient's hair in a quantity sufficient fully to wet the hair. After a short interval, the patient's hair was combed with a louse comb, and then dried with a blow dryer.

Upon inspection of the material removed by combing (*i.e.*, removed prior to drying) in this second treatment, a total of 4 second stage instars and 30 nits were counted. Further microscopic inspection of the 30 removed nits revealed the following results:

Nit Status	Number of Nits	% of Total Nits
empty, with no nit cover in place	8	27%

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embryo inside, with nit cover present	22	73%
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The ratio of embryo-containing to embryo-free nits observed with long-term (7 day) incubation in the presence of dried pediculostatic agent, almost 3:1, is substantially different from that typically seen with shorter (e.g., 8 - 12 hour) incubation, typically about 1:4. This would suggest that hatching of nits - but not the growth and maturation of the embryos therein - is inhibited during contact with the dried pediculostatic agent: as the period of contact is extended, there is thus a progressive accumulation of nits with unhatched embryos. Consistent with this interpretation, the four instars that were observed were all second-stage instars, a stage achieved 5 - 6 days after hatching, consistent with their hatching during the brief period that the dried pediculostatic agent had been solubilized by the patient's inadvertent hair wetting one day into treatment.

The further microscopic observation that two of the embryo-containing nits had covers that were slightly raised, with the dead embryo extending a limb from thereunder, further suggests that a mechanism for such hatching inhibition might include mechanical inhibition of cover removal.

EXAMPLE 5

Prophylactic Use of Pediculostatic Agents

CETAPHIL® Cleanser is applied as in the previous examples, but on a periodic, preferably weekly, basis in order to prevent re-infestation or to

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prevent infestation of persons who are uninfected but at risk for catching head lice.

EXAMPLE 6
Treatment at School

5 Current school policy is immediately to send children home who are discovered to have lice infestation. As an alternative, CETAPHIL® Cleanser is applied to and dried onto the scalp at school and left in place until the child returns home at the end of the
10 day. The agent can then be removed by the child's parents, and the treatment regimen outlined above commenced until the infestation is cured.

 While the foregoing has presented specific embodiments of the present invention, it is to be
15 understood that these embodiments have been presented by way of example only. It is expected that others will perceive and practice variations which, though differing from the foregoing, do not depart from the spirit and scope of the invention as described and
20 claimed herein.

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I claim:

1. A method of removing ectoparasites from a subject, said ectoparasites having an immersion reflex, comprising:

- a) applying to an area of the body having the ectoparasites an effective amount of a driable pediculostatic agent for a time sufficient to trigger the immersion reflex in said ectoparasites;
- b) drying said agent; and
- c) removing said ectoparasites and optionally said agent.

2. The method of Claim 1 in which the ectoparasites are head lice and the subject is a human.

3. The method of Claim 2 which further includes the step of combing the hair after step a) and before step b).

4. The method of Claim 3 in which said combing is performed with a fine-toothed delousing comb.

5. The method of Claim 2 in which the dried agent remains on the body for a time sufficient to kill at least some the lice prior to removal.

6. The method of claim 2 in which the dried agent remains on the body for at least 8 hours.

7. The method of claim 2, in which the dried agent remains on the body for at least 24 hours.

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8. The method of claim 2, in which the dried agent remains on the body for at least 2 days.

9. The method of claim 2, in which the dried agent remains on the body for at least 7 days.

10. The method of claim 2, in which the dried agent remains on the body for longer than 7 days.

11. The method of Claim 2, wherein the dried pediculostatic agent is removed by rinsing the application site with water, optionally with the aid of a soap or shampoo.

12. The method of Claim 2, wherein the drierable pediculostatic agent has an Immersion Reflex Index of 120 or less.

13. The method of Claim 2, wherein the drierable pediculostatic agent is a composition comprising a non-volatile surfactant.

14. The method of Claim 13, wherein the surfactant is selected from the group consisting of anionic agents, cationic agents, amphoteric agents, zwitter ionic agents, nonionic agents and combinations thereof.

15. The method of Claim 13, wherein the surfactant is selected from the group consisting of sodium lauryl sulfate, sorbitan tristearate, sorbitan monostearate, sorbitan monopalmitate and butylene glycol distearate.

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16. The method of Claim 13, in which the composition further includes a polar organic compound.

17. The method of Claim 16, in which the polar organic compound is selected from the group consisting of (C1-C20) alkylene glycols, polyethylene glycols, polyethylene oxides, (C1-C20) polyols, glycerol and combinations thereof.

18. The method of Claim 13 in which the composition solvent is water.

19. The method of Claim 2 in which the drible pediculostatic agent is a composition comprising a non-volatile fatty alcohol.

20. The method of Claim 19 in which the composition is an aqueous composition.

21. The method of Claim 2 in which the drible pediculostatic agent is a composition comprising a non-volatile fatty ester.

22. The method of Claim 21 in which the composition is an aqueous composition.

23. The method of Claim 2 in which the drible pediculostatic agent is a composition comprising an alkanol and a non-volatile surfactant.

24. The method of Claim 23 in which the composition is an aqueous composition.

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25. The method Claim 2 in which the driable pediculostatic agent is CETAPHIL® Cleanser.

26. The method of Claim 2 in which the driable pediculostatic agent includes an effective amount of a pediculicidal agent.

27. The method of Claim 26 in which the pediculicidal agent is selected from the group consisting of pyrethrins, pyrethroids, permethrin, lindane, malathion, carbaryl and ivermectin.

28. A method for the prevention of active lice infestations, comprising:

- a) applying to an area of the body at risk of lice infestation an amount of a driable pediculostatic agent sufficient to soak or saturate the area for a period of time equal to about 1 to 50 times the Immersion Reflex Index of the agent;
- b) drying the agent onto the area of the body;
and
- c) removing the dried agent after the dried agent has remained on the area for a time period sufficient to kill at least some of the lice.

29. A kit for the removal, treatment or prevention of lice or nits, comprising:

- a) an amount of a driable pediculostatic agent sufficient for at least one application;
and
- b) a comb for removing excess agent from the hair.

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30. The kit of Claim 29, further including an amount of a pediculicidal agent sufficient for at least one application.

31. The kit of Claim 29, further including an amount of a dye sufficient for at least one application.

32. A method of treating a lice infestation, comprising the steps of:

- a) applying to the hair of a lice-infested area of the body an effective amount of a drier pediculostatic agent;
- b) allowing the pediculostatic agent to remain on the area for period of time equal to or greater than the Immersion Reflex Index for the agent;
- c) drying the agent onto the application site;
- d) removing the agent; and
- e) repeating steps (a)-(d) at intervals of 1 to 3 times weekly until the lice infestation is cured.

33. The method of Claim 32 further including the step of combing the hair after step b) and prior to step c).

34. The method of Claim 32 further including the step of allowing the dried agent to remain on the application site following step c) for a period of time sufficient to kill at least some of the lice.

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35. A diagnostic method for determining whether an area of the body is infested with lice or nits, comprising:

- a) applying to the hair of an area of the body suspected of having lice or nits an amount of a driable pediculostatic agent sufficient to saturate the hair;
- b) allowing the driable pediculostatic agent to remain on the area for period of time equal to or greater than the Immersion Reflex Index for the agent;
- c) removing a portion of the driable pediculostatic agent from the hair by combing with a fine-toothed delousing comb; and
- d) inspecting the removed driable pediculostatic agent for the presence of lice or nits.

36. A driable pediculostatic agent packaged in association with instructions for use in a method for removing, treating or preventing lice, the instructions comprising:

- a) apply to an area of the body suspected of having lice an amount of a driable pediculostatic sufficient to cover any lice present;
- b) allow the agent to remain on the body for a time period sufficient to trigger the immersion reflex in lice;
- c) dry the agent onto the body; and
- d) remove the dried agent.

37. The agent of Claim 36 in which the instructions further include the step of permitting the

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dried agent to remain on the body for at least 8 hours following step c).

38. A drible pediculostatic agent packaged in association with instructions for use in a method for removing, treating or preventing lice, the instructions comprising:

- a) apply to the hair of an area of the body suspected of having lice an amount of a drible pediculostatic sufficient to saturate the hair;
- b) allow the agent to remain on the hair for at least 2 min.;
- c) dry the agent onto the hair; and
- d) remove the agent.

39. A drible pediculostatic agent packaged in association with instructions for use in a diagnostic method for determining whether an area of the body is infested with lice or nits, the instructions comprising:

- a) apply to the hair of an area of the body suspected of having lice or nits an amount of a drible pediculostatic agent sufficient to saturate the hair;
- b) allow the drible pediculostatic agent to remain on the hair for period of time equal to or greater than the Immersion Reflex Index of the agent;
- c) remove a portion of the drible pediculostatic agent from the hair by combing the hair with a fine-toothed delousing comb; and

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- d) inspect the removed driable pediculostatic agent for the presence of lice or nits.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/01905

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K7/40 A01N25/00 A01N61/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 99 18800 A (PEARLMAN DALE L ;PEARLMAN DARA B (US)) 22 April 1999 (1999-04-22) claims 1-23	1-39
A	US 5 858 383 A (M. J. PRECOPIO) 12 January 1999 (1999-01-12) cited in the application column 2, line 8 - line 12 claims 1-15	1-39
A	WO 91 05561 A (P. H. HULL) 2 May 1991 (1991-05-02) claims 1-10	1-39
A	US 4 927 813 A (J. E. BERNSTEIN) 22 May 1990 (1990-05-22) cited in the application the whole document	1-39
-/-		

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Siatou, E

INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 783 202 A (R. P. TOMLINSON ET AL) 21 July 1998 (1998-07-21) cited in the application claims 1-29 column 2, line 16 - line 54 -----	1-39

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/01905

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9918800 A	22-04-1999	AU 1074299 A	03-05-1999
US 5858383 A	12-01-1999	NONE	
WO 9105561 A	02-05-1991	NONE	
US 4927813 A	22-05-1990	NONE	
US 5783202 A	21-07-1998	NONE	