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<p>(21) International Application Number: PCT/US98/24632 (22) International Filing Date: 18 November 1998 (18.11.98) (30) Priority Data: 08/975,743 20 November 1997 (20.11.97) US (71) Applicant: SYNTHETIC BLOOD INTERNATIONAL, INC. [US/US]; Suite 400, 4667 MacArthur Boulevard, Newport Beach, CA 92660 (US). (72) Inventors: CLARK, Leland, C.; 218 Greendale Avenue, Cincinnati, OH 45220 (US). HOFFMANN, Richard, E.; 1169 Brookside Drive, Beavercreek, OH 45434 (US). (74) Agents: KLEIN, Howard, J. et al.; Klein & Szekeres, LLP, Suite 700, 4199 Campus Drive, Irvine, CA 92612 (US).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>Without international search report and to be republished upon receipt of that report.</i></p>	
<p>(54) Title: SELECTED C₁₀ PERFLUORINATED HYDROCARBONS FOR LIQUID VENTILATION AND ARTIFICIAL BLOOD</p>		
<p>(57) Abstract</p>		
<p>Perfluorinated alkylcyclohexane and alkyl cyclopentane derivatives of the empirical formula C₁₀F₂₀ boil at atmospheric pressure in the range of 144–146 °C and are utilized as mediums for gas transport in liquid ventilation and in artificial blood. Compounds of the C₁₀F₂₀ formula which can exist only as a single stereoisomer are preferred as mediums for gas transport.</p>		

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1 SELECTED C-10 PERFLUORINATED HYDROCARBONS
2 FOR LIQUID VENTILATION AND ARTIFICIAL BLOOD

3 Background of the Invention

4 1. Field of the Invention

5 The present invention is in the field of biological gas exchange in
6 mammals using C-10 perfluorinated hydrocarbons (perfluorocarbons) as
7 a medium of the exchange. More particularly, the present invention is
8 directed to use of those C-10 perfluorinated hydrocarbons in biological
9 gas exchange, primarily in liquid ventilation, which due to their
10 chemical structure can be readily obtained or purified in a state free of
11 isomeric contaminants.

12 2. Brief Description of the Prior Art

13 It has been known for a long time that perfluorocarbons are
14 chemically and biologically inert substances and have the unique
15 capability of dissolving very large volumes of gases, including oxygen
16 and carbon dioxide. Taking advantage of these properties of the
17 perfluorocarbons, it was demonstrated as early as 1966 that the lives of
18 experimental animals, such as mice, can be sustained while the animals
19 are submerged in an oxygenated perfluorocarbon liquid medium.

20 The above-noted pioneering discovery spurred extensive further
21 research in this field by the present inventor, his coworkers and by other
22 scientists as well. As a result, perfluorocarbons emerged as leading
23 candidates for gas-transporting components of artificial blood, and as
24 mediums of gas exchange in liquid ventilation.

25 Specifically, liquid ventilation is a term used for describing gas
26 exchange, *i. e.* breathing of a mammal, where a certain volume of gas
27 transporting liquid is added to fill the entire or partial volume capacity
28 of the lungs, and where the presence of the liquid facilitates the
29 breathing process. The term "tidal liquid ventilation" or "total liquid
30 ventilation" is used to describe liquid ventilation where the lungs of the
31 mammal are completely filled with the liquid which is oxygenated by

1 bubbling or by passing it through a membrane oxygenator. It is now
2 generally accepted in the art that although the feasibility of using
3 perfluorinated hydrocarbons to sustain the lives of experimental animals
4 was initially demonstrated by this method (the animal was submerged in
5 the liquid medium) "total liquid ventilation" is unlikely to become a
6 medically accepted procedure to be used with humans who need
7 respiratory assistance.

8 Another form of liquid ventilation where only the functional
9 residual volume of the lung is filled with the perfluorocarbon and where
10 gas exchange is assisted with the use of a mechanical ventilator, is
11 termed "partial liquid ventilation". In partial liquid ventilation
12 approximately 30 milliliters (ml) of the perfluorocarbon (or mixture of
13 perfluorocarbons) is used per kilogram (kg) body weight of the
14 mammal.

15 Still another form, which has been suggested relatively recently by
16 one of the present inventors is "low volume" or "alveolar" ventilation
17 where the perfluorocarbon (or mixture of perfluorocarbons) is added in
18 sufficient quantity only to fill the *alveoli* (air sacs) of the lung and the
19 mammal is allowed to breath normally, or with the assistance of a
20 mechanical ventilator. In this "low volume" method only approximately
21 0.1 to approximately 10 ml of the perfluorocarbon (or mixture of
22 perfluorocarbons) is used per kg body weight of the mammal.

23 The research prompted by the 1966 discovery of the possibility of
24 "liquid breathing" in a perfluorocarbon medium, resulted in voluminous
25 scientific and patent literature on the medical aspects of the subject. It
26 also led to the development of voluminous literature pertaining to the
27 manufacturing and selecting suitable perfluocarbons for "liquid
28 breathing" and "artificial blood" purposes. A substantial list of scientific
29 papers, publications and patents is provided in an Information

1 Disclosure Statement, which is filed in connection with this application
2 for patent. An article titled "Liquid Ventilation A State of the Art
3 Review" by *Shaffer et al.* in **Pediatric Pulmonology** 14:102-109 (1992)
4 reviews the properties of perfluorocarbons which are pertinent to liquid
5 breathing and provides a long list of references pertinent to the subject.

6 A publication titled "Response of the rabbit lung as a criterion
7 of safety for fluorocarbon breathing and blood substitutes" by *Clark Jr.*
8 *et al.* in **Biomat., Art. Cells & Immob. Biotech** 20(2-4) 1085-1099 (1992)
9 describes hyperinflated non-collapsible lung syndrome (HNCL) which
10 has emerged as a serious problem associated with the use of certain
11 perfluorocarbons in liquid breathing and in artificial blood as well.
12 Briefly, it was found in experimental rabbits, and later in other
13 mammals as well, that when perfluorinated decalin (F-decalin) and
14 certain other perfluorocarbons are administered to rabbits either as an
15 emulsion (artificial blood) or by intratracheal infusion, the animals tend
16 to develop hyperinflated non-collapsible lungs, which can eventually
17 prove to be fatal. The hyperinflated non-collapsible lungs are fatal to
18 the animal because, the lobes completely fill the thorax and are not
19 compliant.

20 The above-noted article in **Biomat., Art. Cells J. Immob. Biotech**
21 and a poster presented by *Clark Jr. et al.* at a symposium **Hot Topics '95**
22 **in Neonatology**, December 3 - 5, 1995, Washington D. C. , titled
23 "Fluorovent™: A New Perfluorocarbon for Liquid Ventilation", describe
24 the scientific quest for perfluorocarbons which would be ideally suited
25 for use in liquid ventilation and artificial blood as well. The criteria
26 mentioned for ideal, or at least better suitability is avoidance of
27 hyperinflated lung syndrome and an acceptably low "body dwell time"
28 after administration of the perfluorocarbon liquid to the mammal.
29 Out of an abundance of caution it is considered desirable for the

1 fluorocarbons to be completely removed from the body after treatment.
2 Alternatively, if complete removal after treatment is impossible, it is in
3 any case desired for the perfluorocarbon to have as short a residual
4 dwell time as possible. In this regard it is noted that the primary
5 mechanism by which the mammalian body eliminates fluorocarbons is
6 through exhalation by the lungs. Although the precise mechanism of
7 this removal by exhalation is not presently known the rate of removal
8 has been recognized to be related to the volatility (vapor pressure at
9 body temperature) of the perfluorocarbon liquid. While, as mentioned
10 above, excessive persistence of the perfluorocarbon in the mammalian
11 body after treatment is undesirable, excessive or too rapid loss by
12 exhalation/evaporation is also undesirable since it requires
13 replenishment of the perfluorocarbon liquid during treatment. As it is
14 readily understood by those skilled in the art, the rate of loss due to
15 exhalation/evaporation is also related to the volatility (vapor pressure at
16 body temperature) of the perfluorocarbon substance.

17 Finally, as manifested in the above-mentioned article by *Clark Jr.*
18 *et al.* in **Biomat., Art. Cells & Immob. Biotech** 20(2-4) 1085-1099 (1992)
19 and in the Abstract of the poster presentation by *Clark Jr. et al.* at a
20 symposium **Hot Topics '95 in Neonatology**, the prior art recognized that
21 causation of hyperinflated non-collapsible lung syndrome (HNCL) is
22 also related to the volatility of the perfluorocarbon liquid, whether it is
23 used in artificial blood or in liquid ventilation. For example,
24 perfluorinated decalin (F-decalin) having a boiling point of 141-142.5°C
25 is known to cause hyperinflated lung syndrome, while perfluorinated
26 methyldecalin (F-methyldecalin) having a boiling point of 161°C does
27 not. F-methyldecalin, however, persists somewhat longer in the body
28 than what is considered desirable. Thus, the article in **Biomat., Art.**
29 **Cells & Immob. Biotech** 20(2-4) 1085-1099 (1992) refers to a search for

1 fluorocarbons "having boiling points between 140°C and 165°C. "in order
2 to find a perfluorinate with the highest transpiration rate, and hence
3 vapor pressure, compatible with an acceptable body dwell time.". The
4 abstract of the presentation at the above-mentioned symposium refers
5 to an evaluation of the properties of many perfluorocarbons (PFCs)
6 ... "to find the optimum PFC for liquid ventilation". The abstract
7 mentions "two properties - boiling point related lung hyperinflation and
8 rapid pulmonary exhalation -, as important selection criteria."

9 As it will become apparent from the ensuing description, the
10 present invention provides perfluorocarbons which avoid the
11 hyperinflated lung syndrome and other problems associated with the
12 prior art, and therefore meet the selection criteria mentioned in the
13 above-quoted abstract. Moreover, still another "important selection
14 criterion" has been discovered in accordance with the present invention,
15 and the perfluorocarbons suggested for use in liquid ventilation and for
16 artificial blood also satisfy the newly suggested criterion.

17 As further background to the present invention applicant cites:

18 United States Patent No. Re: 33,451 to one of the present
19 inventors that describes the use of perfluorocarbons as blood substitutes;

20 U. S. Patent No. 3,911,138 to one of the present inventors that
21 pertains to the search for perfluorocarbons having ideal balance of
22 properties for use in liquid ventilation;

23 PCT Patent application No. 92/19232 to *Faithful et al.* and United
24 States Patent No. 5,437,272 to *Fuhrman* which pertain to liquid
25 breathing utilizing perfluorocarbons to fill the pulmonary functional
26 residual capacity of the mammal;

27 A publication by *Smith et al.* in *Crit Care Med* 1997 Vol. 25, No.
28 7 pp1179 - 1186, titled: Partial liquid ventilation: A comparison using
29 conventional and high frequency techniques in an animal model of

1 acute respiratory failure, and

2 A publication by *Clark, Jr. et al.* in **Mat. Res. Soc. Symp. Proc.**
3 **Vol. 110** (1989) pp129 - 134, titled "Physiological evaluation of
4 fluorocarbon emulsions with notes on F-decalin and pulmonary
5 inflation in the rabbit."

6 **SUMMARY OF THE INVENTION**

7 It is an object of the present invention to provide a
8 perfluorocarbon compound, or several perfluoro compounds which are
9 well suited for use as gas exchange medium in liquid ventilation and as
10 gas exchange medium in artificial blood.

11 More particularly, it is an object of the present invention to
12 provide a perfluorocarbon compound, or several perfluoro compounds
13 which have the appropriate vapor pressure at body temperature so that
14 their use as medium of gas exchange in liquid ventilation or in artificial
15 blood does not cause hyperinflated lung syndrome, and which
16 nevertheless do not unduly persist in the body after treatment or use of
17 the perfluorocarbon is discontinued.

18 It is a further object of the present invention to provide a
19 perfluorocarbon compound, or several perfluoro compounds which
20 satisfy the foregoing objectives, and which, due to their chemical
21 structure, exist only as single isomers, and can be obtained in a state
22 substantially free of isomeric contaminants.

23 The foregoing and other objects and advantages of the invention
24 are attained by selecting and utilizing perfluorocarbon compounds as
25 gas exchange medium in liquid breathing and in artificial blood which
26 have the empirical formula $C_{10}F_{20}$, a molecular weight of approximately
27 500 Daltons, and which have the chemical structure that is selected from
28 the formulas shown below as Formulas 1 through 10.

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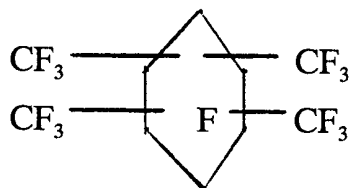
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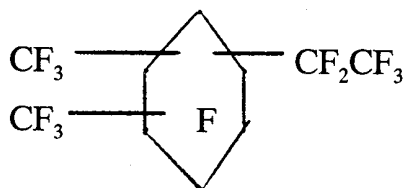
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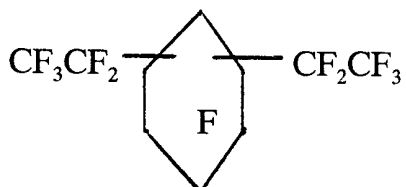
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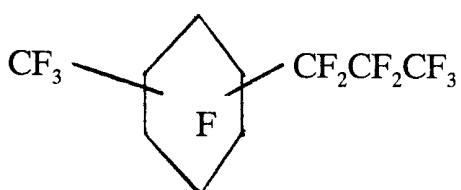
Formula 1



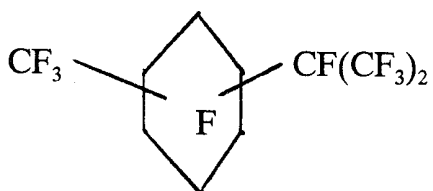
Formula 2



Formula 3



Formula 4



Formula 5

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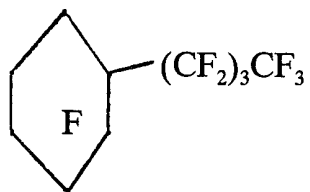
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Formula 6

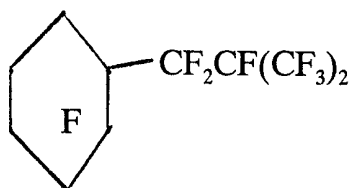
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Formula 7

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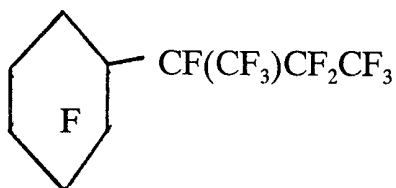
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Formula 8

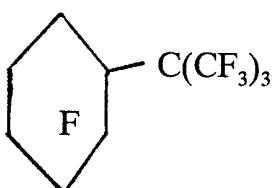
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Formula 9

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Formula 10

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1 In the Formulas 1 - 10 the symbol F in the center of the 5 or 6
2 membered ring represents that all hydrogens of the corresponding
3 cyclohexane or cyclopentane ring have been replaced with fluorine. In
4 other words, F represents that the ring is perfluorinated. The formulas
5 represent all possible positional, stereo (such as *cis* and *trans*) and
6 optical isomers (enantiomers) of the compounds depicted in the
7 formulas. In Formula 10 the symbol C₅F₁₁ * represents not only a
8 perfluorinated pentyl moiety, but any combination of perfluorinated
9 alkyl groups where in the perfluorinated alkyl groups the total number
10 of carbons is 5 and the total number of fluorines is 11. In other words
11 and by way of example in Formula 10 the symbol C₅F₁₁ * represents a
12 CF₃ group in combination with a perfluorinated *n*-butyl, *sec*-butyl, *iso*-
13 butyl or *t*-butyl group, or five CF₃ groups, or combination of a
14 perfluorinated ethyl group with a perfluorinated *n*-propyl or *iso*-propyl
15 group, etc. Moreover, Formula 10 also represents all possible
16 positional, stereo and optical isomers of these compounds.

17 The perfluorinated compounds utilized in accordance with the
18 invention as a gas exchange medium in liquid ventilation and in
19 artificial blood are liquids at ambient temperature and have a vapor
20 pressure at physiological temperature such that the use of these
21 compounds does not result in the development of hyperinflated non-
22 collapsible lung syndrome. Moreover, the vapor pressure and therefore
23 the rate of evaporation/exhalation from the lungs of these
24 perfluorinated compounds is still sufficiently high so that the
25 compounds are satisfactorily cleared from the lungs after use of the
26 compounds (treatment) is discontinued. The boiling point of the
27 compounds is in the range of approximately 144 to 146°C. Preferably
28 those specific perfluorinated compounds are used in accordance with
29 the invention which either can exist only in a single isomeric form and

1 can be purified from other contaminants to attain a pure or substantially
2 pure state, or which, although capable of existing in more than one
3 isomeric form, can be readily purified to attain isomeric purity.

4 BRIEF DESCRIPTION OF THE DRAWING

5 Figure 1 is a graph showing the rate of exhalation of F-1,2,3,5-
6 tetramethylcyclohexane and of F 1-methyl-4-isopropylcyclohexane (F-
7 menthane) from the rat.

8 DETAILED DESCRIPTION OF THE INVENTION

9 DESCRIPTION OF THE PREFERRED EMBODIMENTS

10 The following specification taken in conjunction with the drawings
11 sets forth the preferred embodiments of the present invention. The
12 embodiments of the invention disclosed herein are the best modes
13 contemplated by the inventors for carrying out their invention, although
14 it should be understood that various modifications can be accomplished
15 within the parameters of the present invention.

16 Referring to the Formulas 1 - 9 shown in the Summary section of
17 the present application, it will be apparent to those skilled in the art
18 that these formulas represent perfluorinated cyclohexane derivatives
19 which have perfluoroalkyl substituents having a total of 4 carbons in the
20 alkyl groups. The term "perfluoro" in this regard has the meaning
21 generally accepted in the art, namely it means that all hydrogens of the
22 hydrocarbon skeleton have been replaced with a fluoro atom. It is well
23 known in the art that perfluorinated hydrocarbons, including the ones
24 used in accordance with the present invention, are biologically inert,
25 non-toxic and as far as is presently known they do not undergo
26 metabolic or catabolic transformation in any known mammal. In
27 addition to their inertness, an important property of these compounds
28 which enables them to be utilized as a medium of biological gas
29 exchange is their ability to dissolve a large quantity of gases, including

1 oxygen and carbon dioxide.

2 Formulas 1 through 9 represent all possible positional and stereo
3 isomers of the perfluorinated cyclohexyl derivatives having the empirical
4 formula $C_{10}F_{20}$. Those skilled in the art will readily understand that
5 numerous positional isomers exist. For example, the
6 tetratetrafluoromethyl compounds depicted in Formula 1 can be the
7 following positional isomers: perfluoro 1,2,3,4 tetramethylcyclohexane,
8 perfluoro-1,2,4,5-tetramethylcyclohexane and perfluoro 1,2,3,5
9 tetramethylcyclohexane. For brevity of description the "perfluoro state"
10 of a compound is sometimes indicated here with the symbol "F". Thus,
11 perfluoro 1,2,3,4 tetramethylcyclohexane can also be written as "F 1,2,3,4
12 tetramethylcyclohexane". For the compounds shown in Formula 2 the
13 following positional isomers are possible: F 1,2-dimethyl-3-
14 ethylcyclohexane, F 1,2-dimethyl-4-ethylcyclohexane, F 1,3-dimethyl-2-
15 ethylcyclohexane, F 1,3-dimethyl-4-ethylcyclohexane, F 1,3-dimethyl-5-
16 ethylcyclohexane and F 1,4-dimethyl-2-ethylcyclohexane. For each of
17 the disubstituted cyclohexanes shown in Formulas 3, 4 and 5 three
18 positional isomers are possible, these are where the substituents are in
19 1,2, 1,3 or in the 1,4 (*ortho*, *meta* or *para*) positions.

20 Because of the nature of the cyclohexane ring depicted in
21 Formulas 1 - 9, and of the cyclopentane ring depicted in Formula 10, *cis*
22 and *trans* isomerism (stereoisomerism) and even optical isomerism also
23 exists among the compounds of these formulas, so that the formulas
24 encompass a relatively large number of positional isomers, stereoisomers
25 and for those compounds which include an asymmetric or chiral center,
26 optical isomers as well. For example, each of the disubstituted
27 compounds depicted in Formulas 3, 4 and 5 can exist either as *cis* or as
28 a *trans* isomer. Therefore, Formulas 3, 4 and 5 represent a total of 18
29 different chemical entities not counting possible optical isomers

1 (enantiomers) nor diastereomers.

2 However, it is generally known in the art that compounds of the
3 same molecular weight and of the same type of general structure tend
4 to have similar vapor pressure versus temperature profiles. Vapor
5 pressure is difficult to measure directly, however, it is well known that
6 the boiling temperature of a liquid is directly related to its volatility or
7 vapor pressure. Therefore, compounds of the same molecular weight
8 and of similar structure tend to have same or closely related boiling
9 temperatures. This is known to be particularly true in the field of
10 perfluorocarbons. Among the compounds within the scope of the
11 present invention boiling temperatures measured at atmospheric
12 pressure have become available for the following specific compounds:

13 F-1-ethyl-2,4-dimethylcyclohexane b. p. 146°C;
14 F-1,2,4,5-tetramethylcyclohexane b. p. 146°C;
15 F-1,2,3,5-tetramethylcyclohexane b. p. 146°C;
16 F-1-methyl-4-isopropylcyclohexane b. p. 144°C, and
17 F-*n*-butylcyclohexane b. p. 145°C.

18 As can be seen, the boiling points of the above-noted exemplary
19 compounds, and by analogy of all compounds within the scope of the
20 present invention, are well within the range (approximately 142 to
21 160°C) that is generally considered well suited for compounds utilized
22 as gas exchange medium in liquid ventilation and/or in artificial blood.
23 Perfluoro compounds within this range do not cause hyperinflated lung
24 syndrome, and are transpired from the mammalian body by
25 evaporation/exhalation at an acceptable rate. However, the compounds
26 do not evaporate so rapidly during treatment that undue replenishment
27 would be required.

28 Because measuring boiling points at atmospheric pressure can be
29 difficult or cumbersome, especially when relatively small samples of the

1 liquid are available, a more feasible method has been devised in
2 accordance with the present invention to measure the "volatility" of a
3 liquid. In accordance with this method, which is described in more
4 detail below in the experimental section of this application for patent,
5 the compound to be measured (subject compound) is mixed with a
6 known (preferably equal) quantity of a reference perfluorocarbon the
7 volatility (boiling temperature and/or vapor pressure versus
8 temperature profile) of which is known. A reference compound
9 conveniently employed for this purpose is F-*cis*-decalin which at
10 atmospheric pressure has a boiling point of 141°C. The mixture of the
11 two liquids is maintained in a closed container and the "headspace"
12 above the liquids is allowed to equilibrate with the liquid below. A
13 sample of the saturated gas mixture in the "headspace" is then
14 withdrawn and is analyzed by chromatography to determine the ratios of
15 the two components in the saturated gas mixture. If the two compounds
16 had the same vapor pressure at the temperature of the measurement
17 (usually ambient temperature) then the quantities of the compounds in
18 the saturated gas mixture would also be equal, provided the liquids were
19 mixed in equal quantities. Thus, the ratios of the two components in
20 the saturated gas mixture in the headspace provide a measure of the
21 volatility/vapor pressure of the liquid to be tested, and provide a basis
22 for extrapolation to obtain a boiling point at atmospheric pressure.

23 "Headspace" saturated gas ratio experiments described in
24 principle above, and detailed below, demonstrated that all 5 exemplary
25 C₁₀F₂₀ perfluorocarbons in accordance with the invention have
26 significantly lower vapor pressure at ambient temperature than F-*cis*
27 decalin, signaling that the use of these compounds in liquid ventilation
28 and artificial blood would not cause hyperinflated lung syndrome.

29 C₁₀F₂₀ perfluorocarbons which are preferably used in accordance

1 with the present invention are selected from among the compounds
2 represented by Formulas 1 - 10 with a view to attaining pure or
3 substantially pure substances substantially free of isomers. This is
4 important for practical purposes because it is well known that isomeric
5 compounds, whether they are positional isomers or stereoisomers (such
6 as *cis*, *trans* or diastereomers) are often difficult to separate in
7 substantial quantities. Whereas present day sophisticated analytical
8 techniques, such as gas chromatography (GC) or high pressure liquid
9 chromatography (HPLC) can often *detect* the presence of isomers in a
10 substance, separation of the isomers on a preparative scale is often a
11 more difficult task. Moreover, pertinent laws and regulations by the
12 agencies which permit the use of drugs or related pharmaceuticals in
13 therapy or even experimental use in humans, require certain levels of
14 purity and knowledge of the composition of the substances or
15 compounds to be used. It is much more time consuming and expensive
16 to carry a mixture of isomeric compounds through the appropriate
17 phases of testing in animals and humans, until regulatory approval is
18 obtained, than it is to do the same with pure "single chemical entity"
19 substances. In addition, even during manufacturing and testing phases,
20 quality control of a mixture of isomers is often more difficult than with
21 a single entity compound.

22 For the foregoing and related reasons, use of the following
23 compounds in liquid ventilation and artificial blood is preferred in
24 accordance with the present invention:

- 25 F-*n*-butylcyclohexane (Formula 6);
- 26 F-(2-methylpropyl)cyclohexane (Formula 7, *iso*-butyl);
- 27 F-(1-methylpropyl)cyclohexane (Formula 8, *sec*-butyl);
- 28 F-*t*-butylcyclohexane (Formula 9);
- 29 F-1,1-diethylcyclohexane (Formula 11);

- 1 F-1-methyl-1-*n*-propylcyclohexane (Formula 12);
2 F-1-methyl-1-*iso*-propylcyclohexane (Formula 13);
3 F-1-pentylcyclopentane (Formula 14);
4 F-1-methyl-1-butylcyclopentane (Formula 15);
5 F-1-ethyl-1-propylcyclopentane (Formula 16).

6 In Formulas 14, 15, and 16 the pentyl, butyl and propyl groups
7 represent all possible positional isomers of said groups, for example
8 "propyl" represents *n*-propyl and *iso*-propyl as well, and "butyl"
9 represents *n*-butyl, *t*-butyl and 1-methylpropyl and 2-methylpropyl
10 groups. However, only the use of single chemical entities, not the use
11 of mixtures, is preferred.

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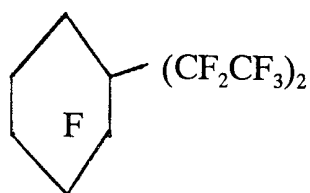
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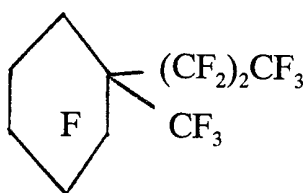
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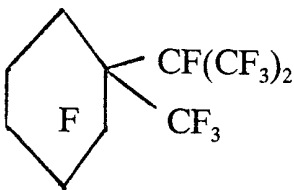
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Formula 11



Formula 12

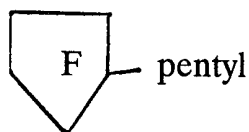


Formula 13

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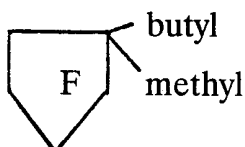
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Formula 14

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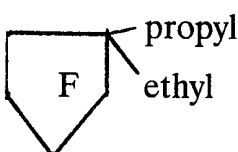
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Formula 15

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Formula 16

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As it can be readily ascertained from their chemical structure, the preferred compounds of Formulas 6 - 9 and 11 - 16 are single positional isomers and *cis* and *trans* isomerism for these compounds is not possible. The compound of Formula 8 and some of the compounds within the scope of Formulas 14 and 15 have one or more chiral centers and therefore exist in enantiomeric and some in diastomeric forms. Enantiomers, however are not expected to give rise in the testing and regulatory approval process to problems of the same magnitude as positional isomers, because a racemic mixture of compounds is often considered acceptable for regulatory purposes. Also in chromatographic and many other analytical techniques, unless the chromatography involves a "chiral column", a racemic mixture is not resolved.

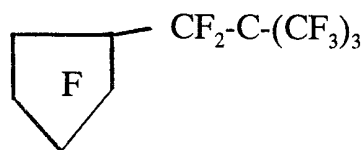
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1 The C₁₀F₂₀ compounds which are presently most preferred in
2 accordance with the present invention are:

3 F-*t*-butylcyclohexane (Formula 9);

4 F-1,1-diethylcyclohexane (Formula 11), and

5 F-neopentylcyclopentane (Formula 17)



10 Formula 17

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12 The C₁₀F₂₀ compounds used within the scope of the present
13 invention, and particularly the preferred compounds shown in Formulas
14 6 - 9 and 11 - 16 can be synthesized from homologous hydrocarbons by
15 well-known techniques, such as reaction with cobalt trifluoride in a
16 furnace. A method of manufacture of F-*tertiary*-butylcyclohexane is
17 described in United States Patent No. 4,453,028, incorporated herein by
18 reference. Further procedures for the synthesis of C₁₀F₂₀ cyclohexane
19 derivatives are described in United States Patent Nos. 5,300,528,
20 4,105,798, and 5,093,432 which are also specifically incorporated herein
21 by reference. Generally speaking the synthesis of perfluorocarbons is
22 described in detail in the book "Chemistry of Organic Fluorine
23 Compounds II. A Critical Review". Edited by Milos Hudlicky and
24 Attila E. Pavlath, published by the American Chemical Society (1995),
25 incorporated herein by reference. The basic technique for cobalt
26 trifluoride fluorination is set forth in U.S. Patent No. 2,631,170. The
27 basic technique of liquid phase fluorination using diluted fluorine gas is
28 set forth in U.S. Patent No. 5,093,432. United States Patent Nos.
29 2,631,170 and 5,093,432 are incorporated herein by reference.

1 In accordance with the present invention, the $C_{10}F_{20}$ compounds,
2 and particularly the preferred embodiments of Formulas 6 - 9 and 11 -
3 16 and still more particularly the most preferred embodiments, are
4 utilized as medium of gas exchange in liquid breathing and in artificial
5 blood. These mediums of gas exchange can be employed in accordance
6 with the present state of the art, namely in "total" or "tidal" liquid
7 ventilation, "partial" liquid ventilation and in "low volume" (alveolar)
8 ventilation as well. For example, the compounds selected in accordance
9 with the present invention can be used to fill the "pulmonary functional
10 residual capacity" of a mammal, in accordance with the methods and
11 apparatus described in United States Patent No. 5,437,272 (*Fuhrman*)
12 which is incorporated herein by reference. A recently issued United
13 States Patent by one of the present inventors No. 5,674,913 describes a
14 method of assisting normal breathing in a mammal having a lung
15 disorder, by introducing a perfluorocarbon into the alveolar sacs of the
16 lung through the trachea. The perfluorocarbons selected in accordance
17 with the present invention can also be used in the method of said
18 application. United States Patent No. 5,674,913 is also incorporated
19 herein by reference. As a medium of gas exchange in artificial blood
20 the compounds can be used for example as described in United States
21 Patent No. Re: 33,451 (incorporated herein by reference) and as is
22 generally known in the state-of-the-art.

23 The $C_{10}F_{20}$ compounds, and particularly examples of the
24 preferred embodiments of Formulas 6 - 9 and 11 - 16 selected for use
25 as a medium of gas exchange in accordance with the present invention
26 do not cause hyperinflated lung syndrome in experimental animals
27 (rabbit and baboon) and are exhaled from the body at an acceptable
28 rate. The ensuing "specific embodiments" (experimental) section of this
29 application describes the animal testing conducted with exemplary

1 compounds, and also experiments wherein the volatility of the
2 compounds selected in accordance with the invention was measured.

3 **Description of Animal Tests and Volatility Measurements**

4 Animal testing is performed in accordance with Protocols 1, 2, 3
5 and 4, which are described below.

6 **PROTOCOL 1: Intratracheal administration of perfluorocarbon neat**
7 **liquids to rats with survival**

8 This protocol is especially useful for the accurate administration
9 of perfluorocarbon neat liquids to the lungs of small animals through a
10 Silastic catheter inserted in the trachea through a tracheotomy. The
11 following protocol and example are specific for rats of the genus *Rattus*,
12 bred for use in research. Adult Sprague Dawley female rats are
13 normally used.

14 The nonfasted rat is weighted and anesthetized with a volatile
15 anesthetic such as enflurane, halothane or similar agent. Surgical plane
16 anesthesia is achieved using an intraperitoneal injection of ketamine
17 hydrochloride in saline (25 mg/ml), at an initial dose of 80 mg/kg.
18 Additional injections of about 20 mg/kg are given as needed to ensure
19 appropriate anesthesia. A single subcutaneous injection of
20 chlorpromazine in saline (25 mg/ml), as a dose of 5 mg/kg, is used for
21 muscle relaxation. The neck area is shaved, and the skin is cleaned with
22 70% alcohol and scrubbed with betadine.

23 The rat is positioned on her back on a padded surgical platform,
24 and humidified 100% oxygen is administered through a mask loosely
25 covering the rat's head. Core temperature is monitored using a small
26 animal rectal Telethermometer probe and meter from Yellow Springs
27 Instruments, Co. A heat lamp is used to maintain body temperature
28 between 35 and 37 degrees Celsius.

29 Sterilized instruments are used for the surgical procedure. A 2

1 cm midline incision is made in the neck over the trachea. The underlying fat and muscle is dissected to expose the trachea. A narrow piece of sterile umbilical tape is passed beneath the trachea and a small hole is made between rings, below the thyroid, using a 21 gauge needle. The hole is enlarged with the scalpel, if needed, to accommodate the Silastic catheter. This Silastic catheter, either single or double lumen and fitted with a 23 gauge tubing adapter, is then inserted about 1 cm into the trachea. The oxygen flow is now directed into, and around, the catheter instead of into the mask.

10 The surgical platform is elevated about 30-40° to facilitate the gravity flow of perfluorocarbon neat liquid into the lungs. The perfluorocarbon neat liquid is then slowly delivered through the catheter from a glass syringe attached to the tubing adapter, at a rate of about 1 ml per minute. Oxygen is concomitantly delivered. The rat can also be rotated to the left and right during dosing to help distribute the liquid. Perfluorocarbon neat liquid doses up to 20 ml/kg have been infused into the lungs by this method. The tracheal catheter is removed, and the board lowered so that the head and neck are kept slightly above the chest to allow any perfluorocarbon neat liquid in the trachea to drain into the lungs. The small opening in the trachea is closed using a single suture of 5-0 silk, as is the muscle layer. The skin is closed with continuous sutures of 4-0 silk. The rat is then kept on humidified 100% oxygen using the mask, and observed until recovery, when it is returned to its cage in the colony.

25 PROTOCOL 2: Intratracheal administration of perfluorocarbon neat
26 liquids to rabbits with survival

- 27 1. The fasted animal is sedated with 2.5 mg/kg subcutaneous
- 28 chlorpromazine (25 mg/ml).
- 29 2. Approximately 30 minutes later the animal is gently

1 restrained and the necessary ear blood vessels catheterized with Teflon
2 catheters, such as an Abbocath T-22 Gaxl 1/4", fitted with a 3-way
3 stopcock. Topical 2% Lidocaine may facilitate the cannulation.

4 3. The animal is anesthetized with intravenous sodium
5 pentobarbital (30 mg/ml in normal saline) at a dose of 30 mg/kg.

6 4. The throat is shaved and disinfected with 70% ethyl alcohol
7 and Betadine.

8 5. The area of the incision is filtrated with 2% Lidocaine.

9 6. With the animal lying on its back, a 1-2' midline incision is
10 made over the trachea below the laryngeal prominence.

11 7. The muscle is incised and the area around the trachea is
12 blunt dissected.

13 8. A length of sterile umbilical tape is passed beneath the
14 trachea to help isolate it and to secure the tracheal cannula.

15 9. The trachea is then cut between rings and a sterilized
16 Silastic tube (5 mm OD) is inserted in the trachea to a point above the
17 bronchial bifurcation.

18 10. The head and shoulders of the animal are elevated for
19 gravity administration of the perfluorocarbon neat liquid. The
20 perfluorocarbon neat liquid is filtered through a sterile, 0.22 micron
21 filter during administration.

22 11. The Silastic tracheal cannula is removed and the trachea
23 closed with two sutures of 5-0 silk.

24 10. A small piece of Gelfoam is placed over the tracheal
25 incision and the muscle and skin are closed with 4-0 silk.

26 The animal is administered humidified, 100% oxygen during the
27 entire procedure and small maintenance doses of intravenous sodium
28 pentobarbital are given when needed.

29 PROTOCOL 3: Gas chromatographic determination of the Exhalation

1 Rate from Rats Having Perfluorocarbon Neat Liquid in the Lungs

2 The rat is placed in a specially designed chamber consisting of a
3 perforated ceramic disk in a 1 liter Pyrex glass dessicator with an oxygen
4 inlet and outlet, and a typical oxygen flow rate of 600ml/min. A
5 magnetic stirring bar below the disk stirs the atmosphere in the
6 dessicator, which has a cover sealed with glycerol.

7 After 20 minutes of equilibration, the gas flow from the outlet of
8 the rat chamber is measured using a Humonics Optiflow 650 digital
9 flowmeter. Samples are then taken from the flow outlet for GC analysis
10 using a Hamilton side port needle syringe.

11 Samples taken from the outlet are injected onto a 20 foot long x
12 1/8 inch stainless steel packed column (30% SE30 on Chromsorb PAW
13 80/100 mesh) in a Hewlett Packard 5890 GC. Head pressure of the 5%
14 methane in argon carrier gas is maintained at 50 pounds/square inch,
15 with an end flow rate of 25 milliliters/minute. Quantitive measurement
16 is accomplished with an electron capture detector. All data is collected
17 and stored using a Hewlett Packard chemstation data system.

18 Quantitation is done by comparison of the measured value of the
19 rat's exhalation to a known standard. The standard is prepared by
20 injecting a 0.1 to 2 microliter (μL) aliquot of perfluorocarbon neat
21 liquid into a sealed 120 milliter (mL) serum vial. It is allowed to stand
22 at room temperature for at least one hour to completely volatilize. This
23 is referred to as the "Stock standard". A $120\mu\text{L}$ aliquot of the stock
24 standard vapor is taken and injected into a second sealed 120mL serum
25 vial, producing a 1000:1 dilution of the original; this is referred to as the
26 "working standard". Accurately measured volumes of the working
27 standard, or the oxygen carrier gas from the rat chamber, are alternately
28 injected onto the GC instrument for quantitation.

29 Calculation of the rate of exhalation is performed using the peak

1 height (or area) from the chromatogram of the rat's breath, the peak
2 height (or area) from the chromatogram of the working standard, the
3 known concentration of the working standard, and the oxygen flow rate
4 through the chamber to give the exhalation rate of the fluorocarbon
5 vapor as microliters of fluorocarbon per day.

6 Figure 1 of the appended drawings shows the rate of exhalation
7 of F-1,2,3,5-tetramethylcyclohexane and of F 1-ethyl-4-
8 isopropylcyclohexane (F-menthane) in the rat, substantially as
9 determined in accordance with Protocol 3. Both of these compounds
10 are $C_{10}F_{20}$ perfluorocarbons the use of which in liquid ventilation is
11 within the scope of the present invention. As it was discussed above,
12 the boiling points of these compounds for practical purposes are
13 virtually the same or very close to the boiling points of all of the
14 perfluorocarbons which are utilized in liquid ventilation and artificial
15 blood in accordance with the present invention. The rate of exhalation
16 indicated in the graph for both of these $C_{10}F_{20}$ perfluoro compounds is
17 considered acceptable, and indicates that undue exposure of the animal
18 to potential long term effect of the perfluorocarbon is likely to be
19 avoided.

20 PROTOCOL 4: Test of intratracheal neat liquid perfluorocarbons for
21 pulmonary hyperinflation in the rabbit

22 Fasted, healthy, Pasteurella-free, young adult female New
23 Zealand white rabbits weighing about 1.8 to 2.2 kilograms, were used.
24 The rabbits were sedated with chlorpromazine, anesthetized with a
25 mixture of ketamine and xylazine, and supported by oxygen breathing.
26 The trachea was cannulated with a soft, sterile Silastic tube stabilized in
27 place with umbilical tape. Filtered, neat liquid fluorocarbon (medical
28 grade) was administered slowly in the doses shown in the table. The
29 cannula was removed, the incision closed and the animal allowed to

1 recover in USDA-approved, air conditioned quarters. The rabbits were
2 observed frequently until sacrifice on the fourth day after infusion.

3 Results of tests conducted substantially as described in Protocol 4,
4 with F-1-ethyl-2,4-dimethylcyclohexane (b. p. 146 °C) and F-1,2,4,5-
5 tetramethylcyclohexane (b. p. 146 °C) caused no pulmonary
6 hyperinflation in the rabbit, whereas F-*cis*-decalin (b. p. 142.5 °C) did.
7 These results are summarized below in Table 1 where the dose of the
8 respective fluorocarbons and the number of animals involved in the test
9 are also indicated.

10 **TABLE 1**

11 Tests of intratracheal neat liquid perfluorocarbons for pulmonary
12 hyperinflation in the rabbit.

Perfluorocarbon Neat Liquid	Dose (cc/kg)	Number of Animals	Hyperinflation
F-ethyl-2,4-dimethylcyclohexane	4	2	None
F-1,2,4,5-tetramethylcyclohexane	4	2	None
" "	6	2	None
" "	8	2	None
" "	10	1	None
F-decalin	4	2	Moderate
" "	6	2	Moderate
" "	8	2	Severe*
" "	10	1	Moderate

23 * Both rabbits died in the morning of the fourth day, shortly after being removed
24 from their cages.

25 By way of further description of the tests summarized in Table 1
26 it is noted that several of the animals which received the F-decalin
27 showed signs of pulmonary distress by the second day. These symptoms
28 included rapid and noticeably labored breathing, and, in general, these
29 animals appeared to be hypoxic and hypercapnic. At necropsy the F-

1 decalin lungs were pale pink and showed various degrees of
2 hyperinflation. The animals which received the F-1,2,4,5-
3 tetramethylcyclohexane and the F-ethyl-dimethyl-cyclohexane showed no
4 signs of distress. At necropsy their lungs were found to be normal in
5 appearance and were not hyperinflated.

6 Test of intratracheal neat liquid perfluorocarbons for pulmonary
7 hyperinflation in the baboon

8 To determine if F-1-ethyl-4,4-dimethylcyclohexane caused
9 hyperinflation in the non-human primate, two fasted, normal, healthy
10 juvenile female baboons weighing about 3.5 to 5 kilograms were given
11 intratracheal neat liquid. An IACUC-approved protocol was followed.
12 The procedure, similar to the description in Protocol 4 was performed
13 under sterile conditions in a USDA-approved primate facility. One
14 baboon received 2cc/kg and the other 4cc/kg of F 1-ethyl-2,4-
15 dimethylcyclohexane via tracheal cannula. Both animals were observed
16 frequently, and no untoward reactions were observed during, or in the
17 days following, the infusion. The animals gained weight, and behaved in
18 a normal fashion in their quarters. Both were sacrificed ten weeks after
19 the infusion. At necropsy their lungs were found to be normal in
20 appearance and were not hyperinflated. Laboratory examination of the
21 lung sections revealed no abnormalities.

22 Measurements comparing the vapor phase concentrations of certain
23 perfluoroalkylcyclohexanes (C₁₀F₂₀) and cis perfluorodecalin (C₁₀F₁₈)
24 with the liquid phase concentration using gas chromatography and
25 electron capture detection

26 A volume (200 microliters) of the perfluorinated liquid under
27 study was mixed with an equal volume of the cis isomer of F-decalin
28 (BP=142.5°C). A stock standard of this mixture was prepared by
29 evaporating two microliters of the liquid in a 120 milliliter glass serum

1 vial sealed with a rubber septum and aluminum cap. This volume was
2 chosen so that complete evaporation of the liquid could take place.
3 After volatilization, this stock standard was diluted by transferring 120
4 microliteres of the vapor to a clean, sealed 120 milliliter serum vial to
5 make the working standard. A 20 microliter sample of the working
6 standard was analyzed using a Hewlett-Packard 5880A gas
7 chromatograph with electron capture detector and column temperature
8 at 80°C. The chromatogram and peak heights were recorded and
9 printed using Hewlett-Packard ChemStation software. This enabled
10 calibration of the electron capture detector for each of the C₁₀F₂₀
11 compounds tested, and the known concentration in the liquid phase
12 could be used to determine the relative sensitivity, R₁ in the table, of
13 the detector to the perfluorinates being used.

14 To obtain the relative concentrations of the perfluorinates in the
15 saturated vapor phase, 30 microliters of the headspace vapor over the
16 50/50 liquid mixture was diluted in a clean, sealed 120 milliliter serum
17 vial. A 20 microliter sample of this diluted headspace was analyzed on
18 the gas chromatograph. The sample volumes and dilutions were
19 selected so that the F-cis-decalin peaks in the working standard and
20 diluted headspace were of similar height in order to avoid any potential
21 problems with a non-linear detector response. The peak height ratio in
22 the vapor phase, R₂, was corrected for sensitivity by dividing by R₁, to
23 give the relative concentration of the C₁₀F₂₀ compound to the F-cis-
24 decalin, R₂/R₁, in the headspace over the liquid; a comparison of the
25 vapor pressures of the liquids in the mixture.

1 Table 2: Direct comparison of the vapor phase concentrations of certain perfluoroalkylcyclohexanes
 2 ($C_{10}F_{20}$) and *cis*-perfluorodecalin ($C_{10}F_{18}$) with the liquid phase concentration using gas chromatography
 3 and electron capture detection.

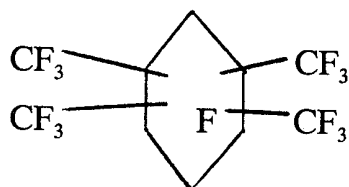
Liquid Phase Peak Heights (thousands) in working standard	Peak Height Ratio <i>cis</i> -decalin/ $C_{10}F_{20}$		Vapor Phase Peak Heights (thousands) in diluted headspace		Peak Height Ratio <i>cis</i> -decalin/ $C_{10}F_{20}$	Fraction of $C_{10}F_{20}$ in vapor phase
	<i>cis</i> -decalin	$C_{10}F_{20}$	<i>cis</i> - decalin	$C_{10}F_{20}$		
	R_1	R_2				R_2/R_1
39.5	41.5 ¹	1.05 ¹	38.7	35.4 ¹	0.91 ¹	0.87 ¹
39.2	22.2 ²	0.57 ²	41.5	18.2 ²	0.44 ²	0.77 ²
37.9	24.9 ³	0.66 ³	39.6	19.5 ³	0.49 ³	0.74 ³
34.4	21.8 ⁴	0.63 ⁴	41.6	23.2 ⁴	0.56 ⁴	0.89 ⁴
37.2	57.3 ⁵	1.54 ⁵	45.3	59.15 ⁵	1.30 ⁵	0.84 ⁵

- 14 1 F ethyl-2,4-dimethylcyclohexane
- 15 2 F 1,2,4,5-tetramethylcyclohexane
- 16 3 F 1,3,4,5-tetramethylcyclohexane
- 17 4 F 1-methyl-4-isopropylcyclohexane
- 18 5 F *n*-butylcyclohexane

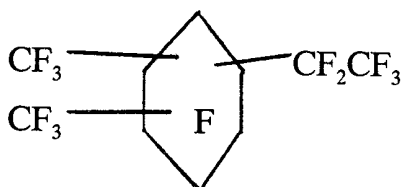
1 Table 2 above shows the results obtained with five separate $C_{10}F_{20}$
2 perfluorocarbons that are utilized in accordance with the present
3 invention. The chemical name of each of the perfluorocarbons
4 measured is indicated by the superscripts over the numerical data. The
5 data of Table 2 clearly demonstrate that the vapor pressure of the 5
6 $C_{10}F_{20}$ compounds are significantly lower than that of F *cis* decalin.

WHAT IS CLAIMED IS:

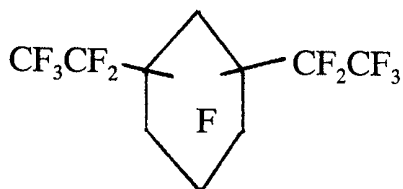
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2 1. A method of facilitating transport of gases in a biological system,
3 comprising using as a medium of gas transport a perfluorocarbon liquid
4 which is selected from the formulas 1 through 10



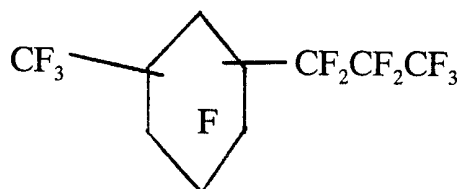
Formula 1



Formula 2

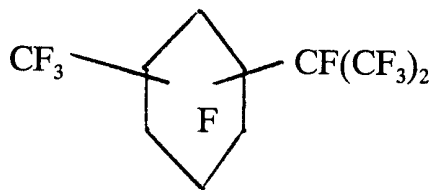


Formula 3

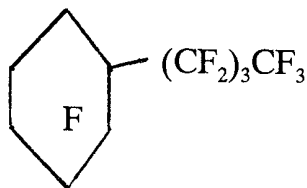


Formula 4

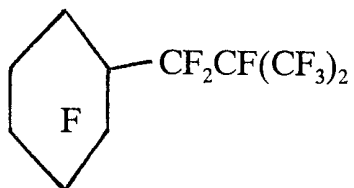
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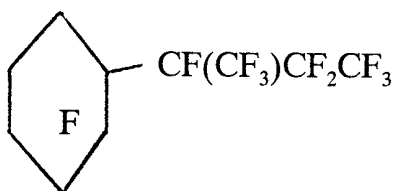
Formula 5



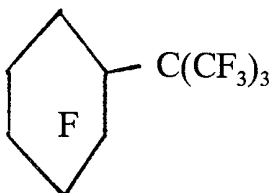
Formula 6



Formula 7



Formula 8



Formula 9

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Formula 10

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wherein the cycloalkyl and rings are fully fluorinated and wherein C_5F_{11} represents any combination of perfluorinated alkyl groups where the total number of carbons is 5 and the total number of fluorines is 11.

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2. The method of Claim 1 where the medium of gas transport is a perfluorocarbon liquid selected from the formulas 1 through 9.

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3. The method of Claim 1 where the medium of gas transport is a perfluorocarbon liquid selected from the formulas 6 through 9 and 11 through 17.

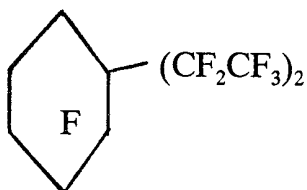
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Formula 11

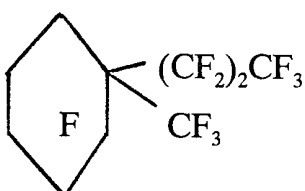
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Formula 12

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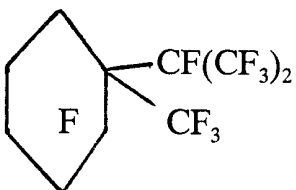
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Formula 13

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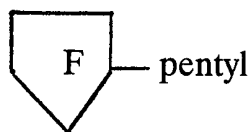
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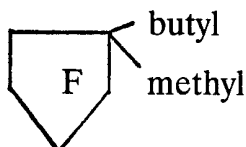
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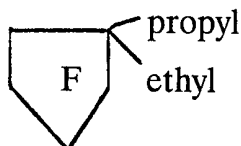
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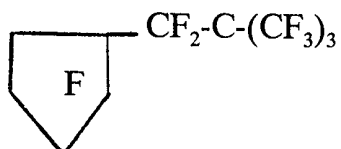
Formula 14



Formula 15



Formula 16



Formula 17

4. The method of Claim 1 where the medium of gas transport is a perfluorocarbon liquid selected from the following compounds:

F-*t*-butylcyclohexane (Formula 9);

F-1,1-diethylcyclohexane (Formula 11), and

F-neopentylcyclopentane (Formula 17)

5. The method of Claim 1 comprising the step of instilling the perfluorocarbon liquid into the lungs of a mammal.

6. The method of Claim 5 where a tidal volume quantity of perfluorocarbon is instilled into the lungs of the mammal.

7. The method of Claim 5 where a quantity of

1 perfluorocarbon is instilled into the lungs of the mammal to fill the
2 functional residual volume of the lungs.

3 8. The method of Claim 5 where a quantity of
4 perfluorocarbon is instilled into the lungs of the mammal to fill the
5 alveoli of the lungs.

6 9. The method of Claim 1 introducing into the blood stream
7 of a mammal a liquid composition containing a perfluorocarbon defined
8 in Claim 1.

9 10. A method of assisting breathing in a mammal in need of
10 such assistance, the method comprising introducing into the lungs of the
11 mammal a perfluorocarbon liquid which is selected from the formulas 1
12 through 10

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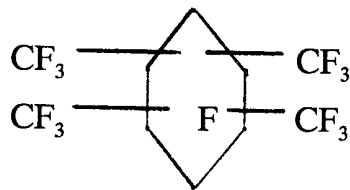
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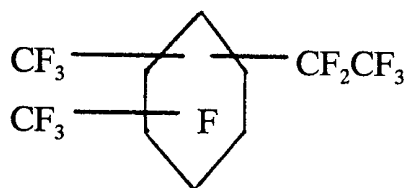
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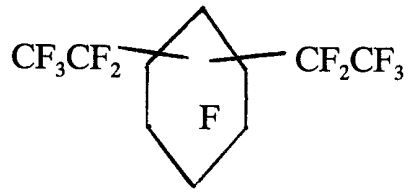


Formula 1

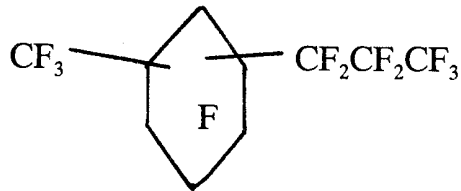


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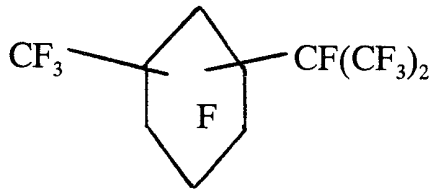
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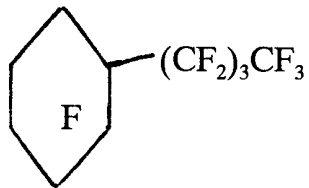
Formula 3



Formula 4



Formula 5



Formula 6

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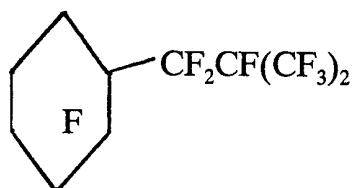
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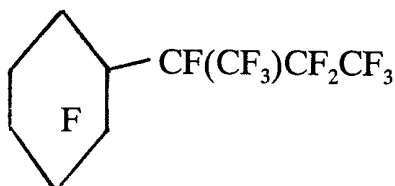
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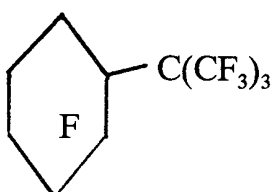
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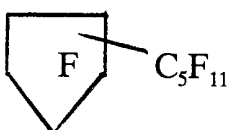
Formula 7



Formula 8



Formula 9



Formula 10

24 wherein the cycloalkyl rings are fully fluorinated and wherein C_5F_{11}
25 represents any combination of perfluorinated alkyl groups where the
26 total number of carbons is 5 and the total number of fluorines is 11, and
27 maintaining a quantity of said perfluorocarbon liquid in the lungs while
28 the mammal breathes.

29 11. The method of Claim 10 where the perfluorocarbon liquid

1 is selected from the formulas 1 through 9.

2 12. The method of Claim 10 where the perfluorocarbon liquid
3 is selected from the Formulas 6 through 9 and 11 through 17.

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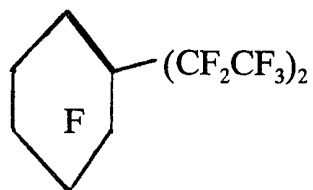
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Formula 11

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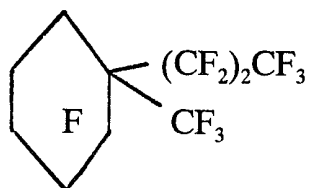
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Formula 12

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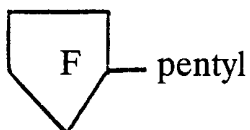
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Formula 14

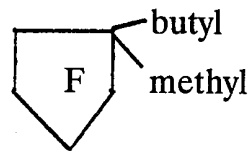
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Formula 15

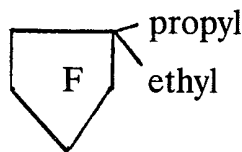
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Formula 16

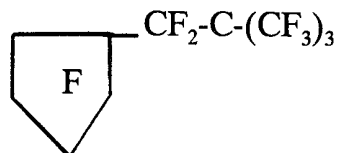
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Formula 17

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13. The method of Claim 10 where the perfluorocarbon liquid is selected from the following compounds:

F-*t*-butylcyclohexane (Formula 9);

F-1,1-diethylcyclohexane (Formula 11), and

F-neopentylcyclopentane (Formula 17)

14. The method of Claim 10 where a tidal volume quantity of perfluorocarbon liquid is introduced into the lungs of the mammal.

15. The method of Claim 10 where a quantity of perfluorocarbon is instilled into the lungs of the mammal to fill the functional residual volume of the lungs.

16. The method of Claim 10 where a quantity of perfluorocarbon is instilled into the lungs of the mammal to fill the alveoli of the lungs.

1 17. A method of assisting breathing in a mammal in need of
2 such assistance, the method comprising introducing into the lungs of the
3 mammal in an amount effective to provide such assistance to breathing
4 a perfluorocarbon liquid selected from the group consisting of

5 F-*t*-butylcyclohexane (Formula 9);
6 F-1,1-diethylcyclohexane (Formula 11), and
7 F-neopentylcyclopentane (Formula 17)

8 18. The method of Claim 17 where the perfluorocarbon liquid
9 is F-*t*-butylcyclohexane (Formula 9).

10 19. The method of Claim 17 where the perfluorocarbon liquid
11 is F-1,1-diethylcyclohexane (Formula 11).

12 20. The method of Claim 17 where the perfluorocarbon liquid
13 is F-neopentylcyclopentane (Formula 17).

