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(71) Applicant *(for all designated States except AE, AG, AU, BB, BH, BN, BW, BZ, CA, CY, EG, GB, GD, GH, GM, IE, IL, IN, KE, KN, LC, LK, LS, MT, MW, MY, NA, NG, NZ, OM, PG, QA, RW, SC, SD, SG, SL, SZ, TT, TZ, UG, US, VC, ZA, ZM, ZW):* **UNILEVER N.V.** [NL/NL]; Weena 455, NL-3013 AL Rotterdam (NL).

(71) Applicant *(for AE, AG, AU, BB, BH, BN, BW, BZ, CA, CY, EG, GB, GD, GH, GM, IE, IL, KE, KN, LC, LK, LS, MT, MW, MY, NA, NG, NZ, OM, PG, QA, RW, SC, SD, SG, SL, SZ, TT, TZ, UG, VC, ZA, ZM, ZW only):* **UNILEVER PLC** [GB/GB]; Unilever House, 100 Victoria Embankment, London EC4Y 0DY (GB).

(71) Applicant *(for IN only):* **HINDUSTAN UNILEVER LIMITED** [IN/IN]; Unilever House, B.D. Sawant Marg Chakala Andheri (East), Mumbai, Maharashtra 400 099 (IN).

(71) Applicant *(for US only):* **CONOPCO, INC., D/B/A UNILEVER** [US/US]; 800 Sylvan Avenue, AG West, S. Wing, Englewood Cliffs, New Jersey 07632 (US).

(72) Inventors: **CORNMELL, Robertjoseph;** Unilever R & D Port Sunlight, Quarry Road East, Bebington, Wirral, Merseyside CH63 3JW (GB). **GOLDING, Stephen;** Unilever R & D Port Sunlight, Quarry Road East, Bebington,Wirral, Merseyside CH63 3JW (GB). **STOTT, Ian,Peter;** Unilever R & D Port Sunlight, Quarry Road East, Bebington, Wirral, Merseyside CH63 3JW (GB). **THOMPSON, Katherine, Mary;** Unilever R & D Port Sunlight, Quarry Road East, Bebington, Wirral, Merseyside CH63 3JW (GB).

(74) Agent: **ROSEN JACOBSON, Frans,** L, **M;** Unilever Patent Group, Olivier van Noortlaan 120, NL-3133 AT Vlaardingen (NL).

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(54) **Title:** ANTIMICROBIAL METHOD AND COMPOSITION

(57) **Abstract:** The present invention relates to a method for disinfection involving an antimicrobial composition, an antimicrobial composition suitable for use in such a method and antimicrobial compounds. It particularly relates to an antimicrobial composition for personal cleaning, oral care or hard surface cleaning applications. It was found that compositions comprising selected substituted cyclohexylpropanediols and a carrier provide antimicrobial action. In a preferred aspect the compositions of the invention also comprise 1 to 80 %-wt of surfactant.

ANTIMICROBIAL METHOD AND COMPOSITION

FIELD OF THE INVENTION

The present invention relates to a method for disinfecting a surface. The invention particularly relates to a method for disinfecting a surface on the human body. The invention also relates to an antimicrobial composition.

BACKGROUND TO THE INVENTION

Sanitising and disinfecting soap or cleaning compositions are of great benefit to individuals, since proper use generally may reduce the number of germs and pathogens the individual is exposed to. Thus, such compositions may for instance play an important role in reducing the occurrence and spread of infectious diseases.

Compounds displaying antimicrobial, disinfecting or sanitising activity are generally known, for example from *"Disinfection, Sterilisation and Preservation",* ed. S S Block, 5th edition, Lippincott, Williams and Wilkins, Philadelphia, 2001

Sanitising and disinfecting soap compositions comprising chlorine-based antimicrobial agent such as triclosan are also known. Such compositions require a rather long contact time to provide efficacious antimicrobial action. In practice, users, in particular children, do not spend a long time on cleansing and as a result cleaning with such compositions does not provide adequate prevention from surface or topical infection or adequate protection against diseases. The user, in spite of cleaning his hands, is generally likely to end up with relatively inadequate bacterial removal from his skin. Therefore, he may cause contamination of further animate and/or inanimate surfaces and contribute to the spreading of pathogens and consequent diseases. Users in general and children in particular who wash contaminated hands before meals with slow-acting antimicrobial compositions for a relatively short time are at risk of contracting diseases.

Similarly in the area of hard surface cleaning, e.g. cleaning of floors, table tops or utensils, the antimicrobial in the compositions are in contact with the substrate for less than a few minutes after which the surface is either wiped off or rinsed with water. These short time scales of cleaning action are ineffective in providing the desired

benefit since most known antimicrobials commonly used in such products take several hours to provide the desired kill of microbes.

Therefore, there is a need of providing a method for disinfection and an antimicrobial composition usable in such a method, wherein the method provides more efficacious antimicrobial action during a relatively short cleaning period, preferably about 30 seconds or less.

Moreover, despite the general availability of antimicrobial compounds and compositions there remains a continuous need to find new or alternative antimicrobial compositions and active compounds that are suitable for use in such compositions. Such alternatives may reduce the dependency on current raw materials. Moreover, in the field of antimicrobials, the availability of alternatives may reduce the risk of development of microbial resistance or insensitivity to particular antimicrobial compounds.

In addition, there is a continued need to reduce the total amount of active ingredients required in such an antimicrobial composition. This need may for instance be driven by the desire for cost-efficiency, because such compositions are particularly relevant to developing countries. Moreover, reducing the amounts may also be beneficial for environmental reasons.

A particular problem of typical terpinoid and phenolic antimicrobial agents is that they are generally well-perceptible due to their olfactory properties. Although the latter may - at least for some species - be appreciated in certain fragrance compositions, they are considered too intense by some users when they are applied at concentrations efficacious in rapid disinfection. Additionally, a lower concentration of odoriferous compounds or the availability of antimicrobial compounds that are less or not odoriferous allows greater flexibility to the manufacturer in providing alternative scents to his composition at lower doses. Hence there is a need to provide alternative antimicrobial compositions and methods that preferably require lower concentrations and/or have a more acceptable sensory profile.

Compounds of the class of 2-(4-alkyl-cyclohexyl)-propane-1 ,2-diols are known as mesogens having amphiphilic properties leading to formation of smectite layers and

applications in liquid crystal displays. [Tschierske, C ; Altmann, H.; Zaschke, H.; Brezesinski, G.; Kuschel, F.; *Molecular Crystals and Liquid Crystals* (1990) , Vol 191 pp 295-300 & F Giesselmann, R Germer and A Saipa, *J. Chem. Phys.,* 2005, Volume 123, issue 3, pp. 034906/1-034906/6]. Patent applications DE 1981 1456 A 1, JP 2009215261 A, and EP 1816180 A 1disclose the use of 2-(4-alkyl-cyclohex-1 -yl)-propane-1 ,2-diols as synthetic intermediates in the synthesis of other LCD-relevant materials.

In view of the above-observed problems and drawbacks of the prior art, it is an object of the present invention to provide a new method for sanitising and/or disinfecting, in particular of surfaces.

It is a particular object of the present invention to provide a new method for disinfecting surfaces based on a new antimicrobial composition.

It is another object of the invention to provide such a method, requiring a lower dose of antimicrobial composition.

It is yet another object of the invention to provide a method for disinfection with a reduced disinfection time.

Similarly, it is an object of the present invention to provide a method based on an antimicrobial composition in which the olfactory contribution of the antimicrobially active compounds is reduced or in which the active compound contributes to providing a consumer-acceptable or even consumer-appreciated scent.

In particular, it is an object of the invention to provide a method for disinfection that gives improved disinfection during cleansing of surfaces, in particular hard surfaces or surfaces of the human body, such as the skin and the oral cavity.

In view of the other objects, it is also an object of this invention to provide antimicrobial compositions that are applicable in a method for disinfection of a surface.

It is a further particular object of the invention to provide such antimicrobial compositions that contribute to reducing the required contact time in a method for disinfection of a surface.

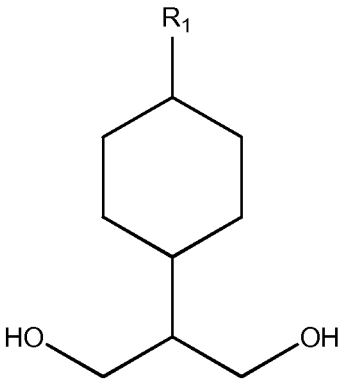
SUMMARY OF THE INVENTION

We have now found that one or more of the above objects are met by the present invention. Thus, we have now found that a method for disinfection involving the step of applying an antimicrobial composition comprising one or more substituted cyclohexyl-propane diols provides for efficacious anti-microbial action. We have consequently also found an antimicrobial composition comprising one or more substituted cyclohexyl-propanediols, whereby the composition is applicable in foresaid method. The substituted cyclohexylpropanediols according to the present invention advantageously have no clearly discernable odour.

Accordingly, in a first aspect the invention provides a method of disinfecting a surface comprising the steps of

a. applying to the surface an antimicrobial composition comprising
   i. 0.001 to 5% by weight of one or more substituted cyclohexyl-propanediols, and
   ii. a carrier; and
b. removing the composition from the surface;

wherein the one or more substituted cyclohexyl-propanediols have the following structure



wherein R_1 is selected from

linear or branched C_1 to C_{10} alkyl, and

linear or branched C_2 to C_{10} alkenyl.

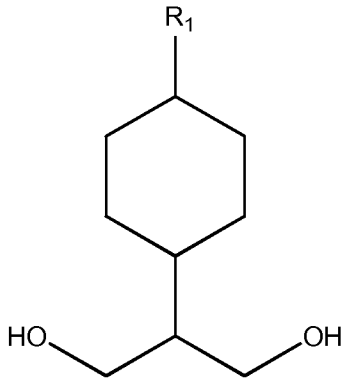
According to a second aspect of the invention, there is provided an antimicrobial composition comprising:

a. 0.001 to 5% by weight of one or more substituted cyclohexyl-propanediols,

b. a carrier, and

c. optionally one or more surfactants;

wherein the carrier is selected from the group consisting of water, ethanol, isopropanol, and mixtures thereof if the composition is free from surfactant; and wherein the one or more substituted cyclohexyl-propanediols have the following structure

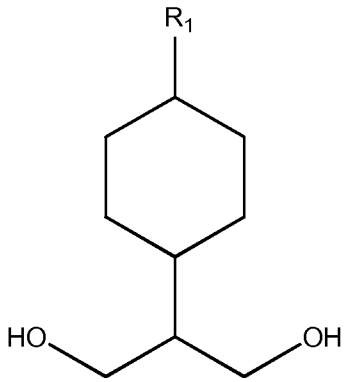


wherein R_1 is selected from

linear or branched C_1 to C_{10} alkyl, and

linear or branched C_2 to C_{10} alkenyl.

In a third aspect, the invention provides use of one or more substituted cyclohexyl-propanediols for improved hygiene, wherein the wherein the substituted cyclohexyl-propanediols have the following structure



wherein R_1 is selected from

linear or branched C_1 to C_{10} alkyl, and

linear or branched C_2 to C_{10} alkenyl.

DETAILED DESCRIPTION

For the avoidance of doubt, any feature of one aspect of the present invention may be utilised in any other aspect of the invention. The word "comprising" is intended to mean "including" but not necessarily "consisting of" or "composed of." Thus, the term "comprising" is meant not to be limiting to any subsequently stated elements but rather to optionally also encompass non-specified elements of major or minor functional importance. In other words, the listed steps or options need not be exhaustive. Whenever the words "including" or "having" are used, these terms are meant to be equivalent to "comprising" as defined above. It is noted that the examples given in the description below are intended to clarify the invention and are not intended to limit the invention to those examples per se.

Except in the operating and comparative examples, or where otherwise explicitly indicated, all numbers in this description indicating amounts of material or conditions of reaction, physical properties of materials and/or use are to be understood as modified by the word "about". Unless specified otherwise, numerical ranges expressed in the format "from x to y" are understood to include x and y. When for a specific feature multiple preferred ranges are described in the format "from x to y", it is understood that all ranges combining the different endpoints are also contemplated.

Throughout this description, the term disinfection refers to reduction of the number of viable microorganisms in a given medium or on a given surface by physical or chemical means. Typically, disinfection involves the destruction or inactivation of said microorganisms.

The antimicrobial method involves a composition comprising one or more substituted cyclohexylpropanediols and a carrier. Various steps of the method and various components of the antimicrobial composition are described below. The method and compositions of the present invention are preferred for non-therapeutic use, and more particularly preferred for use in cleaning surfaces of human body including skin, hair or oral cavity or for hard surface cleaning applications.

Method of disinfecting a surface

According to the first aspect of the invention, there is provided a method of disinfecting a surface. Preferably, the surface is skin. Thus, for example, a surface like the hands, face, body, or the oral cavity is contacted with the composition of the invention. Alternatively, the surface is any hard surface. Typically, such hard surfaces are surfaces that commonly require cleaning and preferably also require sanitisation or disinfection. Such surfaces may be found in many household or industrial environments, and may include for example kitchen and bathroom surfaces, table tops, floors, walls, windows, utensils, cutlery, and crockery. Such surfaces may be made from many different materials, such as for instance plastics, wood, metal, ceramics, glass, concrete, marble, and painted surfaces.

The method according to the first aspect of the present invention includes the step of applying to the surface an antimicrobial composition comprising

a. 0.001 to 5% by weight of one or more substituted cyclohexylpropanediols, and
b. a carrier.

The composition may be applied to the surface by any suitable means known to the skilled person. For instance, a suitable means may be pouring, dropping, spraying or wiping in case of liquid compositions.

Preferably, the method includes diluting or dissolving the composition with a suitable solvent, preferably water, before or whilst applying the composition to the surface. Such dissolving is preferred in particular in case the composition is a solid composition. Alternatively, solid compositions may also be directly spread, rubbed, or sprayed, e.g. in the form of a powder.

Substituted cyclohexylpropanediols of step (i)

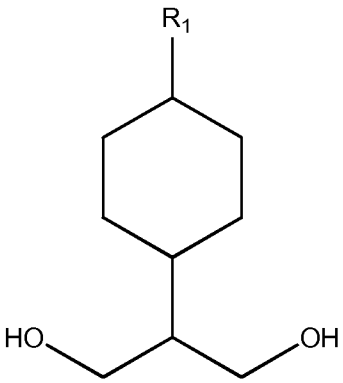
The one or more substituted cyclohexylpropanediols of the composition to be applied are described here, the carrier is described below. The antimicrobial composition to be applied comprises 0.001 to 5% by weight of the one or more substituted cyclohexyl-propanediols. The composition comprises preferably 0.005 to 4.5 wt-%, more preferably 0.01 to 4 wt-%, even more preferably 0.02 to 3 wt-%, yet more preferably 0.03 to 2 wt-%, still more preferably 0.04 to 1 wt-%, even more preferably 0.05 to 0.75 wt-% and still more preferably 0.1 to 0.5 wt-% of the one or more substituted

cyclohexylpropanediols. The concentration of the one or more substituted cyclohexylpropanediols in the antimicrobial composition is preferably such that, when the composition is diluted or dissolved with a suitable medium during use, (e.g. when washing hands with water and a composition according to the invention) the concentration in the diluted or dissolved mixture is still sufficient to be antimicrobially efficacious.

The substituted cyclohexylpropanediol may be a single compound or may be a mixture of the substituted cyclohexylpropanediols as detailed below. In case the composition according to the invention comprises a mixture of such substituted cyclohexylpropanediols, the mixture preferably comprises at least 30%, more preferably at least 50%, even more preferably at least 70% and still more preferably at least 90% by weight of one substituted cyclohexylpropanediol with respect to the total weight of the substituted cyclohexylpropanediols.

At concentration ranges of the one or more substituted cyclohexylpropanediols below their lower concentration limits, the desired fast acting antimicrobial kinetics would not be met. At concentrations higher than the higher preferred concentrations of the one or more substituted cyclohexylpropanediols, while the kinetics of action would not be compromised, the present inventors have found that unlike in therapeutic/pesticidal/herbicidal applications where sensorial aspects are not critical, in the present application, which is preferably a personal cleaning, oral care or hard surface cleaning application, the product is in contact with hands, mouth or other body parts, the sensorial aspects like smell and skin feel would be compromised. Thus, the composition should preferably not be sensorially unpleasant.

The one or more substituted cyclohexyl-propanediols have the following structure



wherein R_1 is selected from linear or branched C_1 to C_{10} alkyl, and linear or branched C_2 to Cio alkenyl.

These compounds can be more specifically described as substituted 2-cyclohexyl-propane-1 ,3-diols. That is, they are selected from 2-(4-alkylcyclohexyl)propane-1 ,3-diols and 2-(4-alkenylcyclohexyl)propane-1 ,3-diols. In case R_1 is an alkenyl group, it comprises a C-C double bond, which may take any position in the alkenyl group. The compound 2-(4-methylcyclohexyl)propane-1 ,3-diol is also known as p-menthane-9,10-diol.

Where applicable, the different stereoisomers of these substituted cyclohexyl-propanediols are contemplated. Thus, compositions comprising enantiomerically pure radicals, racemic mixtures and other mixtures of different stereoisomers are contemplated. In particular the different isomers resulting from cis-trans isomerism across the 1,4-disubstituted cyclohexyl ring are contemplated. However, compounds comprising a trans-(1 ,4)-substituted cyclohexyl moiety are preferred.

Without wishing to be bound by theory, it is believed that the mode of antimicrobial action of the one or more substituted cyclohexylpropanediols is similar.

R_1 is selected from linear or branched C_1 to Cio alkyl, and linear or branched C_2 to Cio alkenyl. Thus, R_1 may for instance be a methyl, ethyl, propyl, isopropyl, ie/f-butyl, allyl, (pent-3-en-2-yl) or n-decyl group. Preferably, R_1 is selected from linear or branched C_1 to C_6 alkyl and linear or branched C_2 to C_6 alkenyl. More preferably, R_1 is selected from linear or branched C_2 to C_5 alkyl and linear or branched C_2 to C_5 alkenyl. R_1 preferably is an alkyl group.

In case the carrier or the dissolution medium during later application is water-based, it may be advantageous if the one or more substituted cyclohexylpropanediols are sufficiently water-soluble. The one or more substituted cyclohexylpropanediols are sufficiently water-soluble if they are soluble to at least the minimum concentration required in the antimicrobial composition according to the invention. Therefore, even more preferably, R_1 is ethyl or propyl.

It is particularly preferred that the one or more substituted cyclohexyl-propanediols are selected from the group consisting of

2-((1 r,4r)-4-ethylcyclohexyl)propane-1 ,3-diol,

2-((1 s,4r)-4-propylcyclohexyl)propane-1 ,3-diol, and

2-((1 r,4s)-4-propylcyclohexyl)propane-1 ,3-diol.

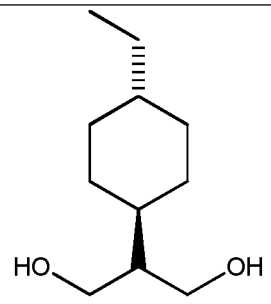
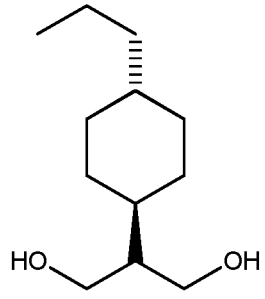
Even more preferably, the one or more substituted cyclohexyl-propanediols are selected from the group consisting of

2-((1 r,4r)-4-ethylcyclohexyl)propane-1 ,3-diol and

2-((1 s,4r)-4-propylcyclohexyl)propane-1 ,3-diol.

The structures of these compounds are given in Table 1.

Table 1

2-((1 r,4r)-4-ethylcyclohexyl)propane-1 ,3-diol	
2-((1 s,4r)-4-propylcyclohexyl)propane-1 ,3-diol	

Mixtures of preferred substituted cyclohexylpropanediols are also preferred.

Suitable substituted cyclohexylpropanediols according to the present invention may be commercially sourced or obtained via synthetic chemical methods. Such methods are generally well-known and are described, for example, by S. Diele *et al* [S Diele, E Geissler, H M Vorbrodt and H Zaschke, *Molecular Crystals and Liquid Crystals,* 1984, Volume 102, Issues 6-7, pp. 181-6].

Method of disinfecting a surface - rinsing step

The method according to the first aspect of the present invention also includes the step of removing the composition from the surface. Here, removing the composition also encompasses partially removing the composition. Preferably, the step of removing the composition comprises rinsing the surface with a suitable solvent or wiping the surface with a suitable wipe, more preferably, this step consists of rinsing the surface with a suitable solvent or wiping the surface with a suitable wipe.

The solvent for rinsing the surface is preferably water but could also be for example a mixture of water and alcohol. It is then rinsed preferably with sufficient amounts of water after a pre-determined period of time to remove any visible or sensory residue of the composition. Alternatively, an alcohol wipe or a water/alcohol impregnated wipe may be used to wipe the surface to be visibly free of the anti-microbial composition. The step of rinsing the substrate is preferably carried out less than 5 minutes, more preferably less than 2 minutes, further more preferably less than a minute and in many cases even more preferably less than 15 seconds after the step of applying the composition on the substrate.

Disinfection time

These times between applying the composition and rinsing or wiping are preferably related to the disinfection time, in order to ensure optimal cleansing and sanitising of the surface. Therefore, the invention preferably relates to a method, wherein the disinfection time T of said method is less than 300 seconds, preferably less than 60 seconds, and more preferably less than 15 seconds; wherein T is defined as the time that elapses from the moment of adding the composition to a microbial culture until the number of microbes per unit volume of the culture is reduced by a factor of 100 000;

and wherein the initial number of microbes preferably exceeds about 100 000 000 microbes per millilitre and wherein the composition is preferably a liquid composition.

The disinfecting action (as may be expressed in terms of the disinfection time T) of the method is preferably determined according to the protocol of Example 1 as described hereinafter. This test relates to a standardised test environment in which the microbial culture is kept in suspension. A similarly suitable test is the standard suspension method described in European Standard EN 1276, with the proviso that the disinfection time is adapted to suit the above criteria as will be clear to a person skilled in the art. Alternatively, one of the test methods as described in WO 2010/046238 may for instance be applied to establish the disinfecting action.

Such test methods may preferably also be used by the skilled person to determine the optimal concentrations of the one or more substituted cyclohexylpropanediols in an antimicrobial composition according to the present invention.

Alternatively, since the method is directed towards surface disinfection, the disinfection time may also be determined by test methods involving a surface. Therefore, the invention preferably relates to a method according to the present invention, wherein the surface disinfection time T2 of said method is less than 60 seconds, preferably less than 15 seconds, wherein T2 is defined as the time starting from the moment of applying the composition to the surface to be disinfected after which the number of microbes per unit area is reduced by a factor of 10000 (i.e. a 4 log reduction), wherein the initial number of microbes preferably exceeds 10^3, more preferably 10^5, and even more preferably 10^7 microbes per square centimeter. Such tests may for instance be performed as described in WO 2010/046238, or as described in European Standards EN 13697:2001 and EN 1500:1997.

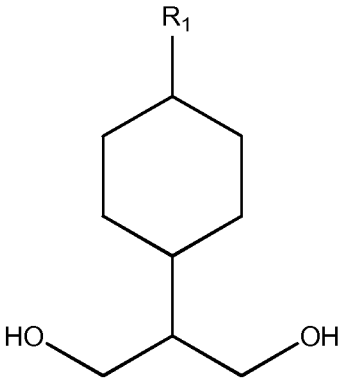
Compositions according to the second aspect of the invention

According to the second aspect of the invention, there is also provided an antimicrobial composition comprising:

a. 0.001 to 5% by weight of one or more substituted cyclohexylpropanediols,
b. a carrier, and
c. optionally one or more surfactants;

wherein the carrier is selected from the group consisting of water, ethanol, isopropanol, and mixtures thereof if the composition is free from surfactant;

and wherein the one or more substituted cyclohexyl-propanediols have the following structure



wherein R_1 is selected from linear or branched C_1 to C_{10} alkyl, and linear or branched C_2 to C_{10} alkenyl.

The antimicrobial composition according to the second aspect of the invention preferably is suitable for use in the method according to the first aspect of the invention.

Therefore, similar to the antimicrobial composition to be applied in the method of the first aspect of the invention, the antimicrobial composition according to the second aspect of the invention comprises 0.001 to 5% by weight of the one or more substituted cyclohexylpropanediols. The composition comprises preferably 0.005 to 4.5 wt-%, more preferably 0.01 to 4 wt-%, even more preferably 0.02 to 3 wt-%, yet more preferably 0.03 to 2 wt-%, still more preferably 0.04 to 1 wt-%, even more preferably 0.05 to 0.75 wt-% and still more preferably 0.1 to 0.5 wt-% of the one or more substituted cyclohexylpropanediols.

The substituted cyclohexylpropanediol may be a single compound or may be a mixture of the selected substituted cyclohexylpropanediols. In case the composition according to the invention comprises a mixture of such substituted cyclohexylpropanediols, the mixture preferably comprises at least 30%, more preferably at least 50%, even more preferably at least 70% and still more preferably at least 90% by weight of one substituted cyclohexylpropanediol with respect to the total weight of the substituted cyclohexylpropanediols.

R_1 is selected from linear or branched C_1 to C_{10} alkyl, and linear or branched C_2 to C_{10} alkenyl. Thus, R_1 may for instance be a methyl, ethyl, propyl, isopropyl, ie/f-butyl, allyl, (pent-3-en-2-yl) or n-decyl group. The different isomers resulting from *cis-trans* isomerism across the 1,4-disubstituted cyclohexyl ring are contemplated. However, compounds comprising a *trans*-(1,4)-substituted cyclohexyl moiety are preferred. Preferably, R_1 is selected from linear or branched C_1 to C_6 alkyl and linear or branched C_2 to C_6 alkenyl. More preferably, R_1 is selected from linear or branched C_2 to C_5 alkyl and linear or branched C_2 to C_5 alkenyl. R_1 preferably is an alkyl group.

In case the carrier or the dissolution medium during later application is water-based, it may be advantageous if the one or more substituted cyclohexylpropanediols are sufficiently water-soluble. The one or more substituted cyclohexylpropanediols are sufficiently water-soluble if they are soluble to at least the minimum concentration required in the antimicrobial composition according to the invention. Therefore, even more preferably, R_1 is ethyl or propyl.

It is particularly preferred that the one or more substituted cyclohexyl-propanediols are selected from the group consisting of

2-((1r,4r)-4-ethylcyclohexyl)propane-1,3-diol,
2-((1s,4r)-4-propylcyclohexyl)propane-1,3-diol, and
2-((1r,4s)-4-propylcyclohexyl)propane-1,3-diol.

Even more preferably, the one or more substituted cyclohexyl-propanediols are selected from the group consisting of

2-((1r,4r)-4-ethylcyclohexyl)propane-1,3-diol and
2-((1s,4r)-4-propylcyclohexyl)propane-1,3-diol.

The structures of the substituted cyclohexylpropanediols of the composition according to the second aspect of the invention are as described above in relation to the substituted cyclohexylpropanediols of the composition to be applied in the method according to the first aspect of the invention.

The carrier in the composition according to the second aspect of the invention can be any carrier as described below. However, if the composition according to the second aspect of the invention is free from surfactant, the carrier is selected from the group

consisting of water, ethanol, isopropanol, and mixtures thereof and more preferably from ethanol, isopropanol and mixtures thereof. Therefore, if the antimicrobial composition is free from surfactant, it preferably comprises from 1 to 99% by weight of the carrier, wherein said carrier is selected from the group consisting of water, ethanol and isopropanol and mixtures thereof and wherein said carrier is preferably selected from ethanol, isopropanol and mixtures thereof.

Additional features of the antimicrobial compositions

The explanations, definitions and further features of antimicrobial compositions described below apply both to the compositions applicable in step (i) of the method according to the first aspect of the invention and to the antimicrobial compositions according to the second aspect of the invention.

Carrier

The antimicrobial compositions according to step (i) of the first aspect of the invention and according to the second aspect of the invention comprise a carrier. The carrier is preferably selected from the group consisting of water, oil, solvent, inorganic particulate material, starch and mixtures thereof. The carrier is preferably from 0.1 to 99% by weight of the composition. The antimicrobial composition may be in form of a solid, liquid, gel, paste or soft solid and the carrier may be selected by a person skilled in the art depending on the format of the antimicrobial composition.

Examples of suitable inorganic particulate materials include clay, talc, calcite, dolomite, silica, and aluminosilicate. Examples of suitable oils include mineral oils, vegetable oils, and petroleum-derived oils and waxes. Examples of solvents include alcohols (in particular ethanol and isopropanol), ethers and acetone. The starch may be natural starch obtained from food grains or may be a modified starch.

Particularly preferred carriers are water or oil/solvent and even more preferred is a carrier that is a mixture of water and oil. Thus, in many of the envisaged applications like personal care/washing, oral care and hard surface cleaning, the antimicrobial composition may be formulated with either an aqueous base or a purely oil/solvent base. Compositions with an aqueous base (water being the carrier), may also for instance be products in gel format. Compositions with a purely oil/solvent base may for instance be products in anhydrous stick form or propellant-containing products.

Thus, the antimicrobial composition may for instance, preferably be an antimicrobial anhydrous stick personal care composition on a purely oil/solvent base wherein the composition has a water content of less than 0.01 % by weight, and wherein the composition preferably is free of water. Alternatively, the antimicrobial composition may for instance, preferably be an antimicrobial propellant-drivable personal care composition, also comprising a propellant.

However, the most preferred product format has an emulsion base (water and oil being the carrier), e.g. soap products in liquid, solid, lotion or semisolid form for hand wash, face wash, body wash, or shaving applications; toothpaste/ dentifrices for oral care applications or products for hard surface cleaning in bars or liquids form.

Surfactants

The antimicrobial composition according to the first or the second aspect of invention preferably comprises from 1 to 80% by weight of one or more surfactants. Surfactants may for instance advantageously contribute to the cleaning efficacy or the formulation stability of a composition.

Thus, the antimicrobial composition according to the second aspect of the invention preferably comprises

a. 0.001 to 5% by weight of the one or more substituted cyclohexylpropanediols according to the invention,
b. a carrier, and
c. from 1 to 80% by weight of one or more surfactants.

In general, the surfactants may be chosen from the surfactants described in well-known textbooks like "Surface Active Agents" Vol. 1, by Schwartz & Perry, Interscience 1949, Vol. 2 by Schwartz, Perry & Berch, Interscience 1958, and/or the current edition of "McCutcheon's Emulsifiers and Detergents" published by Manufacturing Confectioners Company or in "Tenside-Taschenbuch", H. Stache, 2nd Edn., Carl Hauser Verlag, 1981 . Any type of surfactant, i.e. anionic, cationic, nonionic, zwitterionic or amphoteric can be used. Preferably, the surfactant is anionic, nonionic, or a mixture of anionic and nonionic surfactants. More preferably, the surfactant is anionic.

A particularly preferred surfactant is soap. Soap is a suitable surfactant for personal washing applications of the method of disinfecting a surface and the antimicrobial composition according to the invention. The soap is preferably C_8- C_{24} soap, more preferably a C10-C20 soap and most preferably C12- C16 soap. The soap may or may not have one or more carbon-carbon double bonds or triple bonds. The cation of the soap can for instance be an alkali metal, alkaline earth metal or ammonium. Preferably, the cation of the soap is selected from sodium, potassium or ammonium. More preferably the cation of the soap is sodium or potassium.

The soap may be obtained by saponifying a fat and/or a fatty acid. The fats or oils may be fats or oils generally used in soap manufacture, such as tallow, tallow stearines, palm oil, palm stearines, soya bean oil, fish oil, castor oil, rice bran oil, sunflower oil, coconut oil, babassu oil, palm kernel oil, and others. In the above process the fatty acids are derived from oils/fats selected from coconut, rice bran, groundnut, tallow, palm, palm kernel, cotton seed, soyabean, castor etc. The fatty acid soaps can also be synthetically prepared (e.g. by the oxidation of petroleum or by the hydrogenation of carbon monoxide by the Fischer-Tropsch process). Resin acids, such as those present in tall oil, may be used. Naphthenic acids are also suitable.

Tallow fatty acids can be derived from various animal sources and generally comprise about 1 to 8% myristic acid, about 21 to 32 wt-% palmitic acid, about 14 to 31 wt-% stearic acid, about 0 to 4 wt-% palmitoleic acid, about 36 to 50 wt-% oleic acid and about 0 to 5 wt-% linoleic acid. A typical distribution is 2.5 wt-% myristic acid, 29 wt-% palmitic acid, 23 wt-% stearic acid, 2 wt-% palmitoleic acid, 41.5 wt-% oleic acid, and 3 wt-% linoleic acid. Other similar mixtures, such as those from palm oil and those derived from various animal tallow and lard are also included.

Coconut oil refers to fatty acid mixtures having an approximate carbon chain length distribution of 8 wt-% C_8, 7 wt-% C10, 48 wt-% C_{12}, 17 wt-% C_{14}, 8 wt-% C_{16}, 2 wt-% C_{18}, 7 wt-% oleic and 2 wt-% linoleic acids (the first six fatty acids listed being saturated). Other sources having similar carbon chain length distributions, such as palm kernel oil and babassu kernel oil, are included within the term coconut oil.

A typical fatty acid blend consists of 5 to 30 wt-% coconut fatty acids and 70 to 95 wt-% fatty acids ex hardened rice bran oil. Fatty acids derived from other suitable oils/fats such as groundnut, soybean, tallow, palm, palm kernel, etc. may also be used in other

desired proportions. The soap, when present in solid forms of the present invention, is present in an amount of 30 to 80%, preferably from 50 to 80%, more preferably 55 to 75% by weight of the composition. The soap, when present in liquid forms of the composition is present in 0.5 to 20%, preferably from 1 to 10% by weight of the composition.

The method of disinfecting a surface according to the first aspect of the invention and the antimicrobial composition according to the second aspect of the invention are also useful in hard surface cleaning applications. In such applications, preferred surfactants are nonionic surfactants, such as C_8- C_{22}, preferably C_8-Ci_6 fatty alcohol ethoxylates, comprising between 1 and 8 ethylene oxide groups when the product is in the liquid form. When the product for hard surface cleaning applications is in the solid form, surfactants are preferably selected from primary alkyl sulphates, secondary alkyl sulphonates, alkyl benzene sulphonates, or ethoxylated alkyl sulphates. The composition may further comprise an anionic surfactant, such as alkyl ether sulphate preferably those having between 1 and 3 ethylene oxide groups, either from natural or synthetic source and/or sulphonic acid. Especially preferred are sodium lauryl ether sulphates. Alkyl polyglucosides may also be present in the composition, preferably those having a carbon chain length between C6 and C16. Suitable surfactant concentrations in liquid forms of hard surface cleaning application are generally from about from 0.5 to 10%, preferably from 1 to 5 % by weight of the composition. In solid compositions, surfactant is preferably present in 5 to 40%, preferably from 10 to 30% by weight of the composition.

The method of disinfecting a surface according to the first aspect of the invention and the antimicrobial composition according to the second aspect of the invention are also useful in oral care compositions e.g. in a dentifrice/ toothpaste or an oral rinse product. In such applications, preferred surfactants are anionic, nonionic or amphoteric in nature, preferably anionic or amphoteric. The anionic surfactant is preferably an alkali metal alkyl sulphate, more preferably a sodium lauryl sulphate (SLS). Mixtures of anionic surfactants may also be employed. The amphoteric surfactant is preferably a betaine, more preferably an alkylamidopropyl betaine (wherein the alkyl group is a linear C_{10}-Ci_8 chain), and most preferably is cocoamidopropyl betaine (CAPB). Mixtures of amphoteric surfactants may also be employed. Suitable surfactant concentrations in oral care application are generally from about 2% to about 15%,

preferably from about 2.2% to about 10%, more preferably from about 2.5 to about 5% by weight of the total composition.

Thus, it is highly preferred that the antimicrobial compositions include soap, alkyl sulphate or linear alkyl benzene sulphonate as the surfactants. More preferably, the surfactant is a soap, an alkyl sulphate or a linear alkyl benzene sulphonate.

The antimicrobial composition may be in form of a solid, a liquid, a gel or a paste. A person skilled in the art can prepare compositions in various formats by choosing one or more carrier materials and/or surfactant. The antimicrobial compositions of the present invention are useful for cleansing and care, in particular for skin cleansing and skin care. It is envisaged that the antimicrobial composition can be used as a leave-on product or a wash-off product, preferably a wash-off product. The antimicrobial composition of the present invention can also be used for cleansing and care of hard surfaces such as glass, metal, plastic and the like.

Liquid and solid compositions

A particularly preferred carrier in the antimicrobial composition according to the first or the second aspect of the invention is water. When water is present, it is preferably present in at least 1%, more preferably at least 2%, further more preferably at least 5% by weight of the composition. When water is the carrier, a preferred liquid antimicrobial composition according to the first or the second aspect of the invention comprises:

a. 0.05 to 5% by weight of the one or more substituted cyclohexyl-propanediols
b. 10 to 99.9% by weight of water, and;
c. 1 to 30% by weight of surfactant.

The liquid antimicrobial composition is useful for skin cleansing, in particular for hand wash or face wash.

When water is the carrier, a preferred solid antimicrobial composition according to the invention comprises:

a. 0.05 to 5% by weight of the one or more substituted cyclohexyl-propanediols,
b. 5 to 30% by weight of water, and;

c. 30 to 80% by weight of surfactant.

The solid antimicrobial composition is preferably in form of a shaped solid, more preferably a bar. The solid antimicrobial composition is particularly useful for skin cleansing in particular for hand wash or a face wash.

Such a bar-shaped solid antimicrobial composition may for instance be a soap bar. Soap bar compositions are well-known and may be similar to the following non-limiting example composition, comprising 75.6 wt-% of anhydrous sodium soap, 1.0 wt-% of glycerine, 0.5 wt-% of sodium carbonate, 0.2 wt-% of EHDP (ethane-1-hydroxy-1 ,1-disphosphonate) acid, 0.04 wt-% of EDTA (ethylenediaminetetraacetic acid) tetrasodium salt, 8.5 wt-% of hydrated magnesium silicate (Talc), 0.7 wt-% of sodium chloride, 0.05 wt-% of dyes, 0.75 wt-% perfume, 0.05 to 10 wt-% of preservatives and antimicrobial agents including the substituted cyclohexylpropanediols according to the present invention, and water up to 100 wt-%.

Alternatively, inorganic particulate material is also a suitable carrier. When inorganic particulate material is the carrier, the antimicrobial composition is in a solid form. Preferably the inorganic particulate material is talc. When the inorganic particulate material is talc, the solid antimicrobial composition is particularly useful as a talcum powder for application on face or body.

According to another alternative, a solvent is a preferred carrier. Although any solvent can be used, alcohol is a preferred solvent. Short chain alcohols -in particular ethanol, propanol and isopropanol- are particularly preferred as carrier for an antimicrobial wipe or an antimicrobial hand sanitiser composition.

Solvents like ethanol and isopropanol generally show antimicrobial efficacy themselves. However, they are also volatile and may readily evaporate during application of the composition. Thus, their levels on the surface that is treated might even reduce until below the minimum level required for antimicrobial action, before the minimum period needed for disinfection has passed. In contrast, the substituted cyclohexylpropanediols according to the present invention are much less volatile and may therefore yield prolonged antimicrobial action after applying them to the skin.

Additional ingredients

The composition according to the first or second aspect of the invention may further comprise various additional ingredients known to a person skilled in the art. Such additional ingredients include but are not limited to: perfumes, pigments, preservative, emollients, sunscreens, emulsifiers, gelling agents, or thickening agents, humectants (e.g. glycerine, sorbitol), sequestrants (e.g. EDTA) or polymers (e.g. cellulose derivatives for structuring such as methyl cellulose).

Some of the substituted cyclohexylpropanediols according to the invention may contribute to the olfactory properties of the composition. Although some of these compounds might be applied for instance in perfume compositions, the present invention is directed towards antimicrobial compositions. Therefore, the composition is preferably not a perfume composition. Here, a perfume composition is defined as a composition comprising a plurality of olfactory components, where these components are solely intended to provide the composition with a harmonious scent.

Use according to the invention

The invention preferably provides for non-therapeutic benefits.

Thus, according to the third aspect of the invention, there is provided use of one or more substituted cyclohexylpropanediols for improved hygiene. Such use relates for example to use of an antimicrobial composition comprising one or more substituted cyclohexylpropanediols according to the invention for reduction in microbial count, preferably fast reduction of antimicrobial count. Thus, such use preferably is use in a method for disinfection. Fast reduction in antimicrobial count therefore preferably relates to use for disinfection whereby the disinfection time is less than 300 seconds, preferably less than 60 seconds, and more preferably less than 15 seconds. Here, the disinfection is preferably defined similar to the disinfection times T and T2 as described above.

Preferably, the use according to the invention relates to use of one or more substituted cyclohexylpropanediols in an antimicrobial composition. Suitable antimicrobial compositions are for instance compositions according to the first or the second aspect of the invention.

Similarly, the preferences regarding the substituted cyclohexylpropanediols according to the first aspect of the invention also are preferred with respect to the substituted cyclohexylpropanediols according to the third aspect of the invention. Alternatively, the substituted cyclohexylpropanediols according to the second aspect of the invention are preferred.

Thus, there is provided use of one or more substituted cyclohexylpropanediols according to the invention for improved hygiene of surfaces of the human body. Such surfaces include e.g. skin, hands and the oral cavity. According to a preferred aspect, the invention relates to use of one or more substituted cyclohexylpropanediols for improved hand hygiene. According to another preferred aspect, the invention relates to use of one or more substituted cyclohexylpropanediols for improved oral hygiene.

EXAMPLES

The invention is illustrated by the following non-limiting examples.

Example 1: Assessment of antimicrobial efficacy

The efficacies of antimicrobial agents can be usefully compared by determining the Minimum Biocidal Concentration (MBC). The MBC is defined as the absolute lowest concentration of actives that provides complete kill (zero bacterial growth) in a particular test environment.

Experimental method

Antimicrobial efficacy is tested against a representative pathogenic bacterial organism, Gram-negative *Escherichia coii.* Concentrations of actives are expressed in terms of the percentage weight/volume (%w/v) throughout Example 1.

Bacterial stock

An overnight culture of *Escherichia coii* (10536 strain) was prepared in 50 ml total volume of TSB broth, grown for ca. 18 hrs at 37°C and shaken at 150 rpm. 1 ml of this overnight *E. coii* culture was transferred to 50 ml of fresh TSB broth and incubated at 37°C at 150 rpm for ca. 4 hours. This culture was separated into equal volumes and centrifuged at 4000 rpm for 15 minutes, washed with sterile saline (0.85% NaCl), centrifuged once more and re-suspended in saline to give a final concentration of 0.8 OD_{620} equivalent to about 10^8 cells per millilitre for this particular organism. Here,

OD_{620} indicates the absorbance of a sample in a cuvette of 1.0 cm path length at a wavelength of 620 nm. This bacterial stock was used for assaying against antimicrobial actives (in triplicate).

Protocol

The following assay describes the testing of 8 materials using 6 dilutions across half of a 96-well micro titre plate (MTP). Using this approach it is possible to assay 16 actives (without replicates) with one full dilution plate, replicating this set up in two halves of the plate columns, 1-6 and 7-12.

1M solutions of the test actives were prepared in dimethylsulphoxide (DMSO). Stock solutions of the actives at 1.11 times the desired final concentration were prepared by diluting the DMSO solutions in water, so that for example a 0.89% w/v solution was prepared for a desired "in test" concentration of 0.8% w/v in order to allow for the further dilution of the active when the bacterial suspension is added (dilution from 270µl to 300 µl), as described below.

Aliquots (270 µl) of the materials at 1.11 times the final concentration were dispensed into the wells of the MTP along one column (A1-H1). This MTP was labelled as the "Screening plate".

In another MTP, labelled as the "Dilution plate", 270µl of D/E neutralising solution from DIFCO Composition was added to column 1. The composition of the neutralising solution was as follows: pancreatic digest of casein, 5.0g/L; Yeast Extract, 2.5 g/L; Dextrose, 10 g/L, sodium thioglycollate, 1.0 g/L, sodium thiosulphate, 6.0 g/L; sodium bisulphite, 2.5 g/L; Polysorbate 80, 5.0 g/L; lecithin 7.0 g/L; bromocresol purple, 0.02 g/L with a pH in the range 7.6±0.2.

270µl of tryptone diluent solution was added to all the remaining wells of the Dilution MTP (columns 2-6).

Bacterial stock (30 µl) was then added to the prepared 270 µl of the solution of actives in the Screening Plate and mixed, using a multichannel pipette with 8 tips to aspirate and dispense the same volume of bacterial stock in parallel to 8 wells in rows A-H. After a contact time of 15 seconds, the mixtures were quenched by transferring 30µl

volumes of the mixtures into the 270 µl D/E neutralising solution in the prepared dilution plate, using aspiration to mix. After exactly 5 minutes in the D/E neutralising solution, 30µl volumes were transferred from column 1 to column 2 of the Dilution MTP and mixed, before transferring further 30µl volumes from column 2 into column 3. This process was repeated serially diluting the bacteria across the plate to column 6.

30µl volumes from each well in the Dilution MTP were transferred onto pre-labelled segment of Tryptone Soya Agar (TSA) plates starting from the lowest bacterial concentration (highest dilution, column 6) to the highest bacterial concentration (column 1). The TSA plates were allowed to stand for ca. 2 hours so that the 30µl inocula spots could dry and the plates were then inverted and incubated overnight at 37°C before enumerating the bacterial colonies at the labelled dilutions to determine the effects of the actives on bacterial growth.

Calculation of results

Mean bacterial survival numbers N_{MBS} (expressed in Log CFU/ml) are obtained by first determining the segment of the TSA plate where the number of bacterial colonies is countable. From the colony number in this segment, N_{MBS} is calculated by the formula:

$$\mathbf{N_{MBS}} = \log\{ N_{coi} - 10^{DF} - 100 / 3 \}$$

Here, N_{C0}| is the colony count, and DF is the dilution factor taken from the MTP-well corresponding to the TSA plate segment (i.e. DF may range from 1 for the quench, to 6 for the highest dilution). The factor 100/3 is a conversion factor from the volume of the inocula spot to one millilitre.

Every assay test was performed in triplicate. The reported mean bacterial survival results are the average of such a triplet, the error is the corresponding standard deviation.

Thus, a value of N_{MBS} of about 7 corresponds to a count of about 3 colonies from the fifth dilution well, i.e. with DF = 5. Such a count of about 7 is generally observed when bacteria are exposed to non-biocidal materials. In case no surviving colonies are observed in any segment of the TSA plate, this is interpreted as complete kill and a value of $N_{MBS} = 0$ is reported.

Validation

All test results were validated by running every test assay in parallel with four control experiments on the same MTP. All control experiments are executed exactly according to the above protocol, but with the following active ingredients:

A 0.025 %(w/v) thymol

B 0.15 %(w/v) alpha-terpineol

C 0.025 %(w/v) thymol + 0.15 %(w/v) alpha-terpineol

D no active component

The control experiments A, B and D validate a test assay by not showing bacterial kill, whereas control experiment C, comprising a combination of thymol and alpha-terpineol according to WO 2010/046238 A1 validates a test assay by showing complete bacterial kill.

A reference experiment according to the above protocol, but without active component, showed that DMSO does not affect bacterial growth at the concentrations present in the test solutions in this protocol (<5 % (w/v)), as can be seen in Table 2.

Table 2

DMSO in water (% w/v)	Mean bacterial survival [log CFU/ml]	Standard deviation
4.5	8.2	0.1
3.6	8.4	0.2
2.7	8.2	0.1
1.8	8.5	0.2
0.9	8.6	0.1
0.0	8.5	0.1

Results

The above method was applied to assess the antibacterial efficacy of the substituted cyclohexylpropanediols according to the present invention. For each of the below examples, Table 3 shows the antibacterial activities of the substituted cyclohexyl-propanediols.

Table 3: Antibacterial activities of substituted cyclohexylpropanediols

Example	**Concentration of** substituted cyclohexylpropanediols **C (% w/v)**	**N_{MBS} [log CFU/ml]**	**Standard deviation**
1:1	0.6% 2-((1r,4r)-4-ethylcyclohexyl)propane-1,3-diol	0	0
1:2	0.5% 2-((1s,4r)-4-propylcyclohexyl)propane-1,3-diol	0	0

Antimicrobial compositions

As described above, the MBC for an active can be defined as the lowest measured concentration of the active that provides zero bacterial bacterial survival for the particular bacteria in the particular medium. The MBCs determined for the substituted cyclohexylpropanediols are summarised in Table 4 below. The reported MBC values constitute upper boundaries to the MBC in the particular medium used in these examples.

Table 4: Minimum Biocidal concentrations of antimicrobial components

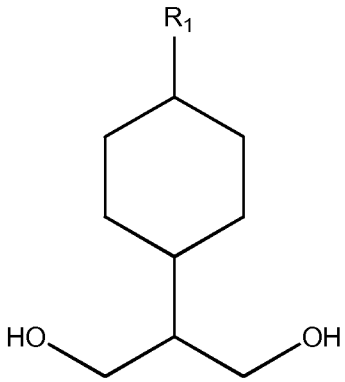
Component	**MBC (% w/v)**
2-((1*r*,4*r*)-4-ethylcyclohexyl)propane-1,3-diol	0.6
2-((1*s*,4*r*)-4-propylcyclohexyl)propane-1,3-diol	0.5

It is clear from the data in Table 4 that the substituted cyclohexylpropanediols according to the present invention are efficacious antimicrobials.

CLAIMS

1. A method of disinfecting a surface comprising the steps of
   a. applying to the surface an antimicrobial composition comprising
      i. 0.001 to 5% by weight of one or more substituted cyclohexyl-propanediols, and
      ii. a carrier; and
   b. removing the composition from the surface;

   wherein the one or more substituted cyclohexyl-propanediols have the following structure



   wherein R_1 is selected from

   linear or branched C_1 to C_{10} alkyl, and

   linear or branched C_2 to C_{10} alkenyl.

2. A method according to claim 1, wherein R_1 is linear or branched C_1 to C_{10} alkyl.

3. A method according to claim 2, wherein R_1 is ethyl or propyl.

4. A method according to claim 3, wherein the one or more substituted cyclohexyl-propanediols are selected from the group consisting of

   2-((1r,4r)-4-ethylcyclohexyl)propane-1,3-diol and

   2-((1s,4r)-4-propylcyclohexyl)propane-1,3-diol.

5. A method according to any one of claims 1 to 4, wherein the antimicrobial composition comprises from 1 to 80% by weight of one or more surfactants.

6. A method according to any one of claims 1 to 5, wherein the surface is skin.

7. A method according to any one of claims 1 to 6, wherein the disinfection time T of said method is less than 300 seconds, preferably less than 60 seconds, and more preferably less than 15 seconds; wherein T is defined as the time that elapses from the moment of adding the antimicrobial composition to a microbial culture until the number of microbes per unit volume of the culture is reduced by a factor of 100 000; and wherein the initial number of microbes preferably exceeds about 100 000 000 microbes per millilitre and wherein the antimicrobial composition is preferably a liquid composition.

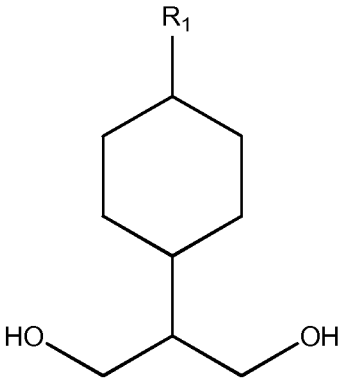
8. An antimicrobial composition comprising:

a. 0.001 to 5% by weight of one or more substituted cyclohexyl-propanediols,

b. a carrier, and

c. optionally one or more surfactants;

wherein the carrier is selected from the group consisting of water, ethanol, isopropanol, and mixtures thereof if the composition is free from surfactant; and wherein the one or more substituted cyclohexyl-propanediols have the following structure



wherein R_1 is selected from

linear or branched C_1 to C_{10} alkyl, and

linear or branched C_2 to C_{10} alkenyl.

9. An antimicrobial composition according to claim 8 wherein R_1 is linear or branched C_1 to Cio alkyl.

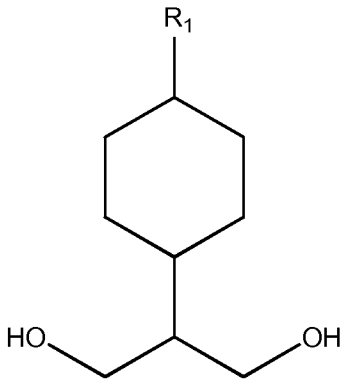
10. An antimicrobial composition according to claim 9 wherein R_1 is ethyl or propyl.

11. An antimicrobial composition according to claim 10, wherein the one or more substituted cyclohexyl-propanediols are selected from the group consisting of
2-((1 r,4r)-4-ethylcyclohexyl)propane-1 ,3-diol and
2-((1 s,4r)-4-propylcyclohexyl)propane-1 ,3-diol.

12. An antimicrobial composition according to any one of claims 8 to 11 comprising from 1 to 80% by weight of the one or more surfactants.

13. An antimicrobial composition according to any one of claims 8 to 12 comprising from 1 to 99% by weight of the carrier, wherein said carrier is selected from the group consisting of water, ethanol and isopropanol.

14. Use of one or more substituted cyclohexyl-propanediols for improved hygiene, wherein the substituted cyclohexyl-propanediols have the following structure



wherein R_1 is selected from
linear or branched C_1 to C_{10} alkyl, and
linear or branched C_2 to C_{10} alkenyl.

15. Use according to claim 14 for improved hand hygiene.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/074964

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K8/34 A61Q17/00 A01N31/04 C11D3/20
ADD.

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)
A61K A61Q A01N C11D

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 practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2011/023582 A2 (BASF SE [DE] ; MI JOLOVIC DARIJO [DE] ; WENDEL VOLKER [DE] ; SUCKERT ANJA) 3 March 2011 (2011-03-03) claim 1	1-15
A	US 5 322 638 A (SCHADT MARTIN [CH] ET AL) 21 June 1994 (1994-06-21) example 4	8-13

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" documentwhich may throw doubts on priority claim(s) orwhich is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 February 2013	25/02/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Vayssié, Stephane

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/074964

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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