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(54) Title: METHODS AND COMPOUNDS FOR REDUCING ALLERGIC REACTIONS TO FRAGRANCED PRODUCTS AND PERFUMES

(57) Abstract: Conventional fragranced products and perfumes often form potent allergens and may also have irritant properties. The invention relates to compounds, compositions, formulations and methods for reducing, avoiding or eliminating allergic contact dermatitis reactions to the oxidation products of odorous chemicals conventionally used in fragranced products and perfumes.
Methods and compounds for reducing allergic reactions to fragranced products and perfumes

The invention relates to compounds, compositions, formulations and methods for: avoiding; eliminating; or reducing i.e. inhibiting the induction and/or decreasing the severity and/or frequency of elicitation of allergic reactions to fragranced and perfume products.

As used herein fragrances are odorous compounds which are included as part of the composition of a variety products such as by way of example only cosmetics, toiletries, soap, deodorants, laundry washing products, laundry aids such as fabric conditioners, cleaning products, air fresheners and deodorising products.

As used herein perfumes are products which comprise one or more odorous chemical which are applied directly to the skin, hair or clothing of an individual or animal to enhance the general attractiveness of the wearer. A secondary role is to hide or mask malodours. The one or more odorous chemical is usually diluted with an organic solvent such as by way of example only ethyl alcohol.

As used herein a hapten is a low molecular weight chemical that is immunogenic only when attached to a carrier protein.

As used herein a prehapten is a chemical that itself is non- or low- sensitising but which may be transformed into a hapten outside the skin by simple chemical transformation (such as air oxidation) without the requirement of a specific enzymatic system.

As used herein a prohapten is a chemical that itself is non- or low-sensitising but which may be transformed into a hapten in the skin by specific enzymatic systems.
The present invention aims to reduce, avoid or eliminate both the induction (sensitisation) of contact allergy and/or the elicitation of allergic contact dermatitis in individuals exposed to fragranced and perfume products.

In a first aspect the invention relates to a method of reducing induction of contact allergy or reducing elicitation of allergic contact dermatitis of, in or on the skin in response to a fragranced product or perfume by inhibiting oxidation of odorous chemicals.

In a second aspect the invention relates to a method as claimed in claim 1 wherein oxidation is inhibited or reversed using an antioxidant.

In a further aspect the invention relates to a method wherein the antioxidant is selected from vitamin C, vitamin E, vitamin C derivatives, vitamin E derivatives, vitamin E acetate, vitamin E linoleate, vitamin E esters, butylated hydroxytoluene, butylated hydroxyanisole or like material.

In a further aspect the invention relates to a method wherein the skin is post-treated to inhibit or reverse oxidation after the application of the fragranced product or perfume.

In a further aspect the invention relates to a method wherein the skin is pre-treated to inhibit or reverse oxidation before the application of the fragranced product or perfume.

In a further aspect the invention relates to a composition for reducing induction of contact allergy or reducing elicitation of allergic contact dermatitis of, in or on the skin in response to a fragranced product or perfume comprising an antioxidant.

In a further aspect the invention relates to a composition wherein the antioxidant is selected from vitamin C, vitamin E, vitamin C derivatives, vitamin E derivatives, vitamin E acetate, vitamin E linoleate, vitamin E esters, butylated hydroxytoluene, butylated hydroxyanisole or like material.
In a further aspect the invention relates to a composition wherein by preventing oxidation, the time taken for the odorous chemicals to dissipate is increased.

**Detailed Description:**

Perfumes have been used in different cultures through the ages. Their main purpose is to enhance the general attractiveness of the wearer. A secondary role is to hide malodours.

There may be as many as 1000 different chemicals in a single fragrance compound each of which plays a different role. The most volatile ("top notes"), with odours such as citrus, green-leafy and spicy give way to longer lasting 'heart' notes with floral odours. The longest lasting ("bottom notes") are often woody or musky in nature.

Current widely used perfumes often consist of a few highly concentrated odorous chemicals.

Many commercially used fragranced products and perfumes for application to or by consumers contain a mixture of organic odorous chemicals one or more of which may undergo chemical changes in or on the skin. Such changes may affect the odour of a chemical, and it may also change it from an innocuous form to a sensitising form which can have irritant properties which in turn give risk to allergic contact dermatitis.

An undesirable consequence of the generation of a number of chemically reactive intermediates is that these can combine with skin proteins rendering them "foreign" and thus activating the immune system into the production of an allergic reaction ie a cell mediated, Type IV hypersensitivity.

Allergic Contact Dermatitis to fragranced products and perfumes takes the form of an inflammatory rash. Subjects can become sensitised to different odorous chemicals, which presents immunologically as an expansion of a population of T-lymphocytes
which recognise and react to epicutaneous contact with the specific odorous chemical (or a chemical with close structural similarities) by producing inflammation within the skin.

Skin sensitization describes an immunological process whereby heightened responsiveness to a chemical allergen is induced. This process involves the chemical being presented to naive T cells and a clone(s) of T cells being produced which will recognise the chemical in the periphery and induce a host inflammatory response to the chemical (elicitation reaction).

Normally an individual only becomes sensitised after one, or more usually, after several exposures to the fragranced or perfume product. Hence, products which are initially well tolerated may, after repeated use, cause an allergic reaction.

Allergic contact dermatitis arises during the elicitation phase (clinical reaction in someone already sensitised or made allergic).

An active sensitisation phase (induction) is required before an allergic response can be elicited. Typically an individual only becomes sensitised to an allergenic chemical following repeated exposures. The number of exposures required for sensitisation to occur is highly variable, the frequency of use of the fragranced or perfume product may mean a period of many months or years precedes the acquisition of sensitisation. Many individuals will never become sensitised.

Classical 'fragrance dermatitis' occurs at sites where fragrances are often applied to the skin, such as on the hands, sides of the neck, behind the ears and on the wrists. However, fragrance dermatitis also occurs on other parts of the body such as the face, axillae and trunk.

Fragrance contact allergy is a clinically significant problem, being the second commonest cause of contact allergy after nickel, and gives rise to a significant degree of morbidity in the general population.
Many of the fragrance chemicals which give rise to allergic contact dermatitis have been well characterised, to the extent that diagnostically, 14 key materials are now present in two mixes, Fragrance Mix 1 (FM I) and Fragrance Mix 2 (FM II) used in routine investigations of possible allergic dermatitis. Johansen, J.D., Lepoittevin, J-P., Basketter, D., McFadden, J. and Sosted, H. (2006) Allergens of special interest. Contact Dermatitis, 4th edition, Eds Frosch PJ, Menne T and Lepoittevin J-P. Springer, Berlin, pp 507 - 536.

Of these 14, only a minority are considered to be directly reactive chemicals (the classical haptens of allergic contact dermatitis). At least half of them require an oxidative process to produce a sensitizing species - these are commonly referred to as prohaptens Dupuis, G. and Benezra, C. (1982) Contact Dermatitis to Simple Chemicals: A Molecular Approach. New York: Marcel Dekker.

In addition to the components of FM I and FM II, other notable fragrance materials such as limonene and linalool also require oxidation to render them allergenic, Karlberg A-T, Basketter DA, Goossens A and Lepoittevin J-P (1999) Regulatory classification of substances oxidized to skin sensitizers by exposure to the air. Contact Dermatitis 40: 183 - 188; and Christensson JB, Matura M, Gruvberger B, Braze M, Karlberg AT (2010) Linalool—a significant contact sensitizer after air exposure. Contact Dermatitis 62: 32 - 41.

To date, the details of the processes by which innocuous fragrance compounds are converted to sensitizing intermediates have not been fully defined. However, for at least some important prehaptens, e.g. limonene and linalool, it is clear that air oxidation is the critical factor Karlberg A-T, Basketter DA, Goossens A and Lepoittevin J-P (1999) Regulatory classification of substances oxidized to skin sensitizers by exposure to the air. Contact Dermatitis 40: 183 - 188; and Matura M, Skold M, Borje A, Andersen KE, Braze M, Frosch P, Goossens A, Johansen JD, Svedman C, White IR, Karlberg AT. (2005) Selected oxidized fragrance terpenes are common contact allergens. Contact Dermatitis 52: 320 - 328.


Prehapten activation as a result of air or auto oxidation is known to be responsible for the generation of hydroperoxides which are some of the most prominent sensitizing agents involved in contact allergy.

Prehapten activation (in contrast to bioactivation of prohaptens) can be reduced by measures adopted in the handling and storage of fragranced products and perfumes for example: perfume compounds may be stored under anaerobic condition (e.g. under nitrogen; and an antioxidant may be added (e.g. BHT) to reduce oxidation. Similarly
fragranced products and perfumes are generally stored in cool dark conditions so as to minimize oxidation. However all there measures are only to preserve the integrity of the odorous compounds during storage not during or after application to the skin.

The fragrance substances that have been investigated so far are all terpenes with oxidizable allylic positions that are able to form sensitising hydroperoxides as primary oxidation products upon air exposure. The primary oxidation products form secondary oxidation products some of which are allergenic Karlberg et al. Chem Res Toxicol 2008: 21:53-69.

linalyl acetate, the main component of lavender oil, creates potent contact allergens. Contact Dermatitis 2008: 58: 9-14.


Non-oxidized limonene and linalool do not (or very rarely) cause allergic reactions. Santucci B et al. Contact Dermatitis 1987: 16: 93-95 (limonene 2%: 0/1200 pos); and Fregert S et al. Contact Dermatitis Newsletter 1969: 5: 85-86. (linalool 10%: 4/792 pos (0.5%); and Frosch PJ et al. Contact Dermatitis 1995: 33: 333-342 (linalool 5% and 1%: 0/100 pos).

Due to the complexity of scented products, which are mixtures of many different fragrance substances, there is no published data on the presence of oxidation products in these consumer products. However numerous clinical studies show a clear connection between contact allergy to oxidized limonene and linalool and contact allergy to other

Other important allergenic products such as aldehydes and epoxides are also produced as a result of both oxidation and bioactivation routes depending on the structure of the compound.

It is not always possible to know whether a particular allergen that is not directly reactive acts as a prehapten or as a prohapten or both because the oxidation and bioactivation product can often give the same compound for example geraniol.

As with geraniol, when haptens are formed from compounds which act as both prohaptens and prehaptens, the impact on the sensitization potency is thought to be higher when an individual is exposed to the oxidized compound compared to the sensitization potency caused by bioactivation.

This effect is likely the result of dosage differences, oxidation giving rise to higher hapten concentrations than bioactivation.

Thus it appears that oxidation either: autooxidation; by the air; or as a result of a specific enzymatic systems in the skin is crucial in converting a range of otherwise innocuous fragrance compounds into sensitizing forms likely to give rise to contact dermatitis.

The present invention relies on this realization and provides methods, and compositions for reducing or eliminating the allergenicity of odorous chemicals by inhibiting, reducing or reversing oxidation.

The present invention provides compositions which contain one or more anti-oxidising agent.

The compositions of the present invention prevent oxidation of odorous chemicals thereby reducing the risk of allergic sensitisation to the fragranced or perfume product.

Preferably the compositions of the present invention have the added benefit of prolonging the pleasant odour by preventing oxidation of odorous chemicals.

Optionally, the compositions for inhibiting oxidation are applied to the skin before or after the application of the fragranced or perfume product in a pre-treatment and/or post treatment step.
Preferably the compositions for inhibiting oxidation are applied only to areas where the allergic reactions are most pronounced, such as on the hands, sides of the neck, behind the ears and on the wrists.
Claims:

1. A method of reducing induction of contact allergy or reducing elicitation of allergic contact dermatitis of, in or on the skin in response to a fragranced product or perfume by inhibiting oxidation of odorous chemicals.

2. A method as claimed in claim 1 wherein oxidation is inhibited or reversed using an antioxidant.

3. A method as claimed in claim 2 wherein the antioxidant is selected from vitamin C, vitamin E, vitamin C derivatives, vitamin E derivatives, vitamin E acetate, vitamin E linoleate, vitamin E esters, butylated hydroxytoluene, butylated hydroxyanisole or like material.

4. A method as claimed in any preceding claim wherein the skin is post-treated to inhibit or reverse oxidation after the application of the fragranced product or perfume.

5. A method as claimed in any preceding claim wherein the skin is pre-treated to inhibit or reverse oxidation before the application of the fragranced product or perfume.

6. A composition for reducing induction of contact allergy or reducing elicitation of allergic contact dermatitis of, in or on the skin in response to a fragranced product or perfume comprising an antioxidant.

7. A composition as claimed in claim 6 wherein the antioxidant is selected from vitamin C, vitamin E, vitamin C derivatives, vitamin E derivatives, vitamin E acetate, vitamin E linoleate, vitamin E esters, butylated hydroxytoluene, butylated hydroxyanisole or like material.
8. A composition as claimed in claims 6 to 7 wherein by preventing oxidation, the time taken for the odorous chemicals to dissipate is increased.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/355 A61K31/375 A61P17/00

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 A61P

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, BIOSIS, EMBASE, SCISEARCH, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>DE 38 26 889 AI (OTTO FUCks GMBH &amp; CO KG H [DE]) 15 February 1990 (1990-02-15) claims; examples</td>
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<td>WO 97/45098 A2 (PANIN GIORGIO [IT]) 4 December 1997 (1997-12-04) claims</td>
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<td>WO 2010/146142 A2 (HDS LTD [GB]; BASKETTER DAVID [GB]; MCFADDAN JOHN [GB]; WHITE IAN [GB]) 23 December 2010 (2010-12-23) claims; examples</td>
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<td>US 2009/258841 AI (MURPHY MICHAEL PATRICK [GB] ET AL) 15 October 2009 (2009-10-15) claims; tables</td>
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X Further documents are listed in the continuation of Box C. X 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

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Date of the actual completion of the international search: 9 November 2012

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Name and mailing address of the ISA:

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk

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Authorized officer: Venturi ni, Francesca

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<td>HAGVALL L; BACKTORP C; SVENSSON S; NYMAN G; BORJE A; KARLBERG AT.: &quot;Fragrance compound geraniol forms contact allergens on air exposure. Identification on and quantification of oxidant products and effect on skin sensitization&quot;, CHEM RES TOXICOL., vol 20, 1 January 2007 (2007-01-01), pages 807-814, XP002686826, cited in the application of the whole document results, discussion</td>
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