COMMONWEALTH OF AUSTRALIA
THE PATENTS ACT 1952

CONVENTION APPLICATION FOR STANDARD
PATENT OR A STANDARD PATENT OF ADDITION

5 6 0 9 4 5

Full name(s) of Applicant(s)
L. GIVAUDAN & CIE
a Societe Anonyme
of 1214 Vernier, Geneva, Switzerland

Address(es) of Applicant(s)

hereby apply for the grant of a standard patent
for an invention entitled

"METHOD FOR THE PREVENTION OF PHOTOTOXIC REACTIONS"

which is described in the accompanying complete specification.

DETAILS OF BASIC APPLICATION(S)
Number(s) of Basic Application(s)
927/83

Name(s) of Convention Country(ies) in which Basic
Application(s) were filed
Switzerland

Date(s) of Basic Application(s)
18 February 1983

APPLICATION ACCEPTED AND AMENDMENTS
ALLOWED

My/Our address for service is:
C/- Spruson & Ferguson
PATENT ATTORNEYS
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AUSTRALIA

Dated this EIGHTH day of FEBRUARY

L. GIVAUDAN & CIE

By: M.P. Anderson
Registered Patent Attorney

To: The Commissioner of Patents

SFP2

11/81
COMMONWEALTH OF AUSTRALIA
THE PATENTS ACT 1952
DECLARATION IN SUPPORT OF A
CONVENTION APPLICATION FOR A PATENT
In support of the Convention Application made for a patent for an invention entitled:

"METHOD FOR THE PREVENTION OF PHOTOTOXIC REACTIONS"

1. Roland Borer
of 10 Stockackerstrasse, 4153 Reinach, Switzerland

do solemnly and sincerely declare as follows:—

1. I am authorised by
   L. GIVAUDAN & CIE (Société Anonyme Vernier-Geneva, Switzerland)

   the applicant(s) for the patent to make this declaration on its/their behalf.

2. The basic application(s) as defined by Section 141 of the Act was/were made
in Switzerland
on February 18, 1983
by X the Applicant L. GIVAUDAN & CIE
   the inventor(s)

3. Georg Klecak, 5 Rheinparkstrasse, Birsfelden, Switzerland
   Peter Schudel, 16 Neugutstrasse, Grüt-Wetzikon, Switzerland
   Hans Ulrich Gonzenbach, 6bis rue de Lyon, Geneva, Switzerland
   Paul Tullen, 12 chemin Pernettes, Satigny, Switzerland

   is/are the actual inventor(s) of the invention and the facts upon
   which the applicant(s) is/are entitled to make the application are
   as follows:

   (X) the Applicant is the assignee of the invention from
   the inventor(s).

4. The basic application(s) referred to in paragraph 2 of this Declaration was/were the first application(s) made in a Convention country in respect of the invention as the subject of the application.

Declared at Basle this 23rd day of January 1984

The Commissioner of Patents,
COMMONWEALTH OF AUSTRALIA

Signature of Declarant(s)
1. A method for the prevention of phototoxic reactions on or in the skin and caused by odorant substances or odorant substance compositions upon exposure to the influence of light, which process comprises bringing into photochemical reaction 4-(1,1-dimethyl)-4'-methoxydibenzoylmethane as such or in solution with said odorant substance or said odorant substance composition in order to photochemically deactivate the phototoxic substance(s) being present in said odorant substance or said odorant substance composition, and then administering this latter odorant substance or odorant substance composition to the skin.

6. An odorant substance composition prone to cause phototoxic reactions which contains at least one of the ingredients of the group consisting of bergamot oil, lemon oil, lime oil, orange oil, grapefruit oil, angelica oil, cumin oil, methyl N-methylantranilate and 5-acetyl-1,1,2,3,3,6-hexamethylindane and also contains 4-(1,1-dimethylthyl)-4'-methoxydibenzoylmethane.
Complete Specification for the invention entitled:

"METHOD FOR THE PREVENTION OF PHOTOTOXIC REACTIONS"

The following statement is a full description of this invention, including the best method of performing it known to me/us:
Abstract

A method for the prevention of phototoxic reactions caused by odorant substances or odorant substance compositions is described. The method comprises using 4-(1,1-dimethylethyl)-4'-methoxydibenzoylmethane for this purpose.
It is known that a series of organoleptically-active substances, especially odorant substances, produce undesired (i.e. phototoxic) reactions on or in the skin when they are applied to the skin (e.g. as components of cosmetic preparations) and are thereupon exposed to the influence of light. These reactions can be accompanied by subjective and objective phenomena of the exposed skin such as itching, inflammations, swellings, reddenings, burnings.

The present invention is concerned with a method for the prevention of such phototoxic reactions caused by odorant substances or odorant substance compositions; the method comprises using for this purpose 4-(1,1-dimethyl-ethyl)-4'-methoxydibenzoylmethane, a substance which has been found to have a very good tolerance both dermally and systemically.

The invention is also concerned with odorant substances or odorant substance compositions which contain 4-(1,1-dimethyl-ethyl)-4'-methoxydibenzoylmethane.

Finally, the invention is also concerned with the use of 4-(1,1-dimethyl-ethyl)-4'-methoxydibenzoylmethane, also referred to hereinafter as "dibenzoylmethane", for the prevention of phototoxic reactions caused by odorant substances or odorant substance compositions.
The most important products which usually produce phototoxic reactions are odorant substance compositions of natural origin, especially a series of citrus oils such as, for example, bergamot oil, lemon oil, lime oil, orange oil and grapefruit oil. However, angelica oil or cumin oil can also be mentioned in this connection.

As synthetic, organoleptically-active substances which usually produce phototoxic reactions there can be mentioned, in particular, methyl N-methylanthranilate and 5-acetyl-1,1,2,3,3,6-hexamethyldiane ("Phantolide").

The amount of dibenzoylmethane to be added conveniently lies in the range of about 0.1 to about 5 weight percent, preferably about 0.1 to about 2 weight percent, of the product to be protected.

The dibenzoylmethane can be added to the product as such or dissolved in a solvent or solvent mixture (e.g. in ethanol).
The following Example illustrates the present invention:

Example

Determination of the phototoxic potential of various products; guinea pigs were used as the experimental animals.

The investigations were carried out under standard conditions. With the exception of the irradiation periods the animals were kept permanently in wire cages at a temperature of 22 ± 2°C and a relative atmospheric humidity of 45 ± 10%. The daylight cycle was 12 hours/day.

Diet: standard feed and fresh water ad libitum.

Light source: UV-Lamp Westinghouse FS 40 "Black Lamp"; energy: \(1 \times 10^4\) erg/cm\(^2\)/sec., spectrum: 320-400 nm, irradiation dosage: 20 j/cm\(^2\).

The male and female guinea pigs used weighed between 300-450 g.

Prior to the experimental periods it was ensured that all experimental animals were healthy.

The test material (with or without added dibenzoylmethane) was applied in the highest possible concentration which was initially non-irritating to the skin. Alcohol, acetone, water, petrolatum or other suitable solvents were used to dilute or suspend the test material. In addition, 2% of dimethyl sulphoxide were added to the solutions or incorporated into the preparation in order to increase the skin penetration.

The test preparations were used as such or optionally diluted.
Dosage: For the experiments the alcoholic, acetic or aqueous solutions were applied to the skin in an amount of 0.025 ml/cm^2 by means of a pipette. In the case of solutions in petrolatum or in the case of preparations such as creams, salves, lotions etc amounts of 0.01 ml/2 cm^2 were applied.

Observation periods: Observation and evaluation of the skin reaction was carried out 4, 24 and 48 hours after the application of the test material.

Experimental procedure: A group of 4 guinea pigs was used to determine the tolerance threshold of the individual test materials prior to the induction phase. In order to determine the highest possible concentration, the test material was applied to the flank (0.25 ml/2 cm^2) not only undiluted but also diluted or suspended in suitable solvents in concentrations of 30%, 10%, 3% and 1% (or when necessary in even lower concentrations) and left uncovered.

Experimental phase (induction phase): Both flanks of at least 10 guinea pigs were shaved at least 2 hours prior to the application of the test material. Thereupon, a maximum of 5 circles each of 2 cm^2 were marked on each flank. On 4 of these circular sites there was applied 0.025 ml of alcoholic, acetic or aqueous test solution (highest initially non-irritating concentration) or 0.01 ml of test solution, which was applied using other solvents or preparations such as creams, salves or lotions.

The fifth application site was in each case treated with a 0.1% alcoholic solution of 8-methoxypsoralen and served as the control.
30 minutes after the application of the test material the left flank of each experimental animal was exposed to a non-erythema producing UV-A irradiation (20 j/cm²). The right flank remained non-irradiated after the application of the test material and served as the control.

Observation and evaluation: The animals were investigated for erythema and oedema formation 4, 24 and 48 hours after the application of the test material. The skin reaction was evaluated either with −, which signified no reaction, or with +, which signified a positive reaction.
Table

Prevention of phototoxic effects by means of "dibenzoylemethane"

Irradiation dosage: 20 J UV-A/cm²

<table>
<thead>
<tr>
<th>&quot;Dibenzoylemethane&quot; %</th>
<th>0</th>
<th>0.25</th>
<th>0.5</th>
<th>0.75</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hours after application</td>
<td>4 24 48</td>
<td>4 24 48</td>
<td>4 24 48</td>
<td>4 24 48</td>
<td>4 24 48</td>
<td>4 24 48</td>
</tr>
<tr>
<td>Bergamot essence</td>
<td>+ + +</td>
<td>+ + -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
</tr>
<tr>
<td>Lemon essence</td>
<td>+ + +</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
</tr>
<tr>
<td>Orange essence</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
</tr>
<tr>
<td>Lime essence</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
</tr>
<tr>
<td>Cumin essence</td>
<td>+ + -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
</tr>
<tr>
<td>Angelica essence</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
</tr>
<tr>
<td>Rue essence</td>
<td>+ + +</td>
<td>+ + -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
</tr>
<tr>
<td>Methyl N-methylanthranilate</td>
<td>+ + -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
</tr>
<tr>
<td>5-Acetyl-1,1,2,3,3,6-hexamethyl-indane</td>
<td>+ + +</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
<td>+ - -</td>
</tr>
</tbody>
</table>
The claims defining the invention are as follows:

1. A method for the prevention of phototoxic reactions on or in the skin and caused by odorant substances or odorant substance compositions upon exposure to the influence of light, which process comprises bringing into photochemical reaction 4-(1,1-dimethyl)-4'-methoxydibenzoylmethane as such or in solution with said odorant substance or said odorant substance composition in order to photochemically deactivate the phototoxic substance(s) being present in said odorant substance or said odorant substance composition, and then administering this latter odorant substance or odorant substance composition to the skin.

2. A method for the prevention of phototoxic reactions caused by odorant substance compositions in accordance with Claim 1.

3. A method according to Claim 2, where bergamot oil is treated with 4-(1,1-dimethylethyl)-4'-methoxydibenzoylmethane.

4. A method according to any one of Claims 1 to 3, wherein 4-(1,1-dimethylethyl)-4'-methoxydibenzoylmethane is used in an amount of 0.1 to 5 weight percent.

5. A method according to Claim 4 wherein 4-(1,1-dimethylethyl)-4'-methoxydibenzoylmethane is used in an amount of 0.1 to 2 weight percent.

6. An odorant substance composition prone to cause phototoxic reactions which contains at least one of the ingredients of the group consisting of bergamot oil, lemon oil, lime oil, orange oil, grapefruit oil, angelica oil, cumin oil, methyl N-methylantranilate and 5-acetyl-1,1,2,3,3,6-hexamethylindane and also contains 4-(1,1-dimethylethyl)-4'-methoxydibenzoylmethane.

7. A composition according to Claim 6, wherein the odorant substance composition contains bergamot oil.

8. A composition according to Claim 5, 6 or 7, which contains 0.1 to 5 weight percent of 4-(1,1-dimethylethyl)-4'-methoxydibenzoylmethane.

9. A composition according to Claim 8 which contains 0.1 to 2 weight percent of 4-(1,1-dimethylethyl)-4'-methoxydibenzoylmethane.

DATED this TWENTY-EIGHTH day of JANUARY 1987
L GIVAUDAN & CIE

Patent Attorneys for the Applicant
SPRUSON & FERGUSON
24450/84