# Annex I to the CLH report

## Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),**
**Annex VI, Part 2**

# International Chemical Identification: Geraniol; (2*E*)-3,7-dimethylocta-2,6-dien-1-ol

**EC Number:** **203-377-1**
**CAS Number:** **106-24-1**
**Index Number:** **-**

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## CONTENTS

# 1 PHYSICAL HAZARDS

Classification for physical hazards is not a part of the CLH proposal for geraniol.

# 2 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

No studies have been located.

# 3 HEALTH HAZARDS

## 3.1 Skin sensitisation

### 3.1.1 Animal data

#### 3.1.1.1 STUDY 1-3 (LLNA, 3 separate assays)

**Study reference:**

Hagwall, L., Bäcktorp, C., Svensson, S., Nyman, G., Börje, A., Karlberg, A.T., 2007. Fragrance compound geraniol forms contact allergens on air exposure. Identification and quantification of oxidation products and effect on skin sensitization. Chemical Research in Toxicology 20, 807-814.

**Detailed study summary and results:**

**Test type**

LLNA, TG/GLP: not reported.

**Test substance**

1) Geraniol (Sigma Aldrich, Germany), purity: 99 %, vehicle: AOO

2) Geraniol (Sigma Aldrich, Germany), purity: 99 %, vehicle: AOO

Air-exposed for 10 weeks prior to testing resulting in 80% geraniol, 2.9% geranial, 0.66% neral, 0.73% geranyl formate, 1.2% 7-hydroperoxy-3,7-dimethyl-octa-2,5-diene-1,7-diol, 3,2% epoxygeraniol and 0,21% 3,7-dimethyl-octa-2,5-diene-1,7-diol.

3) Geraniol (Sigma Aldrich, Germany), purity: 99 %, vehicle: AOO

Air-exposed for 45 weeks prior to testing resulting in 20% geraniol, 3.8% geranial, 1.3% neral, 3.3% geranyl formate, 0.47% 7-hydroperoxy-3,7-dimethyl-octa-2,5-diene-1,7-diol, 3,5% epoxygeraniol and 0,57% 3,7-dimethyl-octa-2,5-diene-1,7-diol.

**Test animals**

Mice (CBA/Ca), female, 3 animals per group, age: 6-12 weeks old

**Administration/exposure**

Each test group received one of 5 concentrations: 1) 5%, 10%, 15%, 20% or 30%; 2) 1%, 3%, 6%, 10% or 20%; 3) 0.5%, 1%, 3%, 6% or 10% of geraniol in acetone:olive oil (AOO) 4:1, or the vehicle alone at a test volume of 25 µl applied on the dorsum of both ears on three consecutive days. On the 5$^{th}$ day after the first treatment, all mice were injected i.v. in the tail vein with 20 µCi of [3H]methyl thymidine. Five hours later the mice were euthanized and the draining auricular lymph nodes were excised and pooled for each test group. After separation of the cellular fraction, the incorporation of [3H]TdR in lymph node cells was measured by ß-scintillation counting and expressed as dpm (disintegrations per minute) per lymph node for each test group. Results were expressed as mean dmp/lymph node for each experimental group and as stimulation index SI, that is, the test group/control group ratio.

**Results**

1) Geraniol was shown to be sensitizing with an EC3 value of 22.4% (1.45 M).

2) Geraniol was shown to be sensitizing with an EC3 value of 4.4% (0.28 M).

3) Geraniol was shown to be sensitizing with an EC3 value of 5.8% (0.37 M).

No information on irritation was reported in any of the 3 studies.

### 3.1.1.2 STUDY 4 (LLNA) (also cited in REACH registration dossier)

**Study references:**

Lalko, J., Api., A.M., 2006. Investigation of the dermal sensitization potential of various essential oils in the local lymph node assay. Food and Chemical Toxicology 44, 739-746.

**Detailed study summary and results:**

**Test type**

LLNA, equivalent or similar to OECD 429

**Test substance**

Geraniol (IFF Inc., USA), purity: 98.5%, vehicle: 1:3 EtOH:DEP

**Test animals**

Mice (CBA/Ca), female, 4 animals per group, age: 8-12 weeks old

**Administration/exposure**

The assay was conducted according to the method of Kimber et al. (1992, 1994) as formalized in OECD Guideline 429 (OECD, 2002). Each group received one of 5 concentrations: 2.5%, 5%, 10%, 25%, or 50% of geraniol in the vehicle, or the vehicle alone at a test volume of 25 µl applied on the dorsum of both ears on

three consecutive days. On the 5th day after the first treatment, all mice were injected i.v. in the tail vein with 20 µCi of [3H]methyl thymidine. Five hours later the mice were euthanized and the draining auricular lymph nodes were excised and pooled for each test group. After separation of the cellular fraction, the incorporation of [3H]TdR in lymph node cells was measured by ß-scintillation counting and expressed as dpm (disintegrations per minute) per lymph node for each test group. For each concentration of test material, a stimulation index (SI) relative to the concurrent vehicle-treated control was calculated. Geraniol was considered a sensitizer if at least one concentration of the test material was observed to have an SI value of 3 (EC3) or more.

**Results**

An EC3 value of 11.4% was reported.

### 3.1.1.3 STUDY 5 (LLNA)

**Study references:**

*RIFM 2003. Local Lymph Node Assay on geraniol in 3:1 EtOH:DEP. RIFM report number 43812 (RIFM, Woodcliff Lake, NJ, USA), cited in:*

SCCS, 2012. Opinion on fragrance allergens in cosmetic products. Scientific Committee on Consumer Safety.

**Detailed study summary and results:**

A detailed summary of the study and results is not available in the SCCS opinion (SCCS 2012).

Geraniol, vehicle: 3:1 EtOH:DEP

An EC3 value of 11.4% was reported (.

### 3.1.1.4 STUDY 6 (LLNA) (also cited in REACH registration dossier)

**Study reference:**

*RIFM 2001j. Local Lymph Node Assay on geraniol in ethanol. RIFM report number 37069*

*(RIFM, Woodcliff Lake, NJ, USA), cited in:*

SCCS, 2012. Opinion on fragrance allergens in cosmetic products. Scientific Committee on Consumer Safety.

Lalko, J., Isola, D., Api, A.M., 2004. Ethanol and Diethyl Phthalate: Vehicle effects in the local lymph node assay. International Journal of Toxicology 23, 1717-177.

**Detailed study summary and results:**

**Test type**

LLNA, equivalent or similar to OECD 429

**Test substance**

Geraniol (Bush Boake Allen Limited, UK), purity: 98.5%, vehicle: EtOH

**Test animals**

Mice CBA/Ca, (male), 4 animals per group, age: 8-12 weeks old

**Administration/exposure**

The assay was conducted according to the method of Kimber et al. (1992, 1994). Each group received one of 5 concentrations: 1%, 3%, 10%, 30%, or 50% of geraniol in the vehicle, or the vehicle alone at a test volume of 25 µl applied on the dorsum of both ears on three consecutive days. On the 5th day after the first treatment, all mice were injected i.v. in the tail vein with 20 µCi of [3H]methyl thymidine. Five hours later the mice were euthanized and the draining auricular lymph nodes were excised and pooled for each test group. After separation of the cellular fraction, the incorporation of [3H]TdR in lymph node cells was measured by ß-scintillation counting and expressed as dpm (disintegrations per minute) per lymph node for each test group. For each concentration of test material, a stimulation index (SI) relative to the concurrent vehicle-treated control was calculated. Geraniol was considered a sensitizer if at least one concentration of the test material was observed to have an SI value of 3 (EC3) or more.

**Results**

An EC3 value of 5.6% was reported.

### 3.1.1.5 STUDY 7 (LLNA) (also cited in REACH registration dossier)

**Study reference:**

*RIFM, 2001k. Local Lymph Node Assay on geraniol in DEP. RIFM report number 37070 (RIFM, Woodcliff Lake, NJ, USA), cited in:*

SCCS, 2012. Opinion on fragrance allergens in cosmetic products. Scientific Committee on Consumer Safety.

Lalko, J., Isola, D., Api, A.M., 2004. Ethanol and Diethyl Phthalate: Vehicle effects in the local lymph node assay. International Journal of Toxicology 23, 1717-177.

**Detailed study summary and results:**

**Test type**

LLNA, equivalent or similar to OECD 429

**Test substance**

Geraniol (Bush Boake Allen Limited, UK), purity: 98.5%, vehicle: DEP

**Test animals**

Mice CBA/Ca, (male), 4 animals per group, age: 8-12 weeks old

**Administration/exposure**

The assay was conducted according to the method of Kimber et al. (1992, 1994). Each group received one of 5 concentrations: 1%, 3%, 10%, 30%, or 50% of geraniol in the vehicle, or the vehicle alone at a test volume of 25 µl applied on the dorsum of both ears on three consecutive days. On the 5th day after the first treatment, all mice were injected i.v. in the tail vein with 20 µCi of [3H]methyl thymidine. Five hours later the mice were euthanized and the draining auricular lymph nodes were excised and pooled for each test group. After separation of the cellular fraction, the incorporation of [3H]TdR in lymph node cells was measured by ß-scintillation counting and expressed as dpm (disintegrations per minute) per lymph node for each test group. For each concentration of test material, a stimulation index (SI) relative to the concurrent vehicle-treated control was calculated. Geraniol was considered a sensitizer if at least one concentration of the test material was observed to have an SI value of 3 (EC3) or more.

**Results**

An EC3 value of 11.8% was reported.

### 3.1.1.6 STUDY 8 (LLNA) (also cited in REACH registration dossier)

**Study reference:**

*RIFM, 2001l. Local Lymph Node Assay on geraniol in 1:3 EtOH:DEP. RIFM report number 37071 (RIFM, Woodcliff Lake, NJ, USA), cited in:*

SCCS, 2012. Opinion on fragrance allergens in cosmetic products. Scientific Committee on Consumer Safety.

Lalko, J., Isola, D., Api, A.M., 2004. Ethanol and Diethyl Phthalate: Vehicle effects in the local lymph node assay. International Journal of Toxicology 23, 1717-177.

**Detailed study summary and results:**

**Test type**

LLNA, equivalent or similar to OECD 429

**Test substance**

Geraniol (Bush Boake Allen Limited, UK), purity: 98.5%, vehicle: EtOH:DEP 1:3

**Test animals**

Mice CBA/Ca, (male), 4 animals per group, age: 8-12 weeks old

**Administration/exposure**

The assay was conducted according to the method of Kimber et al. (1992, 1994). Each group received one of 5 concentrations: 1%, 3%, 10%, 30%, or 50% of geraniol in the vehicle, or the vehicle alone at a test volume of 25 µl applied on the dorsum of both ears on three consecutive days. On the 5th day after the first treatment, all mice were injected i.v. in the tail vein with 20 µCi of [3H]methyl thymidine. Five hours later the mice were euthanized and the draining auricular lymph nodes were excised and pooled for each test group. After separation of the cellular fraction, the incorporation of [3H]TdR in lymph node cells was measured by ß-scintillation counting and expressed as dpm (disintegrations per minute) per lymph node for each test group. For each concentration of test material, a stimulation index (SI) relative to the concurrent vehicle-treated control was calculated. Geraniol was considered a sensitizer if at least one concentration of the test material was observed to have an SI value of 3 (EC3) or more.

**Results**

An EC3 value of 20.4% was reported.

### 3.1.1.7 STUDY 9 (LLNA) (also cited in REACH registration dossier)

**Study reference:**

*RIFM, 2001m. Local Lymph Node Assay on geraniol in 3:1 EtOH:DEP. RIFM report number 37072 (RIFM, Woodcliff Lake, NJ, USA), cited in:*

SCCS, 2012. Opinion on fragrance allergens in cosmetic products. Scientific Committee on Consumer Safety.

Lalko, J., Isola, D., Api, A.M., 2004. Ethanol and Diethyl Phthalate: Vehicle effects in the local lymph node assay. International Journal of Toxicology 23, 1717-177.

**Detailed study summary and results:**

**Test type**

LLNA, equivalent or similar to OECD 429

**Test substance**

Geraniol (Bush Boake Allen Limited, UK), purity: 98.5%, vehicle: EtOH:DEP 3:1

**Test animals**

Mice CBA/Ca, (male), 4 animals per group, age: 8-12 weeks old

**Administration/exposure**

The assay was conducted according to the method of Kimber et al. (1992, 1994). Each group received one of 5 concentrations: 1%, 3%, 10%, 30%, or 50% of geraniol in the vehicle, or the vehicle alone at a test volume of 25 µl applied on the dorsum of both ears on three consecutive days. On the 5th day after the first treatment, all mice were injected i.v. in the tail vein with 20 µCi of [3H]methyl thymidine. Five hours later the mice were euthanized and the draining auricular lymph nodes were excised and pooled for each test group. After separation of the cellular fraction, the incorporation of [3H]TdR in lymph node cells was measured by ß-scintillation counting and expressed as dpm (disintegrations per minute) per lymph node for each test group. For each concentration of test material, a stimulation index (SI) relative to the concurrent vehicle-treated control was calculated. Geraniol was considered a sensitizer if at least one concentration of the test material was observed to have an SI value of 3 (EC3) or more.

**Results**

An EC3 value of 25.8% was reported.

### 3.1.1.8 STUDY 10 (LLNA BrdU ELISA *ex vivo*)

**Study reference:**

Ulker, O.C., Kaymak, Y., Karakaya, A., 2014. Allergenicity evaluation of fragrance mix and its ingredients by using *ex vivo* local lymph node assay-BrdU endpoints. Food and Chemical Toxicology 65, 162-167.

**Detailed study summary and results:**

**Test type**

*Ex vivo* LLNA – BrdU ELISA, GLP compliant

**Test substance**

Geraniol (Fluka, Germany), vehicle: 4:1 acetone:olive oil (AOO)

**Test animals**

Mice (Balb/c), female, 4 animals per group, age: 8-12 weeks old

**Administration/exposure**

Five groups of mice were treated with 2.5, 10, 25 and 50 % geraniol, or the vehicle alone. The test substance or the vehicle alone was applied topically on the dorsum of both ears (25 µl per ear for three consecutive days at the same site). Mice were sacrificed 2 days after treatment, lymph nodes excised and homogenized,

and the released cells suspended in saline. Cells were suspended into 96-well culture plates and labelled with 1uM BrdU and the extent of BrdU incorporations were measured by ELISA. TH1 and TH2 cytokines released from lymph node cell culture were measured as contact sensitization endpoints. The responses to test substances exposure were characterized by stimulation index (SI) calculated as the ratio of the mean *ex vivo* BrdU incorporation (labelling index) for each treatment group vs that of the vehicle control group.

**Results**

Geraniol was shown to be sensitising with an EC3 value of 13.1%. Both TH1 and TH2 cytokines were increased by applied geraniol dose-dependently.

*Calculated stimulation index, geraniol*

| Applied concentration | 2.5% | 10% | 20% | 50% |
|---|---|---|---|---|
| SI | 1.98 | 2.25 | 3.31 | 4.12 |

### 3.1.1.9 STUDY 11-12 (GPMT) (two tests, different vehicles)

**Study reference:**

*RIFM, 1989. The sensitization potential of geraniol in guinea pigs. RIFM Report Number 15429. (RIFM, Woodcliff Lake, NJ, USA), cited in:*

Lapczynski, A., Bhatia, S.P., Foxenberg, R.J., Letizia, C.S., Api, A.M., 2008. Fragrance material review on geraniol. Food and Chemical Toxicology 46 Suppl 11, S160-170.

**Detailed study summary and results:**

A detailed summary of the study and results is not available in the article by Lapczynski *et al.*, which presents a review of the available data on sensitization for geraniol. Only the following data are presented:

**Test type**

Guinea pig maximization test according to the Magnusson and Kligman 1969 method

**Test substance**

Geraniol (no further data)

Vehicle:

1) Dobs/saline for intradermal induction, and acetone:PEG400 for occluded induction and challenge

2) Dobs/saline for intradermal induction, and acetone for occluded induction and challenge

**Test animals**

Guinea pig (albino Dunkin Hartley), 10 animals received test substance, no information on controls.

**Administration/exposure**

Two preliminary irritation tests were conducted prior to a Magnusson and Kligman guinea pig maximization test: Four animals were injected intradermally on the shaved flanks with 0.1 ml of 0.05%, 0.1%, 0.25% or 0.5% geraniol in 0.01 Dobs/saline. The reactions were examined 24 h later. Filter paper patches in aluminium patch test cups were saturated with 2.5%, 5%, 10%, 25% or 50% geraniol in acetone/PEG 400, and then applied to the shaved flanks of 4 guinea pigs. The patches remained in place for 24 h and the reactions sites were examined 24 and 48 h after patch removal.

Guinea pig maximization tests were conducted according to the Magnusson and Kligman (1969) method. Induction consisted of a series of 6 intradermal injections of the test material with and without FCA, followed 6-8 days later by a 48 h occluded patch application. The animals were challenged 12-14 days later by an occluded 24 h patch application. Reactions were read 24 and 48 h after patch removal. Geraniol at 0.1% in Dobs/saline for intradermal induction, at 1) 50% in 70% acetone/30% PEG 400 for occluded induction application and at 10% in 70% acetone/30% PEG 400 for occluded challenge or 2) at 50% in acetone for occluded induction application and at 10% in acetone for occluded challenge was evaluated in 10 albino Dunkin Hartley guinea pigs. Two further challenges were made at weekly intervals. This experiment was repeated three times.

**Results**

Preliminary irritation tests:

No effect was observed at intradermal injections of 0.05% or 0.1% geraniol in Dobs/saline. Irritation was observed at injections of 0.25% and 0.5% geraniol in Dobs/saline. Geraniol at 0.1% was selected for the intradermal induction phase. No effects were observed at 2.5% and 5% geraniol in acetone:PEG400 applied topically. A concentration at 50% was selected as the topical induction dose, and at 10% as the challenge dose.

Guinea pig maximization tests:

1) No sensitization reactions were observed;

2) Sensitization reactions were observed.

### 3.1.1.10 STUDY 13 (GPMT)

**Study reference:**

*RIFM, 1977. Skin irritation and capacity of allergenic sensitization of geraniol on guinea pigs. RIFM Report Number 9473. (RIFM, Woodcliff Lake, NJ, USA), cited in:*

Lapczynski, A., Bhatia, S.P., Foxenberg, R.J., Letizia, C.S., Api, A.M., 2008. Fragrance material review on geraniol. Food and Chemical Toxicology 46 Suppl 11, S160-170.

**Detailed study summary and results:**

A detailed summary of the study and results is not available in the article by Lapczynski *et al.*, which presents a review of the available data on sensitization for geraniol. Only the following data are presented:

**Test type**

Guinea pig maximation test according to the Magnusson and Kligman 1969 method

**Test substance**

Geraniol (no further data), vehicle: petrolatum

**Test animals**

Guinea pig (albino Dunkin Hartley), 6 animals received test substance, no information on controls.

**Administration/exposure**

A primary irritation test was conducted prior to the Guinea pig maximation test. A single application of 0.025 ml of geraniol at 3100% [*stated so in the reference*] in ethanol was made to groups of 6–8 guinea pigs on 2 $cm^2$ area of clipped flank skin. Skin reactions were read 24 h later to determine minimal irritant and maximal non-irritant concentration by all-or-none criterion.

Guinea pig maximization tests were conducted according to the Magnusson and Kligman (1969) method. Induction consisted of a series of 6 intradermal injections of geraniol 5% in petrolatum with and without FCA, followed 6–8 days later by a 48 h occluded patch application. The animals were challenged 12–14 days later by an occluded 24 h patch application. Reactions were read 24 and 48 h after patch removal.

**Results**

Concentration of 10% was selected as the highest non-irritant concentration, and 30% as the lowest irritation concentration in the primary irritation test.

In the Guinea pig maximization tests, three (3/6) sensitization reactions were observed with 5% geraniol for intradermal induction, 30% in petrolatum for occluded induction application and 10% in petrolatum for occluded challenge patch application.

### 3.1.1.11 STUDY 14 (GPMT) (also cited in REACH registration dossier)

**Study reference:**

Klecak, G., Geleick, H., Frey, J.R., 1977. Screening of fragrance materials for allergenicity in the guinea pig I: Comparison of four testing methods. Journal of the Society of Cosmetic Chemists Japan 28, 53-66.

**Detailed study summary and results:**

**Test type**

Guinea pig maximation test according to the Magnusson and Kligman 1969 method

**Test substance**

Geraniol (no further data), vehicle: Petrolatum

**Test animals**

Guinea pig (Himalayan white-spotted), male and female, 400-500 g, male and females

**Administration/exposure**

A preliminary irritation test was conducted. 0.025 ml of undiluted compound and of its progressively diluted solutions were applied to an area measuring 2 $cm^2$ clipped flank skin of 6-8 animals pr. group. The lowest concentrations to produce mild erythema in at least 25% of the animals after single or 21 daily applications were selected as the minimal irritating concentration for the main study.

Guinea pig maximization tests were conducted according to the Magnusson and Kligman (1969) method. Induction consisted of intradermal injections of 5% geraniol in petrolatum with or without FCA, each injection being given twice. In addition, 25% geraniol in petrolatum was applied on day 8 to a clipped skin area of the neck and was kept under occlusive bandage for 2 days (total dose 20 mg intradermally plus 250 mg epicutaneously). On day 21 the animals were challenged by an occluded 24 h patch application, and reactions were read 24 h and 48 h after patch removal.

**Results**

Sensitization reactions were observed with 5% geraniol for intradermal induction, 25% geraniol in petrolatum for patch induction and with geraniol at sub-irritant concentration at challenge.

### 3.1.1.12 STUDY 15 (GPMT) (also cited in REACH registration dossier)

**Study reference:**

*Ishihara, M., Itoh, M., Nishimura, M., Kinoshita, M., Kantoh, H., Nogami, T., Yamada, K., 1986. Closed epicutaneous test. Skin Research 28 (Suppl. 2), 230-240, cited in:*

Lapczynski, A., Bhatia, S.P., Foxenberg, R.J., Letizia, C.S., Api, A.M., 2008. Fragrance material review on geraniol. Food and Chemical Toxicology 46 Suppl 11, S160-170.

**Detailed study summary and results:**

A detailed summary of the study and results is not available in the article by Lapczynski *et al.*, which presents a review of the available data on sensitization for geraniol. Only the following data are presented:

**Test type**

Guinea pig maximation test according to the Magnusson and Kligman 1969 method

**Test substance**

Geraniol (no further data), vehicle: not reported

**Test animals**

Guinea pig, number of animals not reported

**Administration/exposure**

Guinea pig maximization tests were conducted according to the Magnusson and Kligman (1969) method. Induction consisted of a series of 6 intradermal injections of geraniol 5% in petrolatum with and without FCA, followed 6-8 days later by a 48 h occluded patch application. The animals were challenged 12-14 days later by an occluded 24 h patch application. Reactions were read 24 and 48 h after patch removal.

**Results**

Sensitization reactions were observed with 10% geraniol for both intradermal induction and challenge phase of the study.

### 3.1.1.13 STUDY 16 (Buehler)

**Study reference:**

*RIFM, 1992. Delayed contact hypersensitivity study of geraniol in guinea pigs (Buehler Technique). RIFM Report Number 17636. (RIFM, Woodcliff Lake, NJ, USA),* cited in:

Lapczynski, A., Bhatia, S.P., Foxenberg, R.J., Letizia, C.S., Api, A.M., 2008. Fragrance material review on geraniol. Food and Chemical Toxicology 46 Suppl 11, S160-170.

**Detailed study summary and results:**

A detailed summary of the study and results is not available in the article by Lapczynski *et al.*, which presents a review of the available data on sensitisation for geraniol. Only the following data are presented:

**Test type:**

Buehler test

**Test substance**

Geraniol (no further data), vehicle: DEP

**Test animals**

Guinea pig, number of animals per challenge dose not stated, in total 20 animals

**Administration/exposure:**

Animals were induced with 25% geraniol in DEP and challenged with 2.5%, 7.5% or 25% in DEP.

**Results**

No sensitisation observed.

### 3.1.2 Human data

#### 3.1.2.1 STUDY 1 (Patch test, selected)

**Study reference:**

Geier J, Uter W, Lessmann H, Schnuch A: Fragrance mix I and II: results of breakdown tests. Flavour Fragr. J. 2015, 30, 264–247.

**Detailed study summary and results:**

The IVDK (a network of departments of Dermatology in Germany, Austria and Switzerland) has performed a retrospective study of patch test data on the standardised fragrance mixtures Fragrance Mix I and II (FMI and FMII) obtained in the period from 1998-2013 and 2005-2013, respectively. Geraniol is a component of FMI (1% geraniol). In cases where positive reactions were observed for FMI, testing of the full mix breakdown (and other fragrance allergens) have been done. FMI was patch tested in 141,372 patients in 1998–2013. Of these 13,074 patients (9.25%) had a positive reaction. Time trends were analysed by dividing the time span into eight 2-year periods. The FM I full mix breakdown was tested in 2798 patients with a positive reaction to FM I. The results obtained with geraniol alone are based on patch tests with 1% geraniol in petrolatum.

Description of test method as cited from Geier et al. 2015: "*Diagnosing contact sensitization is done by patch testing. Briefly, during this procedure, the incriminated allergen, incorporated in a vehicle (usually petrolatum or water) in a standardized concentration, is filled into a test chamber which is applied occlusively on the patient's upper back for 1 or 2 days. After removal of the patches, reactions in the test areas are observed at least until 3 days after the application. In case of an allergen-specific sensitization, a positive reaction with erythema, infiltration and possibly papules (+), additionally vesicles (++), or even coalescing vesicles (+++) occurs, depending on the degree of sensitization. Patients, who are not sensitized, usually show no reaction at all; however, in some cases, irritant or doubtful reactions can occur, which are coded as 'ir' and '?', respectively. Within the IVDK, patch tests are performed according to international and DKG guidelines [ref]. All patch test preparations were obtained from Almirall Hermal, Reinbek, Germany*."

Patch test results at day three were evaluated (except in a few cases where no reading could be done at day 3, a day 4 reading was chosen instead). Statistical analysis and data management were done using SAS software (SAS 9.3, SAS Institute, Cary, NC, USA).

The results for geraniol showed that during the period 1998-2013 5.5% of the 2798 selected (FMI postitive) patients were tested positive for geraniol. The results divided into time spans are listed in the table below (note that the patient counts of the single time periods to not sum up to 2798 as FMI and its single components were tested in different time periods in 66 patients):

*IVDK results of retrospective analysis of patch tests with geraniol 1% in petrolatum:*

| Year, patient count | 1998-1999 n = 162 | 2000-2001 n = 139 | 2002-2003 n = 249 | 2004-2005 n = 281 | 2006-2007 n = 285 | 2008-2009 n = 469 | 2010-2011 n = 634 | 2012-2013, n = 513 | 1998-2013 n = 2798 |
|---|---|---|---|---|---|---|---|---|---|
| Percent positive reactions (95% conf. intervals) | 4.3% (1.8-8.7) | 2.2% (0.4-6.2) | 7.6% (4.7-11.7) | 4.3% (2.2-7.3) | 5.6% (3.2-9.0) | 4.3% (2.6-6.5) | 6.3% (4.5-8.5) | 5.3% (3.5-7.6) | **5.5% (4.7-6.4)** |

### 3.1.2.2 STUDY 2 (Patch test, selected)

**Study reference:**

Nardelli, A., Carbonez, A., Drieghe, J., Goossens, A., 2013. Results of patch testing with fragrance mix 1, fragrance mix 2, and their ingredients, and Myroxylon pereirae and colophonium, over a 21-year period. Contact Dermatitis 68, 307–313.

**Detailed study summary and results:**

The Department of Dermatology at University Hospital St Rafael, Belgium, has performed a retrospective study of patch test data for 13332 patients who had been patch tested in the period from 1990-2011. A total of 13114 patients were tested with FM I (starting from 1990). The number of patients reacting to FM I (which includes 1% geraniol) was 940. Subsequent patch testing was in done with the individual ingredients of the fragrance mixture.

Description of test method as cited from Nardelli et al., 2013: *"All subjects had been tested with the European baseline series (Trolab, Hermal, Reinbeck, Germany) containing FM 1, M. pereirae (balsam of Peru), and colophonium. Since 2002, 3927 have been tested with HICC 5% pet., and from 2005, 3416 have been tested with FM 2. The patients reacting to FM 1 and FM 2 were, in most cases, tested with the individual ingredients, and some of the subjects were occasionally also tested with other fragrance*

*components. The patch tests were administered with Van der Bend patch test chambers (Van der Bend, Brielle, The Netherlands) applied on the back with Micropore™ (3M Health Care, Borken, Germany), and fixed with Fixomull (Beiersdorf, Hamburg, Germany), and later with Mefix (Mölnlycke Health Care, Göteborg, Sweden). The patch test readings were performed according to the international guidelines of the International Contact Dermatitis Research Group (12) after 2 days, 3 days (exceptionally), and 4 days, and sometimes later."*

Statistical analysis of the patch data were performed with SAS™ version 9.2 (SAS Institute, Cary, NC, USA).

The results showed that 5.5% of the selected patients (52/940) had positive reactions for geraniol (1% in petrolatum).

#### 3.1.2.3 STUDY 3 (Patch test, selected)

**Study reference:**

Turcic, P., Lipozencic, J., Milavec-Puretic, V., Kulisic, S.M., 2011. Contact allergy caused by fragrance mix and Myroxylon pereirae (balsam of Peru) - a retrospective study. Collegium Antropologicum 35, 83-87.

**Detailed study summary and results:**

The aim of the study by Turcic et al., was to determine the incidence of fragrance-induced contact allergy dermatitis (CAD) using a specific fragrance mix. Patch testing was conducted during 2001–2005 in Zagreb, Croatia, and performed on 27815 patients with suspected CAD. Geraniol (5% in petrolatum) was tested in 157 selected patients positive to fragrance mix (FM).

Description of test method as cited from Turcic et al., 2011: "*Patch-test allergens were applied on the patients' upper back with 2-day occlusion. According to the International Contact Dermatitis Research Group (ICDRG) system, the tests were read 48 and 72 hours after their application*[21,22]*. The test results were interpreted using the following scale: negative reaction (0); macular erythema (?); erythema/in filtration and possibly papules (1+); erythematous papules and/or vesicles (2+); spreading blisters and/or crust with ulceration (3+); and irritant reaction (IR); whereby 1+, 2+ and 3+ were considered positive allergic reactions*[21]".

Statistical analysis was performed using the STATISTICA software, Version 7.1. (StatSoft, Inc.).

The results showed that among the 157 selected patients with positive reactions to FM, 20.4% (32/157) had positive reactions to geraniol (5% in petrolatum).

### 3.1.2.4 STUDY 4 (Patch test, selected)

**Study reference:**

Cuesta, L., Silvestre, J.F., Toledo, F., Lucas, A., Pérez-Crespo, M., Ballester, I., 2010. Fragrance contact allergy: a 4-year retrospective study. Contact Dermatitis 63, 77–84.

**Detailed study summary and results:**

The Department of Dermatology, Hospital General Universitario in Alicante, Spain performed a 4-year (2004-2008) retrospective study of patients tested with the Spanish baseline series and/or fragrance series. A total of 1253 patients were patch tested with the baseline Spanish Group series. A total of 86 patients were tested with the Chemotechnique® fragrance series. The objective of the study was to define the characteristics of the population allergic to perfumes, to determine the usefulness of markers of fragrance allergy in the baseline GEIDAC series, and to describe the contribution made by the fragrance series to the data obtained with the baseline series.

Description of test method as cited from Cuesta et al., 2010: *"The allergens used both in the standard series and in the fragrance series were supplied by Chemotechnique Diagnostics®. The markers of the baseline Spanish Group series used in our study to detect fragrance allergic contact dermatitis were: the 'traditional' markers (M. pereirae and FM I), hydroxyisohexyl 3-cyclohexene carboxaldehyde (included as of October 2005), and FM II (included as of January 2007)."*

*"The patches were prepared using Finn Chambers® fixed with Scanpor® adhesive and removed after 2D in contact with the skin. Readings were taken at D2 and D4, with the evaluation criteria (+, ++, and +++) recommended by the ICDRG. If the result was doubtful, a late reading was taken at D7. The relevance was considered current if the clinical picture could be attributed totally or partially to the fragrance obtained, past if this positivity explained only previous dermatitis, and unknown if the clinical picture could not be attributed to the use of these fragrances. Patients who were positive to any fragrance marker in the GEIDAC baseline series (M. pereirae,FM I, hydroxyisohexyl 3-cyclohexene carboxaldehyde,or FM II) were identified, and the percentage of patients positive to each of the markers was determined."*

The results showed that among the patients tested with the Chemotechnique® fragrance series 19.8% of the selected patients (17/86) had positive reactions to geraniol (2% in petrolatum).

It was concluded that the fragrance markers detect the majority of cases of fragrance contact allergy. Furthermore it was recommended to include FM II in the Spanish baseline series, as in the European baseline series, and to use a specific fragrance series to study patients allergic to a fragrance marker.

### 3.1.2.5 STUDY 5 (Patch test, selected)

**Study reference:**

Uter, W., Geier, J., Frosch, P., Schnuch, A., 2010. Contact allergy to fragrances: current patch test results (2005-2008) from the Information Network of Departments of Dermatology. Contact Dermatitis 63, 254-261.

**Detailed study summary and results:**

The IVDK (a network of departments of Dermatology in Germany, Austria and Switzerland) has performed a retrospective study of patch test data from a multicentre project. During 2005-2008, the frequency of contact sensitization to fragrance allergens in patients routinely patch tested for suspected allergic contact dermatitis with the baseline series and special series (including geraniol) was investigated in a total of 40709 patients. Geraniol was tested as a single constituent in 5695 selected patients as part of a special breakdown series of fragrance mix (FM) I.

Description of patch test as cited from Uter et al., 2010: "*The IVDK (www.ivdk.org), a contact allergy surveillance network in Germany, Switzerland and Austria, has been described elsewhere. Briefly, results for all patients patch tested in the participating departments are electronically recorded, along with important demographic and clinical data. The diagnostic procedure follows international guidelines (9) that have been further refined by the German Contact Dermatitis Research Group (10), of which all IVDK participants are members."*

Statistical analysis of the data was performed using the statistical software package SAS (version 9.2, SAS Institute, Cary, NC, USA).

The results showed that 0.87% (95% CI: 0.63-1.1%) of the selected patients (50/5695) were tested positive for geraniol (1% in petrolatum).

### 3.1.2.6 STUDY 6-7 (Patch test, selected)

**Study reference:**

Uter, W., Geier, J., Schnuch, A., Frosch, P.J., 2007. Patch test results with patients' own perfumes, deodorants and shaving lotions: results of the IVDK 1998-2002. Journal of the European Academy of Dermatology and Venerology 21, 374-379.

**Detailed study summary and results:**

The IVDK (a network of departments of Dermatology in Germany, Austria and Switzerland) has performed a retrospective study of patch test data from a multicentre project in order to assess the value of patch testing patients' own perfumes, eau de toilette, deodorants and shaving lotions with regard to diagnosing contact

allergy to fragrances, and an analysis of the spectrum of concurrent patch test reactions to single fragrance allergens. During 1998-2002, a total of 1468 patients (out of 48381 patients) were patch tested with 2557 single products, i.e. the patient's own perfumes, deodorants, shaving lotions etc. Geraniol was tested at 1% in petrolatum in 29 patients tested positive to their own deodorant and in 141 patients tested negative to their own deodorant.

Description of patch test as cited from Uter et al., 2007: *"The methods and objectives of the contact allergy surveillance network IVDK have been described before.[10] In brief; the patch test results along with a standardized set of demographic and clinical data of all patients attending one of the participating centres are collected. The procedure follows current international guidelines[11] further amended by the German Contact Dermatitis Research Group (DKG), [12] of which all IVDK partners are members.*"

Statistical analysis of the data was performed using the statistical software package SAS (version 8.1, SAS Institute, Cary, NC, USA).

The results showed that 6.9% of the patients (2/29) tested positive to their own deodorant were tested positive for geraniol and that 0% of the patients (0/141) tested negative to their own deodorant were tested positive for geraniol (1% in petrolatum).

#### 3.1.2.7 STUDY 8 (Patch test, selected)

**Study reference:**

Vocanson, M., Goujon, C., Chabeau, G., Castelain, M., Valeyrie, M., Floc'h, F., Maliverney, C., Gard, A., Nicolas, J.F., 2006. The skin allergenic properties of chemicals may depend on contaminants - Evidence from studies on coumarin. International Archives of Allergy and Immunology 140, 231-238.

**Detailed study summary and results:**

The aim of the study by Vocanson et al., was to test the importance of purity in the skin allergenic properties of a chemical exemplified by coumarin. A total of 30 patients allergic to their own perfumed product were recruited in 12 months in a multicentre study involving 7 dermatoallergology departments. The inclusion criterion was the presence of a relevant positive patch test to their own perfumed product. Nineteen of the 30 patients were patch tested with the first 8 allergens of the fragrance series (including geraniol) in addition to coumarin.

Description of patch test as cited from Vocanson et al., 2006: "*All patients underwent patch testing. Patch testing was done on the skin on the back using Finn Chambers on Scanpor (dc 8 mm).*" ... "*Readings were done after 48/72 h and results were scored using the International Contact Dermatitis Research Group*

*criteria [7] : – = negative; ? = doubtful; + = weak reaction (no vesicle); ++ = strong reaction (edema and vesicles); +++ = extreme reaction (ulceration, bullies); IR = irritant reaction; NT = not tested*."

The results showed that 21.1% of the patients (4/19) positive to their own perfumed product were tested positive for geraniol (concentration and vehicle not reported).

#### 3.1.2.8 STUDY 9 (Patch test, selected)

**Study reference:**

Temesvari, E., Nemeth, I., Balo-Banga, M.J., Husz, S., Kohanka, V., Somos, Z., Judak, R., Remenyik, E.V.A., Szegedi, A., Nebenfuhrer, L., Meszaros, C., Horvath, A., 2002. Multicentre study of fragrance allergy in Hungary: immediate and late type reactions. Contact Dermatitis 46, 325-330.

**Detailed study summary and results:**

The frequency of fragrance contact sensitisation in Hungary was investigated in a multicentre study from 1998 to 1999 where a total of 3604 patients were tested with fragrance mix (FM). A sub-group of 160 FM hypersensitive patients were also tested with the individuel FM constituents including geraniol.

Description of patch test as cited from Temesvari et al., 2002: "*The methodology and evaluation of the tests followed international standards. The skin lesions were evaluated at 20, 40, and 60 min of testing, and at 24, 48 and 72 h after a 24-h application. In the immediate reactions, we also evaluated those lesions of urticaria as positive that were clearly manifest at 40 min (7, 12).*"

The results showed that 7.5% of the selected patients (12/160) were tested positive for geraniol (concentration and vehicle not reported).

#### 3.1.2.9 STUDY 10 (Patch test, selected)

**Study reference:**

Wohrl, S., Hemmer, W., Focke, M., Gotz, M., Jarisch, R., 2001. The significance of fragrance mix, balsam of Peru, colophony, and propolis as screening tools in the detection of fragrance allergy. British Journal of Dermatology 145, 268-273.

**Detailed study summary and results:**

The aim of the study by Wohrl *et al.* was to determine the usefulness of adding propolis to the European standard series to test for fragrance allergy. For this purpose between 1997 and 2000 a total of 2660 patients were patch tested with a standard patch test series. In a prospective study 747 patients suspected of fragrance allergy were tested further with a special fragrance series (including geraniol at 1% in petrolatum and 1% sorbitan sesquioleate, SSO).

Description of patch test as cited from Wöhrl *et al.* 2001: "*The readings were done after 72 h and scored according to the recommendations of the International Contact Dermatitis Research Group (ICDRG).*"

The results showed that 0.9% of the patients (7/747) suspected of fragrance allergy were tested positive for geraniol.

### 3.1.2.10 STUDY 11 (Patch test, selected)

**Study reference:**

Brites, M.M., Goncalo, M., Figueiredo, A., 2000. Contact allergy to fragrance mix - a 10-year study. Contact Dermatitis 43, 181-182.

**Detailed study summary and results:**

A total of 2600 patients were patch tested with fragrance mix (FM) during a 10-year period from 1989 to 1999. A sub-group of 226 selected FM-reactive patients were also tested with the individuel FM constituents including geraniol at 1% in petrolatum.

The method of patch testing was not described by Brites et al., 2000.

The results of the study showed that 8.4% of the selected patients (19/226) were tested positive for geraniol.

### 3.1.2.11 STUDY 12 (Patch test, selected)

**Study reference:**

Buckley, D.A., Rycroft, R.J.G., White, I. R., McFadden, J.P., 2000. Contact allergy to individual fragrance mix constituents in relation to primary site of dermatitis. Contact Dermatitis 43, 304-305.

**Detailed study summary and results:**

A total of 23660 patients were patch tested with fragrance mix (FM) during a 15-year period from 1984 to 1998. A total of 1811 patients were positive to FM. A sub-group of 1112 patients were tested with the individuel FM constituents including geraniol at 1% in petrolatum. Of these a total of 934 patients had positive patch test reactions to at least one fragrance mix constituent.

The method of patch testing was not described by Buckley et al., 2000.

The results showed that 6.0% of the selected patients (67/1112) were tested positive for geraniol.

### 3.1.2.12 STUDY 13 (Patch test, selected)

**Study reference:**

Kiec-Swierczynska, M., Krecisz, B., 2000. Occupational skin diseases among the nurses in the region of Lodz. International Journal of Occupational Medicine and Environmental Health 13, 179-184.

**Detailed study summary and results:**

The aim of the study by Kiec-Swierczynska & Krecisz 2000 was to assess the sources of occupational dermatopathies among the nurses subjected to medical examinations at the Nofer Institute of Occupational Medicine in Lodz, Poland, during a five-year period from 1995-1999. A total of 223 nurses with suspected occupational skin diseases were patch tested with the European Standard set supplemented with several other chemicals and including geraniol at 2%.

Description of patch test as cited from Kiec-Swierczynska & Krecisz 2000: "*The patch tests were applied and the results interpreted according to the JCDRG recommendations (8).*"

The results showed that 0.4% of the nurses (1/223) were tested positive for geraniol.

### 3.1.2.13 STUDY 14 (Patch test, selected)

**Study reference:**

Sugiura, M., Hayakawa, R., Kato, Y., Sugiura, K., Hashimoto, R., 2000. Results of patch testing with lavender oil in Japan. Contact Dermatitis 43, 157-160.

**Detailed study summary and results:**

A total of 1483 patients with suspected cosmetic contact dermatitis were patch tested with essential oils, including geraniol at 5% in petrolatum, from 1990 to 1998 in Nagoya, Japan.

Description of patch test as cited from Sugiura et al., 2000: "*Using Finn Chambers and Scanpor tape, we performed 2-day closed patch testing with the 10 fragrances on the upper back of patients suspected of having cosmetic contact dermatitis. Readings were done at 1 h and 1 day after removal, according to ICDRG recommendations. We diagnosed contact allergy when patch test reactions were $^{1}$ or $\pm^{1}$ at 1 day after removal (11).*"

The results showed that 0.3% of the patients (4/1483) were tested positive for geraniol.

### 3.1.2.14 STUDY 15 (Patch test, selected)

**Study reference:**

Bordalo O., Pereira, F., Silva, E., Barros, M.A., Goncalo M., Goncalo S., Brandao, M., Silva, R., Faria, A., Correia, T., Brandao, M., Baptista, A., 1999. Dermite de contacto alérgica a perfumes em cosméticos. Bol Inform Grupo Port Estudo Dermites Contacto 13, 22-25..

**Detailed study summary and results:**

A detailed summary of the study and results cannot be presented as the original article is in Portuguese. The following information is based on the abstract in English in the article.

A multicentre study was performed in 10 centres in order to detect and evaluate contact allergy to fragrance in cosmetics in the Portuguese population. From 1990-1997, 21205 patients with suspected contact dermatitis were patch tested with the CPEDC Standard Series. The patients with positive reactions to fragrance mix (FM) were retested, whenever possible, with the individual constituents of the mix. Over this period, 12118 patients had at least one positive reaction, and 1597 reacted to FM. Of these, 542 patients were retested with the 9 individual constituents of the FM.

The results showed that 10.7% of the patients (58/542) were tested positive for geraniol (concentration and vehicle not reported).

### 3.1.2.15 STUDY 16 (Patch test, selected)

**Study reference:**

Hendriks, S.A., van Ginkel, C.J., 1999. Evaluation of the fragrance mix in the European standard series. Contact Dermatitis 41, 161-162.

**Detailed study summary and results:**

In an evaluation of the fragrance mix in the European standard series a total of 757 patients suspected of allergy to cosmetics from University Hospital Utrecht, The Netherlands were patch tested between 1994 and 1998 with the European standard series, including fragrance mix (FM). The 50 fragrance-mix-positive/component-positive patients were tested with the 8 separate components, including geraniol at 2% in sorbitan sesquioleate (SSO, 1%).

The method of patch testing was not described by Hendriks & van Ginkel., 1999.

The results showed that 6.0% of the (3/50) were tested positive for geraniol.

### 3.1.2.16 STUDY 17 (Patch test, selected)

**Study reference:**

Katsarma, G., Gawkrodger, D.J., 1999. Suspected fragrance allergy requires extended patch testing to individual fragrance allergens. Contact Dermatitis 41, 193-197.

**Detailed study summary and results:**

This study was performed to evaluate the efficacy of fragrance mix (FM) as a screen for fragrance allergy. A total of 91 patients with positive allergic reactions to FM, to 1 of the 8 ingredients of FM, to 1 of 14 other fragrance materials, or to their own perfume were identified out of 744 consecutive unselected patients patch tested in 1994-1995 at Department of Dermatology, Royal Hallamshire Hospital, Sheffield, UK. Geraniol was tested in 40 FM-allergic patients identified among the 91 patients with positive allergic reactions to FM, to 1 of the 8 ingredients of FM, to 1 of 14 other fragrance materials, or to their own perfume.

Description of patch test as cited from Katsarma and Gawkrodger, 1999: "*The materials were applied in Finn Chambers on Scanpor to the upper back, left on for 2 days (D), and read at D2 and D4, using the International Contact Dermatitis Research Group's grading system. Data were collected from each patient using a form on which were recorded demographic information (i.e., age, sex and occupation), dermatitis site and type, any personal history of atopy, the test results and the final diagnosis.*"

The results that 0% of the patients (0/40) were tested positive for geraniol (in petrolatum, concentration not reported).

### 3.1.2.17 STUDY 18 (Patch test, selected)

**Study reference:**

Katsarou, A., Armenaka, M., Kalogeromitros, D., Koufou, V., Georgala, S., 1999. Contact reactions to fragrances. Annals of Allergy, Asthma and Immunology 82, 449-455.

**Detailed study summary and results:**

The aim of the study was to investigate the different types of allergic skin reactions to fragrance compounds. A total of 4975 patients with suspected contact dermatitis were patch tested between 1985 and 1996 at the Skin Test Laboratory, Department of Dermatology, University of Athens, "A. Sygros" Hospital, Athens, Greece. Out of the 4975 patients a subgroup of 38 patients positive to fragrance mix were selected to further patch tests with individual components of the fragrance mix, including geraniol at 1% in petrolatum.

Description of patch test as cited from Katsarou et al., 1999: "*Patch testing was always performed when dermatitis was not active. Patch tests were performed according to the International Contact Dermatitis Research Group guidelines. Allergens were supplied by Hermal (Trolab) and applied to the lower back*

*using Finn chambers (Epitest) fixed by Scanpor tape (Norges plaster). Patches were removed at 48 hours and read by a staff dermatologist 30 minutes after removal and again at 92 hours.*"

The results showed that 13.2% of the selected patients (5/38) were tested positive for geraniol.

### 3.1.2.18 STUDY 19 (Patch test, selected) (also cited in REACH registration dossier)

**Study reference:**

Schauder, S., Ippen, H., 1997. Contact and photocontact sensibility to sunscreens. Contact Dermatitis 37, 221-232.

**Detailed study summary and results:**

The aim of the review was to evaluate 15 years of sunscreen allergy and photoallergy clinical testing. From 1981-1996, a total of 402 patients with suspected clinical photosensitivity were patch and photo-patch tested with commercial sunscreens and facial cosmetics at the Photobiology unit, Department of Dermatology, University of Gottingen, Germany. A sub-group of 41 patients sensitive to UV absorbers was tested with geraniol at 1% in petrolatum.

Description of patch test as cited from Schauder and Ippen, 1997: *"Patch tests were performed according to the guidelines of the ICDRG which correspond to those of the DKG."*

The results showed that 2.4% of the selected patients (1/41) were tested positive for geraniol.

### 3.1.2.19 STUDY 20 (Patch test, selected)

**Study reference:**

Larsen, W., Nakayama, H., Lindberg, M., Fischer, T., Elsner, P., Burrows, D., Jordan, W., Shaw, S., Wilkinson, J., Marks, J., Jr., Sugawara, M., Nethercott, J., 1996. Fragrance contact dermatitis: a worldwide multicentre investigation (Part I). American journal of contact dermatitis: official journal of the American Contact Dermatitis Society 7, 77-83.

**Detailed study summary and results:**

The aim of the study was to determine the prevalence of responses to selected fragrance materials in patients with suspect fragrance allergy and to evaluate risk factors and associations with such responses. A total of 167 fragrance sensitive volunteers from seven centres worldwide (Japan, Northern Ireland, United States, England, Switzerland and Sweden) were patch tested with fragrance mix (FM) and its constituents, including geraniol at 5% in petrolatum.

Description of patch test as cited from Larsen et al., 1996: *"The test materials were applied to Finn chambers (Epitest Ltd, Oy, Helsinki, Finland) that were applied to the upper back.[7] The chambers were then further secured to the skin with Scanpor tape (Norgesplaster A/S, Aksjeselskap, Finland). Fifteen to 45 minutes were allowed between the initial patch test removal and the first reading to allow the pressure effect of the patch test appliance to resolve so as not to mask faint responses. The patch test sites were evaluated using the North American Contact Dermatitis Group modification [11] of the International Contact Dermatitis Research Group morphological grading systcm.[12] The patch test sites were evaluated initially at 48 or 72 hours. The test sites were re-examined in the majority of cases, usually between 48 and 120 hours after the first reading. All test site readings were made by the investigators.*"

Statistical analysis of the data was performed using the Statistical Analysis System (release 6.07, SAS Institute, Cary, NC, USA).

The results showed that 3.0% of the selected volunteers (5/167) were tested positive for geraniol (5% in petrolatum).

### 3.1.2.20 STUDY 21 (Patch test, selected)

**Study reference:**

Johansen, J.D., Menne, T., 1995. The fragrance mix and its constituents: a 14-year material. Contact Dermatitis 32, 18-23.

**Detailed study summary and results:**

This study is a review of results from 14 years of patch testing with the fragrance mix (FM) and its constituents and includes 8215 consecutive patients patch tested with FM between 1979 and 1992 at the Department of Dermatology in Gentofte, Denmark. Individual FM constituents were tested in a total of 367 patients reacting to the fragrance mix between 1979 and 1992. Geraniol was tested at 1-2% in petrolatum.

Description of patch test as cited from Johansen & Menné 1995: "*The patches were occluded using Finn Chambers affixed with Scanpor tape." ..." The test substances were applied to the upper back for 2 days. Readings were made on the 2nd, 3rd and 5th- 7th days. In 1987, the scale of readings was adjusted to conform with ICDRG recommendations; before that, a less rigorous scale was used, defining a positive reaction as a definite erythema.*"

The results showed that 4.1% of the selected patients (15/367) were tested positive for geraniol.

### 3.1.2.21 STUDY 22 (Patch test, selected)

**Study reference:**

Becker, K., Temesvari, E., Nemeth, I., 1994. Patch testing with fragrance mix and its constituents in a Hungarian population. Contact Dermatitis 30, 185-186.

**Detailed study summary and results:**

The aim of the study by Becker et al. was to monitor the frequency of fragrance sensitivity and screen for allergy to fragrance mix constituents. Out of 1452 patients patch tested with the Epipharm Hungarian standard series a total of 50 randomly selected fragrance-mix-positive patients were additionally patch tested with the constituents of the fragrance mix including geraniol (concentration and vehicle not reported).

According to Becker et al., reactions to patch tests were evaluated according to international guidelines but no description of the patch test is included in the article.

The results showed that 6.0% of the selected patients (3/50) were tested positive for geraniol.

### 3.1.2.22 STUDY 23 (Patch test, selected)

**Study reference:**

de Groot, A.C., van der Kley, A.M., Bruynzeel, D.P., Meinardi, M.M., Smeenk, G., van Joost, T., Pavel, S., 1993. Frequency of false-negative reactions to the fragrance mix. Contact Dermatitis 28, 139-140.

**Detailed study summary and results:**

The purpose of the study was to determine the frequency of false-negative reactions to fragrance mix (FM). Between September 1991 and December 1991 a total of 677 patients were patch tested with FM at University of Amsterdam and University of Leiden, The Netherlands. Out of the 677 tested patients a total 61 patients were positive to FM. Geraniol (5% in petrolatum) as a single constituent was tested in the FM positive patients.

The method of patch testing was not described by de Groot et al., 1993.

The results showed that 13.1% of the selected patients (8/61) were tested positive for geraniol.

### 3.1.2.23 STUDY 24-26 (Patch test, selected)

**Study reference:**

Haba, Y., Itoh, M., Morita, C., Tsuyuki, S., 1993. Results of patch tests on cosmetic ingredients conducted in 1990 and 1991. Skin Research 35, 65-74.

**Detailed study summary and results:**

A detailed summary of the study and results cannot be presented as the original article is in Japanese. The following information is based on the abstract in English and a table in the article.

Patch tests were conducted on 103 patients with cosmetic contact dermatitis (64 patients), facial melanosis (7 patients), and non-cosmetic dermatitis and eczema (32 patients) in 1990 and 1991 at Department of Dermatology, Toho University School of Medicine, Tokyo, Japan.

The results showed that 4.7% of the patients with cosmetic contact dermatitis (3/64), 0% of the patients with facial melanosis (0/7) and 3.1% of the patients with non-cosmetic dermatitis and eczema (1/32) were tested positive for geraniol (5% in petrolatum).

### 3.1.2.24 STUDY 27-28 (Patch test, selected) (also cited in REACH registration dossier)

**Study reference:**

Abifadel, R., Mortureux, P., Perromat, M., Ducombs, G., Taieb A., 1992. Contact sensitivity to flavourings and perfumes in atopic dermatitis. Contact Dermatitis 27, 43-46.

**Detailed study summary and results:**

This study is a pilot study to investigate whether children with atopic dermatitis might be sensitised by ingesting, inhaling or handling flavouring perfume-containing products. 16 children with atopic dermatitis and 4 children having other dermatoses with a suspicion of contact dermatitis were patch tested with fragrance mix (F) and balsam of Peru (BP). Patients with positive reactions to F or BP were further tested with perfumes and flavourings, including geraniol at 1% in petrolatum.

Description of patch test as cited from Abifadel et al., 1992: *"Patch tests were applied to the upper back, and read at 30 min. and 2, 4 and 10 days. The patch test sites were read according to the criteria of the ICDRG: mild erythema [?+ ];indurated erythema [ + ]; infiltration and vesicles [ + + ]; bullous reaction [ + + + ]; negative reaction [- ]. Initial patch tests comprised (1) the European standard series (Trolab®), which includes fragrance-mix 8% pet. (F) and balsam of Peru 25% pet. (BP), and the additional allergens listed in Table 1. The allergens were tested in Finn Chambers®, except the metal salts, for which Leukotest® was used, and secured with Albupore®. Patients with positive reactions to F or BP were further tested with a perfume and flavourings series (Trolab®), plus sorbitan sesquioleate 20% pet. (Trolab®)"*

The results showed that 0% of the children with atopic dermatitis (0/16) and 0% of the children suspected of having contact dermatitis (0/4) were tested positive for geraniol.

### 3.1.2.25 STUDY 29 (Patch test, selected)

**Study reference:**

Nagareda, T., Sugai, T., Shouji, A., Katoh, J., Mita, T., Utsumi, M., Nakanishi, T., 1992. Incidence of positive reactions to cosmetic products and their ingredients in patch tests and representative cases with cosmetic dermatitis in 1991. Skin Research 34, 176-182.

**Detailed study summary and results:**

A detailed summary of the study and results cannot be presented as the original article is in Japanese. The following information is based on the abstract in English and a table in the article.

Patch tests were conducted on 111 patients with cosmetic dermatitis in 1990 and 1991 at Department of Dermatology, Osaka City University Medical School, Osaka, Japan.

The results showed that 0.9% of the selected patients (1/111) were tested positive for geraniol (5% in petrolatum).

### 3.1.2.26 STUDY 30 (Patch test, selected)

**Study reference:**

Remaut, K., 1992. Contact dermatitis due to cosmetic ingredients. Journal of Applied Cosmetology 10, 73-80.

**Detailed study summary and results:**

Between 1987 and 1988 a total of 310 records from patients registered as cases of contact dermatitis at Department of Dermatology, Ullevaal Hospital, Oslo, Norway, were evaluated. 115 patients with positive reactions to cosmetics or cosmetic ingredients were patch tested with the European standard series, including geraniol at 5% in vaselin.

The method of patch testing was not described by Remaut, 1992.

The results showed that 0% of the selected patients (0/115) were tested positive for geraniol.

### 3.1.2.27 STUDY 31 (Patch test, selected)

**Study reference:**

Roesyanto-Mahadi, I.D., Geursen-Teitsma, A.M., van Joost, Th, van den Akker Th.W., 1990. Sensitization to fragrance material in Indonesian cosmetics. Contact Dermatitis 22, 212-217.

**Detailed study summary and results:**

Seventeen Dutch patients with known patch test reactivity to fragrance-mix were patch tested with geraniol at 1% in petrolatum.

Description of patch test as cited from Roesyanto-Mahadi et al., 1990: *"Standard patch tests were performed using uniform patch tests (Van der Bend) and read at 48 h and 72 h (7, 9). The test results were graded as follows: - = negative (no reaction or dubious reaction) (only slight erythema);+ = positive (erythema, mild edema); ++ = positive (erythema, edema and papules); + + + = strongly positive (erythema, induration, papules, vesicles). Dubious reactions were not included in this study."*

The results showed that 11.8% of the selected patients (2/17) were tested positive for geraniol.

### 3.1.2.28 STUDY 32 (Patch test, selected)

**Study reference:**

Safford, R.J., Basketter, D.A., Allenby, C.F., Goodwin, B.F.J., 1990. Immediate contact reactions to chemicals in the fragrance mix and a study of the quenching action of eugenol. British Journal of Dermatology 123, 595-606.

**Detailed study summary and results:**

Twenty subjects who had previously demonstrated delayed hypersensitivity reactions to fragrance-mix were selected for patch tests, including geraniol at 2%, in petrolatum.

Description of patch test as cited from Safford et al., 1990: "*Delayed hypersensitivity was tested by applying the fragrance mix (16%) and its individual ingredients (at 2% each) to each subject's upper back for 48 h. The reactions were read approximately 1 h after removal and at 96 h using the ICDRG scale. Immediate contact reactions were also assessed on the volar aspect of the forearms to the fragrance mix (16%) and its separate components (2%) at the same time as conventional tests on the back. Test sites were occluded for 40 min using 11-mm Finn Chambers (Epitest Oy, Finland) and on removal of the patches the sites were wiped gently and reactions recorded immediately using a scale of R1-R3 for erythema and U for an urticarial weal. The sites were also inspected 24 and 96 h later, and any type IV allergic reactions noted."*

The results showed that 10.0% of the selected patients (2/20) were tested positive for geraniol.

### 3.1.2.29 STUDY 33 (Patch test, selected) (also cited in REACH registration dossier)

**Study reference:**

Enders, F., Przybilla, B., Ring, J., 1989. Patch testing with fragrance mix at 16% and 8%, and its individual constituents. Contact Dermatitis 20, 237-238.

**Detailed study summary and results:**

A total of 162 patients with a positive reaction to fragrance mix were tested in 1987 with the individual constituents in FM at the Dermatologische Klinik und Poliklinik, Germany, including geraniol at 1% (vehicle not reported).

The method of patch testing was not described by Enders et al., 1989.

The results showed that 2.5% of the selected patients (4/162) were tested positive for geraniol.

### 3.1.2.30 STUDY 34-35 (Patch test, selected)

**Study reference:**

Nethercott, J.R., Nield, G., Holness, D.L., 1989. A review of 79 cases of eyelid dermatitis. Journal of the American Academy of Dermatology 21, 223-230.

**Detailed study summary and results:**

Between January 1980 and May 1987, 1091 patients were assessed and given patch tests in the Contact Dermatitis Clinic of St. Michael's Hospital, Toronto, Canada. Nineteen selected patients with eyelid dermatitis and 70 patients with dermatitis at other sites were patch tested with 25 fragrance materials, including geraniol at 2% in petrolatum.

Description of patch test as cited from Nethercott et al., 1989: *"Chemicals were applied either to A1-Test strips or Finn Chambers, which were then secured to the upper aspect of the back with Scanpor tape. Patch tests were applied on Mondays, Wednesdays or Fridays, and were first read on the 2 days after the tests were applied. When the chambers or strips were removed at the first reading (at 48 or 72 h), sites were scored 30 to 60 minutes after the appliance had been removed. Second reading was scored at 48 or 72 h after the first reading."*

The results showed that 0% of the selected patients with eyelid dermatitis (0/19) and 1.4% of the selected patients with dermatitis at other sites (1/70) were tested positive for geraniol.

### 3.1.2.31 STUDY 36 (Patch test, selected)

**Study reference:**

*Wilkinson, J.D., Andersen, K., Camarasa, J., Ducombs, G., Frosch, P., Lahti, A., Menné, T., Rycroft, R.J.G., White, I., et al., 1989. Preliminary results of the effectiveness of two forms of fragrance mix as screening agents for fragrance sensitivity. In Frosch, P.J. et al. (eds.): Current Topics in contact dermatitis. Heidelberg: Springer-Verlag, 1989: 127-131, cited in:* SCCNFP, 1999

**Detailed study summary and results:**

2455 consecutive patients attending patch test clinics in England, Denmark, Spain, France, Germany and Finland in 1989 were tested with two different fragrance mixes. A total of 78 patients with a positive reaction to one or the other fragrance mix were tested with the individual constituents, including geraniol at 1% in petrolatum.

Description of patch test as cited from SCCNFP, 1999: *Patch test technique and readings were as recommended by the ICDRG and, for positive results an assessment of clinical relevance was also made.*

The results showed that 5.1% of the selected patients (4/78) were tested positive for geraniol.

### 3.1.2.32 STUDY 37 (Patch test, selected)

**Study reference:**

de Groot, A.C., Bruynzeel, D.P., Bos, J.D., van der Meeren, H.L.M., van Joost, T., Jagtman, B.A., Weylan, J.W., 1988. The allergens in cosmetics. Archives in Dermatology 124, 1525-1529.

**Detailed study summary and results:**

In a multicentre study form the Netherlands a total of 119 selected patients suffering from cosmetic-related contact dermatitis were patch tested with a range of preservatives, fragrances, including geraniol at 5% in petrolatum, emulsifiers and miscellaneous substances found in cosmetics.

Description of patch test as cited from de Groot et al., 1988: *"Patch test procedures were carried out according to internationally accepted methods.[12] Van der Bend patch test chambers (van der Bend, Hellevoetsluis, the Netherlands) were used for applying the allergens, and acrylate tape (Fixomull, Beiersdorf, Hamburg, West Germany) for fixation. The materials were removed after two days and the reactions were read after 20 minutes and again one or two days later. Informed consent was obtained from all participants.*"

The results of the study showed that 1.7% of the selected patients (2/119) were tested positive for geraniol.

### 3.1.2.33 STUDY 38 (Patch test, selected)

**Study reference:**

Goncalo, S., Cabral, F., Goncalo, M., 1988. Contact sensitivity to oak moss. Contact Dermatitis 19, 355-357.

**Detailed study summary and results:**

During 1980-1986, 2411 patients at Clinica de Dermatologia e Venereologia dos Hospitals da Universidade de Coimbra, Portugal were patch tested with the standard test series recommended by the ICDRG. A total of

192 patients reacted to the fragrance mix and of these 69 were tested with the individual components of the mixes. 31 patients who reacted to oak moss were also patch tested with individual components, including geraniol (concentration and vehicle not reported).

Description of patch test as cited from de Goncalo et al., 1988: *"Patch tests were performed with Leukotest (Beiersdorf AG, Hamburg) or Finn Chamber (Epitest, Helsmki). Reactions were read at 48 and 96 h."*

The results of the study showed that 16.1% of the selected patients (5/31) were tested positive for geraniol.

### 3.1.2.34 STUDY 39 (Patch test, selected) (also cited in REACH registration dossier)

**Study reference:**

Broeckx, W., Blondeel, A., Dooms-Goossens, A., Achten, G., 1987. Cosmetic intolerance. Contact Dermatitis 16, 189-194.

**Detailed study summary and results:**

A study of cosmetic intolerance was conducted in 5202 patients being tested for contact dermatitis using a standard battery of Belgian Tri-Contact Patch-test series. A group of 156 patients with allergy to cosmetics was tested with dermatitis ingredients, including geraniol (concentration and vehicle not reported).

The method of patch testing was not described by Broeckx et al., 1987.

The results of the study showed that 1.3% of the selected patients (2/156) were tested positive for geraniol.

### 3.1.2.35 STUDY 40 (Patch test, selected)

**Study reference:**

Hirose, O., Arima, Y., Hosokawa, K., Suzuki, M., Matsunaga, K., Hayakawa, R., 1987. Patch test results of cosmetic allergens during recent 30 months. Skin Research 29, 95-100.

**Detailed study summary and results:**

A detailed summary of the study and results cannot be presented as the original article is in Japanese. The following information is based on the abstract in English and a table in the article.

Patch tests were conducted with 20% geraniol in petrolatum on 574 patients with cosmetic contact dermatitis or another eczema in the period 1984-1986.

A positive reaction was observed in 0.9% of the selected patients (5/574).

### 3.1.2.36 STUDY 41-42 (Patch test, selected)

**Study reference:**

Santucci, B., Cristaudo, A., Cannistraci, C., Picardo, M., 1987. Contact dermatitis to fragrances. Contact Dermatitis 16, 93-95.

**Detailed study summary and results:**

The aim of the study by Santucci et al., 1987 was to evaluate the incidence of contact dermatitis to fragrances at Istituto Dermatologico Santa Maria e San Gallicano, Italy and the influence of limited variations in fragrance and perfume mix concentrations on patch test responses. Two large groups of patients with contact dermatitis were patch tested with a range of mixed fragrances including geraniol between 1983 and 1984 (n=1200) and 1984 and 1985 (n=1500). Patients reacting positive to any of the mixed fragrances were tested after 3 months with the individual components of the mix, including geraniol. A total of 63 and 54 patients were tested positive in the first and second group, respectively.

Description of patch test as cited from Santucci et al., 1987: "*Using Finn Chambers on Scanpor'". The tests were read at 48, 72 and 96 h, according to the ICDRG scale; the last reading was taken as definitive*."

The results showed that 6.3% of the selected patients tested with geraniol at 3% (4763) and 7.4% of the selected patients tested with geraniol at 3% (4/54) were tested positive.

### 3.1.2.37 STUDY 43 (Patch test, selected) (also cited in REACH registration dossier)

**Study reference:**

Rudzki, E., Grzywa, Z., 1986. Allergy to perfume mixture. Contact Dermatitis 15, 115-116.

**Detailed study summary and results:**

Out of 5315 patients tested with the ICDRG perfume mixture 299 were found to be sensitive to the fragrance mix. Among these, 42 patients were tested with the 8 individual components of the fragrance mix, including geraniol (concentration and vehicle not reported).

The method of patch testing was not described by Rudzki and Grzywa, 1986.

The results of the study showed that 24.0% of the selected patients (10/42) were tested positive for geraniol.

### 3.1.2.38 STUDY 44 (Patch test, selected)

**Study reference:**

Adams, R.M., Maibach, H.I., 1985. A five-year study of cosmetic reactions. Journal of the American Academy of Dermatology 13, 1062-1069.

**Detailed study summary and results:**

A total of 713 cosmetic related cases were identified among 13216 patch tested contact dermatitis patients from various sections of the United States between 1977 and 1983. To identify the exact cause of their reactions the patients were patch tested with a range of cosmetic ingredients including the cosmetic products used by the patient. A sub-group of 403 selected patients were patch tested with single ingredients including geraniol (concentration and vehicle not reported).

Description of patch test as cited from Adams and Maibach, 1985: "*Patch tests were applied to the upper back for 48 hours according to the methods outlined in the North American Contact Dermatitis Group" and the International Contact Dermatitis Group. Readings were made at 48 hours and 72 hours. In most centres, additional readings at 96 hours or 120 hours were also made. The patch test was either the Al test or the Finn Chamber (Hermal Pharmaceutical Labs., Inc., Oak Hill, NY; Allerderm Laboratories, Mill Valley, CA).*"

The results of the study showed that 2.0% of the selected patients (8/403) were tested positive for geraniol.

### 3.1.2.39 STUDY 45 (Patch test, selected)

**Study reference:**

Angelini, G., Vena, G.A., Giglio, G., Fiordalisi, F., Meneghini, C.L., 1985. Contact dermatitis due to cosmetics. Journal of Applied Cosmetology 3, 223-236.

**Detailed study summary and results:**

Data from 8230 consecutive patients with eczematous forms of dermatitis of various types from 1968 to 1983 were reviewed. 144 patients positive to fragrance mix were tested with individual ingredients, including geraniol at 1% in petrolatum.

The method of patch testing was not described by Angelini et al., 1985.

The results of the study showed that 6.9% of the selected patients (10/144) were tested positive for geraniol.

### 3.1.2.40 STUDY 46 (Patch test, selected)

**Study reference:**

de Groot, A.C., Liem, D.H., Nater, J.P., van Ketel, W.G., 1985. Patch tests with fragrance materials and preservatives. Contact Dermatitis 12, 87-92.

**Detailed study summary and results:**

A total of 179 Dutch patients suspected of cosmetic allergy were patch tested with a series of 16 fragrance materials, including geraniol at 10% in petrolatum.

Description of patch test as cited from de Groot et al., 1985: "*For patch testing we used Silver Patch Testers (van der Bend bv, PO Box 1518, 9701 BM Groningen, The Netherlands). Reactions were read after 48 and 72 hours, and scored according to internationally accepted criteria (4).*"

The results of the study showed that 6.1% of the selected patients (11/179) were tested positive for geraniol.

### 3.1.2.41 STUDY 47-48 (Patch test, selected) (also cited in REACH registration dossier)

**Study reference:**

Emmons, W.W., Marks, J.G., 1985. Immediate and delayed reactions to cosmetic ingredients. Contact Dermatitis 13, 258-265.

**Detailed study summary and results:**

Fifty volunteers, 19 controls, 15 with eczematous dermatitis and 16 with cosmetic sensitivity were patch tested with the North American Contact Dermatitis Group (NACDG) fragrance screening series and 11 other common allergens found in cosmetics, including geraniol at 5% in petrolatum.

Description of patch test as cited from Emmons and Marks, 1985: *"The chemicals were placed in Finn Chambers® and secured to the subject's back with Scanpor® tape. A 3-5 mm ribbon of allergen-petrolatum mixture was used, unless it was an aqueous allergen mixture, in which case one drop was used with a filter paper disc. The patches were removed after 48 h, and the sites were read at 48 and 96 h. The patch test sites were interpreted according to the criteria proposed by the NACDG. A macular erythema was a "?"; an indurated erythema was a "+ 1"; erythema, infiltration and vesicles were a "+ 2"; a bullous reaction or an ulcer was a "+ 3"."*

The data was analysed using $\chi^2$ statistics or, where applicable, the Fisher exact test.

The results of the study showed that 0% of the selected patients with cosmetic sensitivity (0/16) and 6.7% of the selected patients with eczematous dermatitis (1/15) were tested positive for geraniol.

### 3.1.2.42 STUDY 49 (Patch test, selected)

**Study reference:**

Malten, K.E., van Ketel, W.G., Nater, J.P., Liem, D.H., 1984. Reactions in selected patients to 22 fragrance materials. Contact Dermatitis 11, 1-10.

**Detailed study summary and results:**

A total of 182 Dutch patients with suspected contact sensitisation to cosmetics were patch tested with a series of 22 fragrance and flavour raw materials, including geraniol at 1% in petrolatum.

Description of patch test as cited from Malten et al., 1984: "*The patch test reactions were read at 48 and 72 h; the last reading was recorded as definitive*."

The results of the study showed that 1.6% of the selected patients (3/182) were tested positive for geraniol.

### 3.1.2.43 STUDY 50 (Patch test, selected)

**Study reference:**

Hayakawa, R., Ohiwa, K., Ukei, C., Matsunaga, K., 1983. Melanosis faciei feminae in 1982. Skin Research 25, 690-695.

**Detailed study summary and results:**

A detailed summary of the study and results cannot be presented as the original article is in Japanese. The following information is based on the abstract in English and a table in the article.

Patch tests were conducted with 20% geraniol in petrolatum on 181 patients with melanosis faciei feminae from 1977-1982.

A positive reaction was observed in 3.9% of the selected patients (7/181).

### 3.1.2.44 STUDY 51 (Patch test, selected)

**Study reference:**

Sugai, T., 1983. Evaluation of the compound perfume Fleuri 981SA from patch test results. Skin Research 25, 703-706.

**Detailed study summary and results:**

A detailed summary of the study and results cannot be presented as the original article is in Japanese. The following information is based on the abstract in English and a table in the article.

23 patients sensitive to a compound perfume "Fleuri 981SA" were patch tested with 3 ingredients, including geraniol (concentration and vehicle not reported) in 1981.

A positive reaction was observed in 13.0% of the selected patients (3/23).

### 3.1.2.45 STUDY 52 (Patch test, selected)

**Study reference:**

Eiermann, H.J., Larsen, W., Maibach, H.I., Taylor, J.S., 1982. Prospective study of cosmetic reactions: 1977-1980. Journal of the American Academy of Dermatology 6, 909-917.

**Detailed study summary and results:**

In a prospective multicentre study from 1977-1980 in the US a total of 487 patients with cosmetic-related cases of contact dermatitis were patch tested with individual ingredients, including geraniol (concentration and vehicle not reported).

Description of patch test as cited from Eiermann et al., 1982: *"Patch tests were applied to the upper back for 48 h according to methods outlined by the NACDG and the ICDRG. Readings were made at 48 and or 72 hrs. In most centres, delayed readings at 96 or 120 hrs were made. The patch was either A1 test (Astra Pharmaceutical Products, Inc., Worcester, MA) or the Finn Chamber (Epi Test). For most battery tests, positive results were confirmed with a subsequent retest to minimize the potential for the "excited skin stat"."*

The results of the study showed that 1.0% of the selected patients (5/487) were tested positive for geraniol.

### 3.1.2.46 STUDY 53 (Patch test, selected)

**Study reference:**

Itoh, M., 1982. Sensitization potency of some phenolic compounds – with special emphasis on the relationship between chemical structure and allergenicity. The Journal of Dermatology 9, 223-233.

**Detailed study summary and results:**

155 patients with cosmetic dermatitis and female facial melanosis were patch tested with individual fragrance ingredients, including geraniol at 5% in petrolatum.

Description of patch test as cited from Itoh, 1982: *"The test samples were applied on the cloth disks of Torii's adhesive plaster for patch testes. The plaster was applied to the upper back of the patients for 48 hours. Readings were made 1 hour, 24 hours, 1 week and 2 weeks after removal."*

The results of the study showed that 0.6% of the selected patients (1/155) were tested positive for geraniol.

### 3.1.2.47 STUDY 54 (Patch test, selected)

**Study reference:**

*Sugai, T., 1982. Contact dermatitis due to household products. In: Proceedings of the 11th annual meeting, Japanese Society Cutaneous Health, 15-18, cited in:*

Lapczynski, A., Bhatia, S.P., Foxenberg, R.J., Letizia, C.S., Api, A.M., 2008. Fragrance material review on geraniol. Food and Chemical Toxicology 46 Suppl 11, S160-170.

**Detailed study summary and results:**

A detailed summary of the study and results is not available in the article by Lapczynski *et al.*, which presents a review of the available data on sensitization for geraniol. Only the following data are presented:

A total of 1277 patients with contact dermatitis due to the household products, were patch tested with geraniol at 2% in petrolatum.

A positive reaction was observed in 2.2% of the selected patients (28/1277).

### 3.1.2.48 STUDY 55 (Patch test, selected)

**Study reference:**

Larsen, W.G., 1977. Perfume dermatitis. A study of 20 patients. Archives of Dermatology 113, 623-626.

**Detailed study summary and results:**

A total of 20 perfume-sensitive patients were patch tested with several screening sets of fragrance materials, including geraniol at 5% in white petrolatum.

Description of patch test as cited from Larsen, 1977: "*The standard patch-testing technique with use of an aluminium-backed strip was employed. Patch tests were applied to the patient's back and were left for 48 hours. Readings were made at the time of removal or 24 hours after removal. Patients were instructed to return if an additional delayed reaction occurred. All the fragrance allergens were tested on 50 control patients with negative results. To avoid the "angry back" phenomenon, patients were tested during a period of several months.*"

The results of the study showed that 30.0% of the selected patients (6/20) were tested positive for geraniol.

### 3.1.2.49 STUDY 56 (Patch test, selected) (also cited in REACH registration dossier)

**Study reference:**

*Hjorth, N., 1961. Orange peel. In: Eczematous allergy to balsams. Copenhagen, Munksgaard.*

*cited in:* Hostynek, J.J., Maibach, H.I., 2004. Is there evidence that geraniol causes allergic contact dermatitis? Exogenic Dermatology 3, 318-331.

**Detailed study summary and results:**

A detailed summary of the study and results is not available in the article by Hostynek and Maibach, which presents a review of the available clinical data for geraniol. Only the following data are presented as cited:

15 eczema patients sensitive to Peru balsam were patch tested with geraniol at 10% in petrolatum.

A positive reaction was observed in 13.3% of the selected patients (2/15).

### 3.1.2.50 STUDY 57 (Patch test, consecutive)

**Study reference:**

Mann, J., McFadden, J.P., White, J.M.L., White, I.R., Banerjee, P., 2014. Baseline series fragrance markers fail to predict contact allergy. Contact Dermatitis, 70, 276–281.

**Detailed study summary and results:**

The St Johns' Institute of Dermatology at St Thomas' Hospital, UK has performed a retrospective study of patch test data by reviewing the records of 1951 eczema patients, routinely tested with the 26 fragrance substances requiring labelling and with an extended European baseline series (FM I and FM II) in 2011 and 2012. The objective was to determine the frequencies of positive test reactions to the 26 fragrance substances for which labelling is mandatory in the EU, and how effectively reactions to fragrance markers in the baseline series (FM I and FM II) predict positive reactions to the fragrance substances that are labelled. The study thus explored whether routine patch testing with all individual fragrance substances that are labelled above a threshold identified cases of fragrance contact allergy that would have remained undetected when using the baseline series.

Description of test method as cited from Mann et al., 2014: *The patch test records of all eczema patients who underwent routine testing with the fragrance series and the European baseline series during 2011 and 2012 were retrieved from the database at St John's Institute of Dermatology at St Thomas' Hospital, London. The data recorded at the time of consultation included the age, sex and occupation of patients, the primary site affected by eczema, and the duration of eczema. Positive reactions, on or after day 4 of testing, to fragrance markers in the European baseline series (FM I, FMII, Myroxylon pereirae, and HICC) or allergens from the fragrance series (the 26 labelled fragrances and trimethylbenzenepropanol, but excluding HICC) were tabulated with spss™ version 12. Data were also collected for patients who reacted to colophonium and epoxyresin. The concentrations and constituents of the fragrance markers are shown in Table 1, and those of*

*the allergens used in the fragrance series are shown in Table 2. Limonene and linalool were used in their unoxidized forms throughout the study. Patch testing was performed with aluminium Finn Chambers® provided by Bio-Diagnostics® (Upton-Upon-Severn, United Kingdom) and allergens provided by Bio-Diagnostics®, Trolab® (Hermal Almirall, Reinbeck, Germany) and Chemotechnique® (Vellinge, Sweden). Allergens were in petrolatum. Reactions were read on days 2 and 4, according to the recommendations of the International Contact Dermatitis Research Group. Reactions documented as questionable or irritant were considered to be negative.*

The results showed that 0.5% (9/1951) (95% CI: 0.2-0.8%) of the unselected patients had positive reactions to geraniol when tested at 2% in petrolatum.

### 3.1.2.51 STUDY 58-63 (Patch test, consecutive)

**Study reference:**

Hagvall, L., Karlberg, A.-T., Christensson, J.B., 2013. Finding the optimal patch test material and test concentration to detect contact allergy to geraniol. Contact Dermatitis 68, 224-231.

**Detailed study summary and results:**

The Department of Dermatology at Sahlgrenska University Hospital, Gothenburg, Sweden has performed a prospective patch test study to find the optimal patch test substance and concentration for detecting contact allergy to geraniol. Data for geraniol were obtained in the period from 2010-2011. In total 655 consecutive patients were patch tested with pure and oxidized geraniol at 4.0%, 6.0% and 11.0% in petrolatum.

Description of air exposure procedure as cited from Hagvall et al., 2013: "*A distilled sample of geraniol (>98%) was air-exposed in an Erlenmeyer flask, covered with aluminium foil to prevent contamination. It was stirred at room temperature for 1 hr, four times a day, and exposed to light for 12 hr a day, with a daylight fluorescent lamp (Philips; 18 W, Eindhoven, The Netherlands), as previously described (6, 11). Samples were taken on a regular basis, and stored at −20◦C under nitrogen until being analysed by HPLC with ultraviolet detection to determine the concentrations of geraniol and its major oxidation products. The oxidation was interrupted after 10 weeks; where after the oxidation mixture was stored at −20◦C under nitrogen during the patch test study. The oxidation mixture of geraniol was analysed, and found to contain geraniol 48% (wt/wt), geranial 3.9%, neral 1.0%, and geraniol hydroperoxide 3.2%. The nonquantified material consists of other previously identified oxidation products (e.g. geraniol formate and 3,7-dimethyl-octa-2,5-diene-1,7-diol) that do not contribute to the sensitization potency of oxidized geraniol (6) and of polymers formed over time. Samples of the oxidation mixture were taken out and used for patch test preparations.*"

Description of patch test as cited from Hagvall et al., 2013: "*Patch test preparations of ~20 mg were applied in small Finn Chambers® (diameter 8 mm, inner area of 0.5 cm$^2$; Epitest Ltd Oy, Tuusula, Finland) on Scanpor® tape (Norgesplaster A/S, Vennsela, Norway) to the back of the patient, left under occlusion for 2 days, and then removed by the patient. Readings were performed according to the International Contact Dermatitis Research Group recommendations (24) on D3–D4 and D7.*"

Statistical analysis of the data was performed using the statistical software package SPSS™ 15.0 for Windows™ (SPSS Inc., Chicago, IL, USA).

The results from the study are presented in the table below.

| Substance | Concentration (% pet.) | Tested (n) | Positive (n) | Positive (%) |
|---|---|---|---|---|
| **Geraniol** | 4 | 655 | 1 | 0.15 |
| **Geraniol** | 6 | 649 | 3 | 0.46 |
| **Geraniol** | 11 | 655 | 7 | 1.1 |
| **Oxidized geraniol** | 4 | 655 | 6 | 0.92 |
| **Oxidized geraniol** | 6 | 655 | 15 | 2.3 |
| **Oxidized geraniol** | 11 | 653 | 30 | 4.6 |

### 3.1.2.52 STUDY 64-65 (Patch test, consecutive)

**Study reference:**

Hagvall, L., Karlberg, A-T., Christensson, J.B., 2012. Contact allergy to air-exposed geraniol: clinical observations and report of 14 cases. Contact Dermatitis, 67, 20–27.

**Detailed study summary and results:**

The Department of Dermatology at Sahlgrenska University Hospital, Gothenburg, Sweden has performed a prospective study of patch test data for 2227 and 2179 patients who were patch tested with pure geraniol and oxidised geraniol, respectively. Data for geraniol were obtained in the period from 2006-2010. Geraniol (purity: 98%) was obtained from Sigma Aldrich (St Louis, MO, USA) and was distilled prior to use.

Description of air exposure procedure as cited from Hagvall et al., 2012: "*A distilled sample of geraniol (>98%) was air-exposed in an Erlenmeyer flask, covered with aluminium foil to prevent contamination. It was stirred at room temperature for 1 hr, four times a day, as previously described (16). Samples were taken on a regular basis, and stored in the freezer under nitrogen until being analysed with HPLC–ultraviolet to determine the concentrations of geraniol and its major oxidation products. The oxidation was interrupted after 10 weeks, and thereafter the oxidation mixture was stored at −20◦C during the patch test study. The*

*oxidation mixture of geraniol was analysed, and found to contain 48% geraniol, 3.9% geranial, 3.5% geraniol hydroperoxide, and 1.0% neral. Samples were taken and used for patch test preparations.*"

Description of patch test as cited from Hagvall et al., 2012: "*Consecutive patients patch tested with the Swedish baseline series at the Department of Dermatology, Sahlgrenska University Hospital, Gothenburg, Sweden, during the period January 2006 to August 2010, were included in the study. Patch test preparations of approximately 20 mg were applied in small Finn Chambers® (diameter 8 mm, inner area of 0.5 cm2; Epitest Ltd Oy, Tuusula, Finland) on Scanpor® tape (Norgesplaster A/S, Vennsela, Norway) to the back of the patient, left under occlusion for 2 days, and then removed by the patient. Readings were performed according to the International Contact Dermatitis Research Group recommendations (28) on D3–4 and D7.*"

The results showed that 0.1% (3/2227) and 0.6% (12/2179) of the consecutive patients were tested positive for geraniol (2% in petrolatum) and air-oxidised geraniol (2% in petrolatum), respectively.

### 3.1.2.53 STUDY 66 (Patch test, consecutive)

**Study reference:**

Heisterberg, M.V., Menné, T., Johansen, J.D., 2011. Contact allergy to the 26 specific fragrance ingredients to be declared on cosmetic products in accordance with the EU cosmetics directive. Contact Dermatitis 65, 266–275 and corrigendum in: Contact Dermatitis 67 (2012), 58.

**Detailed study summary and results:**

The Department of Dermato-Allergology, Copenhagen University Hospital, Gentofte has performed a retrospective study on consecutive eczema patients patch tested with geraniol. The objective of the study was to investigate frequencies of sensitization to the 26 individual fragrances and evaluate the sensitivity of the standard fragrance screening markers (FM I and FM II), i.e. would testing with the individual substances reveal fragrance allergy that is not detected when using the standard fragrance markers. Patients (n = 1508) were patch tested with at least one of the 26 fragrance ingredients in the period from January 2008 to July 2010 were included in the study. 1502 patients were patch tested with geraniol.

Description of patch test as cited from Heisterberg et al., 2011: "*The patch tests were performed according to international guidelines (9), with Finn Chambers applied on the back with Scanpor tape (Vitalfo Scandinavia, AB, Allerød, Denmark) for a period of 2 days. Readings were performed on days 2, 3 or 4, and 7, according to the recommendations of the International Contact Dermatitis Research Group (10). Not all subjects were patch tested with limonene and linalool, as the patch test material during the study period changed from being the pure compounds (Hermal) to oxidized materials (Göteborg), because several studies have shown that it is the oxidized products that cause allergy (11–17). In this study, we report the results of patch testing with the pure compounds. Methyl 2-octyonate 1% was not patch tested in all of the subjects*

*routinely patch tested, because active sensitization was observed in two patients, and we then stopped patch testing with it; thus only 211 patients were tested (18). Data management and statistical analysis were performed using SPSS™ version 15. Percentages of positive patch test reactions and confidence intervals were calculated with www.openepi.com. Chi-square tests and Fisher's exact tests for characteristic differences were performed, and $p < 0.05$ was considered to be significant."*

The results showed that 0% of the consecutive patients (0/1502) were tested positive for geraniol (1% in petrolatum).

#### 3.1.2.54 STUDY 67 (Patch test, consecutive)

**Study reference:**

Uter, W., Geier, J., Frosch, P., Schnuch, A., 2010. Contact allergy to fragrances: current patch test results (2005-2008) from the Information Network of Departments of Dermatology. Contact Dermatitis 63, 254-261.

**Detailed study summary and results:**

The IVDK (a network of departments of Dermatology in Germany, Austria and Switzerland) has performed a retrospective study of patch test data from a multicentre project. During 2005-2008, the frequency of contact sensitization to fragrance allergens in patients routinely patch tested for suspected allergic contact dermatitis with the baseline series (including geraniol) and special series was investigated in a total of 40709 patients. Geraniol was tested in 1214 consecutive patients as a single constituent as part of a baseline attachment (monitor series).

Description of patch test as cited from Uter et al., 2010: "*The IVDK (www.ivdk.org), a contact allergy surveillance network in Germany, Switzerland and Austria, has been described elsewhere. Briefly, results for all patients patch tested in the participating departments are electronically recorded, along with important demographic and clinical data. The diagnostic procedure follows international guidelines (9) that have been further refined by the German Contact Dermatitis Research Group (10), of which all IVDK participants are members."*

Statistical analysis of the data was performed using the statistical software package SAS (version 9.2, SAS Institute, Cary, NC, USA).

The results showed that 0.4% (95% CI: 0.1-0.69%) of the consecutive patients (5/1214) were tested positive for geraniol (1% in petrolatum).

### 3.1.2.55 STUDY 68 (Patch test, consecutive)

**Study reference:**

Van Oosten, E.J., Schuttelaar, M-L.A., Coenraads, P.J., 2009. Clinical relevance of positive patch test reactions to the 26 EU-labelled fragrances. Contact Dermatitis 61, 217–223.

**Detailed study summary and results:**

The Department of Dermatology, University of Groningen, The Netherlands performed a retrospective study (data obtained in 2995-2007) of patients with eczema suspected of being contact allergy to fragrances or cosmetics. In the study 320 patients were patch tested with the 26 EU-declared fragrance chemicals, FM I and FM II. The objective of the study was to describe frequencies of contact allergy to these 26 fragrance substances, and to evaluate clinical relevance of these positive reactions.

Description of test method as cited from Van Oosten et al., 2009: "*All 320 patients were tested with the series of 26 EU fragrance ingredients that are labelled. Additionally, the European baseline series (TRUE® test, Mekos laboratories, Denmark), which includes FM I, was tested in 295 patients, and the FM II (Hermal/Trolab, Reinbek, Germany) was tested in 227 patients. The fragrance compounds were obtained from Hermal/Trolab and from other international suppliers (International Flavors & Fragrances, USA; Robertet, France; Givaudan, Switzerland, Milennium Speciality Chemicals Inc., USA; Bedoukian Research Inc., USA; Rhodia, France; Symrise, Germany and Firmenich, Switzerland). All fragrances were dissolved in petrolatum, except for Evernia furfuracea which was dissolved in di-ethyl phthalate (Table 1). Patch tests were performed and read according to the guidelines of the International Contact Dermatitis Research Group (ICDRG) (12). The patches were applied for 2D. Final reading was done on D3. (7, 13). Reading of doubtful reactions was done up to D7 after the application of the patch test material. The relevance of the positive reactions (1+ through 3+) was determined and categorized as certain, probable, possible or not relevant. Contact allergy was defined as clinically relevant according to the following criteria: (i) certain exposure to the sensitizer and (ii) the patients dermatitis can be explained by the exposure (8, 11, 14, 15)".*

The results of the study showed that 0.6% of the unselected eczema patients (2/320) had positive reactions to geraniol when tested at 2% in petrolatum.

### 3.1.2.56 STUDY 69 (Patch test, unselected)

**Study reference:**

White, J.M.L., I. R.; Kimber, I.; Basketter, D. A.; Buckley, D. A.; McFadden, J. P., 2009. Atopic dermatitis and allergic reactions to individual fragrance chemicals. Allergy (Oxford, U. K.) 64, 312-316.

**Detailed study summary and results:**

The study was performed to compare rates of atopic dermatitis between patients with allergic contact dermatitis arising out of individual fragrance chemicals with known oral/cutaneous exposure against

exclusively cutaneous exposure. Between 1982 and 2007, 37065 dermatitis patients attending the Department of Cutaneous Allergy at St John's Institute of Dermatology, London, were tested with Fragrance mix (FM) I. Those patients who were FM1 patch test positive were furthermore patch tested with each of the single fragrance chemicals. (The study furthermore addressed rates of atopic dermatitis between patients with allergic contact dermatitis arising out of individual fragrance chemicals with known oral/cutaneous exposure against exclusively cutaneous exposure).

Description of patch test as cited from White et al., 2009: "*Allergens were applied to the skin on 8 mm Finn chambers$^{R}$ (Epitest Oy; Tuusula, Finland) under Scanpor$^{R}$ tape (Beiersdorf, Hamburg, Germany). Patch-test readings were performed at days 2/3 and 4/5, according to standard ICDRG criteria (6). A positive (+, ++, +++) patch-test reaction signified allergy. Wherever possible, patients who were allergic (patch-test positive) to FM1 were then patch tested to the individual ingredients of the mix, all at 1% pet.*"

The results of the study showed that 0.2% (89/37065) of the consecutive patients were tested positive for geraniol in 1% petrolatum.

### 3.1.2.57 STUDY 70 (Patch test, consecutive)

**Study reference:**

Schnuch, A., Uter, W., Geier, J., Lessmann, H., Frosch, P.J., 2007. Sensitization to 26 fragrances to be labelled according to current European regulation. Contact Dermatitis 57, 1–10.

**Detailed study summary and results:**

The IVDK (a network of departments of Dermatology in Germany, Austria and Switzerland) has performed a retrospective study of patch test data from a multicentre project. During 2003-2004, 26 fragrances were patch tested additionally to the standard series in a total of 21325 patients; the number of (consecutive, unselected) patients tested with each of the fragrances ranged from 1658 to 4238.

Description of patch test as cited from Schnuch et al., 2007: "*Patch tests are performed in accordance with the recommendations of the International Contact Dermatitis Research Group (12) and the German Contact Dermatitis Research Group (DKG) (13). Patch test material is obtained from Hermal/Trolab, Reinbek, Germany. Patch test preparations are applied for 24 or 48 hr. Readings are done until at least 72 hr using the following grading based on international standards (14), further refined by the German Contact Dermatitis Group (13): neg, ?, +, ++, +++, irritant, follicular. The patch test results of every reading, a standardized history (including age, sex, atopic diseases, current and former occupation(s), presumptive causal exposures), along with final diagnoses and site(s) of dermatitis are assessed and documented.*
*All data are transferred to the data centre in Gottingen in an anonymized format every 6 months. During 4 periods of 6 months each, from 1 January 2003 to 31 December 2004, 25 fragrances (Table 1) were*

*successively patch tested additionally to the standard series, i.e. in unselected patients, by departments of the IVDK. In the first period 8, in the second 6, in the third 3, and in the last period 8 compounds were added to the standard series, the number of patients tested with each preparation ranging from 1658 (tree moss) to 4238 (farnesol; tested during 2 periods).”*

Statistical analysis of the data was performed using the statistical software package SAS (version 9.1, SAS Institute, Cary, NC, USA).

The results showed that 0.5% (95% CI: 0.1-0.7%) of the consecutive patients (10/2063) were tested positive for geraniol at 1% in petrolatum.

### 3.1.2.58 STUDY 71 (Patch test, consecutive)

**Study reference:**

Heydorn, S., Johansen, J.D., Andersen, K.E., Bruze, M., Svedman, C., White, I.R., Basketter, D.A., Menné, T., 2003. Fragrance allergy in patients with hand eczema – a clinical study. Contact Dermatitis 48, 317–323.

**Detailed study summary and results:**

A study of fragrance allergy in hand eczema patients from three dermatological departments in Denmark and Sweden (Gentofte, Odense, Malmö) was done in 2001-2002. A total of 658 consecutive patients presenting with hand eczema were patch tested with the European standard series and the developed selection of fragrances. The aim of the study was to investigate patients referred with hand eczema concerning their frequency of positive patch tests to allergens in a selection of fragrances and to the European standard series. Geraniol (98%) was obtained from Dr. D. Basketter, Unilever Research (Sharnbrook, UK).

Description of patch test as cited from Heydorn et al., 2003: “*The patch tests were applied to the skin of the upper back for 2 D, using Finn Chambers® (Epitest,Helsinki,Finland)on Scanpor® tape (Norgesplaster A/S, Vennesla, Norway). Readings were taken on D2 and/or D3–4 and on D7. ICDRG recommendations were followed (10). A patch test was considered positive when the reading was +, ++ or +++. A + patch-test reaction was defined as homogeneous erythema and infiltration, whereas only erythema was not. The standard series used in Gentofte was from Hermal® (Reinbek, Germany) apart from sesquiterpene lactone mix, which became unavailable from Hermal® and was therefore obtained from Chemotechnique® (Malmö, Sweden). In Odense, the standard series was TRUE TestTM (Chemotechnique®), supplemented by test substances from Hermal®. In Malmö, the standard series was from Chemotechnique®. In Odense, they tested 229, in Gentofte 220 and in Malmö 209 patients with hand eczema. As seen in tables 2 and 3, patch-test results from Hermal®, Chemotechnique® and TRUE TestTM were combined for each allergen in the standard series.*”

Statistical analysis of the data was performed using the SAS® system for Windows® release 8.02 TS level 02MO© 1999–2001 by SAS Institute Inc. (Cary, NC, USA).
The results showed that 0.9% (6/658) of the consecutive patients were tested positive for geraniol at 5% in petrolatum.

### 3.1.2.59 STUDY 72 (Patch test, consecutive)

**Study reference:**

Schnuch, A., Geier, J., Uter, W., Frosch, P.J., 2002. Another look at allergies to fragrances: Frequencies of sensitisation to the fragrance mix and its constituents. Results from the Information Network on Departments of Dermatology (IVDK). Exogenous Dermatology 1, 231-237.

**Detailed study summary and results:**

The IVDK ((InformationsVerbund Dermatologischer Kliniken) a network of departments of Dermatology in Germany, Austria and Switzerland) has performed a retrospective study of patch test data from a multicentre project. During 1996-1999, fragrance mix (FM) (including geraniol) was tested in a total of 35599 unselected patients and its single constituents were tested at 1% in petrolatum in a subgroup of 4900 patients.

Description of patch test as cited from Schnuch et al., 2002: "*The multicentre project 'Information Network of Departments of Dermatology' ('Informationsverbund dermatologischer Kliniken', IVDK) is an instrument of epidemiological surveillance of contact allergy and has been described in detail elsewhere [2, 8, 9]. Basically, patch tests are performed in accordance with the recommendations of the ICDRG, the International Contact Dermatitis Research Group [10] and the DKG, the German Contact Dermatitis Research Group [11]. Patch test material is obtained from Hermal/Reinbek, Germany, and applied for 24 or 48 h. Readings are performed until at least 72 h. All patch test results and a standardised history of all patients tested in the participating centres (see footnote) are recorded and transferred to the data centre in Göttingen.*"

Statistical analysis of the data was performed using the statistical software package SAS (version 6.12, SAS Institute, Cary, N.C., USA).

The results showed that 1.2% of the consecutive patients (60/4900) were tested positive for geraniol.

### 3.1.2.60 STUDY 73 (Patch test, consecutive)

**Study reference:**

Frosch, P.J., Pilz, B., Burrows, D., Camarasa, J.G., Lachapelle, J.M., Lahti, A., Menné, T., Wilkinson, J.D., 1995a. Testing with fragrance mix. Is the addition of sorbitan sesquioleate to the constituents useful? Results

of a multicentre trial of the European Environmental and Contact Dermatitis Research Group (EECDRG). Contact Dermatitis 32, 266-272.

**Detailed study summary and results:**

A prospective multicentre study involving a total of 702 patients tested in 7 centres located in Europe was performed. The study involved testing of two types of fragrance mix (FM), its 8 constituents with 1% sorbitan sesquioleate (SSO) and its 8 constituents without SSO and 20% SSO. The concentration of geraniol was 1% when tested as individual constituent.

Description of patch test as cited from Frosch et al., 1995a: *"The series was applied for 2 days to the back with Finn Chambers on Scanpor tape. Readings were made at 2 and 3 days (4 days in some centres), according to published guidelines (3). 7 centres participated in the study: Amersham in England (100 patients), Barcelona in Spain (100 patients), Belfast in Northern Ireland (100 patients), Brussels in Belgium (100 patients), Hellerup in Denmark (124 patients), Oulu in Finland (85 patients) and Dortmund in Germany (100 patients). The patients were unselected consecutive patients patch tested because of suspected contact dermatitis.*"

The results showed that 0.7% (5/702) and 0.4% (3/702) of the consecutive patients were tested positive for geraniol at 1% with and without SSO, respectively.

### 3.1.2.61 STUDY 74-75 (Patch test, consecutive)

**Study reference:**

Frosch, P.J., Pilz, B., Andersen, K.E., Burrows, D., Camarasa, J.G., Dooms-Goossens, A., Ducombs, G., Fuchs, T., Hannuksela, M., Lachapelle, J.M., Lahti, A., Maibach, H.I., Menné, T., Rycroft, R.J.G., Shaw, S., Wahlberg, J.E., White, I.R., Wilkinson, J.D., 1995b. Patch testing with fragrances: results of a multicentre study of the European Environmental and Contact Dermatitis Research Group with 48 frequently used constituents of perfumes. Contact Dermatitis 33, 333-342.

**Detailed study summary and results:**

A prospective multicentre study involving a total of 1323 patients tested in 11 centres located in Europe was performed. The study involved testing of 48 frequently used constituents of perfumes, as well as patch testing with a standard series fragrance mix (FM) containing geraniol. In total 106 patients were patch tested with geraniol (0.1 or 1% in petrolatum) in the Barcelona centre and 1072 patients were patch tested with geraniol (1% in petrolatum with sorbitan sesquioleate (SSO)).

Description of patch test as cited from Frosch et al., 1995b: *"In each centre, a minimum of 100 consecutive patients were tested with the allocated FF* (Fenn fragrance) *materials and the 8% FM with its constituents.*

*For each patient positive to any 1 of the FF materials, a questionnaire was filled out regarding clinical relevance and other sensitizations. Patch testing was performed with Finn Chambers on Scanpor tape applied for 2 days to the back. Readings were made following the guidelines of the ICDRG (16) on days 2 and 3, or in some centres on days 2 and 4".*

The results showed that 0% of the consecutive patients from the Barcelona centre (0/106) were tested positive for geraniol at 0.1% or 1% geraniol (in petrolatum) and that 0.8% of the consecutive patients from a total of 9 European centres (8/1072) were tested positive for geraniol at 1% geraniol (in petrolatum with 1% SSO).

### 3.1.2.62 STUDY 76 (Patch test, selected)

**Study reference:**

Malanin, G., Ohela, K., 1989. Allergic reactions to fragrance-mix and its components. Contact Dermatitis 21, 62-63.

**Detailed study summary and results:**

Each patient patch tested with a standard series at Department of Dermatology, South-Saimaa Central Hospital, Lappeenranta, Finland during the years 1982 and 1985 was simultaneously tested with fragrance-mix and its individual constituents, including geraniol at 3-1% in petrolatum.

Description of patch test as cited from Malanin, G. and Ohela, K., 1989: *A total of 1967 patients were tested using Finn Chambers. The chambers were applied to the upper back for 24 or 48 h, and the results were read about 1 h after removing the test and further on the 3$^{rd}$ (or 4$^{th}$), 5$^{th}$ (or 6$^{th}$) and 7$^{th}$ days after application. Palpable erythema or a stronger reaction, seen on the 3$^{rd}$ day or later, was considered positive.*

The results showed that 0.7% of the patients (14/1967) were tested positive for geraniol.

### 3.1.2.63 STUDY 77 (Patch test, consecutive)

**Study reference:**

Itoh, M., Ishirara, M., Hosono, K., Kantoh, H., Kinoshita, M., Yamada, K., Nishimura, M., 1986. Results of patch tests conducted between 1978 and 1985 using cosmetic ingredients. Skin Research 28 Suppl 2, 230-240.

**Detailed study summary and results:**

A detailed summary of the study and results cannot be presented as the original article is in Japanese. The following information is based on a table in the article.

Patch tests were conducted from 1978-1985 with 5% geraniol (vehicle not reported) on 680 patients with eczema or dermatitis.

A positive reaction was observed in 0.4% (3/680).

### 3.1.2.64 STUDY 78 (Patch test, consecutive)

**Study reference:**

Ferguson, J., Sharma, S., 1984. Cinnamic aldehyde test concentrations. Contact Dermatitis 10, 191-192.

**Detailed study summary and results:**

A detailed summary of the study and results cannot be presented as the original article is a letter to the editor.

In a perfume screening series for sensitivity to fragrances in 241 consecutive patients, October 1981 - June 1983, geraniol were tested at 2% in yellow soft paraffin using the Finn Chamber technique.

A positive reaction was observed in 4.1% of the patients (10/241).

### 3.1.2.65 STUDY 79-81 (Patch test, consecutive)

**Study reference:**

Nishimura, M., Ishihara, M., Itoh, M., Hosono, K., Kantoh, H., 1984. Results of patch tests on cosmetic ingredients conducted between 1979 and 1982. Skin Research 26, 945-954.

**Detailed study summary and results:**

A detailed summary of the study and results cannot be presented as the original article is in Japanese. The following information is based on a table in the article.

Patch tests were conducted on 522 patients with cosmetic dermatitis (212 patients), facial melanosis (35 patients) or non-cosmetic dermatitis or eczema (275 patients).

A positive reaction was observed in 0.5% of the patients with cosmetic dermatitis (1/212), in 0% of the patients with facial melanosis (0/35), and in 0.7% of the patients with non-cosmetic dermatitis or eczema (2/275) for geraniol at 5% (vehicle not reported).

### 3.1.2.66 STUDY 82 (Patch test, consecutive)

**Study reference:**

van Joost, T.H., Stolz, D., van der Hoek, J.S.V., Prens, E.P., 1984. Sensitivity to woodtar. Contact Dermatitis 11, 248.

**Detailed study summary and results:**

A group of 667 patients randomly selected for allergic contact dermatitis were tested with the ICDRG standard battery (wood tar 12%, balsam of Peru 25% and colophony 20%, all in petrolatum), and 1 month later with perfume compounds, including geraniol at 1% in petrolatum.

No sensitisation reaction to geraniol was reported.

### 3.1.2.67 STUDY 83-84 (Patch test, consecutive)

**Study reference:**

Ishihara, M., Itoh, S., Hayashi, S., Satake, T., 1979. Methods of diagnosis in cases of cosmetic dermatitis and facial melanosis in females. Nishinihon Journal of Dermatology 41, 426-439.

**Detailed study summary and results:**

A detailed summary of the study and results cannot be presented as the original article is in Japanese. The following information is based on the abstract in English and a table in the article.

Patch tests were conducted with 2% or 5% geraniol in vaseline on female patients with cosmetic dermatitis (120 patients) or facial melanosis (45 patients).

A positive reaction was observed in 1.7% of the patients with cosmetic dermatitis (2/120) with geraniol at 5%; no reactions were observed with 2%. No sensitisation reactions to geraniol were reported in patients with facial melanosis.

### 3.1.2.68 STUDY 85-87 (Patch test, consecutive)

**Study reference:**

Cronin, E., 1978. Allergy to cosmetics. Acta Dermato-Venereologica, Stockholm 134, 77-82.

**Detailed study summary and results:**

No detailed information on patch test methods is presented in the original article.

Between 1979 and 1980, 2461 patients were tested at St. John's Hospital for Diseases of the Skin, London, UK, and in 1984, 803 male patients and 1033 female patients were tested with geraniol at 2% in petrolatum.

A positive reaction was observed in 0.5% of the male patients in 1984 (4/803), in 0.6% of the female patients in 1984 (6/1033), and in 0.3% of the patients in 1979-1980 (7/2461).

### 3.1.2.69 STUDY 88 (Patch test, consecutive)

**Study reference:**

*Fregert, S., Hjorth, N., 1969. Results of standard patch tests with substances abandoned. Contact Dermatitis Newsletters 5, 85, cited in:*

Hostynek, J.J., Maibach, H.I., 2004. Is there evidence that geraniol causes allergic contact dermatitis? Exogenic Dermatology 3, 318-331.

**Detailed study summary and results:**

A detailed summary of the study and results is not available in the article by Hostynek and Maibach, which presents a review of the available clinical data for geraniol. Only the following data are presented as cited:

In a group of 792 eczematous patients, 0.5% (4/792) showed positive reactions to 10% geraniol in petrolatum.

### 3.1.2.70 STUDY 89 (Patch test, other)

**Study reference:**

Nagtegaal, M.J.C., Pentinga, S.E., Kuik, J., Kezic, S., Rustemeyer, T., 2012. The role of the skin irritation response in polysensitization to fragrances. Contact Dermatitis 67, 28–35.

**Detailed study summary and results:**

The Department of Dermatology of the VU University Medical Centre, The Netherlands, has performed a prospective study of 100 selected patients with contact allergy who were patch tested with 25 individual fragrance chemicals and FM I and II in the period from 2005-2010. The objective of the study was to investigate whether enhanced skin irritability is a risk factor for the development of polysensitisation to fragrance chemicals.

Description of test method as cited from Nagtegaal et al., 2012:

Patch tests: "*Patch tests were performed in accordance with the recommendations of the ICDRG (12). Preparations of test materials in petrolatum were obtained from Trolab® (Almirall-Hermal, Reinbeck, Germany) or Chemotechnique Diagnostics® (Vellinge, Sweden). Van der Bend® patch test chambers (Van der Bend BV, Brielle, The Netherlands) on Fixomull® tape were used. Test chambers were manually filled by a specially trained investigator. The test substances consisted of 27 commercial patch test materials of fragrance chemicals, including FM I (8%) and FM II (14%), and were coded to ensure that the study could be performed in a double-blind fashion. The materials were supplied in polypropylene syringes, and stored in a refrigerator at 5◦C. The patches were applied for 2 days on the upper back, and readings were performed on day 2(48 hr), day 3 (72 hr), and day 7 (144 hr). Methodological and observer errors were minimized, as preparation and reading of the test were performed by only one specially trained person.*

*Polysensitization was defined as three or more allergic reactions to non-cross-reacting fragrance allergens."*

Skin irritation tests: "*This test consisted of the application of SLS at five sites in a row on the non-dominant upper arm for 1 day (24 hr). Van der Bend® patch test chambers on Fixomull® tape were filled with 20 µl of test solution. The SLS test concentrations were 0.0%, 0.45%, 0.67%, 1% and 1.5% in water. New test solutions were prepared every 3 weeks. The participants removed the patches themselves 24 hr after application, after which the test was assessed at day 2, day 3 and day 7 by bioengineering techniques. This included a non-invasive measurement of TEWL by means of a TEWAmeter® (TM300; Courage & Khazaka, Cologne, Germany) and of redness of the skin (erythema index) by means of a DermaSpectrometer® (Cortex Technology, Hadsund, Denmark). The increase in TEWL and erythema index reflects the sensitivity of the skin to SLS irritation. As baseline values of erythema index and TEWL are known to vary day to day, these values were measured every visit. The existing guidelines for assessment of these parameters were followed (13, 14), meaning that the volunteers rested for at least 15 min with uncovered arms before measurement, in a room with a temperature of 20–22◦C, a relative humidity of 35–45%, and no direct incursion of sunlight."*

Statistical analysis: "*All data were analysed for significance by paired samples t-test or Mann–Whitney U-test with SPSS™ statistical software (version 17). The distribution of data was tested by the Shapiro–Wilk normality test. For non-normally distributed data, we applied the Mann–Whitney test. For testing the differences in TEWL between different SLS concentrations and the control site, we used a non-parametric Friedman test followed by Dunn's multicomparison test ($p < 0.001$)."*

Although not a clinical diagnostic patch test study, patch tests were nevertheless performed according to the guidelines of the International Contact Dermatitis Research Group. The results showed that specifically for geraniol 9.0% (95% CI: 4.2-16.4%) of the selected patients (9/100) had positive reactions when tested at 1% in petrolatum.

Individuals with polysensitization (defined as multiple patch test reactions to > 3 non-related allergens) showed significantly higher irritation responses to SLS 1% and 1.5% (as assessed by transepidermal water loss). It was concluded that an enhanced skin irritation response is associated with polysensitization, and that it could be a phenotype for susceptibility to contact allergy.

### 3.1.2.71 STUDY 90 (Patch test, other)

**Study reference:**

Foti, C., Bonamonte, D., Conserva, A., Stingeni, L., Lisi, P., Lionetti, N., Rigano, L., Angelini, G., 2008. Allergic and photoallergic contact dermatitis from ketoprofen: evaluation of cross-reactivities by a

combination of photopatch testing and computerized conformational analysis. Current Pharmaceutical Design 14, 2833-2839.

**Detailed study summary and results:**

The aim of the study by Foti et al., was to identify the substances most frequently associated with sensitization to ketoprofen (KP), and to evaluate, by means of computerized conformational analysis, whether this association could be due to cross-allergy. A total of 15 patients with allergic contact dermatitis and photo-allergic contact dermatitis to KP were patch tested with Società Italiana di Dermatologia Alergologica Professionale ed Ambientale patch test standard series including fragrance mix (FM) and its constituents (including geraniol 2% in petrolatum). Data was collected between 2006 and 2007 in Italy.

Description of the patch test is limited to the photo-patch test as cited here from Foti et al., 2008: *"Photo-patch tests were carried out by applying the allergens on one side of the back and leaving them under occlusion for 2 days; readings were performed at 48 and 96 h (D2 and D4). Simultaneously photopatch tests were carried out by applying the allergens on the other side of the back, taking the bandages off at 24 h and exposing them to UVA rays at the dose of 5 J/cm$^2$(UV 801 KL, PUVA/TLOI, Photochemotherapy Herbert Waldman, Werk für Lichttechnik, Germany), whereas the opposite side of the back was covered with a black cloth. Test reactions were read at 1 and 3 days after irradiation (D2 and D4)."*

The results of the study showed that 0% of the patients with allergic contact dermatitis and photo-allergic contact dermatitis to KP (0/15) were tested positive for geraniol.

### 3.1.2.72 STUDY 91 (Patch test, other)

**Study reference:**

van Joost, T.H., Stolz, E., van der Hoek, J.C.S., 1985. Simultaneous allergy to perfume ingredients. Contact Dermatitis 12, 115-116.

**Detailed study summary and results:**

A detailed summary of the study and results cannot be presented as the original article is a short communication.

242 patients with contact allergy was patch tested with geraniol at 7% (vehicle not reported).

A positive reaction was observed in 0.4% of the patients (1/242).

### 3.1.2.73 STUDY 92 (Patch test, other)

**Study reference:**

Ohela, K., Saramies J., 1983. Perfume sensitivity. Duodecim 99, 215-220.

**Detailed study summary and results:**

A detailed summary of the study and results cannot be presented as the original article is in Finnish. The following information is based on the abstract in English and a table in the article.

467 patients were patch tested with 2% geraniol (vehicle not reported).

A positive reaction was observed in 0.2% of the patients (1/467).

### 3.1.2.74 STUDY 93 (HRIPT)

**Study reference:**

*RIFM, 2000. Repeated insult patch test of geraniol in humans. RIFM Report Number 36679 (RIFM, Woodcliff Lake, NJ, USA), cited in*:

Lapczynski, A., Bhatia, S.P., Foxenberg, R.J., Letizia, C.S., Api, A.M., 2008. Fragrance material review on geraniol. Food and Chemical Toxicology 46 Suppl 11, S160-170.

**Detailed study summary and results:**

A detailed summary of the study and results is not available in the article by Lapczynski et al., 2008 which presents a review of the available data on sensitisation for geraniol. Only the following data are presented:

Description of test method as cited from Lapczynski et al., 2008: "*Human repeated insult patch test (HRIPT). Several repeated insult patch tests were conducted to determine if geraniol would induce dermal sensitization in human volunteers. During the induction phase, a 0.3 ml aliquot of geraniol was applied onto 25 mm Hilltop® Chamber patches which were then applied to test sites on the upper right arm. Patches were allowed to volatilize for 15–40 minutes prior to application. Induction applications were made to the same site on Monday, Wednesday and Friday for a total of nine applications during a 3 weeks period. Following a 10-14-days rest period, a challenge patch was applied to a site not previously exposed on the left upper arm. Patches were applied as in the induction phase and kept in place for 24 h after which time they were removed. Reactions to challenge were scored at 24, 48 and 72 h after application.*

110 volunteers were patch tested with 2% (2362 µg/cm$^2$) geraniol in DEP:EtOH 3:1.

A positive reaction was observed in 0% of the volunteers (0/110).

### 3.1.2.75 STUDY 94 (HRIPT)

**Study reference:**

*RIFM, 2002. Repeated insult patch test (RIPT) with geraniol. RIFM Report Number 44248, (RIFM, Woodcliff Lake, NJ, USA), cited in*:

Lapczynski, A., Bhatia, S.P., Foxenberg, R.J., Letizia, C.S., Api, A.M., 2008. Fragrance material review on geraniol. Food and Chemical Toxicology 46 Suppl 11, S160-170.

**Detailed study summary and results:**

A detailed summary of the study and results is not available in the article by Lapczynski et al., 2008 which presents a review of the available data on sensitisation for geraniol. Only the following data are presented:

Description of test method as cited from Lapczynski et al., 2008: "*Human repeated insult patch test (HRIPT). Several repeated insult patch tests were conducted to determine if geraniol would induce dermal sensitization in human volunteers. During the induction phase, a 0.3 ml aliquot of geraniol was applied onto 25 mm Hilltop® Chamber patches which were then applied to test sites on the upper right arm. Patches were allowed to volatilize for 15–40 minutes prior to application. Induction applications were made to the same site on Monday, Wednesday and Friday for a total of nine applications during a 3 weeks period. Following a 10-14-days rest period, a challenge patch was applied to a site not previously exposed on the left upper arm. Patches were applied as in the induction phase and kept in place for 24 h after which time they were removed. Reactions to challenge were scored at 24, 48 and 72 h after application.*

109 volunteers were patch tested with 5% (5905 μg/cm$^2$) geraniol plus 0.5% tocopherol in DEP:EtOH 3:1.

A positive reaction was observed in 0.9% of the volunteers (1/109).

### 3.1.2.76 STUDY 95 (HRIPT)

**Study reference:**

*RIFM, 2004. Human repeated insult patch test with geraniol (Modified Draize procedure). RIFM Report Number 46888, Woodcliff Lake, NJ, USA), cited in*:

Lapczynski, A., Bhatia, S.P., Foxenberg, R.J., Letizia, C.S., Api, A.M., 2008. Fragrance material review on geraniol. Food and Chemical Toxicology 46 Suppl 11, S160-170.

**Detailed study summary and results:**

A detailed summary of the study and results is not available in the article by Lapczynski et al., 2008 which presents a review of the available data on sensitisation for geraniol. Only the following data are presented:

Description of test method as cited from Lapczynski et al., 2008: "*Human repeated insult patch test (HRIPT). Several repeated insult patch tests were conducted to determine if geraniol would induce dermal sensitization in human volunteers. During the induction phase, a 0.3 ml aliquot of geraniol was applied onto 25 mm Hilltop® Chamber patches which were then applied to test sites on the upper right arm. Patches were allowed to volatilize for 15–40 minutes prior to application. Induction applications were made to the same site on Monday, Wednesday and Friday for a total of nine applications during a 3 weeks period. Following a 10-14-days rest period, a challenge patch was applied to a site not previously exposed on the left upper arm. Patches were applied as in the induction phase and kept in place for 24 h after which time they were removed. Reactions to challenge were scored at 24, 48 and 72 h after application.*

112 volunteers were patch tested with 10% (11810 μg/cm$^2$) geraniol in DEP:EtOH 3:1.

A positive reaction was observed in 2.7% of the volunteers (3/112).

### 3.1.2.77 STUDY 96 (HRIPT)

**Study reference:**

*RIFM, 1964. Repeated insult patch test with geraniol. RIFM Report Number 51135 (RIFM, Woodcliff Lake, NJ, USA, cited in*:

Lapczynski, A., Bhatia, S.P., Foxenberg, R.J., Letizia, C.S., Api, A.M., 2008. Fragrance material review on geraniol. Food and Chemical Toxicology 46 Suppl 11, S160-170.

**Detailed study summary and results:**

A detailed summary of the study and results is not available in the article by Lapczynski et al., 2008 which presents a review of the available data on sensitisation for geraniol. Only the following data are presented:

Description of test method as cited from Lapczynski et al., 2008: "*A 0.5 ml aliquot of geraniol was applied to a Webril swatch (1-in. square of Webril affixed to the center of a 1x 3 in. strip of adhesive bandage) which was then applied to the upper arm of the volunteers."*

40 volunteers were patch tested with 5% (3876 μg/cm$^2$) geraniol in alcohol SDA 39C.

A positive reaction was observed in 0% of the volunteers (0/40).

### 3.1.2.78 STUDY 97 (HRIPT)

**Study reference:**

*RIFM, 1964a. Repeated insult patch test with geraniol. RIFM Report Number 14094 (RIFM, Woodcliff Lake, NJ, USA, cited in*:

Lapczynski, A., Bhatia, S.P., Foxenberg, R.J., Letizia, C.S., Api, A.M., 2008. Fragrance material review on geraniol. Food and Chemical Toxicology 46 Suppl 11, S160-170.

**Detailed study summary and results:**

A detailed summary of the study and results is not available in the article by Lapczynski et al., 2008 which presents a review of the available data on sensitisation for geraniol. Only the following data are presented:

Description of test method as cited from Lapczynski et al., 2008: "*A 0.5 ml aliquot of geraniol was applied to a Webril swatch (1-in. square of Webril affixed to the center of a 1x 3 in. strip of adhesive bandage) which was then applied to the upper arm of the volunteers."*

41 volunteers were patch tested with 12.5% (9690 μg/cm$^2$) geraniol in ethanol.

A positive reaction was observed in 0% of the volunteers (0/41).

### 3.1.2.79 STUDY 98-99 (HRIPT, modified Draize procedure) (also cited in REACH registration dossier)

**Study reference:**

Marzulli, F.N., Maibach, H.I., 1980. Contact allergy: predictive testing of fragrance ingredients in humans by Draize and the maximization methods. Journal of Environmental Pathology and Toxicology 3, 235-245.

**Detailed study summary and results:**

HRIPT, modified Draize procedure.

Description of test method as cited from Marzulli and Maibach, 1980: "*Test substance: Apply 0.2 ml or 0.2 g at highest tolerable concentration. Skin site: Arm or upper back. Patch type: Square occlusive Band Aid®; no perforations. Induction: Ten patches, 48-72 hr each. Rest period: 2 weeks. Challenge: Apply 72 hr patch on new skin site with nonirritating concentration. Rechallenge if test was conducted with other positives. Scoring: Grade 1, erythema; Grade 2, erythema and induration; Grade 3, vesiculation; Grade 4, bulla formation. Grade 2 or greater is evidence of skin sensitization. Results: Reported as response fraction or percent positive (sensitization index).*"

104 volunteers were patch tested with 10% geraniol in petrolatum and 73 volunteers were patch tested with 10% geraniol in ethanol.

A positive reaction was observed in 0% of the volunteers (0/104) at 10% geraniol in petrolatum and in 2.7% of the volunteers (2/73) at 10% geraniol in ethanol.

### 3.1.2.80 STUDY 100 (HMT) (as cited in REACH registration dossier)

**Study reference:**

Study report from 1986.

**Detailed study summary and results:**

A detailed summary of the study and results is not available in the REACH registration dossier. It is mentioned "*Original reference not translated (Japanese); English abstract available.*" Only the following data are presented:

Human maximisation test. Study with 25 volunteers. Geraniol at 6% (vehicle not reported)

A positive reaction was observed in 0% of the volunteers (0/25).

### 3.1.2.81 STUDY 101 (HMT) (also cited in REACH registration dossier)

**Study reference:**

Marzulli, F.N., Maibach, H.I., 1980. Contact allergy: predictive testing of fragrance ingredients in humans by Draize and the maximization methods. Journal of Environmental Pathology and Toxicology 3, 235-245.

**Detailed study summary and results:**

Description of test method as cited from Marzulli and Maibach, 1980: "*Test substance: Apply 0.3 ml or 0.3 g at 10 times the use concentration. Apply 1% SLS 24 hr before the first 48 hr exposure (in Caucacians) except do not use SLS with irritating substances. Vehicle: Petrolatum. Skin site: Forearm for induction. Patch type: 2 cm square non-woven cotton cloth (Webril®, Curity) covered with plastic tape (3M Blenderm®) over which is a final cover of Micropore® or Dermiclear® tape Uohnson & Johnson). Induction: Five 48 hr patches. Rest period:10 days to 2 weeks. Challenge: Apply 5% SLS for a half hour before challenge with the test material on the shoulder. Use control SLS patch, and use the back for challenge. Apply one 48 hr patch and read at 48 and 72 hr.*

25 volunteers were patch tested with 6% geraniol in petrolatum.

A positive reaction was observed in 0% of the volunteers (0/25).

### 3.1.2.82 STUDY 102 (HMT)

**Study reference:**

*RIFM, 1979. Report on human maximization studies. RIFM Report Number 1697, June 18 (RIFM, Woodcliff Lake, NJ, USA), cited in*:

Lapczynski, A., Bhatia, S.P., Foxenberg, R.J., Letizia, C.S., Api, A.M., 2008. Fragrance material review on geraniol. Food and Chemical Toxicology 46 Suppl 11, S160-170.

**Detailed study summary and results:**

A detailed summary of the study and results is not available in the article by Lapczynski et al., 2008 which presents a review of the available data on sensitisation for geraniol. The following data are presented:

Description of test method as cited from Lapczynski et al., 2008: "M*aximization tests were carried out with geraniol. Application was under occlusion to the same site on the forearms of the subjects for five alternate-days 48 h periods. Patch sites were pretreated for 24 h with 1% or 5% aqueous SLS under occlusion for the initial patch only. Following a 10–14 days rest period, challenge patches were applied under occlusion to fresh sites for 48 h. Challenge applications were preceded by 30-minute applications of 5% or 10% aqueous SLS under occlusion on the left side whereas the test material was applied without SLS treatment on the right side."*

24 volunteers were patch tested with 6% (4140 μg/cm$^2$) geraniol in petrolatum.

A positive reaction was observed in 0% of the volunteers (0/24).

### 3.1.2.83 STUDY 103 (HMT)

**Study reference:**

*RIFM, 1979a. Report on human maximization studies. RIFM Report Number 1697, July 6 (RIFM, Woodcliff Lake, NJ, USA), cited in*:

Lapczynski, A., Bhatia, S.P., Foxenberg, R.J., Letizia, C.S., Api, A.M., 2008. Fragrance material review on geraniol. Food and Chemical Toxicology 46 Suppl 11, S160-170.

**Detailed study summary and results:**

A detailed summary of the study and results is not available in the article by Lapczynski et al., 2008 which presents a review of the available data on sensitisation for geraniol. The following data are presented:

Description of test method as cited from Lapczynski et al., 2008: "M*aximization tests were carried out with geraniol. Application was under occlusion to the same site on the forearms of the subjects for five alternate-days 48 h periods. Patch sites were pretreated for 24 h with 1% or 5% aqueous SLS under occlusion for the initial patch only. Following a 10–14 days rest period, challenge patches were applied under occlusion to fresh sites for 48 h. Challenge applications were preceded by 30-minute applications of 5% or 10% aqueous SLS under occlusion on the left side whereas the test material was applied without SLS treatment on the right side."*

26 volunteers were patch tested with 6% (4140 μg/cm$^2$) geraniol in petrolatum.

A positive reaction was observed in 3.8% of the volunteers (1/26).

### 3.1.2.84 STUDY 104 (HMT) (also cited in REACH registration dossier)

**Study reference:**

*Grief, N. 1967. Cutaneous safety of fragrance material as measured by the maximization test. American Perfumer and Cosmetics 82, 54–57), cited in*:

Lapczynski, A., Bhatia, S.P., Foxenberg, R.J., Letizia, C.S., Api, A.M., 2008. Fragrance material review on geraniol. Food and Chemical Toxicology 46 Suppl 11, S160-170.

**Detailed study summary and results:**

A detailed summary of the study and results is not available in the article by Lapczynski et al., 2008 which presents a review of the available data on sensitisation for geraniol. The following data are presented:

Description of test method as cited from Lapczynski et al., 2008: "M*aximization tests were carried out with geraniol. Application was under occlusion to the same site on the forearms of the subjects for five alternate-days 48 h periods. Patch sites were pretreated for 24 h with 1% or 5% aqueous SLS under occlusion for the initial patch only. Following a 10–14 days rest period, challenge patches were applied under occlusion to fresh sites for 48 h. Challenge applications were preceded by 30-minute applications of 5% or 10% aqueous SLS under occlusion on the left side whereas the test material was applied without SLS treatment on the right side."*

25 volunteers were patch tested with 6% (4140 μg/cm$^2$) geraniol in petrolatum.

A positive reaction was observed in 0% of the volunteers (0/25).

### 3.1.2.85 STUDY 105 (Case study)

**Study reference:**

Swerdlin, A., Rainey, D., Storrs, F.J., 2010. Fragrance mix reactions and lime allergic contact dermatitis. Dermatitis 21, 214-216.

**Detailed study summary and results:**

At the Department of Dermatology, Oregon Health & State University, Portland, OR, USA a 54-year-old female bartender with chronic hand dermatitis was patch tested with the Department's standard and supplemental trays and with several of the patients' personal items including geraniol at 2% in petrolatum.

Description of patch test as cited from Swerdlin et al., 2010: "*With the exception of the peels, which were applied directly to Scanpor tape (Norgesplaster Alpharma A/S, Vennesla, Norway), the allergens were first*

*placed into Finn Chambers (Epitest Ltd Oy, Tuusula, Finland) before application to Scanpor tape. The tape was then applied to normal uninvolved skin on the patient's upper back. The allergens were removed after 48 hours, and reactions were assessed.*"

The result of the patch tests showed positive reactions to lime peel (both endocarp and exocarp in confirmatory tests), geraniol, fragrance mix I and fragrance mix II all of which were clinically relevant to her work as a bartender. The patient had negative patch tests towards D-limonene and lemon peel and according to the authors patch tests with citral were not available. The authors speculated that the patient may possibly have had a false-negative reaction to lemon peel since the allergen within the peel does not always reach the skin during patch testing.

### 3.1.2.86 STUDY 106 (Case study)

**Study reference:**

Tanko, Z., Shab, A., Diepgen, T.L., Weisshaar, E., 2009. Polyvalent type IV sensitizations to multiple fragrances and a skin protection cream in a metal worker. Journal of the German Society of Dermatology 7, 541-543.

**Detailed study summary and results:**

At the Department of Clinical Social Medicine, Occupational and Environmental Dermatology, University Hospital Heidelberg, Germany a 48-year-old male metalworker with chronic recurrent hand dermatitis (symptoms were maximal from Wednesday to Friday and improved during weekends) was patch tested with the patch test series of the German Contact Dermatits Research Group and 18 further fragrances including geraniol.

There is no description of the patch test in Tanko et al., 2009.

The result of the patch tests showed positive reactions to fragrance mix, Balsam of Peru, epoxy resin, fragrance mix II, skin protection cream Travabon®, hydroxycitronellal, lilial, tree moss, geraniol, oak moss absolute, citral, citronellol, farnesol and lyral®.

The patient was submitted to a three-week inpatient occupational dermatologic treatment and the patient's workplace was inspected including all technical emulsions and oils. None of the positively tested contact allergens were identified in any product from the workplace. The patient returned to work after complete healing of the hand dermatitis but was diagnosed with irritant hand dermatitis four weeks later. According to the authors "*Mixed forms of irritant and allergic contact dermatitis are frequent in occupational dermatology and in many cases difficult to differentiate. Most likely, initially irritant contact dermatitis of*

*the hand developed and subsequently type IV sensitizations to the skin protection cream Travabon® and two contained fragrances, geraniol and citronellol, were acquired.*"

### 3.1.2.87 STUDY 107 (Case study)

**Study reference:**

Goossens, A., Merckx, L., 1997. Allergic contact dermatits from farnesol in a deodorant. Contact Dermatitis 37, 179-189.

**Detailed study summary and results:**

In a study of the association between contact allergy to farnesol and contact allergy to balsam of Peru a total of 7 subjects sensitive to farnesol were patch tested with balsam of Peru, fragrance mix and other perfume ingredients (including geraniol at 20% in petrolatum).

The method of patch testing was not described by Goossens & Merckx 1997.

The results of the study showed that 43% of the patients (3/7) were tested positive for geraniol.

### 3.1.2.88 STUDY 108 (Case study) (also cited in REACH registration dossier)

**Study reference:**

Keil, H., 1947. Contact dermatitis due to oil of citronella. The Journal of Investigate Dermatology 8, 327-334.

**Detailed study summary and results:**

Three cases of eczematous contact-type hypersensitivitity were patch tested with geraniol at 1% in acetone.

The method of patch testing was not described by Goossens & Merckx 1997.

The results of the study showed that 33% of the patients (1/3) were tested positive.

## 4 ENVIRONMENTAL HAZARDS

Classification for environmental hazards is not a part of the CLH proposal for geraniol.