

**Committee for Risk Assessment
RAC**

Annex 1

Background document

to the Opinion proposing harmonised classification
and labelling at EU level of

geraniol; (2E)-3,7-dimethylocta-2,6-dien-1-ol

EC Number: 203-377-1

CAS Number: 106-24-1

CLH-O-0000001412-86-224/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

14 September 2018

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; (2E)- 3,7-dimethylocta-2,6-dien-1-ol

EC Number: 203-377-1

CAS Number: 106-24-1

Index Number: -

Contact details for dossier submitter:

Danish Environmental Protection Agency

Haraldsgade 53, 2100 Kbh Ø, Denmark

e-mail: mst@mst.dk

Version number: 2

Date: 30 August 2017

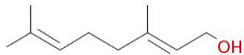
CONTENTS

| | | |
|-----------|--|-----------|
| 1 | IDENTITY OF THE SUBSTANCE | 3 |
| 1.1 | NAME AND OTHER IDENTIFIERS OF THE SUBSTANCE..... | 3 |
| 1.2 | COMPOSITION OF THE SUBSTANCE | 4 |
| 2 | PROPOSED HARMONISED CLASSIFICATION AND LABELLING..... | 5 |
| 2.1 | PROPOSED HARMONISED CLASSIFICATION AND LABELLING ACCORDING TO THE CLP CRITERIA | 5 |
| 3 | HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING | 7 |
| 4 | JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL..... | 7 |
| 5 | IDENTIFIED USES | 8 |
| 6 | DATA SOURCES..... | 8 |
| 7 | PHYSICOCHEMICAL PROPERTIES..... | 9 |
| 8 | EVALUATION OF PHYSICAL HAZARDS | 9 |
| 9 | TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION) | 10 |
| 10 | EVALUATION OF HEALTH HAZARDS..... | 10 |
| 10.1 | ACUTE TOXICITY - ORAL ROUTE | 10 |
| 10.2 | ACUTE TOXICITY - DERMAL ROUTE | 10 |
| 10.3 | ACUTE TOXICITY - INHALATION ROUTE | 10 |
| 10.4 | SKIN CORROSION/IRRITATION | 10 |
| 10.5 | SERIOUS EYE DAMAGE/EYE IRRITATION | 10 |
| 10.6 | RESPIRATORY SENSITISATION..... | 10 |
| 10.7 | SKIN SENSITISATION | 10 |
| 10.8 | SHORT SUMMARY AND OVERALL RELEVANCE OF THE PROVIDED INFORMATION ON SKIN SENSITISATION..... | 25 |
| 10.8.1 | <i>Animal data</i> | 26 |
| 10.8.2 | <i>Human data</i> | 27 |
| 10.8.3 | <i>Human exposure</i> | 28 |
| 10.9 | COMPARISON WITH THE CLP CRITERIA | 30 |
| 10.9.1 | <i>Animal data</i> | 30 |
| 10.9.2 | <i>Human data</i> | 31 |
| 10.9.3 | <i>Exposure considerations</i> | 32 |
| 10.9.1 | <i>Weight of Evidence</i> | 33 |
| 10.10 | CONCLUSION ON CLASSIFICATION AND LABELLING FOR SKIN SENSITISATION | 34 |
| 10.11 | GERM CELL MUTAGENICITY | 44 |
| 10.12 | CARCINOGENICITY | 44 |
| 10.13 | REPRODUCTIVE TOXICITY..... | 44 |
| 10.14 | SPECIFIC TARGET ORGAN TOXICITY-SINGLE EXPOSURE | 44 |
| 10.15 | SPECIFIC TARGET ORGAN TOXICITY-REPEATED EXPOSURE | 44 |
| 10.16 | ASPIRATION HAZARD..... | 44 |
| 11 | EVALUATION OF ENVIRONMENTAL HAZARDS..... | 44 |
| 12 | EVALUATION OF ADDITIONAL HAZARDS | 44 |
| 13 | ADDITIONAL LABELLING | 44 |
| 14 | REFERENCES..... | 44 |
| 15 | ANNEXES..... | 49 |

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

| | |
|--|---|
| Name(s) in the IUPAC nomenclature or other international chemical name(s) | Geraniol; (2E)-3,7-dimethylocta-2,6-dien-1-ol |
| Other names (usual name, trade name, abbreviation) | (E)-3,7-Dimethyl-2,6-octadien-1-ol 3,7-Dimethyl-trans-2,6-octadien-1-ol; Trans-3,7-Dimethyl-2,6-octadien-1-ol; Trans-Geraniol; β-Geraniol; (E)-Geraniol; (E)-Nerol; Geraniol, Geranyl alcohol; Lemonol; MosquitoSafe; NSC 9279 (SCCS 2012) |
| ISO common name (if available and appropriate) | |
| EC number (if available and appropriate) | 203-377-1 |
| EC name (if available and appropriate) | Geraniol |
| CAS number (if available) | 106-24-1 |
| Other identity code (if available) | |
| Molecular formula | C ₁₀ H ₁₈ O |
| Structural formula |  |
| SMILES notation (if available) | CC(=CCC/C(=C/CO)/C)C |
| Molecular weight or molecular weight range | 154.2493 Da |
| Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate) | Not applicable |
| Description of the manufacturing process and identity of the source (for UVCB substances only) | Not applicable |
| Degree of purity (%) (if relevant for the entry in Annex VI) | ≥ 98.0 (commercially available geraniol) |

Geraniol; (2E)-3,7-dimethylocta-2,6-dien-1-ol, hereafter referred to as “geraniol”, is a component of palmarosa oil, geranium oil, citronella oil, rose oil, lavender oil and jasmine oil (SCCS 2012).

Geraniol forms oxidation products with increased sensitizing capacity both via spontaneous autoxidization at air exposure and via metabolic oxidation. Geranial and neral together with hydroperoxide have been identified as oxidation products when geraniol autoxidizes. Geranial and neral were also identified as metabolites of geraniol (SCCS 2012).

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

Geranial and neral constitute the two cis-trans stereo-isomers of the substance citral (CAS 5392-40-5), for which a separate CLH proposal is submitted by the DK EPA (simultaneously with the current CLH proposal for geraniol).

Geraniol is commonly used as a fragrance, mainly in cosmetics but also in various cleaning and maintenance products.

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

| Constituent (Name and numerical identifier) | Concentration range (% w/w minimum and maximum in multi-constituent substances) | Current CLH in Annex VI Table 3.1 (CLP) | Current self-classification and labelling (CLP) |
|---|---|---|---|
| (2E)-3,7-dimethylocta-2,6-dien-1-ol CAS No: 106-24-1 | ≥ 98.0 | None | Skin sens. 1 or 1B; H317 Skin irrit. 2; H315 Eye dam. 1; H318 or eye irrit. 2; H319 STOT SE 3; H335(RT1) Aquatic Acute 2 Aquatic Chronic 2; H411 |

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

| Impurity (Name and numerical identifier) | Concentration range (% w/w minimum and maximum) | Current CLH in Annex VI Table 3.1 (CLP) | Current self-classification and labelling (CLP) | The impurity contributes to the classification and labelling |
|--|---|---|---|--|
| Not applicable | - | - | - | - |

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

| Additive (Name and numerical identifier) | Function | Concentration range (% w/w minimum and maximum) | Current CLH in Annex VI Table 3.1 (CLP) | Current self-classification and labelling (CLP) | The additive contributes to the classification and labelling |
|--|----------|---|---|---|--|
| Not applicable | | | | | |

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5:

| | Index No | International Chemical Identification | EC No | CAS No | Classification | | Labelling | | | Specific Conc. Limits, M-factors | Notes |
|---|----------|---------------------------------------|-----------|----------|-----------------------------------|--------------------------|--------------------------------|--------------------------|---------------------------------|----------------------------------|-------|
| | | | | | Hazard Class and Category Code(s) | Hazard statement Code(s) | Pictogram, Signal Word Code(s) | Hazard statement Code(s) | Suppl. Hazard statement Code(s) | | |
| Current Annex VI entry | | | | | | | | | | | |
| Dossier submitters proposal | | Geraniol | 203-377-1 | 106-24-1 | Skin Sens. 1A | H317 | GHS07 Wng | H317 | | | |
| Resulting Annex VI entry if agreed by RAC and COM | | Geraniol | 203-377-1 | 106-24-1 | Skin Sens. 1A | H317 | GHS07 Wng | H317 | | | |

Table 6: Reason for not proposing harmonised classification and status under public consultation

| Hazard class | Reason for no classification | Within the scope of public consultation |
|--|---|--|
| Explosives | hazard class not assessed in this dossier | No |
| Flammable gases (including chemically unstable gases) | hazard class not assessed in this dossier | No |
| Oxidising gases | hazard class not assessed in this dossier | No |
| Gases under pressure | hazard class not assessed in this dossier | No |
| Flammable liquids | hazard class not assessed in this dossier | No |
| Flammable solids | hazard class not assessed in this dossier | No |
| Self-reactive substances | hazard class not assessed in this dossier | No |
| Pyrophoric liquids | hazard class not assessed in this dossier | No |
| Pyrophoric solids | hazard class not assessed in this dossier | No |
| Self-heating substances | hazard class not assessed in this dossier | No |
| Substances which in contact with water emit flammable gases | hazard class not assessed in this dossier | No |
| Oxidising liquids | hazard class not assessed in this dossier | No |
| Oxidising solids | hazard class not assessed in this dossier | No |
| Organic peroxides | hazard class not assessed in this dossier | No |
| Corrosive to metals | hazard class not assessed in this dossier | No |
| Acute toxicity via oral route | hazard class not assessed in this dossier | No |
| Acute toxicity via dermal route | hazard class not assessed in this dossier | No |
| Acute toxicity via inhalation route | hazard class not assessed in this dossier | No |
| Skin corrosion/irritation | hazard class not assessed in this dossier | No |
| Serious eye damage/eye irritation | hazard class not assessed in this dossier | No |
| Respiratory sensitisation | hazard class not assessed in this dossier | No |
| Skin sensitisation | new harmonised classification proposed | Yes |
| Germ cell mutagenicity | hazard class not assessed in this dossier | No |
| Carcinogenicity | hazard class not assessed in this dossier | No |
| Reproductive toxicity | hazard class not assessed in this dossier | No |
| Specific target organ toxicity-single exposure | hazard class not assessed in this dossier | No |
| Specific target organ toxicity-repeated exposure | hazard class not assessed in this dossier | No |
| Aspiration hazard | hazard class not assessed in this dossier | No |
| Hazardous to the aquatic environment | hazard class not assessed in this dossier | No |
| Hazardous to the ozone layer | hazard class not assessed in this dossier | No |

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Geraniol has no classification and labelling history under Directive 67/548/EEC or Regulation (EC) No 1272/2008.

Geraniol is one of the 26 fragrance substances for which individual labelling is required under the Cosmetics Regulation (EC no. 1223/2009) and the Detergents Regulation (EC no 648/2004). Geraniol is also among the 13 allergenic fragrance substances listed in the SCCS opinion which have been frequently reported as well-recognised contact allergens in consumers and thus of most concern (SCCS 2012).

In 2012 the Scientific Committee on Consumer Safety (SCCS) published an opinion on fragrance allergens in cosmetic products. In this opinion geraniol has been categorised as an established contact allergen in humans which has given rise to a significant number (>100-1000) of published cases on contact allergy (SCCS 2012).

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Justification that action is needed at Community level is required.

Reason for a need for action at Community level:

Differences in self-classification
Disagreement by DS with current self-classification

Further detail on need of action at Community level

New classification criteria and difference in self-classification

With the 2nd ATP to CLP new classification criteria were introduced for skin sensitisation allowing sub-categorisation of skin sensitisers into Category 1A (strong sensitisers) and Category 1B (other sensitisers, corresponding to the existing Category 1). A classification in Cat. 1A will lead to more stringent labelling requirements for mixtures containing the substance and is currently regarded as the most important risk management measure for such substances. Correct identification of Category 1A skin sensitisers is thus expected to increase the human protection level for strong sensitisers due to the requirement of labelling of mixtures containing Cat 1A sensitisers $\geq 0.01\%$ with EUH208: “Contains [name of sensitising substance]. May produce an allergic reaction”.

In the REACH registration dossier the registrants have selfclassified geraniol as a Category 1 skin sensitiser. The same is true for 91.8% (1506 of 1641) of the notifiers in the C&L Inventory (May 2017). Of the remaining notifiers 4.0% (66 of 1641) has notified geraniol as a skin sensitiser in Category 1B, 1.6% (26 of 1641) have not stated the hazard class for sensitisation but have indicated H317 as a labelling hazard statement, and 2.6% (43 of 1641) have not notified a classification for skin sensitisation.

Widespread use in low concentrations

Geraniol is a fragrance that is manufactured in or imported to the EU in amounts of 1000-10.000 tonnes/year and is widely used in products on the EU market. The registered categories of use for consumers are mainly cosmetics, a variety of household products for cleaning and maintenance and biocidal products. The registered uses for professionals are cleaning agents and polishes and wax blends (see section 5 below on identified uses). As geraniol is widely used in a range of frequently used consumer products the general population can be exposed from many different sources.

Geraniol is generally present in low concentrations in individual consumer products. The International Fragrance Association (IFRA) has established maximum recommended limits of geraniol in specific product categories based on a quantitative risk assessment approach. The maximum limits of geraniol in leave-on cosmetic products are between 0.3-5.3% depending on the specific product category. The recommended limits for rinse-off cosmetic products are between 5.0-8.6% and the recommended

maximum limit for non-cosmetic products with direct skin contact is 2.5% (see Table 10 in section 10.8.3 on human exposure) (IFRA 2007).

The SCCS opinion refers to a number of surveys on the presence and content of various allergenic fragrances in various consumer products. Geraniol has been found to be present in 12-49% of the products investigated in different surveys of consumer products. It was concluded by SCCS that taking the total exposure into account, exposure to all 26 allergenic fragrances is foreseeable in daily life (SCCS 2012). The Danish EPA has conducted surveys and assessments of a broad range of consumer products over the last decades. Geraniol has been identified in different types of products, such as cosmetic products (adults and children), household products, and in toys for small children. Generally geraniol is found in low concentrations (>0 - <0.15%) in the investigated products with some exceptions (see also section 10.8.3 on human exposure) (DK EPA database, search February 2017). Data from the Danish Product Register further show that geraniol is present in various products for professional use (mainly cleaning products) and mostly in low concentrations <0.1% (The Danish Product Register, 2016).

Human exposure to geraniol seems to be low based on the IFRA recommendations and reported contents in various consumer products. However, the exposure is assessed to be frequent due to the widespread uses and the high tonnage level of geraniol. It is thus difficult for consumers to avoid exposure.

Human data confirm strong potency of geraniol

Positive patch test frequencies from 92 human patch tests range from 0.1-30% and frequencies equal to or exceeding 2% for selected dermatitis patients and 1% for consecutive (unselected) dermatitis patients are reported in a number of studies. The total number of positive reactions in published cases is > 100 (more than 900). Overall the human data confirm the potency of geraniol.

5 IDENTIFIED USES

Geraniol is used as a fragrance mainly in cosmetics but also in cleaning and maintenance products. Registered uses for consumers include: cosmetics, personal care products, perfumes, fragrances, washing and cleaning products, water softeners, polishes and waxes, air care products, biocidal products, coatings and paints, thinners and paint removers, fillers, plasters, putties and modelling clay, finger paints, inks and toners. Registered uses for professionals include: washing and cleaning products and polishes and waxes.

6 DATA SOURCES

One of the primary sources of information for this CLH report is the SCCS opinion on fragrance allergens from 2012 which contains the most recent and comprehensive assessment of available information on geraniol as well as other fragrance allergens up to year 2011 (SCCS 2012). References on the data cited in this opinion for geraniol have been retrieved when possible.

A supplementary search in the open literature has been done for the period from January 2009 and until November 2016 in order to ensure that potentially relevant studies published after the SCCS opinion are taken into account. The searches have included literature databases such as SciFinder, PubMed and Scopus as well as searches in sources such as OECD SIDS, IPCS INCHEM.

Data in the publicly available part of the REACH registration dossier for geraniol have been assessed as well.

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

| Property | Value | Reference | Comment (e.g. measured or estimated) |
|--|---|----------------------------|--------------------------------------|
| Physical state at 20 °C and 1013 hPa | Colourless to pale yellow, oily liquid with a pleasant floral odour | REACH registration dossier | Measured |
| Melting/freezing point | -15 °C | REACH registration dossier | Measured |
| Boiling point | >204 °C at 2013 hPa (decomposition) | REACH registration dossier | Measured |
| Relative density | 0.89 g/cm ³ at 20 °C | REACH registration dossier | Measured |
| Vapour pressure | 0.266 hPa at 20 °C | REACH registration dossier | Measured |
| Surface tension | No data | REACH registration dossier | - |
| Water solubility | 100 mg/L at 25 °C | REACH registration dossier | Measured |
| Partition coefficient n-octanol/water | 2.6 at 25 °C | REACH registration dossier | Measured |
| Flash point | >100 °C at 1013 hPa | REACH registration dossier | Measured |
| Flammability | No data | REACH registration dossier | - |
| Explosive properties | No data | REACH registration dossier | - |
| Self-ignition temperature | 250 °C at >1002 - <1018 hPa | REACH registration dossier | Measured |
| Oxidising properties | No data | REACH registration dossier | - |
| Granulometry | No data/not applicable | REACH registration dossier | - |
| Stability in organic solvents and identity of relevant degradation products | No data | REACH registration dossier | - |
| Dissociation constant | No data | REACH registration dossier | - |
| Viscosity (dynamic) | 8.4 mPa*s (dynamic) at 17 °C | REACH registration dossier | Measured |

8 EVALUATION OF PHYSICAL HAZARDS

Physical hazards have not been assessed in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

No relevant non-human or human information has been located.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Hazard class not assessed in this dossier.

10.2 Acute toxicity - dermal route

Hazard class not assessed in this dossier.

10.3 Acute toxicity - inhalation route

Hazard class not assessed in this dossier.

10.4 Skin corrosion/irritation

Hazard class not assessed in this dossier.

10.5 Serious eye damage/eye irritation

Hazard class not assessed in this dossier.

10.6 Respiratory sensitisation

Hazard class not assessed in this dossier.

10.7 Skin sensitisation

Table 8 summarises relevant animal studies with geraniol which include a total of 16 studies: 9 LLNAs, 1 *ex vivo* LLNA-BrdU ELISA, 5 GPMTs, and 1 Buehler test. Seven of the below reported studies are included in the REACH Registration dossier.

Table 8: Summary table of animal studies on skin sensitisation (chronological order)

| Method, guideline, deviations if any | Species, strain, sex, no/group | Test substance, | Dose levels duration of exposure | Results | Reference |
|--------------------------------------|--------------------------------------|---|---|-------------------------|----------------------|
| LLNA | | | | | |
| LLNA TG/GLP: no information | Mice (CBA/Ca), female n = 3/group | Geraniol (in AOO 4:1) Purity 99% | 0, 5, 10, 15, 20 and 30% Exp: 3 days | EC3: 22.4%, sensitising | Hagvall et al., 2007 |
| LLNA TG/GLP: no information | Mice (CBA/Ca), female n = 3/group | Geraniol air-exposed for 10 weeks (in AOO 4:1) Purity 99% | 0, 1, 3, 6, 10 and 20% Exp: 3 days | EC3: 4.4%, sensitising | Hagvall et al., 2007 |

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

| Method, guideline, deviations if any | Species, strain, sex, no/group | Test substance, | Dose levels duration of exposure | Results | Reference |
|--|--------------------------------------|--|--|--|---|
| | | at start, 80% after 10 weeks | | | |
| LLNA TG/GLP: no information | Mice (CBA/Ca), female n = 3/group | Geraniol air-exposed for 45 weeks (in AOO 4:1) Purity 99% at start, 20% after 45 weeks | 0, 0.5, 1, 3, 6 and 10% Exp: 3 days | EC3: 5.8%, sensitising | Hagvall et al., 2007 |
| LLNA OECD TG 429 | Mice (CBA/Ca), female n = 4/dose | Geraniol (in 1:3 EtOH:DEP) Purity 98.5% | 0, 2.5, 5, 10, 25 and 50% | EC3: 11.4%, sensitising | Lalko & Api, 2006 (also cited in REACH reg.) |
| LLNA | Mice (no further info) n = 4/dose | Geraniol (in 3:1 EtOH:DEP) | 2.5, 5, 10, 25 and 50% | EC3: 11.4%, sensitising <i>NB: The EC3 value, test concentrations and no. of animals tested are identical to the study above but the vehicles are reported differently. From the references cited it is not possible to identify whether the identical results may actually refer to the same study (but with a mistake reported for the use of vehicle).</i> | Unpublished summary report RIFM 2009 (RIFM 2003t), as cited in SCCS 2012 |
| LLNA (no reported deviations from OECD TG 429) | Mice (CBA/Ca), male n = 4/dose | Geraniol (in EtOH) Purity 98.5% | 0, 1, 3, 10, 30 and 50% | EC3: 5.6%, sensitising | Unpublished summary report RIFM 2009 (RIFM 2001j), as cited in SCCS 2012; Lalko et al., 2004 (also cited in REACH reg.) |
| LLNA (no reported deviations from OECD TG 429) | Mice (CBA/Ca), male n = 4/dose | Geraniol (in DEP) Purity 98.5% | 0, 1, 3, 10, 30 and 50% | EC3: 11.8%, sensitising | Unpublished summary report RIFM 2009 (RIFM 2001k), as cited in SCCS 2012; Lalko et al., 2004 (also cited in REACH reg.) |
| LLNA (no reported deviations from OECD TG 429) | Mice (CBA/Ca), male n = 4/dose | Geraniol (EtOH:DEP 1:3) | 0, 1, 3, 10, 30 and 50% | EC3: 20.4%, sensitising | Unpublished summary report RIFM 2009 (RIFM |

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

| Method, guideline, deviations if any | Species, strain, sex, no/group | Test substance, | Dose levels duration of exposure | Results | Reference |
|--|---|---|--|--|---|
| | | Purity 98.5% | | | 2001), as cited in SCCS 2012; Lalko et al., 2004 (also cited in REACH reg.) |
| LLNA (no reported deviations from OECD TG 429) | Mice (CBA/Ca), male n = 4/dose | Geraniol (EtOH:DEP 3:1) Purity 98.5% | 0, 1, 3, 10, 30 and 50% | EC3: 25.8%, sensitising | Unpublished summary report RIFM 2009 (RIFM 2001m), as cited in SCCS 2012; Lalko et al., 2004 (also cited in REACH reg.) |
| <i>Ex vivo</i> LLNA-BrdU ELISA TG/GLP: no information | Mice (Balb/c), female n = 4/dose | Geraniol (in AOO 4:1) | 0, 2.5, 10, 20 and 50% Exp: 3 days, duration 5 days | EC3: 13.1%, sensitising | Ulker et al., 2014 |
| GPMT | | | | | |
| GPMT (acc. to Magnusson and Kligman 1969) | Guinea pig (Dunkin Hartley) 10 animals | Geraniol (in Dobs/saline for intradermal induction; in 70/30 acetone/PEG 400 for topical induction and challenge) | Intradermal ind.: 0.1% Topical ind.: 50% Chall. conc.: 10% | No sensitisation observed | Unpublished report RIFM 1989, as cited in Lapczynski et al., 2008 |
| GPMT (acc. to Magnusson and Kligman 1969) | Guinea pig (Dunkin Hartley) 10 animals | Geraniol (in Dobs/saline for intradermal induction; in acetone for topical induction and challenge) | Intradermal ind.: 0.1% Topical ind.: 50% Chall. conc.: 10% | Sensitisation observed | Unpublished report RIFM 1989, as cited in Lapczynski et al., 2008 |
| GPMT (acc. to Magnusson and Kligman 1969) | Guinea pig (Dunkin Hartley) 6 animals | Geraniol (in petrolatum) | Intradermal ind.: 5% Topical ind.: 30% Chall. conc.: 10% | Sensitisation observed, positive reactions seen in 3/6 animals | Unpublished report RIFM 1977, as cited in Lapczynski et al., 2008 |
| GPMT | Guinea pig (Himalayan) | Geraniol (in | Intradermal ind.: | Sensitisation observed | Klecak et al., 1977 (also |

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

| Method, guideline, deviations if any | Species, strain, sex, no/group | Test substance, | Dose levels duration of exposure | Results | Reference |
|---|-----------------------------------|---------------------------------|---|---------------------------|---|
| (acc. to Magnusson and Kligman 1969) | white-spotted male/female | petrolatum) | 5% Topical ind.: 25% Chall. conc.: subirritant | | cited in REACH reg.) |
| GPMT (acc. to Magnusson and Kligman 1969) | Guinea pig | Geraniol (vehicle not reported) | Intradermal ind.: 10% Topical ind.: 10% Chall. conc.: 10% | Sensitisation observed | Ishihara et al., 1986, as cited in Lapczynski et al., 2008 (also cited in REACH reg.) |
| Buehler test | | | | | |
| Buehler delayed contact hypersensitivity test | Guinea pig 20 animals in total | Geraniol (in DEP) | Induction: 25% Chall. conc.: 2.5, 7.5, 25% | No sensitisation observed | Unpublished report RIFM 1992, as cited in Lapczynski et al., 2008 |

Table 9 summarises relevant human tests with geraniol which include 92 patch test studies, 7 HRIPTs, 5 HMTs and 4 case studies. The studies involve thousands of dermatitis patients from different EU countries, North America, and Asia. The majority of the references cited below are not included in the REACH registration dossier.

Table 9: Summary table of human data on skin sensitisation (chronological order)

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---------------------------------------|------------------------|--|---|-----------------------|
| Patch tests, selected patients | | | | |
| Patch test data, selected patients | Geraniol, 1% (in pet.) | Study of 2798 selected Fragrance mix (FM) I positive patients patch tested with geraniol. Data from IVDK multicentre project (IVDK: Information Network of Departments of Dermatology in Germany, Austria and Switzerland). Data obtained 1998-2013. | 5.5% were tested positive (n = 2798) | Geier et al., 2015 |
| Patch test data, selected patients | Geraniol, 1% (in pet.) | Study of 940 selected patients with positive reactions to FM I patch tested with geraniol. Data from Department of Dermatology, University Hospital St Rafaël, Belgium. Data obtained 1990-2011. | 5.5% were tested positive (52/940) | Nardelli et al., 2013 |
| Patch test data, selected patients | Geraniol, 5% (in pet.) | Study of 157 selected patients positive to fragrance mix patch tested with geraniol. Data from | 20.4% were tested positive (32/157) | Turcic et al., 2011 |

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|------------------------------------|--|--|---|-----------------------|
| | | the Allergy Clinic of the Department of Dermatology and Venereology, Zagreb University Hospital Center and School of Medicine, Zagreb, Croatia. Data obtained 2001-2005. | | |
| Patch test data, selected patients | Geraniol, 2% (in pet.) | Study of 86 selected patients patch tested with geraniol. Data from the Cutaneous Allergy Unit of a tertiary referral hospital, Spain. Data obtained 2004-2008. | 19.7% were tested positive (17/86) | Cuesta et al., 2010 |
| Patch test data, selected patients | Geraniol, 1% (in pet.) | Study of 5695 selected patients patch tested with geraniol. Data from IVDK multicentre project (IVDK: Information Network of Departments of Dermatology in Germany, Austria and Switzerland). Data obtained 2005-2008. | 0.9% (95% CI: 0.63-1.1%) were tested positive (50/5695) | Uter et al., 2010 |
| Patch test data, selected patients | Geraniol, 1% (in pet.) | Study of 29 selected patients tested positive to their own deodorant patch tested with geraniol. Data from IVDK multicentre project (IVDK: Information Network of Departments of Dermatology in Germany, Austria and Switzerland). Data obtained 1998-2002. | 6.9% were tested positive (2/29) | Uter et al., 2007 |
| Patch test data, selected patients | Geraniol, 1% (in pet.) | Study of 141 selected patients tested negative to their own deodorant patch tested with geraniol. Data from IVDK multicentre project (IVDK: Information Network of Departments of Dermatology in Germany, Austria and Switzerland). Data obtained 1998-2002. | 0% were tested positive (0/141) | Uter et al., 2007 |
| Patch test data, selected patients | Geraniol, (concentration and vehicle not reported) | Study of 30 selected patients allergic to their own perfumed product, 19 of these patch tested with geraniol. | 21.1% were tested positive (4/19) | Vocanson et al., 2006 |
| Patch test data, selected patients | Geraniol, (concentration and vehicle not reported) | Multicentre study, a total of 3604 patients tested with FM, subgroup of 160 patients hypersensitive to FM patch tested with geraniol. Data from members of the Hungarian Contact Dermatitis Research Group. Data obtained 1998-1999. | 7.5% were tested positive (12/160) | Temesvari al., 2002 |
| Patch test data, selected patients | Geraniol, 1% (in pet. and 1% SSO) | A total of 2660 patients patch tested with a standard patch test series, 747 patients suspected of | 0.9% were tested positive (7/747) | Wohrl et al., 2001 |

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|------------------------------------|--|--|--|----------------------------------|
| | | fragrance allergy tested further with a special fragrance series including geraniol. Data from FAZ-Floridsdorf Allergy Centre, Austria. Data obtained 1997-2000. | | |
| Patch test data, selected patients | Geraniol, 1% (in pet.) | A total of 2600 patients patch tested with FM, 226 selected FM-reactive patients patch tested with geraniol. Data from Department of Dermatology, University Hospital, 3000-075 Coimbra, Portugal. Data obtained 1989-1999. | 8.4% were tested positive (19/226) | Brites et al., 2000 |
| Patch test data, selected patients | Geraniol, 1% (in pet.) | A total of 23660 patients patch tested with FM, a sub-group of 1112 patients patch tested with geraniol. Data from St John's Institute of Dermatology, St Thomas's Hospital, London SE1 7EH, UK. Data obtained 1984-1998. | 6.0% were tested positive (67/1112) | Buckley et al., 2000 |
| Patch test data, selected patients | Geraniol, 2% (vehicle not reported) | A total of 223 nurses with suspected occupational skin disease patch tested with geraniol. Data from the Department of Occupational Diseases, The Nofer Institute of Occupational Medicine, Łódź, Poland. Data obtained 1995-1999. | 0.4% were tested positive (1/223) | Kiec-Swierczynska & Krecisz 2000 |
| Patch test data, selected patients | Geraniol, 5% (in pet.) | A total of 1483 patients with suspected cosmetic contact dermatitis patch tested with geraniol. Data from Nagoya, Japan. Data obtained 1990-1998. | 0.3% were tested positive (4/1483) | Sugiura et al., 2000 |
| Patch test data, selected patients | Geraniol, (concentration and vehicle not reported) | Study of 542 selected patients positive to FM patch tested with geraniol. Data from Portugal. Data obtained 1990-1997. | 10.7% were tested positive (58/542) | Bordalo et al., 1999 |
| Patch test data, selected patients | Geraniol, 2% (in 1% sorbitan sesquioleate) | Study of 50 patients positive to FM patch tested with geraniol. Data from University Hospital Utrecht, The Netherlands. Data obtained 1994-1998. | 6.0% were tested positive (3/50) | Hendriks & van Ginkel 1999 |
| Patch test data, selected patients | Geraniol, concentration not reported (in pet.) | Study of 40 patients positive to FM patch tested with geraniol. Data from Department of Dermatology, Royal Hallamshire Hospital, Sheffield, UK. Data obtained 1994-1995. | 0% were tested positive (0/40) | Katsarma & Gawkrödger 1999 |
| Patch test data, selected patients | Geraniol, 1% (in pet.) | Study of 38 patients positive to FM patch tested with geraniol. Data from the Skin Test | 13.2% were tested positive (5/38) | Katsarou et al., 1999 |

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|------------------------------------|--|--|---|--|
| | | Laboratory, Department of Dermatology, University of Athens, "A. Sygros" Hospital, Athens, Greece. Data obtained 1985-1996. | | |
| Patch test data, selected patients | Geraniol, 1% (in pet.) | Study of 41 patients sensitive to UV absorbers patch tested with geraniol. Data from the Photobiology unit, Department of Dermatology, University of Gottingen, Germany. Data obtained 1981-1996. | 2.4% were tested positive (1/41) | Schauder & Ippen 1997 (also cited in REACH reg.) |
| Patch test data, selected patients | Geraniol, 5% (in pet.) | Study of 167 fragrance sensitive volunteer patients patch tested with geraniol. Data from seven centers located in Japan, Northern Ireland, United States, England, Switzerland and Sweden. | 3.0% were tested positive (5/167) | Larsen et al., 1996 |
| Patch test data, selected patients | Geraniol, 1-2% (in pet.) | Study of 367 patients reacting to FM patch tested with geraniol. Data from Department of Dermatology, Gentofte Hospital, Denmark. Data obtained 1979-1992. | 4.1% were tested positive (15/367) | Johansen & Menne 1995 |
| Patch test data, selected patients | Geraniol, (concentration and vehicle not reported) | Study of 50 selected patients sensitive to FM patch tested with geraniol. Data from Department of Dermatology and Venereology, Hungary. | 6.0% were tested positive (3/50) | Becker et al., 1994 |
| Patch test data, selected patients | Geraniol, 5% (pet.) | Study of 61 selected patients sensitive to FM patch tested with geraniol. Data from University of Amsterdam and University of Leiden, The Netherlands. Data obtained in 1991. | 13.1% were tested positive (8/61) | De Groot et al., 1993 |
| Patch test data, selected patients | Geraniol, 5% (pet.) | Study of 64 selected patients with cosmetic dermatitis patch tested with geraniol. Data from Department of Dermatology, Toho University School of Medicine, Tokyo, Japan. Data obtained 1990-1991. | 4.7% were tested positive (3/64) | Haba et al., 1993 |
| Patch test data, selected patients | Geraniol, 5% (pet.) | Study of 7 selected patients with facial melanosis patch tested with geraniol. Data from Department of Dermatology, Toho University School of Medicine, Tokyo, Japan. Data obtained 1990-1991. | 0% were tested positive (0/7) | Haba et al., 1993 |
| Patch test data, selected patients | Geraniol, 5% (pet.) | Study of 32 selected patients with non-cosmetic dermatitis and eczema patch tested with geraniol. Data from Department of Dermatology, Toho University | 3.1% were tested positive (1/32) | Haba et al., 1993 |

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|------------------------------------|-------------------------------------|---|--|--|
| | | School of Medicine, Tokyo, Japan. Data obtained 1990-1991. | | |
| Patch test data, selected patients | Geraniol, 1% (pet.) | Study of 16 selected children with atopic dermatitis patch tested with geraniol. | 0% were tested positive (0/16) | Abifadel et al., 1992 (also cited in REACH reg.) |
| Patch test data, selected patients | Geraniol, 1% (pet.) | Study of 4 selected children with a suspicion of contact dermatitis patch tested with geraniol. | 0% were tested positive (0/4) | Abifadel et al., 1992 (also cited in REACH reg.) |
| Patch test data, selected patients | Geraniol, 5% (pet.) | Study of 111 selected patients with contact dermatitis patch tested with geraniol. Data from Department of Dermatology, Osaka City University Medical School, Osaka, Japan. Data obtained 1990-1991. | 0.9% were tested positive (1/111) | Nagareda et al., 1992 |
| Patch test data, selected patients | Geraniol, 5% (vaselin) | Study of 115 selected patients positive to cosmetics or cosmetic ingredients patch tested with geraniol. Data from Department of Dermatology, Ullevaal Hospital, Oslo, Norway. Data obtained 1987-1988. | 0% were tested positive (0/115) | Remaut 1992 |
| Patch test data, selected patients | Geraniol, 1% (pet.) | Study of 17 selected patients sensitive to FM patch tested with geraniol. Data from the Netherlands. | 11.8% were tested positive (2/17) | Roesyanto-Mahadi et al., 1990 |
| Patch test data, selected patients | Geraniol, 2% (pet.) | Study of 20 selected patients sensitive to FM patch tested with geraniol. | 10.0% were tested positive (2/20) | Safford et al., 1990 |
| Patch test data, selected patients | Geraniol, 1% (vehicle not reported) | Study of 162 selected patients sensitive to FM patch tested with geraniol. Data from Dermatologische Klinik und Poliklinik, Germany. Data obtained 1987. | 2.5% were tested positive (4/162) | Enders et al., 1989 (also cited in REACH reg.) |
| Patch test data, selected patients | Geraniol, 2% (pet.) | Study of 19 selected patients with eyelid dermatitis patch tested with geraniol. Data from Contact Dermatitis Clinic of St. Michael's Hospital, Toronto, Canada. Data obtained 1980-1987. | 0% were tested positive (0/19) | Nethercott et al., 1989 |
| Patch test data, selected patients | Geraniol, 2% (pet.) | Study of 70 selected patients with dermatitis patch tested with geraniol. Data from Contact Dermatitis Clinic of St. Michael's Hospital, Toronto, Canada. Data obtained 1980-1987. | 1.4% were tested positive (1/70) | Nethercott et al., 1989 |
| Patch test data, selected patients | Geraniol, 1% (pet.) | Study of 78 selected patients sensitive to FM patch tested with geraniol. Data from multicenter study involving 6 countries. Data | 5.1% were tested positive (4/78) | Wilkinson et al., 1989, as cited in SCCNFP 1999 |

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|------------------------------------|--|---|---|---|
| | | obtained 1989. | | |
| Patch test data, selected patients | Geraniol, 5% (pet.) | Study of 119 selected patients suffering from cosmetic-related contact dermatitis patch tested with geraniol. Data from a multicentre study performed in the Netherlands. Data obtained 1986-1987. | 1.7% were tested positive (2/119) | De Groot et al., 1988 |
| Patch test data, selected patients | Geraniol, (concentration and vehicle not reported) | Study of 31 selected patients sensitive to oak moss patch tested with geraniol. Data from Clinica de Dermatologia e Venereologia dos Hospitais da Universidade de Coimbra, Portugal. Data obtained 1980-1986. | 16.1% were tested positive (5/31) | Goncalo et al., 1988 |
| Patch test data, selected patients | Geraniol, (concentration and vehicle not reported) | Study of 156 selected patients with pure contact allergy to cosmetic products patch tested with geraniol. | 1.3% were tested positive (2/156) | Broeckx et al., 1987 (also cited in REACH reg.) |
| Patch test data, selected patients | Geraniol, 20% (pet.) | Study of 574 selected patients with cosmetic contact dermatitis or another eczema patch tested with geraniol. Data obtained 1984-1986. | 0.9% were tested positive (5/574) | Hirose et al., 1987 |
| Patch test data, selected patients | Geraniol, 3% (pet.) | Study of 63 selected dermatitis patients positive to perfume mixture patch tested with geraniol. Data from Istituto Dermatologico Santa Maria e San Gallicano, Italy. Data obtained 1983-1984. | 6.3% were tested positive (4/63) | Santucci et al., 1987 |
| Patch test data, selected patients | Geraniol, 1% (pet.) | Study of 54 selected dermatitis patients positive to perfume mixture patch tested with geraniol. Data from Istituto Dermatologico Santa Maria e San Gallicano, Italy. Data obtained 1984-1985. | 7.4% were tested positive (4/54) | Santucci et al., 1987 |
| Patch test data, selected patients | Geraniol, (concentration and vehicle not reported) | Study of 42 selected patients sensitive to perfume mixture patch tested with geraniol. | 24.0% were tested positive (10/42) | Rudzki & Grzywa 1986 (also cited in REACH reg.) |
| Patch test data, selected patients | Geraniol, (concentration and vehicle not reported) | Study of 403 selected patients with cutaneous reactions to cosmetic products patch tested with geraniol. Data from the North American Contact Dermatitis Group, a task force of the American Academy of Dermatology. Data obtained 1977-1983. | 2.0% were tested positive (8/403) | Adams & Maibach 1985 |
| Patch test data, selected | Geraniol, 1% | Study of 144 selected patients | 6.9% were tested | Angelini et al., |

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---|--|---|--|---|
| patients | (pet.) | sensitive to FM patch tested with geraniol. | positive (10/144) | 1985 |
| Patch test data, selected patients | Geraniol, 10% (pet.) | Study of 179 selected patients suspected of cosmetic allergy patch tested with geraniol. Data from the Netherlands. | 6.1% were tested positive (11/179) | De Groot et al., 1985 |
| Patch test data, selected patients | Geraniol, 5% (pet.) | Study of 16 selected patients with cosmetic sensitivity patch tested with geraniol. | 0% were tested positive (0/16) | Emmons and Marks 1985 (also cited in REACH reg.) |
| Patch test data, selected patients | Geraniol, 5% (pet.) | Study of 15 selected patients with eczematous dermatitis patch tested with geraniol. | 6.7% were tested positive (1/15) | Emmons and Marks 1985 (also cited in REACH reg.) |
| Patch test data, selected patients | Geraniol, 1% (pet.) | Study of 182 selected patients suspected of contact allergy to cosmetics patch tested with geraniol. Data from the Netherlands. Data obtained 1977. | 1.6% were tested positive (3/182) | Malten et al., 1984 |
| Patch test data, selected patients | Geraniol, 20% (pet.) | Study of 181 selected patients with melanosia faciei feminae patch tested with geraniol. Data obtained 1977-1982 | 3.9% were tested positive (7/181) | Hayakawa et al., 1983 |
| Patch test data, selected patients | Geraniol, (concentration vehicle not reported) | Study of 23 selected fragrance sensitive patients patch tested with geraniol. | 13.0% were tested positive (3/23) | Sugai 1983 |
| Patch test data, selected patients | Geraniol, (concentration and vehicle not reported) | Multicentre study of 487 patients allergic to cosmetic patch tested with geraniol. Data from US. Data obtained 1977-1980 | 1.0% were tested positive (5/487) | Eiermann et al., 1982 |
| Patch test data, selected patients | Geraniol, 5% (pet.) | Study of 155 selected cosmetic dermatitis patients patch tested with geraniol. | 0.6% were tested positive (1/155) | Itoh 1982 |
| Patch test data, selected patients | Geraniol, 2% (pet.) | Study of 1277 selected patients with contact dermatitis due to household products patch tested with geraniol. | 2.2% were tested positive (28/1277) | Sugai 1982, as cited in Lapczynski et al., 2008 |
| Patch test data, selected patients | Geraniol, 5% (white petrolatum) | Study of 20 selected perfume sensitive patients patch tested with geraniol. | 30.0% were tested positive (6/20) | Larsen et al., 1977 |
| Patch test data, selected patients | Geraniol, 10% (pet.) | Study of 15 selected eczema patients allergic to Balsam of Peru patch tested with geraniol. | 13.3% were tested positive (2/15) | Hjorth 1961, as cited in Hostynek & Maibach 2004 (also cited in REACH reg.) |
| Patch tests, consecutive (unselected) patients | | | | |
| Patch test data, consecutive patients | Geraniol, 2% (in pet.) | Study of patch test data by reviewing records of 1951 | 0.5% (95% CI: 0.2-0.8%) were tested | Mann et al., 2014 |

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---------------------------------------|---|---|------------------------------------|----------------------|
| | | eczema unselected patients patch tested with geraniol. Data from St Johns Institute of Dermatology at St Thomas Hospital, UK. Data obtained 2011-2012. | positive (9/1951) | |
| Patch test data, consecutive patients | Geraniol, 4% (in pet.) | Study of 655 unselected patients patch tested with geraniol. Data from Department of Dermatology, Sahlgrenska University Hospital, Gothenburg, Sweden. Data obtained 2010-2011. | 0.2% were tested positive (1/655) | Hagvall et al., 2013 |
| Patch test data, consecutive patients | Geraniol, 6% (in pet.) | Study of 649 unselected patients patch tested with geraniol. Data from Department of Dermatology, Sahlgrenska University Hospital, Gothenburg, Sweden. Data obtained 2010-2011. | 0.5% were tested positive (3/649) | Hagvall et al., 2013 |
| Patch test data, consecutive patients | Geraniol, 11% (in pet.) | Study of 655 unselected patients patch tested with geraniol. Data from Department of Dermatology, Sahlgrenska University Hospital, Gothenburg, Sweden. Data obtained 2010-2011. | 1.1% were tested positive (7/655) | Hagvall et al., 2013 |
| Patch test data, consecutive patients | Geraniol, air-exposed for 10 weeks , 4% (in pet.) | Study of 655 unselected patients patch tested with geraniol. Data from Department of Dermatology, Sahlgrenska University Hospital, Gothenburg, Sweden. Data obtained 2010-2011. | 0.9% were tested positive (6/655) | Hagvall et al., 2013 |
| Patch test data, consecutive patients | Geraniol, air-exposed for 10 weeks , 6% (in pet.) | Study of 655 unselected patients patch tested with geraniol. Data from Department of Dermatology, Sahlgrenska University Hospital, Gothenburg, Sweden. Data obtained 2010-2011. | 2.3% were tested positive (15/655) | Hagvall et al., 2013 |
| Patch test data, consecutive patients | Geraniol, air-exposed for 10 weeks , 11% (in pet.) | Study of 653 unselected patients patch tested with geraniol. Data from Department of Dermatology, Sahlgrenska University Hospital, Gothenburg, Sweden. Data obtained 2010-2011. | 4.6% were tested positive (30/653) | Hagvall et al., 2013 |
| Patch test data, consecutive patients | Geraniol, 2% (in pet.) | Study of 2227 unselected patients patch tested with geraniol. Data from Department of Dermatology, Sahlgrenska University Hospital, Gothenburg, Sweden. Data obtained 2006- | 0.1% were tested positive (3/2227) | Hagvall et al., 2012 |

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---------------------------------------|--|--|--|--------------------------|
| | | 2010. | | |
| Patch test data, consecutive patients | Geraniol, air-exposed for 10 weeks , 2% (in pet.) | Study of 2179 unselected patients patch tested with geraniol. Data from Department of Dermatology, Sahlgrenska University Hospital, Gothenburg, Sweden. Data obtained 2006-2010. | 0.6% were tested positive (12/2179) | Hagvall et al., 2012 |
| Patch test data, consecutive patients | Geraniol, 1% (in pet.) | Study of 1502 unselected eczema patients patch tested with geraniol. Data from Department of Dermato-Allergology, Copenhagen University Hospital Gentofte, Denmark. Data obtained 2008-2010. | 0% were tested positive (0/1502) | Heisterberg et al., 2011 |
| Patch test data, consecutive patients | Geraniol, 1% (in pet.) | Study of 1214 unselected patients patch tested with geraniol. Data from IVDK multicentre project (IVDK: Information Network of Departments of Dermatology in Germany, Austria and Switzerland). Data obtained 2005-2008. | 0.4% (95% CI: 0.1-0.69%) were tested positive (5/1214) | Uter et al., 2010 |
| Patch test data, consecutive patients | Geraniol, 2% (in pet.) | Study of 320 eczema patients suspected of being contact allergic to fragrances or cosmetics patch tested with geraniol. Data from the University Medical Centre in Groningen, the Netherlands. Data obtained 2005-2007. | 0.6% were tested positive (2/320) | Van Oosten et al., 2009 |
| Patch test data, consecutive patients | Geraniol, 1% (in pet.) | Study of 37065 unselected dermatitis patients patch tested with geraniol. Data from the Department of Cutaneous Allergy at St John's Institute of Dermatology, UK. Data obtained 1982-2007. | 0.2% were tested positive (89/37065) | White et al., 2009 |
| Patch test data, consecutive patients | Geraniol, 1% (in pet.) | Study on 2063 unselected patients patch tested with geraniol. Data from IVDK multicentre project (IVDK: Information Network of Departments of Dermatology in Germany, Austria and Switzerland). Data obtained 2003-2004. | 0.5% (95% CI: 0.1-0.7%) were tested positive (10/2063) | Schnuch et al., 2007 |
| Patch test data, consecutive patients | Geraniol, 5% (in pet.) | A study on fragrance allergy in 658 hand eczema patients from three dermatological departments in Denmark and Sweden (Gentofte, Odense, Malmö). Data obtained in 2001-2002. | 0.9% were tested positive (6/658) | Heydorn et al., 2003 |
| Patch test data, | Geraniol, 1% | Study of 4900 unselected patients | 1.2% were tested | Schnuch al., |

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---------------------------------------|---|---|--|------------------------|
| consecutive patients | (in pet.) | patch tested with geraniol. Data from IVDK multicentre project (IVDK: Information Network of Departments of Dermatology in Germany, Austria and Switzerland). Data obtained 1996-1999. | positive (60/4900) | 2002 |
| Patch test data, consecutive patients | Geraniol, 1% (in pet. with or without SSO (1%)) | Study of 702 unselected patients patch tested with geraniol. Data from a multicentre study of the European Environmental and Contact Dermatitis Research Group. | 0.7% (5/702) and 0.4% (3/702) were tested positive with and without SSO, respectively. | Frosch et al., 1995a |
| Patch test data, consecutive patients | Geraniol, 0.1 and 1% (in pet.) | Study of 106 unselected patients patch tested with geraniol. Data from Test centre Camarasa, Barcelona, as part of a multicentre study of the European Environmental and Contact Dermatitis Research Group. | 0% were tested positive at both concentrations (0/106) | Frosch et al., 1995b |
| Patch test data, consecutive patients | Geraniol, 1% (in pet. with SSO 1%) | Study of 1072 unselected patients patch tested with geraniol. Data from a multicentre study involving 9 European centres of the European Environmental and Contact Dermatitis Research Group. | 0.8% were tested positive (8/1072) | Frosch et al., 1995b |
| Patch test data, consecutive patients | Geraniol, 3-1% (pet.) | Study of 1967 patients patch tested with geraniol. Data from Department of Dermatology, South-Saimaa Central Hospital, Lappeenranta, Finland. Data obtained 1982-1985. | 0.7% were tested positive (14/200) | Malanin & Ohela 1989 |
| Patch test data, consecutive patients | Geraniol, 5% (vehicle not reported) | Study of 680 unselected patients with eczema or dermatitis patch tested with geraniol. Data obtained 1978-1985. | 0.4% were tested positive (3/680) | Itoh et al., 1986 |
| Patch test data, consecutive patients | Geraniol, 2% (yellow soft paraffin) | Study of 241 unselected patients patch tested with geraniol. Data obtained 1981-1983. | 4.1% were tested positive (10/241) | Ferguson & Sharma 1984 |
| Patch test data, consecutive patients | Geraniol, 5% (vehicle not reported) | Study of 212 unselected patients with cosmetic dermatitis patch tested with geraniol. Data obtained 1979-1982. | 0.5% were tested positive (1/212) | Nishimura et al., 1984 |
| Patch test data, consecutive patients | Geraniol, 5% (vehicle not reported) | Study of 35 unselected patients with facial patch tested with geraniol. Data obtained 1979-1982. | 0% were tested positive (0/35) | Nishimura et al., 1984 |
| Patch test data, consecutive patients | Geraniol, 5% (vehicle not reported) | Study of 275 unselected patients non-cosmetic dermatitis or eczema patch tested with geraniol. Data obtained 1979- | 0.7% were tested positive (2/275) | Nishimura et al., 1984 |

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|--|-------------------------------------|---|------------------------------------|--|
| | | 1982. | | |
| Patch test data, consecutive patients | Geraniol, 1% (pet.) | Study of 242 unselected patients patch tested with geraniol. | 0% were tested positive (0/667) | Van Joost et al., 1984 |
| Patch test data, consecutive patients | Geraniol, 2% (vaseline) | Study of 120 unselected patients with cosmetic dermatitis patch tested with geraniol. | 0% were tested positive (0/120) | Ishihara et al., 1979 |
| Patch test data, consecutive patients | Geraniol, 5% (vaseline) | Study of 120 unselected patients with cosmetic dermatitis patch tested with geraniol. | 1.7% were tested positive (2/120) | Ishihara et al., 1979 |
| Patch test data, consecutive patients | Geraniol, 2% (pet.) | Study of 1033 unselected female patients patch tested with geraniol. Data from St. John's Hospital for Diseases of the Skin, London, UK. Data obtained 1984. | 0.6% were tested positive (6/1033) | Cronin 1978 |
| Patch test data, consecutive patients | Geraniol, 2% (pet.) | Study of 803 unselected male patients patch tested with geraniol. Data from St. John's Hospital for Diseases of the Skin, London, UK. Data obtained 1984. | 0.5% were tested positive (4/803) | Cronin 1978 |
| Patch test data, consecutive patients | Geraniol, 2% (pet.) | Study of 2461 unselected patients patch tested with geraniol. Data from St. John's Hospital for Diseases of the Skin, London, UK. Data obtained 1979-1980. | 0.3% were tested positive (7/2461) | Cronin 1978 |
| Patch test data, consecutive patients | Geraniol, 10% (pet.) | Study of 792 unselected eczema patients patch tested with geraniol. | 0.5% were tested positive (4/792) | Fregert & Hjorth 1969, as cited in Hostynek & Maibach 2004 |
| Patch Tests, other patients/studies | | | | |
| Experimental study, selected patients | Geraniol, 1% (in pet.) | Single-centre, double-blind volunteer study of 100 selected patients with contact allergy to FM I and/or FM II. The patients were patch tested with commercial patch test fragrances incl. geraniol. Data from Department of Dermatology of the VU University Medical Centre, The Netherlands. Data obtained 2005-2010. | 9.0% (9/100) | Nagtegaal et al., 2012 |
| Patch test data, patients | Geraniol, 2% (in pet.) | Study of 15 patients with eczematous reactions from ketoprofen-containing gels concerning cross-reactivity and concomitant reactions patch tested with geraniol. Data from Italy. Data obtained 2006-2007. | 0% were tested positive (0/15) | Foti et al., 2008 |
| Patch test data, patients | Geraniol, 7% (vehicle not reported) | Study of 242 patients with contact allergy patch tested with geraniol. | 0.4% were tested positive (1/242) | Van Joost et al., 1985 |

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|--|---|--|-----------------------------------|--|
| Patch test data, patients | Geraniol, 2% (vehicle not reported) | Study of 467 patients patch tested with geraniol. | 0.2% were tested positive (1/467) | Ohela & Saramies |
| Human Repeat Insult Patch Tests (HRIPT's) | | | | |
| HRIPT | Geraniol 2% (3:1 DEP:EtOH) (2362 µg/cm ²) | Study of 110 volunteers patch tested with geraniol. | 0% were tested positive (0/110) | Unpublished report RIFM 2000, as cited in Lapczynski et al., 2008 |
| HRIPT | Geraniol 5% and 0.5% tocopherol (3:1 DEP:EtOH) (5905 µg/cm ²) | Study of 109 volunteers patch tested with geraniol. | 0.9% were tested positive (1/109) | Unpublished report RIFM 2002, as cited in Lapczynski et al., 2008 |
| HRIPT | Geraniol 10% (3:1 DEP:EtOH) (11810 µg/cm ²) | Study of 112 volunteers patch tested with geraniol. | 2.7% were tested positive (3/112) | Unpublished report RIFM 2004, as cited in Lapczynski et al., 2008 |
| HRIPT | Geraniol 5% (alcohol SDA 39C) (3876 µg/cm ²) | Study of 40 volunteers patch tested with geraniol. | 0% were tested positive (0/40) | Unpublished report RIFM 1964, as cited in Lapczynski et al., 2008 |
| HRIPT | Geraniol 12.5% (EtOH) (9690 µg/cm ²) | Study of 41 volunteers patch tested with geraniol. | 0% were tested positive (0/41) | Unpublished report RIFM 1964a, as cited in Lapczynski et al., 2008 |
| HRIPT (modified Draize procedure) | Geraniol 10% (pet.) | Study of 104 volunteers patch tested with geraniol. | 0% were tested positive (0/104) | Marzulli & Maibach, 1980 (also cited in REACH reg.) |
| HRIPT (modified Draize procedure) | Geraniol 10% (ethanol) | Study of 73 volunteers patch tested with geraniol. | 2.7% were tested positive (2/73) | Marzulli & Maibach, 1980 (also cited in REACH reg.) |
| Human Maximation Tests (HMT's) | | | | |
| HMT | Geraniol 6% (vehicle not reported) | Study of 25 volunteers patch tested with geraniol. | 0% tests were positive (0/25) | Study report from 1986, as cited in REACH reg. |
| HMT | Geraniol 6% (pet.) | Study of 25 volunteers patch tested with geraniol. | 0% were tested positive (0/25) | Marzulli & Maibach, 1980 |
| HMT | Geraniol 6% | Study of 24 volunteers patch tested with geraniol. | 0% tests were positive (0/24) | Unpublished report RIFM |

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

| Type of data/report | Test substance, | Relevant information about the study (as applicable) | Observations | Reference |
|---------------------|---|--|---------------------------------|---|
| | (pet.) (4140 µg/cm ²) | | | 1979, as cited in Lapczynski et al., 2008 |
| HMT | Geraniol 6% (pet.) (4140 µg/cm ²) | Study of 26 volunteers patch tested with geraniol. | 3.8% tests were positive (1/26) | Unpublished report RIFM 1979a, as cited in Lapczynski et al., 2008 |
| HMT | Geraniol 6% (pet.) (4140 µg/cm ²) | Study of 25 volunteers patch tested with geraniol. | 0% tests were positive (0/25) | Grief 1967, cited from Lapczynski et al., 2008 (also cited in REACH reg.) |
| Case studies | | | | |
| Case study | Geraniol 2% (pet.) | Patch test, one 54-year old female bartender with chronic hand dermatitis (Department of Dermatology, Oregon Health & State University, Portland, OR, USA, year not reported) | Positive reaction to geraniol | Swerdlin et al., 2010 |
| Case study | Geraniol (concentration and vehicle not reported) | Patch test, one 48-year old male metalworker with recurrent hand dermatitis (Germany, 2007-2008) | Positive reaction to geraniol | Tanko et al., 2009 |
| Case study | Geraniol, 20% (in pet.) | Patch test, 7 patients sensitive to farnesol patch tested with geraniol. Data from the Contact Allergy Unit, Department of Dermatits, University Hospital St. Rafaël, Kapucijnenvoer 33, B-3000 Leuven, Belgium. | 43% were tested positive (3/7) | Goossens & Merckx 1997 |
| Case study | Geraniol, 1% (acetone) | Study of 3 eczema patients patch tested with geraniol. | 33% were tested positive (1/3) | Keil 1947 (also cited in REACH reg.) |

10.8 Short summary and overall relevance of the provided information on skin sensitisation

The sensitising properties of geraniol have been intensively studied in both animals and humans. Numerous animal studies confirming the sensitising properties of geraniol are available. The animal studies reported in table 8 represent guideline studies as well as older studies based on testing principles that are equivalent to current test guidelines for skin sensitisation. According to the CLP criteria the results of LLNA (OECD 429), GPMT and Buehler tests (OECD 406) are directly applicable for classification and sub-categorisation of skin sensitisation.

Furthermore, a large number of publications are available on the sensitising properties of geraniol seen in human patch tests. For diagnostic testing of contact allergy to fragrances in humans, standardised fragrance mixtures (FM I and FM II) are used in the European baseline series used for standardised patch testing in dermatological clinics. Geraniol is a component of FM I, which has routinely been used for diagnostic patch testing in Europe (and elsewhere). FM I contains 1% geraniol and a total of 8% fragrance allergens (SCCS

2012), when tested individually the recommended concentration for geraniol in petrolatum is 2% (Recommendation of the European Society of Contact Dermatitis). Follow-up testing of the single fragrance substances showing positive reactions in patch tests with FM I and FM II is routinely done in many dermatological clinics and the sensitising properties of geraniol are well documented in humans. Patch tests with geraniol involving several thousand dermatitis patients from dermatological clinics in various countries in Europe, North America and Asia are thus available. Diagnostic patch test data are generally seen as the primary source of clinical information on the occurrence of skin sensitisation and are considered to represent the most important human data in relation to this classification proposal.

Results of human volunteer studies (which are no longer performed due to ethical reasons) are also available for geraniol and may according to the guideline of the application of the CLP criteria be used as weight of evidence for sub-categorisation (ECHA 2015).

10.8.1 Animal data

A total of 9 LLNAs, 1 *ex vivo* LLNA-BrdU ELISA, 5 GPMTs, and 1 Buehler test were identified for geraniol (Table 8).

The reported EC3 values in the LLNAs range between 5.6% and 25.8% in different vehicles. Most LLNAs were reported as being conducted according to or as being equivalent to OECD TG 429. The lowest EC3 value obtained with (non-oxidised) Geraniol (EC3 = 5.6%) was observed in a study where EtOH was used as a vehicle (SCCS 2012, Lalko et al., 2004). In two tests with the vehicle EtOH:DEP 3:1, the EC3 values were 11.4 and 25.8%, respectively (SCCS 2012, Lalko et al., 2004), whereas in two other tests with the same vehicle but in the ratio 1:3, the EC3 values were 11.4 and 20.4%, respectively (Lalko and Api 2006, SCCS 2012, Lalko et al., 2004). In one study with DEP as vehicle, the EC3 value was 11.8% (SCCS 2012, Lalko et al., 2004). In the study with AOO as the vehicle the EC3 value was 22.4% (Hagvall et al., 2007). A potential influence on the EC3 values of the vehicle used in the different tests cannot be evaluated. In the LLNA *ex vivo* BrdU tests an EC3 value of 13.1% was reported (Ulker et al., 2014). In two LLNA studies using air-exposed geraniol the EC3 values obtained were in the lower range compared to the results of the other LLNA studies (EC3 values of 4.4% and 5.8%, respectively) (Hagvall et al., 2007). As described in the SCCS opinion geraniol can be activated to other substances with increased sensitising capacity (such as geranial) both through autoxidation and metabolic oxidation. This may explain that lower EC3 values seem to be obtained with air exposed geraniol.

A positive reaction was observed in a GPMT with geraniol at an intradermal induction concentration of 0.1% in Dobs saline followed by topical application at 50% in acetone whereas no sensitisation was observed when followed by topical application at 50% in 70/30 acetone/PEG 400 (Lapczynski et al., 2008). Positive reactions were also observed in two GPMTs with geraniol (3/6 animals in one test) at intradermal induction concentrations of 5% in petrolatum followed by topical application of 25 or 30% in petrolatum, and in one GPMTs at an intradermal induction concentration of 10% followed by topical application at 10% (vehicle not reported) (Lapczynski et al., 2008, Klecak et al., 1977).

No sensitisation was observed in a Buehler test with an induction concentration of 25% in DEP (Lapczynski et al., 2008).

The above reported animal studies are relevant in terms of classification and generally confirm the sensitising properties of geraniol except from two of the studies (one GPMT and the Buehler test) in which no sensitisation was observed. For a number of the studies robust information is not available and the results are cited from reviews. Although the quality and reliability cannot be assessed in detail the results of the tests are, however, relatively consistent.

Other (and older) animal studies on the skin sensitising properties of geraniol have also been identified but have not been included in table 8. Such studies include Draize tests, Open Epicutaneous Tests (OET), Freund's Complete Adjuvant Tests (FCAT) and sensitisation tests. Both positive and negative results have been obtained in these studies. However, as these studies are not directly applicable for classification and sub-categorisation of skin sensitisers according to the CLP criteria and guidance, they are not included in the current CLH report as several currently accepted guideline studies are available.

10.8.2 Human data

A total of 88 diagnostic patch tests, 4 other patch test studies, 7 HRIPTs, 5 HMTs and 4 case studies were identified for geraniol (Table 9).

Diagnostic patch testing is conducted in order to diagnose contact allergy to a substance and is performed according to international standards by dermatologists (Johansen et al. 2015). The results of such patch tests are usually reported as number of patients/subjects having positive reactions in relation to the total number tested, i.e. the frequency of positive patch tests. An important factor when assessing the prevalence of positive reactions in diagnostic patch tests is how the group of patients are defined, i.e. selected patients versus consecutive (unselected) patients. Selected patients can be e.g. patients with dermatitis suspected of having contact allergy to fragrances or cosmetics or special occupational groups (aimed testing). Consecutive (unselected) patients are groups of patients for whom allergic contact dermatitis (ACD) is generally suspected.

The positive patch test frequencies from the 88 reported diagnostic patch tests vary between 0.1 and 30% in all dermatitis patients and the highest frequencies of positive patch test reactions with geraniol were generally seen in patch tests with selected patients. In the 56 patch tests with selected dermatitis patients the frequency of positive reactions ranges between 0.3 and 30%. Complete absence of positive reactions was observed in 8 of these tests. Whereas some of the highest frequencies of positive reactions (e.g. above 10%) were seen in tests including groups of less than 100 selected patients, high frequencies of positive reactions were also observed in patch tests with larger patient groups. In 36 out of 56 patch tests with selected patients positive patch test frequencies $\geq 2\%$ were observed. In the 32 patch tests with consecutive (unselected) dermatitis patients the frequency of positive reactions was generally lower, ranging from 0.1 and 4.6%. Complete absence of positive reactions was only observed in 5 of these tests whereas relatively high frequencies of positive reactions ($\geq 1.0\%$) were seen in 6 of these tests. In 2 of these 6 tests the patients were, however, exposed to air-oxidised geraniol (see below). Most of the patch tests with selected patients included large patient groups > 500 patients. Geraniol was typically tested in concentrations of 1-5% (in petrolatum) in the diagnostic patch tests. A concentration of 2% is currently recommended by the European Society of Contact Dermatitis. The total number of positive reactions in the published cases is > 900 .

In some of the reported patch test studies both geraniol and air-exposed geraniol were tested in consecutive patients at different concentrations (Hagvall et al., 2012 and 2013). As geraniol can be activated to other substances with increased sensitising capacity (e.g. geranial) both through autoxidation and metabolic oxidation (SCCS 2012), patch testing with air-exposed geraniol may be foreseen to yield a higher response when compared to patch tests with unexposed geraniol. The results of the few available patch test studies using both air-exposed and unexposed geraniol seem to confirm that the air-exposed form generally increases the frequency of positive reactions relative to the unexposed form of geraniol and that testing with oxidised geraniol detects more cases of contact allergy than testing with pure geraniol (Hagvall et al., 2012, Hagvall et al., 2013). In relation to classification of geraniol for skin sensitisation the results obtained in patch tests using air-exposed geraniol are not directly applicable, as the increased sensitisation potential is considered to be a consequence of the transformation into more reactive metabolites/oxidation products of geraniol.

Four "other" patch test studies were identified. In an experimental study the possible role of skin irritation response in relation to polysensitisation to fragrances was investigated in 100 volunteer patients with confirmed fragrance contact allergy. All patients were patch tested (on the back) with 27 fragrance chemicals including geraniol. Furthermore a simultaneous patch test was done with sodium lauryl sulphate (a known skin irritant) on the upper arm of the patients. The study was not a clinical diagnostic patch test but the tests were nevertheless performed according to the guidelines of the International Contact Dermatitis Research Group. In this study 9.0% of the patients had positive reactions to geraniol (in 1% petrolatum). This result thus confirms the high frequencies of positive reactions to geraniol found in routine diagnostic patch testing with selected patients (Nagtegaal et al. 2012). In the three other studies sufficient information for identifying the nature of the patch test or the patient group was not available. Positive patch test frequencies between 0-0.4% were obtained for geraniol in these three studies.

The results of the many patch tests confirm that positive reactions to geraniol are commonly observed in dermatitis patients and with relatively high frequencies observed in a number of tests. The patch test data

collectively cover information from the last 3-4 decades and from many different dermatological clinics in different countries. Although it is not possible to directly compare these findings and draw conclusions on any tendencies in the sensitisation rates, it is obvious that high sensitisation frequencies have been observed for geraniol in recent years and that patients in many countries are affected.

Induction of sensitisation was also reported in 3 of 7 HRIPT studies after exposures to between 5-10% (>500 µg/cm²) geraniol (different vehicles). Sensitisation was observed in 1 of 5 HMT studies after exposure to 6% (>500 µg/cm²) geraniol (vehicle: petrolatum or not reported). The number of volunteers tested ranged from 40-112 in the HRIPT studies and 24-26 in the HMT studies. Concentrations lower than 500 µg/cm² geraniol were not tested in any of these studies. Robust study information is not available for these studies (Marzulli & Maibach, 1980, Lapczynski et al., 2008).

Four case studies are reported which confirm the general picture observed in the other patch tests with dermatitis patients described above.

The human tests identified are all relevant in terms of classification and confirm the sensitising properties of geraniol. The comprehensive set of diagnostic patch test data covering the last 3-4 decades with several of the tests being published very recently are seen as the key information for this classification proposal. The four case studies confirm the general picture observed in the other patch tests with dermatitis patients. For the HRIPTs and HMTs (older volunteer tests) robust study information is not available and the results are primarily cited from an older publication (Marzulli & Maibach, 1980) and a review article (Lapczynski et al., 2008). These data are seen as supporting evidence.

10.8.3 Human exposure

Geraniol is a fragrance that is manufactured in or imported to the EU in amounts of 1000-10,000 tonnes/year and is widely used in products on the EU market. The registered categories of use for consumers are cosmetics and a variety of household and professional cleaning and maintenance products. Data from the fragrance industry (cited in SCCS 2012) indicate that 80% of the total fragrance chemical volume is used in cosmetics and 20% in household products. Although cosmetics are assessed to be the main use category for geraniol, the use in other products (household and other products) may thus account for a substantial volume. As geraniol is widely used in many different types of consumer products the general population can be exposed from many different sources.

Geraniol is generally present in low concentrations in individual consumer products. The International Fragrance Association (IFRA) has established maximum recommended limits of geraniol in leave-on cosmetic products between 0.3-5.3% depending on the product category, between 5.0-8.6% in rinse-off cosmetic products, and of 2.5% for non-cosmetic consumer products with direct skin contact, as shown in Table 10 (IFRA 2007). (Note that other product types than those specifically mentioned in the table driving the category consumer exposure level are also covered under the different categories).

Table 10: The IFRA standard limits for geraniol in IFRA QRA (Quantitative Risk Assessment) product categories (IFRA 2007):

| IFRA QRA product category | Product type that drives the category consumer exposure level | IFRA standard limits |
|---------------------------|---|----------------------|
| Category 1 | Lip products | 0.3% |
| Category 2 | Deodorants/antiperspirants | 0.4% |
| Category 3 | Hydroalcoholics for shaved skin | 1.8% |
| Category 4 | Hydroalcoholics for unshaved skin | 5.3% |
| Category 5 | Hand cream | 2.8% |
| Category 6 | Mouthwash | 8.6% |

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

| IFRA QRA product category | Product type that drives the category consumer exposure level | IFRA standard limits |
|---------------------------|---|----------------------|
| Category 7 | Intimate wipes | 0.9% |
| Category 8 | Hair styling aids | 2.0% |
| Category 9 | Rinse-off hair conditioners | 5.0% |
| Category 10 | Hard surface cleaners | 2.5% |
| Category 11 | Incidental or non-skin contact | Not restricted |

The SCCS opinion (SCCS 2012) refers to a number of surveys on the presence and content of the 26 fragrances subject to labelling requirements (for cosmetics and detergents) in various consumer products. The reported occurrence of the fragrances is mostly based on labelling information alone, i.e. whether the substances are mentioned on the label of the product. In one survey the content was verified by chemical analysis. Table 11 summarises the results of the surveys with respect to the occurrence of geraniol in various consumer products.

Table 11: Occurrence of geraniol in consumer products, different surveys (cited from SCCS 2012):

| Product type | Number of products investigated | % products labelled to contain geraniol | Reference in SCCS 2012 |
|---|---------------------------------|--|------------------------|
| Children's cosmetics | n.a | 12% | Table 10.1, p. 74 |
| Deodorants | 88 | 48.9% (87% products found to contain geraniol; measured conc. from 1-399 ppm) | Table 10.2, p. 75 |
| Consumer products (cosmetics, household products) | 300 | 42% | Table 10.3, p. 77 |
| Consumer products | 516 | 22.1% | Table 10.4, p. 77 |
| Consumer products | 3000 | Approx. 20% | Figure 10.1, p 78 |

Geraniol was found to be present in 12-49% of the products covered in the different surveys based on labelling information alone. One study of deodorants showed that the occurrence of geraniol was even more frequent than expected based on subsequent chemical analysis. It was concluded by SCCS (SCCS 2012) that taking the total exposure into account, exposure to all 26 allergenic fragrances is foreseeable in daily life.

The Danish EPA has conducted surveys and assessments of a broad range of consumer products on the Danish market over the last decades. Geraniol has been identified in many different types of products but mostly in cosmetic products, including day-to-day cosmetic products such as deodorants, soaps, shampoos/conditioner, lotions and creams as well as in e.g. massage oils. Geraniol has also been found in household products such as cleaning agents, stain removers and air care products and in articles such as pens. Generally geraniol is found in low concentrations (>0 - <0.15%) in the investigated products except air fresheners (up to 0.9%) and massage oils (up to 23%) (DK EPA database, search February 2017).

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

The Danish Product Register contains information of hazardous substances in mixtures for professional use. Data from the Register confirm that geraniol is used in a wide range of products on the market, especially cleaning products. The concentrations are generally lower than 0.1% in the majority of the products. However, concentrations above 1% are found in fragrance mixtures and scented oils (Danish Product Register, 2016).

Human exposure to geraniol generally seems to be low based on the IFRA recommendations and reported contents in various consumer products. The exposure is, however, assessed to be frequent due to the widespread uses, primarily as a fragrance in consumer products, and the high tonnage level of geraniol. It is thus difficult for consumers to avoid exposure. According to the data from IFRA the exposure to geraniol when used as a fragrance in cosmetics is relatively low with established maximum recommended limits in most leave-on products being below 2-3% (except for IFRA QRA Product Category 4 and 5). For rinse-off cosmetics higher maximum recommended limits (5.0-8.6%) have been established, but a lower exposure is expected due to the intermediant character of the exposure and shorter duration of exposure compared to leave-on products. For non-cosmetic consumer products with direct skin contact a maximum recommended limit of 2.5% has been established.

10.9 Comparison with the CLP criteria

Geraniol is a widely used fragrance and a well known skin sensitizer. Geraniol has no harmonized classification but is generally self-classified as a Category 1 Skin sensitizer according to the C&L Inventory. An assessment of the skin sensitizing properties of geraniol has been conducted according to the current classification criteria including an assessment of the appropriate sub-category for this hazard class

According to the classification criteria sub-category 1A represent “*Substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitisation in humans. Severity of reaction may also be considered*” (CLP table 3.4.2).

According to the classification criteria sub-category 1B represent “*Substances showing a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals can be presumed to have the potential to produce sensitisation in humans. Severity of reaction may also be considered*” (CLP table 3.4.2).

10.9.1 Animal data

According to the classification criteria evidence from animal tests for sub-category 1A and 1B, respectively, can include the following types of data and results (CLP Tables 3.4.3 and 3.4.4):

| | Animal data | |
|------------------------|-------------|---|
| Sub-category 1A | LLNA | EC3 value \leq 2 % |
| | GPMT | \geq 30 % responding at \leq 0,1 % intradermal induction dose or \geq 60 % responding at $>$ 0,1 % to \leq 1 % intradermal induction dose |
| | Buehler | \geq 15 % responding at \leq 0,2 % topical induction dose or \geq 60 % responding at $>$ 0,2 % to \leq 20 % topical induction dose |
| Sub-category 1B | LLNA | EC3 value $>$ 2 % |
| | GPMT | \geq 30 % to $<$ 60 % responding at $>$ 0,1 % to \leq 1 % intradermal induction dose or \geq 30 % responding at $>$ 1 % intradermal induction dose |
| | Buehler | \geq 15 % to $<$ 60 % responding at $>$ 0,2 % to \leq 20 % topical induction dose or \geq 15 % responding at $>$ 20 % topical induction dose |

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

Test results from the LLNA, GPMT and Buehler tests can be used directly for classification and potency assessment. The reported EC3 values in the LLNAs (n=7) performed with geraniol range between 5.6% and 25.8% indicating a moderate skin sensitisation potency of geraniol (i.e. Cat 1B). The reported EC3 values in the LLNAs (n=2) performed with geraniol air-exposed for 10 or 45 weeks, respectively, were 4.4% and 5.8%, respectively, indicating a moderate skin sensitisation potency of air-exposed geraniol (i.e. Cat 1B). The reported EC3 value in the *ex vivo* LLNA-BrdU ELISA performed with geraniol was 13.1%; however, the result of this study cannot be used for sub-categorisation according to the CLP guidance (ECHA 2015).

Five GPMTs are available. In one GPMT with an intradermal induction concentration of 5%, a positive response was seen in 50% of the animals (3/6), indicating a moderate potency (i.e. Cat 1B). In three GPMTs with intradermal induction doses of 0.1, 5 and 10% geraniol, respectively, sensitisation was observed but not quantified (i.e. the number of animals affected was not reported) and a decision on sub-categorisation is thus not possible based on these studies. In one GPMT with an intradermal induction concentration of 0.1%, no sensitisation was observed.

No sensitisation was observed in a Buehler test with an induction concentration of 25% indicating that geraniol was not identified as a skin sensitizer in this test.

Other and older animal tests on the skin sensitising properties of geraniol show conflicting results. However, such tests are not directly applicable for sub-categorisation of skin sensitizers according to the CLP criteria and guidance.

In summary the animal data either indicate that geraniol is a skin sensitizer of moderate potency or do not allow conclusions on potency due to the design of the tests (doses used, lack of quantification of response). For most of the tests robust study information is not available to assess the quality more precisely. Caution should thus be exerted in drawing firm conclusions on sub-categorisation based on the animal data alone. Collectively, the results of the animal tests confirm the sensitizing properties of geraniol in a relatively consistent manner with a moderate potency.

10.9.2 Human data

According to the classification criteria human evidence for sub-category 1A and 1B, respectively, can include the following types of data (CLP section 3.4.2.2.2):

| | Human data |
|------------------------|--|
| Sub-category 1A | (a) positive responses at $\leq 500 \mu\text{g}/\text{cm}^2$ (HRIPT, HMT — induction threshold); (b) diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure; (c) other epidemiological evidence where there is a relatively high and substantial incidence of allergic contact dermatitis in relation to relatively low exposure. |
| Sub-category 1B | (a) positive responses at $> 500 \mu\text{g}/\text{cm}^2$ (HRIPT, HMT — induction threshold); (b) diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure; (c) other epidemiological evidence where there is a relatively low but substantial incidence of allergic contact dermatitis in relation to relatively high exposure. |

The guidance on the application of the CLP criteria further outlines how high or low frequency of occurrence of skin sensitization shall be assessed. The exposure level is determined according to Table 3.4.2-b in the guidance as shown below (ECHA 2015).

Table 3.4.2-b Relatively high or low exposure* (copied from ECHA 2015)

| Human diagnostic patch test data | High frequency | Low frequency |
|---|----------------|---------------|
| General population studies | ≥ 0.2 % | < 0.2 % |
| Dermatitis patients (unselected, consecutive) | ≥ 1.0 % | < 1.0 % |
| Selected dermatitis patients (aimed testing, usually special test series) | ≥ 2.0 % | < 2.0 % |
| Work place studies: | | |
| 1: all or randomly selected workers | ≥ 0.4 % | < 0.4 % |
| 2: selected workers with known exposure or dermatitis | ≥ 1.0 % | < 1.0 % |
| Number of published cases | ≥ 100 cases | < 100 cases |

* Only one or two types of information may be sufficient for sub-categorisation.

The key evidence for the assessment of the potency of geraniol in this classification proposal is the human data from diagnostic patch tests. Patch test data are available from several dermatological clinics in many different countries in and outside EU. In the patch tests summarized in Table 9, relatively high frequencies of positive reactions are seen upon exposure to geraniol in a high number of published cases. For selected dermatitis patients positive reactions range between 0.3 and 30% with frequencies ≥2% in 36 of 56 tests. For consecutive (unselected) dermatitis patients positive reactions range between 0.1 and 4.6% with 6* of 32 tests reporting frequencies ≥1% (*hereof two patch tests with oxidized geraniol). These tests represent more than 900 published cases of positive patch test reactions to geraniol.

The collected data from patch tests thus show that

- a high frequency (≥1%) of occurrence of skin sensitization is observed in some (6* of 32) of the patch tests with consecutive (unselected) dermatitis patients (*hereof two patch tests with oxidized geraniol).
- a high frequency (≥2%) of occurrence of skin sensitization is observed in the majority (36 of 56) of the patch tests with selected dermatitis patients
- the number of tested dermatitis patients showing positive reactions to geraniol is well above 100 (>900 cases)

These findings show a high frequency of occurrence of sensitization for geraniol in humans. For deciding on the appropriate sub-category the data from patch tests need to be seen in conjunction with the estimated exposure (see chapter 10.9.1.3 below).

Furthermore, four case studies of ACD are available. Geraniol was found to be among the causative agents of the dermatitis. These case studies are seen as supportive evidence for the findings of the patch tests.

The positive responses reported at relatively high concentrations > 500 µg/cm² in three HRIPTs and in one HMT indicate a moderate sensitisation potential of geraniol. The HRIPTs and HMTs are non-clinical tests based on healthy volunteers representing the general population (and are no longer conducted due to ethical reasons). Robust study information is not available for the HRIPTs and HMTs. The estimated induction concentrations (>500 µg/cm²) are calculated by fragrance industry and the original data have not been published. They are considered of low relevance for this classification proposal.

In an experimental volunteer study sensitisation to geraniol was reported in 9% of the fragrance allergy patients patch tested with 27 fragrance chemicals.

10.9.3 Exposure considerations

The occurrence of skin sensitization in human tests needs to be seen in conjunction with the level of exposure in order to make a decision on sub-categorisation of skin sensitizers. As described in chapter 10.8.3 the exposure to geraniol is generally considered to be relatively low, partly based on the current IFRA standard limits and on information of the actual concentrations of geraniol in various consumer products reported in different surveys.

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

According to the guidance on the application of the CLP criteria an additive exposure index shall be set in order to decide on the appropriate sub-category for skin sensitisers (when based on human data). An additive exposure index of 1-4 equates to relatively low exposure, whereas 5-6 reflects relatively high exposure. The exposure index is determined according to Table 3.4.2-c in the guidance as shown below (ECHA 2015).

Table 3.4.2-c Relatively high or low exposure (adapted from ECHA 2015)

| Exposure data | Relatively low exposure (weighting) | Relatively high exposure (weighting) | Score for geraniol |
|---|--|--|--------------------|
| Concentration / dose | < 1.0% < 500µg/cm ² (score 0) | ≥ 1.0% ≥ 500µg/cm ² (score 2) | 0 |
| Repeated exposure | < once/daily (score 1) | ≥ once/daily (score 2) | 2 |
| Number of exposures (irrespective of concentration of sensitizer) | <100 exposures (score 0) | ≥ 100 exposures (score 2) | 2 |

To achieve the exposure index a response in each row in Table 3.4.2-c above is necessary. The exposure index of geraniol is estimated based on the following assumptions:

- **Score 0** for concentration/dose: based on expected and observed concentrations < 1.0% of geraniol in relevant (consumer) products on the market.
- **Score 2** for repeated exposure: based on the frequent occurrence of geraniol in consumer products with estimated daily use.
- **Score 2** for number of exposures: based on an anticipated exposure of sensitised individuals to geraniol at least more than 100 times.

An additive exposure index of maximum 4 (0+2+2) is thus estimated indicating a relatively low exposure. A decision on the appropriate sub-category for skin sensitisers based on human data is done according to Table 3.4.2-d in the guidance:

Table 3.4.2-d Sub-categorisation decision table (from ECHA 2015)

| Exposure data | Relatively low frequency of occurrence of skin sensitisation | Relatively high frequency of occurrence of skin sensitisation |
|--------------------------------------|--|---|
| Relatively high exposure (score 5-6) | Sub-category 1B | Category 1 or case by case evaluation |
| Relatively low exposure (score 1-4) | Category 1 or case by case evaluation | Sub-category 1A |

10.9.1 Weight of Evidence

Both animal and human data are available documenting the skin sensitizing properties of geraniol. These data are considered in a weight of evidence assessment (WoE) according to the CLP criteria and guidance.

The animal data either indicate that geraniol is a skin sensitizer of moderate potency or do not allow conclusions on potency due to the design of the tests (doses used, lack of quantification of response). Among the standardized animal tests for skin sensitization the LLNA is considered best suited for potency assessment (Basketter et al., 2005 and ECHA 2015). All the available LLNAs suitable for classification of geraniol (i.e. excluding the LLNA BrdU ELISA and the LLNAs with air-exposed geraniol) show a moderate

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

potency with EC3 values >2%. Whereas one GPMT indicates a moderate potency, the remaining animal studies only indicate “sensitization” (3 GPMTs) or “no sensitization” (1 GPMT and 1 Buehler test). For most of the animal studies robust study information is not available to assess the quality more precisely. Collectively, the results of the animal tests confirm the sensitizing properties of geraniol in a relatively consistent manner with a moderate potency.

The human data available provide substantial evidence of strong sensitising effects of geraniol especially based on the results of patch tests with selected patients. Diagnostic patch test data obtained from eczema patients attending individual dermatology clinics or collected clinic data is the primary source of clinical information on the occurrence of skin sensitisation (ECHA 2015) and diagnostic patch tests are generally performed under internationally standardised conditions. Human patch tests with geraniol show a high frequency of occurrence of skin sensitisation of geraniol according to the classification criteria. According to the guidance the following three types of human information confirm the high frequency of occurrence of skin sensitisation: Data from unselected and selected dermatitis patients as well as a high number of published cases (>100). The comprehensive set of patch test data include thousands of dermatitis patients tested in dermatological clinics in different countries, mostly in EU. The four case studies confirm the general picture observed in the other patch tests with dermatitis patients. Some of the older volunteer tests in humans (HRIPTs and HMTs) generally confirm the sensitising properties of geraniol and indicate a moderate potency; however, original study information is generally not available for these non-clinical experimental studies.

Although frequent/daily exposure to geraniol is anticipated the overall exposure to geraniol is estimated to be relatively low based on information on the use in consumer products such as cosmetics and cleaning agents, but also in professional cleaning products.

Based on the high frequency of skin sensitisation observed in human patch tests with geraniol ($\geq 2.0\%$ in 36 of 56 patch tests with selected dermatitis patients and $\geq 1.0\%$ in 6* of 32 patch tests with unselected dermatitis patients [*hereof two tests with oxidised geraniol]) and the high number of published cases combined with the estimated relatively low exposure, a classification of geraniol as a strong skin sensitizer in sub-category 1A is justified.

10.10 Conclusion on classification and labelling for skin sensitisation

Based on the high frequency of skin sensitisation observed in a large number of human patch tests (approximately 90 tests) combined with the relatively low estimated exposure to geraniol, a classification in sub-category 1A is justified.

Specific concentration limits can be set for skin sensitizers when reliable and adequate information is available to support that the specific hazard is evident below (or above) the GCL. The setting of an SCL for sensitizers is based on potency. For skin sensitizers the guidance clearly describes how an SCL can be set based on the results of certain animal studies (i.e. when a high response level is observed below a certain low dose). Further, relevant information e.g. from workplaces with known exposure levels can be used to justify a different SCL than those recommended based on the results of the animal studies.

The guidance does not provide any information on how an SCL may be set based on human data alone. Whereas the human patch test data support that geraniol is a strong sensitizer fulfilling the criteria for Category 1A these data do not provide clear dose-response information or specific information on the previous exposure regime for these patients. These data alone are thus not considered to support the establishment of an SCL.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The sensitising properties of geraniol have been intensively studied in both animals and humans. Guideline and non-guideline studies in animals are available; the positive results of numerous local lymph node assays, Guinea pig maximisation and Buehler tests are directly applicable for classification and sub-categorisation. A large number of human patch tests are also available. Geraniol is a component of one of the standardised fragrance mixtures used in the European baseline series used for diagnostic patch testing. Follow-up testing with the single fragrance substances is done routinely in many clinics; the sensitising properties of geraniol are well documented. Results of historical human volunteer studies are also available for geraniol and provide supporting evidence for sub-categorisation.

All the available local lymph node assays (LLNAs) suitable for classification of geraniol show a moderate potency with EC values > 2%. Whereas one maximisation test indicates a moderate potency, the remaining Guinea pig tests only indicate positive, with no indication of potency, or negative results.

The human data provide substantial evidence of strong sensitising effects of geraniol, especially based on the results of patch tests with selected dermatitis patients. Human patch tests with geraniol show a high frequency of occurrence of skin sensitisation. There are data from thousands of unselected and selected patients, and well over 100 published cases. Although original study reports are rarely available, some of the older volunteer tests in humans (human repeat insult patch tests and maximisation tests: HRIPTs and HMTs) generally confirm the sensitising properties of geraniol and indicate a moderate potency.

There is widespread use of geraniol as a fragrance in cosmetics and other consumer products and a high tonnage is placed on the market (1000 - 10000 tonnes/annum). Although frequent or daily exposure to geraniol is anticipated, the overall exposure to geraniol is estimated to be relatively low based on information on how the geraniol is used in these products.

Overall, there is a high frequency of skin sensitisation in human patch tests ($\geq 2.0\%$ in 36 of the 56 patch tests with selected patients and $\geq 1.0\%$ in 6 of 32 patch tests with unselected patients) and a high number of published cases, set against an estimated low exposure. In accordance with the CLP criteria and guidance, classification of geraniol as a strong skin sensitiser (Skin Sens. 1A) is justified on the basis of this human evidence.

Comments received during public consultation

Comments were received from 3 Member State Competent Authorities (MSCAs), a Downstream User company (DU) and a Manufacturer, 3 non-governmental groups of dermatologists and one expert individual. In all cases there was an agreement that geraniol should be classified as a skin sensitiser based on both animal and human data. However, differing perspectives were offered in relation to potency and sub-categorisation. The most challenging aspects related to the interpretation of clinical data and information on the extent of human exposure.

One of the commenting MSCA agreed with the Dossier Submitter (DS) that although the animal data indicated low or moderate potency, the clinical information and exposure assessment were typical of a high potency sensitiser. In their view a category 1A classification would have been appropriate. All 3 groups of dermatologists, including clinicians from across the EU, also supported the proposal to classify geraniol as a skin sensitiser in category 1A. In contrast, 2 further MSCAs were not convinced that a sufficiently clear case had been made to support this level of classification. They queried especially the DS's assertion that human exposure to geraniol had been low.

The expert individual, a clinician based in Germany, did not support classification in category 1A. He regarded the strength of the human evidence to be insufficient. He argued against use of the data from selected patients for hazard or risk assessment given the heterogeneous nature of the selection process. Of the fragrances in the standard series used for patch testing, he observed that geraniol had not given an especially high frequency of responses in non-selected patients; several substances had given higher response rates. When sensitising frequencies (clinical data) and exposure frequencies (volumes in consumer products) were compared for the standard series, as an indicator of risk, geraniol appeared not to be of high concern.

The DU did not support the DS, favouring classification in category 1 without a sub-category. Results of 10 mouse LLNAs showed geraniol to be a weak sensitiser, and this was supported by the Guinea pig tests. The mouse data were considered especially relevant because, as for human skin, several forms of cytochrome P450 known to oxidise geraniol to allergenic metabolites were active in mouse skin. Therefore, according to the DU, allergenic metabolites of geraniol would have been most likely produced under the conditions of the LLNA. Whilst some oxidation products or metabolites of geraniol were potent sensitisers when tested in the LLNA, these findings were not representative for exposure to geraniol itself because the tested concentrations would not have been generated in human skin. Similarly, according to the DU, the auto-oxidation of geraniol that had been found under extreme experimental conditions (> 10 weeks exposure to air) could not occur under conditions of normal storage, handling and use of geraniol-containing products.

Detailed comments provided by the Manufacturer of geraniol supported their view that data from the animal and human volunteer studies were consistent with the criteria for a category 1B classification. Four HRIPTs of mixed quality had shown no skin sensitisation reactions after repeated application of 2362, 3876 and 9690 µg geraniol/cm². Positive reactions had been seen in 4/221 volunteers exposed to dose levels of 5905 or 11810 µg/cm², but these could be attributed either to an individual being pre-sensitised or to irritant responses. Further, the tested concentrations were above the threshold for differentiating between sub-categories 1A and 1B.

Both the Manufacturer and DU regarded clinical patch test data to be unsuitable for hazard classification because the induction concentrations for all subjects were unknown. The Manufacturer accepted that the highly variable cumulative data on selected dermatitis patients indicated a high frequency of occurrence of skin sensitisation, as defined by CLP guidance (3.3% positive: 653/19800 patients). However, a meta-analysis for all the studies of unselected patients, including 2 new studies published in 2017 (see Additional Key Elements), met the criteria for low frequency. According to this analysis, the positive response rate was 0.44% (327/74381 patients tested).

The Manufacturer further commented on the DS's assessment that exposure of consumers to

geraniol could be classed as low. Whilst the DS had indicated that frequent/daily exposure was anticipated amongst consumers due to widespread use and the high tonnage of geraniol, the manufacturer suggested that the content of this substance in consumer products on the market leading to the induction of skin sensitisation had been under-estimated. The Manufacturer commented that it was not possible to know if those patients who had responded positively on patch testing with geraniol had mostly been induced by low concentrations. The reports showing the highest frequencies of positive patch test results in unselected patients were published before 2007. Although the International Fragrance Association (IFRA) had issued a limit of 1% on the content of geraniol in many consumer products in 2007, this would not have impacted on many of the products actually being used until some years later, and potentially as late as 2015.

The Manufacturer argued that the DS had not provided adequate justification for excluding from their analysis those current products and historical exposures to other products with > 1% content of geraniol.

The Manufacturer concluded that the low frequency of positive patch test results on unselected patients (0.44%) combined with clear evidence for a strong potential for high estimated exposure levels (> 1% in products) indicated that a classification in category 1B would be more appropriate than category 1A.

Analysis of further information received during the public consultation

The Manufacturer provided information on two relatively large, additional clinical studies of non-selected dermatitis patients.

In the first, patch testing was conducted in a single Danish clinic (Bennike *et al.*, 2017). Positive reactions to 1% geraniol were seen in 0.25% of patients (15/6004), tested between 2010 and 2015. The authors reported a steady to decreasing prevalence trend during this period.

In the second, clinical patch testing with 2% geraniol in Sweden produced positive responses in 0.4% of patients tested between 2009 and 2012 (8/2235), and 0.6% between 2013 and 2015 (14/2248) (Mowitz *et al.*, 2017).

The Manufacturer also provided further details (including study reports) of the various human volunteer repeated insult patch tests (HRIPTs) and human maximisation tests (HMTs) conducted with geraniol. This information is summarised in the table below.

Unless otherwise indicated, the HRIPTs involved nine 24h occluded induction applications (3 times a week for 3 weeks) followed approximately two weeks later by a 24h occluded challenge application to a virgin site. Reactions were read at patch removal and 48, 72 and 96 hours after application. The HMTs were conducted with occluded applications to the same site for five alternate-day 48-hour periods, followed 10-14 days later with a 48 hours occluded challenge application.

Generally, information on the age and ethnicity of the volunteers was not provided.

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

| Additional information on the Human Repeat Insult Patch and Maximisation tests | | | |
|---|----------------------------------|-------------------|---|
| Study details | Volunteer participants | Reactions | RAC Observations |
| <i>HRIPT</i> 2% geraniol in 1:3 ethanol:Diethylphthalate (DEP) | 110 (24 male, 86 female) | 0/110 | No evidence of sensitising potential. |
| <i>HRIPT</i> 5% geraniol in 1:3 ethanol:DEP | 109 (20 male and 89 female) | 1/109 | The single positive response was not considered a case of sensitisation; subject did not respond when re-challenged 3 weeks later using occlusive and semi-occlusive patches |
| <i>HRIPT</i> 10% geraniol in 1:3 ethanol:DEP Reactions assessed at 24 and 72 h only | 102 (30 male and 82 female) | 3/112 | None of the 3 respondents was considered to be a case of sensitisation. 1 st : reacted to both geraniol and vehicle after first induction and reacted strongly at challenge to geraniol, solvent and saline control. 2 nd : reacted to both geraniol and vehicle during last 2 induction applications, exhibited mild erythema during challenge; considered to be cumulative irritant response 3 rd : comparable level of irritation seen at induction and challenge. |
| <i>HRIPT</i> 5% geraniol in alcohol SDA 39C Semi-occluded challenge. | 40 (12 male and 28 female) | 0/40 | No evidence of sensitising potential. Relatively small group size limits statistical power of the study. |
| <i>HRIPT</i> 12.5% geraniol in alcohol SDA 39C Semi-occluded challenge. | 41 (14 male and 27 female) | 0/41 | No evidence of sensitising potential. Relatively small group size limits statistical power of the study. |
| <i>Modified Draize Procedure</i> 10% "semi pure" geraniol in petrolatum 10% "semi pure" geraniol in alcohol Ten (48-72 h) occluded induction applications; 72 h occluded challenge 2 weeks later | 104 73 | 0/104 2/73 | This study reviewed data on 21 fragrance ingredients to compare the predictive potential of a Modified Draize Procedure (involving the use of high induction and challenge test concentrations) with the Maximisation test. Two volunteers responded positive to geraniol. |
| <i>HMT</i> 6% geraniol in petrolatum | 24 (Japanese-American ethnicity) | 0/24 | Another test material (name not provided) gave a clear positive allergic result in 20 of the volunteers. |
| <i>HMT</i> 6% geraniol in petrolatum | 26 | 1/26 | One volunteer responded positively to geraniol. |

| | | | |
|---|-------------------------------|------|--|
| | (Japanese-American ethnicity) | | Another test substance (name not provided) gave a clear positive allergic reaction in 7 of the volunteers. |
| HMT 6% geraniol (solvent not stated) | 25 | 0/25 | No evidence of a sensitising potential. |

Assessment and comparison with the classification criteria

Animal data

The sensitising potential of geraniol has been tested comprehensively in both Guinea pigs and mice. As shown in the following tables, limited reporting of the results from some of the Guinea pig studies makes it difficult to assess them against the CLP criteria. However, overall there does appear to be sufficient, reproducible evidence from both species to demonstrate that geraniol should be classified as a skin sensitiser. Where the data are sufficient to allow an assessment to be made, the potency of geraniol does not appear to be high.

| Guinea pig studies | | |
|--|---|--|
| Method (study date) | Result | RAC assessment against CLP criteria |
| Maximisation (1989) Induction: 0.1% (intra-dermal) Challenge: 10% | 0/10 animals sensitised when solvent was acetone:PEG400 for occluded induction and challenge. "Sensitisation observed" in another group of 10 animals when solvent was acetone only. Response rate not specified. In preliminary studies, intra-dermal doses of 0.25% and 0.5% evoked an irritant response. | Not possible, as the number of animals responding with a positive result is unclear. |
| Maximisation (1977) Induction: 5% (intra-dermal) Challenge: 10% | 3/6 animals sensitized 50% response rate | Classification as a sensitiser (low potency, but lacking data to exclude high potency) |
| Maximisation (1977) Induction: 5% (intra-dermal) Challenge: "sub-irritant" | "Sensitisation observed" (n=10) Response rate not specified. | Not possible; insufficient information. |
| Maximisation (1986) Induction: 10% (intra-dermal) Challenge: 10% | "Sensitisation observed" (n=10) Response rate not specified. | Not possible; insufficient information. |
| Buehler Induction: 25% Challenge: 2.5, 7.5 & 25% | 0/20 animals sensitised | Not classified |

| Mouse studies | | |
|---|--|---|
| Method (study date) | Results | Assessment against CLP criteria |
| LLNA (OECD TG 429) Eight tests conducted between 2001 and 2007 | EC3: 22.4% - sensitising EC3: 4.4% - sensitising (test substance had been air-exposed for 4 weeks) EC3: 5.8% - sensitising EC3: 11.4% - sensitising* EC3: 5.6% - sensitising EC3: 11.8% - sensitising EC3: 20.4% - sensitising EC3: 25.8% - sensitising | Classification, sub-category 1B (low or moderate potency) |
| Ex vivo LLNA -BrdU/Elisa (2014) | EC3: 13.1% - sensitising | Classification, sub-category 1B (low potency) |

**This study was summarised twice by the DS – it seemed to them from the literature originally available that 2 different studies with identical methodology and results had been conducted.*

Human data

In a number of human volunteer studies the skin sensitisation potential of geraniol has been assessed. As summarised in the following table, these include Repeat Insult Patch tests (HRIPT), Maximisation tests and a modified Draize procedure. Although the conduct of such studies is not permitted for compliance with CLP for ethical reasons, it is possible to take account of such data as part of a weight of evidence analysis if it is available historically. The comparable findings from study to study provide some confidence in the results seen.

| Human Repeat Insult Patch Tests | | |
|--|--------------------------------------|--|
| Geraniol test concentration | % Positive (No. positive/No. tested) | Summary |
| 2% (2362 µg/cm ²) | 0% (0/110) | Induction of sensitisation was seen in 3/7 studies (6/589 volunteers; 1%). |
| 5% (plus 0.5% tocopherol) (5905 µg/cm ²) | 0.9% (1/109) | |
| 10% (11810 µg/cm ²) | 2.7 % (3/112) | All exposures were > 500 µg/cm ² Various different solvents were used. |
| 5% (3876 µg/cm ²) | 0 % (0/40) | |
| 12.5% (9690 µg/cm ²) | 0 % (0/41) | |
| 10% (modified Draize procedure) | 0 % (0/104) | |
| 10% (modified Draize procedure) | 2.7% (2/73) | |

| Human Maximisation Tests | | |
|-------------------------------|--------------------------------------|---|
| Geraniol test concentration | % Positive (No. positive/No. tested) | Summary |
| 6% | 0 % (0/25) | Induction of sensitisation was seen in 1/5 studies (1/125 volunteers; < 0.1%). All exposures were > 500 µg/cm ² |
| 6% | 0% (0/25) | |
| 6% (4140 µg/cm ²) | 0% (0/24) | |
| 6% (4140 µg/cm ²) | 3.8 % (1/26) | |
| 6% (4140 µg/cm ²) | 0% (0/25) | |

According to CLP guidance, the exposure concentrations used in volunteer tests like these can contribute to an assessment of potency and the possible sub-categorisation of a sensitiser. High potency, supporting sub-category 1A, is shown when exposures below 500 µg/cm² induce a positive response. Lower potency, supporting sub-category 1B, is shown when induction occurs at higher exposure levels. The small numbers of individuals who did respond in these studies were exposed to 4140-11810 µg/cm² geraniol, suggesting that sub-category 1B may be appropriate. However, it is not possible to know whether lower test concentrations could also have induced sensitisation in some volunteers. Thus, overall, these data do not provide unambiguous support for sub-categorisation.

Four case studies from within the EU are summarised in the CLH report. They describe how positive patch test reactions to geraniol were seen in a 54-year old female bartender with chronic hand dermatitis, a 48-year old male metalworker with recurrent hand dermatitis, 3/7 patients who were referred to a clinic with sensitivity to farnesol, and 1/3 eczema patients. The patch test concentrations ranged from 1-20%. These studies are consistent with diagnostic patch test data available from various groups of selected and non-selected dermatology clinic patients.

The many reports of diagnostic patch tests available for geraniol provide supporting information to the classification assessment and may, potentially, steer the conclusion towards sub-categorisation. The studies date from the 1960s. Such tests are conducted according to standardised guidelines and with well-defined challenge conditions. The DS cited 56 reports of patch tests conducted on selected dermatitis patients. These patients included those suspected of having contact allergy to fragrances or cosmetic products and those from certain relevant occupational groups. The CLH report also included 32 publications summarising the results of similar patch tests conducted on non-selected (consecutive) contact allergy patients and a further 4 patch test studies. Data from unselected, consecutive dermatitis patients is more standardised than testing which is undertaken on a specific patient group. Additionally, 2 recent publications reporting incidence of contact allergy to geraniol in consecutive patients were provided through the public consultation (see above).

As shown clearly in the CLH report, there is no obvious trend related to the date of the study, the positive response rates being highly variable (range: 0-30%). In total, the data presented in the CLH report show 654 cases out of 20023 patients tested, a response rate of 3.3%. The studies with the higher response rates would appear to have selected particularly well for individuals who had been exposed and sensitised to geraniol before they attended the clinics. In accordance with the CLP criteria, these data overall show a "high frequency" of cases (response rate ≥ 2.0%).

The studies with non-selected (i.e. consecutive) patients showed much less variable positive response rates, ranging from 0-4.6%. Again, there were no obvious trends relating to the date of study. It is noted that 4 of the 32 studies reported by the DS used geraniol that had been air-

exposed for 10 weeks; these studies showed some of the highest response rates (0.6, 0.9, 2.3, 4.6). It is possible that this aged material was more potent as a sensitiser than geraniol itself, possibly due to oxidation, but this is circumstantial and the findings are not definitive. Overall, taking into account data provided in the CLH report and the public consultation, there has been a positive response rate of approximately 325 reported cases/74400 patients tested (approx. 0.45%). This meets the criteria for "low frequency" according to the CLP guidance (< 1%). Only 6 of the individual studies with non-selected patients met the criteria for "high frequency" (rates were 1.1, 1.2, 1.7, 2.3, 4.1 and 4.6%).

As it is not possible to establish the induction doses encountered by those patients who responded positively to geraniol, the CLP guidance describes principles for deriving an exposure index leading to an assessment of relatively high or low exposure for a substance that can be matched against patch test data to inform on potency and sub-categorisation.

Geraniol is a fragrance that is used widely in consumer products found on the EU market. It is imported in amounts of 1000-10,000 tonnes/year and the registered categories for use for consumers are cosmetics and a variety of household and professional cleaning products. Individuals can be exposed to geraniol from many different sources.

In 2007, IFRA established maximum recommended limits of geraniol in leave-on cosmetic products between 0.3 - 5.5%, depending on product category, between 5.0-8.6% in rinse-off cosmetic products, and of 2.5% for non-cosmetic consumer products with direct skin contact. However, it is not clear how quickly or completely products on the market came to adhere to these recommendations. In 2012, the Scientific Committee on Consumer Safety (SCCS) considered a number of surveys on the presence and content of certain fragrances in consumer products, based mostly on labelling information. Geraniol was found present in 12-49% of the products covered; the SCCS concluded that exposure to geraniol is foreseeable in daily life. Further surveys have shown geraniol to be present in deodorants, soaps, shampoos, conditioners, lotions and creams, and also cleaning agents, stain removers and air care products. A Danish database (2017) generally describes low levels of geraniol in consumer products marketed currently and in the past, although up to 23% was found in certain massage oils. A further database, a Danish register of hazardous substances in professional products, reports concentrations below 0.1% in the majority of cleaning products, but above this value in fragrance mixtures and scented oils.

In characterising the nature of the exposure of EU citizens to geraniol in order to make a comparison with the numbers of positive patch tested individuals, RAC is mindful that there is much uncertainty about the nature of the products that may have induced sensitisation, the periods during which the induction occurred, and the concentrations encountered by those individuals in which sensitisation was induced. Although according to the DS the IFRA guidelines have helped to reduce exposure, it is possible that patients may have been exposed to consumer products containing unrestricted concentrations of geraniol well into 2015 (according to comments received from industry during the public consultation).

RAC finds this all this general information to be relevant for the assessment of skin exposure to geraniol of sensitised patients before they became symptomatic. In accordance with the CLP guidance, RAC makes the following conclusions about the nature of the exposures encountered.

| Consumer exposure to geraniol (skin) | | | |
|---|--------------------------------------|---------------------------------------|---|
| Exposure data | Indicator of relatively low exposure | Indicator of relatively high exposure | Assessment by RAC |
| Concentration/dose at induction | < 1.0% < 500 µg/cm ² | ≥ 1.0% ≥ 500 µg/cm ² | The content of geraniol in many consumer and professional products appears to have decreased significantly in recent years; surveys suggest that current levels may generally be very low. However, it also appears that higher content levels (≥1.0%) will have prevailed during the periods when most of the contact allergy patients were induced to geraniol. <i>Conclusion: Some uncertainty: overall, relatively high exposure</i> |
| Repeated exposure | < once/daily | ≥ once/daily | Given the wide range of consumer products shown to contain geraniol, repeated exposure every day seems very likely. <i>Conclusion: Relatively high exposure</i> |
| Number of exposures (irrespective of the concentration of the sensitiser) | < 100 exposures | ≥ 100 exposures | Given the types of consumer and professional products shown to contain geraniol, it is highly likely that individuals will have been exposed 100s of times. <i>Conclusion: Relatively high exposure</i> |

This assessment contrasts with the view of the DS, who concluded that concentration/dose levels at induction were relatively low.

In accordance with the CLP criteria, this assessment of relatively high skin exposure indicates that geraniol should not be regarded as a high potency skin sensitiser in spite of the high number of positive patch test results reported.

Conclusion

RAC concludes that geraniol should be classified as a skin sensitiser. This is justified by a considerable volume of animal and human data.

Although there are some indicators of possible high potency (most notably the very high numbers of positive patch test results in clinics, and the number of published cases), other data suggest geraniol has low or moderate potency (e.g. local lymph node assays). Human volunteer studies have also tended to indicate low to moderate potency, although the possibility of high potency cannot be excluded completely given the nature of these studies. Further, although the numbers of positive patch tests are undoubtedly high, the exposures responsible for inducing the sensitised state in these individuals also may have been relatively high – it is not entirely clear. Given this uncertainty about the potency of geraniol, RAC concludes that no sub-categorisation is warranted for this endpoint.

Overall, RAC concludes that classification as **Skin Sens. 1; H317 (may cause an allergic skin reaction)** is warranted for geraniol.

The available data are not sufficient to support the establishment of a specific concentration limit. Furthermore, the data do not suggest that geraniol has an extreme potency. Overall, an SCL is not justified.

10.11 Germ cell mutagenicity

Hazard class not assessed in this dossier.

10.12 Carcinogenicity

Hazard class not assessed in this dossier.

10.13 Reproductive toxicity

Hazard class not assessed in this dossier.

10.14 Specific target organ toxicity-single exposure

Hazard class not assessed in this dossier.

10.15 Specific target organ toxicity-repeated exposure

Hazard class not assessed in this dossier.

10.16 Aspiration hazard

Hazard class not assessed in this dossier.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Environmental hazards have not been assessed in this dossier.

12 EVALUATION OF ADDITIONAL HAZARDS

Additional hazards have not been assessed in this dossier.

13 ADDITIONAL LABELLING

Given that geraniol is classified as a skin sensitizer in Category 1A, labelling with EUH 208 will apply when geraniol is present in mixtures in concentrations $\geq 0.01\%$.

14 REFERENCES

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.

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

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.

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

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 Dermite Contacto* 13, 22-25.

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

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

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

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.

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

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.

Danish Product Register: Search results for geraniol and its presence in hazardous mixtures on the Danish market 2016 (the register contains information on hazardous mixtures for professional use only, data are not publically available).

DK EPA database. Danish Environmental Protection Agency database of chemicals reported and analysed in various consumer products (incl. links to the original survey reports). <http://www2.mst.dk/databaser/Vidensbank/vidensbank.aspx>

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.

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.

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.

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.

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

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.

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

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.

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.

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.

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 multicenter study of the European Environmental and Contact Dermatitis Research Group with 48 frequently used constituents of perfumes. *Contact Dermatitis* 33, 333-342.

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

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

- Goncalo, S., Cabral, F., Goncalo, M., 1988. Contact sensitivity to oak moss. *Contact Dermatitis* 19, 355-357.
- Goossens, A., Merckx, L., 1997. Allergic contact dermatitis from farnesol in a deodorant. *Contact Dermatitis* 37, 179-189.
- 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.
- 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.
- 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.
- 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.
- Hayakawa, R., Ohiwa, K., Ukei, C., Matsunaga, K., 1983. Melanosis faciei feminae in 1982. *Skin Research* 25, 690-695.
- 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.
- Hendriks, S.A., van Ginkel, C.J., 1999. Evaluation of the fragrance mix in the European standard series. *Contact Dermatitis* 41, 161-162.
- 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.
- Hiroso, 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.
- 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.
- Hostynek, J.J., Maibach, H.I., 2004. Is there evidence that geraniol causes allergic contact dermatitis? *Exogenic Dermatology* 3, 318-331.
- IFRA, 2007: IFRA Standard Geraniol. 42nd amendment to the IFRA code of practice, International Fragrance Association. <http://www.ifraorg.org/en-us/standards>
- Isihara, M., Itoh, S., Hayashi, S., Satake, T., 1979. Methods of diagnosis in cases of cosmetic dermatitis and facial melanosis in females. *Nishinon Journal of Dermatology* 41, 426-439
- 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.
- 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.
- 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.
- Johansen, J.D., Menne, T., 1995. The fragrance mix and its constituents: a 14-year material. *Contact Dermatitis* 32, 18-23.
- Johansen JD, Aalto-Korte K, Agner T, Andersen KE, Bircher A, Bruze M, Cannavó A, Giménez-Arnau A, Goncalo M, Goossens A, John SM, Lidén C, Lindberg M, Mahler V, Matura M, Rustermeier T, Serup J, Spiewak R, Thyssen JP, Vigan M, White IR, Wilkinson M, Uter W: European Society of Contact Dermatitis

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

guideline for diagnostic patch testing – recommendations on best practice. *Contact Dermatitis* 2015: vol. 73 issue 4, 195-221. Katsarma, G., Gawkrödger, D.J., 1999. Suspected fragrance allergy requires extended patch testing to individual fragrance allergens. *Contact Dermatitis* 41, 193-197.

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

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

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.

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.

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.

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.

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

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

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 multicenter investigation (Part I). *American journal of contact dermatitis : official journal of the American Contact Dermatitis Society* 7, 77-83.

Magnusson, B., Kligman, A.M., 1969. The identification of contact allergens by animal assay. The guinea pig maximization test. *Journal of Investigative Dermatology* 52, 268.

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

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.

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.

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.

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.

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.

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.

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.

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.

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

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

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

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.

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

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.

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

SCCFNP, 1999. Opinion concerning fragrance allergy in consumers. A review of the problem. Analysis of the need for appropriate consumer information and identification of consumer allergens. The Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers.

SCCS, 2012. SCCS (Scientific Committee on Consumer Safety), opinion on fragrance allergens in cosmetic products, 26-27 June 2012.

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

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.

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.

Sharp, D.W., 1978. The sensitization potential of some perfume ingredients tested using a modified Draize procedure. *Toxicology* 9, 261-271. *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.

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.

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

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.

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

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.

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. Multicenter study of fragrance allergy in Hungary: immediate and late type reactions. *Contact Dermatitis* 46, 325-330.

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.

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.

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

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.

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.

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

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

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.

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.

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.

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 127-131. *Cited in: SCCNFP*, 1999.

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.

Additional references

Bennike, Zachariae and Johansen (2017). Non-mix fragrances are top sensitizers in consecutive dermatitis patients – a cross-sectional study of the 26 EU-labelled fragrance allergens. *Contact Dermatitis*, 77, 270-279.

Mowitz, Svedman, Zimerson, Isaksson, Pontén and Bruze (2017). Simultaneous patch testing with fragrance mix I, fragrance mix II and their ingredients in southern Sweden between 2009 and 2015. *Contact Dermatitis*, 77, 280-287.

15 ANNEXES

Annex I: detailed study summaries

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; (2E)- 3,7-dimethylocta-2,6-dien-1-ol

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

Contact details for dossier submitter:

Danish Environmental Protection Agency

Haraldsgade 53, 2100 Kbh Ø, Denmark

E-mail: mst@mst.dk

Version number: 2

Date: 30 August 2017

CONTENTS

| | | |
|----------|--|----------|
| 1 | PHYSICAL HAZARDS | 4 |
| 2 | TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION) | 4 |
| 3 | HEALTH HAZARDS | 4 |
| 3.1 | SKIN SENSITISATION..... | 4 |
| 3.1.1 | <i>Animal data</i> | 4 |
| 3.1.1.1 | STUDY 1-3 (LLNA, 3 separate assays)..... | 4 |
| 3.1.1.2 | STUDY 4 (LLNA) (also cited in REACH registration dossier)..... | 5 |
| 3.1.1.3 | STUDY 5 (LLNA)..... | 6 |
| 3.1.1.4 | STUDY 6 (LLNA) (also cited in REACH registration dossier)..... | 6 |
| 3.1.1.5 | STUDY 7 (LLNA) (also cited in REACH registration dossier)..... | 7 |
| 3.1.1.6 | STUDY 8 (LLNA) (also cited in REACH registration dossier)..... | 8 |
| 3.1.1.7 | STUDY 9 (LLNA) (also cited in REACH registration dossier)..... | 9 |
| 3.1.1.8 | STUDY 10 (LLNA BrdU ELISA <i>ex vivo</i>)..... | 10 |
| 3.1.1.9 | STUDY 11-12 (GPMT) (two tests, different vehicles) | 11 |
| 3.1.1.10 | STUDY 13 (GPMT) | 12 |
| 3.1.1.11 | STUDY 14 (GPMT) (also cited in REACH registration dossier)..... | 13 |
| 3.1.1.12 | STUDY 15 (GPMT) (also cited in REACH registration dossier)..... | 14 |
| 3.1.1.13 | STUDY 16 (Buehler)..... | 15 |
| 3.1.2 | <i>Human data</i> | 16 |
| 3.1.2.1 | STUDY 1 (Patch test, selected) | 16 |
| 3.1.2.2 | STUDY 2 (Patch test, selected) | 17 |
| 3.1.2.3 | STUDY 3 (Patch test, selected) | 18 |
| 3.1.2.4 | STUDY 4 (Patch test, selected) | 19 |
| 3.1.2.5 | STUDY 5 (Patch test, selected) | 20 |
| 3.1.2.6 | STUDY 6-7 (Patch test, selected)..... | 20 |
| 3.1.2.7 | STUDY 8 (Patch test, selected) | 21 |
| 3.1.2.8 | STUDY 9 (Patch test, selected) | 22 |
| 3.1.2.9 | STUDY 10 (Patch test, selected) | 22 |
| 3.1.2.10 | STUDY 11 (Patch test, selected) | 23 |
| 3.1.2.11 | STUDY 12 (Patch test, selected) | 23 |
| 3.1.2.12 | STUDY 13 (Patch test, selected) | 24 |
| 3.1.2.13 | STUDY 14 (Patch test, selected) | 24 |
| 3.1.2.14 | STUDY 15 (Patch test, selected)..... | 25 |
| 3.1.2.15 | STUDY 16 (Patch test, selected)..... | 25 |
| 3.1.2.16 | STUDY 17 (Patch test, selected)..... | 26 |
| 3.1.2.17 | STUDY 18 (Patch test, selected)..... | 26 |
| 3.1.2.18 | STUDY 19 (Patch test, selected) (also cited in REACH registration dossier)..... | 27 |
| 3.1.2.19 | STUDY 20 (Patch test, selected) | 27 |
| 3.1.2.20 | STUDY 21 (Patch test, selected) | 28 |
| 3.1.2.21 | STUDY 22 (Patch test, selected)..... | 29 |
| 3.1.2.22 | STUDY 23 (Patch test, selected)..... | 29 |
| 3.1.2.23 | STUDY 24-26 (Patch test, selected)..... | 29 |
| 3.1.2.24 | STUDY 27-28 (Patch test, selected) (also cited in REACH registration dossier)..... | 30 |
| 3.1.2.25 | STUDY 29 (Patch test, selected) | 31 |
| 3.1.2.26 | STUDY 30 (Patch test, selected) | 31 |
| 3.1.2.27 | STUDY 31 (Patch test, selected)..... | 31 |
| 3.1.2.28 | STUDY 32 (Patch test, selected)..... | 32 |
| 3.1.2.29 | STUDY 33 (Patch test, selected) (also cited in REACH registration dossier)..... | 32 |
| 3.1.2.30 | STUDY 34-35 (Patch test, selected)..... | 33 |
| 3.1.2.31 | STUDY 36 (Patch test, selected)..... | 33 |
| 3.1.2.32 | STUDY 37 (Patch test, selected) | 34 |
| 3.1.2.33 | STUDY 38 (Patch test, selected)..... | 34 |
| 3.1.2.34 | STUDY 39 (Patch test, selected) (also cited in REACH registration dossier)..... | 35 |

ANNEX TO ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

| | | |
|----------|--|----|
| 3.1.2.35 | STUDY 40 (Patch test, selected) | 35 |
| 3.1.2.36 | STUDY 41-42 (Patch test, selected)..... | 36 |
| 3.1.2.37 | STUDY 43 (Patch test, selected) (also cited in REACH registration dossier)..... | 36 |
| 3.1.2.38 | STUDY 44 (Patch test, selected) | 36 |
| 3.1.2.39 | STUDY 45 (Patch test, selected) | 37 |
| 3.1.2.40 | STUDY 46 (Patch test, selected) | 37 |
| 3.1.2.41 | STUDY 47-48 (Patch test, selected) (also cited in REACH registration dossier)..... | 38 |
| 3.1.2.42 | STUDY 49 (Patch test, selected) | 38 |
| 3.1.2.43 | STUDY 50 (Patch test, selected) | 39 |
| 3.1.2.44 | STUDY 51 (Patch test, selected) | 39 |
| 3.1.2.45 | STUDY 52 (Patch test, selected) | 40 |
| 3.1.2.46 | STUDY 53 (Patch test, selected) | 40 |
| 3.1.2.47 | STUDY 54 (Patch test, selected) | 41 |
| 3.1.2.48 | STUDY 55 (Patch test, selected) | 41 |
| 3.1.2.49 | STUDY 56 (Patch test, selected) (also cited in REACH registration dossier)..... | 41 |
| 3.1.2.50 | STUDY 57 (Patch test, consecutive) | 42 |
| 3.1.2.51 | STUDY 58-63 (Patch test, consecutive) | 43 |
| 3.1.2.52 | STUDY 64-65 (Patch test, consecutive) | 44 |
| 3.1.2.53 | STUDY 66 (Patch test, consecutive) | 45 |
| 3.1.2.54 | STUDY 67 (Patch test, consecutive) | 46 |
| 3.1.2.55 | STUDY 68 (Patch test, consecutive) | 47 |
| 3.1.2.56 | STUDY 69 (Patch test, unselected) | 47 |
| 3.1.2.57 | STUDY 70 (Patch test, consecutive) | 48 |
| 3.1.2.58 | STUDY 71 (Patch test, consecutive) | 49 |
| 3.1.2.59 | STUDY 72 (Patch test, consecutive) | 50 |
| 3.1.2.60 | STUDY 73 (Patch test, consecutive) | 50 |
| 3.1.2.61 | STUDY 74-75 (Patch test, consecutive) | 51 |
| 3.1.2.62 | STUDY 76 (Patch test, selected) | 52 |
| 3.1.2.63 | STUDY 77 (Patch test, consecutive) | 52 |
| 3.1.2.64 | STUDY 78 (Patch test, consecutive) | 53 |
| 3.1.2.65 | STUDY 79-81 (Patch test, consecutive) | 53 |
| 3.1.2.66 | STUDY 82 (Patch test, consecutive) | 53 |
| 3.1.2.67 | STUDY 83-84 (Patch test, consecutive)..... | 54 |
| 3.1.2.68 | STUDY 85-87 (Patch test, consecutive)..... | 54 |
| 3.1.2.69 | STUDY 88 (Patch test, consecutive) | 55 |
| 3.1.2.70 | STUDY 89 (Patch test, other)..... | 55 |
| 3.1.2.71 | STUDY 90 (Patch test, other)..... | 56 |
| 3.1.2.72 | STUDY 91 (Patch test, other)..... | 57 |
| 3.1.2.73 | STUDY 92 (Patch test, other)..... | 58 |
| 3.1.2.74 | STUDY 93 (HRIPT)..... | 58 |
| 3.1.2.75 | STUDY 94 (HRIPT)..... | 59 |
| 3.1.2.76 | STUDY 95 (HRIPT)..... | 59 |
| 3.1.2.77 | STUDY 96 (HRIPT)..... | 60 |
| 3.1.2.78 | STUDY 97 (HRIPT)..... | 60 |
| 3.1.2.79 | STUDY 98-99 (HRIPT, modified Draize procedure) (also cited in REACH registration dossier)..... | 61 |
| 3.1.2.80 | STUDY 100 (HMT) (as cited in REACH registration dossier) | 62 |
| 3.1.2.81 | STUDY 101 (HMT) (also cited in REACH registration dossier) | 62 |
| 3.1.2.82 | STUDY 102 (HMT) | 62 |
| 3.1.2.83 | STUDY 103 (HMT) | 63 |
| 3.1.2.84 | STUDY 104 (HMT) (also cited in REACH registration dossier) | 64 |
| 3.1.2.85 | STUDY 105 (Case study)..... | 64 |
| 3.1.2.86 | STUDY 106 (Case study)..... | 65 |
| 3.1.2.87 | STUDY 107 (Case study)..... | 66 |
| 3.1.2.88 | STUDY 108 (Case study) (also cited in REACH registration dossier)..... | 66 |

4 ENVIRONMENTAL HAZARDS..... 66

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 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 β-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

ANNEX TO ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

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 β-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 β-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 β-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 β-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 β-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,

ANNEX TO ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

and the released cells suspended in saline. Cells were suspended into 96-well culture plates and labelled with 1µM 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 maximization 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 maximization 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 cm² 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 cm² 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 maximization 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.*”

ANNEX TO ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

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 positive) 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 do 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 reactions²¹”.*

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 guidelines¹¹ 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 dermatology 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 individual 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).

ANNEX TO ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

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 individual 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 individual 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 Dermite 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., Gawkrödger, 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 Gawkrödger, 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*

ANNEX TO ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

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.

ANNEX TO ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

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 modification¹¹ of the International Contact Dermatitis Research Group morphological grading system.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 Alupore®. 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 AI-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 from 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 Hospitais da Universidade de Coimbra, Portugal were patch tested with the standard test series recommended by the ICDRG. A total of

ANNEX TO ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

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% (4/63) 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 AI 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 χ^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), geraniol 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-dimethylocta-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.”

ANNEX TO ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

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 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 (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

ANNEX TO ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

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 1995-2007) 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, Millennium 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

ANNEX TO ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

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 Göttingen 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*

ANNEX TO ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

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 Test™ (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 Test™ 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 3rd (or 4th), 5th (or 6th) and 7th days after application. Palpable erythema or a stronger reaction, seen on the 3rd 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.

ANNEX TO ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

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. *Nishinohon 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: *“Photopatch 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/cm²(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/cm²) 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/cm²) 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:

ANNEX TO ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON GERANIOL; (2E)-3,7-DIMETHYLOCTA-2,6-DIEN-1-OL

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/cm²) 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/cm²) 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/cm²) 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 Caucasians) 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 Blendederm®) 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: “*Maximization 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/cm²) 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: “*Maximization 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/cm²) 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: “*Maximization 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/cm²) 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 Alpha 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 Dermatitis 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 dermatitis 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 hypersensitivity 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.