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:

benzyl alcohol

EC Number: **202-859-9**

CAS Number: **100-51-6**

Index Number: **603-057-00-5**

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1 PHYSICAL HAZARDS

Not assessed in this dossier.

2 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Not assessed in this dossier.

3 HEALTH HAZARDS

***Note:** The following summaries are a blend of excerpts from the original publications, complemented with text written by the DS.*

Acute toxicity

3.1 Acute toxicity - oral route

3.1.1 Animal data

3.1.1.1 Study summaries

Study reference:

RIFM (1992a): Acute oral toxicity study in rats with benzyl alcohol. Unpublished report from Proctor and Gamble. Report No. 20505 (RIFM, Woodcliff Lake, NJ, USA)

Study summary and results:

The acute oral LD50 of benzyl alcohol in rats was determined to be 1.57 g/kg (1.4–1.76 g/kg) when Sprague Dawley rats (5/sex/dose) were given single gavage doses of neat benzyl alcohol at 1.00, 1.41, 2.00, and 2.83 g/kg. Mortalities were 0/10, 3/10, 9/10, and 10/10 from low dose to high, respectively. Several died during the day of dosing, but the majority was found dead between 24 and 48 h post-dosing. Adverse clinical signs commonly noted during the study were lethargy, prostration, and ataxia in all treated groups. Animals treated at the highest two doses experienced increased respiration, piloerection, tremors, and half closed eyes. All animals that survived appeared normal by day 3. No macroscopic abnormalities were noted at necropsy in any survivors. Animals dying during the study, however, commonly showed abnormalities associated with the gastrointestinal tract, liver, and lungs.

Study reference:

Jenner P.M., Hagan E.C., Taylor J.N.M., Cook E.L., and Fitzhugh O.G. (1964): Food flavourings and compounds of related structure I. acute oral toxicity. Fd. Cosmet. Toxicol. 2, 327-343

Study summary and results:

In a study of the acute oral toxicity of 107 flavor ingredients, it was reported that the LD50 for benzyl alcohol in 10 Osborne-Mendel rats was 1.23 g/kg (1.13–1.33 g/kg) in fasted rats and 1.58 g/kg (1.41–1.77 g/kg) in unfasted mice. Test article was administered undiluted to rats and at 25% in corn oil to mice. Clinical signs of toxicity in rats included coma and depression within 10–15 min with death times occurring between 1 h and 4 days. Clinical signs of toxicity in mice included depression, with animals dying within 18 h.

Study reference:

Smyth H.F., Jr., Carpenter C.P., and Weil C.S. (1951): Range-finding toxicity data: List IV. AMA Arch Ind Hyg Occup Med 4 (2), 119-122

Study summary and results:

The acute oral LD50 in unfasted rats was reported to be 3.10 g/kg (2.85–3.37 g/kg).

Study reference:

Graham B.E. and Kuizenga M.H. (1945): Toxicity studies on benzyl benzoate and related benzyl compounds. J Pharmacol Exp Ther 84, 358-362

Study summary and results:

The LD50 was 2.08 g/kg when neat benzyl alcohol was administered by gavage to 20 rats (5/dose) at doses of LD50 ±0.5 g/kg from an unpublished preliminary study followed by a 14-day observation period. Clinical signs of toxicity included complete prostration within a half hour following administration and stayed in this condition until death. No necropsy was performed. Groups of three rabbits were also observed to have an LD50 of 1.04 g/kg when administered in the same study. Clinical signs of toxicity and necropsy results all mirrored those found in the rat.

Study reference:

Carter D.V., Charlton P.T., Fenton A.H., Housley J.R., and Lessel B. (1958): The preparation and the antibacterial and antifungal properties of some substituted benzyl alcohols. Journal of Pharmacy and Pharmacology 10 (Supp), 149-157T; discussion 157-159T. DOI: 10.1111/j.2042-7158.1958.tb10394.x

Study summary and results:

The acute oral LD50 of aqueous solution of benzyl alcohol was reported to be 1150 mg/kg in mice.

Study reference:

Macht D.I. (1918): A Pharmacological and therapeutic study of benzyl alcohol as a local anesthetic. Journal of Pharmacology and Experimental Therapeutics 11 (3), 263-279

Study summary and results:

The acute oral LD50 in unfasted rats was reported to be >1400- <3120 mg/kg bw in rat, 1040 mg/kg bw in mice and >1040- <2600 mg/kg bw in guinea pig.

3.2 Acute toxicity - dermal route

3.2.1 Animal data

3.2.1.1 Study summaries

Study reference:

NPIRI (1974). Raw Material Data Handbook 1 (Organic Solvents), 6

Study summary and results:

The acute dermal LD50 in rabbit was reported to be > 2.0 g/ kg.

Study reference:

Opdyke D.L. (1973): Monographs on fragrance raw materials. Food and Cosmetics Toxicology 11 (6), 1011-1013. DOI: 10.1016/0015-6264(73)90228-9

Study summary and results:

The acute dermal LD50 in guinea pigs was reported to be < 5.0 ml/ kg.

Study reference:

Graham B.E. and Kuizenga M.H. (1945): Toxicity studies on benzyl benzoate and related benzyl compounds. J Pharmacol Exp Ther 84, 358-362

Study summary and results:

In a series of studies of the toxicities of benzyl benzoate and related compounds, 20 ml of neat benzyl alcohol was applied dermally to two cats. Both cats died within 22 h of application. They exhibited excessive salivation and twitching of the treated areas of their backs, followed somewhat later by generalized tremor, muscular incoordination, paralysis of the hind limbs, and finally violent convulsions followed by respiratory failure and death. Based on an average 15-lb cat, the LD50 calculates to 2.93 g/kg.

3.3 Acute toxicity - inhalation route

3.3.1 Animal data

3.3.1.1 Study summaries

Study reference:

Clayton (1982). In: Patty's Industrial hygiene and toxicology (Patty F.A., Clayton G.D., Clayton F.E., and Battigelli M.C., eds.), ed. Third Revised Edition, pp. 4636-4641. John Wiley and Sons, New York

Study summary and results:

Exposure of rats to saturated vapours (~200 ppm) resulted in an LC_0 of 2 hours, an LC_{33} of 4 hours and an LC_{100} of 8 hours ((Smyth et al., 1951); personal communication). No fatalities or symptoms were found in rats when exposed 6 hours to a calculated concentration of 61 ppm, nor were symptoms produced by exposures obtained by bubbling air through the liquid heated to 100°C and 150°C (personal communication). The approximate lethal concentration (ALC) 4 or 8 hour exposures was found to be >250 ppm (nominal). Gross and histopathology were negative (unpublished data). Subacute exposure of 216 to 270 ppm to six male rats for 4 hour periods produced no clinical or pathologic signs of toxicity (unpublished data).

Study reference:

Smyth H.F., Jr., Carpenter C.P., and Weil C.S. (1951): Range-finding toxicity data: List IV. AMA Arch Ind Hyg Occup Med 4 (2), 119-122

Study summary and results:

In a report of toxicity screening test results for a number of chemicals, it was reported that in rats, the minimal lethal exposure time to benzyl alcohol saturated vapours was 2 h and that inhalation exposure to 1000 pm (4422 mg/m^3) for 8 hours resulted in 3/6 deaths during the 14 day observation period. No additional details reported.

Study reference:

Carpenter C.P., Smyth H.F., Jr., and Pozzani U.C. (1949): The assay of acute vapor toxicity, and the grading and interpretation of results on 96 chemical compounds. J Ind Hyg Toxicol 31 (6), 343-346

Study summary and results:

In a study of 96 different chemicals, male or female rats of the Sherman strain weighing 100–150 g, 6 per dose, were exposed by inhalation for 4 h and observed for 14 days. Benzyl alcohol was included in the list of chemicals which caused death of 2, 3, and 4 of the 6 animals at 2000 ppm (8845 mg/m^3). No analytical checks were made on the concentration of the prepared vapour. The concentration is based upon empirical calculation. Careful observation of flowmeter reading, Monodrum delivery and vaporizer performance is relied upon to eliminate errors. Experience indicates that the calculated concentrations are slightly higher than would actually be found if it were practical to determine them analytically on the exposure air.

3.4 Skin corrosion/irritation

Not assessed in this dossier.

3.5 Serious eye damage/eye irritation

Not assessed in this dossier.

3.6 Respiratory sensitisation

Not assessed in this dossier.

3.7 Skin sensitisation

3.7.1 Animal data

3.7.1.1 Study summaries for LLNA and Guinea pig data

Study reference:

Scognamiglio J., Jones L., Vitale D., Letizia C.S., and Api A.M. (2012): Fragrance material review on benzyl alcohol. Food and Chemical Toxicology 50 Suppl 2, S140-160. DOI: 10.1016/j.fct.2011.10.013

Detailed study summaries and results:

Various animal studies were described in the review by (Scognamiglio et al., 2012).

Benzyl alcohol was assessed for its skin sensitization potential using the mouse Local Lymph Node Assay. Benzyl alcohol was applied as 2.5%, 5%, 10%, 25%, or 50% w/v preparations in 1:3 ethanol:diethyl phthalate (1:3 EtOH:DEP) vehicle control was 1:3 EtOH:DEP. The study was conducted in CBA/Ca/Ola/Hsd female mice that were 8–12 weeks of age using four mice per group. Benzyl alcohol in 1:3 EtOH:DEP did not have the capacity to cause skin sensitization at any of the doses applied. The EC3 value giving rise to a 3-fold increase in lymphocyte proliferation was estimated to be greater than 50% w/v (greater than 12 500 µg/cm^2). In a positive control study, hexyl cinnamaldehyde was shown to have the capacity to cause skin sensitization when applied as 10 or 25% in acetone:olive oil (4:1), confirming the validity of the protocol used for this study (RIFM, 2005b).

In an investigation of the potentially sensitizing components of Balsam of Peru, benzyl alcohol was tested in a modified Freunds Complete Adjuvant study. Applied dose was 15 mg. Challenge doses were 1% or 3% in acetone. The authors classified benzyl alcohol as a weak to moderate sensitizer (Hausen et al., 1992).

Ishihara et al. (1981) reported that benzyl alcohol when tested for sensitization in guinea pigs was positive in the Open Epicutaneous Test, negative in the Draize test, negative in the maximization test, and positive in the complete adjuvant test (article in Japanese, details not available in English).

In a comparison of the relative predictive values of the Freunds Complete Adjuvant and Open Epicutaneous Tests in guinea pigs, it was reported that 10% benzyl alcohol gave negative results in human testing (HMT or HRIPT) and in the guinea pig Open Epicutaneous Test (Klecak, 1979; Klecak, 1985).

Benzyl alcohol was reported to be positive for sensitization in the guinea pig Open Epicutaneous Test and the Freunds Complete Adjuvant test, but negative in the Draize and Maximization tests. The minimizing sensitizing and elicitation concentrations were reported to be 30% and 10%, respectively (Klecak et al., 1977).

Using 10% for induction and challenge, benzyl alcohol was found to be sensitizing in a guinea pig maximization test but negative (n = 25) in a human maximization test. Using 30% for induction and 1% for challenge, benzyl alcohol was negative for sensitization in a guinea pig closed epicutaneous test (Ishihara et al., 1986).

Benzyl alcohol was reported to be positive for sensitization in the guinea pig Open Epicutaneous Test and the Freunds Complete Adjuvant test, but negative in the Draize and Maximization tests. The minimizing sensitizing and elicitation concentrations were reported to be 30% and 10%, respectively (Klecak et al., 1977).

In an investigation of the potentially allergenic components of propolis and Balsam of Peru, it was reported that 10% benzyl alcohol is a moderate sensitizer in the guinea pig Freunds Complete Adjuvant test (Hausen et al., 1992).

Benzyl alcohol was reported to be non-sensitizing at an injection challenge concentration of 0.25% and an application challenge concentration of 10% in a guinea pig modified Draize procedure (Sharp, 1978).

In a delayed contact hypersensitivity test (modified cumulative contact enhancement test), benzyl alcohol was considered a weak allergen in the five female guinea pigs tested. Induction consisted of a 30% intradermal injection in FCA with a 24 h patch of 30% concentration in ethanol as the topical injection at intervals of 4–6 days. Guinea pigs were challenged 3 weeks later with non-occlusive patches of 10% benzyl alcohol in ethanol (Kashima et al., 1993).

3.7.2 Human data

3.7.2.1 Study summaries for human experimental data

Study reference:

Scognamiglio J., Jones L., Vitale D., Letizia C.S., and Api A.M. (2012): Fragrance material review on benzyl alcohol. Food and Chemical Toxicology 50 Suppl 2, S140-160. DOI: 10.1016/j.fct.2011.10.013

Detailed study summaries and results:

Various human studies were described in the review by Scognamiglio et al. (2012).

3.7.2.1.1 HRIPT studies

Repeated Insult Patch Tests (HRIPT) were conducted to determine if benzyl alcohol would induce dermal sensitization in human volunteers. During the induction phase, 0.3 ml of benzyl alcohol was applied onto an occlusive patch and applied to the upper arm or back of each volunteer for 24 h. Induction applications were made to the same site on Monday, Wednesday and Friday for a total of nine applications during a 3- week period. Following a 10- to 14-day rest period, a challenge patch was applied to a site previously unexposed.

Patches were applied as in the induction phase and kept in place for 24 h before removal. Reactions to the challenge were scored at 24, 48, 72, and/or 96 h after application. The following results were obtained.

A Human Repeat Insult Patch Test (HRIPT) with 56 subjects, five subjects exhibited edematous reactions to 20% benzyl alcohol in 3:1 DEP:EtOH when applied at 0.3 ml occlusively with a 25 mm Hill Top chamber (23 622 µg/cm^2). Patching was discontinued for the remainder of the induction phase of the study for four of the subjects who reacted again when patched on a new test site but was continued for one subject who exhibited only transient +/- reaction when patched on a new site. At challenge with the same test material, two subjects exhibited level 2+ edema reactions. Three subjects exhibited level 1+ edema reactions. Other subjects exhibited transient (±/1) reactions. Upon rechallenge, one subject exhibited level 2+ edema and one subject exhibited level 1+ edema at both occlusive and semi-occlusive test sites. One subject exhibited low level (+/-) reaction at the occlusive site and no reaction at the semi-occlusive site. No reactions were exhibited in these subjects when test material was applied ‘‘under use conditions’’ to the antecubital fossa of the left arm three times per day for five days, the antecubital fossa of the right arm serving as vehicle control. No reactions were exhibited by the three remaining subjects who were re-challenged (RIFM, 2002a).

During the induction phase of a HRIPT with 46 subjects, five subjects exhibited edematous reactions to 15% benzyl alcohol in 3:1 DEP:EtOH when applied at 0.3 ml occlusively with a 25 mm Hill Top chamber (17 717 µg/cm^2). Patching was discontinued for two of the subjects who reacted again when patched on a new test site but was continued for one subject who exhibited only transient +/- reaction when patched on a new site. At challenge with the same test material, level 2+ edematous reactions were induced in four subjects, level 1+ edematous reaction in one subject, and transient (+/-) reaction in one subject. The level 2+ and 1+ reactions in the five subjects was considered indicative of dermal sensitization (RIFM, 2003a).

During the induction phase of a Human Repeat Insult Patch Test (HRIPT) with 110 subjects using 7.5% benzyl alcohol in 3:1 DEP:EtOH applied at 0.3 ml occlusively with a 25 mm Hill Top chamber (8 858 µg/cm^2), one subject experienced severe irritation that required moving the test article application site. This subject also experienced grade-2 reaction at the 96 h reading after challenge. Two other subjects also experienced reactions at challenge. These three subjects were re-challenged with occlusive, semi-occlusive, and antecubital fossa sites. At re-challenge, one of them exhibited a reaction at all three sites indicative of sensitization, but the other two did not, although minimal erythema was observed at the occluded site (RIFM, 2004b).

During the induction phase of a HRIPT with 101 subjects, two subjects exhibited edematous reactions to 5% benzyl alcohol in 3:1 DEP:EtOH when applied at 0.3 ml occlusively with a 25 mm Hill Top chamber (5 906 µg/cm^2). Patching was discontinued for both of the subjects after they reacted again when patched on a new test site. Patching was continued for one subject who exhibited only a low level (+/-) reaction. At challenge, one of these subjects exhibited a 3+ edematous reaction and one exhibited a 1+ edematous reaction, both indicative of pre-sensitization. No other reactions were observed at challenge (RIFM, 2005a). During the induction phase of a HRIPT with 107 subjects, no sensitization reactions were observed to 3% benzyl alcohol in 3:1 DEP:EtOH when applied at 0.3 ml occlusively with a 25 mm Hill Top chamber (3 543 µg/cm^2) (RIFM, 2004c).

3.7.2.1.2 HMT

Human maximization tests (HMT) according to (Magnusson and Kligman, 1969) and (Kligman and Epstein, 1975) were carried out with benzyl alcohol in petrolatum on various panels of volunteers. Application was

under occlusion to the same site on the forearms or backs of all subjects for five alternate-day 48-h periods. Patch sites were pre-treated for 24 h with 5% aqueous sodium lauryl sulfate (SLS) under occlusion. Following a 10– 14 day rest period, challenge patches were applied under occlusion to fresh sites for 48 h. Challenge applications were preceded by SLS treatment. Reactions were read at patch removal and again at 48 and 72 h. The following results were obtained. Ten percentage of benzyl alcohol in petrolatum on the volar forearm of 25 subjects for five alternate-day 48 h periods (6 900 µg/cm^2). No subject exhibited any reaction during challenge (RIFM, 1970a). There was no evidence of irritation or contact sensitization to 10% benzyl alcohol in petrolatum (6 900 µg/cm^2) (RIFM, 1979a).

3.7.2.2 Study summaries for clinical data (human patch test studies)

Human patch test studies as described by various authors and summarized in reviews.

Study reference:

Goossens A. (2016): Cosmetic contact allergens. Cosmetics 3 (1), 5. DOI: 10.3390/cosmetics3010005

Detailed study summary and results:

The data were retrieved from, and evaluated with, a patient database developed in-house in our Contact Allergy Unit of the University Hospitals of Leuven. This database contains patient information and results of all contact allergy investigations for patients with suspicion of allergic contact dermatitis, or with other diseases, such as irritant dermatitis or other forms of eczema for which an allergenic cause needed to be excluded.

During the 25-year period from January 1990 until December 2014, 14 911 patients presenting with an eczematous dermatitis were patch-tested with a modified European baseline series and those with a presumed cosmetic cause were also tested with a cosmetic series, or in case of a presumed photo-induced reaction, with a photo-patch test series. Most, if not all, subjects were also tested (or photo-patch tested) with the products to which they had been exposed and, whenever possible, also their ingredients. Formerly, the patch-test chambers applied on the upper back of the patients were Vander Bend® (Brielle, The Netherlands) fixed on Micropore® (3M Health Care, Borken, Germany), later on IQ Ultra® patch test chambers (Chemotechnique Diagnostics, Vellinge, Sweden), covered with Mefix® (Mölnlycke, Göteborg, Sweden). Following occlusion for two days, readings were performed at Day (D) 2 and D4, sometimes also at D7, according to the recently published guidelines from the European Society of Contact Dermatitis (ESCD) [1]. A +, ++, or +++ reaction at either reading was recorded as a positive patch test reaction; an irritant, doubtful, or negative response was recorded as a negative result. Some patients also received prick tests with the cosmetic products and the ingredients, in order to diagnose immediate contact urticarial reactions. Concerning the cosmetic allergens identified, we will consider here the latest period, i.e., between January 2010 and November 2015. For each test substance, the proportion of positive patch-test results over the total number of patch tests and the percentages (%) were calculated.

Results of patch testing for benzyl alcohol showed the following frequencies of sensitisation: 1/147 (0.68 % of positive reactions).

Study reference:

Schnuch A., Uter W., Lessmann H., and Geier J. (2015): Risk of sensitization to fragrances estimated on the basis of patch test data and exposure, according to volume used and a sample of 5451 cosmetic products. Flavour and Fragrance Journal 30 (3), 208-217. DOI: 10.1002/ffj.3241

Detailed study summary and results:

Total use volume: IFRA kindly provided us with the quantity (in tonnes) of the 26 single fragrance materials relevant here, sold for use in cosmetics Europe-wide in 2008. The total amount (the sum of all volumes of single fragrances) was set at 100%, and the share of single fragrances (in %) (i.e. the volume of a single fragrance related to the total of volumes) was calculated.

Fragrances contained in cosmetics: The labelling of cosmetic products (n = 5451) purchased at random between 2007 and 2009 was documented by the CVUA (Chemisches und Veterinär- Untersuchungsamt Karlsruhe/Germany), aggregated into 24 product classes. The total products (5451) and leave-on products (n = 3541) were considered for analysis. 15500 and 9568 occurrences of fragrances were documented, respectively. Thus a product contained 2.8 fragrance compounds on average. As the frequency of occurrence of a fragrance is regarded as indicator of actual exposure, it is used as the basis for further analysis.

The total frequency of use of fragrances (n = 15 500 and n = 9568, respectively) was set at 100% and the relative frequency of use of single fragrances was calculated yielding the thus standardized share of products (%) containing the respective fragrance. Data on labelled cosmetics (n=516) put together from different smaller studies were used for similar calculations of the SEQ. There were 1800 occurrences of single fragrances, 3.5 times on the products on average. Exposure to fragrances through different product categories (total: n = 300) and more specifically to deodorants (n = 88) was also assessed by documenting labelling. There were 5.9 and 6.4 labelled fragrances on average. In all these labelling statistics, a distinction between high and low volume products was not possible. With a few high volume products the labelling based estimate of exposure would underestimate actual exposure.

Frequency of sensitization: Data on sensitization frequency generated by the IVDK network between 2007 and 2009 and specifically 2008 were considered for specific analyses (For a more detailed description of the methods used by the IVDK see Geier et al. To characterize the study population, the factors of the MOAHLFA-Index are given where M stands for the proportion of men, O for the proportion of occupational dermatitis, A for the proportion of patients with atopic dermatitis, H with hand dermatitis (H), L with leg dermatitis, F with face dermatitis (F) and A being at least 40 years old.

Results of patch testing FMI and FMII in the standard series and the results of break down testing in mix positives for the period 1 September 2007 to 31 December 31 2009 were analysed. During this period, a specific fragrance series (Almirall/ Hermal, 'further fragrances') containing those of the '26 EU' fragrances not covered by FM I and FM II were applied in 1870 patients (in 2008: n=823). These were defined as the study population further considered. The proportion of reactions to single constituents in breakdown testing in mix positives from testing the standard series was extrapolated to the study population (n = 1870) yielding the frequency of sensitization to single constituents.

The relative frequency of sensitization was calculated as the share of sensitization to a single allergen (%) relative to the total of sensitization (=100%) to fragrances.

Sensitization exposure quotient (SEQ): As an estimate of sensitization risk associated with exposure to the respective fragrance the SEQ is calculated as the quotient of the relative frequency of sensitization divided by the relative frequency of use.

0.7% of the patients sensitised to the fragrances mix tested positive for benzyl alcohol. This corresponded with a frequency of 0.16% when extrapolated to all 1870 patients.

Study reference:

Mann J., McFadden J.P., White J.M., White I.R., and Banerjee P. (2014): Baseline series fragrance markers fail to predict contact allergy. Contact Dermatitis 70 (5), 276-281. DOI: 10.1111/cod.12171

Detailed study summary and results:

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. The concentrations and constituents of the fragrance markers are shown, and those of the allergens used in the fragrance series are shown as well. 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.

Results of patch testing for 10% benzyl alcohol showed the following frequencies of sensitisation: 4/ 1951 (0.21 % of positive reactions).

Study reference:

Chow E.T., Avolio A.M., Lee A., and Nixon R. (2013): Frequency of positive patch test reactions to preservatives: The Australian experience. Australasian Journal of Dermatology 54 (1), 31-35. DOI: 10.1111/j.1440-0960.2012.00958.x

Detailed study summary and results:

A retrospective review of patch test data from 6845 patients across four clinics situated in three centres was performed: the Contact and Occupational Dermatitis Clinic, Skin and Cancer Foundation (SCF-NSW) comprising clinics at Westmead and Darlinghurst, Sydney, NSW; the Contact Dermatitis Clinic, (SCF-VIC) and the Occupational Dermatology Clinic (OCC) all located at the Skin and Cancer Foundation, Melbourne Victoria. Data were collected for a minimum of 5 years from each centre (SCF-NSW: 2002–2006; SCF-VIC: 2000–2006; OCC: 1993–2006). This study was classified as clinical audit and as such, ethics approval was not required. These are tertiary referral clinics where patients are referred for patch testing, predominantly by dermatologists. Patch testing was performed with allergens purchased from Chemotechnique Diagnostics (Malmo, Sweden) or Trolab (Hermal, Germany); applied with Finn Chambers on Scanpor tape (Epitest, Oy,

Finland) to the upper back and evaluated on day 2 and day 4 according to the International Contact Dermatitis Research Group scoring system.

Results of patch testing for 1% benzyl alcohol showed the following frequencies of sensitisation: 18/ 4'552 (0.4 % of positive reactions). The authors list benzyl alcohol as one of the least frequent sensitizers in Australia.

Study reference:

Schnuch A., Lessmann H., Geier J., and Uter W. (2011a): Contact allergy to preservatives. Analysis of IVDK data 1996–2009. British Journal Of Dermatology 164 (6), 1316-1325. DOI: 10.1111/j.1365-2133.2011.10253.x

Detailed study summary and results:

The IVDK (http://www.ivdk.gwdg.de/), a contact allergy surveillance network in Germany, Switzerland and Austria, has been described elsewhere. Briefly, results of all patients patch tested in the participating departments are electronically recorded, along with important demographic and clinical data. The diagnostic procedure follows international guidelines, further refined by the German Contact Dermatitis Research Group, of which all IVDK participants are members. All data are transmitted to the data centre in Göttingen in an anonymous format twice yearly, where they are checked and, if satisfying internal quality control criteria, are analysed according to international guidelines.

For the present analysis, data of all patients patch tested with the preservatives listed between January 1996 and December 2009 were included. Patch test preparations (except PHMB) were provided by Almirall- Hermal /Trolab (Reinbek, Germany). Weak (+) to strong (+++) positive patch test reactions on the third day after application of the test or, if this was not read, after the fourth day, were aggregated as 'positive' outcome and contrasted with non-positive (non-allergic) reactions, comprising negative, doubtful and irritant reactions. Frequencies of sensitization (as percentage of patients tested) were calculated both as crude proportions and as proportions standardized for sex and age, the latter accompanied by the 95% confidence interval (CI). Patch test results were generally analysed regarding (i) the total period, and (ii) stratified for sex.

Results of patch testing for 1% benzyl alcohol showed the following frequencies of sensitisation overall: 258/ 79'770 (0.28 % of positive reactions standardised for sex and age). Women showed a higher incidence for positive reactions than men, namely 194/ 50'251 women (0.34% of positive reactions standardised for age) compared to 64/ 29'519 men (0.18% of positive reactions standardised for age). According to the authors benzyl alcohol is associated with leg dermatitis.

Study reference:

Schnuch A., Mildau G., Kratz E.M., and Uter W. (2011b): Risk of sensitization to preservatives estimated on the basis of patch test data and exposure, according to a sample of 3541 leave-on products. Contact Dermatitis 65 (3), 167-174. DOI: 10.1111/j.1600-0536.2011.01939.x

Detailed study summary and results:

Data for patients tested with the standard series and the preservative series between 2006 and 2009 in the departments of the IVDK were analysed with a focus on the frequency of sensitization to preservatives contained in these series. Patients with suspected occupational dermatitis or leg dermatitis were excluded from

analysis, as in both cases important non-cosmetic risk factors would interfere. Thus, the population considered can be regarded as exposed to cosmetics in sensu strictu. To characterize the study population, the remaining factors (M, A, H, F, A) of the MOAHLFA index were analysed [MOAHLFA: the proportion of men (M), and of patients with occupational dermatitis (O), with atopic dermatitis (A), with hand dermatitis (H), with leg dermatitis (L),with face dermatitis (F), and being at least 40 years old (A)], comparing those with at least one positive reaction to a preservative with those showing no reactions to preservatives. The frequency of sensitization to MI is given (i) as is and (ii) corrected for the proportion of MI-positives not reacting concomitantly toMCI/MI (33%). Frequencies of sensitization to single preservatives were added up to give the total frequency of sensitization to preservatives.

Results of patch testing for benzyl alcohol showed the following frequencies of sensitisation: 17 740 patients (0.17 % of positive reactions, SEQ 0.3 %).

Study reference:

Heisterberg M.V., Menne T., and 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 (5), 266-275. DOI: 10.1111/j.1600-0536.2011.01962.x

Detailed study summary and results:

Data were retrieved from the database at the Dermato- Allergology Department of Copenhagen University Hospital Gentofte. This contains structured information from the patient files, including patch test results, patient demographics, exposures, and clinical relevance of the patch test. In January 2008, we began patch testing with the 26 fragrance ingredients on the EU Cosmetics Directive's list of mandatory labelling. From January 2009 to July 2009 (6 months), only subjects suspected of having fragrance allergy were tested with the 26 individual ingredients; otherwise, all eczema patients suspected of having contact allergy were tested consecutively. We included all subjects (n = 1508) patch tested with at least one of the 26 fragrance ingredients in the period from January 2008 to July 2010. The majority were women [1056 women (70%) versus 452 men (30%)]. The mean age was 46 years (standard deviation, ±16.9). The patch test material was obtained from Hermal (Reinbek, Germany). The subjects were also patch tested with the European baseline series, which, in that period, included four fragrance screening markers: fragrance mix I (FM I), fragrance mix II (FM II), M. pereirae (balsam of Peru), and hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC). The clinical relevance of a positive patch test reaction is evaluated routinely, and registered according to standardized guidelines, which are based on: (i) medical history; (ii) results of patch test and/or use test; (iii) ingredient labelling; or (iv) chemical analysis. Relevant exposure sources causing allergic contact dermatitis are registered in the database. The exposure sources are categorized into specific cosmetic product groups. One subject could have more than one exposure listed as the cause of allergic contact dermatitis. The patch tests were performed according to international guidelines, 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. 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.

Results of patch testing for 1% benzyl alcohol showed the following frequencies of sensitisation: 2/ 1508 (0.1 % of positive reactions). 3 patients had doubtful reactions and 1 had an irritant reaction.

Study reference:

Uter W., Geier J., Frosch P., and Schnuch A. (2010): Contact allergy to fragrances: current patch test results (2005-2008) from the Information Network of Departments of Dermatology. Contact Dermatitis 63 (5), 254-261. DOI: 10.1111/j.1600-0536.2010.01759.x

Detailed study summary and results:

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 that have been further refined by the German Contact Dermatitis Research Group, of which all IVDK participants are members. All data are transmitted to the data centre in Göttingen in an anonymous format twice yearly, where they are checked and, if satisfying internal quality control criteria, analysed according to international guidelines using sas software (version 9.2; SAS Institute, Cary, NC, USA). For the present analysis, data of all patients patch tested between January 2005 and December 2008 were included (n = 40 709 in the course of 41 656 consultations). In cases of multiple consultations of one patient, the strongest of the possible multiple test results was considered for analysis. Allergens were provided by Almirall-Hermal/Trolab, Reinbek, Germany. As the composition of these series changed, and for other reasons, such as the temporary unavailability of allergens, the number of patients actually tested with the allergens varies. Weak (+) to strong (+++) positive patch test reactions on the third day after application of the test or, if this was not read, after the fourth day were aggregated as 'positive' outcomes and contrasted with non-positive (non-allergic) reactions, comprising negative, doubtful and irritant reactions. For information on INCI nomenclature and CAS numbers, the 'CosIng' database (http://ec.europa.eu/enterprise/cosmetics/cosing/, last accessed December 2009) and the list of fragrances that have to be labelled in the EU were utilized.

Results of patch testing for 1% benzyl alcohol showed the following frequencies of sensitisation overall: 51/ 23'257 (0.22 % of positive reactions). In the 1999 Scientific Committee on Cosmetic Products and Non-Food Products opinion, benzyl alcohol is classified as an allergen frequently causing allergic reactions, having been found to cause allergic reactions in 1.2–15% of patients with eczema resulting from cosmetic products. The current International Fragrance Association (IFRA) standard recommends a limit ranging from 0.2% in deodorants, to 1.4% in hand creams, and 5% in rinse-off hair conditioners (http://www.ifraorg.org, last accessed December 2009). The German 'Rote Liste' (http://www.rote-liste.de, last accessed November 2009) lists 205 drug specialties (products) containing benzyl alcohol as an excipient, pointing to topical medications as a possible source of exposure, in addition to (perfumed) cosmetics. In some cases, uses beyond perfuming or masking do occur, as in the case of benzyl alcohol, which is widely used as a preservative.

Study reference:

Ada S. and Seckin D. (2010): Patch testing in allergic contact dermatitis: is it useful to perform the cosmetic series in addition to the European standard series? J Eur Acad Dermatol Venereol 24 (10), 1192-1196. DOI: 10.1111/j.1468-3083.2010.03619.x

Detailed study summary and results:

This prospective study included 93 consecutive patients suspected of having ACD (67 women and 26 men) who applied to the Dermatology Department, Baskent University Faculty of Medicine, Ankara, Turkey between April 2005 and April 2006. Local ethical committee approval was obtained. The age, sex, localization of the contact dermatitis and the cosmetic-related products used if any were recorded. The patients with a suspicion of ACD caused by cosmetics were determined by the disease history, and clinical examination based on a standard textbook. Once the acute phase of the dermatitis was under control with appropriate treatment and the test site was free of any lesion, all patients were patch tested with European standard series (25 allergens) and simultaneously with cosmetic series (Chemotechnique Diagnostics AB, Malmö, Sweden) including 45 allergens which were selected excluding those already present in European standard series. Exclusion criteria included the use of systemic corticosteroids or any other immunosuppressive therapy, UV exposure in the test area within the last 1 month and pregnancy. Test allergens were applied with IQ_Chambers (Chemotechnique Diagnostics AB) to the upper back of the patients. The strips were removed after 48 h and the readings were recorded after 15–30 min. The sites were re-examined after 96 h. The criteria of International Contact Dermatitis Research Group were used for assessment of the patch test results.

Results of patch testing for 10% benzyl alcohol showed the following frequencies of sensitisation: 1/ 93 (1.1 % of positive reactions). The result was categorised as clinically relevant by the authors.

Study reference:

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

Detailed study summary and results:

This is a retrospective and descriptive study carried out at the Cutaneous Allergy Unit of a tertiary referral hospital, between October 2004 and June 2008. All patients tested with the baseline Spanish Group series were reviewed, as well as patients tested with the fragrance series either because they were positive to the baseline series or because there was clinical suspicion. The clinical data recorded on each patient were age, sex, profession, site of lesions, series tested, positive allergens and number of positive reactions, their relevance, origin of the sensitization, and patient's diagnosis. The allergens used both in the standard series and in the fragrance series were supplied by Chemotechnique Diagnostics®. 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.

Results of patch testing for 1% benzyl alcohol showed the following frequencies of sensitisation: 2/ 86 (2.3 % of positive reactions).

Study reference:

Schnuch A., Uter W., Geier J., Lessmann H., and Frosch P.J. (2007): Sensitization to 26 fragrances to be labelled according to current European regulation: Results of the IVDK and review of the literature. Contact Dermatitis 57 (1), 1-10. DOI: 10.1111/j.1600-0536.2007.01088.x

Detailed study summary and results:

The multicentre project IVDK (Information Network of Departments of Dermatology) is an instrument of epidemiological surveillance of CA and has been described in detail elsewhere. Patch tests are performed in accordance with the recommendations of the International Contact Dermatitis Research Group and the German Contact Dermatitis Research Group (DKG). 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, further refined by the German Contact Dermatitis Group: 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 Goettingen in an anonymized format every 6 months.

During 4 periods of 6 months each, from 1 January 2003 to 31 December 2004, 25 fragrances were successively patch tested additionally to the standard series, i.e. in unselected patients, by departments of the IVDK. In the first period 8, in the second 6, in the third 3, and in the last period 8 compounds were added to the standard series, the number of patients tested with each preparation ranging from 1658 (tree moss) to 4238 (farnesol; tested during 2 periods). HMPCC was tested in the standard series in 21 325 patients throughout the study period.

For the description of the demographic characteristics of patients tested the MOAHLFA index is used. MOAHLFA is the acronym for male, occupational dermatitis, atopic dermatitis, hand dermatitis, leg dermatitis, face dermatitis, and age>40.

Frequencies of sensitization (as % of patients tested) were calculated both as crude proportions and proportions standardized for sex and age. Subgroups of patients defined by sensitization to an index allergen were analysed for concomitant reactions (crude proportions). The reaction index (RI) (16), relating the number of allergic reactions to the number of doubtful or irritant reactions, ranging from RI = -1 (all reactions nonallergic) to RI= +1 (all reactions being allergic), and the positivity ratio (PR), as the proportion (%) of + reactions out of the total number of allergic reactions, were calculated as parameters to assess the patch test preparation. A low RI (e.g. -0.8) together with a high PR (e.g. 100%) is indicative of a 'problematic' patch test preparation, where a number of the '+' reactions may be suspected to be falsely positive. For data management and analysis, the statistical software package SAS (version 9.1, SAS Institute, Cary, NC, USA) was used.

Results of patch testing for benzyl alcohol showed the following frequencies of sensitisation: 0.3 % of positive reactions in 2166 patients associated with leg dermatitis.

Study reference:

Hasan T., Rantanen T., Alanko K., Harvima R.J., Jolanki R., Kalimo K., Lahti A., Lammintausta K., Lauerma A.I., Laukkanen A., Luukkaala T., Riekki R., Turjanmaa K., Varjonen E., and Vuorela A.-M. (2005): Patch test reactions to cosmetic allergens in 1995-1997 and 2000-2002 in Finland - a multicentre study. Contact Dermatitis 53, 40-45

Detailed study summary and results:

This retrospective survey is based on patch test results of the 7 Finnish dermatological clinics representing the Finnish Contact Dermatitis Group: all the 5 university hospitals, 1 central hospital and the Finnish Institute of Occupational Health. We compared the patch test results of extended standard series and hairdressing series

in 1995–96 and cosmetic series in 1995–97 with the corresponding ones in 2000–02. Only allergens that were tested during both time periods were included in the analyses. Patch testing was performed according to the guidelines of the International Contact Dermatitis Research Group. Occlusion time was 2 days, and readings were done when the patches were removed (Finn Chambers on Scanpor, Epitest Ltd Oy, Tuusula, Finland; diameter 10 mm) and at days 4 or 5 and, when necessary, at day 7. Patch test substances were purchased from Chemotechnique Diagnostics AB (Malmö, Sweden), Hermal (Reinbeck/Hamburg, Germany) or Epikon Oy (Helsinki, Finland). The concentrations and the vehicles of the test substances underwent minor changes during the years but mostly followed the recommendations of the European Environmental and Contact Dermatitis Research Group. The total number and percentages of allergic patch test reactions (scored as +, ++ or +++) were calculated and compared between the 2 time periods. For this comparison, Pearson's Chi-square or Fisher's Exact tests were used. To avoid multiple comparison problems, Bonferroni correction was performed. Thus, a significance level of $P < 0.001$ was considered statistically significant, and P values between Bonferroni corrected significance level (i.e. 0.001) and 0.05 were considered to express a tendency of a change. The analyses were performed with SPSS 11.5 for Windows (SPSS Inc., Chicago, IL, USA).

Results of patch testing for 1% benzyl alcohol showed the following frequencies of sensitisation: 0.1 % of positive reactions in 4922 patients in the years 1995-1996 and no positive reactions in tested patients from 2000-2002.

Study reference:

Jappe U., Schnuch A., and Uter W. (2003): Frequency of sensitization to antimicrobials in patients with atopic eczema compared with nonatopic individuals: analysis of multicentre surveillance data, 1995-1999. Br J Dermatol 149 (1), 87-93. DOI: 10.1046/j.1365-2133.2003.05290.x

Detailed study summary and results:

Data of all patients patch tested in the Departments of Dermatology participating in the IVDK between 1995 and 1999 were analysed. The frequency of sensitization to selected antimicrobials was compared between patients with current or previous atopic eczema (those who were suffering only from allergic rhinitis and⁄or asthma were not included according to guidelines of the IVDK) and patients without past or current atopic eczema. Leg ulcer or stasis dermatitis, which is age-related, predisposes patients to contact allergy in general, and to allergy to antibiotics and antiseptics in particular. Because atopy, as defined here, is also age-related, albeit inversely, confounding effects-despite age standardization and adjustment, respectively, see below-were anticipated. Thus, patients with existing leg ulcer or stasis dermatitis were excluded from further analyses. Patch tests were performed according to the international guidelines of the ICDRG further extended by the German Contact Dermatitis Research Group (Deutsche Kontaktallergie-Gruppe, DKG). Patch test substances were obtained from Hermal (Reinbek, Germany). Results presented are based on readings 72 h (day 3) after application of patch test material. Allergens included here comprise some from the standard series, which is usually applied to every patient patch tested. However, the majority of agents are contained in supplementary test trays, which are tested in a more aimed way, i.e. if previous exposure to one of the allergens is suspected. The test series are regularly updated by the DKG to account for changes in the general exposure profile. All test substances except formaldehyde and chlorhexidine digluconate, which were diluted in water, were applied in petrolatum. Patch test reactions between + and +++ at day 3 were considered to be positive. The proportion of patients with positive reactions out of all patients tested with the respective allergen were calculated in a stratified descriptive analysis for the subgroup of atopics and nonatopics, respectively. This analysis was

standardized for age (50% age 40 and above) and sex (65% women) to account for the potentially confounding effect of these factors.

Results of patch testing for 1% benzyl alcohol showed the following frequencies of sensitisation: 5 183 atopic patients (0.28 % of positive reactions) and 14 722 nonatopic patients (0.3 % of positive reactions). In their multicentre study, which did not differentiate between atopics and nonatopics, Schnuch and coworkers showed 0.4% positive reactions towards benzyl alcohol and benzoate. These proportions are similar to the overall proportions we found in the present analysis.

Study reference:

Trattner A., Farchi Y., and David M. (2002): Cosmetics patch tests: first report from Israel. Contact Dermatitis 47 (3), 180-181. DOI: DOI 10.1034/j.1600-0536.2002.470308_16.x

Detailed study summary and results:

Our study sample consisted of 244 patients (204 female, 40 male) aged 12–80 years (mean 52.4 years) with clinical suspicion of cosmetic contact dermatitis. All were patch tested at the Contact Dermatitis Clinic of Rabin Medical Center in Israel between January 1997 and December 2000. The tests were done on the upper back with the European standard series and a cosmetics series (Chemotechnique Diagnostics, AB, Malmö, Sweden) using Finn Chambers on Scanpor tape (Epitest, Tuusula, Finland). The patches were removed after 2days, and readings made on day 2 (D2) and D3 as recommended by the ICDRG.

Results of patch testing for benzyl alcohol showed the following frequencies of sensitisation: 5/244 patients (2.0 % of positive reactions).

Study reference:

Schnuch A., Geier J., Uter W., and Frosch P.J. (1998): Patch testing with preservatives, antimicrobials and industrial biocides. Results from a multicentre study. Br J Dermatol 138 (3), 467-476. DOI: 10.1046/j.1365-2133.1998.02126.x

Detailed study summary and results:

Data (patch test results and important items of patients' history) are continuously recorded in the 24 allergy departments participating in the IVDK. Records contain patients' history (e.g. occupational background, suspected allergen exposure), personal data (age, sex, geographical origin), clinical data (present skin disease(s), present or past atopic diseases) and patch test results together with a judgement on their relevance. Patch tests were performed according to recommendations of the International Contact Dermatitis Research Group and the German Contact Dermatitis Group. Finn Chambers on Scan-por were used in 19 departments, and other systems (Leukotest, Hal, Curatest, Haye, Intradex Service BV, Alphenaanden Riyn, The Netherlands) were used in five departments. The test substances were delivered by Hermal/Reinbek (Germany). Nine of 24 centres applied patch tests for 24 h, the remainder (15 of 24) for 48 h. Readings were done until at least 72 h after application of the test chambers. For this study, only readings at 72 h were considered. Preservatives and industrial biocides were included in three series: a standard series (SS), a preservative series (PS) and an industrial biocide tray (IB). Statistical analysis was performed using the SASTM system (SAS Institute, Cary, NC,U.S.A.) on the IBM host computer of the Department of Medical Informatics of the University of Göttingen.

Results of patch testing for 1 % benzyl alcohol showed the following frequencies of sensitisation: 46/11 373 patients (0.4 % of positive reactions).

Study reference:

Broeckx W., Blondeel A., Dooms-Goossens A., and Achten G. (1987): Cosmetic intolerance. Contact Dermatitis 16 (4), 189-194. DOI: DOI 10.1111/j.1600-0536.1987.tb01422.x

Detailed study summary and results:

A study of cosmetic inolerance has been undertaken in 5202 patients (3330 (64.0%) women and 1872 (36.0%) men) being tested for contact dermatitis using computer analysis of extensive medical histories and epicutaneous tests, following the program developed at the Catholic University of Leuven by Dooms et al.. Almost all the patients have been tested with a standard battery, i.e., the Belgian Tri-Contact Patch-test series. In about 3/4 of the cases, this has been completed by testing the patients' own products. Other patch test series were less frequently used such as the Belgian Tri-Contact Pharmaceutical and Cosmetic Tests series, fragrance materials and hair preparations.

Results of patch testing for benzyl alcohol showed the following frequencies of sensitisation: 48/5 202 patients (0.9 % of positive reactions).

Study reference:

Eiermann H.J., Larsen W., Maibach H.I., and Taylor J.S. (1982): Prospective study of cosmetic reactions: 1977-1980. North American Contact Dermatitis Group. J Am Acad Dermatol 6 (5), 909-917. DOI: 10.1016/S0190-9622(82)70080-5

Detailed study summary and results:

The study extended over the 40 months from May 15, 1977, to Sept. 15, 1980, and involved eleven dermatologists (nine during any reporting period) with a special interest in contact dermatitis. The patients were those of individual or group private practices or of university dermatology clinics. Some patients had been referred to a participating dermatologist specifically for patch tests; in one city (Richmond, VA), one third of the patients were from an emergency department. The participating dermatologists evaluated the patients personally. A minimum evaluation consisted of a determination of the medical history and a cutaneous examination. One or more of the following substances were used for patch tests in most patients: (1) the standard screening, perfume, or vehicle-preservative series of the North American Contact Dermatitis Group (NACDG), (2) most of the cosmetic products used by the patient, and (3) when possible, several or all of a product's individual ingredients. Patch tests were applied to the upper back for 48 hours according to methods outlined by the NACDG and the International Contact Dermatitis Group. Readings were made at 48 and/or 72 hours. In most centers, delayed readings at 96 or 120 hours were made. The patch was either the 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 state" ("angry back").

Results of patch testing for benzyl alcohol showed the following frequencies of sensitisation: 2/487 patients (0.4 % of positive reactions).

Study reference:

Mitchell J.C. (1977): Multiple concomitant positive patch test reactions. Contact Dermatitis 3 (6), 315-320. DOI: 10.1111/j.1600-0536.1977.tb03695.x

Detailed study summary and results:

Patients sent by dermatologists in the community were tested at a patch test unit at Shaughnessy Hospital, Vancouver, to chemical compounds recommended by the North American Contact Dermatitis Research Group. Reactions on the upper back were read at Day 2 (D2) and Day 7 (D7). It was found to be difficult to recall patients for retesting at a later date and therefore the following method of testing was used. The patches were removed at D2 and reactions were graded at D2 and D7 according to the method of the International Contact Dermatitis Research Group (Wilkinson et al. 1970). ± reactions were disregarded. In 23 cases where one or more + + reactions and one or more + reactions were observed at D2, the chemical compound(s) which had produced + reaction(s) at D2 were re-applied at D7 and read at D9. In 12 cases where two or more + reactions were observed at D2, the chemical compound(s) which had produced + reaction(s) at D2 were re-applied at D7 and read at D9.

Results of patch testing for benzyl alcohol showed the following frequencies of sensitisation: 2/35 patients (6 % of positive reactions).

Study reference:

Scognamiglio J., Jones L., Vitale D., Letizia C.S., and Api A.M. (2012): Fragrance material review on benzyl alcohol. Food and Chemical Toxicology 50 Suppl 2, S140-160. DOI: 10.1016/j.fct.2011.10.013

Detailed study summaries and results:

- Of 2273 patients tested with the standard European series, 445 reacted to Balsam of Peru. Of these, 102 patients agreed to further testing and 8/ 102 reacted to benzyl alcohol, 5% in petrolatum, with one having a +++ reaction and seven having a ++ reaction. The authors reported that Balsm of Peru contains about 1–2% benzyl alcohol (Hausen, 2001).

- Mitchell et al. (1982) reported no positive reactions to benzyl alcohol, 5% in petrolatum, in 1934 dermatology patients tested in 1978–79 by the North American Contact Dermatits Group.

- In a study to determine if SLS irritancy could be useful in interpreting weak positive diagnostic patch test reactions as allergic or irritant, 0.1% (0.0–0.3%) of 1082 patients had a positive reaction to benzyl alcohol, 1% in petrolatum (Geier et al., 2003).

- In a retrospective computer analysis of standard diagnostic patch test screening results for 991 patients (877 white and 114 black), it was reported that 0.3% of whites and no blacks reacted to benzyl alcohol, 5% in petrolatum. Significance of the difference between whites and blacks for benzyl alcohol was not reported. However, based on results for all 33 materials that were tested, the authors concluded that except for phenylenediamine, they found no epidemiologic evidence for a significant difference in prevalence of contact dermatitis between black and white skin (Dickel et al., 2001).

- When 669 patients with contact dermatitis were tested with benzyl alcohol, 5% in petrolatum, 3 (0.4%) had a positive reaction (Katoh et al., 1995).

- Benzyl alcohol (5% in petrolatum) was included in a study of 667 patients with allergic contact dermatitis to identify fragrance ingredients that cross-react with wood tar. There was no evidence of benzyl alcohol cross reaction with wood tar. Frequency of reaction to benzyl alcohol was not reported (van Joost et al., 1984).

- When dermatology patients were tested from 1978 to 1986 with 5% benzyl alcohol in petrolatum, 4/270 (1.5%) with cosmetic dermatitis, 1/28 (3.6%) with facial melanosis, and 4/363 (1.1%) with non-cosmetic dermatitis and eczema had a positive reaction, for a total of 6/661 (0.9%) tested (Itoh et al., 1988).

- When dermatology patients were tested with 5% benzyl alcohol in petrolatum, 4/248 (1.6%) with cosmetic dermatitis, 1/26 (3.8%) with facial melanosis, and 4/311 (1.3%) with non-cosmetic dermatitis and eczema had a positive reaction, for a total of 9/585 (1.5%) tested (Itoh et al., 1986).

- There were no positive reactions when 10% benzyl alcohol in petrolatum was included in a diagnostic patch test study of 14 preservatives in 501 consecutive dermatology patients with suspected contact dermatitis (De Groot et al., 1986).

- Between 1992 and 1993, benzyl alcohol, 5% in petrolatum, elicited positive reaction in 1/479 (0.2%) of Japanese dermatology patients (Nagareda, 1996).

- Nishimura et al. (1984) reported positive reaction to 5% benzyl alcohol in 8/427 (1.9%) dermatology patients tested between 1978 and 1982. These included 3/172 (1.7%) of cases diagnosed with cosmetic dermatitis, 4/230 (4.0%) of cases with facial melanosis, and 4/230 (1.7%) of cases with non-cosmetic dermatitis and eczema.

- In a study of Japanese patients with contact dermatitis 3/425 (0.71%) (0.2%) had a positive test reaction to benzyl alcohol, 5% in petrolatum (Nagareda et al., 1992).

- In a diagnostic patch test study of 422 Korean dermatology patients between April 2002 and June, 2003, there were no positive reactions to 1% benzyl alcohol reported (An et al., 2005).

- In 1994, benzyl alcohol at 5% in petrolatum gave 1 positive diagnostic patch test results in 398 (0.3%) dermatology patients with suspected contact dermatitis from cosmetic and toiletry products (Sugai, 1996).

- In a study to determine optimum allergen test concentration for diagnostic patch testing, benzyl alcohol was tested at 10%, 5%, and 1% in petrolatum in 394 patients with various facial dermatoses. Positive allergic reactions were reported in 0.5%, 0.3%, and 0% of the population and irritation reactions were reported in 2.3%, 1.5%, and 0.8% of the population at 10%, 5%, and 1%, respectively (Mid-Japan Contact Dermatitis Research Group, 1984).

- When 394 Japanese dermatology patients were tested with 10% benzyl alcohol, 6 (1.5%) had a ?/+ reaction, 2 (0.5%) had a + reaction, 0 had a ++ reaction, and 9 (2.3%) had irritant reaction. At 5%, there were 5 (1.3%) ?/+, 1 (0.3%) +, 0 ++, and 6 (1.5%) irritant reactions. At 1% there were 2 (0.5%)

?/+, 0 +, 0 ++, and 3 (0.8%) irritant. The authors recommended, based on the low incidence of irritancy, that 10% be used for future patch testing (Ueda, 1994).

- Positive diagnostic patch test reaction to 5% benzyl alcohol was reported for 4/242 patients with allergic contact dermatitis of different origins (van Joost et al., 1984).

- Benzyl alcohol at 5% in petrolatum gave no positive diagnostic patch test results in 241 dermatology patients (Ferguson and Sharma, 1984).

- In a report of the management of cases of pigmented cosmetic dermatitis in Japanese patients, it was reported that 20% benzyl alcohol in petrolatum resulted in positive patch test results in 5%, 4%, and 1% of cosmetic dermatitis patients in 1971–74, 1975–77, and 1978–80, respectively. In non-cosmetic dermatitis patients results for the same time periods were 1%, 2%, and 0% for the same time periods. The number of patients tested varied from 136 to 230 per category per time period (Nakayama et al., 1984).

- When benzyl alcohol, 5% in petrolatum was tested in 200 dermatology patients suspected of having allergic contact dermatitis, a positive reaction was elicited in 1% (Nethercott, 1982).

- Benzyl alcohol, 10%, vehicle not specified, elicited positive reactions in 1.6% of 182 patients with suspected contact sensitization to cosmetic products (Malten et al., 1984).

- There were no positive reactions when benzyl alcohol, 5%, was included as part of the North American Standard Series and tested on 178 Japanese dermatology patients with a clinical diagnosis of contact dermatitis (Hirano and Yoshikawa, 1982).

- Benzyl alcohol, 5%, vehicle not specified, was tested in 167 patients with suspected fragrance allergy. Positive response rate was 3.6% on the first reading and 1.8% on the second reading. The authors interpreted the results to indicate 3.6% irritant response and 1.2% allergic response (Larsen et al., 1996).

- When dermatology patients were tested with 5% benzyl alcohol, 3/78 (3.8%) with cosmetic dermatitis, 0/30 (0%) with facial melanosis, and 1/51 (2.0%) with non-cosmetic dermatitis and eczema had a positive reaction. When tested at 2%, 2/78 (2.6%) with cosmetic dermatitis, 0/30 (0%) with facial melanosis, and 0/51 (0%) with non-cosmetic dermatitis and eczema had a positive reaction. When tested at 1%, 2/78 (2.6%) with cosmetic dermatitis, 0/30 (0%) with facial melanosis, and 0/51 (0%) with non-cosmetic dermatitis and eczema had a positive reaction. A total of 159 patients were tested (Ishihara et al., 1979).

- Among 95 dermatology patients sensitive to Balsam of Peru and tested for sensitivity to benzyl alcohol, 5% in petrolatum or 10% in alcohol, 19 were positive and 76 negative (Hjorth, 1961).

- There were seven positive reactions when 1% benzyl alcohol in petrolatum was tested for frequency of contact allergy in a multicenter study on a demographic of males with occupational dermatitis, atopic dermatitis, hand dermatitis, leg dermatitis, face dermatitis and age >40 (Schnuch et al., 2007).

- A series of 390 patients with oral disease or oral symptoms were tested to determine the role of contact allergy in oral cavity disease. There was only one positive reactions reported (Torgerson et al., 2007).

3.7.3 Other data

3.7.3.1 Study summaries of in chemico and in vitro data

Study reference:

Urbisch D., Mehling A., Guth K., Ramirez T., Honarvar N., Kolle S., Landsiedel R., Jaworska J., Kern P.S., and Gerberick F. (2015): Assessing skin sensitization hazard in mice and men using non-animal test methods. Regulatory Toxicology and Pharmacology 71 (2), 337-351. DOI: https://doi.org/10.1016/j.yrtph.2014.12.008

Detailed study summary and results:

Direct peptide reactivity assay (DPRA): Peptide reactivity data were generated using a method to measure reactivity of a test chemical with model hepta-peptides containing lysine (Ac-RFAAKAA-COOH) or cysteine (Ac- RFAACAACOOH) (Gerberick et al., 2004). Peptide reactivity was reported as percent depletion based on the decrease in non-reacted peptide concentration in the sample relative to the average concentration measured in the control.

Peptides were prepared and purified by the SynPep Corporation (Dublin, CA, USA) to >90% purity as measured by HPLC, and molecular weight confirmation was determined by flow injection positive- ion electrospray mass spectrometry. Briefly, 400 µL of a 1.25 mM peptide stock solution prepared in buffer and a 100 mM test chemical stock solution prepared in either acetonitrile or DMSO/acetonitrile were added to 100 mM ammonium acetate buffer (pH 10.2) for the lysine peptide or 100 mM sodium phosphate buffer (pH 7.5) for the cysteine peptide. The final reaction, containing 0.5 mM of the peptide and 5 or 25 mM of the test chemical, representing 1:10 and 1:50 M ratios, was mixed and incubated in the dark for 24 h at 25 °C. Control samples and standards used for defining the calibration curve for each analysis were prepared without test chemical for each peptide and ranged from 0.0156 to 1.0 mM. All samples were prepared in triplicate. Following incubation, the peptide was quantified by reverse-phase HPLC (Waters 2695 Alliance) on a Zorbax SB-C18 column (3.5 lm, 100 x 2.1 mm) with UV detection at 220 nm (Waters 996 PDA detector) using an external standard linear calibration curve. The UV spectrum was collected from 210 to 400 nm to permit verification of the peptide peak identity. Results for 199 substances were generated by P&G (referred to in Supplementary Table as DPRA I) or BASF (DPRA II) and thus available for this study. Five substances were not considered for further analyses due to discordant results in the two independent labs.

KeratinoSens™ assay: The standard operating procedure described (Natsch et al., 2011) and published online (ECVAM, 2014) was used to test additional substances in the KeratinoSens™ assay. Briefly, cells were grown for 24 h in 96-well plates. The medium was then replaced with medium containing the test substance and a final level of 1% of the solvent DMSO. Each test substance was subsequently tested at 12 twofold dilutions (0.98–2000 µM). In each repetition, three parallel replicate plates were run for luciferase determination and a fourth parallel plate was prepared for cytotoxicity determination. Cells were incubated for 48 h with the test substances, and then luciferase activity and cytotoxicity (with the 3-(4,5- dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromid (MTT) assay (Mosmann, 1983)) were determined. For each chemical the EC1.5, EC2 and EC3 values (concentration in µM for 1.5, 2 and 3-fold induction of the luciferase activity) were calculated along with IC50 values for the concentration yielding 50% reduction in cellular viability. Substances were tested in at least two independent experiments. A substance is considered to have a sensitizing potential

if an induction equal to or exceeding 1.5-fold compared to the vehicle control is observed at a concentration below 1000 µM and at which cells remain >70% viable. If the results of the two experiments were concordant, a prediction according to the prediction model was derived. Substances with discordant results or results close to the 1.5-fold threshold (borderline) were tested in additional independent experiments. The number of experiments and the number of positive results for each chemical is given in the database. Results for 195 substances were generated by Givaudan (referred to in Supplementary Table as KeratinoSens assay I) or BASF (KeratinoSens assay II) and thus available for this study. Eight substances were not considered for further analyses due to discordant results in the two independent labs.

LuSens assay: The LuSens assay is a keratinocyte-based assay which utilizes the luciferase gene under the control of the antioxidant response element (ARE) originating from the rat NQO1 gene as the reporter construct. The LuSens assay used in this paper is similar to that described in Bauch et al., 2012 with some modifications (Ramirez et al., 2014). In brief, a cytotoxicity range finding experiment (consisting of twelve concentrations) was performed, to calculate the concentration in which cell viability corresponds to no less than 75% (CV75). Following the range finder experiment, a main experiment was set up using six concentrations of test substance (in triplicates), the highest tested concentration was 1.2x CV75 (or 2000 µM if no cytotoxicity was observed). After 48 h treatment, luminescence and cytotoxicity were measured. A test substance is considered to have skin sensitization potential when the luciferase induction is above or equal to 1.5-fold compared to the vehicle control in two (or more than) consecutive non-cytotoxic tested concentrations whereby at least three tested concentrations must be non-cytotoxic (viability ≥70%). A test compound is considered not to have sensitizing potential if the above effects are not observed. The skin sensitization potential of a test substance is determined by the result of the majority of the repetitions of an experiment. If two of two or two of three repetitions are negative/ positive, the substance is considered as negative/positive. In order to come to a conclusion on the skin sensitization hazard of a substance, one complete experiment needs to be conducted. A complete experiment consists of two valid independent repetitions (Ramirez et al., 2014). Results for 77 substances were obtained by BASF and considered for this study.

Human cell line activation test (h-CLAT): In the h-CLAT assay, THP-1 cells (American Type Culture Collection, Manassas, VA, USA) were used as surrogate for dermal dendritic cells. For dose finding, cytotoxicity tests were conducted and the concentration resulting in 75% cell viability, termed CV75, was calculated based on the analysis of viable cells. THP-1 cells were treated with eight different concentrations, decided based on dose finding cytotoxicity test, for 24 h. After removing the test substance, the expression of CD86 and CD54 on the cell surface was measured by flow cytometry. The relative fluorescence intensity (RFI) was used as an indicator of CD86 and CD54 expression. If the RFI of CD86 or CD54 was greater than 150% or 200% at any dose in at least two out of three experiments, the substance was judged as a sensitizer. Otherwise, it was considered a non-sensitizer (Ashikaga et al., 2006). From the dose-dependency curves of three experiments, the median concentration inducing 150% of CD86 RFI and/or 200% of CD54 RFI (EC150 or EC200) was calculated like EC3 value determination in the LLNA. The lower EC value was defined as minimal induction threshold (MIT) (Nukada et al., 2013). Results for 166 substances were available for this study and for the determination of Cooper statistics; data generated by the respective method developer was used.

Myeloid U937 skin sensitization test (MUSST) and modified MUSST: The MUSST uses the U937 cell-line purchased from the American Type Culture Collection (Rockville, MD, USA). Four to six concentrations are chosen based on preliminary propidium iodide cytotoxicity experiments and are applied in duplicate for 48 h. The highest tested concentration in the main experiment is twice the concentration causing a cytotoxicity of

25% (CV75) determined in a pretest. A test substance is predicted to have a dendritic cell activating potential indicative of being a sensitizer when CD86 induction (measured by flow cytometry) exceeds the threshold of 1.5-fold with respect to vehicle treated cells at any tested concentration showing sufficient cell viability (P70%) in at least two independent experiments (Natsch et al., 2013). Results for 145 substances were made available for this study by P&G (referred to in Supplementary Table as U-937 Test).

A modified version of the MUSST (mMUSST) uses the U937 cell line from German Resource Center for Biological Material DSMZ, Braunschweig, Germany. In the mMUSST, a test substance is predicted to have a dendritic cell activating potential when CD86 induction exceeds a threshold of 1.2-fold (Bauch et al., 2012). Data for 65 substances were generated in the mMUSST by BASF (referred to in Supplementary Table as mMUSST). For the analyses within this study, the results from the MUSST and mMUSST were taken together to create a dataset of 161 substances. Data for 12 substances were not further considered for analyses due to discordant results being obtained in both tests.

'2 out of 3' prediction model: The least complicated way to assess the skin sensitization hazard potential of a substance is to use the results of single assays which reflect key steps of the AOP within a '2 out of 3' prediction model. For the assays addressing the three key events described in the OECD AOP on skin sensitization mentioned above, a '2 out of 3' assessment was introduced for the first time by Bauch et al. (2012). In the current study, this prediction model was applied using DPRA, KeratinoSens™ and h-CLAT data. Any two congruent results of the three tests rule the overall assessment: If at least two of the three assays were positive, the substance was rated to be a skin sensitizer. If at least two of the three assays were negative, the substance was rated to be a non-sensitizer. The classification as a sensitizer or non-sensitizer is therefore based on a weight of evidence pertaining to key events of the AOP. Cooper statistics for this classification were determined in comparison to LLNA or human data. Results for 180 or 101 substances, respectively, were obtained using this prediction model.

3.8 Germ cell mutagenicity

Not assessed in this dossier.

3.9 Carcinogenicity

Not assessed in this dossier.

3.10 Reproductive toxicity

Not assessed in this dossier.

3.11 Specific target organ toxicity – single exposure

Not assessed in this dossier.

3.12 Specific target organ toxicity – repeated exposure

Not assessed in this dossier.

3.13 Aspiration hazard

Not assessed in this dossier.

4 ENVIRONMENTAL HAZARDS

Not assessed in this dossier.

5 REFERENCES

Ada S. and Seckin D. (2010): Patch testing in allergic contact dermatitis: is it useful to perform the cosmetic series in addition to the European standard series? J Eur Acad Dermatol Venereol 24 (10), 1192-1196. DOI: 10.1111/j.1468-3083.2010.03619.x

An S., Lee A.Y., Lee C.H., Kim D.W., Hahm J.H., Kim K.J., Moon K.C., Won Y.H., Ro Y.S., and Eun H.C. (2005): Fragrance contact dermatitis in Korea: a joint study. Contact Dermatitis 53 (6), 320-323. DOI: 10.1111/j.0105-1873.2005.00720.x

Broeckx W., Blondeel A., Dooms-Goossens A., and Achten G. (1987): Cosmetic intolerance. Contact Dermatitis 16 (4), 189-194. DOI: DOI 10.1111/j.1600-0536.1987.tb01422.x

Carpenter C.P., Smyth H.F., Jr., and Pozzani U.C. (1949): The assay of acute vapor toxicity, and the grading and interpretation of results on 96 chemical compounds. J Ind Hyg Toxicol 31 (6), 343-346

Carter D.V., Charlton P.T., Fenton A.H., Housley J.R., and Lessel B. (1958): The preparation and the antibacterial and antifungal properties of some substituted benzyl alcohols. Journal of Pharmacy and Pharmacology 10 (Supp), 149-157T; discussion 157-159T. DOI: 10.1111/j.2042-7158.1958.tb10394.x

Chow E.T., Avolio A.M., Lee A., and Nixon R. (2013): Frequency of positive patch test reactions to preservatives: The Australian experience. Australasian Journal of Dermatology 54 (1), 31-35. DOI: 10.1111/j.1440-0960.2012.00958.x

Clayton (1982). In: Patty's Industrial hygiene and toxicology (Patty F.A., Clayton G.D., Clayton F.E., and Battigelli M.C., eds.), ed. Third Revised Edition, pp. 4636-4641. John Wiley and Sons, New York

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

De Groot A.C., Bos J.D., and Jagtman B.A. (1986): Contact allergy to preservatives - II. Contact Dermatitis 15 (4), 218-222. DOI: 10.1111/j.1600-0536.1986.tb01340.x

Dickel H., Taylor J.S., Evey P., and Merk H.F. (2001): Comparison of patch test results with a standard series among white and black racial groups. Am J Contact Dermat 12 (2), 77-82. DOI: 10.1053/ajcd.2001.20110

Eiermann H.J., Larsen W., Maibach H.I., and Taylor J.S. (1982): Prospective study of cosmetic reactions: 1977-1980. North American Contact Dermatitis Group. J Am Acad Dermatol 6 (5), 909-917. DOI: 10.1016/S0190-9622(82)70080-5

Ferguson J. and Sharma S. (1984): Cinnamic Aldehyde Test Concentrations. Contact Dermatitis 10 (3), 191-192. DOI: DOI 10.1111/j.1600-0536.1984.tb00039.x

Geier J., Uter W., Pirker C., and Frosch P.J. (2003): Patch testing with the irritant sodium lauryl sulfate (SLS) is useful in interpreting weak reactions to contact allergens as allergic or irritant. Contact Dermatitis 48 (2), 99-107. DOI: DOI 10.1034/j.1600-0536.2003.480209.x

Goossens A. (2016): Cosmetic contact allergens. Cosmetics 3 (1), 5. DOI: 10.3390/cosmetics3010005

Graham B.E. and Kuizenga M.H. (1945): Toxicity studies on benzyl benzoate and related benzyl compounds. J Pharmacol Exp Ther 84, 358-362

Hasan T., Rantanen T., Alanko K., Harvima R.J., Jolanki R., Kalimo K., Lahti A., Lammintausta K., Lauerma A.I., Laukkanen A., Luukkaala T., Riekki R., Turjanmaa K., Varjonen E., and Vuorela A.-M. (2005): Patch test reactions to cosmetic allergens in 1995-1997 and 2000-2002 in Finland - a multicentre study. Contact Dermatitis 53, 40-45

Hausen B.M. (2001): Contact allergy to balsam of Peru. II. Patch test results in 102 patients with selected balsam of Peru constituents. American Journal of Contact Dermatitis 12 (2), 93-102. DOI: http://dx.doi.org/10.1053/ajcd.2001.19314

Hausen B.M., Evers P., Stuwe H.T., Konig W.A., and Wollenweber E. (1992): Propolis allergy (IV). Studies with further sensitizers from propolis and constituents common to propolis, poplar buds and balsam of Peru. Contact Dermatitis 26 (1), 34-44

Heisterberg M.V., Menne T., and 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 (5), 266-275. DOI: 10.1111/j.1600-0536.2011.01962.x

Hirano S. and Yoshikawa K. (1982): Patch testing with European and American standard allergens in Japanese patients. Contact Dermatitis 8 (1), 48-50

Hjorth N. (1961): Eczematous allergy to balsams, perfumes and flavouring agents. Dan Med Bull 8, 143-144

Ishihara M., Ito M., Hosono K., and Nishimura M. (1981): Some Problems With Patch Tests Using Fragrance Materials. Skin research 23 (6), 808-817. DOI: 10.11340/skinresearch1959.23.808

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

Ishihara M., Itoh S., Hayashi S., and Satake T. (1979): Methods of diagnosis in cases of cosmetic dermatitis and facial melanosis in females. Nishinihon Journal of Dermatology 41 (3), 426-439

Itoh M., Hosono K., Kantoh H., Kinoshita M., Yamada K., Kurosaka R., and Nishimura M. (1988): Patch test results with cosmetic ingredients conducted between 1978 and 1986. Journal Society Cosmetic Science 12 (1), 27-41

Itoh M., Ishihara M., Hosono K., Kantoh H., Kinoshita M., Yamada K., and Nishimura M. (1986): Results of patch tests conducted between 1978 and 1985 using cosmetic ingredients. Skin research 28 (suppl 2), 110-119

Jappe U., Schnuch A., and Uter W. (2003): Frequency of sensitization to antimicrobials in patients with atopic eczema compared with nonatopic individuals: analysis of multicentre surveillance data, 1995-1999. Br J Dermatol 149 (1), 87-93. DOI: 10.1046/j.1365-2133.2003.05290.x

Jenner P.M., Hagan E.C., Taylor J.N.M., Cook E.L., and Fitzhugh O.G. (1964): Food flavourings and compounds of related structure I. acute oral toxicity. Fd. Cosmet. Toxicol. 2, 327-343

Kashima R., Oyake Y., Okada J., and Ikeda Y. (1993): STUDIES OF NEW SHORT-PERIOD METHOD FOR DELAYED CONTACT HYPERSENSITIVITY ASSAY IN THE GUINEA-PIG .1. DEVELOPMENT AND COMPARISON WITH OTHER METHODS. Contact Dermatitis 28 (4), 235-242. DOI: 10.1111/j.1600-0536.1993.tb03409.x

Katoh J., Sugai T., Syoji A., Nagareda T., and Kuwano A. (1995): Multiple sensitization from fragrance materials during the last one and a half year period at the Osaka Kaisei Hospital. Environmental Dermatology 2 (3)

Klecak G. (1979): The open epicutaneous test (OET), a predictive test procedure in the guinea pig for estimation of allergenic properties of simple chemical compounds, their mixtures and of finished cosmetic preparations. International Federation Societies Cosmetic Chemists

Klecak G. (1985): The Freund's Complete Adjuvant Test and the Open Epicutaneous Test. A complementary test procedure for realistic assessment of allergenic potential. Curr Probl Dermatol 14, 152-171. https://www.ncbi.nlm.nih.gov/pubmed/4064742

Klecak G., Geleick H., and 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 28 (2), 53-64

Kligman A.M. and Epstein W. (1975): Updating the maximization test for identifying contact allergens. Contact Dermatitis 1 (4), 231-239. https://www.ncbi.nlm.nih.gov/pubmed/1235254

Larsen W., Nakayama H., Lindberg M., Fischer T., Elsner P., Burrows D., Jordan W., Shaw S., Wilkinson J., Marks J., Jr., Sugawara M., and Nethercott J. (1996): Fragrance contact dermatitis: a worldwide multicenter investigation (Part I). Am J Contact Dermat 7 (2), 77-83

Macht D.I. (1918): A PHARMACOLOGICAL AND THERAPEUTIC STUDY OF BENZYL ALCOHOL AS A LOCAL ANESTHETIC. Journal of Pharmacology and Experimental Therapeutics 11 (3), 263-279

Magnusson B. and Kligman A.M. (1969): The identification of contact allergens by animal assay. The guinea pig maximization test. J Invest Dermatol 52 (3), 268-276. https://www.ncbi.nlm.nih.gov/pubmed/5774356

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

Mann J., McFadden J.P., White J.M., White I.R., and Banerjee P. (2014): Baseline series fragrance markers fail to predict contact allergy. Contact Dermatitis 70 (5), 276-281. DOI: 10.1111/cod.12171

Mid-Japan Contact Dermatitis Research Group (1984): Determination of suitable concentrations for patch testing of various fragrance materials. The Journal of Dermatology 11 (1), 31-35. DOI: 10.1111/j.1346-8138.1984.tb01437.x

Mitchell J.C. (1977): Multiple concomitant positive patch test reactions. Contact Dermatitis 3 (6), 315-320. DOI: 10.1111/j.1600-0536.1977.tb03695.x

Mitchell J.C., Adams R.M., Glendenning W.E., Fisher A., Kanof N., Larsen W., Maibach H.I., Rudner E.J., Schnorr W., Storrs F., and Taylor J.S. (1982): Results of standard patch tests with substances abandoned. Contact Dermatitis 8 (5), 336-337

Nagareda T., Sugai T., Shouji A., Katoh J., Mita T., Utsumi M., Nakanishi T., and Mochida K. (1992): Incidence of positive reactions to cosmetic products and theri ingredients in patch tests and representative cases with cosmetic dermatitis in 1991. Skin research 34 (SUPPL. 14), 176-182

Nagareda T., Sugai, T., Shoji, A., Katoh, J., Kuwano, A., Teramae, K., Nakanishi, T., (1996): Incidence of positive reactions to cosmetic products and their ingredients in patch tests and a representative case of cosmetic dermatitis in 1993. Environmental Dermatology 3 (1), 16-24

Nakayama H., Matsuo S., Hayakawa K., Takhashi K., Shigematsu T., and Ota S. (1984): Pigmented cosmetic dermatitis. Int J Dermatol 23 (5), 299-305

Nethercott J.R. (1982): Results of routine patch testing of 200 patients in Toronto, Canada. Contact Dermatitis 8 (6), 389-395

Nishimura M., Ishihara M., Itoh M., Hosono K., and Kantoh H. (1984): Results of patch tests on cosmetic ingredients conducted between 1979 and 1982. Skin research 26 (4), 945–954

NPIRI (1974). Raw Material Data Handbook 1 (Organic Solvents), 6

Opdyke D.L. (1973): Monographs on fragrance raw materials. Food and Cosmetics Toxicology 11 (6), 1011-1013. DOI: 10.1016/0015-6264(73)90228-9

RIFM (1970a): The contact sensitizing potential of fragrance materials in humans. RIFM report No. 1760, October 07 (RIFM, Woodcliff Lake, NJ, USA)

RIFM (1979a): Report on human maximization studies. . RIFM report No. 1697, May 25 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (1992a): Acute oral toxicity study in rats with benzyl alcohol. Unpublished report from Proctor and Gamble. Report No. 20505 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (2002a): Repeated insult patch test (RIPT) with benzyl alcohol. RIFM report No. 44247, March 03 (RIFM, Woodcliff Lake, NJ, USA)

RIFM (2003a): Repeated insult patch test (RIPT) with benzyl alcohol. RIFM report No. 44246, November 03 (RIFM, Woodcliff Lake, NJ, USA)

RIFM (2004b): Repeated insult patch test with benzyl alcohol (modified Draize procedure). RIFM report No. 45131, April 30 (RIFM, Woodcliff Lake, NJ, USA)

RIFM (2004c): Repeated insult patch test with benzyl alcohol. RIFM report No. 47046, July 07 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (2005b): Benzyl alcohol diluted with vehicle 1:3 ETOH:DEP: Local Lymph Node Assay. RIFM report No. 47376, January 20 (RIFM, Woodcliff Lake, NJ, USA)

Schnuch A., Geier J., Uter W., and Frosch P.J. (1998): Patch testing with preservatives, antimicrobials and industrial biocides. Results from a multicentre study. Br J Dermatol 138 (3), 467-476. DOI: 10.1046/j.1365-2133.1998.02126.x

Schnuch A., Lessmann H., Geier J., and Uter W. (2011a): Contact allergy to preservatives. Analysis of IVDK data 1996–2009. British Journal Of Dermatology 164 (6), 1316-1325. DOI: 10.1111/j.1365-2133.2011.10253.x

Schnuch A., Mildau G., Kratz E.M., and Uter W. (2011b): Risk of sensitization to preservatives estimated on the basis of patch test data and exposure, according to a sample of 3541 leave-on products. Contact Dermatitis 65 (3), 167-174. DOI: 10.1111/j.1600-0536.2011.01939.x

Schnuch A., Uter W., Geier J., Lessmann H., and Frosch P.J. (2007): Sensitization to 26 fragrances to be labelled according to current European regulation: Results of the IVDK and review of the literature. Contact Dermatitis 57 (1), 1-10. DOI: 10.1111/j.1600-0536.2007.01088.x

Schnuch A., Uter W., Lessmann H., and Geier J. (2015): Risk of sensitization to fragrances estimated on the basis of patch test data and exposure, according to volume used and a sample of 5451 cosmetic products. Flavour and Fragrance Journal 30 (3), 208-217. DOI: 10.1002/ffj.3241

Scognamiglio J., Jones L., Vitale D., Letizia C.S., and Api A.M. (2012): Fragrance material review on benzyl alcohol. Food and Chemical Toxicology 50 Suppl 2, S140-160. DOI: 10.1016/j.fct.2011.10.013

Sharp D.W. (1978): The sensitization potential of some perfume ingredients tested using a modified draize procedure. Toxicology 9 (3), 261-271. DOI: 10.1016/0300-483X(78)90009-4

Smyth H.F., Jr., Carpenter C.P., and Weil C.S. (1951): Range-finding toxicity data: List IV. AMA Arch Ind Hyg Occup Med 4 (2), 119-122

Sugai T. (1996): Cosmetic skin diseases in 1994. Environmental Dermatology 3 (1), 1-7

Torgerson R.R., Davis M.D., Bruce A.J., Farmer S.A., and Rogers R.S., 3rd (2007): Contact allergy in oral disease. J Am Acad Dermatol 57 (2), 315-321. DOI: 10.1016/j.jaad.2007.04.017

Trattner A., Farchi Y., and David M. (2002): Cosmetics patch tests: first report from Israel. Contact Dermatitis 47 (3), 180-181. DOI: DOI 10.1034/j.1600-0536.2002.470308_16.x

Ueda H. (1994): Historical data of the JSCD Group study II and III. Fragrance materials (I) (II). Environmental Dermatology 2 (1), 156-157

Urbisch D., Mehling A., Guth K., Ramirez T., Honarvar N., Kolle S., Landsiedel R., Jaworska J., Kern P.S., and Gerberick F. (2015): Assessing skin sensitization hazard in mice and men using non-animal test methods. Regulatory Toxicology and Pharmacology 71 (2), 337-351. DOI: https://doi.org/10.1016/j.yrtph.2014.12.008

Uter W., Geier J., Frosch P., and Schnuch A. (2010): Contact allergy to fragrances: current patch test results (2005-2008) from the Information Network of Departments of Dermatology. Contact Dermatitis 63 (5), 254-261. DOI: 10.1111/j.1600-0536.2010.01759.x

van Joost T., Stolz E., van der Hoek J.C., and Prens E.P. (1984): Sensitivity to woodtar. Contact Dermatitis 11 (4), 248