The MAK Collection for Occupational Health and Safety

Benzyl alcohol

MAK Value Documentation, addendum – Translation of the German version from 2017

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Benzyl alcohol / phenylmethanol

MAK Value Documentation

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated benzyl alcohol [100-51-6] to derive a maximum concentration at the workplace (MAK value), considering all toxicological endpoints. Available publications and study reports are described in detail.
Benzyl alcohol is irritating to the eyes and the airways. In a 4-week inhalation study in rats, microscopic lesions in the airways, especially in the lung, occurred at 1072 mg/m³. The NAEC is estimated to be 300 mg/m³, a concentration at which benzyl alcohol can occur as vapour, corresponding to 67 ml/m³. A MAK value of 5 ml/m³ has been derived. As local effects are critical, benzyl alcohol is classified in Peak Limitation Category I with an excursion factor of 2.
In developmental toxicity studies with benzyl alcohol in mice, foetotoxic effects occurred at 750 mg/kg body weight and day in the presence of marked maternal toxicity. The NOAEL was 550 mg/kg body weight and day; however, teratogenicity was not examined. Benzoic acid is the main metabolite of benzyl alcohol. Considering the developmental toxicity studies with sodium benzoate, the differences between the NOAEL for rats, mice, rabbits and hamsters scaled to an inhalation concentration at the workplace and the MAK value are considered so large that damage to the embryo or foetus is unlikely when the MAK value is observed. Therefore, benzyl alcohol is classified in Pregnancy Risk Group C.
Benzyl alcohol is not regarded to be genotoxic or carcinogenic. Sensitization is not expected as benzyl alcohol was not a contact sensitizer in a local lymph node assay and there were no conclusive positive clinical findings of sensitizing effects on the skin. Skin contact is expected to contribute significantly to the systemic toxicity. Therefore, benzyl alcohol is designated with an "H".
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Keywords

benzyl alcohol; phenyl methanol; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub) chronic toxicity; irritation; allergenic effects; reproductive toxicity; fertility; developmental toxicity; genotoxicity; carcinogenicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Benzyl alcohol[1)]

[100-51-6]
Supplement 2017

MAK value (2016)	**5 ml/m³ (ppm) ≙ 22 mg/m³**
Peak limitation (2016)	**Category I, excursion factor 2**
Absorption through the skin (2016)	**H**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2016)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
Molar mass	108.14 g/mol
Vapour pressure at 25 °C Vapour pressure at 20 °C	0.13 hPa (NLM 2015 a; ECHA 2014) 0.07 hPa (ECHA 2014); 0.027 hPa (IFA 2015)
1 ml/m³ (ppm) ≙ 4.487 mg/m³	**1 mg/m³ ≙ 0.223 ml/m³ (ppm)**
Stability	Benzyl alcohol is sensitive to light and air (Merck KGaA 2014)
Production	Hydrolysis of benzyl chloride with aqueous sodium or potassium carbonate (NLM 2015 b)
Purity	99.5% (Merck KGaA 2013)
Impurities	Benzaldehyde (≤ 0.1%; Merck KGaA 2013)

1) The substance may be present simultaneously as vapour and aerosol.

Uses	For curing epoxy resins, as a solvent in waterborne coatings, in paint strippers, in cosmetics and as a preservative and flavour in food (OECD 2004). Approved since 2009 as an active ingredient in a lotion for treating head lice in the USA (FDA 2009).

Documentation for benzyl alcohol is available from 2006 (documentation "Benzylalkohol" 2006, available in German only). This supplement takes into account the new data.

1 Toxic Effects and Mode of Action

The toxic effects and mode of action of benzyl alcohol are described in the 2006 documentation (documentation "Benzylalkohol" 2006, available in German only). In a recently published 4-week inhalation study with rats, histopathological changes in the lungs occurred at a concentration of 1072 mg/m^3.

In vitro and in vivo studies with benzyl alcohol did not reveal gene mutations. Clastogenic effects were found only in vitro at high concentrations. In micronucleus tests in vivo, neither benzyl alcohol nor its main metabolite benzoic acid was found to have clastogenic effects.

When administered by gavage using doses of 750 mg benzyl alcohol/kg body weight and day, reduced foetal body weights with simultaneous maternal toxicity were found in mice. In recent studies of the developmental toxicity of benzyl alcohol in rats and rabbits, foetotoxic effects, but not teratogenic effects, were observed with simultaneous maternal toxicity after subcutaneous administration of 500 and 400 mg/kg body weight and day, respectively.

In humans, only few cases of sensitization to benzyl alcohol after application to healthy skin have been reported. Also in animals its sensitization potential is, at most, very low. No data are available for sensitization of the airways.

2 Mechanism of Action

The toxicity of benzyl alcohol in premature neonates is attributed to their reduced metabolic capacity (see Section 4). This is assumed to be the result of lower glycine acyltransferase activity and a depletion in glycine (LeBel et al. 1988). Extrapolation of the effects in premature neonates to those in adults is difficult due to the different metabolic capacity. In an intraperitoneal study with adult and neonatal mice, no difference in the toxicity of benzyl alcohol could be found, however. In both age groups there were toxic effects such as sedation, dyspnoea or the loss of the righting reflex. The LD_{50} value for adult and newborn mice was 1000 mg/kg body weight. The authors assume that the increased susceptibility to benzyl alcohol (with effects such as gasping) in the premature neonates compared with in the adults may be

related to an excessive body burden relative to weight, rather than to metabolic differences between neonates and adults. (McCloskey et al. 1986).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

There is no information available for the toxicokinetics of benzyl alcohol after inhalation. Data from the documentation of 2006 (documentation "Benzylalkohol" 2006, available in German only) show that orally administered benzyl alcohol is rapidly and presumably almost completely absorbed via the gastrointestinal tract and 75% to 85% is eliminated with the urine after metabolism

Since the documentation from 2006 (documentation "Benzylalkohol" 2006, available in German only), three new studies of its dermal penetration have been published. A summary of all the available studies of dermal penetration is shown in Table 1.

In a study with repeated dermal treatment of rats and dogs for 6 hours a day over 14 days, benzyl alcohol was investigated as the active ingredient (5%) in a lotion to treat head lice. The benzyl alcohol doses used were 5, 10 and 15 mg/kg body weight and day. The concentrations of benzyl alcohol in the plasma were investigated after 1 day and after 14 days. The highest level of benzyl alcohol (3.59 µg/ml) was found in the high dose group in rats after 14 days. The concentrations in the plasma of dogs were similarly low after 14 days; 10.2 µg/ml was determined in the high dose group (FDA 2009).

In an in vitro study of dermal penetration, benzyl alcohol in ethanol was applied to human split skin (300 µm) in concentrations of 0.9 µg/cm^2 to 10.6 mg/cm^2. A maximum flux of 100 µg/cm^2 and hour at a concentration of 990 µg/cm^2 was determined. This would correspond to the total absorption of 200 mg by both hands and forearms (about 2000 cm^2) after exposure for one hour. In the study it was also found that at low concentrations (< 300 µg/cm^2) the maximum absorption occurs within the first hour after application of the substance, and at higher concentrations (≥ 990 µg/cm^2) the time taken to reach maximum absorption increases. The cumulative amount absorbed after 24 hours was between 20% (0.9 µg/cm^2) and 29% (–10.6 mg/cm^2 (Miller et al. 2006).

In another in vitro study, no significant difference in dermal penetration was found between undiluted benzyl alcohol and saturated aqueous solutions (540 ± 240 µg/cm^2 and hour and 610 ± 530 µg/cm^2 and hour, respectively) (Barry et al. 1985 b).

In an inadequately documented investigation, 7 mg benzyl alcohol/cm^2 was applied to human split skin for 24 hours. The cumulative amount absorbed per area, divided by the concentration in the solvent (mg/cm^2 / mg/cm^3), was given as 40.1 ± 4.3 × 10^3 cm and 41.0 ± 10 × 10^3 cm for benzyl alcohol (Grégoire et al. 2009).

No new data for the half-life of benzyl alcohol were found. After intravenous administration of 52 or 150 mg/kg body weight (2.5% in saline solution), the half-life in the plasma of dogs was 1.5 hours (Rowe and McCollister 1982).

Table 1 Summary of the studies of the dermal penetration of benzyl alcohol

Test system, species	Receptor phase	Solvent	Occlusion	Skin thickness [µm]	Flux [µg/cm²/h]	Total uptake [mg][a)]	References
in vivo, rhesus monkey (*Macaca mulatta*)	–	acetone	with and without covering	–	0.1[b)]	0.2	Bronaugh et al. 1990
in vivo, rat, dog	–	5% in lotion for head lice	no data; 5, 10, 15 mg/kg body weight and day, 6 hours/day, 14 days	–	n.c.	n.c.; 15 mg/kg body weight and day: 3.59 (rat) or 10.2 µg/ml (dog) in the plasma after 14 days	FDA 2009
in vitro, humans	saline solution	undiluted	test chamber covered with parafilm	no data	275	550	Jimbo 1983; Jimbo et al. 1983
in vitro, humans	buffer solution	ethanol	no[c)]	300	29	57.9	Saiyasombati and Kasting 2003
in vitro, humans	saline solution	benzene	no data	5000	n.c.	n.c.	Menzel and Maibach 1970
in vitro, humans	no data	no data	no data	no data	73	146	FDA 2009
in vitro, humans	buffer solution	ethanol	test chamber covered some of the time	300	100	200	Miller et al. 2006
in vitro, humans	ethanol (50%)[d)]	undiluted	no data	400	50^{VF}	100	Barry et al. 1985 a
in vitro, humans	ethanol (50%)[d)]	undiluted water (saturated)	no data	400	52^{VF} 540^{LF} 610^{SF}	104 1080 1220	Barry et al. 1985 b

Table 1 (continued)

Test system, species	Receptor phase	Solvent	Occlusion	Skin thickness [µm]	Flux [µg/cm²/h]	Total uptake [mg][a)]	References
in vitro, humans	physiological receptor solution	no data	no	390 ± 80	n.c.	n.c.	Grégoire et al. 2009

[a)] one-hour exposure of both hands and forearms (about 2000 cm²), calculated;
[b)] mean value from open and occlusive application;
[c)] apparatus with continuous air removal;
[d)] study not valid as receptor phase not physiological;
[VF]: vapour flux;
[LF]: liquid flux;
[SF]: flux of saturated aqueous solution;
n.c.: not calculable, as data are lacking

3.2 Metabolism

After absorption, in humans as well as in rats and rabbits, benzyl alcohol is rapidly oxidized via benzaldehyde to benzoic acid. After conjugation with glycine, 80% is eliminated as hippuric acid and up to 20% as glucuronide (see documentation "Benzylalkohol" 2006, available in German only). In adult mice, alcohol dehydrogenase and aldehyde dehydrogenase could be identified as the metabolizing enzymes (McCloskey et al. 1986). In human liver microsomes, on the other hand, cytochrome P450 and not alcohol dehydrogenase has been described as the metabolizing enzyme of benzyl alcohol (Chapman et al. 1990).

4 Effects in Humans

There are no new data available for repeated exposure and there are still no data for reproductive toxicity, genotoxicity and carcinogenicity.

4.1 Single exposures

Benzyl alcohol was added to isotonic saline solution as a preserving agent. Therefore, toxic effects such as gasping, depression of the central nervous system or kidney and liver failure were observed in premature neonates (documentation "Benzylalkohol" 2006, available in German only). From the significantly increased levels of benzoic acid in the plasma and the significantly reduced urinary hippuric acid values in the premature neonates compared with term newborns, a reduced metabolic capacity in the premature neonates can be concluded. Lower glycine acyltransferase activity and a depletion in glycine are assumed (LeBel et al. 1988).

4.2 Local effects on skin and mucous membranes

In earlier studies, benzyl alcohol was described as irritating to human skin (documentation "Benzylalkohol" 2006, available in German only). In a review it is reported that 9 female subjects were exposed to subcutaneous injections of benzyl alcohol on their backs (3%, no other data) on 4 consecutive days. After visual evaluation according to the Frosch-Kligman assessment system the effects were described as irritative (Nair 2001).

4.3 Allergenic effects

In the documentation from 2006 (documentation "Benzylalkohol" 2006, available in German only), in addition to some case reports, most of which were not occupation-related, numerous clinical epidemiological studies are described in which patch tests were carried out with benzyl alcohol concentrations of between 1% and 10%. In the tests with concentrations of 5% or 10% in collectives of up to 4246 and 2028 patients, reactions were obtained in up to about 2.5% and 1.6% of the persons, respectively. A higher percentage of about 5% was found only in a collective of 652

patients with eczema on the lower leg or ulcus cruris (documentation "Benzylalkohol" 2006, available in German only).

In a more recent review of the toxicological properties of benzyl alcohol, other studies, in particular Japanese, are cited, in which a similarly high percentage of reactions was obtained with 5% or 10% test concentrations (Scognamiglio et al. 2012). However, in the tests using a 1% preparation (mostly in petrolatum), either a markedly lower percentage of reactions of below 1%, for example in about 0.4% of 11373 tested persons, were observed, or no reactions at all (documentation "Benzylalkohol" 2006, available in German only).

As a result of the more frequent occurrence of irritative reactions at higher concentrations, in the meantime a 1% preparation in petrolatum has been recommended for testing by the DKG (German Contact Dermatitis Research Group). The reaction index (RI)[2)] of –0.15 and the positivity ratio (PR)[3)] of 74.9% (Schnuch et al. 2008) indicate that this preparation is sufficiently suitable for this purpose.

In a comparative evaluation, no increased incidence of positive or questionable erythematous reactions was found in 441 patients who reacted to sodium lauryl sulfate (SLS) tested as an irritant control in the clinics of the IVDK (Information Network of Departments of Dermatology) compared with in 641 patients who did not react to SLS (Geier et al. 2003 b).

Only a low percentage of reactions was found also in more recent clinical epidemiological studies. For example, a reaction to benzyl alcohol was found in 0.1% of 4922 patients in Finland between 1995 and 1996, whereas there were no reactions at all in any of 6125 patients in the period between 2000 and 2002 (Hasan et al. 2005).

In a Danish and a Dutch study of sensitization to fragrance components, a reaction to benzyl alcohol was found in 2 of 1508 patients between January 2008 and July 2010 and in 1 of 320 patients between April 2005 and June 2007, that is in about 0.1% of the tested persons in each case (Heisterberg et al. 2011; van Oosten et al. 2009).

In a Spanish study, 2 of 86 patients with diagnostic or anamnestic evidence of fragrance intolerance reacted to 1% benzyl alcohol (no other details) in the period between October 2004 and June 2008 (Cuesta et al. 2010).

Between 2011 and 2012, in two British dermatological centres, 1951 patients were tested with the standard series and with a fragrance series. Here, 4 persons reacted to a 10% benzyl alcohol preparation (Mann et al. 2014).

A similarly low percentage of reactions was recorded also in the clinics of the IVDK in corresponding studies, with reactions in 1 of 1059 persons (tested in 2003 and 2004) and 7 of 2166 persons (tested between 2005 and 2008) (Schnuch et al. 2007; Uter et al. 2010).

When benzyl alcohol was tested in the clinics of the IVDK in persons with suspected sensitization to preservatives, only a low percentage of reactions occurred, with 0.24% of 23 257 and 0.18% of 17 740 tested persons between 2005 and 2008,

2) The reaction index is defined as the quotient: (a – d – i) / (a + d + i); with: a = number of allergic reactions, d = number of questionable reactions, i = number of irritative reactions (Brasch and Henseler 1992).

3) The positivity ratio is defined as the percentage of 1+ test reactions among the total positive test reactions (Geier et al. 2003 a).

and between 2006 and 2009, respectively. In the larger collective, the reactions were classified as irritative or questionable in 0.53% of the patients (Schnuch et al. 2011; Uter et al. 2010).

An evaluation of the patch test results from 5183 patients with and 14 722 patients without atopic eczema documented between 1995 and 1999 in the clinics of the IVDK showed that in these collectives there is practically no difference in the incidence of reactions at 0.28% and 0.30%, respectively. A positive result was, however, strongly associated with a more advanced age (> 40 years). Patients with ulcus cruris or chronic eczema on the leg were not included in this study (Jappe et al. 2003).

In total, more than 120 000 patients were patch tested in the clinics of the IVDK during the twelve years between 1996 and 2007, more than 60 000 of whom were also tested with a preservative series in addition to the standard series. A reaction to 1% benzyl alcohol in petrolatum was observed in 223 of 65 398 patients (0.3%). (Schnuch et al. 2008).

A similarly low frequency (0.4%) of reactions to 1% benzyl alcohol in petrolatum was described in an Australian study with 4552 tested patients. Less than a third of the reactions were considered by the authors to be relevant (Chow et al. 2013).

Patch tests with 1% benzyl alcohol in petrolatum produced a reaction only in 1 of 290 patients with suspected perioral symptoms of allergic origin. However, the authors did not regard this as relevant (Torgerson et al. 2007).

No reactions to 1% benzyl alcohol in petrolatum were observed in the testing of 232 patients with dermatitis of various origin on the eyelids and in an Indian study with 436 patients with suspected intolerance to cosmetics (Cooper and Shaw 2000; Penchalaiah et al. 2000).

In five photo-contact allergy studies, benzyl alcohol concentrations of 5% were investigated in photopatch tests and produced only one reaction in a total of 2365 tested persons (Scognamiglio et al. 2012).

In addition, also a number of case reports have been published which, however, were always in connection with (possibly) non-occupational exposure, as with one patient (female) who produced a 2+ reaction to benzyl alcohol contained in a semi-permanent hair-dye preparation (Carrascosa et al. 2006). One female patient, who had had dermatitis of the arms and legs for ten years and had undergone repeated topical antibiotic and corticoid treatment for her chronic leg eczema, reacted in the patch test to benzyl alcohol, several external agents and cosmetics containing benzyl alcohol as a preservative, and a number of other substances, including wool alcohol and neomycin (Curry and Warshaw 2005).

In another female patient with intolerance to a topical pimecrolismus preparation (balsam of Peru), the authors suspected the benzyl alcohol used as a preservative to be the cause, and described sudden exacerbation of the dermatitis in the eye area after provocation with a product containing benzyl alcohol (Jacob and Stechschulte 2008). In view of the multiple 1+ reactions of this patient to 13 test substances, including benzoic acid and dodecyl gallate, the relevance of the reaction to benzyl alcohol is, however, questionable.

A female patient who suffered from peri-genital pruritus and recurrent erythematous oedema after the application of different topical antimycotics and antibiotics, reacted in the patch test to numerous substances, including *p*-phenylenediamine, benzocaine, parabene mix, several fragrances and balsam of Peru, and also to sever-

al external agents preserved with benzyl alcohol and to 5% benzyl alcohol in petrolatum (Sestini et al. 2004).

Reactions to benzyl alcohol were reported without giving details in 2 patients who reacted following an injection of botulinum toxin A preparations containing benzyl alcohol with dermatitis of the eyelids (Amado and Jacob 2007).

Repeated insult patch tests with benzyl alcohol preparations in a mixture of diethyl phthalate/ethanol (3:1) were carried out in groups of 46 to 110 volunteers. For induction, 0.3 ml of the respective preparation was applied occlusively to the upper arm or back in a 25 mm test chamber for 24 hours on 9 alternate days over a period of 3 weeks. After a 10 to 14-day treatment-free interval, a corresponding challenge test was performed on a previously untreated area of skin with readings after 24 and 48 hours and once more after 72 or 96 hours. The substance concentrations used and the amount applied per cm^2 were 20%/23 622 µg (group 1); 15%/17 717 µg (group 2); 7.5%/8858 µg (group 3); 5%/5906 µg (group 4) and 3%/3543 µg (group 5). In group 1, oedematous reactions were found in 7 volunteers during the induction phase. In 4 of them, the induction treatment was discontinued, as they also reacted in a repeated test. At the challenge, 2 and 3 of the 56 volunteers had 2+ or 1+ reactions; these were also reproducible in one of the volunteers in each case in a challenge repeated both on an occlusive and a semi-occlusive basis. Neither of the two volunteers, however, reacted to a repeated open application test (ROAT) applied to the forearm 3 times daily for 5 days. Five of the 46 volunteers in group 2 had oedematous reactions during the induction phase. In 2 of these volunteers, a reaction occurred also on testing a previously untreated area, which led to the discontinuation of the induction treatment. In this test, one of the volunteers had a questionable (+/–) transient reaction, so that induction was continued. The challenge treatment produced 2+ reactions in 4 volunteers and a 1+ or questionable reaction in 1 volunteer in each case. The 2+ and 1+ reactions were regarded by the investigators as an expression of sensitization. In group 3, 1 of the 110 volunteers developed pronounced irritation, which made the removal of the test material necessary. This volunteer also had a 2+ reaction after challenge treatment in the 96-hour reading. Two other volunteers reacted to the challenge treatment in the same way. Repeated occlusive and semi-occlusive challenge treatment produced a reaction in 1 of these 3 volunteers on all test areas, which was regarded as sensitization, whereas the two others developed a very minor erythematous reaction only to the occlusive challenge. Two of the 101 volunteers in group 4 produced an oedematous reaction during induction. As repeated testing on an untreated area also produced a reaction, further treatment was discontinued. The challenge treatment produced a 3+ oedematous reaction in 1 of the 2 volunteers and a 1+ oedematous reaction in the other, which the investigators considered to be the expression of previously existing sensitization. In group 5, no reaction occurred in any of the 107 volunteers (Scognamiglio et al. 2012). It is not specified whether the volunteers were tested prior to the investigation for already existing sensitization to benzyl alcohol.

A maximization test carried out with one-day intervals between each of a total of 5 48-hour applications of a 10% benzyl alcohol preparation in petrolatum did not lead to sensitization in any of the 25 volunteers (documentation "Benzylalkohol" 2006, available in German only; Nair 2001; Scognamiglio et al. 2012).

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

Based on a saturation vapour pressure of 0.13 hPa at 25 °C, a saturation concentration of 567 mg/m³ (126 ml/m³) is obtained for benzyl alcohol. It can therefore be assumed that, independent of the generation of an exposure atmosphere above 500 to 600 mg benzyl alcohol/m³ (111–133 ml/m³), equilibrium exists between the aerosol and vapour phase. At concentrations markedly below these levels, benzyl alcohol is presumably present mainly in vapour form.

In the documentation from 2006 (documentation "Benzylalkohol" 2006, available in German only), an 8-hour LC_{50} of 1000 ml/m³ (4492 mg/m³) is reported for rats. Another study gives an LC_{50} of 1059 mg/m³, after 4 rats inhaled a benzyl alcohol aerosol for 6 hours. The animals that died were found to have asthenia, hyperthermia, tremor and disturbed locomotion and paresis in the hind limbs. Discoloration in the nasal region occurred in all animals of the high concentration group. Neither substance-related effects nor gross-pathological changes could be found in the animals that had inhaled 182, 357 or 781 mg benzyl alcohol/m³ (no further details; Katz and Fennikoh 1983). In all other short-term inhalation studies with exposure times between 4 and 6 hours, no mortality was observed; the investigated concentrations were between 61 ml/m³ (274 mg/m³) and 4178 mg/m³. In a valid study carried out according to OECD Test Guideline 403, in which rats were exposed nose-only to benzyl alcohol concentrations of 4178 mg/m³ for 4 hours, unkempt fur and slower breathing was described; this was interpreted as mild sensory irritation in the upper respiratory tract (Bayer AG 1990 a).

No deaths occurred in rats in a 4-week inhalation study (see Section 5.2.1) at concentrations of up to 1072 mg/m³.

5.1.2 Oral administration

There are no new data available.

5.1.3 Dermal application

There are no new data available.

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

In a study, groups of 4 rats were exposed by inhalation to benzyl alcohol concentrations of 0, 190, 334, 643 or 1119 mg/m³ for 6 hours a day, on 3 days. The recovery period was 16 days. In the high concentration group one animal died after the first exposure, a further animal became moribund and was killed after the second exposure. The clinical symptom observed in these animals was a disturbance in locomo-

tor coordination of the hind limbs. In all animals of the group exposed to 1119 mg/m³ and in 2 animals of the group exposed to 334 mg/m³, discoloration of the nasal region was found. There were no gross-pathological changes in any group (no other details; Katz and Fennikoh 1983).

In a 2-week study in which groups of 6 male rats were exposed in whole-animal chambers to benzyl alcohol concentrations of 971 to 1214 mg /m³ for 4 hours, no clinical symptoms or pathological findings were observed (documentation "Benzylalkohol" 2006, available in German only). The study gives no details of a histopathological evaluation, although microscopic examinations are reported in an additional short-term oral toxicity study. It is therefore possible that a microscopic examination was carried out also in the 2-week study. However, no information is provided as to whether the lungs were examined.

In a 4-week study carried out according to OECD Test Guideline 412, groups of 10 male and 10 female Sprague Dawley rats were exposed nose-only to benzyl alcohol concentrations of 0, 41, 102, 290 or 1072 mg/m³ for 6 hours a day, on 5 days per week. The exposure atmosphere was generated from the undiluted substance. The mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) could be determined only for the concentration of 1072 mg/m³ (MMAD: 3.3 µm; GSD: 2.39), a mass balance was not carried out. The parameters investigated included the number of survivors, body weights, food consumption, haematology and coagulation, serum chemistry, ophthalmic examinations, organ weights, and gross-pathological and histopathological changes. Clinical symptoms such as local irritation were not described. The only significant effect, a concentration-dependent increase in the relative weight of the epididymis, was found at 290 and 1072 mg/m³.

In Table 2, the histological changes after exposure to 1072 mg/m³ and those in the control group are given. The effect with the highest incidence was minimal mononuclear infiltrates in the lungs in 5 of 10 males from the high concentration group, but not in any animals of the control group. Lung weights were decreased in a concentration-dependent but not significant manner. In addition, in the males of the high concentration group, slight hyperplasia (2/10) of the squamous cells (nasal level I) and minimal acute (1/10) and subacute (1/10) inflammation (nasal level II) were seen in sections from the nasal cavity; these were found in the control group with a lower incidence. Histological examination of the lymph nodes in the respiratory tract of the males revealed minimal hyperplasia (1/10, mandibular region) and haemorrhage (1/10, 2/9, mandibular and mediastinal region) in the animals of the 1072 mg/m³ group, and in either no or only one animal of the control group.

In one of the females of the high concentration group, a slight increase in eosinophilic and mononuclear infiltrates was found in the lungs, but in no animal of the control group. Examination of the sections from the nasal cavities revealed minimal hyperplasia of squamous cells (2/10, nasal level I), minimal subacute inflammation (2/10, nasal level I) and minimal mononuclear infiltrates (2/10 and 1/10, nasal level I and II) with a higher incidence compared with that in the control group. Minimal hyperplasia was seen in the lymph nodes of the mandibular region in 3 of 10 females, but in none of the controls. Histopathological examinations were carried out only in the high concentration group, in which the exposure was in aerosol form.

Table 2 Histological changes after 4-week inhalation exposure to 1072 mg benzyl alcohol/m³ (The Personal Care Products Council 2010)

	♂		♀	
Concentration (mg/m³)	0	1072	0	1072
Number of investigated animals	10	10	10	10
lungs				
hyperplasia (type II PC[a])	0	1	0	0
minimal		1		
hypertrophy (bronchiolar)	0	1		
slight		1		
infiltrates (eosinophilic)	2	0	0	1
minimal	2			
slight				1
infiltrates (mononuclear)	**0**	**5**	0	1
minimal		**5**		
slight				1
nasal cavity (nasal level I)				
hyperplasia (squamous cells)	1	2	0	2
minimal				2
slight	1	2		
inflammation (subacute)	3	1	0	2
minimal	2	1		2
slight	1			
infiltrates (mononuclear)			1	2
minimal			1	2

Table 2 (continued)

	♂		♀	
Concentration (mg/m³)	0	1072	0	1072
nasal cavity (nasal level II)				
inflammation (acute)	0	1		
minimal		1		
inflammation (subacute)	0	1		
minimal		1		
infiltrates (mononuclear)			0	1
minimal				1
nasal cavity (nasal level III)				
inflammation (subacute)	1	0	0	0
minimal	1			
nasal cavity (nasal level V)				
inflammation (nasolacrimal duct)	1	0	0	0
slight	1			
LN[b] (mandibular)				
hyperplasia (lymphatic)	0	1	0	3
minimal		1		3
haemorrhage	0	1		
slight		1		
LN[b] (mediastinal)				
haemorrhage	1	2[c]		
minimal	1	2		

[a] PC: pneumocytes;
[b] LN: lymph nodes;
[c] only 9 instead of 10 lymph nodes examined; planes of section IV and VI were normal in ♂ and ♀

All findings were regarded as not substance-related and the NOAEC (no observed adverse effect concentration) was established at the highest concentration tested of 1072 mg/m^3 (The Personal Care Products Council 2010).

The study wascritically evaluated by the Commission. It was noticed that: The study was not carried out and described in accordance with OECD Guideline 39 (2009). No real-time monitoring to demonstrate the presence of aerosols was carried out. There are no reproducible data available for the measurement of particles. The concentration was determined using two wash bottles arranged in series, where only the first was analyzed, without ensuring that the second wash bottle was free of the test substance. The wash bottles used in the measurement system were filled with volatile isopropanol. Its evaporation can lead to volumetric errors, and the exposure concentration calculated is then false. There are no data regarding the validation of the method or information about the collection efficiency. Furthermore, the inhalation chamber was operated at reduced pressure, as a result of which the concentration in the chamber could be influenced by the inflow of air from outside. Investigations of the rebreathing of used air and the exchange of exhaust air are lacking. The Commission is particularly critical of the lack of histopathological examinations in the middle and low concentration groups exposed to the vapour.

The inhalation study was not carried out in accordance with present-day standards in all aspects; this fact has been taken into account in the assessment of the study. Nevertheless, the study can be used to derive a threshold value.

Conclusions:

The microscopic changes in the respiratory tract, especially in the lungs, in the females and with an increased incidence in the males at 1072 mg benzyl alcohol/m^3 represent, in the view of the Commission, at least the beginning of an effect, and the concentration of 1072 mg/m^3 is therefore considered to be the LOAEC (lowest observed adverse effect concentration). As no histopathological examinations were carried out in the animals of the middle and low concentration groups, the course of the concentration–effect relationship is not evident. However, in view of the low severity of the microscopic changes in the respiratory tract at the highest tested concentration, the NAEC (no adverse effect concentration) can be estimated as the LOAEC/3 (ECETOC 2003) to be in the range of 300 mg/m^3.

5.2.2 Oral administration

In a valid 16-day study, groups of 5 male and 5 female F344/N rats and B6C3F1 mice were given oral doses of benzyl alcohol of 0, 125, 250, 500, 1000 or 2000 mg/kg body weight and day for 12 days. In the high dose group, all rats and mice died. At 1000 mg/kg body weight and day, 2/5 male and 3/5 female rats and 1/5 male and 2/5 female mice died. In the two high dose groups, lethargy and blood around the mouth and nose, subcutaneous haemorrhage, and blood in the urine, bladder and gastrointestinal tract occurred. Animals treated with lower doses (125, 250, 500 mg/kg body weight and day), displayed no clinical symptoms and there were no histopathological findings attributable to the administration of benzyl alcohol (NTP 1989).

As described in the documentation from 2006 (documentation "Benzylalkohol" 2006, available in German only), oral benzyl alcohol doses of 50, 100, 200, 400 or 800 mg/kg body weight and day (on 5 days a week) for 13 weeks produced symptoms of intoxication in F344/N rats such as lethargy or laboured breathing and histopathological changes in the brain, thymus, skeletal muscles and kidneys in the high dose group. In females given 200 mg/kg body weight and day and 400 mg/kg body weight and day, the relative body weight gains were reduced (by 7% and 9%, respectively, compared with the values in the controls). In the males, this was found at 800 mg/kg body weight and day (7% reduction compared with in the controls). The body weight gains were not reduced in F344/N rats after doses of 200 and 400 mg/kg body weight and day in the 2-year study with benzyl alcohol (NTP 1989). For this reason, the effect at 200 and 400 mg/kg body weight and day in the 13-week study is not considered adverse (OECD 2004).

In mice, after oral benzyl alcohol doses of 0, 50, 100, 200, 400 or 800 mg/kg body weight and day for 13 weeks (on 5 days per week), clinical symptoms of intoxication occurred in both sexes only in the high dose group. The relative body weight gains in the females were reduced at dose levels of 200 mg/kg body weight and day and above (by 4.8% compared with the values in the controls), and at 400 mg/kg body weight and day and above in the males (by 4.7% compared with in the controls) (documentation "Benzylalkohol" 2006, available in German only). The treatment of male and female B6C3F1 mice in the 2-year study (NTP 1989) with 100 and 200 mg benzyl alcohol/kg body weight and day had no effect on the body weight gains of these animals, so that the slight decrease at 200 mg/kg body weight and day in the 13-week study is not considered adverse (OECD 2004).

In the 2-year oral studies (NTP 1989), F344/N rats and B6C3F1 mice were treated with benzyl alcohol on 5 days per week. The NOAEL (no observed adverse effect level) in rats was 400 mg/kg body weight and day, the highest dose that was tested. In B6C3F1 mice, the NOAEL was the highest tested dose of 200 mg/kg body weight and day (documentation "Benzylalkohol" 2006, available in German only).

Conclusions:

In both mice and rats, the most sensitive end point for systemic effects is the reduction in body weight gains. The 2-year studies yielded a NOAEL of 200 mg/kg body weight and day for mice, and 400 mg/kg body weight and day for rats.

5.2.3 Dermal application

There are no new data available.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

New data for skin irritation in rabbits and guinea pigs (Nair 2001) and from in vitro studies (Cotovio et al. 2005; ECHA 2014) have been published since the documentation from 2006 (documentation "Benzylalkohol" 2006, available in German only).

A study in nude mice has not been used in the evaluation of dermal irritation. A summary of all available studies is shown in Table 3.

Irritation of the skin by benzyl alcohol in vivo was found only in inadequate studies: in some cases details of the observation period and method of covering the treated area are lacking, so that an evaluation of the results is difficult (Opdyke 1973). Furthermore, in an open epicutaneous test, the result was judged as positive as soon as 25% of the tested animals displayed slight erythema formation after an exposure period of 24 hours or 21 consecutive days (Klecak et al. 1977). In one study with rabbits, benzyl alcohol was assessed as being moderately irritating; however, benzyl alcohol was applied twice, and the primary irritation index was made up of several end points (Motoyoshi et al. 1979). Both the evaluation methods and the multiple applications do not meet present-day requirements. All in all, these studies cannot be considered relevant to the evaluation.

In all the other available in vivo studies in rabbits, guinea pigs and miniature swine, one of which was carried out according to OECD Test Guideline 404 (Bayer AG 1990 b), benzyl alcohol was not found to be irritating to the skin.

From in vitro studies with human epidermis, benzyl alcohol cannot be concluded to cause skin irritation. Although one of the two studies yielded a positive result, this was regarded as being falsely positive without giving any reasons (ECHA 2014).

Conclusions:

On the basis of the available in vitro and in vivo data, benzyl alcohol is not regarded as irritating to the skin.

5.3.2 Eyes

In the documentation from 2006 (documentation "Benzylalkohol" 2006, available in German only), benzyl alcohol is described as irritating to the eyes. This has been confirmed by new data. In a study carried out in accordance with OECD Test Guideline 405, benzyl alcohol is described as irritating in the eyes of rabbits (ECHA 2014). All the available data for the irritating effects of benzyl alcohol in the eyes are shown in Table 4.

Conclusions:

Based on the available data with rabbits, benzyl alcohol is regarded as irritating to the eyes.

Table 3 Summary of the studies of the irritating effects of benzyl alcohol on the skin

Test system, species (number)	Exposure time [h]	Examination time [h]	Concentration/method	Result	References
In vivo					
rabbit	24	no other data	0.05 ml/no other data	slightly irritating	Smyth et al. 1951
guinea pig	24	no other data	undiluted/no other data	irritating	Opdyke 1973
guinea pig	24	24	0.1 ml (10%)/no other data	not irritating	Sharp 1978
rabbit (6); guinea pig (6)	1st application: 24 2nd application: 24	24, 48, 72	0.1 g (100%)/ rabbit: open guinea pigs: no other data	rabbit: moderately irritating[a] guinea pigs: not irritating[a]	Motoyoshi et al. 1979
miniature swine (6)	48	no other data	0.05 g/semi-occlusive	not irritating	Motoyoshi et al. 1979
rabbit (3)	4	1, 24, 48, 72 hours, and 7 and 14 days	0.5 ml (100%)/semi-occlusive	not irritating[b]	Bayer AG 1990 b
guinea pig (6–8)	24	24	30%, 10%/open	30%: irritating[c] 10%: not irritating	Klecak et al. 1977
guinea pig (6–8)	repeated application, 21 days, no other data	24	3%, 1%/open	3%: irritating[c] 1%:not irritating	Klecak et al. 1977
mouse	24	no other data	10%/occlusive	highly irritating	Lashmar et al. 1989
rabbit	24	24, 72	0.3 ml (10% in squalane)/occlusive	not irritating[d]	Nair 2001
guinea pig	repeated application, 3 days, 24 hours	24	0.3 ml (10% in squalane)/open	not irritating to slightly irritating[e]	Nair 2001

Table 3 (continued)

Test system, species (number)	Exposure time [h]	Examination time [h]	Concentration/method	Result	References
In vitro					
human epidermis	3 min, 60 min	no other data	50 µl (undiluted)	positive[f)]	ECHA 2014
human epidermis	no other data	no other data	10 µl	not irritating	Cotovio et al. 2005

[a)] primary irritation index based on: extent of blood vessel distension, oedema formation, erythema formation, blue colouring of the capillaries after injection of 40 mg/g "Evans Blue"
[b)] erythema score (24, 48, 72 hours; maximum score 4) animal 1: 0; animal 2: 0; animal 3: 0.6; oedema score (24, 48, 72 hours; maximum score 4) animal 1: 0; animal 2: 0; animal 3: 0; in accordance with OECD Test Guideline 404
[c)] given as the minimal irritating concentration, at which at least 25% of the animals produced slight erythema
[d)] score of 0 (maximum score: 8)
[e)] score 0.4 (maximum score: 4)
[f)] the authors judged the result to be falsely positive

Table 4 Summary of the studies of the irritating effects of benzyl alcohol in the eyes

Test system, species (number)	Exposure time	Examination time	Quantity, concentration/ method	Result	References
rabbit (not specified)	no data	no data	750 µg/no other data	highly irritating to the eyes	NTP 1989
rabbit (3)	24 hours	1, 24, 48, 72 hours, and 7, 14 and 21 days	100 µl (100%)/rinsing out after 24 hours	moderately irritating to the eyes[a), b)]	Bayer AG 1990 b
rabbit (not specified)	no data	no data	4% aqueous solution/no other data	not irritating to the eyes	OECD 2004
rabbit (2)	7 days	1, 24, 48 hours, and 7 days	100 µl (100%)	moderately irritating to the eyes	ECHA 2014
rabbit (3)	without rinsing out	1, 24, 48, 72 hours, and 7 and 18 days	100 µl (100%)	irritating to the eyes[b), c)]	ECHA 2014

[a)] corneal opacity (24, 48, 72 hours; maximum score 4): animal 1: 1; animal 2: 1; animal 3: 1; iris (24, 48, 72 hours; maximum score 2): animal 1: 0; animal 2: 0.3; animal 3: 0; redness (24, 48, 72 hours; maximum score 3): animal 1: 2; animal 2: 2; animal 3: 2; swelling (24, 48, 72 hours; maximum score 4): animal 1: 1; animal 2: 0.6; animal 3: 0.6; exudation (24, 48, 72 hours; maximum score 3): animal 1: 0.6; animal 2: 1.3; animal 3: 1; effects reversible, after 3 weeks at the latest

[b)] in accordance with OECD Test Guideline 405

[c)] corneal opacity (24, 48, 72 hours; maximum score 4): animal 1: 2; animal 2: 2; animal 3: 2; iris (24, 48, 72 hours; maximum score 2): animal 1: 1; animal 2: 1; animal 3: 1; redness (24, 48, 72 hours; maximum score 3): animal 1: 2; animal 2: 3; animal 3: 2–3; swelling (24, 48, 72 hours; maximum score 4): animal 1: 1–2; animal 2: 3; animal 3: 2; effects reversible, by day 18 at the latest

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

In a local lymph node assay (LLNA) in female CBA/Ca/Ola/Hsd mice, a 3-fold increase in lymphocyte proliferation was not obtained after the application of 2.5%, 5%, 10%, 25% and 50% benzyl alcohol in diethyl phthalate/ethanol (3:1). This means that no EC3 value could be determined and the result was evaluated as negative. At concentrations of 10% and 25%, the hexyl cinnamaldehyde included as positive control produced a more than 3-fold increase in lymphocyte proliferation (Scognamiglio et al. 2012).

Benzyl alcohol was also included in vitro in a screening test in cultures of mouse Hepa1C1C7 hepatoma cells to determine the luciferase activity after activating the antioxidant response element without metabolic activation ("KeratinoSens assay") and in a modified procedure for detecting potential prohaptens by means of the addition of an S9 fraction from Aroclor-induced rat liver. The results of both tests were negative (Emter et al. 2010; Natsch and Emter 2008; Natsch and Haupt 2013). The results for benzyl alcohol were negative also in a similar in vitro experiment using a human skin cell line (HaCaT) and in studies investigating chemical reactivity by measuring glutathione depletion (McKim et al. 2010).

A no expected sensitization induction level (NESIL) of 5900 μg/cm^2 was derived for benzyl alcohol (IFRA 2009); on the basis of quantitative structure-activity relationship (QSAR) observations, the substance was classified, however, as not reactive, and any sensitization occurring in spite of this was attributed to possible unnamed impurities (Safford et al. 2011). In a comparison of mutagenic and (contact-) sensitizing substances, benzyl alcohol was listed as a sensitizer on the basis of internal company studies (maximization test or LLNA) not documented in any greater detail (Wolfreys and Basketter 2004).

Conclusions:

Overall, the new experimental data do not indicate skin sensitizing potential.

5.4.2 Sensitizing effects on the airways

There are no new data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

There are no studies specifically investigating the effects of benzyl alcohol on fertility. In the 2-year studies (NTP 1989) with repeated oral administration to rats and mice, no effects on the reproductive organs were observed.

5.5.2 Developmental toxicity

In the documentation from 2006, the NOAEL for developmental toxicity in mice was given as 550 mg/kg body weight and day. Teratogenicity was not investigated. Because of reduced birth weights and marked maternal toxicity, the LOAEL (lowest observed effect level) given in a second study was 750 mg/kg body weight and day. These studies are not available as original reports (documentation "Benzylalkohol" 2006, available in German only).

Since then published developmental toxicity studies on benzyl alcohol are not available as original reports and are only inadequately described. Benzyl alcohol in corn oil was administered subcutaneously from gestation days 6 to 17 in doses of 100, 250 or 500 mg/kg body weight to groups of 25 Sprague Dawley rats. A range-finding study revealed significant maternal mortality at 1000 mg/kg body weight and day. In the main study, the authors reported a NOEL for maternal toxicity of 250 mg/kg body weight and day because of decreased body weights (8%) and reduced body weight gains (17%), and a NOEL for foetal toxicity of 250 mg/kg body weight and day as a result of reduced foetal body weights relative to the weights for control foetuses. Investigation of the soft tissue, skeleton and other parameters in the foetuses did not reveal any substance-related effects up to the high dose of 500 mg/kg body weight and day (FDA 2009).

Benzyl alcohol was administered subcutaneously to groups of 23 New Zealand White rabbits in doses of 100, 250 or 400 mg/kg body weight from days 6 to 18 of gestation. In a range-finding study, significant maternal mortality was found after doses of 1000, 750 and 650 mg/kg body weight and day. In the main study, at 400 mg/kg body weight and day, mortality (7/23), decreased body weights (7%), reduced body weight gains (31%), and an increase in clinical symptoms (for example decreased activity, breathing difficulties) were observed in the dams. In the middle dose group, mortality (2/23) and reduced body weight gains (20%) were found. No maternal toxicity occurred after 100 mg/kg body weight and day. In the foetuses, body weights were decreased (by 9% for both sexes combined), presumably as a result of the maternal toxicity. The authors gave a NOEL of 250 mg/kg body weight and day. No teratogenic effects could be found at the high dose of 400 mg/kg body weight and day (FDA 2009).

Conclusions:

In the available studies, although they are inadequately described, the most sensitive end point for benzyl alcohol was found to be decreased body weights of the foetuses at maternally toxic doses after gavage administration of 750 mg/kg body weight and day in mice, and subcutaneous administration of 500 and 400 mg/kg body weight and day in rats and rabbits. No teratogenicity occurred in the study with subcutaneous administration. In the oral study, teratogenicity was not tested.

5.6 Genotoxicity

5.6.1 In vitro

Since the documentation from 2006 (documentation "Benzylalkohol" 2006, available in German only) new data have been published for the mutagenicity in bacteria, the induction of micronuclei and the formation of DNA double strand breaks caused by benzyl alcohol. There was no increase in mutations in bacterial strains after incubation with 100 to 5000 µg benzyl alcohol/plate, either with or without metabolic activation (Fall et al. 2007). In a comet assay under alkaline conditions, human lymphocytes were incubated with benzyl alcohol in concentrations of 1 to 50 nM both with and without metabolic activation. The results were evaluated as positive at 25 and 50 nM, although without a dose–response relationship and without giving data for cytotoxicity (Demir et al. 2010). In CHL (Chinese hamster lung) cells and TK6 cells, 3-hour incubation with 10 mM benzyl alcohol under metabolic activation did not increase the micronucleus frequency. No cytotoxicity was found. Further details of the study methods are lacking (Fowler et al. 2012). All available data for the genotoxicity of benzyl alcohol in vitro are summarized in Table 5 (see also documentation "Benzylalkohol" 2006, available in German only).

5.6.2 In vivo

Since the documentation from 2006 (documentation "Benzylalkohol" 2006, available in German only), a wing somatic mutation and recombination test (SMART) has been carried out in Drosophila melanogaster with benzyl alcohol. This test yielded positive results in trans-heterozygous wings (mwh/flr3) at a concentration of 50 mM benzyl alcohol (Demir et al. 2008). A test for sex-linked recessive lethal mutations (SLRL) in the germ cells of Drosophila melanogaster at comparable concentrations (46.1 mM, 73.8 mM), however, did not reveal genotoxic effects for benzyl alcohol (Foureman et al. 1994). A summary of the studies of the genotoxicity of benzyl alcohol in vivo is given in Table 6 (see also documentation "Benzylalkohol" 2006, available in German only).

Summary and conclusions:

Studies of DNA repair using the rec assay/pol $A^{+/-}$ assay in bacteria yielded a positive and a negative result. In both studies data for cytotoxicity were not given, therefore it is possible that the result was falsely positive. The induction of DNA strand breaks was tested using alkaline elution and an alkaline comet assay. DNA double strand breaks were found with metabolic activation in primary rat hepatocytes at the high concentration (1084 mg/ml). A re-evaluation using improved assessment criteria indicated the result was falsely positive. A positive result using an alkaline comet assay was obtained in human lymphocytes in the two high dose groups (2710, 5420 µg/ml) without a dose–response relationship. Data for cytotoxicity are lacking, so that a falsely positive result likewise cannot be excluded.

Table 5 The genotoxicity of benzyl alcohol in vitro

End point	Test system	Concentration	Effective concentration	Result		Remarks	References
				–m.a.	+m.a.		
DNA repair (pol $A^{+/-}$ assay)	Escherichia coli	10, 25, 50 µl (without solvent)	–	–	–	controls: dimethyl sulfate, ampicillin and colistin, no data for cytotoxicity	Fluck et al. 1976
DNA repair (rec assay)	Bacillus subtilis M45 (rec–), H17 (rec+)	20 µl/plate	20 µl/plate	+[a)]		DNA damage: weakly positive, no data for cytotoxicity	Kuroda et al. 1984; Yoo 1985
gene mutation (bacterial mutagenicity test)	Escherichia coli Wp2 uvrA	–	–	–[a)]		positive control: AF-2, cytotoxicity negative	Kuroda et al. 1984; Yoo 1985
gene mutation (bacterial mutagenicity test)	Salmonella typhimurium TA100	100, 250, 500, 1000 µg/plate	–	–[a)]		positive control: methylmethane sulfonate, cytotoxicity negative	Ball et al. 1984
gene mutation (bacterial mutagenicity test)	Salmonella typhimurium TA98, TA100, TA1535, TA1537	3 µmol/plate	–	–	–	positive controls: benz[a]pyrene, chrysene, benz[a]anthracene, perylene, β-naphthylamine, cytotoxicity negative	Florin et al. 1980
gene mutation (bacterial mutagenicity test)	Salmonella typhimurium TA92, TA94, TA98, TA100, TA1535, TA1537	10 000 µg/plate	–	–	–	preincubation method, cytotoxicity negative	Ishidate et al. 1984
gene mutation (bacterial mutagenicity test)	Salmonella typhimurium TA98, TA100, TA1535, TA1538	5 µl (no other data)	–	–[a)]		no data for cytotoxicity	Milvy and Garro 1976

Table 5 (continued)

End point	Test system	Concentration	Effective concentration	Result		Remarks	References
				–m.a.	+m.a.		
gene mutation (bacterial mutagenicity test)	Salmonella typhimurium TA98, TA100, TA1535, TA1538	100, 333, 1000, 3333, 5000, 6666 µg/plate	–	–	–	preincubation method, negative control: potassium chloride, positive controls: 9-aminoacridine hydrochloride, 4-nitro-o-phenylenediamine, tris(1,3-dichloro-2-propyl)phosphate, cytotoxicity negative	Mortelmans et al. 1986
gene mutation (bacterial mutagenicity test)	Salmonella typhimurium TA98, TA100	100, 500, 1000, 2500, 5000 µg/plate	–	–	–	positive controls: 2-nitrofluorene, sodium acid, 2-amineoanthracene	Fall et al. 2007
DNA DSB (alkaline elution[b)])	primary rat hepatocytes (liver perfusion)	108.4, 325.2, 1084 µg/ml (1, 3, 10 mM)	1084 µg/ml	n.i.	+/–	cytotoxicity negative, trypan blue staining without recovery time: ≥ 70%, trypan blue staining after 3 hours recovery: ≥ 70%, intracellular ATP content ≥ 50%, DNA DSB positive (Elia et al. 1994): increased by 2.5% relative to solvent control but less than positive control (40 Gy gamma radiation) DSB falsely positive (Storer et al. 1996): according to new evaluation criteria	Elia et al. 1994; Storer et al. 1996
DNA SB (alkaline comet assay)	human lymphocytes	108.4–5420 µg/ml (1–50 mM)	2710, 5420 µg/ml	n.i.	+	positive control: EMS, lymphocytes of two healthy volunteers, tail moment given,% tail DNA, not tail length, no data for cytotoxicity, no dose-response relationship	Demir et al. 2010

Table 5 (continued)

End point	Test system	Concentration	Effective concentration	Result		Remarks	References
				–m.a.	+m.a.		
sister chromatid exchange	CHO cells	16 to 4000 µg/ml	1250 µg/ml (–m.a.), 4000 µg/ml (+m.a.)	+[w]	+[w]	positive controls: mitomycin, cyclophosphamide, 4000 µg/ml (+m.a.): total number of chromosomes was 647 compared with 1045 in the solvent control, otherwise no cytotoxicity	Anderson et al. 1990
chromosomal aberration	CHL cells	1000 µg/ml	–	–	n.i.	cytotoxicity: by means of number of cells, not by mitotic index; no data for positive control, cytotoxicity negative	Ishidate et al. 1984, 1988
chromosomal aberration	CHO cells	50–5000 µg/ml	4000 µg/ml	–	+	positive controls: mitomycin, cyclophosphamide, +m.a.: cytotoxicity negative, –m.a.: 5000 µg/ml cytotoxicity (20 instead of 100 cells in metaphase)	Anderson et al. 1990
micronucleus test	CHL cells, TK6 cells	1084 µg/ml (10 mM)	–	n.i.	–	cytotoxicity: negative, 3-hour exposure, no other details	Fowler et al. 2012
gene mutation ($TK^{+/-}$ mutation test)	L5178Y mouse lymphoma cells	156–5000 µg/ml	4500 µg/ml	–	+	positive controls: EMS, 3-MC, significant positive effect at cytotoxic concentrations (RTG: 20%), at and above 5000 mg/ml lethal dose, no data for colony size	McGregor et al. 1988

[a] no details of metabolic activation; [b] lysis under neutral conditions; AF-2: furyl furamide; DSB: double strand breaks; Pol A^-: DNA polymerase of deficient strain; Pol A^+: DNA polymerase proficient strain; m.a.: metabolic activation; n.i.: not investigated; RTG: relative total growth ; SB: strand break; $+^w$: weakly positive

Table 6 The genotoxicity of benzyl alcohol in vivo

Test system	Species (number)	Dose, administration	Result	Remarks	References
Somatic cells					
SMART (Drosophila wing spot test)	Drosophila melanogaster	0, 0.1, 0.5, 1, 10, 25, 50 mM	+	positive control: EMS, 80 wings per group, trans-heterozygous wings (mwh/flr3): positive: 50 mM (small size spots, total mwh spots, total spots), balancer-heterozygous wings (mwh/TM3): positive: 1, 10, 50 mM (large size spots), no dose–response relationship	Demir et al. 2008
micronucleus test	mice, (6 ♂/group)	0, 50, 100, 200 mg/kg body weight, intraperitoneal	–	bone marrow cells, positive control: MMC, sampling time: 24 hours, PCE (%): 0: 48.8 ± 6.2 50: 55.5 ± 4.0 100: 51.8 ± 9.5 200: 48.7 ± 5.2 no cytotoxicity	Hayashi et al. 1988
Germ cells					
SLRL (test for x-chromosomal recessive lethal mutation)	Drosophila melanogaster	feeding: 0, 46.1 mM (5000 mg/l), injection: 0, 73.8 mM (8000 mg/l)	–		Foureman et al. 1994

EMS: ethylmethane sulfonate; MMC: mitomycin C; mwh: multiple wing hair; PCE: polychromatic erythrocytes; SLRL: sex-linked recessive lethal mutations; SMART: somatic mutation and recombination test

The results of gene mutation tests in vitro in different strains of Salmonella typhimurium and Escherichia coli Wp2 uvrA were negative. The $TK^{+/-}$ mutation test in mouse lymphoma cells with metabolic activation yielded a positive result, however at clearly cytotoxic concentrations, so that the effect can be attributed to the toxicity of benzyl alcohol and not to its mutagenic potential. In vivo, although a positive result was obtained in somatic cells tested for gene mutations using the wing spot test (SMART) in Drosophila melanogaster at the high concentration (50 nM), a negative result was found in the test for sex-linked recessive lethal mutations in germ cells at a comparable concentration.

A test for sister chromatid exchange in CHO cells (a cell line derived from Chinese hamster ovary) yielded a positive result without metabolic activation at a concentration of 1250 µg/ml without detectable cytotoxicity. With metabolic activation, a positive result was obtained at 4000 µg/ml. The number of chromosomes evaluated was reduced compared with that in the solvent controls, which can be interpreted as an indication that the concentration range was cytotoxic. In an inadequately documented study (there was, for example, no data regarding a positive control) for clastogenicity of benzyl alcohol, no increase in chromosomal aberrations was detected in CHL cells at a concentration of 1000 µg/ml without metabolic activation. In a second study with CHO cells, an increase in chromosomal aberrations was found at high, yet not cytotoxic concentrations of 4000 µg/ml with metabolic activation. Other cytogenetic studies in vitro and in vivo yielded negative results. For example, in a micronucleus test in CHL and TK6 cells with metabolic activation, no increase in the incidence of micronuclei at the non-cytotoxic concentration of 1084 µg/ml was found. However, details of the experimental conditions are lacking. This result was confirmed in vivo in the bone marrow cells of mice. After intraperitoneal injection of benzyl alcohol in doses of up to 200 mg/kg body weight, the incidence of micronuclei was not increased compared with that in the controls; the positive control, mitomycin C, produced the expected increase in micronuclei. No cytotoxicity was found after the administration of benzyl alcohol, therefore a falsely negative result cannot be excluded. However, in the case of benzoic acid, the metabolite of benzyl alcohol, there was likewise no evidence of a clastogenic effect in vivo (see supplement "Benzoic acid and alkali benzoates" 2017).

The in vitro and in vivo studies of benzyl alcohol did not reveal mutagenic effects. Clastogenic effects occurred only in vitro at high concentrations. In vivo, no clastogenicity was found in micronucleus tests; however, there was no cytotoxicity up to the highest tested dose. For the main metabolite of benzyl alcohol, benzoic acid, no evidence of a clastogenic effect in vivo was found. To summarize, no genotoxic effects in somatic cells or in germ cells are to be suspected for benzyl alcohol.

5.7 Carcinogenicity

In the NTP two-year studies with oral administration to rats and mice, no increases in tumour incidences were observed (documentation "Benzylalkohol" 2006, available in German only). There are still no new data available.

5.8 Other effects

Benzyl alcohol produced necrosis and apoptosis in cells of the retinal pigment epithelium in vitro (Chang et al. 2011). In vivo studies in the rabbit eye with intravitreal injection of 0.073%, 0.222% and 0.733% benzyl alcohol revealed changes in the outer retina including the loss and shortening of outer segments and photoreceptors (Morrison et al. 2006). Intravitreal injection of 0.1 ml benzyl alcohol into the eyes of rabbits produced structural and functional changes mainly in the inner retinal layer. The most severe damage was found in the ganglion cell layer, and in the inner and outer nuclear layer (Macky et al. 2007). Examination of the eye with a light microscope after intravitreal injection of the pharmaceutical substance triamcinolone hexacetonide containing 0.132% benzyl alcohol as a preservative revealed necrosis and atrophy of the retina and structural damage in the photoreceptors (Li et al. 2008). In contrast, after the injection into the rabbit eye of 0.1 ml (0.99 mg) benzyl alcohol, no morphological or functional changes could be found (Ruiz-Mereno et al. 2007).

6 Manifesto (MAK value/classification)

The critical effect is the local irritation in the lungs of rats with minimal hyperplasia of type II pneumocytes and slight bronchiolar hypertrophy, particularly with mononuclear infiltrates. The main systemic effect is reduced body weight gains.

MAK value. No suitable data in humans are available for the derivation of a MAK value. For benzyl alcohol, the NOAEL for systemic toxicity was found to be 200 mg/kg body weight and day in the mouse and 400 mg/kg body weight and day in the rat after 2-year oral administration on 5 days per week. The following toxicokinetic data are taken into consideration for the extrapolation of these NOAELs to a concentration in workplace air: the species-specific correction values for the mouse and the rat (1:7 and 1:4), the demonstrated very good oral absorption (100%), the body weight (70 kg) and respiratory volume (10 m^3) of the person, and the assumed 100% absorption by inhalation. The concentrations calculated from this are 200 mg/m^3 (44 ml/m^3) and 700 mg/m^3 (155 ml/m^3), respectively.

In addition to its systemic toxicity, however, attention has to be paid especially to the local effects of benzyl alcohol. Data in humans (BIBRA 1991) and rabbits show that the substance is irritating to the eyes. Furthermore, in animal studies, irritative effects were reported after short-term inhalation exposure (lacrimation at 450 mg/m^3, discolored nasal region at 1059 mg/m^3, slower breathing at 4178 mg/m^3) and after medium-term inhalation exposure (discolored nasal region at 334 mg/m^3 and 1119 mg/m^3).

In the documentation from 2006 (documentation "Benzylalkohol" 2006, available in German only), no MAK value could be established as data for the determination of a concentration without irritative effects after inhalation exposure were lacking. In the meantime, a 4-week inhalation study with rats is available (The Personal Care Products Council 2010). Although the study has some methodological deficiencies and does not meet present-day standards in all aspects, it is considered adequate for

the derivation of a threshold value. On the basis of microscopic changes in the respiratory tract (especially in the lungs) after concentrations of 1072 mg/m³, a NAEC (1:3) in the range of 300 mg benzyl alcohol/m³ can be estimated. At this concentration, benzyl alcohol can be present in vapour form (67 ml/m³).It is not evident from the available data whether the effects in the lungs increase with longer exposure duration, thus the long-term NAEC (1:6) is therefore in the range of 11 ml/m³. As this NAEC was obtained from animal studies (animal–human extrapolation 1:2), a MAK value of 5 ml/m³ (22 mg/m³) can be derived in accordance with the procedure of the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (see Section I of the List of MAK and BAT Values) and the preferred value approach.

Peak limitation. Because the substance causes local irritation, Peak Limitation Category I applies for benzyl alcohol. The irritation in the lungs was only of minimal to slight severity at the highest concentration tested of 1072 mg/m³. As the lungs are the preferred target organ, and sensory irritation mainly affects the nose, it is assumed that the histopathological changes in the lungs observed in the 4-week inhalation study (The Personal Care Products Council 2010) are more dependent on the concentration–time product than on a higher short-term peak concentration.

Furthermore, from the NOAEC of 1072 mg/m³ in the nose of rats, a long-term NAEC (1:6) of 179 mg/m³ and from this a NAEC of 60 mg/m³ (13 ml/m³) for sensory irritation (1:3) is obtained according to Brüning et al. (2014). As a 2-fold increase in the MAK value would result in a concentration which is below this NAEC of 13 ml/m³ (10 ml/m³), an excursion factor of 2 has been set.

Prenatal effects. In two developmental toxicity studies with benzyl alcohol in mice with gavage administration, reduced body weights of the offspring accompanied by considerable maternal toxicity, such as increased mortality, and decreased body weights and body weight gains, were found after doses of 750 mg/kg body weight and day. The dose of 550 mg/kg body weight and day had no effects on the offspring. However, teratogenic effects were not investigated (OECD 2004). The systemic effects of benzoic acid, the main metabolite of benzyl alcohol, are similar to those of the salt, as the effects are mediated by the benzoate. For sodium benzoate, concentrations in air of 2345 (rat), 175 (mouse), 730 (rabbit) and 382 (hamster) mg/m³ were calculated from the NOAELs for developmental toxicity (supplement "Benzoic acid and alkali benzoates" 2017). On the basis of the molecular weights of sodium benzoate and benzyl alcohol the following concentrations in air are obtained for benzyl alcohol: 1760 (rat), 131 (mouse), 563 (rabbit) and 289 mg/m³ (hamster). These concentrations are therefore higher than the MAK value of 22 mg/m³ by factors of 80 (rat), 6 (mouse), 25 (rabbit) and 12 (hamster). As, in the mouse study 750 mg/kg body weight and day was the highest dose and therefore the true NAEL (no adverse effect level) is higher, and all other differences to the MAK value are sufficiently large, benzyl alcohol is classified in Pregnancy Risk Group C.

Carcinogenicity. Since the documentation from 2006 (documentation "Benzylalkohol" 2006, available in German only), no recent data have become available. Benzyl alcohol therefore remains without classification in one of the categories for carcinogens.

Germ cell mutagenicity. Benzyl alcohol did not induce gene mutations in bacteria and mammalian cells. Clastogenic effects were observed only at high concentrations in vitro. In vivo, in micronucleus tests, no clastogenicity could be detected, but there was also no cytotoxicity up to the highest concentration tested. Investigation of the main metabolite of benzyl alcohol, benzoic acid, provided no evidence of clastogenic effects in vivo. Benzyl alcohol is therefore not suspected to be a germ cell mutagen and is not classified in one of the categories for germ cell mutagens.

Absorption through the skin.
From the available in vitro studies of the penetration of benzyl alcohol through the human skin, flux values of 29 to 275 μg/cm^2 and hour were obtained when using physiological receptor media. In vivo, a considerably lower flux of 0.1 μg/cm^2 and hour was found in monkeys, in this case, however, only a very small absolute amount of substance was applied (4 μg). Assuming the worst case, with a maximum flux of 275 μg/cm^2 and hour, the amount dermally absorbed (one-hour exposure of both hands and forearms with a penetration area of about 2000 cm^2) would be 550 mg. On the basis of the NOAEL of 200 mg/kg body weight and day for mice obtained following long-term oral administration, a systemically tolerable dose of 1015 mg can be estimated for humans. This extrapolation takes into consideration the species-specific correction value (1:7) for the mouse, the body weight of 70 kg of the person, the halving of the dose when extrapolating from animal results to humans (1:2) (see Section I of the List of MAK and BAT Values) and the assumed complete absorption after oral ingestion. The dermal uptake of benzyl alcohol estimated from this is more than 25% of the tolerable dose; the possible contribution of dermal absorption to systemic toxicity is therefore not considered to be negligible. Benzyl alcohol is therefore designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. No recent case reports are available for occupational contact allergy to benzyl alcohol. There are no other new case reports following non-occupational exposure or results from patch tests with benzyl alcohol in larger collectives which would indicate a significant skin-sensitizing potential. All in all, the more recent findings also confirm that, although benzyl alcohol may produce reactions, this is frequently in connection with the application of topical preparations on damaged skin. The results of earlier animal studies indicate only a low sensitization potential, and the results of a more recent local lymph node assay were negative. Therefore, designation of benzyl alcohol with "Sh" (for substances which cause sensitization of the skin) is not justified. As there are no data available for its sensitizing effects on the airways, benzyl alcohol is not designated with "Sa" (for substances which cause sensitization of the airways).

7 References

Amado A, Jacob SE (2007) Letter: Benzyl alcohol preserved saline used to dilute injectables poses a risk of contact dermatitis in fragrance-sensitive patients. Dermatol Surg 33: 1396–1397

Anderson BE, Zeiger E, Shelby MD, Resnick MA, Gulati DK, Ivett JL, Loveday KS (1990) Chromosome aberration and sister chromatid exchange test results with 42 chemicals. Environ Mol Mutagen 16: 55–137

Ball JC, Foxall-VanAken S, Jensen TE (1984) Mutagenicity studies of p-substituted benzyl derivates in the Ames Salmonella plate-incorporation assay. Mutat Res 138: 145–151

Barry BW, Harrison SM, Dugard PH (1985 a) Correlation of thermodynamic activity and vapour diffusion through human skin for the model compound, benzyl alcohol. J Pharm Pharmacol 37: 94–90

Barry BW, Harrison SM, Dugard PH (1985 b) Vapour and liquid diffusion of model penetrants through human skin; correlation with thermodynamic activity. J Pharm Pharmacol 37: 226–235

Bayer AG (1990 a) Benzylalkohol. Untersuchungen zur akuten Inhalationstoxizität an der Ratte (Benzyl alcohol. Investigations of the acute inhalation toxicity in the rat) (German). Report No. 19799, 12th Dec 1990, unpublished

Bayer AG (1990 b) Benzyl alcohol. Study for skin and eye irritation/corrosion in rabbits according to OECD guideline no. 404 and 405. Report No. 19232, 6th July 1990, unpublished

BIBRA (The British Industrial Biological Research Association) (1991) Toxicity profile on benzyl alcohol. BIBRA, Carshalton, UK

Brasch J, Henseler T (1992) The reaction index: a parameter to assess the quality of patch test preparations. Contact Dermatitis 27: 203–204

Bronaugh RL, Wester RC, Bucks D, Maibach HI, Sarason R (1990) In vivo percutaneous absorption of fragrance ingredients in rhesus monkeys and humans. Food Chem Toxicol 28: 369–373

Brüning T, Bartsch R, Bolt HM, Desel H, Drexler H, Gundert-Remy U, Hartwig A, Jäckh R, Leibold E, Pallapies D, Rettenmeier AW, Schlüter G, Stropp G, Sucker K, Triebig G, Westphal G, van Thriel C (2014) Sensory irritation as a basis for setting occupational exposure limits. Arch Toxicol 88: 1855–1879

Carrascosa JM, Domingo H, Soria X, Ferrándiz C (2006) Allergic contact dermatitis due to benzyl alcohol in a hair dye. Contact Dermatitis 55: 124–125

Chang YS, Lin CF, Wu CL, Kuo PY, Wu FS, Shieh CC, Gean PW, Chen ST, Chen MS, Wu WC, Tai MH, Tseng SH (2011) Mechanisms underlying benzyl alcohol cytotoxicity (triamcinolone acetonide preservative) in human retinal pigment epithelial cells. Invest Ophthalmol Vis Sci 52: 4214–4222

Chapman DE, Moore TJ, Michener SR, Powis G (1990) Metabolism and covalent binding of [14C]toluene by human and rat liver microsomal fractions and liver slices. Drug Metab Dispos 18: 929–936

Chow ET, Avolio AM, Lee A, Nixon R (2013) Frequency of positive patch test reactions to preservatives: The Australian experience. Australas J Dermatol 54: 31–35

Cooper SM, Shaw S (2000) Eyelid dermatitis: an evaluation of 232 patch test patients over 5 years. Contact Dermatitis 42: 291–293

Cotovio J, Grandidier M-H, Portes P, Roguet R, Rubinstenn G (2005) The in vitro acute skin irritation of chemicals: Optimisation of the EPISKIN prediction model within the framework of the ECVAM validation process. Altern Lab Anim 33: 329–349

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

Curry EJ, Warshaw EM (2005) Benzyl alcohol allergy: importance of patch testing with personal products. Dermatitis 16: 203–208

Demir E, Kocaoglu S, Kaya B (2008) Genotoxicity testing of four benzyl derivatives in the Drosophila wing spot test. Food Chem Toxicol 46: 1034–1041

Demir E, Kocaoglu S, Kaya B (2010) Assessment of genotoxic effects of benzyl derivatives by the comet assay. Food Chem Toxicol 48: 1239–1242

ECHA (European Chemicals Agency) (2014) Information on registered substances. Dataset on Benzyl alcohol (CAS Number 100-51-6), joint submission, first publication 03.03.2011, last modification 26.05.2014,
http://echa.europa.eu/web/guest/information-on-chemicals

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) (2003) Derivation of assessment factors for human health risk assessment. Monograph No. 86, ECETOC, Brussels, Belgium

Elia MC, Storer RD, McKelvey TW, Kraynak AR, Barnum JE, Harmon LS, DeLuca JG, Nichols WW (1994) Rapid DNA degradation in primary rat hepatocytes treated with diverse cytotoxic chemicals: analysis by pulsed field gel electrophoresis and implications for alkaline elution assays. Environ Mol Mutagen 24: 181–191

Emter R, Ellis G, Natsch A (2010) Performance of a novel keratinocyte-based reporter cell line to screen skin sensitizers in vitro. Toxicol Appl Pharmacol 245: 281–290

Fall M, Haddouk H, Morin JP, Forster R (2007) Mutagenicity of benzyl chloride in the Salmonella/microsome mutagenesis assay depends on exposure conditions. Mutat Res 633: 13–20

FDA (US Food and Drug Administration) (2009) Pharmacology/Toxicology review and evaluation, application number 22-129, Silver Spring, MD, USA,
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022129s000_PharmR.pdf

Florin I, Rutberg L, Curvall M, Enzell CR (1980) Screening of tobacco smoke constituents for mutagenicity using the Ames test. Toxicology 15: 219–232

Fluck ER, Poirier LA, Ruelius HW (1976) Evaluation of a DNA polymerase-deficient mutant of E. coli for the rapid detection of carcinogens. Chem Biol Interact 15: 219–231

Foureman P, Mason JM, Valencia R, Zimmering S (1994) Chemical mutagenesis testing in Drosophila. IX. Results of 50 coded compounds tested for the National Toxicology Program. Environ Mol Mutagen 23: 51–63

Fowler P, Smith K, Young J, Jeffrey L, Kirkland D, Pfuhler S, Carmichael P (2012) Reduction of misleading ("false") positive results in mammalian cell genotoxicity assays. I. Choice of cell type. Mutat Res 742: 11–25

Geier J, Uter W, Lessmann H, Schnuch A (2003 a) The positivity ratio – another parameter to assess the diagnostic quality of a patch test preparation. Contact Dermatitis 48: 280–282

Geier J, Uter W, Pirker C, Frosch PF (2003 b) 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: 99–107

Grégoire S, Ribaud C, Benech F, Meunier JR, Garrigues-Mazert A, Guy RH (2009) Prediction of chemical absorption into and through the skin from cosmetic and dermatological formulations. Br J Dermatol 160: 80–91

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

Hayashi M, Kishi M, Sofuni T, Ishidate M Jr (1988) Micronucleus tests in mice on 39 food additives and eight miscellaneous chemicals. Food Chem Toxicol 26: 487–500

Heisterberg MV, Menné T, Johansen JD (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

IFA (Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung) (Institute for Occupational Safety and Health of the German Social Accidence Insurance) (2015) Benzyl alcohol, GESTIS data base, http://www.dguv.de/en/data_bases/index.jsp

IFRA (International Fragrance Association) (2009) IFRA standard – Benzyl alcohol. 42nd Amendment, 14.10.2009, http://www.ifraorg.org/en-us/search/s/NESIL_benzyl_alcohol

Ishidate M Jr, Sofuni T, Yoshikawa K, Hayashi M, Nohmi T, Sawada M, Matsuoka A (1984) Primary mutagenicity screening of food additives currently used in Japan. Food Chem Toxicol 22: 623–636

Ishidate M Jr, Harnois MC, Sofuni T (1988) A comparative analysis of data on the clastogenicity of 951 chemical substances tested in mammalian cell cultures. Mutat Res 195: 151–213

Jacob SE, Stechschulte S (2008) Eyelid dermatitis associated with balsam of Peru constituents: benzoic acid and benzyl alcohol. Contact Dermatitis 58: 111–112

Jappe U, Schnuch A, Uter W (2003) Frequency of sensitization to antimicrobials in patients with atopic eczema compared with non-atopic individuals: analysis of multicentre surveillance data, 1995–1999. Br J Dermatol 149: 87–93

Jimbo Y (1983) Penetration of fragrance compounds through human epidermis. J Dermatol 10: 229–239

Jimbo Y, Ishihara M, Osamura H, Takano M, Ohara M (1983) Influence of vehicles on penetration through human epidermis of benzyl alcohol, isoeugenol and methyl isoeugenol. J Dermatol 10: 241–250

Katz GV, Fennikoh FW (1983) Acute inhalation toxicity of benzyl alcohol in rats following single or multiple vapor or aerosol exposure. Study number TX-83-04, 22nd March 1983, unpublished

Klecak G, Geleick H, Frey JR (1977) Screening of fragrance materials for allergenicity in the guinea pig. I. Comparison of four testing methods. J Soc Cosmet Chem 28: 53–64

Kuroda K, Yoo YS, Ishibashi T (1984) Antimutagenic activity of food additives. Mutat Res 130: 369

Lashmar U, Hadgraft J, Thomas N (1989) Topical application of penetration enhancers to the skin of nude mice: a histopathological study. J Pharm Pharmacol 41:118–122

LeBel M, Ferron L, Masson M, Pichette J, Carrier C (1988) Benzyl alcohol metabolism and elimination in neonates. Dev Pharmacol Ther 11: 347–356

Li Q, Wang J, Yang L, Mo B, Zeng H, Lui W (2008) A morphologic study of retinal toxicity induced by triamcinolone acetonide vehicles in rabbit eyes. Retina 28: 504–510

Macky TA, Helmy D, El Shazly N (2007) Retinal toxicity of triamcinolone's vehicle (benzyl alcohol): an electrophysiologic and electron microscopic study. Graefes Arch Clin Exp Ophthalmol 245: 817–824

Mann J, McFadden, JP, White JML, White IR, Banerjee P (2014) Baseline series fragrance markers fail to predict contact allergy. Contact Dermatitis 70: 276–281

McCloskey SE, Gershanik JJ, Lertora JJ, White L, George WJ (1986) Toxicity of benzyl alcohol in adult and neonatal mice. J Pharm Sci 75: 702–705

McGregor DB, Brown A, Cattanach P, Edwards I, McBride D, Riach C, Caspary WJ (1988) Responses of the L5178Y tk+/tk– mouse lymphoma cell forward mutation assay: III. 72 coded chemicals. Environ Mol Mutagen 12: 85–154, 345

McKim Jr JM, Keller DJ III, Gorski JR (2010) A new in vitro method for identifying chemical sensitizers combining peptide binding with ARE/EpRE-mediated gene expression in human skin cells. Cutan Ocul Toxicol 29: 171–192

Menzel E, Maibach HI (1970) In vitro human percutaneous penetration of benzyl alcohol and testosterone: epidermal-dermal retention. J Invest Dermatol 54: 386–394

Merck KGaA (2013) Benzyl alcohol. Specification (16.05.2013), http://www.merckmillipore.com/DE/en/product/Benzyl-alcohol,MDA_CHEM-109626

Merck KGaA (2014) Benzyl alcohol. Safety data sheet (16.09.2014), http://www.merckmillipore.com/DE/de/product/Benzyl-alcohol,MDA_CHEM-109626

Miller MA, Bhatt V, Kasting GB (2006) Dose and airflow dependence of benzyl alcohol disposition on skin. J Pharm Sci 95: 281–291

Milvy P, Garro AJ (1976) Mutagenic activity of styrene oxide (1,2-epoxyethylbenzene), a presumed styrene metabolite. Mutat Res 40: 15–18

Morrison VL, Koh HJ, Cheng L, Bessho K, Davidson MC, Freeman WR (2006) Intravitreal toxicity of the Kenalog vehicle (benzyl alcohol) in rabbits. Retina 26: 339–344

Mortelmans K, Haworth S, Lawlor T, Speck W, Tainer B, Zeiger E (1986) Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. Environ Mutagen 8: 1–119

Motoyoshi K, Toyoshima Y, Sato M, Yoshimura M (1979) Comparative studies on the irritancy of oils and synthetic perfumes to the skin of rabbit, guinea pig, rat, miniature swine and man. Cosmet Toilet 94: 41–48

Nair B (2001) Final report on the safety assessment of benzyl alcohol, benzoic acid, and sodium benzoate. Int J Toxicol 20, Suppl 3: 23–50

Natsch A, Emter R (2008) Skin sensitizers induce antioxidant response element dependent genes: Application to the in vitro testing of the sensitization potential of chemicals. Toxicol Sci 102: 110–119

Natsch A, Haupt T (2013) Utility of rat liver S9 fractions to study skin-sensitizing prohaptens in a modified KeratinoSens assay. Toxicol Sci 135: 356–368

NLM (National Library of Medicine) (2015 a) Benzyl alcohol. ChemIDplus Database, http://chem.sis.nlm.nih.gov/chemidplus/

NLM (2015 b) Benzyl alcohol. Hazardous Substances Data Bank, http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB

NTP (National Toxicology Program) (1989) Toxicology and carcinogenesis studies of benzyl alcohol. NTP Technical Report Series No. TR 343, US Department of Health and Human Services, National Institutes of Health, Bethesda, MD, USA

Penchalaiah K, Handa S, Lakshmi SB, Sharma VK, Kumar B (2000) Sensitizers commonly causing allergic contact dermatitis from cosmetics. Contact Dermatitis 43: 311–313

OECD (Organisation for Economic Co-operation and Development) (2004) Benzoates, OECD SIDS Initial Assessment Report, UNEP (United Nations Environment Programme), Geneva, http://www.inchem.org/documents/sids/sids/benzoates.pdf

Opdyke DL (1973) Monographs on fragrance raw materials. Food Cosmet Toxicol 11: 1011–1081

Rowe VK, McCollister SB (1982) Benzenemethanol. in: Clayton GD, Clayton FE (Eds) Patty's industrial hygiene and toxicology, Vol 2C, Wiley, New York, USA, 4636–4641

Ruiz-Mereno JM, Montero JA, Bayon A, Rueda J, Vidal M (2007) Retinal toxicity of intravitreal triamcinolone acetonide at high doses in the rabbit. Exp Eye Res 84: 342–348

Safford RJ, Aptula AO, Gilmour N (2011) Refinement of the dermal sensitisation threshold (DST) approach using a larger dataset and incorporating mechanistic chemistry domains. Regul Toxicol Pharmacol 60: 218–224

Saiyasombati P, Kasting GB (2003) Disposition of benzyl alcohol after topical application to human skin in vitro. J Pharm Sci 92: 2128–2139

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

Schnuch A, Uter W, Lessmann H, Geier J (2008) Kontaktallergien gegen Konservierungsmittel. Ergebnisse des Informationsverbundes Dermatologischer Kliniken (IVDK) 1996 bis 2007 (Contact allergies to preservatives. Results of the IVDK (Information Network of Departments of Dermatology) from 1996 to 2007) (German). Allergo J 17: 631–638

Schnuch A, Mildau G, Kratz EM, Uter W (2011) 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: 167–174

Scognamiglio J, Jones L, Vitale D, Letizia CS, Api AM (2012) Fragrance material review on benzyl alcohol. Food Chem Toxicol 50: 140–160

Sestini S, Mori M, Francalanci S (2004) Allergic contact dermatitis from benzyl alcohol in multiple medicaments. Contact Dermatitis 50: 316–317

Sharp DW (1978) The sensitization potential of some perfume ingredients tested using a modified Draize procedure. Toxicology 9: 261–271

Smyth HF Jr, Carpenter CP, Weil CS (1951) Range-finding toxicity data: List IV. AMA Arch Ind Hyg Occup Med 4: 119–122

Storer RD, McKelvey TW, Kraynak AR, Elia MC, Barnum JE, Harmon LS, Nichols WW, DeLuca JG (1996) Revalidation of the in vitro alkaline elution/rat hepatocyte assay for DNA damage: improved criteria for assessment of cytotoxicity and genotoxicity and results for 81 compounds. Mutat Res 12: 59–101

The Personal Care Products Council (2010) A 4-week inhalation toxicity study of aerosolized benzyl alcohol and benzoic acid in Sprague-Dawley rats. Study number WIL-703002, 8. Feb. 2010, unpublished

Torgerson RR, Davis MDP, Bruce AJ, Farmer SA, Rogers RS (2007) Contact allergy in oral disease. J Am Acad Dermatol 57: 315–321

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 Oosten EJ, Schuttelaar ML, Coenraads PJ (2009) Clinical relevance of positive patch test reactions to the 26 EU-labelled fragrances. Contact Dermatitis 61: 217–223

Wolfreys AM, Basketter DA (2004) Mutagens and sensitizers – An unequal relationship? J Toxicol Cutaneous Ocul Toxicol 23: 197–205

Yoo YS (1985) Mutagenic and antimutagenic activities of flavoring agents used in foodstuffs. Osaka City Med J 34: 267–288

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