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Review

A toxicological and dermatological assessment of aryl alkyl alcohols when used as fragrance ingredients ☆

The RIFM Expert Panel
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ABSTRACT

The aryl alkyl alcohol (AAA) fragrance ingredients are a diverse group of chemical structures with similar metabolic and toxicity profiles. The AAA fragrances demonstrate low acute and subchronic dermal and oral toxicity. No carcinogenicity in rats or mice was observed in 2-year chronic testing of benzyl alcohol or α-methylbenzyl alcohol; the latter did induce species and gender-specific renal adenomas in male rats at the high dose. There was no to little genotoxicity, mutagenicity, or clastogenicity in the mutagenic *in vitro* bacterial assays, and *in vitro* mammalian cell assays. All *in vivo* micronucleus assays were negative. NOAELs for maternal and developmental toxicity are far in excess of current human exposure levels. At concentrations likely to be encountered by consumers, AAA fragrance ingredients are non-irritating to the skin. The potential for eye irritation is minimal. With the exception of benzyl alcohol and to a lesser extent phenethyl and 2-phenoxyethyl AAA alcohols, human sensitization studies, diagnostic patch tests and human induction studies, indicate that AAA fragrance ingredients generally have no or low sensitization potential. Available data indicate that the potential for photosensitization is low. It is concluded that these materials would not present a safety concern at current levels of use as fragrance ingredients.

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1. Introduction

In 2009, complete literature searches were conducted for alkyl aryl alcohols (AAAs). This document provides safety assessment and critical evaluation of the pertinent data of the AAAs used as fragrance ingredients. The scientific evaluation focuses on dermal exposure, which is considered to be the primary route for fragrance materials. Toxicity, metabolism, and biological fate data from other exposures have been considered where relevant.

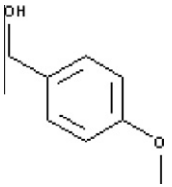
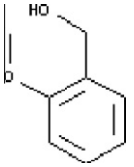
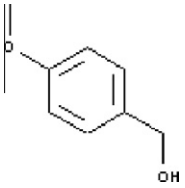
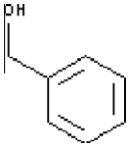
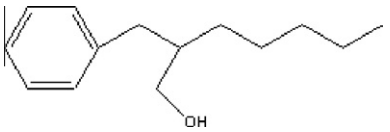
The evaluation of the AAA fragrance materials in this safety assessment is supported by more detailed Fragrance Material Reviews (FMR) that will be published concurrently for each of the AAA fragrance ingredients. The group summary is an evaluation of relevant data selected from the large bibliography of studies and reports on the individual chemicals. The selected data were deemed to be relevant based on the currency of protocols, quality of the data, statistical significance, and appropriate exposure. These are identified in tabular form in the group summary. Details that are provided in the tables are not always discussed in the text of the group summary. The Fragrance Material Reviews contain a more comprehensive description of all published reports including complete bibliographies (Scognamiglio, in press a-dd).

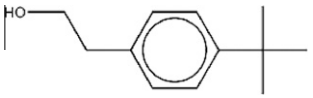
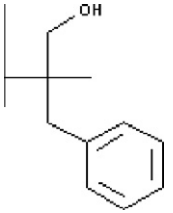
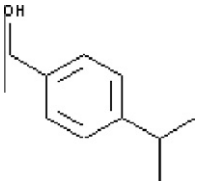
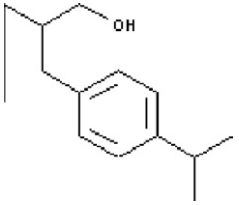
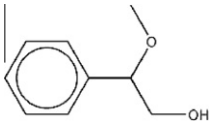
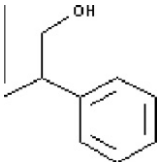
2. Chemical identity, regulatory status and exposure

The AAA compounds discussed in this report are blended with other AAA compounds, and/or chemical classes of fragrance ingredients, and may be used in decorative cosmetics, fine fragrances, personal care products such as shampoos, soaps, and other toiletries, and in household products such as cleaners and detergents.

This safety assessment summarizes the animal and human toxicology data for oral, dermal and inhalation exposures. These data were integrated to determine the potential for human health effects and risks associated with the use of the AAA fragrance ingredients. The AAA risk evaluation focuses primarily on dermal exposure, which is considered to be the major route by which consumers may be exposed to fragrance materials. If available, toxicity, metabolism, and kinetic data for other important routes of potential consumer exposures to fragrance ingredients, such as inhalation, are also evaluated.

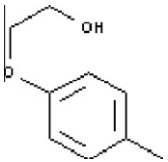
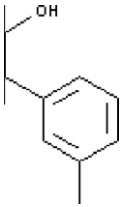
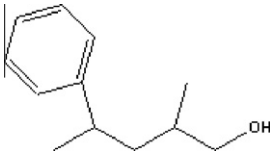
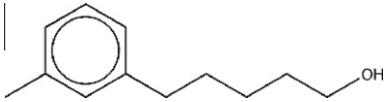
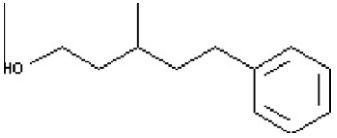
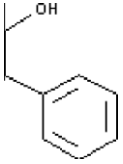
Table 1
Aryl alkyl alcohols material identification, summary of volume of use, and dermal exposure.

Material	Synonyms	Structure	Worldwide Metric Tons (annual)[a]	Dermal Exposure (mg/kg/day)[b]	Maximum Skin Level (%)[c,d]
1-6 **Primary aryl alkyl alcohol**					
Anisyl alcohol (*o*-*m*-*p*-) $C_8H_{10}O_2$ CAS#: 1331-81-3 Log K_{ow}(calculated): 1.16 Molecular Weight: 138.66 Vapor Pressure: 0.00246 mm Hg @ 25 °C Water Solubility: 31710 mg/l @ 25 °C	Benzenemethanol, ar-methoxy-; (4-Methoxyphenyl)methanol		0.01–0.1	0.0033	0.77
2-Methoxybenzyl alcohol[f] $C_8H_{10}O_2$ CAS#: 612-16-8 Log K_{ow}(calculated): 1.16 Molecular Weight: 138.66 Vapor Pressure: 0.00474 mm Hg @ 25 °C Water Solubility: 29890 mg/l @ 25 °C	Benzenemethanol, 2-methoxy-; (2-Methoxyphenyl)methanol; Rosethyl (*o*-anisyl ethyl ether)		0	0	0
Anisyl alcohol $C_8H_{10}O_2$ CAS#: 105-13-5 Log K_{ow}(calculated): 1.16 Molecular Weight: 138.17 Vapor Pressure: <0.001 mm Hg @ 20 °C Water Solubility: 31710 mg/l @ 25 °C	Anise alcohol; Benzyl alcohol, *p*-methoxy-; (4-Methoxyphenyl)methanol		10–100	0.0081	0.96
Benzyl alcohol C_7H_8 O CAS#: 100-51-6 Log K_{ow}(calculated): 1.08 Molecular Weight: 108.14 Vapor Pressure: 0.07 mm Hg @ 20 °C Water Solubility: 41050 mg/l @ 25 °C	Benzenemethanol; α-Hydroxytoluene; Phenyl carbinol; Phenylmethanol; α-Toluenol		100–1000	0.042	3.89
2-Benzylheptanol $C_{14}H_{22}$ O CAS#: 92368-90-6 Log K_{ow}(calculated): 4.44 Molecular Weight: 206.29 Vapor Pressure: 0.0000292 mm Hg @ 25 °C Water Solubility: 21.23 mg/l @ 25 °C	Benzenepropanol, β-pentyl-		1–10	0.0293	0.03

2-(4-*tert*.Butyl phenyl) ethanol[f] $C_{12}H_{18}O$ CAS#: 5406-86-0 Log K_{ow}(calculated): 3.48 Molecular Weight: 178.28 Vapor Pressure: 0.000335 mm Hg @ 25 °C Water Solubility: 195.3 mg/l @ 25 °C	None		0	0	0
2,2-Dimethyl-3-phenylpropanol $C_{11}H_{16}O$ CAS#: 13351-61-6 Log K_{ow}(calculated): 2.93 Molecular Weight: 164.48 Vapor Pressure: 0.143 mm Hg @ 25 °C Water Solubility: 667.7 mg/l @ 25 °C	Benzenepropanol, β,β-dimethyl-; Dimethyl phenylpropanol; 2,2-Dimethyl-3-phenylpropan-1-ol; Dimethyl-3-Phenylpropanol; Muguetalcohol; 1-Propanol, 2,2-dimethyl-3-phenyl-		0.1–1	0.1911	0.84
***p*-Isopropylbenzyl alcohol** $C_{10}H_{14}O$ CAS#: 536-60-7 Log K_{ow}(calculated): 2.53 Molecular Weight: 150.22 Vapor Pressure: 0.02 mm Hg @ 20 °C Water Solubility: 1687 mg/l @ 25 °C	Benzenemethaynol, 4-(1-methylethyl)-; Cuminyl alcohol; (4-Isopropylphenyl)methanol		1–10	0.0021	0.06
3-(*p*-Isopropyl)phenyl-2-methyl-1-propanol[f] $C_{13}H_{20}O$ CAS#: 4756-19-8 Log K_{ow}(calculated): 3.93 Molecular Weight: 192.3 Vapor Pressure: <0.001 mm Hg @ 20 °C Water Solubility: 68.03 mg/l @ 25 °C	Benzenepropanol, β-methyl-4-(1-methylethyl)-; 3-(4-Isopropylphenyl)-2-methylpropan-1-ol; cyclamen alcohol		IFRA Prohibited		
***β*-Methoxy benzeneethanol** $C_9H_{12}O_2$ CAS#: 2979-22-8 Log K_{ow}(calculated): 0.73 Molecular Weight: 152.19 Vapor Pressure: 0.00308 mm Hg @ 25 °C Water Solubility: 57420 mg/l @ 25 °C	2-Hydroxy-1-methoxy-1-phenylethane; β-methoxybenzeneethanol; β-methoxyphenethyl alcohol; 2-Methoxy-2-phenylethanol		0.01–0.1	0.0005[e]	0.02[e]
***β*-Methylphenethyl alcohol** $C_9H_{12}O$ CAS#: 1123-85-9 Log K_{ow}(calculated): 1.98 Molecular Weight: 136.19 Vapor Pressure: 0.02 mm Hg @ 20 °C Water Solubility: 5677 mg/l @ 25 °C	Benzeneethanol, α-methyl-; Hydratropic alcohol; 2-Phenyl-1-propanol; 2-Phenylpropan-1-ol		1–10	0.0925	.0.31

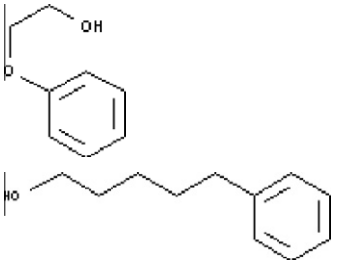
(*continued on next page*)

Table 1 (*continued*)

Material	Synonyms	Structure	Worldwide Metric Tons (annual)[a]	Dermal Exposure (mg/kg/day)[b]	Maximum Skin Level (%)[c,d]
1-6 **Primary aryl alkyl alcohol**					
2-(4-Methylphenoxy)ethanol $C_9H_{12}O_2$ CAS#: 15149-10-7 Log K_{ow}(calculated): 1.65 Molecular Weight: 152.19 Vapor Pressure: 0.00117 mm Hg @ 25 °C Water Solubility: 9407 mg/l @ 25 °C	Ethanol, 2-(4-methylphenoxy)-; Ethylene glycol mono-*p*-tolyl ether; 2-(*p*-Tolyloxy)ethanol; Methyl *para* phenoxy ethanol		0.01–0.1	0.011	0.08
2-(3-Methylphenyl)ethanol $C_9H_{12}O$ CAS#: 1875-89-4 Log K_{ow}(calculated): 2.11 Molecular Weight: 136.94 Vapor Pressure: 0.00505 mm Hg @ 25 °C Water Solubility: 4399 mg/l @ 25 °C	Benzeneethanol, 3-methyl-; 3-Methylphenethyl alcohol; 2-*m*-Tolylethanol		<0.01	0.0285	0.05
2-Methyl-4-phenylpentanol $C_{12}H_{18}O$ CAS#: 92585-24-5 Log K_{ow}(calculated): 3.38 Molecular Weight: 178.75 Vapor Pressure: 0.00227 mm Hg @ 25 °C Water Solubility: 801 mg/l @ 25 °C	Benzenebutanol, β, δ-dimethyl-; Pamplefleur		1–10	0.0288	0.08
2-Methyl-5-phenylpentanol $C_{12}H_{18}O$ CAS#: 25634-93-9 Log K_{ow}(calculated): 3.59 Molecular Weight: 178.28 Vapor Pressure: 0.000116 mm Hg @ 25 °C Water Solubility: 157 mg/l @ 25 °C	Rosaphen		10–100	0.0005[e]	0.02[e]
3-Methyl-5-phenylpentanol $C_{12}H_{18}O$ CAS#: 55066-48-3 Log K_{ow}(calculated): 3.46 Molecular Weight: 178.75 Vapor Pressure: 0.000299 mm Hg @ 25 °C Water Solubility: 202.6 mg/l @ 25 °C	Benzenepentanol, γ-methyl-; 3-Methyl-5-phenylpentan-1-ol; Phenylisohexanol; Phenoxanol		100–1000	0.0912	1.76
Phenethyl alcohol $C_8H_{10}O$ CAS#: 60-12-8 Log K_{ow}(calculated): 1.57 Molecular Weight: 122.17 Vapor Pressure: 0.03 mm Hg @ 20 °C Water Solubility: 21990 mg/l @ 25 °C	Benzeneethanol; Benzyl carbinol; (2-Hydroxyethyl)benzene; 1-Phenyl-2-ethanol; 2-Phenylethanol; Phenylethyl alcohol; Etaphen		>1000	0.3198	11.72

2-Phenoxyethanol $C_8H_{12}O_2$
CAS#: 122-99-6
Log K_{ow}(calculated): 1.1
Molecular Weight: 138.17
Vapor Pressure: 0.006 mm Hg @ 20 °C
Water Solubility: 28180 mg/l @ 25 °C

Ethanol, 2-phenoxy-; Phenoxyethanol; CoSept PHE; Dowanol Eph; Emeressence 1160; Igepal OD 410; Phenoxen; Polioxol F-01; Protacide P-OH; REWOPAL MPG 10; Sepicide LD; Tri-K



100–1000 | 0.0476 | 4.09

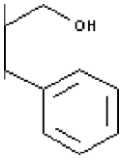
0 | 0 | 0

5-Phenylpentanol[f] $C_{11}H_{16}O_2$
CAS#: 10521-91-2
Log K_{ow}(calculated): 3.04
Molecular Weight: 164.25
Vapor Pressure: 0.000445 mm Hg @ 25 °C
Water Solubility: 536.7 mg/l @ 25 °C

Benzenepentanol; Phenylamyl alcohol; 5-Phenylpentan-1-ol

Phenylpropanol[f] $C_9H_{12}O$
CAS#: 1335-12-2
Log K_{ow}(calculated): 2.06
Molecular Weight: 136.94
Vapor Pressure: 0.000592 mm Hg @ 25 °C
Water Solubility: 6969 mg/l @ 25 °C

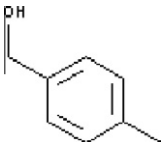
1-Phenylpropan-1-ol; 1-Propanol, phenyl-



0 | 0 | 0

***p*-Tolyl alcohol** $C_8H_{10}O$
CAS#: 589-18-4
Log K_{ow}(calculated): 1.62
Molecular Weight: 122.17
Vapor Pressure: 0.0109 mm Hg @ 25 °C
Water Solubility: 14260 mg/l @ 25 °C

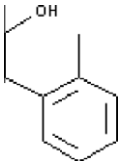
Benzenemethanol, 4-methyl-; 4-Methylbenzyl alcohol; (4-Methylphenyl)methanol; 4-Tolylcarbinol



0.01-0.1 | 0.0061 | 0.15

***o*-Tolylethanol** $C_9H_{12}O$
CAS#: 19819-98-8
Log K_{ow}(calculated): 2.11
Molecular Weight: 136.94
Vapor Pressure: 0.00494 mm Hg @ 25 °C
Water Solubility: 4399 mg/l @ 25 °C

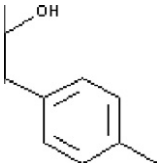
Benzeneethanol, 2-methyl-; 2-(2-Methylphenyl)ethanol; Blanc Rose; Peomosa



1–10 | 0.0846 | 0.62

2-*p*-Tolylethanol $C_9H_{12}O$
CAS#: 699-02-5
Log K_{ow}(calculated): 2.11
Molecular Weight: 136.94
Vapor Pressure: 0.0169 mm Hg @ 25 °C
Water Solubility: 4399 mg/l @ 25 °C

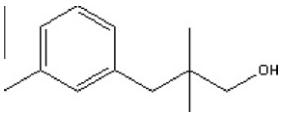
Benzeneethanol, 4-methyl-; 2-(4-Methylphenyl)ethanol



<0.01 | 0.0043 | 0.06

***β*, *β*, 3-Trimethyl benzenepropanol** $C_{12}H_{18}O$
CAS#: 103694-68-4
Log K_{ow}(calculated): 3.48
Molecular Weight: 178.28
Vapor Pressure: 0.000335 mm Hg @ 25 °C
Water Solubility: 256.8 mg/l @ 25 °C

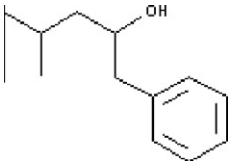
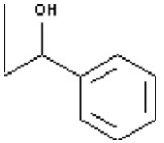
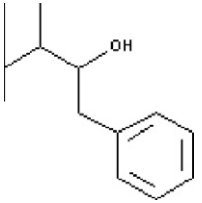
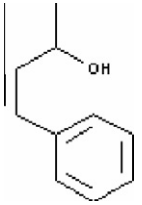
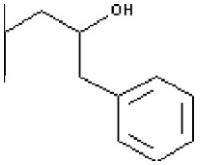
2,2-Dimethyl-3-(3-methylphenyl)propanol; 2,2-Dimethyl-3-(3-tolyl)propan-1-ol; Majantol

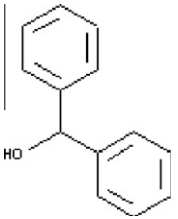
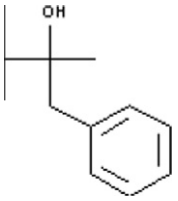
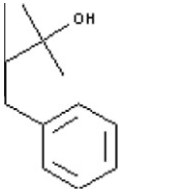
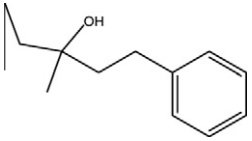
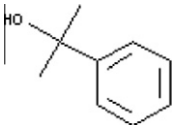
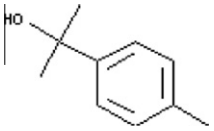


10-100 | 0.1368 | 1.81

(*continued on next page*)

Table 1 (*continued*)

Material	Synonyms	Structure	Worldwide Metric Tons (annual)[a]	Dermal Exposure (mg/kg/day)[b]	Maximum Skin Level (%)[c,d]
1-6 **Primary aryl alkyl alcohol**					
Secondary aryl alkyl alcohol **α-Isobutylphenethyl alcohol** $C_{12}H_{18}O$ CAS#: 7779-78-4 Log K_{ow}(calculated): 3.38 Molecular Weight: 178.28 Vapor Pressure: 0.02 mm Hg @ 20 °C Water Solubility: 234 mg/l @ 25 °C	Benzyl isoamyl alcohol; Benzyl isobutyl carbinol; Isobutyl benzyl carbinol; 4-Methyl-1-phenyl-2-pentanol; 4-Methyl-1-phenylpentan-2-ol; 2-Pentanol, 4-methyl-1-phenyl-; 2-Methylpropyl benzyl carbinol		0.1-1	0.0076	0.16
α-Methylbenzyl alcohol $C_8H_{10}O$ CAS#: 98-85-1 Log K_{ow}(calculated): 1.49 Molecular Weight: 122.17 Vapor Pressure: 0.2 mm Hg @ 20 °C Water Solubility: 19,540 mg/l @ 25 °C	Benzenemethanol, α-methyl-; Methyl phenyl carbinol; 1-Phenylethanol; α-Phenylethyl alcohol; Styralyl alcohol		1–10	0.0004	0.09
3-Methyl-1-phenylbutan-2-ol $C_{11}H_{16}O$ CAS#: 705-58-8 Log K_{ow}(calculated): 2.89 Molecular Weight: 164.48 Vapor Pressure: 0.00296 mm Hg @ 25 °C Water Solubility: 716.5 mg/l @ 25 °C	Benzeneethanol, α-(1-methylethyl)-; Isopropyl benzyl carbinol		0 < 0.01	0.0531	0.42
4-Phenyl-3-buten-2-ol $C_{10}H_{12}O$ CAS#: 17488-65-2 Log K_{ow}(calculated): 2.26 Molecular Weight: 148.21 Vapor Pressure: 0.00327 mm Hg @ 25 °C Water Solubility: 2935 mg/l @ 25 °C	3-Buten-2-ol, 4-phenyl-; Methyl styryl carbinol; 4-Phenyl-3-buten-2-ol; 4-Phenylbut-3-en-2-ol		0.001-0.01	0.0005[e]	0.02[e]
α-Propylphenethyl alcohol $C_{11}H_{16}O$ CAS#: 705-73-7 Log K_{ow}(calculated): 2.97 Molecular Weight: 164.25 Vapor Pressure: 0.001 mm Hg @ 20 °C Water Solubility: 620.1 mg/l @ 25 °C	Benzeneethanol, α-propyl-; 1-Phenyl-2-pentanol; 1-Phenylpentan-2-ol; Benzylbutyl alcohol; Benzylpropyl carbinol		0.01-0.1	0.0115	0.09

Benzhydrol[f] $C_{13}H_{12}O$ CAS#: 91-01-0 Log K_{ow}(calculated): 2.71 Molecular Weight: 184.24 Vapor Pressure: 0.317 mm Hg @ 25 °C Water Solubility: 891.1 mg/l @ 25 °C	Benzenemethanol, α-phenyl-; Diphenylmethanol		0	0	0
Tertiary aryl alkyl alcohols **α, α-Dimethylphenethyl alcohol** $C_{10}H_{14}O$ CAS#: 100-86-7 Log K_{ow}(calculated): 2.44 Molecular Weight: 150.22 Vapor Pressure: 0.04 mm Hg @ 20 °C Water Solubility: 2029 mg/l @ 25 °C	Benzeneethanol, α,α-dimethyl-; Benzyl dimethyl carbinol; 2-Benzyl-2-propanol; Dimethylbenzyl carbinol; α,α-Dimethylphenethanol; α,α-Dimethylphenethyl alcohol; α-Dimethyl-β-phenethyl alcohol; 2-Hydroxy-2-methyl-1-phenylpropane; 2-Methyl-1-phenyl-2-propanol; 2-Methyl-1-phenylpropan-2-ol		10–100	0.0199	0.29
2-Methyl-4-phenyl-2-butanol $C_{11}H_{16}O$ CAS#: 103-05-9 Log K_{ow}(calculated): 2.93 Molecular Weight: 164.25 Vapor Pressure: 0.009 mm Hg @ 20 °C Water Solubility: 667.7 mg/l @ 25 °C	Butanol, 2-methyl-4-phenyl-; Benzyl-*tert*-butanol; Dimethylphenylethyl carbinol; Methyl phenylbutanol; 2-Methyl-4-phenylbutan-2-ol; Dimethyl Phenyl Ethyl Carbinol		10–100	0.0894	2.97
1-Phenyl-3-methyl-3-pentanol $C_{12}H_{18}O$ CAS#: 10415-87-9 Log K_{ow}(calculated): 3.42 Molecular Weight: 178.28 Vapor Pressure: 0.004 mm Hg @ 20 °C Water Solubility: 218.1 mg/l @ 25 °C	3-Methyl-1-phenyl-3-pentanol; 3-Methyl-1-phenylpentan-3-ol; 3-Pentanol, 3-methyl-1-phenyl-; Phenylethyl methyl ethyl carbinol		1–10	0.0583	0.60
2-Phenyl-2-propanol $C_9H_{12}O$ CAS#: 617-94-7 Log K_{ow}(calculated): 1.95 Molecular Weight: 136.19 Vapor Pressure: 0.0468 mm Hg @ 25 °C Water Solubility: 6113 mg/l @ 25 °C	Benzenemethanol, α,α-dimethyl-; α,α-Dimethylbenzyl alcohol; Dimethyl phenyl carbinol; 2-Phenylpropan-2-ol		0.01–0.1	0.0024	0.004
***p*-α, α-Trimethylbenzyl alcohol** $C_{10}H_{14}O$ CAS#: 1197-01-9 Log K_{ow}(calculated): 2.49 Molecular Weight: 150.22 Vapor Pressure: 0.02 mm Hg @ 20 °C Water Solubility: 1817 mg/l @ 25 °C	Benzenemethanol, α,α-4-trimethyl-; *p*-Cymen-8-ol; 2-(4-Methylphenyl)propan-2-ol; α,α-4-Trimethylbenzyl alcohol		0.1–1	0.0008	0.009

(*continued on next page*)

Table 1 (*continued*)

Material	Synonyms	Structure	Worldwide Metric Tons (annual)[a]	Dermal Exposure (mg/kg/day)[b]	Maximum Skin Level (%)[c,d]
1-6 **Primary aryl alkyl alcohol**					
α, α, 4-Trimethylphenethyl alcohol $C_{11}H_{16}O$ CAS#: 20834-59-7 Log K_{ow}(calculated): 2.99 Molecular Weight: 164.48 Vapor Pressure: 0.00302 mm Hg @ 25 °C Water Solubility: 597.8 mg/l @ 25 °C	Benzeneethanol, α,α-4-trimethyl-; 2-Methyl-1-(4-methylphenyl)propan-2-ol; Methyl-*p* Dimethyl Benzyl Carbinol		<0.01	0.0013	0.006

[a] 2008 Volume of use survey (IFRA, 2008).
[b] Based on a 60 kg adult.
[c] Upper 97.5 percentile levels of the fragrance ingredient in the fragrance mixture used in these products.
[d] 2004 Use level survey (IFRA, 2004).
[e] A default value of 0.02% was used to calculate dermal systemic exposure.
[f] These materials are structurally related to the AAA group; they are not reviewed in the text because there is no reported use of these materials as fragrance ingredients.

The AAA safety assessment provides a comprehensive review of all the available information selected from a large bibliography of AAA studies and reports, which is maintained by the Research Institute of Fragrance Materials (RIFM). The AAA data included published and unpublished reports and are deemed to be appropriate and relevant for the objectives of this report based on the following criteria: the nature of the protocols, the quality of the data, and the route of potential exposure. The RIFM and published AAA toxicology data are summarized in Tables 2–10.

In 2001, 2002, and 2003, the International Joint FAO/WHO Expert Committee on Food Additives (JECFA) conducted and published the *Safety Evaluation of Certain Food Additives and Contaminant* evaluations which included aromatic substituted secondary alcohols, ketones and related esters (JECFA, 2002a), benzyl derivatives (JECFA, 2002b), hydroxy- and alkoxy-substituted benzyl derivatives (JECFA, 2002c), and phenylethyl alcohol, aldehyde, acid and related acetals and esters and related substances (JECFA, 2003). Based on these publications, the substances, some of which include AAA fragrance ingredients, were judged by the WHO Expert Committee not to present a human health safety concern at the current levels of estimated human exposure.

In the United States, the regulatory status of 11 of these materials includes approval (21 CFR 172.515) by the Food and Drug Administration (FDA) and Generally Recognized as Safe (GRAS) as flavor ingredients [15 materials] by the Flavor and Extract Manufacturers Association (FEMA, 1965; FEMA, 1970, 1979, 2009). Eleven of these materials were also included in the Council of Europe's list of substances which may be used in foodstuffs (Council of Europe, 2000). Finally, the international Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2002, 2003, 2006, 2008) has evaluated 13 of these materials and found them to have no safety concerns based on current levels of intake as food flavors.

Table 1 provides a list of the AAAs and structures being evaluated in this report. The AAA compounds are organized based on whether the aryl portion of the molecule includes a primary, secondary, or tertiary alkyl alcohol group. For the AAA primary and tertiary alkyl alcohols, the aryl ring may be either an unsubstituted or substituted benzene; for the AAA secondary alkyl alcohols, the benzene is unsubstituted. Table 1 may also include compounds that are currently not used as fragrance ingredients. These zero use compounds, are included with the AAA fragrances because their toxicology is relevant for the AAA fragrance ingredients. The AAA primary alcohols consist of 24 compounds and include the economically important anisyl, benzyl, and phenethyl alcohols fragrance ingredients (and their congeners).

Table 1 includes the following data for each of the listed compounds: Chemical Abstract Service registry numbers (CAS RN); synonyms (alternative nomenclature); molecular formulas; molecular weight; physiochemical properties that are relevant for adsorption and biological activity (calculated Log K_{ow}, vapor pressure, water solubility); the annual worldwide production as determined by International Fragrance Association (IFRA); and dermal systemic exposure data.

Tables 2–10 provide summaries of the AAA toxicology data in the RIFM database. These include both the publically available peer reviewed literature and studies sponsored by RIFM. As previously noted, Tables 2–10 may also contain data for AAA compounds that are not used as fragrance ingredients (Volume of Use Survey, IFRA, 2008). These zero use compounds include the primary alcohols 2-methoxybenzyl alcohol; 2-(4-*tert*-butylphenyl) ethanol; 5-phenylpentanol; phenylpropanol, and the secondary alcohol benzhydrol. Toxicology data for the compounds with no fragrance use are included in Tables 2–10, but are not reviewed in the text of the safety report.

2.1. Rationale for grouping aryl alkyl alcohols

The AAAs are a structurally diverse class of fragrance ingredients that includes primary, secondary, and tertiary alkyl alcohols covalently bonded to an aryl (Ar) group, which may be either a substituted or unsubstituted benzene ring. The common structural element for the AAA fragrance ingredients listed in Table 1 is an alcohol group -C-(R1)(R2) OH and generically the AAA fragrances can be represented as an Ar-Alkyl-C-(R1)(R2) OH group. The structural details of the AAA primary, secondary, and tertiary alcohol fragrances are depicted in Figs. 1–3 in Section 2, under metabolism. Cinnamic alcohol is, structurally, a part of this group; however, because it was reviewed in a separate group summary (along with cinnamic aldehyde and cinnamic acid), it has not been included here.

For the primary alkyl alcohols, R1 and R2 are both hydrogen (H) and the alkyl may be a linear or branched carbon chain of 1–8 carbons (C1–C8). The resultant AAA primary alcohol generic formula can be represented as Ar-Alkyl-CH_2OH. Table 1 also includes three structurally AAA primary alcohols that are not covered by the generic AAA primary alkyl alcohol formula: β-methoxybenzene ethanol and 2-phenoxyethanol, both of which are congeners of phenethyl alcohol, and 2-(4-methylphenoxy)-ethanol, which is a congener of 2-*p*-tolylethanol.

For the secondary alkyl alcohols, the alkyl substituent is a linear carbon chain of 1–2 carbons and R1 is a methyl, *n*-propyl, *iso*-propyl, or sec-butyl. The resultant simplified AAA secondary alcohol generic formula can be represented as Ar-Alkyl-CH (R_1) OH.

For the tertiary alcohols, R1 and R2 may either both be methyl groups or R1 may be a methyl and R2 may be an ethyl group. In the case where R1 and R2 are equal to methyl, the alkyl substituent is a linear chain of 1 or 2 carbons and for R1 methyl and R2 ethyl the alkyl is a linear chain of 2 carbons groups. The resultant tertiary alcohol AAA generic formula can be represented, Ar-Alkyl-(R1)(R2) OH.

As noted above, the AAA aryl (aromatic) group for the primary and tertiary alcohols may be an unsubstituted or a substituted benzene ring. If substituted, the benzene ring is generally mono substituted in the para position. Additionally, substituted benzene ring derivatives may also include mono substituted ortho or meta isomers or a mixture of ortho, meta and para isomers in which the para-isomer is the major component. The AAA benzene ring substituents include methyl, isopropyl, tertiary butyl, and methoxy groups.

The primary path of metabolism for the AAA fragrance ingredients is contingent on whether the AAA fragrance ingredient includes a primary, secondary, or tertiary alkyl alcohol. The metabolic pathways for the AAA primary, secondary, or tertiary alkyl alcohols are illustrated in Figs. 1–3 in Section 2 on metabolism. Published studies have generally confirmed that the AAA primary and secondary alkyl alcohols may either be conjugated and excreted directly, or oxidized to benzoic acids before being conjugated and excreted (JECFA, 2002, 2003 and additional references cited in Section 2). AAA tertiary alkyl alcohols are not metabolized and are conjugated and excreted unchanged. The aryl (benzene) ring substituent may also be degraded, but generally the metabolic degradation of the aryl ring substituent is not a primary pathway and does not affect the metabolism and or conjugation/excretion of AAA primary or secondary alkyl alcohols and any related metabolites. This review will illustrate that these materials have similar metabolic pathways suggesting that their toxicity profiles may be similar.

Considering that the parent compounds tested in the different systems are hydrolysed and form the alcohol and the acid it can be concluded that the test result apply to both the parent compounds and the resulting metabolites. Since all the short term and repeated dose studies, revealed a low toxicity this conclusion applies to the group of the AAA primary and secondary alkyl alcohols including their metabolites. This seems also to apply to the AAA tertiary alcohols as well, although they are less readily metabolized.

The molecular weights of the 24 AAA primary alcohol fragrance ingredients listed in Table 1 vary appreciably, and ranged from a high of 206.29 g/mol for 2-benzylheptanol to a low of 108.14 for benzyl alcohol. Log K_{ow} increased with increasing carbon chain length of the primary alkyl alcohol and with alkyl aryl ring substitution and ranged from Log K_{ow} = 4.44 for 2-benzylheptanol to Log K_{ow} = 0.73 for β-methoxy benzeneethanol. As a group, the 24 AAA primary alcohol fragrances have low to essentially no volatility in air. Water solubility, which is generally inversely proportional to Log K_{ow}, ranged from 21.23 mg/L @25 °C for 2-benzylheptanol to 57,420 mg/L at 25 °C for β-methoxy benzeneethanol.

The molecular weights of the six AAA secondary alcohol fragrance ingredients listed in Table 1 ranged from 122.17 g/mol for α-methylbenzyl alcohol, to 178.28 g/mol for α-isobutylphenethyl alcohol, excluding the two zero use materials. Log K_{ow} also increased with increasing carbon chain of the secondary alkyl alcohol length and ranged from Log K_{ow} = 3.38 for α-isobutylphenethyl alcohol to Log K_{ow} = 1.49 for α-methylbenzyl alcohol. There are no alkyl substituted aryl ring AAA secondary alcohol congeners. As a group, the aryl alkyl secondary alcohol fragrances have generally low volatility. Water solubility, which is generally inversely proportional to Log K_{ow}, ranged from 234 mg/L at 25 °C for α-isobutylphenethyl alcohol to 19,540 mg/L for α-methylbenzyl alcohol.

The molecular weights of the 6 AAA tertiary alcohol fragrance ingredients listed in Table 1 ranged from a high of 178.28 g/mol for 1-phenyl-3-methyl-3-pentanol to a low of 136.19 g/mol for 2-phenyl-2 propanol. The Log K_{ow} generally increased with increasing tertiary alkyl carbon chain length of the alcohol and alkyl aryl ring substitution and ranged from Log K_{ow} = 3.42 for the 1-phenyl-3-methyl-3-pentanol, to a low of Log K_{ow} = 1.95 for 2-phenyl-2-propanol. As a group, the AAA tertiary alcohol fragrances have generally low volatility. Water solubility, which is generally inversely related to Log K_{ow}, ranged from 218.1 mg/L at 25 °C for 1-phenyl-3-methyl-3-pentanol to 6.113 mg/L at 25 °C for 2-phenyl-2-propanol.

2.2. Occurrence and use

While the AAA compounds are predominately used as fragrance ingredients, some of the AAA primary alkyl alcohols are used as flavoring agents. These include anisyl alcohol, benzyl alcohol and phenethyl alcohol and the FDA has designated these compounds as GRAS for use as flavor ingredients in food products. The annual worldwide production of the individual AAA fragrance and flavoring ingredients varies from less than 0.01 to greater than 1000 metric tons.

Several fragrance ingredients in the aryl alkyl alcohols group have been reported to occur in nature. Benzyl Alcohol (CAS RN 100-51-6), α-methylbenzyl alcohol (CAS RN 98-85-1), and phenethyl alcohol (CAS RN 60-12-8) have been reported to occur in species of allium plants. α,α-dimethylphenethyl alcohol (CAS RN 100-86-7), α-methylbenzyl alcohol (CAS RN 98-85-1), 2-phenyl-2-propanol (CAS RN 617-94-7), and α-propylphenethyl alcohol (705-73-7) have been reported to occur in various types of cheese and cocoa. Anisyl Alcohol (CAS RN 105-13-5), *p*-isopropylbenzyl alcohol (CAS RN 536-60-7), phenethyl alcohol (CAS RN 60-12-8), and *p*-α,α-trimethylbenzyl alcohol (CAS RN 1197-01-9) have been reported to occur in anise and angelica. 2-Phenoxyethanol (CAS RN 122-99-6) has been reported to occur in species of mangifera plant and 2-*p*-tolylethanol (CAS RN 699-02-5) has been reported to occur in mushrooms (VCF, 2010).

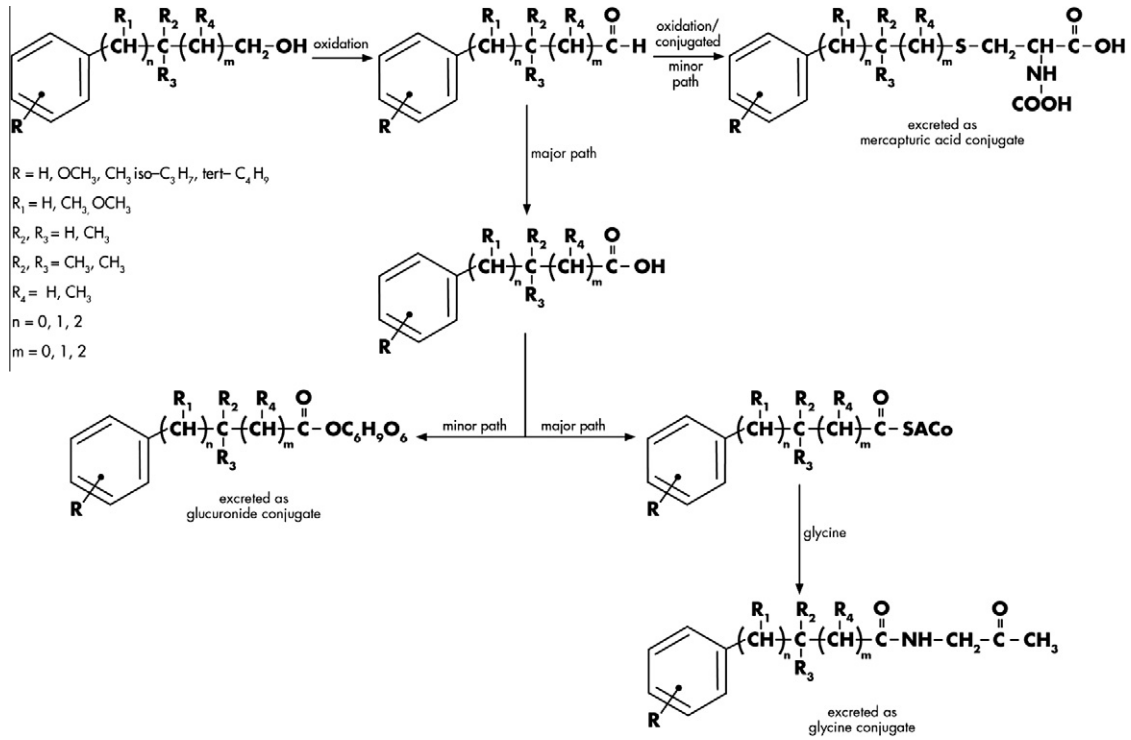
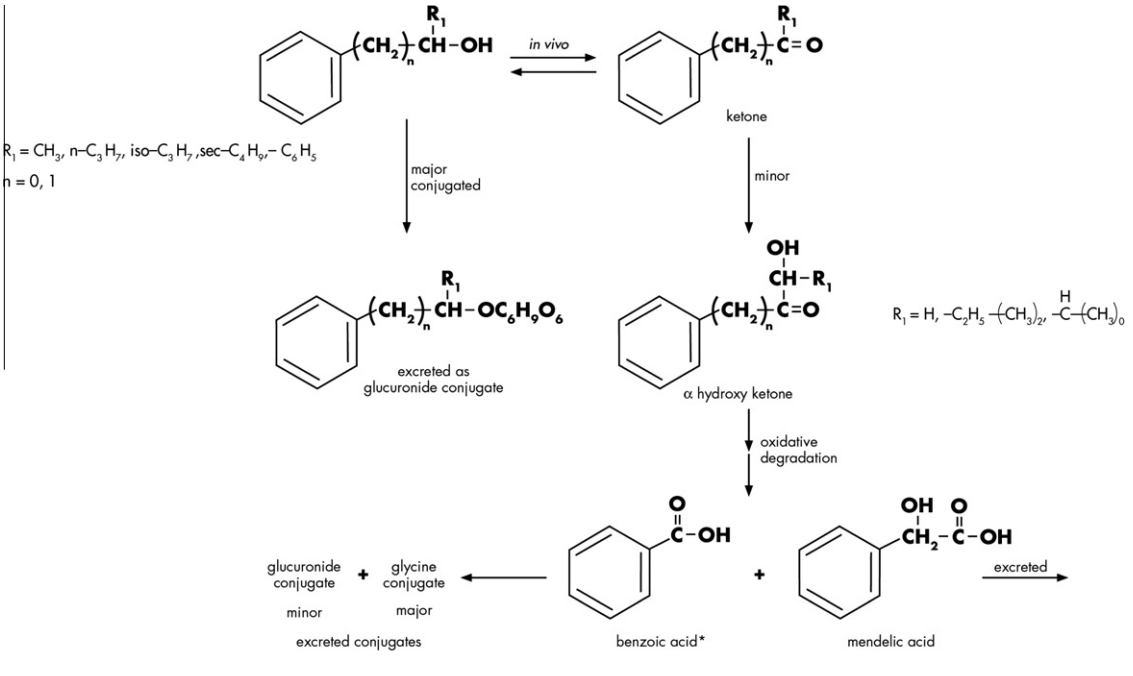


Fig. 1. Aryl alkyl primary alcohol metabolism.



* Oxidative degradation of aryl alkyl secondary alcohols with even carbon chain length will generate phenethyl acetic acid which is excreted as glycine, laurine, and or glutamine conjugates.

Fig. 2. Proposed aryl alkyl secondary alcohol metabolism.

2.3. Estimated consumer exposure

All of the AAA exposure data in Table 1 were provided by the fragrance industry. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).

Potential consumer exposure to fragrance materials occurs through the dermal and/or inhalation routes of exposure. When conservative estimates for evaporation, rinsing and other forms of product removal are taken into account (Cadby et al., 2002), worst-case scenario calculations indicate that application to skin following use of cosmetics represents the major route of exposure

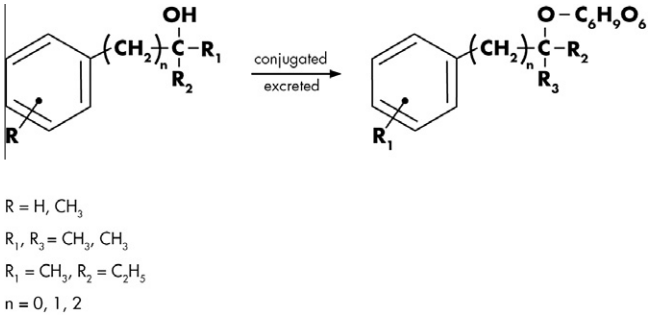


Fig. 3. Proposed aryl alkyl tertiary alcohol metabolism and glucuronic acid excretion.

to fragrance ingredients. Therefore, the dermal route was the major route in assessing the safety of these compounds.

The fragrance industry has developed three types of approaches to estimate potential exposure for consumers to fragrance materials. All three types of exposure are summarized in Table 1. The first is volume of use. The total worldwide volume of use for fragrance materials for the AAA fragrance ingredients ranges from less than 0.01 metric tons per year for 2-(3-methylphenyl) ethanol, 2-*p*-tolylethanol and α,α,4-trimethylphenethyl alcohol and to greater than 1000 metric tons per year for phenethyl alcohol (IFRA, 2008). The reported volume for each of the AAA fragrance ingredient represents the annual volume used in formulated mixtures of fragrances in all the finished consumer product categories. The volume of use is determined by IFRA approximately every four years through a comprehensive survey of IFRA and RIFM member companies. As such the volume of use data from this survey provides volume of use of fragrance ingredients for the majority of the fragrance industry.

The second method estimates potential percutaneous (total human skin exposure) absorption from the entire body based on the use of multiple consumer personal care products containing the same fragrance ingredient. The dermal systemic exposure in cosmetic products is calculated based on the concentrations in the ten types of the most frequently used personal care and cosmetic products (anti-perspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap).

The concentration of the fragrance ingredient in fine fragrances is obtained from examination of several thousand commercial formulations. The upper 97.5 percentile concentration is calculated from the data based on these. This upper 97.5 percentile concentration is then used to estimate the concentrations of fragrances for all 10 consumer products. These concentrations are multiplied by the amount of product applied, the number of applications per day for each product type, and a "retention factor" (ranging from 0.001 to 1.0) to account for the length of time a product may remain on the skin and/or the likelihood of the fragrance ingredient being removed by washing. The resultant calculation represents the total consumer exposure (mg/kg/day) (Cadby et al., 2002; Ford et al., 2000). In view of all of the above assumptions, the total calculated consumer exposure is a conservative estimate of daily consumer exposure. It is unlikely that a consumer will consistently use on a daily basis a number of the different consumer products which are all perfumed with the upper 97.5 percentile level of the fragrance ingredient from a fine fragrance type products (Cadby et al., 2002, Ford et al., 2000). The total consumer exposures to the AAA fragrance ingredients ranges from 0.0004 mg/kg body weight/day for α-methylbenzyl alcohol to 0.3198 mg/kg body weight/day for phenethyl alcohol in the high-end user of cosmetic products containing these materials (see Table 1) (IFRA, 2004).

The third method provides maximum skin levels. For consideration of potential sensitization, the exposure is calculated as the percent concentration of the fragrance ingredient applied to the skin based on the use of 20% of the fragrance mixture in the fine fragrance consumer product (IFRA, 2004). The maximum skin exposure levels of the AAA compounds that form part of the formulae of fine fragrances vary widely and have been reported to range from 0.004% for 2-phenyl-2-propanol to 11.72 % for phenethyl alcohol. The maximum skin exposure for the AAA compounds in fine fragrance products are listed in Table 1 (IFRA, 2004).

The recently revised IFRA Standards on anisyl alcohol; benzyl alcohol; and β,β-3-trimethyl benzenepropanol are based on the dermal sensitization quantitative risk assessment (QRA) approach for fragrance ingredients (Api and Vey, 2008). The details of the Standard can be found in Section 5.8 of this fragrance review. Additionally, the material 3-(*p*-Isopropyl) phenyl-2-methyl-1-propanol has an IFRA Standard prohibiting its use as a fragrance ingredient based on the sensitizing potential of the alcohol. As discussed earlier, since this material is not used as a fragrance material it will not be discussed in the safety report.

Exposure data were not available for all the AAA fragrance materials. These materials include β-methoxybenzeneethanol; 2-methyl-5-phenylpentanol; and 4-phenyl-3-buten-2-ol, and a default value of 0.02% was then used to calculate the maximum daily exposure on the skin which is 0.0005 mg/kg body weight for high end users of these products.

In assessing safety, the calculated dermal systemic exposure in cosmetic products can then be compared to the indices of systemic toxicity such as NOAEL and LOAEL that are obtained from the repeat dose sub-chronic, chronic and reproductive toxicity studies to derive a margin of exposure (MOE). Systemic exposures (i.e., the dose absorbed through the skin and available to the systemic circulation) were estimated based on dermal absorption rates. Where such data were lacking, as a conservative measure, dermal absorption was considered to be 100% (i.e., the maximum skin exposure value was considered as the estimate of systemic exposure).

All exposure data were provided by the fragrance industry. Further explanation of how the data were obtained and of how exposures were determined has been previously reported by Cadby et al. (2002) and Ford et al. (2000).

3. Metabolism

AAA metabolism is dependent on whether the alcohol group is primary, secondary or tertiary. Aryl ring substitution should have little or no effect on the principle metabolic pathways depicted in Figs. 1–3 (adapted from Adams et al., 2005a). Carbon chain length of the alcohol should also not affect the overall metabolism (JECFA, 2002a).

The metabolism of the aryl primary alkyl alcohols, such as anisyl alcohol; benzyl alcohol; and phenethyl alcohol and the aryl alkyl secondary alcohols, such as α-methylbenzyl alcohol, have been extensively studied and published in summary food safety evaluations by FEMA and JECFA (Adams et al., 2005a,b, 2007; JECFA, 2002a–c; 2003) and as individual metabolism studies in other publications. Metabolism data for the tertiary alcohols is limited to 2-phenyl-2-propanol and *p*-α,α-trimethylbenzyl alcohol, which have been identified metabolite pathways for cumene and *p*-cymene respectively.

3.1. Primary alcohols

The general metabolic pathway for the aryl primary alkyl alcohols (Adams et al., 2005a,b; JECFA, 2002b,c, 2003) serves as a rep-

resentative pathway for all of the primary alcohols included in Table 1 (Fig. 1). Initial metabolism results in oxidation of the primary alcohol to an aldehyde which is typically rapidly oxidized to the corresponding carboxylic acid and excreted primarily in the urine, mainly as the glycine conjugate, or to a lesser extent as glucuronide. On a minor pathway the aldehyde may be excreted as the mercapturic acid conjugate primarily in urine. It has been reported that phenethyl acetic acid, derived from the oxidation of phenethyl alcohol, is conjugated with taurine and glutamine in addition to glycine (JECFA, 2003). 2-Phenoxyethanol is rapidly absorbed after either topical or oral administration and excreted in the urine as phenoxy acetic acid (Howes, 1988a,b; JECFA, 2003).

In addition to the FEMA and JECFA food safety evaluations and the metabolism studies summarized therein, metabolism studies are available for some of the more commercially important aryl primary alkyl alcohols: *o*- and *p*-anisyl alcohol; benzyl alcohol; *p*-isopropylbenzyl alcohol; β-methylphenethyl alcohol; phenethyl alcohol; and 2-phenoxyethanol. The pathways and metabolites described are consistent with Fig. 1. The isopropyl group of *p*-isopropybenzyl alcohol was reported to undergo oxidation (Walde et al., 1983).

As expected, benzyl alcohol is metabolized in the skin to benzoic acid in a two step reaction: first benzyl alcohol is metabolized to benzaldehyde by alcohol dehydrogenase using NAD^+ as a cofactor; next benzaldehyde is converted to benzoic acid by aldehyde dehydrogenase also using NAD^+ as a cofactor. Benzoic acid can also conjugate with glycine to form hippuric acid (Van Hulst et al., 1997). Oral exposures of rats and rabbits to benzyl alcohol yielded similar metabolic profiles (Bray et al., 1951; Diack and Lewis, 1928).

In a study investigating the metabolites of halogenoalkyl benzenes and their corresponding alcohols, anisyl alcohol (250 mg/kg), benzyl alcohol (250 mg/kg), or phenethyl alcohol (300 mg/kg) was administered by gavage to rabbits (Bray et al., 1958). Urinary metabolites of anisyl alcohol were said to include 53% glucosiduronic acid conjugate, 49% glucuronic acid conjugate, 32% unconjugated *p*-methoxybenzoic acid and 19% glycine conjugate (the gross overestimate of the total dose was unexplained). Metabolites of benzyl alcohol included 74% of the glycine conjugate, 14% of the glucosiduronic acid conjugate, and 8% of both the glucuronic acid and unconjugated benzoic acid. Phenethyl alcohol metabolites included 42% glycine conjugate, 19% unconjugated phenylacetic acid, and 5% glucusiduronic acid conjugate (not all of the metabolites were accounted for in the urine). None of these fragrances resulted in significant amounts of mercapturic acids or sulfate esters.

In a male volunteer, 26% of a 4000 mg oral dose of phenethyl alcohol was excreted in the urine mostly as phenylacetylglutamine within 24 h. Most of the dose was presumed, but not demonstrated, to be excreted as phenylacetic acid (Thierfelder and Schempp, 1917). In 2 males exposed dermally (site open for first hour and semi-occluded thereafter) to 10 mg/100 cm^2 radiolabeled phenethyl alcohol in ethanol for 6 h/day for 5 days, two metabolites were detected in the urine. The major metabolite (4.1% of the dose) was identified as phenylacetylglutamine, the glutamine conjugate of phenylacetic acid. The second metabolite (2.7% of the dose) was a glucuronide conjugate of phenylacetic acid (RIFM, 1987a).

Oral (gavage) administration of 460 mg/kg phenethyl alcohol to rabbits resulted in urinary excretion of 7% of the dose conjugated with glucuronide and none of the dose conjugated to sulfate (Smith et al., 1954). Phenethyl alcohol is a metabolite of ethylbenzene, and to better understand its metabolism, 2 mmol/kg (244 mg/kg) of phenethyl alcohol was orally administered to three rabbits. Urine was collected 24 h after the dose (El Masry et al., 1956). Only 3% was excreted as the hippuric acid, and a trace amount as phenaceturic acid, which indicates that very little-oxidation takes place.

In a series of studies evaluating the dermal application of radiolabeled phenethyl alcohol in rats, phenylacetic acid was the primary entity in the urine associated with radioactivity, regardless of dosage. The major metabolite in the urine excreted over 24 h after a single dose or five consecutive doses was phenaceturic acid which accounted for 73–87% of the urinary radioactivity. Hippuric acid accounted for 4–6%, phenylacetic acid accounted for 4% of urine radioactivity and phenethyl alcohol accounted for 1–2% of urine radioactivity (RIFM, 1986a). After dermal application of phenethyl alcohol in rabbits, the plasma phenylacetic acid concentration-time profile after a dose of 700 mg/kg differed markedly from that of the 140 mg/kg dose. At the high dose, the peak plasma radioactivity of 623 μ/ml at 6 h only gradually declined by 24 h, while at the low dose peak plasma radioactivity of 91.2 μg/ml at 4 h rapidly declined by 12 h. The results suggest that the high dose saturated the glycine pathway by which phenylacetic acid is excreted (RIFM, 1988a).

In humans, 61% of an oral dose of 2-phenoxyethanol was excreted in the urine as the parent compound; no metabolites were identified (in dogs the percentage of the dose was 55%) (Thierfelder and Schempp, 1917). In rats receiving an oral dose of radiolabelled 2-phenoxyethanol, 90% of the dose of ^{14}C was rapidly excreted in the urine. The main metabolite of excretion through the urine was phenoxyacetic acid, with conjugates of phenoxyethanol and phenoxyacetic acid present at lower levels, and trace amounts of the parental phenoxyethanol and ring hydroxylated metabolites detected (Howes, 1988a,b). Serum samples from New Zealand White rabbits (3 female per group) administered 2-phenoxyethanol by gavage at 100 or 300 mg/kg body weight/kg day for 4 (300 mg/kg group) or 11 (100 mg/kg group) consecutive days contained phenoxyethanol (0–7 mg/L), phenoxyacetic acid (700–1000 mg/L), and trace amounts of phenol. Significant conjugation of phenoxyethanol and its metabolites with glucuronide was found (RIFM, 1986c). In serum samples from rabbits gavaged with a single dose of 800 mg/kg body weight phenoxyethanol, high levels of phenoxyacetic acid were observed in serum at all time periods (1, 3, 6 and 24 h after dosing), peaking at 3 h after dosing (1.45 mg/mL) (Breslin et al., 1991). Lower concentrations of phenoxyethanol were observed in all samples (0–0.025 mg/mL). After 2 days of dosing with 600 mg/kg/day, the metabolite phenol was observed in serum (<1 μg/mL). In addition, 90% of the phenoxyethanol and 50% of the phenoxyacetic acid observed in serum from these animals was glucuronide or sulfate conjugates.

The primary alcohol *p*-isopropylbenzyl alcohol has been identified as a minor metabolite of *p*-cymene when given to rats and guinea pigs via gavage and is known to be excreted as isopropylbenzoic acid (cumic acid and its glycine conjugate) (Walde et al., 1983; Bakke and Scheline, 1970). *p*-Isopropylbenzyl alcohol represented 1% of the cymene dose given to rats and 6% of the dose given to guinea pigs (Walde et al., 1983). In a supplementary metabolism experiment by Walde et al. (1983) in which *p*-isopropylbenzyl alcohol was administered by gavage to a rat, three routes of metabolism were hypothesized with associated metabolites: (1) further oxidation of the methyl group to produce *p*-isopropylbenzoic acid and its glycine conjugate (*p*-isopropyl hippuric acid); (2) further hydroxylation of one of the two available sites of the isopropyl group will form a diol (2-*p*-(hydroxymethyl) phenylpropan-2-ol) and subsequent oxidation of each hydroxyl group 2-*p*-carboxyphenylpropionic acid; or (3) further hydroxylation of the other available sites on the isopropyl group forming another diol (2-*p*-(hydroxymethyl) phenylpropan-1-ol, followed by oxidation of the methanol group on the ring and reduction to *p*-isopropenylbenzoic acid (the unconjugated acid) and its glycine conjugate.

In a study investigating the metabolic products in urine and bile of β-methylphenethyl alcohol after oral administration in a human subject, dogs (4) or rabbits (7) most of the metabolites were excreted in the urine within 3 h and very little was excreted in the bile (Gruneberg and Langecker, 1957). Only 18% of the compound was

accounted for in the human subject (10% as the glucuronic acid conjugate, 6% as the parent compound, and 2.3 % as the ketone propiophenone). In dogs 57.5% was accounted for (20% as the glucuronic acid conjugate, 20% as the *p*-oxyphenyl propyl alcohol, 14.5% hippuric acid and 3% as unchanged compound). The percent hippuric acid excretion was larger after a lower dose than after a high one indicating that a certain capacity of glycine conjugation cannot be exceeded. In the rabbits 50% of the dose was accounted for (25% as the glucuronic acid conjugate 18% as the hippuric acid, 4% as the *p*-oxyphenyl propyl alcohol, and 3% as the unchanged compound). In addition, β-methylphenethyl alcohol is a $\dot{\omega}$-oxidation metabolite (25%) of cumene (isopropylbenzene), when cumene is fed to rabbits (Robinson et al., 1954). To further identify the form of the metabolites, β-methylphenethyl alcohol (500 mg/kg) was administered by gavage to rabbits (4) to determine the identity of subsequent metabolites. The major metabolites identified were the ester and ether glucuronides (6:1) which represented an average of 73% of the dose (Robinson et al., 1954).

3.2. Secondary alcohols

The general metabolic pathway for the three aryl alkyl secondary alcohols (Adams et al., 2007; JECFA, 2002), is illustrated in Fig. 2 and serves as the representative pathway for all of the secondary alcohols included in Table 1. Generally, the secondary alkyl alcohols are either excreted in the urine as glucuronic acid conjugates or further oxidized to a ketone metabolite which is interconvertable *in vivo* with the parent alcohol. With the exception of benzhydrol, which is not a fragrance ingredient and would be conjugated and excreted as the glycine conjugate, as a minor pathway, the AAA ketone metabolite is either further oxidized to a hydroxy aldehyde type metabolite, which may be converted to a carboxylic acid and excreted as the glycine conjugate, or a mandelic acid type metabolite and excreted as the glycine conjugate. For α-methylbenzyl alcohol and α-propylphenethyl alcohol, secondary alcohols having an alkyl group of odd carbon chain length, the carboxylic acid is benzoic acid; whereas for α-isobutylphenethyl alcohol, and secondary alcohols having an alkyl group of even chain length, the carboxylic acid is phenethylacetic acid.

In addition to the FEMA and JECFA food safety evaluations and the metabolism studies summarized therein, metabolism studies were identified for one commercially important secondary alcohol, α-methylbenzyl alcohol. The pathways and metabolites described in these papers are consistent with Fig. 2. α-Methylbenzyl alcohol, was identified as a metabolite of ethylbenzene and acetophenone when administered by gavage to rabbits or rats. The D (+) isomer subsequently became glucuronidated and excreted and the L (−) isomer became mandelic acid (Kiese and Lenk, 1974; Bakke and Scheline, 1970). Oral administration of 460 mg/kg α-methylbenzyl alcohol L (−) isomer to rabbits led to 50% of the dose excreted as glucuronic acid conjugate and 3% of the dose as ethereal sulfate conjugate (Kiese and Lenk, 1974; Smith et al., 1954). Similar findings have been found after oral exposure of rats (McMahon and Sullivan, 1966). α-Methyl benzyl alcohol can also metabolize to acetophenone, which can undergo hydroxylation to become hydroacetophenone, or -oxidation to -hydroxyacetphenone, which becomes phenylglyoxal then phenylglyoxylic acid. Further decarboxylation and conjugation with glycine led to hippuric acid (Kiese and Lenk, 1974). This latter pathway appears to be minor, less than 1% of the dose in rabbits after oral or intraperitoneal administration to rabbits (Kiese and Lenk, 1974) or subcutaneous injection in rats (0.15% of the dose) (Hopkins et al., 1972). To better understand α-methylbenzyl alcohol metabolism, 2 mmol/kg (244 mg/kg) was orally administered to rabbits (3) and urine was collected 24 h after the dose (El Masry et al., 1956). On average 28% was excreted as the hippuric acid and no phenaceturic acid was excreted indicating that $\dot{\omega}$-oxidation was most likely not a part of the metabolic pathway.

3.3. Tertiary alcohols

There are currently limited studies that are relevant for AAA tertiary alcohol metabolism. Thus, it is proposed, based on the published literature for tertiary alcohol metabolism, that the AAA tertiary alcohols listed in Table 1 should not be oxidatively degraded (Williams, 1959). Rather, as illustrated in Fig. 3, it is postulated that these compounds would be conjugated with glucuronic acid and excreted in the urine similarly as reported for the AAA secondary alcohols (Adams et al., 2007; JECFA, 2002).

A metabolism study in which cumene, i.e., isopropylbenzene, was fed to rabbits substantiates that AAA tertiary alcohols would be conjugated and excreted as the guluronide (Robinson et al., 1954). Robinson reported that the metabolism of cumene in rabbits resulted in a mixture of metabolites in which ω – oxidation predominated to produce 25% hydrotropic alcohol and 25 % hydrotropic acid. The other metabolite, 40% 2-phenyl-2-propanol, which is an AAA tertiary alcohol, was reported to be conjugated and excreted as the glucuronide.

The other tertiary alcohol with metabolic data is *p*-α,α-trimethylbenzyl alcohol, which is a minor metabolite of *p*-cymene (Walde et al., 1983). As noted above, cymene was given to rats and guinea pigs via gavage. The metabolite *p*-α,α-trimethylbenzyl alcohol represented 9% of the cymene given to rats and 14% of the dose given to guinea pigs. This metabolite was hypothesized to be further oxidized either by the addition of a hydroxyl group on one of the methyl groups adjacent to the alcohol, or by the addition of a hydroxyl group on the methyl substituent on the benzyl ring. This latter oxidation is a shared metabolite of *p*-isopropylbenzyl alcohol described above (metabolic route 3).

4. Toxicokinetics

4.1. Dermal route of exposure

4.1.1. Human studies

Two healthy male volunteers (36 and 27 years old) received 10 mg (in ethanol) of radiolabeled phenethyl alcohol applied to 100;cm^2 area of skin on the upper chest with occlusion for 6 h/day for 5 days (RIFM, 1987a). The skin was tape stripped, blood and urine samples were collected up to 120 h after treatment and feces were collected at 24 h intervals for 5 days. Samples were analyzed for radioactivity. The C_{max} was achieved at 1.5 h with radioactivity undetectable by 4 h. There was recovery of 7.6% of the dose in the urine within 48 h after application; radioactivity was undetectable in the feces. Approximately 90% of the radioactivity was lost from the skin during the 6-h exposure period. The authors presumed this was due to evaporation; 2.6% was recovered from the dressing and 0.64% from the skin washes.

A single dose of 40 g of skin cream containing 1.2% 2-phenoxyethanol was applied topically to four hospitalized volunteers with skin complaints. Recovery of phenylacetic acid in the urine of these patients over 3 days was used to measure skin penetration of the test material. The results were variable, at 8.5, 31, 33, and 48% of the applied dose (Howes, 1988a,b).

4.1.2. Animal studies

In a series of experiments by RIFM, unlabeled phenethyl alcohol was administered in one topical occlusive dosage of either 700 or 1400 mg/kg to rats (4/time point; 32/dose) to determine plasma levels of phenylethanol and phenylacetic acid (RIFM, 1988b). Radiolabeled phenethyl alcohol was applied in a similar manner to rats

at levels of 140 or 700 mg/kg (for measurement of plasma, urine and feces content) (RIFM, 1986a). In a supplemental study rats (2) were administered a single topical dose of 700 mg/kg radiolabeled phenethyl alcohol and housed in closed metabolism cages to monitor expired air (RIFM, 1986a). Rats (4/dose) received radiolabeled phenethyl alcohol in daily topical doses of 140 or 700 mg/kg for five days and urine/feces were collected up to 24 h during the last treatment (RIFM, 1986a).

In rats exposed to 700 or 1400 mg/kg of unlabeled phenethyl alcohol, the mean plasma concentrations of phenylacetic acid greatly exceeded those of phenethyl alcohol for most of the 24 h sampling period, indicating that rats were exposed for longer time periods to much higher concentrations of metabolite than unchanged phenethyl alcohol. Plasma phenethyl alcohol levels peaked at 0.5 h, whereas phenylacetic acid levels peaked at 4 h for both the 1400 and 700 mg/kg doses (RIFM, 1988b).

In rats exposed to 140 or 700 mg/kg of radiolabeled phenethyl alcohol and its metabolites, plasma levels indicated that a dermal dose of 140 mg/kg was rapidly absorbed and excreted in rats (C_{max} achieved at 2 h dropping to the limit of detection at 72–120 h post treatment) and that the 700 mg/kg dose was more slowly absorbed and excreted (C_{max} achieved at 4 h dropping to limit of detection at 96–120 h). Radiolabeled phenethyl alcohol and its metabolites were excreted predominantly via the kidneys into the urine; less than 1.8% was excreted in the feces. It appeared that a large loss resulted from evaporation at the applications site. Repeat-dose dermal application did not change the excretion pattern observed after a single dose.

In another study, a single dose of 430 mg/kg phenethyl alcohol was applied dermally to 40 female CD rats. Approximately 27% of the dose was recovered in the urine as phenylacetic acid. This recovery was much less than after oral administration of the same dose (70% recovered in urine as phenylacetic acid) (RIFM, 1990a). Presumably this was due to evaporation from the dermal application site and differing pharmacokinetics via the two routes of exposure.

Tissue distribution was determined after a 6-h dermal application of radiolabeled phenethyl alcohol (140 mg/kg) to male Long Evans rats (12). Tissues from pairs of rats were analyzed 3, 6, 12, 24, 48 or 73 h after treatment. Male Long Evans rats were chosen because this was the strain tested in a prior study (Mankes et al., 1983, 1984, 1985). At 72 h post treatment radiolabeled phenethyl alcohol appeared to have been rapidly absorbed and eliminated from most tissues, although some radioactivity was detected in fat, kidneys, pancreas, liver and treated skin (RIFM, 1986a).

Tissue distribution was also examined after 6-h dermal application of 140 and 700 mg/kg radiolabeled phenethyl alcohol to pregnant CD rats on gestation day (GD) 6–15. Single animals were sacrificed for whole body autoradiography at 2 h (140 mg/kg group) and 4 h (700 mg/kg group) after doses on GD 6, 10, or 15 and at 24 h and 48 h after the dose at GD15. In these rats, autoradiography confirmed the tissue distribution profile seen in the male Long Evans rats. Radioactivity initially was associated with the dermal application site, the gastrointestinal tract, kidneys and urinary tract, liver, blood and a number of endocrine and secretory organs. In rats examined at GD5 and 10, embryos were not clearly evident. However, after 10 doses, on GD15, radioactivity was observed in fetuses 2 h after dosing (RIFM, 1986a).

In New Zealand White rabbits, single unoccluded topical dosages of 140 or 700 mg/kg radiolabeled phenethyl alcohol resulted in mean plasma C_{max} 4 h after the 140 mg/kg dose and 6 h after the 700 mg/kg dose. Phenylacetic acid was identified as the radioactive metabolite with only minimal levels of phenethyl alcohol and additional metabolites. Mean radioactivity totals of 47% of the 140 mg/kg dose and 57% of the 700 mg/kg dose were recovered, the remainder was considered to have been lost by evaporation.

Radiolabeled 2-phenoxyethanol in ethanol was applied, dried, and covered with an occlusive patch at 94 mg/10 cm^2 or 108 mg/10 cm^2 to Colworth Wistar male rats. Approximately 62–72% of the dose was absorbed through the skin (Howes, 1988a,b). Most of the radiolabel was found in the urine at 24 and 48 h (55–60%); levels were higher during the first 24 h compared to the second 48-h time period. Of the remaining applied dose, 1–5% remained on the skin, 1–1.5% was expired in the air, 1–2% was found in the feces, 1–3% was found in the carcass and 5–7% remained on the patch. Recovery of radiolabeled 2-phenoxyethanol in skin cream applied to female rats was much higher with approximately 80–85% of the dose found in the urine in the first 24 h. Radiolabeled 2-phenoxyethanol in shampoo (0.928 mg/10 cm^2) was applied to female rats (3/dose) for 1, 5, or 10 min after which the excess was rinsed off with distilled water, dried with warm air and covered with a non-occlusive patch. After 10 min, 3% of the applied phenoxyethanol had penetrated the skin, whereas after 1 min, only 1.7% penetrated the skin (Howes, 1988a,b).

4.2. Oral route of exposure

4.2.1. Humans

After oral administration of benzyl alcohol to humans, 80–90% of the dose was converted within 6 h to benzoic acid and excreted as hippuric acid (Snapper et al., 1925). In a single male volunteer orally administered 10 mg of nonradioactive 2-phenoxyethanol dissolved in water, urine collected three days after dosing indicated it was rapidly excreted in the urine as phenoxyacetic acid, with no conjugates identified (Howes, 1988a,b).

4.2.2. Animal studies

Blood samples from juvenile rats (PND 28) treated with 0, 100, 300 or 600 mg/kg body weight/day benzyl alcohol from PND 22 were analyzed by HPLC-UV for the parent compound and metabolites (Foulon et al., 2005; DeJouffrey et al., 2004). Benzyl alcohol was not at measurable levels in the blood (detection limit was 0.5 μg/mL), but its oxidation product benzoic acid was present in significant amounts. Benzoic acid levels were proportional to the administered doses and maximum plasma levels were achieved 0.5 to 2.0 h after administration in both males and females, indicating an efficient first-pass metabolism after oral administration.

The pharmacokinetics in rats after oral administration of phenethyl alcohol has recently been studied (RIFM, 1990). In one study, phenethyl alcohol was administered by gavage as a single dose (430 mg/kg in an aqueous PEG200 solution) to female CD rats (4/time point [44]). Female CD rats (4/time point [40]) rats were also fed *ad libitum* for up to 24 h a diet containing encapsulated phenethyl alcohol in a gum Arabic matrix providing a nominal dose of 430 mg/kg. For both studies, concentrations of phenylethanol and phenylacetic acid in plasma, and total phenylacetic acid (+ conjugates) in urine were determined by GC/MS. In the gavage study, maximum plasma concentration of phenylethanol was reached in 0.25 h; for plasma phenyl acetic acid, maximum plasma concentration was reached in 4 h; 74% of the dose of phenethyl alcohol was excreted in urine as phenylacetic acid. In the diet study, maximum plasma concentration of phenylethanol was reached in 4 h; maximum concentration of plasma phenylacetic acid was reached in 10hr; 70% of the dose of phenethyl alcohol was excreted in urine as phenylacetic acid.

In Colworth Wistar rats (4 male, 4 female), radiolabeled 2-phenoxyethanol orally administered by gavage at doses of 16, 27 or 160 mg/kg body weight was extensively absorbed with 90% excreted rapidly in the urine as phenoxyacetic acid and conjugated phenoxyacetic acid. Only 1.8–2% was expired in the air, and even less excreted in the feces. After four days of dosing, and 2 h after the last dose less than 2% remained in the carcass (Howes, 1988a,b).

4.2.3. Secondary alcohols

The secondary alcohol, α-methylbenzyl alcohol, was reported to be absorbed much more efficiently from the abdominal cavity than from subcutaneous tissues, but no data were given (Theirfelder and Klenk, 1924).

4.3. Other routes of exposure

4.3.1. Humans

Benzyl alcohol is sometimes used as a preservative in medications and has been reported to cause "gasping syndrome" often accompanied by death in premature neonates. To address concerns about neonatal exposure in humans, 14 term and 9 preterm (gestational age 29 weeks for intravenous administration; gestational age 30.7 weeks for intramuscular administration) babies were given loading doses of phenobarbital containing benzyl alcohol (0.116–0.208 μmol/kg intravenous; or 0.141–0.153 μmol/kg intramuscular) to better understand the concentrations of benzoic acid that may exceed the capacity of the immature liver or kidney for detoxification through glycine conjugation to form hippuric acid (LeBel et al., 1988). After intravenous administration, there was a greater accumulation of benzoic acid in the serum of preterm neonates compared to the term neonates as measured by normalized peak levels, 2130.3 kg/L and 237.8 kg/L, respectively, and by normalized AUC_{it}, 1253.2 versus 483.0 kg-h/L. Higher levels of benzoic acid and lower levels of hippuric acid were found in the urine of preterm neonates compared to term neonates.

4.3.2. Animals

To determine plasma levels of test material following inhalation exposure, groups of 4 mice were exposed to benzyl alcohol. Air was passed into the cage through a glass tube containing 1.5 ml test material. Total test material volume was 20–50 mg. After 1 h of exposure, benzyl alcohol concentration in blood samples was 1.21 ng/ml. (Buchbauer et al., 1993).

5. Toxicological studies

5.1. Acute toxicity

Acute dermal toxicity studies have been performed with 12 primary, 1 secondary, and 4 tertiary alcohols; all, but two materials, in rabbits. The dermal LD_{50} values in rabbits range from 1680 to >5000 mg/kg body weight. All the compounds are of low acute toxicity by the dermal route (Table 2-1).

Acute oral toxicity studies have been performed with 13 primary, 2 secondary, and 5 tertiary alcohols. Two materials had two studies where LD_{50}s were under 1000 mg/kg body weight, including the primary alcohol phenethyl alcohol (650 mg/kg body weight in female rats and 400–800 mg/kg body weight in guinea pigs) and the secondary α-methyl benzyl alcohol (400 mg/kg body weight in rats and 250 mg/kg body weight in mice). However, in all other studies, the oral LD_{50} values in rats, mice, guinea pigs and rabbits are in the range of 1000 to <5000 mg/kg body weight. The overall weight of evidence in these and the other AAAs indicates a low acute toxicity when administered via the oral route (Table 2-2).

Acute toxicity data obtained from studies using exposure other than dermal or oral routes are summarized in Table 2-3. In an inhalation test with phenethyl alcohol, the LC_{50} was greater than 4600 mg/m^3 (RIFM, 1980d). The LC_{50} for benzyl alcohol was < 2000 ppm (8845 mg/m^3) (Carpenter et al., 1949). In an inhalation test with 2-phenoxyethanol rats exposed to concentrated vapor (no concentration reported) for 8 h and observed for 14 days showed no alterations (RIFM, 1983b). LC_{50} value was not determined.

5.2. Repeat-dose toxicity

The evaluation of repeat-dose systemic toxicity is based on oral studies with 7 primary alcohols, 2 secondary alcohols, and 1 tertiary alcohol, and on dermal studies with only primary alcohols. The metabolic pathways of the materials in this group appear to yield innocuous metabolites. Other studies can be found in Section 5.4 Carcinogenicity.

5.2.1. Dermal studies

Dermal studies with the aryl alkyl alcohols are summarized in Table 3-1.

5.2.1.1. Primary alcohols. In a screening study, anisyl alcohol was administered as a subcutaneous injection for 7 days at 100 mg/kg body weight/day to assess the effect on liver regeneration in partially hepatectomized rats ($n = 11$). Anisyl alcohol had no effect on liver regeneration (Gershbein, 1977).

Phenethyl alcohol was administered dermally to groups of Sprague–Dawley rats (15/sex) for 90 days at 0, 0.25, 0.5, 1.0, or 2.0 mL/kg of pure phenethyl alcohol (equivalent to 0, 250, 500, 1000, or 2000 mg/kg body weight/day). Among animals treated with 1000 or 2000 mg/kg body weight/day, body weights and weight gains were significantly decreased after 1 week of treatment and throughout the experiment. In males exposed to 1000 or 2000 mg/kg body weight/day, hemoglobin concentrations and leukocyte counts were decreased. Significant increases in the relative weights of the brain, kidneys, and gonads occurred in rats of both sexes that were given 2000 mg/kg body weight/day. No changes in blood biochemistry or urinary analyses were reported. The systemic NOAEL was 500 mg/kg body weight/day (Owston et al., 1981).

New Zealand White female rabbits (10) received daily occlusive dorsal application of 1000 mg/kg weight/day 2-phenoxyethanol to assess hematological effects (RIFM, 1985b). By day 8 of the study 3 animals were found dead and 4 were moribund and sacrificed. All exhibited hemoglobinuria, pale livers, dark kidneys, and dark spleens as a result of intravascular hemolysis. In a 90-day study with the same material, rabbits (10/sex/dose) receiving a dermal dose of 0, 50, 150 or 500 mg/kg body weight/day, showed sporadic erythema and scaling at the highest dose (RIFM, 1986b).

5.2.2. Oral studies

Toxicity studies with AAA fragrance ingredients via the oral route (gavage or diet) are summarized in Table 3-2.

5.2.2.1. Primary alcohols. Six repeat-dose oral toxicity studies were conducted with benzyl alcohol. In a series of tests by NTP, 16-day, 90-day and 2-year studies were performed with benzyl alcohol. In the 16-day studies (range finding) in which male and female F344 rats and B6C3F1 mice (5/sex/dose) received 0, 125, 250, 500, 1000 and 2000 mg/kg body weight/day by oral gavage in corn oil (NTP, 1980a), high mortality was observed at the two high dose groups in both species. Weight loss was observed at all doses with signs of toxicity observed at 250 mg/kg body weight/day for rats and 500 mg/kg body weight/day in mice. In the 90-day studies, benzyl alcohol was administered by gavage in corn oil to F344 rats and B6C3F1 mice at 0, 50, 100, 200, 400, or 800 mg/kg body weight/day (NTP, 1980b). Mortality was observed in the high dose male (8/10 dead at week 8) and female rats (1/10 dead at week 12). Survivors had decreased mean body weight and body weight gain, neurotoxicity (staggering after dosing), skeletal muscle atrophy, thymic toxicity (congestion, hemorrhage and atrophy), and nephrosis. An apparent decrease in mean body weight was reported for female mice receiving 200 or 800 mg/kg/day and male mice receiving 400 mg/kg/day (statistics were not reported for

Table 2-1
Acute toxicity studies – dermal.

	Species (No./dose)	LD_{50}*** (95% Confidence Interval)	References
Primary alcohols			
Anisyl alcohol	Rabbits (4)	3000 mg/kg (19,400–4060 mg/kg)	RIFM (1973a)
Anisyl alcohol	Mice (10)	>10,000 mg/kg*	Draize et al. (1948)
Benzyl alcohol	Cats (2)	<20 mL of 100% solution (both died) (2930 mg/kg based on average 15 lb. cat)	Graham and Kuizenga (1945)
2,2-Dimethyl-3-phenylpropanol	Rats (5/sex)	>15 mL/kg (1500 mg/kg)	RIFM (1981a)
p-Isopropylbenzyl alcohol	Rabbits (4)	2500 mg/kg (500–3000 mg/kg)	RIFM (1973a)
β-Methoxy benzeneethanol	Rabbits (3/sex)	>2000 mg/kg	RIFM (1979a)
β-Methylphenethyl alcohol	Rabbits (5)	>5000 mg/kg	RIFM (1974a)
2-Methyl-4-phenylpentanol	Rabbits (5/sex)	>2000 mg/kg	RIFM (1988c)
2-Methyl-5-phenylpentanol	Rats (10)	>2000 mg/kg	RIFM (1989a)
3-Methyl-5-phenylpentanol	Rats (8M)	>5000 mg/kg males	RIFM (1980a)
3-Methyl-5-phenylpentanol	Rats (8F)	3100 mg/kg females (2900–3320 mg/kg)	RIFM (1980a)
Phenethyl alcohol	Rabbits (4)	1680 mL/kg (1100–2570 mL/kg)	Carpenter et al. (1974)
Phenethyl alcohol	Rabbits (4/sex)	2535 mg/kg (1769–3364 mg/kg)	RIFM (1983a)
Phenethyl alcohol	Rats (10)	>5000 mg/kg	RIFM (1982a)
2-Phenoxyethanol	Rabbits (10 M)	3440 mg/kg (2990–3920 mg/kg)**	RIFM (1983b)
2-Phenoxyethanol	Rabbits	3290 mg/kg (2940–3600 mg/kg)**	RIFM (1983b)
2-Phenoxyethanol	Rabbits (10)	>5000 mg/kg	RIFM (1982a)
2-Phenoxyethanol	Rabbits (10)	>5000 mg/kg	RIFM (1978a)
2-Phenoxyethanol	Guinea pigs	>20 mL/kg (concentration not reported)	RIFM (1984a)
p-Tolyl alcohol	Rabbits (10)	>5000 mg/kg	RIFM (1978a)
β,*β*-3-Trimethyl benzenepropanol	Rabbits (5/sex)*	>5000 mg/kg	RIFM (1987b)
Secondary alcohols			
α-Methylbenzyl alcohol	Rabbits (4–6)	>2500 mg/kg	RIFM (1973a)
α-Methylbenzyl alcohol	Guinea pigs (6)	>15000 mg/kg	Smyth and Carpenter (1944)
Tertiary alcohols			
α,α-Dimethylphenethyl alcohol	Rabbits (10)	>5000 mg/kg	RIFM (1973a)
2-Methyl-4-phenyl-2-butanol	Rabbits (6)	<5000 mg/kg	RIFM (1973b)
1-Phenyl-3-methyl-3-pentanol	Rabbits (10)	>5000 mg/kg	RIFM (1975a)
2-Phenyl-2-propanol	Rabbits (4)	4300 mg/kg (2700–6900 mg/kg)	RIFM (1977a)

* OECD 402.
** Assume 100% solution.
*** For the purpose of comparison some units have been changed from the reported units in the original study.

the 13-week studies). The apparent NOAEL was 100 mg/kg body weight/day for rats and for mice. In the 2-year gavage study rats received 0, 200 or 400 mg/kg body weight/day and mice received 0, 100, or 200 mg/kg body weight/day 5 days a week (NTP, 1989; Zeiger et al., 1990). No apparent compound-related neoplastic or non-neoplastic lesions were observed. The NOAEL was 400 and 200 mg/kg body weight/day for rats and mice, respectively.

β-Methylphenethyl alcohol was administered to Wistar rats (15/sex/dose) in the diet at 0, 10, 40, or 160 mg/kg body weight/day for 90 days (Gaunt et al., 1982). Increased liver weight at the highest dose level in both sexes and increased kidney weight at the two highest dose levels in males were considered to be treatment-related. The NOAEL was 10 mg/kg body weight/day.

In a 28-day repeat dose toxicity study, 2-methyl-4-phenylpentanol was administered by gavage in corn oil to rats (5/sex/dose) at 0, 5, 55 or 500 mg/kg body weight/day (RIFM, 1988f). The NOAEL was determined to be 55 mg/kg body weight/day based on serum chemistry changes, increased kidney, and liver weights in both sexes at 500 mg/kg body weight/day.

In another 28-day repeat dose toxicity study, 2-methyl-5-phenylpentanol, was administered by gavage in polyethylene glycol 400 (PEG 400) to rats (6/sex/dose) at 10, 200 and 1000 mg/kg body weight/day. The NOAEL was determined to be 10 mg/kg body weight/day in males and 200 mg/kg body weight/day in females, based on slightly reduced body weight gains (RIFM, 1990b).

SD rats (2/sex) were given phenethyl alcohol by gavage at 500, 1600 and 5000 mg/kg body weight in 0.25% methylcellulose for 14 days. The LOAEL of 500 mg/kg body weight/day was based on inactivity, ptosis, diarrhea, decreased activity and body tone, poor grooming, abnormal stance, hypersensitivity, piloerection, chromodacryorrhea and prostration (RIFM, 1982b). Phenethyl alcohol was administered to male rats (12) by gavage for 4 months at 50.8 mg/kg body weight/day in order to determine the functional state of the liver (Zaitsev and Rakhmanina, 1974). Compared to control animals, treated animals showed increased blood cholinesterase, alanine aminotransferase, content of serum thiols, and decreased protein content. Histopathological studies were not performed.

New Zealand White rabbits (3 females) were administered 2-phenoxyethanol by gavage with 100, 300, 600, or 1000 mg/kg body weight/day for 10 days (RIFM, 1986c). Blood, urine, and selected tissue samples were taken for histopathology. 100% mortality was observed at 600 and 1000 mg/kg body weight/day. Effects at 100 mg/kg/day and above included decreased body weight and changes in hematologic parameters. Organs from rabbits receiving 600 or 1000 mg/kg body weight/day had gross and microscopic abnormalities consistent with hemolytic anemia and decreased hematopoiesis. The LOAEL was 100 mg/kg body weight/day. F344 rats (2 females/dose) received 2-phenoxyethanol by gavage at, 1250, or 2500 mg/kg body weight/day for 14 days (RIFM, 1986c). In another gavage study, rats (5/dose) were given 2-phenoxyethanol at 100, 300, or 1000 mg/kg body weight/day for 15 days (RIFM, 1984a). There were enlarged Peyer's patches and a decrease in AST and ALT in the 1000 mg/kg body weight/day animals: no other changes in hematology or histopathology were identified. The systemic NOAEL appeared to be 100 mg/kg body weight/day. Full details of the study were not disclosed.

2-Phenoxyethanol was administered 0, 1, 2.5, 5, 7.5, or 10% in the diet to CD-1 mice (8/sex/dose) for a 14-day range finding study (NTP, 1984), which is equivalent to 1500, 3750, 7500, 11,250, or

Table 2-2
Acute toxicity studies – oral.

Material	Species (No./dose)	LD_{50}** (95% Confidence Interval)	References
Primary alcohols			
Anisyl alcohol	Rats (50)	1.2 mL/kg (1330 mg/kg)	Draize et al. (1948)
Anisyl alcohol	Mice (90)	1.6 mL/kg (1780 mg/kg)	Draize et al. (1948)
Benzyl alcohol	Rabbits (3)	1040 mg/kg	Graham and Kuizenga (1945)
Benzyl alcohol	Rats	1230 mg/kg	Bar and Griepentrog (1967)
Benzyl alcohol	Rats (5/sex)	2490 mg/kg (1040–3040 mg/kg)	Jenner et al. (1964)
Benzyl alcohol	Rats (2/sex)	1570 mg/kg (1400–1760 mg/kg)	RIFM (1992a)
Benzyl alcohol	Rats	1230 mg/kg	Nishimura et al. (1994); Koch et al. (1993)
Benzyl alcohol	Rats (5)	2800 mg/kg	Graham and Kuizenga (1945)
Benzyl alcohol	Rats	3100 mg/kg (2850–3370 mg/kg)	Smyth et al. (1951)
Benzyl alcohol	Mice (5/sex)	1580 mg/kg (1410–1770 mg/kg)	Jenner et al. (1964)
2,2-Dimethyl-3-phenylpropanol	Rats (5/sex)	1.97 mL/kg (1970 mg/kg)	RIFM (1981b)
p-Isopropylbenzyl alcohol	Rats (10)	1020 mg/kg (900–1140 mg/kg)	RIFM (1973a)
β-Methoxy benzeneethanol	Rats (5M)	2030 mg/kg (1530–2670 mg/kg)	RIFM (1979b)
β-Methylphenethyl alcohol	Rats (10)	2300 mg/kg (1893–2707 mg/kg)	RIFM (1974a)
2-(4-Methylphenoxy)ethanol	Rats (5F)*	1110 mg/kg	RIFM (2000a)
2-(4-Methylphenoxy)ethanol	Rats (5M)	>2000 mg/kg	RIFM (2000a)
2-Methyl-4-phenylpentanol	Rats (5/sex)	3600 mg/kg (3100–4200 mg/kg)	RIFM (1988d)
2-Methyl-4-phenylpentanol	Mice (2/sex or 5/sex)	>800 ⩽1600 mg/kg	RIFM (1988e)
2-Methyl-5-phenylpentanol	Rats (10)	>2000 mg/kg	?RIFM (1988)
3-Methyl-5-phenylpentanol	Rats (10F)	2300 mg/kg (1560–3380 mg/kg)	RIFM (1980b)
3-Methyl-5-phenylpentanol	Rats (8/sex)	2300 mg/kg (1760–3010 mg/kg)	RIFM (1980c)
Phenethyl alcohol	Guinea pigs	400–800 mg/kg	Treon (1963a)
Phenethyl alcohol	Guinea pigs, Rats, Mice,	2540 mg/kg	Zaitsev and Rakhmanina (1974)
Phenethyl alcohol	Rats	1790 mg/kg	Bar and Griepentrog (1967)
Phenethyl alcohol	Rats (5/sex)	1790 mg/kg (1580–2020 mg/kg)	Jenner et al. (1964)
Phenethyl alcohol	Rats (10)	1500 mg/kg (1200–2000 mg/kg)	RIFM (1982a)
Phenethyl alcohol	Rats	1609 mg/kg (1400–1850 mg/kg)	RIFM (1982b)
Phenethyl alcohol	Rats	1800 mg/kg (1340–2450 mg/kg)	Rumyantsev et al. (1987)
Phenethyl alcohol	Rats (4F)	650 mg/kg females (310–1360 mg/kg)	Purchase (1969)
Phenethyl alcohol	Rats (4M)	1430 mg/kg males (650–2940 mg/kg)	Purchase (1969)
Phenethyl alcohol	Rats	2460 mL/kg (1790–3390 mL/kg)	Carpenter et al. (1974)
Phenethyl alcohol	Mice	2190 mg/kg (1827–2658 mg/kg)	RIFM (1974b)
Phenethyl alcohol	Mice	800–1500 mg/kg	Treon (1963a)
2-Phenoxyethanol	Rats	>3000 mg/kg	RIFM (1983c)
2-Phenoxyethanol	Rats (5/sex)	1345 mg/kg (M); 1902 mg/kg (F)	RIFM (1984a)
2-Phenoxyethanol	Rats (10M)	2580 mg/kg (2390–2770 mg/kg)	RIFM (1983b)
2-Phenoxyethanol	Rats	1260 mg/kg (1120–1420 mg/kg)	RIFM (1983b); Smyth et al. (1951)
2-Phenoxyethanol	Rats	2210 mg/kg (2010–2420 mg/kg)	RIFM (1983b)
2-Phenoxyethanol	Rats (10M)	2200 mg/kg (1400–3400 mg/kg)	RIFM (1982a)
2-Phenoxyethanol	Rats (10)	2000 mg/kg (1300–3200 mg/kg)	RIFM (1978a)
p-Tolyl alcohol	Rats (10)	3900 mg/kg (2700–5500 mg/kg)	RIFM (1978a)
β,*β*-3-Trimethyl benzenepropanol	Rats (5/sex)*	3570 mg/kg (3120–4030 mg/kg)	RIFM (1985a)
Secondary alcohols			
α-Methylbenzyl alcohol	Rats	400 mg/kg	Bar and Griepentrog (1967)
α-Methylbenzyl alcohol	Rats (6M)	400 mg/kg	Smyth and Carpenter (1944)
α-Methylbenzyl alcohol	Rats (5/sex)	>1250 and <2500 mg/kg	NTP (1990)
α-Methylbenzyl alcohol	Mice (5/sex)	>1250 and <2500 mg/kg	NTP (1990)
α-Propylphenethyl alcohol	Rats (5/sex)*	>2000 mg/kg	RIFM (2000b)
Tertiary alcohols			
α,α-Dimethylphenethyl alcohol	Guinea pigs (5/sex)	988 mg/kg (705–1380 mg/kg)	Jenner et al. (1964)
α,α-Dimethylphenethyl alcohol	Rats (10)	1350 mg/kg (1020–1680 mg/kg)	RIFM (1973a)
α,α-Dimethylphenethyl alcohol	Rats (5/sex)	1280 mg/kg (934–1770 mg/kg)	Jenner et al. (1964)
α,α-Dimethylphenethyl alcohol	Rats	1280 mg/kg	Bar and Griepentrog (1967)
2-Methyl-4-phenyl-2-butanol	Rats (10)	<5000 mg/kg	RIFM (1973b)
1-Phenyl-3-methyl-3-pentanol	Rats (10)	2950 mg/kg (2350–3550 mg/kg)	RIFM (1975a)
2-Phenyl-2-propanol	Rats (10)	1300 mg/kg (1000–1700 mg/kg)	RIFM (1977a)
p-α,α-trimethylbenzyl alcohol	Rats (5/sex)*	>2000 mg/kg	RIFM (2000c)

* OECD 401.
** For the purpose of comparison some units have been changed from the reported units in the original study.

15,000 mg/kg body weight/day. Decreased weight gain for both sexes was observed at 7500 mg/kg body weight/day, and mortality was increased at the two higher doses. The NOAEL was 3750 mg/kg body weight/day when administered in the diet based on body weight and weight gain.

β,*β*-3-Trimethyl-benzenepropanol was administered to Wistar rats (10/dose) at 0, 800, 3000 or 10000 ppm (0, 80, 300, 100 mg/kg body weight/day) in a 28 day dietary study. A NOEL of 800 ppm (80 mg/kg body weight/day) was based on minor observations considered not of toxicological significance (RIFM, 1987c).

5.2.2.2. Secondary alcohols. In a 90-day study Sprague–Dawley rats were fed diets to provide intakes of the secondary alcohol α-isobutylphenethyl alcohol at 0, 10, 40 or 160 mg/kg body weight/day (Ford et al., 1983). At the high dose a reduction in weight gain (potentially resulting from unpalatability), mild proteinuria in females, increased relative liver weight in males, and reduced serum glucose and a low reticulocyte count were observed. Serum glucose was decreased at 40 mg/kg body weight/day; however, the significance of this effect was questioned. Due to that small reduction in serum glucose (5.5%) at the 40 mg/kg body weight/day dose, the

Table 2-3
Acute toxicity studies – inhalation and miscellaneous.

Material	Species-route (No./dose)	LD50* (95% Confidence Interval)	References
Primary alcohols			
Benzyl alcohol	Dogs - iv	>5.0 and <5.1 mg/kg	Kimura et al. (1971)
Benzyl alcohol	Cat (1) - iv	600 mg/kg (100% mortality)	Macht (1920)
Benzyl alcohol	Rats – iv (0.9% solution, fast iv)	301 mg/kg (272–331 mg/kg)	Kimura et al. (1971)
Benzyl alcohol	Rats – iv (94% solution, slow iv)	47–75 mg/kg	Kimura et al. (1971)
Benzyl alcohol	Rats (6) - inh	⩽2000 ppm (<8845 mg/m^3)	Carpenter et al. (1949)
Benzyl alcohol	Rats (6) – inh	1000 ppm (4422 mg/m^3); minimal lethal exposure time=2h (3/6 deaths)	Smyth et al. (1951)
Benzyl alcohol	Mice (10; 3 strains used) - iv	>100–400 mg/kg	Montaguti et al. (1994)
Benzyl alcohol	Mice (10) - iv	>450 and <470 mg/kg	Kimura et al. (1971)
Benzyl alcohol	Mice - iv	38 mg/kg	Chvapil et al. (1962)
Benzyl alcohol	Mice (4; adults & juveniles) - ip	1000 mg/kg	McCloskey (1987)
Benzyl alcohol	Mice - sc	1000 mg/kg	Koch et al. (1993)
Phenethyl alcohol	Guinea pigs - ip	400–800 mg/kg	Treon (1963a)
Phenethyl alcohol	Rat (10) ip	520 mg/kg (270–1000 mg/kg)	RIFM (1982a)
Phenethyl alcohol	Rat (5/sex) - inh	>600 mg/m^3	RIFM (1980d)
Phenethyl alcohol	Mice - ip	454 mg/kg (297–695 mg/kg)	RIFM (1974c)
Phenethyl alcohol	Mice - ip	200–400 mg/kg	Treon (1963a)

Notes: ip – intraperitoneal, iv – intravenous, sc – subcutaneous, inh – inhalation.
* For the purpose of comparison some units have been changed from the reported units in the original study.

Table 3-1
Repeat-dose toxicity studies – dermal.

Material	Route and Duration	Dose	Species (No./dose)	Results	References
Primary alcohols					
Anisyl alcohol	7-day subcutaneous injection	150 mg/kg/day	Rats (partially hepatectomized Charles River, *n* = 11)	No significant difference from controls in regenerating liver	Gershbein (1977)
Phenethyl alcohol	90-day dermal	250, 500, 1000 or 2000 mg/kg/day	Rats (15/sex)	NOAEL 500 mg/kg/day based on decreased body weight gain after 1 week of treatment; decreased hemoglobin concentration, and white blood cell count in males 1000 and 2000 mg/kg/day	Owston et al. (1981)
2-Phenoxyethanol	14-day dermal application	1000 mg/kg/day	Rabbit (10F)	Mortality, morbidity and intravascular hemolysis	RIFM (1985b)
2-Phenoxyethanol	90-day dermal	0, 50, 150, 500 mg/kg/d	Rabbit (10/sex/dose)	Only treatment related effect was sporadic observation of erythema and slight scaling at highest dose	RIFM (1986b)

NOAEL was considered to be 10 mg/kg body weight/day. The true value may be closer to 40 mg/kg body weight/day.

In a series of repeat dose toxicity tests, NTP (1990) tested α-methylbenzyl alcohol in F344/N rats and B6C3F1 mice for 16 days, 90 days and 2 years. In a 16-day study, the animals (5/sex/dose) were gavaged with the alcohol in corn oil at 0, 125, 250, 500, 1000, or 2000 mg/kg body weight/day. For both species, the NOAEL was 500 mg/kg body weight/day based on mortality at the two higher doses. In the 90-day study, the rats (10/sex/dose) were gavaged with 0, 93, 187, 750, or 1500 mg/kg body weight/day and the mice (10/sex/dose) with 0, 47, 93, 187, or 750 mg/kg body weight/day. The NOAEL was 187 mg/kg/day for the male rats, based on increased liver weights at 375 mg/kg/day. However, female rats exhibited decreased liver weights at all dose levels, hence a NOAEL was not established, but the LOEL was 93 mg/kg/day for liver effects in females. In mice, there were no lasting toxic effects, but labored breathing, ataxia and lethargy were observed at the two high doses, but effects were reversible. In the 2-year studies, rats and mice were administered α-methylbenzyl alcohol at 0, 375, or 750 mg/kg body weight/day by gavage. In rats, excessive mortality in the 2-year study in males reduced the sensitivity of the study. α-Methylbenzyl alcohol was toxic to the kidney, causing an exacerbation of the spontaneous age-related nephropathy resulting in a carcinogenic response (see Section 5.4). A NOAEL was not established for the rats. In mice, no long term effects were observed, so the NOAEL was 750 mg/kg body weight/day.

5.2.2.3. Tertiary alcohols. The tertiary alcohol α,α-dimethylphenethyl alcohol was fed to weanling Osborne-Mendel rats for 16 weeks at 10,000 ppm (500 mg/kg body weight/day) or 1000 ppm for 28 weeks (50 mg/kg body weight/day) (Hagan et al., 1967). No effects were reported for either dose.

5.2.3. Inhalation studies

Rats were exposed to benzyl alcohol by nose-only inhalation over a 5-day period (RIFM, 2001). The concentrations were 0, 0.051, 0.73 or 2.1 mg/L for 6 h/day, which provided an intake of 0, 10, 42, or 146 mg/kg/day). Animals in the high dose group exhibited decreased body weights; reduced food consumption; reduced spleen, liver, and brain weights; and increased adrenal glands weights. The NOAEL for this experiment was 42 mg/kg body weight/day based on effects at the high dose (Table 3-3). In a 4-week inhalation study, rats (10/sex/dose) were exposed to 41, 102, 290 and 1072 mg/m^3 for 6 h/day for 5 days/week (RIFM, 2009). There were no observed effects and the NOEL and NOAEL were determined to be 1072 mg/m^3.

5.3. Genotoxicity

5.3.1. In vitro studies

5.3.1.1. Indicator studies. The primary alcohols benzyl alcohol and phenethyl alcohol have been screened with repair-deficient bacterial assays based on the differential inhibition of growth by repair-

Table 3-2
Repeat-dose toxicity studies – oral.

Material	Route and Duration	Dose*	Species (No./dose)	Results	References
Primary alcohols					
Benzyl alcohol	16-day gavage	125, 250, 500, 1000, or 2000 mg/kg/day in corn oil	F344 rats (5/sex)	All rats died at highest dose. "Clinical signs of toxicity" observed in all rats receiving 1000 mg/kg/day along with mortality (5/10) during the study. Dose range finding study (no statistical analyses performed)	NTP (in press-a), NTP (1989)
Benzyl alcohol	16-day gavage	125, 250, 500, 1000 or 2000 mg/kg/day in corn oil	B6C3F1 mice (5/sex)	All mice died at highest dose. Dose range finding study (no statistical analyses performed)	NTP (in press-a), NTP (1989)
Benzyl alcohol	13-week gavage	50, 100, 200, 400, 800 mg/kg/day in corn oil	F344 rats (10/sex)	NOAEL 100 mg/kg/day based on male mortality (8/10) and decreased weight gain in male rats at 800 mg/kg/day and female rats at 200 mg/kg/day and above; Other toxicity observed at high dose (no statistical analyses performed)	NTP (in press-b); NTP (1989)
Benzyl alcohol	13-week gavage	50, 100, 200, 400, 800 mg/kg/day in corn oil	B6C3F1 mice (10/sex)	NOAEL 100 mg/kg/day based on significant depression in relative weight gain in male mice receiving 400 mg/kg/day or more and females receiving 200 mg/kg/day and above	NTP (in press-b), NTP (1989)
Benzyl alcohol	2-year gavage	200 or 400 mg/kg/day in corn oil	F344 rats (50/sex)	No effects. Survival in both groups of female rats was 50% of controls resulting primarily from gavage-related deaths	NTP (1989), Zeiger et al. (1990)
Benzyl alcohol	2-year gavage	100 or 200 mg/kg/day in corn oil	B6C3F1 mice (50/sex)	No effects	NTP (1989), Zeiger et al. (1990)
β-Methylphenethyl alcohol	13-week diet	10, 40, 160 mg/kg/day	Wistar rats (15/sex)	NOAEL 10 mg/kg/day based on increased kidney weights at 40 mg/kg/day in the males	RIFM (1979c), Gaunt et al. (1982)
2-Methyl-4-phenylpentanol	28-day gavage	5, 55, or 500 mg/kg/day in corn oil	Chales River Crl:CD (SD) BR rats (5/sex)	NOAEL 55 mg/kg/day based on higher albumin and lower globulin serum levels in males and increased urea nitrogen in males; increased glutamic-pyruvic transaminase levels and increased kidney weights in females; and lower calcium levels and increased liver weights in both sexes at 500 mg/kg/day (LOAEL)	RIFM (1988f)
2-Methyl-5-phenylpentanol	28-day gavage	10, 200 and 1000 mg/kg/day	Rats (6/sex)	NOAEL in males of 10 mg/kg/d; NOAEL in females 200 mg/kg/d based on slight body weight changes	RIFM (1990b)
Phenethyl alcohol	4-month gavage	50.8 mg/kg (0.02 × previously determined LD_{50} of 2540 mg/kg)	Rats (12M)	LOAEL 50.8 mg/kg/day based on blood serum changes (increased cholinesterase, ALT, protein thiols and decreased protein content)	Zaitsev and Rakhmanina (1974)
Phenethyl alcohol	56-week diet	0.12% in drinking water (120 mg/kg/day)	Wistar rats (20/sex)	No differences in organ weights or histopathology	Johannsen and Purchase (1969)
2-Phenoxyethanol	10-day gavage	100, 300, 600, 1000 mg/kg/day	New Zealand White rabbits (6F)	LOAEL 100 mg/kg/day based on decreased body weight and hemolytic anemia	RIFM (1986c), RIFM (1992b)
2-Phenoxyethanol	14-day gavage	1250 or 2500 mg/kg/day	Fischer 344 rats (3/sex)	LOAEL 1250 mg/kg/day based on mortality	RIFM (1986c)
2-Phenoxyethanol	15-day gavage (11 doses)	100, 300, 1000 mg/kg/day	Rats (5M)	NOAEL appeared to be 100 mg/kg/day based increased incidences of enlarged Peyer's patches in males	RIFM (1984a)
2-Phenoxyethanol	14-day diet	1, 2.5, 5, 7.5, 10% in diet (1500, 3750, 7500, 11250, or 15000 mg/kg/day)	CD-1 mice (8/sex)	NOAEL 3750 mg/kg/day based on decreased weight gain and mortality at 7500 mg/kg/day and above (LOAEL)	NTP (1984)
β,β-3-trimethyl-benzenepropanol	28-day diet	0, 800, 3000, or 10,000 ppm (0, 80, 300, 1000 mg/kg/day)	Wistar Rat (10)	NOEL was 80 mg/kg/day following minor observations considered not of toxicological significance	RIFM (1987c)
Secondary alcohols					
α-Isobutylphenethyl alcohol	90-day diet	10, 40, 160 mg/kg/day in diet	SPF Sprague–Dawley rats (15/sex)	NOAEL 10 mg/kg/day based on lower serum glucose levels in males at 40 mg/kg/day (LOAEL) (may be	RIFM (1981c), Ford et al. (1983)

(*continued on next page*)

Table 3-2 (*continued*)

Material	Route and Duration	Dose*	Species (No./dose)	Results	References
				questioned)	
α-Methylbenzyl alcohol	16-day gavage	125, 250, 500, 1000 or 2000 mg/kg/day in corn oil	F344/N rats (5/sex)	NOAEL 500 mg/kg day based on mortality at 1000 and 2000 mg/kg bodyweight/day	NTP (1990)
α-Methylbenzyl alcohol	16-day gavage	125, 250, 500, 1000 or 2000 mg/kg/day in corn oil	B6C3F1 mice (4–5/sex)	NOAEL 500 mg/kg day based on mortality at 1000 and 2000 mg/kg bodyweight/day	NTP (1990)
α-Methylbenzyl alcohol	13-week gavage	93, 187, 375, 750, or 1500 mg/kg/day in corn oil	F344/N rats (10/sex)	NOEL 187 mg/kg/day in males based on increased relative liver weights, LOEL in females 93 mg/kg/day based on increased liver weight; mortality observed at 1500 mg/kg/day; labored breathing, ataxia, and lethargy observed at 375 or 750 mg/kg/day for up to 30 min after dosing	NTP (1990)
α-Methylbenzyl alcohol	13-week gavage	46.9, 93.8, 187.5, 375, or 750 mg/kg/day in corn oil	B6C3F1 mice (10/sex)	No effects. Labored breathing, ataxia and lethargy observed at 375 or 750 mg/kg/day for up to 30 min but reversible	NTP (1990)
α-Methylbenzyl alcohol	2-year gavage	375 or 750 mg/kg/day in corn oil	F344/N rats (50/sex)	LOAEL 375 mg/kg/day based on increased incidences at 750 mg/kg/day of renal tubular cell adenomas in male rats; increased nephropathy in treated males and low dose females; secondary responses from renal imbalance observed in parathyroid, heart, glandular stomach and bone in low dose animals; Excessive mortality of treated animals was believed to be accidental	NTP (1990)
α-Methylbenzyl alcohol	2-year gavage	375 or 750 mg/kg/day in corn oil	B6C3F1 mice (49–50/sex)	No effects NOAEL 750 mg/kg/d	NTP (1990)
Tertiary alcohols					
α,α-Dimethylphenethyl alcohol	16-week diet	10,000 ppm (500 mg/kg/day)	Osborne Mendel rats (5/sex)	No effect	Hagan et al. (1967); Bar and Griepentrog (1967)
α,α-Dimethylphenethyl alcohol	28-week diet	1000 ppm (50 mg/kg/day)	Osborne Mendel rats (10/sex)	No effect	Hagan et al. (1967)

* For the purpose of comparison some units have been changed from the reported units in the original study.

proficient and repair deficient strains (Table 4-1). In the rec-assay with *B. subtillis H17(rec+)/M45(rec⁻)*, benzyl alcohol gave both negative and weak positive results (Yoo, 1986; Kuroda et al., 1984a,b; Oda et al., 1978). In *E. coli* P3110 (polA+)/P3478 (polA-) strains, benzyl alcohol did not interfere with DNA repair (Fluck et al., 1976). In experiments with *E. coli* strains Hr30 (wildtype for DNA repair) versus strains with different DNA repair capacities, NG30(rec A), R15(polA) and H/r30(thy⁻), phenethyl alcohol did not increase survival in the Hs30(uvrB) and R15(polA) strains, indicating that there was no further damage in UV-irradiated *E. coli;* however, survival was decreased in the wild type and NG30(rec A) strains. In addition, phenethyl alcohol inhibited the removal of thymine dimers from DNA in the H/r30(thy⁻) strain. The authors indicated that the mechanism of DNA repair in these strains illustrated that phenethyl alcohol interfered with the incision step of excision repair by dissociating the DNA-membrane complex in bacteria, but did not interact with the DNA itself (Tomiyama et al., 1986).

Benzyl alcohol gave negative results in a light absorption umu test, which is based on the ability of a chemical to induce expression of the umu operon in *S. typhimurium* TA1535/psk1002 umuDC-lacZ both with and without metabolic activation (Yasunaga et al., 2004).

5.3.1.2. Mutation studies. Ten primary AAA fragrance ingredients (anisyl alcohol; benzyl alcohol; *p*-isopropylbenyl alcohol; *β*-methyl phenethyl alcohol; 2-methyl-4-phenylpentyl alcohol; 2-methyl-5-phenylpentyl alcohol; phenethyl alcohol; 2-phenoxyethanol; *p*-tolyl alcohol and *β*,*β*-3-trimethyl benzene propanol); three secondary alcohols (α-methylbenzyl alcohol, 4-phenyl-3-buten-2-ol and α-propyl phenethyl alcohol); and two tertiary alcohols, (1-phenyl-3-methyl-3-pentanol and *p*-α,α-trimethylbenzyl alcohol) were inactive when tested for reverse mutation in at least one Ames test with *Salmonella typhimurium* TA97, TA98, TA100, TA1535, TA1537, or TA1538; most were tested with and without metabolic activation (Table 4-1). In *E. coli* WP2 uvrA cells, reverse mutation was not observed with the primary alcohol 2-methyl-4-phenyl pentanol. In *E. coli* SD-4-73 cells, reverse mutation was not observed with the secondary alcohol α-methylbenzyl alcohol.

In two forward mutation assays, the primary AAA, benzyl alcohol, was negative in a mammalian cell system (mouse lymphoma L5178Y ± TK cells) with metabolic activation but showed positive and equivocal response without metabolic activation (NTP, 1989; Zeiger et al., 1990; Myhr et al., 1990; McGregor et al., 1988). The secondary α-methylbenzy alcohol was active without microsomal activation (NTP, 1990) (Table 4-2).

5.3.1.3. Sister chromatid exchange and chromosome aberration studies. The primary AAA, benzyl alcohol, as well as the secondary alcohol α-methylbenzyl alcohol, did not induce chromosomal aberrations *in vitro* when incubated with Chinese hamster ovary cells without metabolic activation; however, with metabolic activation, both of these fragrances tested positive (NTP, 1990; NTP, 1989; Zeiger et al., 1990; Anderson et al., 1990; Ishidate et al., 1984) (Table 4-2). An equivocal response in sister chromatid exchanges was reported for benzyl alcohol *in vitro* with metabolically activated Chinese hamster ovary (CHO) cells; a positive response was found with non-activated cells (NTP, 1989; Zeiger et al., 1990; Myhr et al., 1990). Phenethyl alcohol did not produce sister chromatid exchanges *in vitro* with human peripheral lymphocytes (Norppa and Vainio, 1983) (Table 4-2).

5.3.2. In vivo studies

After *in vivo* exposure, neither the four primary alcohols (benzyl alcohol; 2-methyl-4-phenyl pentanol; 2-methyl-5-phenyl pentanol; or *β*, *β*, 3-trimethyl-benzenepropanol), nor the tertiary alcohol 1-phenyl-3-methyl-3-pentanol were clastogenic in the mouse bone marrow micronucleus assay (Hayashi et al., 1988; RIFM, 1988e,h, 1987k; Wild et al., 1983) (Table 4-3).

5.4. Carcinogenicity

The available carcinogenicity studies are summarized in Table 5.

5.4.1. Primary alcohols

The primary alcohol, benzyl alcohol, was given by gavage in corn oil to F344/N rats (50/sex/dose) 5 days per week for 103 weeks at 0, 200, or 400 mg/kg body weight/day (NTP, 1989). NTP (1989) conducted a similar study in B6C3F1 mice (50/sex/dose) at gavage doses of 0, 100, or 200 mg/kg body weight/day. Administration of benzyl alcohol to both rats and mice did not affect survival, or result in statistically significant neoplastic or non-neoplastic lesions. NTP concluded that "…there was no evidence of carcinogenic activity" for both rats and mice at the doses tested.

In separate experiments, the primary alcohols benzyl alcohol and anisyl alcohol were administered to male B6C3F1 mice (30–35/species) for 4 weeks with preweaning intraperitoneal injections of 0.25, 0.5, 1.0, and 2.0 μmol on post natal days (PNDs) 1, 8, 15, and 22, respectively for a total dose of 3.75 μmol (total dose of 406 mg for benzyl alcohol; 518 mm g for anisyl alcohol) (Miller et al., 1983). At sacrifice, no significant difference in the number of hepatoma-bearing mice between untreated, vehicle-treated, and treated was reported with either compound.

5.4.2. Secondary alcohols

In the two-year gavage study with α-methylbenzyl alcohol, rats (50/sex/dose) were administered 0, 375, or 750 mg/kg body weight/day by gavage in corn oil 5 days/week (NTP, 1990). For males, NTP concluded that there was some evidence of carcinogenic activity of α-methylbenzyl alcohol for male F344/N rats, as shown by increased incidences of renal tubular cell adenomas and adenomas or adenocarcinomas combined. Renal toxicity was characterized by severe nephropathy and related secondary lesions

Table 3-3
Repeat-dose toxicity studies – inhalation.

Material	Route and Duration	Dose*	Species (No. per dose group)	Results	References
Primary alcohols					
Benzyl alcohol	5-day inhalation	10, 42, 146 mg/kg/day (0.051, 0.73, 2.1 mg/L)	Wistar rat (5/sex)	NOAEL 42 mg/kg/day based on decreased body weight and gain and spleen atrophy at 146 mg/kg/day)	RIFM (2001)
Benzyl alcohol	4- week inhalation (6 h/day, 5 days/week)	41, 102, 290 and 1072 mg/m^3	Rats (10/sex)	NOEL and NOAEL 1072 mg/m^3	RIFM (2009)

* For the purpose of comparison some units have been changed from the reported units in the original study.

Table 4-1
Genotoxicity in bacteria.

Material	Test	Bacterial strain	Concentration*	Results	References
Primary alcohols					
Anisyl alcohol	Ames reverse mutation	Salmonella typhimurium TA98 or TA100 (no S9)	up to 500 μg/plate	Negative	Ball et al. (1984)
Benzyl alcohol	Ames reverse mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537, or TA1538 ±S9	up to 50,000 μg/plate	Negative	Heck et al. (1989)
Benzyl alcohol	Ames reverse mutation	Salmonella typhimurium TA92, TA94, TA98, TA100, or TA1537 ±S9	10,000 μg/plate	Negative	Ishidate et al. (1984)
Benzyl alcohol	Ames reverse mutation	Salmonella typhimurium TA98, TA100, TA1535, or TA1537 ±S9	3333 μg/plate	Negative	NTP (1989k); Zeiger et al. (1990)
Benzyl alcohol	Ames reverse mutation	Salmonella typhimurium TA98, TA100, TA1535, or TA 1537 ±S9	up to 3333 μg/plate	Negative	Mortlemans et al. (1986)
Benzyl alcohol	Ames reverse mutation	Salmonella typhimurium TA98 or TA100 (no S9)	up to 1000 μg/plate	Negative	Ball et al. (1984)
Benzyl alcohol	Ames reverse mutation	Salmonella typhimurium TA98 or TA100 (no S9)	up to 100 nmol/plate	Negative	Rogan et al. (1986)
Benzyl alcohol	Ames reverse mutation	Salmonella typhimurium TA98, TA100, TA1535, or TA1537 ±S9	324 μg/plate	Negative	Florin et al. (1980)
Benzyl alcohol	Ames reverse mutation	Salmonella typhimurium TA98 or TA100 (±S9)	up to 10 μg/plate	Negative	Kubo et al. (2002)
Benzyl alcohol	Ames reverse mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537, or TA1538	5 μL/plate (5 μg/plate)	Negative	Milvy and Garro (1976)
Benzyl alcohol	DNA damage (umu test)	Salmonella typhimurium TA1535/pSK1002 umuDC-lacZ ±S9	5000 μg/plate	Negative	Yasunaga et al. (2004)
Benzyl alcohol	DNA damage	*Escherichia coli* pol A/W3110-P3478 (±S9)	50 μL/well (−S9) 10 μL/well (+S9)	Negative	Fluck et al. (1976)
Benzyl alcohol	Rec assay	Bacillus subtilis H17 (rec+) and M45 (rec−) ± S9	>20 μL/disc	Negative	Yoo (1986)
Benzyl alcohol	Rec assay	Bacillus subtilis H17 (rec+) and M45 (rec−) ± S9	>10 μL/disc	Positive	Kuroda et al. (1984a,b)
Benzyl alcohol	Rec assay	Bacillus subtilis H17 (rec+) and M45 (rec−)	21 μg/disc	Negative	Oda et al. (1978)
p-Isopropylbenzyl alcohol	Ames reverse mutation	Salmonella typhimurium TA98, TA100 +S9	0.5–100 μL/plate	Negative	Rockwell and Raw (1979)
β-Methylphenethyl alcohol	Ames reverse mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537, or TA1538 ±S9	up to 3600 μg/plate	Negative	Wild et al. (1983)
2-Methyl-4-phenylpentanol	Ames reverse mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537, or TA1538 ±S9	up to 1000 μg/plate	Negative	RIFM (1987d)
2-Methyl-4-phenylpentanol	Reverse mutation	*Escherichia coli* WP2 uvrA ± S9	up to 1000 μg/plate	Negative	RIFM (1987d)
2-Methyl-5-phenylpentanol	Ames reverse mutation	Salmonella typhimurium TA98, TA100, TA1535 or TA1538 ±S9	up to 300 μg/plate	Negative	RIFM (1988g)
Phenethyl alcohol	Ames reverse mutation	Salmonella typhimurium TA98, TA100, TA1535, or TA1537 ±S9	3 μmol/plate	Negative	Florin et al. (1980)
Phenethyl alcohol	DNA excision repair	*Escherichia coli* Hs30 (uvrB)	33mM (0.4%)	Negative	Tomiyama et al. (1986)
Phenethyl alcohol	DNA excision repair	*Escherichia coli* R15 (polA)	33mM (0.4%)	Negative	Tomiyama et al. (1986)
Phenethyl alcohol	DNA excision repair	*Escherichia coli* H/r30 (wildtype)	33mM (0.4%)	Positive	Tomiyama et al. (1986), Tachibana and Yonei (1985)
Phenethyl alcohol	DNA excision repair	*Escherichia coli* NG30 (rec A)	33mM (0.4%)	Positive	Tomiyama et al. (1986), Tachibana and Yonei (1985)
Phenethyl alcohol	DNA excision repair	*Escherichia coli* H/r30thy-	(0.15%)	Postive	Tomiyama et al. (1986)
Phenethyl alcohol	DNA repair	*Escherichia coli* $polA_1^-$ (−S9)	NR	Negative	Rosenkranz and Leifer (1980)
Phenethyl alcohol	Genetic transformation	Bacillus subtilis 168 ind ± thy or str-r	(0.3%)	Positive	Urban and Wyss (1969)
2-Phenoxyethanol	Ames reverse mutation	Salmonella typhimurium TA98, TA100, TA1535, or TA1537 +S9	25–500 μl solvent/plate	Negative	Maron et al. (1981)
p-Tolyl alcohol	Ames reverse mutation	Salmonella typhimurium TA97, TA98, TA100, TA1535, or TA1537 ±S9	up to 10,000 μg/plate	Negative	Zeiger et al. (1992)
p-Tolyl alcohol	Ames reverse mutation	Salmonella typhimurium TA98 or TA100 −S9 only	up to 500 μg/plate	Negative	Ball et al. (1984)
β,*β*-3-Trimethyl benzenepropanol	Ames reverse mutation*	Salmonella typhimurium TA98, TA100, TA1535, orTA1537 ± S9	up to 500 μg/plate	Negative	RIFM (1987e)
Secondary alcohols					
α-Methylbenzyl alcohol	Ames reverse mutation	Salmonella typhimurium TA98, TA100, TA1535, or TA 1537 ±S9	up to 6666 μg/plate	Negative	NTP (1990), Zeiger et al. (1987)
α-Methylbenzyl alcohol	DNA damage	*Escherichia coli* pol A/W3110-P3478 (no metabolic activation)	up to 50 μL/well (50 μg/well)	Negative	Fluck et al. (1976)
α-Methylbenzyl alcohol	Reverse mutation	*Escherichia coli* SD-4-73	0.01–0.025 μL/disc or plate	Negative	Szybalski (1958)
4-Phenyl-3-buten-2-ol	Ames reverse mutation	Salmonella typhimurium TA98, TA100, TA1535, or TA 1537 ±S9	Up to 1000 μg/plate	Negative	Wilde et al. (1983)
α-Propylphenethyl alcohol	Ames reverse mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537, or TA1538 ±S9	up to 3600 μg/plate	Negative	Wild et al. (1983)

Table 4-1 (*continued*)

Material	Test	Bacterial strain	Concentration*	Results	References
Tertiary alcohols					
1-Phenyl-3-methyl-3-pentanol	Ames reverse mutation	Salmonella typhimurium TA98, TA100, TA1535, TA1537, or TA1538 ±S9	up to 3600 μg/plate	Negative	Wild et al. (1983)
p-α,α-Trimethylbenzyl alcohol	Ames reverse mutation	Salmonella typhimurium TA97, TA98, TA100 or TA1535 ±S9	up to 10,000 μg/plate	Negative	Zeiger and Margolin (2000)

* For the purpose of comparison some units have been changed from the reported units in the original study.

were observed in the dosed rats. Poor survival reduced the sensitivity for detecting the presence in all male rats and the high dose group of female rats. For females, NTP concluded that there was no evidence of carcinogenic activity for female F344/n rats administered 375 or 750 mg/kg/day. There was no evidence of carcinogenic activity of α-methylbenzyl alcohol for male or female B6C3F1 mice administered 375 or 750 mg/kg/day for 2 years.

5.4.3. Tertiary alcohols

No carcinogenic studies with the tertiary alcohols were identified.

5.5. Reproductive toxicity

Reproductive and developmental toxicity after dermal and oral exposure has been studied with 4 primary alcohols. Reproductive and or developmental studies with dermal exposures are listed in Table 6-1, those with oral exposure are in Table 6-2 and miscellaneous exposures are listed in Table 6–3.

5.5.1. Reproductive studies

5.5.1.1. Oral exposure. Dietary levels of 0, 0.25, 1.25, and 2.5% 2-phenoxyethanol were fed to CD1 mice (0, 400, 2000, or 4000 mg/kg body weight per day) for 7 days prior to and during a 98-day cohabitation period (NTP, 1984; Morrissey et al., 1989; Heindel et al., 1990). There was no reduction in the number of litters 2-phenoxyethanol treated animals produced during the continuous breeding but there was a significant, small decrease in the number of pups/litter and in pup weight in the high dose group. Though fertility was minimally compromised, severe neonatal toxicity was observed in the mid- and high-dose groups. For the F0 male mice, it appeared that a dose of 4000 mg/kg/day was the reproductive NOAEL for decreased body weight and increased liver weight; the reproductive NOAEL for the F0 females was 400 mg/kg/day. By weaning at PND 21, the weights of mid- and high-dose group F1 pups were reduced and remained lower at the time of mating, with resulting postnatal mortality of F2 pups. The cross-over mating trial indicated that the reproductive effects could be attributed primarily to effects on the female (Heindel et al., 1990).

In a 5 week subchronic study, groups of mice (5/dose) were given 2-phenoxyethanol at 500 or 1000 mg/kg body weight/day. No changes in testes weight nor in hematologic parameters were observed and a NOAEL of 1000 mg/kg body weight/day was established (Nagano et al., 1979, 1984).

5.5.2. Developmental toxicity studies

Developmental toxicity of the primary alcohols, benzyl alcohol; phenethyl alcohol; and 2-phenoxyethanol has been reported.

Table 4-2
Genotoxicity* in mammalian cells.

Material	Test system	Cell line	Concentration	Results	References
Primary alcohols					
Benzyl alcohol	Sister chromatid Exchange	Chinese Hamster Ovary cells ± S9	up to 4000 (+S9) or 5000 (−S9) μg/mL	Equivocal/ Positive	NTP (1989), Zeiger et al. (1990), Anderson et al. (1990)
Benzyl alcohol	Chromosome aberrations	Chinese Hamster Ovary cells ± S9	up to 5000 μg/mL	Negative −S9 Positive +S9	NTP (1989), Zeiger et al. (1990), Anderson et al. (1990)
Benzyl alcohol	Chromosome aberrations	Chinese Hamster fibroblast cells (CHL) no S9	up to 1000 μg/mL	Negative	Ishidate et al. (1984)
Benzyl alcohol	Forward mutation assay	Mouse L5178Y ± TK lymphoma cells ±S9	up to 5000 μg/mL	Negative +S9 Equivocal −S9	McGregor et al. (1988)
Benzyl alcohol	Forward mutation assay	Mouse L5178Y ± TK lymphoma cells ±S9	up to 2500 μg/mL	Negative +S9 Positive −S9/Equivocal	NTP (1989), Zeiger et al. (1990), Myhr et al. (1990)
Benzyl alcohol	Replicative DNA synthesis	Rat and mouse hepatocytes	MTD and 1/2 MTD	Negative	Yoshikawa (1996)
Benzyl alcohol	Replicative DNA synthesis	Mouse hepatocytes	400 or 800 mg/kg (MTD)	Negative	Miyagawa et al. (1995)
Benzyl alcohol	Replicative DNA synthesis	Rat hepatocytes	300 or 600 mg/kg	Negative	Uno et al. (1994)
Benzyl alcohol	Alkaline elution assay (DNA strand breaks)	Rat hepatocytes	1, 3, or 10 mM	Negative (with false positive result)	Storer et al. (1996)
Phenethyl alcohol	Sister chromatid Exchange	Human peripheral lymphocytes	up to 10mM	Negative	Norppa and Vainio (1983)
Secondary alcohols					
α-Methylbenzyl alcohol	Sister chromatid Exchange	Chinese Hamster Ovary cells ±S9	33–1000 μg/mL	Negative	NTP (1990)
α-Methylbenzyl alcohol	Chromosome aberrations	Chinese Hamster Ovary cells ±S9	1000–3000 μg/mL	Negative −S9 Positive +S9	NTP (1990)
α-Methylbenzyl alcohol	Forward mutation assay	Mouse L5178Y ± TK lymphoma cells (no s9)	250–1250 nl/mL	Positive	NTP (1990)

MTD: Maximum tolerated dose.

Table 4-3
Genotoxicity in mice.

Material	Test system	Mouse strain	Dose	Results	References
Primary alcohols					
Benzyl alcohol	Micronucleus test (bone marrow cells)	ddYY (M)	50, 100, or 200 mg/kg	Negative	Hayashi et al. (1988)
2-Methyl-4-phenylpentanol	Micronucleus test (erythrocytes)	CD-1 mice (20/sex)	871 mg/kg	Negative	RIFM (1988e)
2-Methyl-5-phenylpentanol	Micronucleus test (erythrocytes)	NMRI mice (5/sex/dose)	250, 500 and 1000 mg/kg	Negative	RIFM (1988h)
β,β,3-trimethyl-benzenepropanol	Micronucleus Test (erythrocytes)	NMRI mice (5/sex/dose)	1000 mg/kg	Negative	RIFM (1987k)
Tertiary alcohols					
1-Phenyl-3-methyl-3-pentanol	Micronucleus test (erythrocytes)	NMRI mice (M and F, 4/dose)	357, 624, 891, or 1416 mg/kg	Negative	Wild et al. (1983)

Table 5
Carcinogenicity.

Material	Method	Dose*	Species (No./dose)	Results	References
Primary alcohols					
Anisyl alcohol	4-week preweaning IP injections 1/week	Total 3.75 μmol (518 mg) (weekly dose in the ratio of 1:2:4:8 on post natal day 1,8,15 and 22)	Mice (Male B6C3F, $n = 32$)	No significant difference of the number of hepatoma-bearing mice (treated 16/32, untreated 15/35, and vehicle-treated 15/32)	Miller et al. (1983)
Benzyl alcohol	4-week preweaning IP injections 1/week	Total 3.75 μmol (406 mg) (weekly dose in the ratio of 1:2:4:8 on post natal day 1,8,15 and 22)	Male B6C3F mice ($n = 30$)	No significant difference of the number of hepatoma-bearing mice (treated 10/30, untreated 15/35, and vehicle-treated 15/32)	Miller et al. (1983)
Benzyl alcohol	2-year gavage	200 or 400 mg/kg/day in corn oil	F344 rats (50/sex)	"No evidence of carcinogenic activity"	NTP (1989)
Benzyl alcohol	2-year gavage	100 or 200 mg/kg/day in corn oil	B6C3F1 mice (50/sex)	"No evidence of carcinogenic activity"	NTP (1989)
Secondary alcohols					
α-Methylbenzyl alcohol	2-year gavage	375 or 750 mg/kg/day in corn oil	F344/N rats (50/sex)	LOAEL 375 mg/kg/day based on significantly increased incidences of renal tubular cell adenomas or adenomas and adenocarcinomas combined in male rats; no evidence of carcinogenic activity in females	NTP (1990)
α-Methylbenzyl alcohol	2-year gavage	375 or 750 mg/kg/day in corn oil	B6C3F1 mice (49–50/sex)	"No evidence of carcinogenic activity"	NTP (1990)

* For the purpose of comparison some units have been changed from the reported units in the original study.

5.5.2.1. Dermal exposure. Phenethyl alcohol was tested for developmental toxicity by applying it to the skin of female Crl:COBS CD (SD) BR rats on GD6-15 at dosages of 0, 140, 430, or 1400 mg/kg body weight/day in one study ($n = 25–35$/dose) and 0, 70, 140, 280, 430, or 700 mg/kg/day on females in a corroborative study ($n = 10$/dose). The dermal maternal and developmental NOAELs were 70 mg/kg/day, based on dermal irritation and reductions (not statistically significant) in fetal body weights (Ford et al., 1987; RIFM, 1988i). Recently this study has been repeated, under current guidelines, with additional parameters measured, including reversibility of the effects in pups euthanized on postnatal day 21 (RIFM, 2010). In this study, female rats were dosed on GD 7-20 at dosages of 0, 140, 430, or 1400 mg/kg body weight/day ($n = 40$/dose). Twenty rats/group were Caesarean-sectioned on GD 21 and the remaining 20 rats/group were allowed to naturally deliver their litters and were euthanized on postnatal day 21. In this repeated study, the maternal NOAEL was 430 mg/kg body weight/day based on reductions in body weight and feed consumption at the 1400 mg/kg body weight/day. The developmental NOAEL was 140 mg/kg body weight/day. Maternal dosages of 430 and 1400 mg/kg body weight/day caused reductions in fetal weight with corresponding delays in fetal skeletal ossification and an increase in the incidences of cervical ribs in fetuses from the rats selected for Caesarean delivery. However, all apparent delays in ossification and increased numbers of cervical ribs that were observed in the fetuses Caesarean-sectioned at GD 21 in the 430 mg/kg body weight/day were resolved in pups from rats selected for natural deliver by postnatal day 21 (RIFM, 2010).

2-Phenoxyethanol was evaluated for developmental toxicity by occluded topical administration to rabbits at 0, 300, 600, or 1000 mg/kg body weight/day on GD6-18 (Scortichini et al., 1987). See Table 6-1. Embryo/fetotoxic or teratogenic effects were not observed. There was a dose-related intravascular hemolytic anemia in maternal rabbits exposed to 600 or 1000 mg/kg body weight/day. The maternal NOAEL was 300 mg/kg/day based on hemoglobiuriniuria, pale livers, dark kidneys, and dark blood in the bladder at 600 mg/kg/day. The developmental NOAEL was 1000 mg/kg/day, the highest dose tested.

Table 6-1
Reproductive toxicity studies – dermal.

Material	Method	Dose*	Species (No./dose)	Results	References
Primary alcohols					
Phenethyl alcohol	Developmental study: dermal during GD6-GD15	140, 430, or 1400 mg/kg/day (100% neat)	Crl:COBS CD (SD)BR rats (25–35F)	Maternal NOAEL 430 mg/kg/day based on reduced mean feed consumption and body weight gain at LOAEL 1400 mg/kg/day; Developmental NOAEL 140 mg/kg/day based on morphological changes in fetuses at LOAEL 430 mg/kg/day. Similar fetal changes occurred at 140 mg/kg/day; however, differences from control were slight; findings were equivocal	RIFM (1986d)
Phenethyl alcohol	Developmental study: dermal during GD6-15, sacrifice GD20	70, 140, 280, 430, or 700 mL/kg/day (99.6% pure; 70, 140, 280, 430 or 700 mg/kg/day))	Crl:COBS CD (SD)BR rats (10F)	Maternal NOAEL 70 mg/kg/day based on dermal irritation at ⩾140 mg/kg/day; Developmental NOAEL 70 mg/kg/day based on small reduction (not statistically significant) of fetal body weights at 140 mg/kg/days. Note: reversible delays in ossification observed at 70 mg/kg/day but dose dependent pattern not demonstrated	RIFM (1988i)
Phenethyl alcohol	Developmental study: dermal during GD7-20; sacrifice at GD 20 or PND 21	140, 430, 1400 mg/kg/day (100%)	Crl:CD(SD) rats (40F)	Maternal NOAEL 430 mg/kg/day based on mortality and reduced body weight and feed consumption at 1400 mg/kg/day. Developmental NOAEL 140 mg/kg/day based on reduced fetal weight and delay in fetal skeletal ossification and increase incidence of cervical ribs. Reproductive NOAEL 430 mg/kg/day based on increased incidence in perinatal mortality at 1400 mg/kg/day. Note: delays in ossification observed with caesarean delivered fetuses at 430mg/kg/day were resolved by PND 21 in natural delivered pups	RIFM (2010)
2-Phenoxyethanol	Developmental study: dermal GD6-18	300, 600, or 1000 mg/kg/day	New Zealand White rabbits (10F)	Maternal NOAEL 300 mg/kg/day based on hemolytic anemia with hemoglobinuria, pale livers, dark kidneys and dark blood in bladder at 600 mg/kg/day; Developmental NOAEL 1000 mg/kg/day	Scortichini et al. (1987)

* For the purpose of comparison some units have been changed from the reported units in the original study.

5.5.2.2. Oral exposure. In a preliminary screening test, benzyl alcohol was administered by gavage to CD1 mice (50 females) at 750 mg/kg body weight/day from gestational days 6–13 (Hardin et al., 1987; RIFM, 1986e; NIOSH, 1983). See 7Table 6-2. Only 62% of the dams survived, and they showed a decrease in body weight. There were no changes in reproductive or gestation indices. Statistically significant reduction in litter weight, birth weight and weight gain of pups were also reported. Benzyl alcohol was administered by gavage daily at 0 (corn oil), 100, 300, or 600 mg/kg body weight/day to groups of rat pups (10/sex) for a period of 6 weeks from PND 22 to PND 64 (sexual maturity) in order to understand the metabolic and pharmacokinetic handling of benzoic acid in neonates (Foulon et al., 2005; DeJouffrey et al., 2004). Treatment resulted in respiratory problems with varying severity; dypsnea with onset after 3 weeks of treatment (PND 42) at the two higher doses. The effects appeared to be associated with bronchoconstriction. Males had slight but significant decreases in body weight gain at the high-dose level. There were no treatment-related histopathology findings including the lungs. The NOAEL was 100 mg/kg body weight/day based on respiratory function at 300 and 600 mg/kg/day.

The effects of phenethyl alcohol were tested by administration by gavage in pregnant Long Evans rats during GD6-15 at 0, 4.3, 43, or 432 mg/kg body weight/day. Maternal NOAEL was 43 mg/kg body weight/day based on visible signs of severe intoxication (no details provided) at 432 mg/kg/day. The fetal LOAEL (no NOAEL established) was 4.3 mg/kg/day based on decreased birth weight, pup size, embyolethality, and increased number of malformed pups (Mankes et al., 1983, 1984, 1985). In another study, phenethyl alcohol (508 mg/kg body weight/day in sunflower oil) was given to pregnant rats (75) on gestational days 4, 10, 11 or 12. A LOAEL of 508 mg/kg body weight/day was determined based on a delay in the ossification of bones in the pups (Maganova and Saitsev, 1973). The effects of phenethyl alcohol were evaluated on female Crl:COBS CD (SD) BR rats ($n = 28$) that were administered 1000, 3000, or 10,000 ppm phenethyl alcohol in the diet during GD 6-15 (equivalent to 83, 266, or 799 mg/kg body weight/day). The maternal NOAEL was 799 mg/kg/day, the highest dose tested, and the developmental NOAEL was 266 mg/kg/day based on delays in fetal ossification and increased incomplete ossification in rats at 799 mg/kg/day (Burdock et al., 1987; RIFM, 1985c).

5.6. Skin irritation

5.6.1. Human studies

Fourteen primary alcohols, 1 secondary alcohols and 6 tertiary alcohols have been studied for their potential to produce dermal irritation in humans (Table 7-1).

The following substances did not induce skin irritation in pretests for a maximization study with single occlusive application for 48 h at the highest concentrations tested: 5% anisyl alcohol, 10% benzyl alcohol, 4% *p*-isopropylbenzyl alcohol, 6% β-methylphenethyl alcohol, 10% 2-phenoxyethanol, 4% *p*-Tolyl alcohol, 8% α-methylbenzyl alcohol, 8% α,α-dimethyl phenethyl alcohol, 4% 2-methyl-4-phenyl-2-butanol, 10% 1-phenyl-3-methyl-3-pentanol, and 4% 2-phenyl-2-propanol.

No irritation was observed with 15% β-methoxy benzeneethanol; 2.5% 2-(4-methylphenoxy) ethanol; 3% 2-methyl-4-phenylpentanol; an unknown concentration of 2-methyl-5-phenylpentanol; 5% 3-methyl-5-phenylpentanol; 15% 2-phenoxyethanol; 6.25% *o*-toly-

Table 6-2
Reproductive toxicity studies – oral.

Material	Method	Dose*	Species (No. per dose)	Results	References
Primary alcohols					
Benzyl alcohol	Developmental study: Oral (gavage) GD 6-13, sacrificed PND3	750 mg/kg/day	CD1 mice (50F)	Maternal toxicity: Decreased maternal body weight and 38% mortlality; Fetal toxicity: decreased birth weight and weight gain per pup	Hardin et al. (1987), RIFM (1986e)
Benzyl alcohol	Developmental study: oral gavage GD7-14	750 mg/kg/day	CD1 mice (50F)	Decreased maternal body weight, maternal body weight gain; decreased litter size and mean litter and pup weight at PND1-3. No significant difference in other reproductive indices or gestation indices	NIOSH (1983)
Benzyl alcohol	Juvenile study: oral gavage PND22 to PND 64	100, 300, 600 mg/kg/day in corn oil	Rats (10/sex)	NOAEL 100 mg/kg-day based on observed respiratory disfunction due to bronchoconstriction at PND 42 and thereafter at two high doses; decreased bodyweight gain at high dose	DeJouffrey et al. (2004), Foulon et al. (2005)
Phenethyl alcohol	Developmental study: gavage during GD6-15	4.3, 43, 432 mg/kg/day	Long Evans rats (5–7F)	Maternal toxicity NOAEL 43 mg/kg/day based on visible intoxication (no further details provided) at 432 mg/kg/day; Developmental LOAEL 4.3 mg/kg/day based on decreased birth weight, pup size, % dead, and increased number of malformed pups	Mankes et al. (1983, 1984, 1985)
Phenethyl alcohol	Developmental study: diet during GD6-15	83, 266, or 799 mg/kg/day in diet (1000, 3000, or 10000 ppm)	Crl:COBS CD (SD)BR rats (28F)	Maternal NOAEL 799 mg/kg/day; Developmental NOAEL 266 mg/kg/day based on delays in fetal ossification, increased incomplete ossification (LOAEL 799 mg/kg/day)	Burdock et al. (1987), RIFM (1985c)
Phenethyl alcohol	Developmental study: gavage on GD4 or GD10, 11 or 12	508 mg/kg/day in sunflower oil	Rats (75)	LOAEL 508 mg/kg/day (delay in ossification of bones)	Maganova and Saitsev (1973)
2-Phenoxyethanol	Reproductive study: diet	400, 2000, and 4000 mg/kg/day (0.25, 1.25, 2.5% in diet)	CD-1 mice (38, 20, 19, 18 pairs/dose)	Reproductive NOAEL for males: 4000 mg/kg/day (with decreased body weight and increased liver weight); Reproductive NOAEL for females was 400 mg/kg/day based on decreased pup weight gain and lethality	NTP (1984), Morrissey et al. (1989), Heindel et al. (1990)
2-Phenoxyethanol	Reproductive study: subchronic oral (5-weeks)	500 or 1000 mg/kg/day	Mice (5M)	NOAEL 1000 mg/kg/day (no statistically significant changes in testes weight or hematological parameters)	Nagano et al. (1979, 1984)

* For the purpose of comparison some units have been changed from the reported units in the original study.

lethanol; 2.5% *p*-α,α-trimethylbenzyl alcohol; 2.5% 1-phenyl-3-methyl-3-pentanol; or 5% α,α-4-trimethylphenethyl alcohol during the induction phase of a human repeat insult patch test (HRIPT). However the repeated application of 5, 7.5, 15, or 20% (not 3%) benzyl alcohol during the induction phase led to a dose-dependent incidence and severity of erythema in subjects among the 4 tests (RIFM, 2004b, 2003a, 2002a). Phenethyl alcohol (25% in EtOH) produced a strong reaction during repeated applications of a HRIPT (RIFM, 1964b, 1983d,e). 2-Methyl-4-phenylpentanol and α,α-dimethylphenethyl alcohol produced negative and positive responses to repeated applications during separate HRIPTs (RIFM, 1987f,g; RIFM, 1985d, 1964d). β,β-Trimethyl benzenepropanol at 10 or 18% produced irritation at rates from 1.9% to 3% during repeated applications of a HRIPT (RIFM, 2005c, 2007). In a closed patch study (24–48 h) conducted with healthy Japanese volunteers, irritation was observed between 0.2 and 1.9% of the subjects tested with the primary alcohols anisyl alcohol; benzyl alcohol; phenethyl alcohol and *p*-Tolyl alcohol. With the tertiary alcohols, the incidence was between 1.2% and 6.6% for α,α-dimethyl phenethyl alcohol; 2-methyl-4-phenyl-2-butanol; and 2-phenyl-2-propanol.

Further details on studies of dermal irritation in humans are provided in Table 7-1.

5.6.2. Animal studies

Rabbits, guinea pigs, mice and miniature swine were tested for irritation for 12 primary aryl alkyl alcohols, 1 secondary alcohol, and 4 tertiary alcohols. Reactions ranged from none to severe (Table 7-2). Irritation studies on animals included observations from acute dermal toxicity tests, primary irritation tests on the skin of rabbits and rats, and preliminary irritation tests to find the dose range for maximization tests with guinea pigs.

Single application of neat primary alcohols during acute dermal toxicity tests with 2,2-dimethyl-3-phenylpropanol with rats (RIFM, 1981a), β-methylphenethyl alcohol with rabbits (RIFM, 1974a), phenethyl alcohol with miniature swine (Motoyoshi et al., 1979), rabbits (RIFM, 1985e), rats (RIFM, 1982a), *p*-tolyl alcohol with rabbits (RIFM, 1989a), and 2-methyl-4-phenyl-2-butanol with rabbits (RIFM, 1988c) did not produce dermal irritation. If applied undiluted as a single application, primary anisyl alcohol (RIFM, 1973a; Draize et al., 1948), *p*-isopropyl benzyl alcohol (RIFM, 1973a), β,β-3-trimethylbenzenepropanol, secondary alcohol α-methyl benzyl alcohol, and tertiary alcohol 1-phenyl-3-methyl-3-pentanol produced moderate irritation. 2-Phenoxyethanol; *p*-tolyl alcohol; and tertiary 2-methyl-4-phenyl-2-butanol; and 2-phenyl-2-propanol produced moderate to severe irritation when applied undiluted (see Table 7-2).

Table 7-1
Skin irritation in humans.

Material	Method	Concentration	Results	References
Primary alcohols				
Anisyl alcohol	Closed patch 24- or 48-h	0.05–0.5% in cream base or 99% ethanol	16/465	Takenaka et al. (1968)
Anisyl alcohol	Maximization pretest	5% in petrolatum	0/7	RIFM (1971a)
2-Methoxybenzyl alcohol[a]	HRIPT induction	1.25% in EtOH	4/39 slight erythema at one reading only	RIFM (1965a)
Benzyl alcohol	Closed patch 24 to 72-h	2% in ointment	0/30	Fujii et al. (1972)
Benzyl alcohol	Closed patch 48-h	20% in petrolatum and ointment	0/35	Fujii et al. (1972)
Benzyl alcohol	Closed patch 24- or 48-h	0.05–0.5% in cream base or 99% ethanol	18/614	Takenaka et al. (1968)
Benzyl alcohol	Semi-occluded patch 48-h	32% in acetone	1/50	Motoyoshi et al. (1979)
Benzyl alcohol	Primary irritation 4-h	NR	1/31	Basketter et al. (1997)
Benzyl alcohol	Primary irritation 4-h	NR	2/31	Basketter et al. (2004)
Benzyl alcohol	Modified Primary dermal irritation	20% in 3:1 DEP:EtOH	0/12	RIFM (2004a)
Benzyl alcohol	Modified Primary dermal irritation	20% in 3:1 EtOH:DEP (different sample)	2/12	RIFM (2004a)
Benzyl alcohol	HRIPT induction	20% in 3:1 DEP:EtOH	7/56	RIFM (2002a)
Benzyl alcohol	HRIPT induction	15% in 3:1 DEP:EtOH	7/46	RIFM (2003a)
Benzyl alcohol	HRIPT induction	7.5% in 3:1 DEP:EtOH	3/110	RIFM (2004b)
Benzyl alcohol	HRIPT induction	5% in 3:1 DEP:EtOH	1/101	RIFM (2005a)
Benzyl alcohol	HRIPT induction	3% in 3:1 DEP:EtOH	0/107	RIFM (2004c)
Benzyl alcohol	Maximization pretest	10% in petrolatum	0/24	RIFM (1979d)
p-Isopropylbenzyl alcohol	Maximization pretest	4% in petrolatum	0/24	RIFM (1973c)
β-Methoxy benzeneethanol	HRIPT induction	15% in petrolatum	0/50	RIFM (1979e)
β-Methylphenethyl alcohol	HRIPT induction	6.25% in 95% Ethanol	3/37	RIFM (1964a)
β-Methylphenethyl alcohol	Maximization pretest	6% in petrolatum	0/5	RIFM (1974c)
2-(4-Methylphenoxy)ethanol	HRIPT induction	2.5% in Alcohol SDA 39C	0/10	RIFM (1971b)
2-(4-Methylphenoxy)ethanol	HRIPT induction	2.5% in Alcohol SDA 39C	0/34	RIFM (1972)
2-Methyl-4-phenylpentanol	HRIPT induction	3% in EtOH	0/55	RIFM (1987f)
2-Methyl-4-phenylpentanol	HRIPT induction	3% in EtOH	17/52	RIFM (1987g)
2-Methyl-5-phenylpentanol	HRIPT induction	Unknown concentration in EtOH:DEP	0/50	RIFM (1997)
3-Methyl-5-phenylpentanol	HRIPT induction	5% in EtOH	0/39	RIFM (1975b)
3-Methyl-5-phenylpentanol	HRIPT induction	5% in petrolatum	0/41	RIFM (1975c)
Phenethyl alcohol	Closed patch 24 to 72-h	2% in ointment and cream base	0/30	Fujii et al. (1972)
Phenethyl alcohol	Closed patch 48-h	20% in petrolatum and ointment	1/47	Fujii et al. (1972)
Phenethyl alcohol	Closed patch 24- or 48-h	0.05–0.5% in cream base or 99% ethanol	1/82	Takenaka et al. (1968)
Phenethyl alcohol	Closed patch 24-h	100%	0/20	Katz (1946)
Phenethyl alcohol	Semi-occluded patch 48-h	32% in acetone	0/50	Motoyoshi et al. (1979)
Phenethyl alcohol	HRIPT induction	25% in EtOH	52/93	RIFM (1983d) IFF a
Phenethyl alcohol	HRIPT induction	25% in EtOH	3/50	RIFM (1983e)
Phenethyl alcohol	HRIPT induction	25% in EtOH	0/39	RIFM (1964b)
Phenethyl alcohol	HRIPT induction	8% in DEP	0/103	RIFM (1989c)
2-Phenoxyethanol	HRIPT induction	15% in 85% EtOH	0/41	RIFM (1978b)
2-Phenoxyethanol	Maximization pretest	10% in petrolatum	0/26	RIFM (1982c)
2-Phenoxyethanol	Maximization pretest	10% in petrolatum	0/18	RIFM (1982c)
2-Phenoxyethanol	Maximization pretest	10% in petrolatum	0/30	RIFM (1978c)
p-Tolyl alcohol	Closed patch 24- or 48-h	0.05–5% in cream base or 99% ethanol	8/416	Takenaka et al. (1968)
p-Tolyl alcohol	HRIPT induction	5% in 65% EtOH	0/39	RIFM (1964c)
p-Tolyl alcohol	Maximization pretest	4% in petrolatum	0/49	RIFM (1978c)
o-Tolylethanol	HRIPT induction	6.25% in EtOH	0/53	RIFM (1990c)
β,*β*-3-Trimethyl benzenepropanol	Primary irritation 48-h	10% in 3:1 DEP:EtOH in skin lotion	2/52 Mild	RIFM (2005b)
β,*β*-3-Trimethyl benzenepropanol	HRIPT induction	18% in 3:1 DEP:EtOH	2/98	RIFM (2007)
β,*β*-3-Trimethyl benzenepropanol	HRIPT induction	10% in 3:1 DEP:EtOH in skin lotion	2/103	RIFM (2005c)
Secondary alcohols				
α-Methylbenzyl alcohol	Maximization pretest	8% in petrolatum	0/5	RIFM (1973d)
Tertiary alcohols				
α,α-Dimethylphenethyl alcohol	Closed patch 24- or 48-h	0.05–0.5% in cream base or 99% ethanol	1/86	Takenaka et al. (1968)
α,α-Dimethylphenethyl alcohol	HRIPT induction	2.5% in Ethanol	9/42	RIFM (1964d) IFF
α,α-Dimethylphenethyl alcohol	HRIPT induction	2% in unspecified vehicle	0/48	RIFM (1985d)

(*continued on next page*)

Table 7-1 (*continued*)

Material	Method	Concentration	Results	References
α,α-Dimethylphenethyl alcohol	Maximization pretest	8% in petrolatum	0/5	RIFM (1973d)
α,α-Dimethylphenethyl alcohol	Maximization pretest	4% in petrolatum	0/5	RIFM (1974)
2-Methyl-4-phenyl-2-butanol	Closed patch 24- or 48-h	0.05–0.5% in cream base or 99% ethanol	14/212	Takenaka et al. (1968)
2-Methyl-4-phenyl-2-butanol	Maximization pretest	4% in petrolatum	0/5	RIFM (1973d)
1-Phenyl-3-methyl-3-pentanol	HRIPT induction	2.5% in Alcohol SDA 39C	0/37	RIFM (1964e)
1-Phenyl-3-methyl-3-pentanol	Maximization pretest	10% in petrolatum	0/25	RIFM (1975d)
2-Phenyl-2-propanol	Closed patch 24- or 48-h	0.05–5% in cream base or 99% ethanol	14/212	Takenaka et al. (1968)
2-Phenyl-2-propanol	Maximization pretest	4% in petrolatum	0/25	RIFM (1977c)
p-α,α-trimethylbenzyl alcohol	HRIPT induction	2.5% in ethanol	0/37	RIFM (1966a)
α,α,4-Trimethylphenethyl alcohol	HRIPT induction	5% in EtOH	0/39	RIFM (1964f)

[a] This material is not one of the materials being reviewed, as it is not used in fragrances, but it is included in this table because it is structurally related.

5.7. Mucous membrane (eye) irritation

Studies regarding eye irritation in humans and animals can be found in Table 8.

5.7.1. Human studies

Drops of phenethyl alcohol (6 g/L) were administered to human eyes with and without the preservative phenylmercuric borate (Boer, 1981). All six volunteers reported irritation of the eye including the skin around the eye. In another study, 50 volunteers received drops of 0.5% phenethyl alcohol in the eyes (Barkman et al., 1969). Thirty-nine subjects reported subjective irritation or "smarting" and 6 showed slight conjunctive hyperemia.

5.7.2. Animal studies

The eye irritation potential for 12 primary alcohols, 2 secondary alcohol and 4 tertiary alcohols has been evaluated by the Draize rabbit eye irritation test. Undiluted benzyl alcohol (Thomson et al., 1989; Stern et al., 1998) and 2-phenoxyethanol were moderate to severe eye irritants. Undiluted 2-methyl-4-phenylpentanol, 2-methyl-5-phenylpentanol and phenethyl alcohol produced conjunctive irritation, which was gone by day 7 or 10 (RIFM, 1988o,p, 1979h). Undiluted β,β-3-Trimethyl benzenepropanol was not irritating to the eyes of rabbits (RIFM, 1987i).

The primary alcohols, β-methoxybenzene ethanol (0.1 g washed out within 5–30 s), and 2, 2-dimethyl-3-phenylpropanol (20%) produced mild to moderate conjunctival irritation, which was gone by day 7. Several substances produced more severe reactions with increasing dose, such as benzyl alcohol (Morrison et al., 2006), β-methoxybenzene ethanol (0.1 g not washed out), and 3-methyl-5-phenylpentanol (1% and 5% in EtOH showed increased duration of conjunctival effects, but no effects were produced with 5% in petrolatum). Phenethyl alcohol (1%) caused minimal irritation that was clear in 24 h; however, 25% in EtOH resulted in moderate to severe conjunctive irritation with corneal opacity and iris congestion. 2-Phenoxyethanol at 5% produced very slight transient conjunctive inflammation; however, 15% in EtOH produced conjunctive irritation and 15% in propylene glycol produced severe corneal necrosis (RIFM, 1977e, 1983b). *p*-Tolyl alcohol (0.5%) produced slight irritation that was clear by day 7, but 5% *p*-tolyl alcohol resulted in severe conjunctive injury (RIFM, 1963a, 1964i). The secondary alcohol α-methylbenzylalcohol produced injury at 15% and severe injury and necrosis at 40% (Carpenter and Smyth, 1946). 3-Methyl-1-phenylbutan-2-ol (7.6%) produced corneal opacity, iris congestion and conjunctival irritation (RIFM, 1964j). The tertiary alcohol, α,α-trimethylphenethyl alcohol produced mild conjunctival irritation clear by day 4 at 0.5% but corneal opacity and severe conjunctive irritation not clear by day 7 with 5% (RIFM, 1963b,c). The tertiary alcohol *p*-α,α-trimethylbenzyl alcohol produced conjunctival irritation at 2.5%, which cleared by day 7 (RIFM, 1966b).

After intravitreal injection of rabbit eyes ($n = 9$) with 0.0073, 0.022, 0.073, 0.222, or 0.733% which included 1.5% benzyl alcohol (in carboxycellulose and 0.08% polysorbate 80) caused a loss of and shortening of outer segments and photoreceptors of the outer retina occurred in the highest three doses (Morrison et al., 2006).

5.8. Skin sensitization

Three of the materials in the AAA group of fragrance ingredients, anisyl alcohol, benzyl alcohol and β,β-3-Trimethyl benzenepropanol have IFRA Standards based on sensitization. The RIFM Expert Panel reviewed the critical effect data for these materials, and based on weight of evidence, established no expected sensitization induction levels (NESILs) of 1500 μg/cm^2 for anisyl alcohol (IFRA Standard, 42nd Amendment); 5900 μg/cm^2 for benzyl alcohol (IFRA Standard, 42nd Amendment); and 9900 μg/cm^2 for β,β-3-Trimethyl benzenepropanol. The NESILs were derived from the application of the exposure based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006. They recommended the limits for the 11 different product categories, which are the acceptable use levels of these 3 materials in the various product categories. These limits range from 0.04% (lip products and toys) to 5% (shampoos and liquid soap) for anisyl alcohol; 0.02% (lip products and toys, and also deodorant and anti-perpirant products) to 5% (shampoos and liquid soaps) for benzyl alcohol; and 0.28% (lip products and toys) to 7.2% (mouthwash and toothpaste) for β,β-3-Trimethyl benzenepropanol.

5.8.1. Human studies

5.8.1.1. Induction of human sensitization. Human sensitization data, from approximately 3200 volunteers, are available for 15 of the primary aryl alkyl alcohols and all 6 of the tertiary alcohols (Table 9-1a). Of the 15 primary alcohols only benzyl alcohol and phenethyl alcohol produced positive results in at least one HRIPT assay. Out of 74 volunteers, 2-phenoxyethanol produced only 1 positive reaction in the Maximization test. Overall, as a class, it can be concluded, on the basis of the large majority of AAA primary and tertiary alcohol data, that with the exception of benzyl alcohol and phenethyl alcohol, the AAA fragrance ingredients are not human sensitizers. Benzyl alcohol was evaluated in five human repeat in-

Table 7-2
Skin irritation in animals.

Material	Method	Concentration*	Species	Results	References
Primary alcohols					
Anisyl alcohol	LD_{50}	100%	Mice (10)	Moderate irritation (primary irritation score =4.0)	Draize et al. (1948)
Anisyl alcohol	LD_{50}	1250, 2500, or 5000 mg/kg in unknown vehicle	Rabbits (4)	Moderate erythma and edema	RIFM (1973a)
Anisyl alcohol	Modified Draize topical pretest	10% in suitable vehicle	Hartley guinea pigs (4)	0/4	Sharp (1978)
Anisyl alcohol	Modified Draize intradermal injection pretest	0.25% in suitable vehicle	Hartley guinea pigs (4)	4/4 slight irritation	Sharp (1978)
Benzyl alcohol	Primary irritation 4-h occlusive	100%	Rabbits (3)	2/3 very slight erythema	RIFM (1984b)
Benzyl alcohol	Primary irritation 4-h occlusive	100%	New Zealand White rabbits (4)	1/3 very slight erythema and edema	RIFM (1985e)
Benzyl alcohol	24-h occlusive patch	10% in water	Nude mice (3)	3/3 severe irritation	Lashmar et al. (1989)
Benzyl alcohol	24-h semi-occlusive patch	100%	Angora rabbits (6)	2/6 mild irritation	Motoyoshi et al. (1979)
Benzyl alcohol	24-h semi-occlusive patch	100%	Hartley guinea pigs (6)	0/6	Motoyoshi et al. (1979)
Benzyl alcohol	48-h occlusive patch	100%	Pitman–Moore miniature swine 1 month old (6)	0/6	Motoyoshi et al. (1979)
Benzyl alcohol	Modified Draize topical pretest	10% in suitable vehicle	Hartley guinea pigs (4)	0/3	Sharp, 1978)
Benzyl alcohol	Modified Draize intradermal injection pretest	0.25% in suitable vehicle	Hartley guinea pigs (4)	4/4 slight irritation	Sharp (1978)
Benzyl alcohol	OET 24-h pretest	0.03, 0.1, 0.3, 1, 3, 10, 30, or 100% in acetone, EtOH, DEP, etc.	Himalayan guinea pigs (6–8)	minimal irritating application after single application: 30%	Klecak et al. (1977)
Benzyl alcohol	OET induction (21 daily applications)	0.03, 0.1, 0.3, 1, 3, 10, 30, or 100% in acetone, EtOH, DEP, etc.	Himalayan guinea pigs (6–8)	minimal irritating concentration after 21 applications: 3%	Klecak et al. (1977)
2,2-Dimethyl-3-phenylpropanol	6-h occlusive patch	20% in peanut oil	Guinea pigs	0/20	RIFM (1981f)
2,2-Dimethyl-3-phenylpropanol	LD_{50}	100% (15 ml/kg; approximately 14.7 mg/kg)	Wistar rats (5/sex)	0/5	RIFM (1981a)
2,2-Dimethyl-3-phenylpropanol	6-h occlusive patch	20% in peanut oil	Guinea pigs	0/20	RIFM (1981f)
p-Isopropylbenzyl alcohol	LD_{50}	100% (5000 mg/kg)	Guinea pigs (4)	Moderate irritation	RIFM (1973a)
β-Methoxy benzeneethanol	Primary irritation 4-h	0.5 g	Rabbits (6)	0/6	RIFM (1979f)
β-Methylphenethyl alcohol	LD_{50}	100%	Rabbits (5)	0/5	RIFM (1974a)
2-Methyl-4-phenylpentanol	Primary irritation 4-h (OECD 404)	100%	New Zealand White rabbits (3)	0/3 (irritation score 1.3 erythema, 0.66 edema)	RIFM (1987h)
2-Methyl-4-phenylpentanol	LD_{50}	40% in unknown vehicle	New Zealand White rabbits (5/sex)	0/10	RIFM (1988c)
2-Methyl-4-phenylpentanol	Delayed-Contact Hypersensitivity pre test	2, 4, 8, or 16% in EtOH	Hartley guinea pigs (4)	0/4, 3/4, 3/4, 4/4	RIFM (1988j)
2-Methyl-4-phenylpentanol	Delayed-Contact Hypersensitivity induction	3% in EtOH	Hartley guinea pigs (10/sex)	16/20 slight to moderate erythema	RIFM (1988j)
2-Methyl-5-phenylpentanol	Primary irritation 4-h semi-occlusive	100%	Rabbits (3)	Well defined and slight edema extending beyond treatment site; desquamation in 2/3 animals and hyperkeratinization in 1/3 animals	RIFM (1988k)
2-Methyl-5-phenylpentanol	Primary irritation 4-h semi-occlusive	100, 50, 25, 10 and 2% in DEP	Rabbits (4)	Very slight to slight erythema in all animals, resolving by 48 h	RIFM (1990d)
2-Methyl-5-phenylpentanol	Maximization pre-test	10% in arachis oil BP with and without FCA	Guinea pigs (20)	0/20	RIFM (1988l)
3-Methyl-5-phenylpentanol	Irritation 24-h	5% in EtOH	Rabbits (3)	0/3	RIFM (1975e)
3-Methyl-5-phenylpentanol	Irritation 24-h	5% in petrolatum	Rabbits (3)	0/3	RIFM (1975f)
Phenethyl alcohol	Irritation 48-h	100%	1 month old Pitman–Moore miniature swine (6)	0/6	Motoyoshi et al. (1979)

(*continued on next page*)

Table 7-2 (*continued*)

Material	Method	Concentration*	Species	Results	References
Phenethyl alcohol	Irritation 24-h	100%	Angora rabbits (6)	2/6	Motoyoshi et al. (1979)
Phenethyl alcohol	Irritation 24-h	100%	Hartley guinea pigs (6)	2/6	Motoyoshi et al. (1979)
Phenethyl alcohol	Primary irritation 4-h semi-occlusive	100%	Rabbits (4)	0/4	RIFM (1985e)
Phenethyl alcohol	Primary irritation 4-h semi-occlusive	25, 50% in acetone/PEG; 100%	Guinea pigs (4)	0/4	RIFM (1983f)
Phenethyl alcohol	Primary irritation 4-h	100%	Rabbits (3)	1/3	RIFM (1984b)
Phenethyl alcohol	Irritation 1–6 h	100%	Rabbits (3)	0/3 by day 6	RIFM (1988m)
Phenethyl alcohol	LD_{50}	100% (5000 mg/kg)	Rats (10)	0/10	RIFM (1982a) Moreno
2-Phenoxyethanol	Irritation 24-h occluded patch	100%	Guinea Pigs (3)	Slight irritation (3/3)	RIFM (1984a)
2-Phenoxyethanol	Irritation 24-h patch	15% in 80%EtOH	Rabbits (3)	0/3	RIFM (1977b)
2-Phenoxyethanol	Irritation	100%	Rabbits (5)	Moderate erythema (3/5)	RIFM (1983b)
2-Phenoxyethanol	Irritation (no details)	100%	Rabbit (1)	Very slight irritation (1/1)	RIFM (1983c)
2-Phenoxyethanol	LD_{50}	100%	Rabbits (10)	Moderate to severe (10/10)	RIFM (1978a)
2-Phenoxyethanol	LD_{50}	100%	Rabbit (10M)	Skin erythema	RIFM (1983b)
2-Phenoxyethanol	LD_{50}	100%	New Zealand White rabbits (10/sex/dose)	Erythema and very slight to slight scaling of the skin	Breslin (1991)
2-Phenoxyethanol	Repeated open patch (10 applications)	100%	Guinea pigs (5)	Slight erythema with no exacerbation (5/5)	RIFM (1984a)
p-Tolyl alcohol	Primary irritation	100% (0.5g/0.5 mL)	Rabbits (4)	0/4 (irritation score 0.04)	RIFM (1989b)
p-Tolyl alcohol	LD_{50}	100%	Rabbits (10)	10/10 (moderate-severe erythema and slight to severe edema)	RIFM (1978a)
p-Tolyl alcohol	Modified Draize topical pretest	30% in suitable vehicle	Hartley guinea pigs (4)	0/4	Sharp (1978)
p-Tolyl alcohol	Modified Draize intradermal injection pretest	0.25% in suitable vehicle	Hartley guinea pigs (4)	Slight irritation	Sharp (1978)
β,*β*-3-Trimethyl benzenepropanol	Irritation 24-h OECD 404	97%	Rabbits (8)	0/8	RIFM (1985f)
β,*β*-3-Trimethyl benzenepropanol	LD_{50}	100%	New Zealand White rabbits (5/sex)	Moderate erythema and slight edema (8/10 on day 2)	RIFM (1987b)
β,*β*-3-Trimethyl benzenepropanol	Maximization intradermal induction	5% in 80% EtOH or FCA/ oleum arachidis	Pirbright guinea pigs (20)	0/20	RIFM (1985g)
β,*β*-3-Trimethyl benzenepropanol	Maximization closed patch induction	5% in 80% EtOH	Pirbright guinea pigs (20)	0/20	RIFM (1985g)
Secondary alcohols					
α-Methylbenzyl alcohol	LD_{50}	1250 mg/kg and up in unknown vehicle	Rabbits (4–6)	Moderate erythema (3/6) and edema (5/6)	RIFM (1973a)
α-Methylbenzyl alcohol	Modified Draize topical pretest	30% in suitable vehicle	Hartley guinea pigs (4)	0/4	Sharp (1978)
α-Methylbenzyl alcohol	Modified Draize intradermal injection pretest	0.25% in suitable vehicle	Hartley guinea pigs (4)	4/4 slight	Sharp (1978)
Tertiary alcohols					
α,α-Dimethylphenethyl alcohol	OET 24-h pretest	0.03, 0.1, 0.3, 1, 3, 10, 30, or 100% in acetone, EtOH, DEP, etc.	Himalayan guinea pigs (6–8)	Minimal irritating concentration=30%	Klecak et al. (1977)
α,α-Dimethylphenethyl alcohol	OET induction	0.03, 0.1, 0.3, 1, 3, 10, 30, or 100% in acetone, EtOH, DEP, etc.	Himalayan guinea pigs (6–8)	Minimal irritating concentration = 1%	Klecak et al. (1977)
α,α-Dimethylphenethyl alcohol	OET induction	0.3, 1, 3, 10, 30, or 100% in acetone	Guinea Pigs (4/dose)	No irritation	RIFM (1978d)
2-Methyl-4-phenyl-2-butanol	Primary irritation 4-h	100%	New Zealand White rabbits (4)	0/4 no irritation (irritation score 1.3 erythema, 0.3 edema)	RIFM (1988n)
2-Methyl-4-phenyl-2-butanol	LD_{50}	100%	Rabbits (6)	Moderate to severe erythema/eschar	RIFM (1973b)
1-Phenyl-3-methyl-3-pentanol	LD_{50}	100%	Rabbits (10)	Moderate erythema (9/10) and moderate/marked edema 10/10	RIFM (1975a)
2-Phenyl-2-propanol	LD_{50}	1250, 2500, 5000 mg/kg	Rabbits (4)	1250 mg/kg: Mild erythema (4/4) and edema (1/4)	RIFM (1977a)

Table 7-2 (*continued*)

Material	Method	Concentration*	Species	Results	References
				2500 mg/kg: Moderate (1/4) and severe (3/4) erythema and moderate edema (4/4) 5000 mg/kg: Severe erythema (2/4) and moderate (1/4) to severe (1/4) edemal	

* For the purpose of comparison some units have been changed from the reported units in the original study.

sult patch tests (HRIPT) with 420 volunteers with induction concentrations including 3, 5, 7.5, 15 or 20% in 3:1 DEP:EtOH. From these tests, 10/420 reactions were considered sensitizing, none of which occurred at the lowest concentration. In the HRIPT with 7.5% benzyl alcohol 1/110 reactions were reported plus two questionable reactions (RIFM, 2004b). All three subjects participated in a rechallenge that consisted of a 24-h occluded patch, a 24-h semi-occluded patch, and a repeat open application test (ROAT, 3 times a day for 5 days). Only 1 subject reacted under occlusion, semi-occlusion and ROAT. In another HRIPT with 20% benzyl alcohol 5/56 tested positive; however, only 2 of these five reacted to the occluded and semi-occluded applications and not reacted to the ROAT indicating that the reaction may not be sensitizing (RIFM, 2002a). Three maximization tests (74 subjects) with 10% benzyl alcohol in petrolatum resulted in no reactions (RIFM, 1979; RIFM, 1970; Ishihara et al., 1986). Similarly, phenethyl alcohol had 2/108, 1/89 (after rechallenge), 1/50 (after rechallenge) and 1/50 positive HRIPT results (RIFM, 1989c, 1983d,e, 1964b).

The primary alcohol, 2-(4-methylphenoxy) ethanol, was evaluated for sensitization in 2 HRIPT studies, at 2.5% in alcohol SDA. None of the 44 volunteers exhibited a positive reaction (RIFM, 1971b, 1972).

The secondary alcohol, α-methylbenzyl alcohol was evaluated for sensitization in a maximization test, at 8% in petrolatum. None of the 25 volunteers had a positive reaction (RIFM, 1973d).

Four of the tertiary alcohols, α,α-dimethylphenethyl alcohol; 2-methyl-4-phenyl-2-butanol; 1-phenyl-3-methyl-3-pentanol; and 2-phenyl-2-propanol did not induce positive reactions in maximization tests (RIFM, 1974c, 1973d, 1975d, 1977c). Four tertiary alcohols, α,α-dimethylphenethyl alcohol; 1-phenyl-3-methyl-3-pentanol; *p*-α,α-trimethylbenzyl alcohol; and α,α,4-trimethylphenethyl alcohol also did not produce positive reactions in a HRIPT (RIFM, 1964f; RIFM, 1985d).

5.8.1.2. Diagnostic patch-test studies. Diagnostic patch-test studies on dermatological patients have been reported for 6 of the primary aryl alkyl alcohols used as fragrances, anisyl alcohol; benzyl alcohol; 2,2-dimethyl-3-phenylpropanol; phenethyl alcohol; 2-phenoxyethanol; and β,β-trimethyl benzenepropanol (Table 9-1b). Benzyl alcohol was tested in 35 studies with dermatitis patients and incidence ranged from 0 to 3.8%, averaging around 1%. One outlying study with benzyl alcohol was reported for a group of patients allergic to balsam of Peru with an incidence of 7.8% (8/102) (Hausen, 2001). Reported reactions to anisyl alcohol, and phenoxyethanol were less than 1.8%. In one test, there were 2/20 (10%) positive reactions to phenethyl alcohol in perfume-sensitive patients (Larsen, 1977). In 2 separate studies with β,β-trimethyl benzenepropanol (dose not specified and 5% in petrolatum), there were 7/217 (3.2%) and 36/6573 (0.5%) positive reactions, respectively.

Diagnostic patch test studies were also performed on individual patients with histories of contact dermatitis or eczema for three of the AAA materials (phenethyl alcohol, 2-phenoxyethanol, and *p*-tolyl alcohol). The individuals did not react to phenethyl alcohol or *p*-tolyl alcohol. One patient did react to 2-phenoxyethanol and one did not (see FMRs for more detail).

5.8.2. Animal studies

Nine primary aryl alkyl alcohols, 1 secondary alcohols and 1 tertiary alcohols were evaluated for sensitization in guinea pigs with various test methods that included the Magnusson–Kligman maximization test, an open epicutaneous test, the Buehler delayed hypersensitivity test, Freund complete adjuvant test, and a Draize or modified Draize test (Table 9-2a).

Overall, the primary alcohols showed weak to no sensitization in animal studies. Among the primary alcohols, benzyl alcohol; 2-methyl-4-phenyl pentanol; phenethyl alcohol; and 2-phenoxyethanol had positive, but weak, sensitization reactions; however, the other five showed no sensitization Benzyl alcohol had both negative and weak to moderate positive responses.

The secondary alcohol α-methylbenzyl alcohol was not sensitizing in an open epicutaneous test or the modified Draize test. The tertiary alcohol α,α-dimethylphenethyl alcohol was not sensitizing in an open epicutaneous test, in a Draize test, or in a maximization test with guinea pigs (Table 9-2a).

Sensitization was evaluated using the murine local lymph node assay conducted with 6 primary and 1 secondary aryl alkyl alcohols (Table 9-2b). Of all the alcohols evaluated, only **anisyl alcohol**, with an EC_3 value of 5.9%, indicated sensitization.

5.9. Phototoxicity and photosensitization

Limited phototoxicity and photosensitization data are available for the AAA fragrance ingredients (Table 10-1a, 10-1b, 10-2a and 10-2b).

5.9.1. Phototoxicity in humans

In the phototoxicity portion of two HRIPT studies, β-methoxybenzeethanol (15% in petrolatum) and 2-phenoxyethanol (10% in mineral oil) showed no phototoxicity with or without UVA irradiation (RIFM, 1979e; RIFM, 1987j), see Table 10-1a.

5.9.2. Phototoxicity in animals

The primary alcohol, 2,2-dimethyl-3-phenylpropanol, was tested in guinea pigs in two studies for phototoxicity with 10% in peanut oil in a daily open application followed by UVA irradiation (energy not reported, 30 seconds at 30 cm) for two weeks (RIFM, 1982d,e). One study was negative for all 15 animals; the other study was inconclusive as a result of irritation from the vehicle (see Table 10-1b). In a study with 5% β, β, 3-trimethyl benzenepropanol in 80% ethanol, guinea pigs (10/sex) did not exhibit signs of phototoxicity (RIFM, 1985h).

5.9.3. Photosensitization in humans

In HRIPTs performed to investigate the photosensitization potential of β-methoxybenzeethanol (15% in petrolatum) and 2-phenoxyethanol (10% in mineral oil), no photosensization was shown with or without UVA irradiation (RIFM, 1979e, 1987j).

Table 8
Mucous membrane (eye) irritation studies.

Material	Method (Vol., %, No. animals)	Results	References
Primary alcohols			
2-Methoxybenzyl alcohol[a]	0.1ml (concentration and vehicle NR) (n = 3)	definite conjunctival irritation, not clear until day 7	RIFM (1964g)
Benzyl alcohol	Neural red test 100% (n = 6)	6/6 severe irritant	Thomson et al. (1989)
Benzyl alcohol	100%	Moderate irritant	Stern et al. (1998)
Benzyl alcohol	In vitro eye irritation test 1, 10, 100%	Maximum average score: 1% = 0 (non-irritant) 10% = 23 (mild irritant) 100% = 31 (moderate irritant)	Ohno et al. (1999)
Benzyl alcohol	0.0073, 0.022, 0.073, 0.222, 0.733% in 1.5% carboxycellulose and 0.08% polysorbate 80 (n = 9)	After intravitreal injection, loss of and shortening of outer segments and photoreceptors of the outer retina in 3 high doses	Morrison et al. (2006)
2,2-Dimethyl-3-phenylpropanol	20% in peanut oil (n = 6)	0/6 (clear by 24 h)	RIFM (1981d)
β-Methoxy benzeneethanol	0.1 g washed out after 5 seconds (n = 3)	3/3 conjuctival irritation (clear by day 3)	RIFM (1979g)
β-Methoxy benzeneethanol	0.1 g washed out after 30 seconds (n = 3)	3/3 conjunctival irritation (2/3 clear by day 5), corneal and iris irritation 3/3 (day 1), 2/3 (day 2), 1/3 (day 3), clear by day 5	RIFM (1979g)
β-Methoxy benzeneethanol	0.1 g no wash (n = 6)	3/3 severe irritation (not clear by day 7)	RIFM (1979g)
β-Methylphenethyl alcohol	0.1 ml no wash (n = 3) 0.625% in unspecified vehicle	Conjunctival redness, chemosis and discharge were observed in all 3 animals, resolving by day 7	RIFM (1964h)
2-(4-Methylphenoxy)ethanol	2.5% in Alcohol SDA 39C (n = 3)	Moderate to mild conjunctival irritation, resolving by day 4	RIFM (1971c)
2-Methyl-4-phenylpentanol	100% (n = 4)	1/4 (not clear by day 7); 4/4 irritation clear by day 3; 2/4 conjunctival irritation clear by day 4	RIFM (1988o)
2-Methyl-5-phenylpentanol	0.1 ml of 100% (n = 3)	3/3 diffuse and translucent corneal opacity, iridial inflammation and moderate to severe conjunctival iiritation, resolving by day 7	RIFM (1988p)
2-Methyl-5-phenylpentanol	15% in Alcohol SDA 39C (n = 3)	Conjunctival irritation and corneal involvement not cleared by day 10; results similar to control	RIFM (1988p)
3-Methyl-5-phenylpentanol	5% in EtOH (n = 3)	3/3 conjuctival irritation with corneal involvement not clear by day 10	RIFM (1975g)
3-Methyl-5-phenylpentanol	5% in petrolatum (n = 3)	0/3	RIFM (1975h)
3-Methyl-5-phenylpentanol	1% in EtOH (n = 3)	3/3 conjuctival irritation with corneal involvement not clear by day 7	RIFM (1977d)
Phenethyl alcohol	HUMAN: 0.5% in saline (n = 50 people)	39/50 reported subjective symptoms of irritation "smarting"; 6/50 showed slight conjunctive hyperaemia	Barkman et al. (1969)
Phenethyl alcohol	HUMAN: drops of 6 g/L (n = 6 people) with and without phenylmercuric borate	6/6 reported irritation (including the skin around the eye)	Boer (1981)
Phenethyl alcohol	100% (n = 6)	6/6 mild conjuctival irritation with corneal opacity clear by day 10	RIFM (1979h)
Phenethyl alcohol	25% in EtOH (n = 3)	3/3 moderate to severe conjunctival irritation with cornea opacity and iris congestion	RIFM (1965b)
Phenethyl alcohol	1% in unknown vehicle (n = 3)	3/3 minimal irritation clear by 24 h	RIFM (1988q)
2-Phenoxyethanol	100% washed or unwashed (n = 3)	Unwashed: 3/3 Strong acute eye irritation; Washed: 2/3 slight 1/3 moderate irritation	RIFM (1984a)
2-Phenoxyethanol	15% in 80% EtOH (n = 3)	3/3 conjunctival irritation with corneal involvement not clear by day 10	RIFM (1977e)
2-Phenoxyethanol	15% in propylene glycol (n = 5)	Severe corneal necrosis	RIFM (1983b)
2-Phenoxyethanol	5% in propylene glycol	Very slight transient conjunctival inflammation	RIFM (1983c)
2-Phenoxyethanol	5% in propylene glycol (n = 5)	Minor damage	RIFM (1983b)
p-Tolyl alcohol	5% in EtOH (n = 3)	3/3 severe conjunctival injury	RIFM (1963a)
p-Tolyl alcohol	0.5% in EtOH (n = 3)	0/3 (clear by day 7)	RIFM (1964i)
β,β-3-Trimethyl benzenepropanol	100% (n = 6)	0/6	RIFM (1987i)
β,β,3-Trimethyl-benzenepropanol	10% in CMC	6/6 conjunctival irritation (cleared within 48 h)	RIFM (1985)
Secondary alcohols			
α-Methylbenzyl alcohol	40% in propylene glycol (0.005 mL) (n = 5)	Severe injury and necrosis (grade 7)	Carpenter and Smyth (1946)
α-Methylbenzyl alcohol	15% in propylene glycol (0.005 mL) (n = 5)	Less than severe injury (grade 7)	Carpenter and Smyth (1946)
3-Methyl-1-phenylbutan-2-ol	7.6% in unspecified vehicle (n = 3)	3/3 corneal opacity, iris congestion and conjunctival irritation	RIFM (1964j)
Tertiary alcohols			
α,α-Dimethylphenethyl alcohol	2.5% in unspecified vehicle (n = 3)	pronounced conjunctival irritation as evidenced by intense vessel injection, obvious chemosis, and mild discharge, resolving by day 3	RIFM (1963b)

Table 8 (*continued*)

Material	Method (Vol., %, No. animals)	Results	References
1-Phenyl-3-methyl-3-pentanol	2.5% in Alcohol SDA 39C ($n = 3$)	Intense conjunctival reactions occurred within all animals within 24 h. By the seventh day, severe vessel injection and chemosis was still present	RIFM (1963c)
1-Phenyl-3-methyl-3-pentanol	0.25% in Alcohol SDA 39C ($n = 3$)	Definite conjunctival irriation, completely resolving by day 7	RIFM (1964j)
p-α,α-Trimethylbenzyl alcohol	2.5% in unspecified vehicle ($n = 3$)	Conjunctival irritation observed in 3/3, clear by day 7	RIFM (1966b)
α,α,4-Trimethylphenethyl alcohol	5% in unknown vehicle ($n = 3$)	3/3 corneal opacity and severe conjuctival irritation (not cleared by day 7)	RIFM (1963d)
α,α,4-Trimethylphenethyl alcohol	0.5% in unknown vehicle ($n = 3$)	3/3 mild conjunctival irritation clear by day 4	RIFM (1964k)

[a] This material is not one of the materials being reviewed as it is not used in fragrances, but it is included in this table because it is structurally related.

In a series of photopatch studies with 5% benzyl alcohol in petrolatum on patients with contact dermatitis (Sugai, 1996; Nagareda et al., 1996), or normal volunteers (Nagareda et al., 1992) all reported no incidence of photosensitivity. Among patients with contact sensitivity (Katoh et al., 1995) or photosensitivity dermatitis with actinic reticuloid syndrome (Addo et al., 1982) 1/669 and 1/50 patients, respectively, showed a reaction to the photopatch test.

5.9.4. Photosensitization in animals

2,2-Dimethyl-3-phenylpropanol was also tested for photosensitization in a Maximization test with guinea pigs (RIFM, 1981g). At concentrations of 20% in peanut oil, no photosensitization was seen in the animals either induced or challenged by UVA irradiation (the level of energy not reported; see Table 10-2b). β, β, 3-Trimethylbenzenepropanol was tested for photosensitization at 5% in ethanol at a wavelength of 370–450 nm. It was not found to be a photosensitizer (RIFM, 1985i).

5.9.5. UV spectra

UV spectra have been obtained for 6 aryl alkyl alcohol fragrance ingredients. All of them absorbed UV light peaking in the UVC range (<290 nm). Based on the UV spectra (see Table 11) and review of the phototoxicity/photosensitization data, aryl alkyl alcohol fragrance ingredients would not be expected to elicit phototoxicity or photosensitization under the current conditions of use as a fragrance ingredient.

6. Conclusion

The AAA fragrance ingredients are structurally diverse and include primary, secondary and tertiary aryl alkyl alcohols.

The metabolism of the AAA fragrance ingredients is contingent on whether the AAA fragrance ingredient includes a primary, secondary or tertiary alkyl alcohol. Metabolism studies were available for the AAA primary alkyl alcohols, anisyl alcohol; benzyl alcohol; phenethyl alcohol; and 2-phenoxyethanol; and for the AAA secondary alcohol α-methylbenzyl alcohol.

- AAA primary and secondary alkyl alcohols may either be conjugated and excreted directly, or oxidized to benzoic acids before being conjugated and excreted.
- Although there are no available metabolism studies on the AAA tertiary alkyl alcohols, it is expected that tertiary alcohols would be conjugated and excreted unchanged.
- Aryl (benzene) ring substituents may be metabolized, but generally this is not a primary pathway and does not affect the overall metabolism and/or conjugation/excretion of AAA primary and secondary alkyl alcohols and any related metabolites.

The metabolism of the AAA fragrance ingredients does not produce toxic metabolites; the conjugated metabolites or unmetabolized AAA conjugates are excreted in the urine and feces.

The available data indicate that there are no safety concerns regarding the use of AAA fragrance ingredients under the presently declared levels of exposure. Use of these fragrance ingredients beyond the higher maximum dermal levels or higher systemic exposure levels requires re-evaluation by the Panel. For the compounds for which systemic uptake in consumers (Table 1) has been estimated by RIFM, the margin of safety is between 70 and 25,000. There is an adequate margin of safety for the alcohols under review when applied in consumer personal care products at the currently recommended concentrations. Since all the short term and repeated dose studies revealed a low toxicity, this conclusion applies to the AAA group of fragrance ingredients including their metabolites.

This recommendation was based on the following rationale:

- Testing results for 21 compounds indicate that the AAAs have a low acute oral toxicity.
- Low systemic repeat dose toxicity was observed for 7 primary aryl alkyl alcohols, 2 secondary alcohols and 1 tertiary alcohol tested (see Table 3-2). Renal effects and plasma biochemistry (decreased serum glucose and other enzyme level changes) have been observed at doses of 40 mg/kg body weight/day and more. The lowest NOAEL of all subacute and subchronic oral toxicity studies available were with 90-day dietary administration of β-methylphenethyl alcohol and α-isobutylphenethyl alcohol and was 10 mg/kg/body weight/day. This value is taken as representative for all members of the group as a worst-case.
- *In vitro* and *in vivo* evaluation for 14 aryl alkyl alcohols did not result in evidence of genotoxic effects for primary, secondary and tertiary alcohol AAA fragrance ingredients.
- Chronic carcinogenicity testing showed that benzyl alcohol is not carcinogenic to rats and mice. α-Methylbenzyl alcohol was shown to induce renal tubular cell adenomas in male rats but not in female rats or mice of either sex. The authors of this study remarked that renal toxicity was characterized by severe nephropathy and related secondary lesions and that excessive deaths occurred during the last quarter of the study. The poor survival reduced the sensitivity of the study for detecting the presence of a carcinogenic response (NTP, 1990). JECFA reviewed this study and others and noted that α-methylbenzyl alcohol administered by gavage in corn oil was associated with a higher incidence of renal tubule-cell adenomas in male rats than in untreated controls, but not in female rats or in mice, at dose levels at or exceeding the maximum tolerated dose (MTD) and in the presence of factors that exacerbated a high incidence of age-related chronic progressive nephropathy. The intake of this compound from all sources is extremely low. On

Table 9-1a
Skin sensitization in humans.

Material	Method	Concentration*	Results	References
Primary alcohols				
Anisyl alcohol	Maximization[b]	5% in petrolatum (3450 μg/cm[b])	0/25	RIFM (1971a)
2-Methoxybenzyl alcohol[c]	HRIPT[a]	1.25% in EtOH (969 μg/cm[b])	0/39	RIFM (1965a)
Benzyl alcohol	HRIPT[a] plus rechallenge	20% in 3:1 DEP EtOH (23,622 μg/cm[b])	5/56 (2/5 reacted to rechallenge)	RIFM (2004a)
Benzyl alcohol	HRIPT[a]	15% in 3:1 DEP EtOH (17,717 μg/cm[b])	5/46	RIFM (2003a)
Benzyl alcohol	HRIPT[a] plus rechallenge	7.5% in 3:1 DEP:EtOH (8858 μg/cm[b])	3/110 (1/3 reacted to rechallenge)	RIFM (2004b)
Benzyl alcohol	HRIPT[a]	5% in 3:1 DEP:EtOH (5906 μg/cm[b])	2/101	RIFM (2005a)
Benzyl alcohol	HRIPT[a]	3% in 3:1 DEP:EtOH (3543 μg/cm[b])	0/107	RIFM (2004)
Benzyl alcohol	Maximization[b]	10% in petrolatum (6900 μg/cm[b])	0/25	Ishihara et al. (1986)
Benzyl alcohol	Maximization[b]	10% in petrolatum (6900 μg/cm[b])	0/24	RIFM (1979d)
Benzyl alcohol	Maximization[b]	10% in petrolatum (6900 μg/cm[b])	0/25	RIFM (1970)
Benzyl alcohol	Patch test	5% in petrolatum	1/104	Itoh et al. (1988)
Benzyl alcohol	Patch test	5% in petrolatum	1/97	Itoh et al. (1986)
Benzyl alcohol	Patch test	5% in petrolatum	1/83	Nishimura et al. (1984)
Benzyl alcohol	Patch test	5% in petrolatum	2/34	Ishihara et al. (1981)
Benzyl alcohol	Patch test	5, 2 or 1% in petrolatum	0/17	Ishihara et al. (1979)
p-Isopropylbenzyl alcohol	Maximization[b]	4% in petrolatum (2760 μg/cm^2)	0/24	RIFM (1973c)
β-Methoxy benzeneethanol	HRIPT[a]	15% in petrolatum (17,715 μg/cm^2)	0/50	RIFM (1979e)
β-Methylphenethyl alcohol	HRIPT[a]	6.25% in petrolatum (4845 μg/cm[b])	0/37	RIFM (1964a)
β-Methylphenethyl alcohol	Maximization[b]	6% in petrolatum (4140 μg/cm[b])	0/25	RIFM (1974c)
2-(4-Methylphenoxy)ethanol	HRIPT[a]	2.5% in Alcohol SDA 39C (1938 μg/cm[b])	0/10	RIFM (1971b)
2-(4-Methylphenoxy)ethanol	HRIPT[a]	2.5% in Alcohol SDA 39C (1938 μg/cm[b])	0/34	RIFM (1972)
2-Methyl-4-phenylpentanol	HRIPT[a]	3% in EtOH (3543 μg/cm[b])	0/55	RIFM (1987f)
2-Methyl-4-phenylpentanol	HRIPT[a]	3% in EtOH (3543 μg/cm[b])	0/52	RIFM (1987g)
2-Methyl-5-phenylpentanol	HRIPT[a]	NR in EtOH:DEP	0/50	RIFM (1997)
3-Methyl-5-phenylpentanol	HRIPT[a]	5% in EtOH (5905 μg/cm[b])	0/39	RIFM (1975b)
3-Methyl-5-phenylpentanol	HRIPT[a]	5% in petrolatum (5905 μg/cm[b])	0/41	RIFM (1975c)
Phenethyl alcohol	HRIPT[a] plus rechallenge	25% in EtOH (12,500 μg/cm[b])	3/89 (1/3 reacted to rechallenge)	RIFM (1983d)
Phenethyl alcohol	HRIPT[a] plus rechallenge	25% in EtOH (12,500 μg/cm[b])	1/50 (1/1 reacted to rechallenge)	RIFM (1983e)
Phenethyl alcohol	HRIPT[a]	25% in EtOH (19,380 μg/cm[b])	0/39	RIFM (1964b)
Phenethyl alcohol	HRIPT[a]	8% in DEP (9448 μg/cm[b])	2/108	RIFM (1989c)
Phenethyl alcohol	Maximization[b]	8% in EtOH (5520 μg/cm[b])	0/25	Grief (1967)
2-Phenoxyethanol	HRIPT[a]	15% in EtOH (15,000 μg/cm[b])	0/41	RIFM (1978b)
2-Phenoxyethanol	HRIPT[a]	10% in mineral oil	0/30	RIFM (1987j)
2-Phenoxyethanol	Maximization[b]	10% in petrolatum (6900 μg/cm[b])	0/26	RIFM (1982c)
2-Phenoxyethanol	Maximization[b]	10% in petrolatum (6900 μg/cm[b])	1/18	RIFM (1982c)
2-Phenoxyethanol	Maximization[b]	10% in petrolatum (6900 μg/cm[b])	0/30	RIFM (1982c)
2-Phenoxyethanol	Patch test 4 month	5% in petrolatum	1/501	DeGroot et al. (1986)
2-Phenoxyethanol	Patch test	5% in petrolatum	1/281	Motolese et al. (1992)
p-Tolyl alcohol	HRIPT[a]	5% in EtOH (5905 μg/cm[b])	0/39	RIFM (1964) IFF
p-Tolyl alcohol	Maximization	4% in petrolatum (2760 μg/cm[b])	0/23	RIFM (1978c)
o-Tolylethanol	HRIPT[a]	6.25% in EtOH (7381 μg/cm[b])	0/53	RIFM (1990c)
β,*β*-3-Trimethyl benzenepropanol	HRIPT[a]	18% in 3:1 DEP:EtOH (9920 μg/cm[b])	0/98	RIFM (2007)
β,*β*-3-Trimethyl benzenepropanol	HRIPT[a]	10% in 3:1 DEP:EtOH in skin lotion (5510 μg/cm[b])	0/103	RIFM (2005c)
Secondary alcohols				
α-Methylbenzyl alcohol	Maximization	8% in petrolatum (5520 μg/cm[b])	0/25	RIFM (1973d)
Tertiary alcohols				
α,α-Dimethylphenethyl alcohol	HRIPT[a]	2.5% in EtOH (1938 μg/cm[b])	0/42	RIFM (1964d)
α,α-Dimethylphenethyl alcohol	HRIPT[a]	2% in unspecified vehicle (1000 μg/cm[b])	0/48	RIFM (1985d)
α,α-Dimethylphenethyl alcohol	Maximization[b]	8% in petrolatum (5520 μg/cm[b])	0/25	RIFM (1973d)
α,α-Dimethylphenethyl alcohol	Maximization[b]	4% in petrolatum (2760 μg/cm[b])	0/25	RIFM (1974c)
2-Methyl-4-phenyl-2-butanol	Maximization[b]	4% in petrolatum (2760 μg/cm[b])	0/25	RIFM (1973d)
1-Phenyl-3-methyl-3-pentanol	HRIPT[a]	2.5% in Alcohol SDA 39C (2953 μg/cm[b])	0/37	RIFM (1964e)
1-Phenyl-3-methyl-3-pentanol	Maximization[b]	10% in petrolatum (6900 μg/cm[b])	0/25	RIFM (1975d)
2-Phenyl-2-propanol	Maximization[b]	4% in petrolatum (2760 μg/cm[b])	0/25	RIFM (1977c)
p-α,α-trimethylbenzyl alcohol	HRIPT[a]	2.5% in ethanol (1938 μg/cm[b])	0/37	RIFM (1966a)
α,α-4-Trimethylphenethyl alcohol	HRIPT[a]	5% in EtOH (5905 μg/cm[b])	0/39	RIFM (1964f)

[a] Human repeat insult patch test (HRIPT) generally consists of nine occluded induction patches (3 times/week) for 3 weeks and one occluded challenge patch. Sensitization reported during challenge phase only. Patch applications are 24 h in duration unless noted.

[b] Maximization generally consists of 5 induction 48-h 2 cm^2 patches every other day with 0.3 g or 0.3 mL at 10 times the use concentration in petrolatum (1% SLS for 24-h prior to the first pathc). After 5% SLS for 30 min, challenge consists of 48-h occluded patch given 10–14 days later; rechallenge if necessary one week later.

[c] This material is not one of the materials being reviewed as it is not used in fragrances, but it is included in this table because it is structurally related.

* For the purpose of comparison some units have been changed from the reported units in the original study.

Table 9-1b
Diagnostic patch tests.

Material	Concentration	Subjects	Results (frequency)	References
Primary alcohols				
Anisyl alcohol	5%	Patients with eczema suspected of a contact allergy to fragrances or cosmetics	0/320	VanOosten et al. (2009)
Anisyl alcohol	5% in petrolatum	Patients sensitive to fragrance allergens and suspected of contact dermatitis	3/167 (1.8%)	Larsen et al. (1996)
Anisyl alcohol	5% in petrolatum	Patients with contact dermatitis	0/115	Remaut (1992)
Anisyl alcohol	5% in petrolatum	Perfume sensitive patients	4/20 (20%)	Larsen (1977)
Anisyl alcohol	1% in petrolatum	Patients with dermatitis	1/2004 (0.05%)	Schnuch et al. (2007)
Benzyl alcohol	10% in petrolatum	Patients with contact dermatitis	0/501	DeGroot et al. (1986)
Benzyl alcohol	10% in petrolatum	Patients sensitive to cosmetics	3/182 (1.6%)	Malten et al. (1984)
Benzyl alcohol	1, 5, 10% in petrolatum	Patients with eczema, contact dermatitis, etc.	1/392 (0.3%), 6/392 (1.5%), or 9/394 (2.3%)	Ueda (1994)
Benzyl alcohol	1, 5, or 10% in petrolatum	Patients with facial dermatoses	0/394 at 1%; 1/394 (0.25%) at 5%; 2/394 (0.51%) at 10%	MJCDRG (1984)
Benzyl alcohol	5% in petrolatum	Patients with allergy to Balsam of Peru	8/102 (7.8%)	Hausen (2001)
Benzyl alcohol	5% in petrolatum	Patients with facial and or hand dermatitits	0/145	Suzuki et al. (1997)
Benzyl alcohol	5% in petrolatum	Patients sensitive to fragrance allergens and suspect to contact dermatitis	3/167 (1.8%)	Larsen et al. (1996)
Benzyl alcohol	5% in petrolatum	Patients with contact dermatitis	1/398 (0.3%)	Sugai (1996)
Benzyl alcohol	5% in petrolatum	Patients with dermatitis	1/479 (0.2%)	Nagareda et al. (1996)
Benzyl alcohol	5% in petrolatum	Patients with contact dermatitis	3/669 (0.4%)	Katoh et al. (1995)
Benzyl alcohol	5% in absorption ointment	Patients with eczema and dermatitis [subgroups of patients with cosmetic dermatitis; facial melanosis; non-cosmetic dermatitis & eczema]	1/81 (1.2%), [1/47 (2.1%),0/6, 0/28]	Haba et al. (1993)
Benzyl alcohol	5% in petrolatum	Patients with dermatitis (1990–1991)	3/425 (0.7%)	Nagareda et al. (1992)
Benzyl alcohol	5% in petrolatum	Patients with eczema and dermatitis	6/661 (0.9%)	Itoh et al. (1988)
Benzyl alcohol	5% in petrolatum	Patients with eczema and dermatitis	0/574	Hirose et al. (1987)
Benzyl alcohol	5% in petrolatum	Patients with eczema and dermatitis [subgroups of patients with: cosmetic dermatitis; facial melanosis; non-cosmetic dermatitis & eczema]	9/585 (1.5%); [4/248 (1.6%), 1/26 (3.8%), 45/311 (14.5%)]	Itoh et al. (1986)
Benzyl alcohol	5% in petrolatum	Patients with eczema	0/3037	Angelini et al. (1985)
Benzyl alcohol	5% in PMF	Patients with dermatitis	0/241	Ferguson and Sharma (1984)
Benzyl alcohol	5% in petrolatum	Patients with contact dermatitis	0/667	vanJoost et al. (1984)
Benzyl alcohol	5% in petrolatum	Patients with skin disease	1/84 (1.2%)	Takase et al. (1984)
Benzyl alcohol	5% in petrolatum	Patients with eczema and dermatitis [subgroups of patients with: cosmetic dermatitis; facial melanosis; non-cosmetic dermatitis & eczema] (1979–1982)	8/427 (1.2%)[3/172 (1.7%, 1/25 (4%), 4/230 (1.9%]	Nishimura et al. (1984)
Benzyl alcohol	5% in vehicle	Patients with contact dermatitis	0/178	Hirano and Yoshikawa (1982)
Benzyl alcohol	5% in petrolatum	Patients with skin disease	13/1206 (1.1%)	Sugai (1982)
Benzyl alcohol	5% in petrolatum	Patients with dermatitis	~2/200 (1%)	Nethercott (1982)
Benzyl alcohol	5% in petrolatum	Patients with contact dermatiti s	1/457 (0.2%)	Addo et al. (1982)
Benzyl alcohol	5% in petrolatum	Patients with eczema (1978/79)	~22/2261 (1%)	Mitchell et al. (1982)
Benzyl alcohol	5% in petrolatum	Patients with eczema (1979/80)	0/1934	Mitchell et al. (1982)
Benzyl alcohol	5% in petrolatum	Patients with eczema and dermatitis [subgroups of patients with: cosmetic dermatitis; non-cosmetic dermatitis & eczema]	6/220 (2.7%) [2/105 (1.9%), 4/115 (3.5%)]	Ishihara et al. (1981)
Benzyl alcohol	5, 2 or 1% in petrolatum	Patients with eczema and dermatitis [subgroups of patients with: cosmetic dermatitis; facial melanosis; non-cosmetic dermatitis & eczema]	5%: [3/78 (3.8%), 0/30, 1/51 (2.0%)]; 2%: [2/78 (2.6%), 0/30, 0/51]; 1: [2/78 (2.6%), 0/30, 0/51]	Ishihara et al. (1979)
Benzyl alcohol	1% in petrolatum	Patients with eczema suspected of contact dermatitis to fragrances	1/320 (0.3%)	vanOosten et al. (2009)
Benzyl alcohol	1% in petrolatum	Patients with dermatitis	7/2166 (0.3%)	Schnuch et al. (2007a)
Benzyl alcohol	1% in petrolatum	Patients with oral sensitivity or disease	1/390 (0.3%)	Torgerson et al. (2007)
Benzyl alcohol	1% in petrolatum	Patients with sensitive skin	1/1082 (0.1%)	Geier et al. (2003)
Benzyl alcohol	1% in petrolatum	Patients with dermatitis [subgroup with eyelid dermatitis]	0/3115 [0/232]	Cooper and Shaw (2000)

(*continued on next page*)

Table 9-1b (*continued*)

Material	Concentration	Subjects	Results (frequency)	References
Benzyl alcohol	1% in petrolatum	Patients with dermatitis	0/436	Penchalaiah et al. (2000)
Benzyl alcohol	0.2% in 99% EtOH and non irritant cream base	Patients with dermatoses	18/614 (2.9%)	Fujii et al. (1972)
2,2-Dimethyl-3-phenylpropanol	20% in petrolatum	50 patients, 40 of whom had eczema of various kinds	0/50	RIFM (1981e)
Phenethyl alcohol	25% in petrolatum	Patients suspected of cosmetic allergy	1/179 (0.6%)	DeGroot et al. (1985)
Phenylethyl alcohol	5% in petrolatum	20 perfume-sensitive patients	2/20 (10%)	Larsen (1977)
Phenethyl alcohol	1% in petrolatum	Dermatitis patients	0/100	Frosch et al. (1995)
2-Phenoxyethanol	5% in petrolatum	Patients with suspected contact dermatitis	1/501 (0.2%)	DeGroot et al. (1986)
2-Phenoxyethanol	5% in petrolatum	Patients with suspected contact dermatitis	1/343 (0.003%)	Vigan et al. (1992)
2-Phenoxyethanol	5% in petrolatum	Patients with contact dermatitis	1/281 (0.4%)	Motolese et al. (1992)
2-Phenoxyethanol	1% in petrolatum	Patients with contact dermatitis	7/3492 (0.2%)	Marks et al. (1995)
2-Phenoxyethanol	1% in petrolatum	Patients with contact dermatitis	0/3080	Marks et al. (1998)
2-Phenoxyethanol	1% in petrolatum	Patients with suspected contact dermatitis	8/8521 (0.09%)	Goosens et al. (1998)
2-Phenoxyethanol	1% in petrolatum	34 patients (10 with asthma, 13 with rhinitis, 11 with both) treated with corticosteroids or nasal inhalers	0/34	Isaksson et al. (1999)
2-Phenoxyethanol	1% in petrolatum	Patients with suspected contact dermatitis	0/2943	Thompson and Belsito (2002)
2-Phenoxyethanol	1% in petrolatum	Patients with suspected contact dermatitis	0/141	Thompson and Belsito (2002)
2-Phenoxyethanol	1% in petrolatum	Metal workers with contact dermatitis	2/199 (1%)	Geier et al. (2004)
β,β-3-Trimethyl benzenepropanol	5%	Dermatology patients with proven sensitization to fragrance ingredients	7/217 (3.2%)	Larsen et al. (2002)
β,β-3-Trimethyl benzenepropanol	5% in petrolatum	Dermatology patients	36/6573 (0.5%)	Schnuch et al. (2007b)

the basis of the evidence available, the Committee concluded that the higher incidence of benign neoplasms in the kidney of male rats is not relevant to humans; it is a species and gender-specific effect that does not occur in humans. Indeed, in view of the low use of α-methylbenzyl alcohol in cosmetic products (1–10 t/y) and the very low systemic exposure estimated by RIFM (0.0004 mg/kg body weight/day), the margin of exposure is 937,500 compared to the LOAEL for renal tubular cell adenomas in male rats of 375 mg/kg body weight/day, which is considered to be sufficient for a non-genotoxic compound.

- 2-phenoxyethanol adverse effects on reproduction were noted at a high oral doses where maternal toxicity was observed (2000 mg/kg body weight/day) with a NOAEL of 400 mg/kg body weight/day. For this compound the estimated systemic dose is 0.0476 mg/kg body weight for consumers (Table 1) leading to a margin of safety of 8400. Phenethyl alcohol induced fetotoxic and teratogenic effects at a low oral dose of 4.3 mg/kg body weight/day in rats, giving a margin of safety of 13.5. It should be noted that in a dermal study with phenethyl alcohol, increased perinatal mortality was observed at the highest dose tested (1400 mg/kg body weight/day) with a developmental NOAEL of 140 mg/kg body weight/day. This corresponds to a margin of safety of > 400. It is important to note, though, that in a dermal absorption study in humans under simulated exposure conditions, in which 10 mg of phenethyl alcohol was applied to the chest, an average of only 7.6% of the total dosage was absorbed, compared to 77% in the rat (after 24 h) (see Section 4.1). Based on the results from a pharmacokinetic study in rats, the rat and human dermal absorption data can be used to revise the developmental toxicity margin of safety. This revision takes into account the estimated daily human exposure, and the percent of applied dermal dose that is absorbed by humans. These are then compared to the rat maternal and developmental NOAEL and the percent of applied dermal dose that is absorbed by rats. The margin of safety is calculated to be greater than 2600. When peak plasma concentration is also taken into account in the estimation of a developmental toxicity margin of safety, the margin of safety is greater than 6000. Based on the accumulated conservative data, it is concluded that phenethyl alcohol, under the declared levels of use as a fragrance ingredient, would not produce developmental or reproductive effects in humans.
- Evaluations of 21 AAA fragrance ingredients at concentrations of 2–10%, which are above the concentrations currently used in personal care products, resulted in no, or only minimal, evidence of skin irritation in humans.
- Evaluation of 18 AAA fragrance ingredients for eye irritation showed that the undiluted materials cause moderate to severe eye irritation. However, since the AAAs are diluted and not used as a concentrate in personal care end products, the AAA should pose minimal concern for eye irritation at the concentrations currently used in the marketplace.
- Available sensitization data for 21 of AAA fragrance ingredients generally demonstrated no or low sensitizing potential.
  - Anisyl alcohol, benzyl alcohol and β,β-3-trimethyl benzenepropanol have IFRA Standards based on their weak sensitization potential (see Section 5.8). These Standards dictate the concentrations of these materials in various product categories. The limits range from 0.04% (lip products and toys) to 5% (shampoos and liquid soap) for anisyl alcohol; 0.02% (lip products and toys, and also deodorant and anti-perpirant products) to 5% (shampoos and liquid soaps) for benzyl alcohol; and 0.28% (lip products and toys) to 7.2% (mouthwash and toothpaste) for β,β-3-Trimethyl benzenepropanol.
  - AAA fragrances do not form hydroperoxides, but may be oxidized to aldehydes or ketones. At the recommended use levels and expected exposure in personal care products, the

Table 9-2a
Skin sensitization in animals.

Material	Method	Induction	Challenge	Species (No./group)	Results	References
Primary alcohols						
Anisyl alcohol	Open epicutaneous Test[b]	1, 3, 10, 30 or 100% in water, acetone, alcohol, petrolatum, PEG, etc.	5% in water, acetone, alcohol, petrolatum, PEG, etc.	Guinea pigs (6–8)	0/(6–8)	Klecak (1985), Klecak (1979)
Anisyl alcohol	Modified Draize[f]	0.625% in unknown vehicle	10% in unknown vehicle	Guinea pigs (4)	0/4	Sharp (1978)
Benzyl alcohol	Open epicutaneous Test[b]	1, 3, 10, or 30% in water, acetone, alcohol, petrolatum, PEG, etc.	10% in water, acetone, alcohol, petrolatum, PEG, etc.	Guinea pigs (6–8)	0/(6–8)	RIFM (1985); RIFM (1979)
Benzyl alcohol	Closed epicutaneous test	30% in unknown vehilcle	1% in unknown vehicle	Guinea pigs (10)	0/10	Ishihara et al. (1986)
Benzyl alcohol	Delayed contact hypersensitivty (Modified CCET)[h]	30% in FCA (injection) and 30% in EtOH (topical)	10% in EtOH	Hartley guinea pigs (5F)	"Weak allergen"	Kashima et al. (1993)
Benzyl alcohol	Maximization[a]	10% in unknown vehicle	10% in unknown vehicle	Guinea pigs	Moderate	Ishihara et al. (1986)
Benzyl alcohol	Maximization[a]	5% ± FCA (injection), 25% in petrolatum (topical)	subirritant concentration in petrolatum	Himalayan guinea pigs (6–8)	0/(6–8)	Klecak et al. (1977)
Benzyl alcohol	Modified Draize[f]	0.03, 0.1, 0.3, 1, 3, 10, 30, or 100% in acetone, EtOH, or DEP, etc.	3% in acetone, EtOH, or DEP, etc.	Himalayan guinea pigs (6–8)	Elicitation at $\geqslant$ 10% induction	Klecak et al. (1977)
Benzyl alcohol	Modified Draize[f]	Previously published	3% in acetone	Guinea pigs (10)	"Weak sensitizer"	Hausen et al. (1992)
Benzyl alcohol	Modified Draize[f]	0.25% (injection)	10% in unknown vehicle	Guinea pigs (4)	0/4	Sharp (1978)
Benzyl alcohol	Modified FCAT[g]	50% in FCA	1 or 3% in acetone	Himalayan guinea pigs (6–8)	Sensitization observed	Klecak et al. (1977)
2,2-Dimethyl-3-phenylpropanol	Modified Buehler[c]	20% in peanut oil	20% in peanut oil	Pirbright guinea pigs (20)	0/20	RIFM (1981f)
2-Methyl-4-phenylpentanol	Delayed contact sensitizaton[e]	3% in EtOH	3% in EtOH	Hartley guinea pigs (10/sex)	3/19 (slight reaction)	RIFM (1988j)
2-Methyl-5-phenylpentanol	Maximization[a]	10% in arachis oil BP with and without FCA (injection)	75% in EtOH	Guinea pigs (20)	0/20	RIFM (1988l)
3-Methyl-5-phenylpentanol	Maximization[a]	0.5% in FCA (injection); 10% in petrolatum (topical)	100%	Guinea pigs (12M)	0/12	RIFM (1980e)
Phenethyl alcohol	Open epicutaneous Test[b]	1, 3, 10, 30 or 100% in water, acetone, alcohol, petrolatum, PEG, etc.	8% in water, acetone, alcohol, petrolatum, PEG, etc.	Guinea pigs (6–8)	0/(6–8)	Klecak (1985), Klecak (1979)
2-Phenoxyethanol	Maximization[a]	0.5% in propylene glycol	0.5% in EtOH	Dunkin–Hartley guinea pigs (24F)-2 series	3/24 (similar to control) 0/24	Bruze et al. (1988)
2-Phenoxyethanol	FCAT	5 g/8 mL in FCA/saline	2 or 10% in saline	Guinea pigs (10)	0/10	Hausen (1993)
p-Tolyl alcohol	Modified Draize[f]	0.1% in unknown vehicle	10% in unknown vehicle	Guinea pigs (10)	0/10	Sharp (1978)
β,β-3-Trimethyl benzenepropanol	Maximization[a]	5% in 80% EtOH or FCA/oleum arachidis	5% in 80% EtOH	Pirbright guinea pigs (20)	0/20	RIFM (1985g)
β, β,3-Trimethyl-benzenepropanol	Maximization[a]	5% in–FCA intradermal 1% in oleum arachidis topical	1% in oleum arachidis	Pirbright guinea Pigs (20)	0/20	RIFM (1987)
Secondary alcohols						
α-Methylbenzyl alcohol	Open epicutaneous Test[b]	1, 3, 10, 30 or 100% in water, acetone, alcohol, petrolatum, PEG, etc.	8% in water, acetone, alcohol, petrolatum, PEG, etc.	Guinea pigs (6–8)	0/(6–8)	Klecak (1985), Klecak (1979)
α-Methylbenzyl alcohol	Modified Draize[f]	0.625% in unknown vehicle	30% in unknown vehicle	Guinea pigs (4)	0/4	Sharp (1978)

(*continued on next page*)

Table 9-2a (*continued*)

Material	Method	Induction	Challenge	Species (No./group)	Results	References
Tertiary alcohols						
α,α-Dimethylphenethyl alcohol	Open epicutaneous Test[b]	1, 3, 10, or 30% in water, acetone, alcohol, petrolatum, PEG, etc.	8% in water, acetone, alcohol, petrolatum, PEG, etc.	Guinea pigs (6–8)	0/(6–8)	RIFM (1985); RIFM (1979)
α,α-Dimethylphenethyl alcohol	Open epicutaneous Test[b]	0.3,1, 3, 10, 30, or 100% in water, acetone, alcohol, petrolatum, PEG, etc.	0.3,1, 3, 10, 30, or 100% in water, acetone, alcohol, petrolatum, PEG, etc	Guinea Pigs (4/dose)	0/4 at all doses	RIFM (1978d)
α,α-Dimethylphenethyl alcohol	Guinea Pig Maximization Test	3% in FCA – intradermal 25% in petrolatum – topical	10% in petrolatum	Guinea Pigs (6)	0/6	RIFM (1978d)
α,α-Dimethylphenethyl alcohol	Draize Test	0.1% in saline	0.1% in saline	Guinea Pigs (8)	0/8	RIFM (1978d)

Notes: 4 Draize – Guinea pigs inducted with 10 intradermal injections of the test material at the ICC over a 3 week period; challenge with injection of same concentration

[a] Maximization – Guinea pigs induced with intradermal injections of test material ± Freund's adjuvant/oleum arachidis on day 1 then with a closed patch test topical application on day 7; challenge is with closed patch test on day 21.

[b] OET – Guinea pigs inducted daily for 3 weeks with open topical applications of the test material; challenge by open application of the threshold irritating concentration and read after 24 h.

[c] Modified Buehler – Guinea pigs induced with 0.5 mL test material to 4 cm^2 occluded patch for 6 h repeated 1/week for 3 weeks; 2 weeks later primary challenge.

[e] Delayed contact hypersensitivity test – Guinea pigs induced 1/week for 3 weeks with 6-h semi-occlusive patch; challenge 14 days later in same manner; rechallenge 8 days later.

[f] Modified Draize – Guinea pigs inducted day 1 with 4 intradermal injections of 2.5x ICC (ICC [injection challenge concentration] gives a slight but perceptible irritation with no edema); challenge on day 14 performed with intradermal injection of ICC on one flank and topical application of the ACC (application challenge concentration] is the highest open topical concentration which caused no irritation in the pretest); rechallenge performed at day 21.

[g] FCAT – Guinea pigs inducted with 0.1 mL intradermal injection of 5% in FCA 3 times (day 1, 5 and 9) or 5 times (day 0, 2, 4, 7,or 9) on 8 cm^2; Challenge by open epicutaneous application in appropriate vehicle (water, acetone, alcohol, petrolatum, polyethylene glycol, etc.) at days 21 and 35.

[h] Modified CCET (cumulative contact enhancement test) – induction consists of FCA id injection and 24-h patch 2X at an inteval of 4–6 days followed by non-occlusive patches 3 weeks later.

Table 9-2b
Murine local lymph node assay (LLNA).

Material	Method	Dose	Species (No./group)	Results	References
Primary alcohols					
Anisyl alcohol	LLNA	2.5, 5, 10, 25, or 50% in DEP:EtOH (3:1)	CBA/Ca Mice (4)	EC_3 = 5.9% w/v (1475 μg/cm^2)	RIFM (2005d)
Benzyl alcohol	LLNA	2.5, 5, 10, 25, or 50% in DEP:EtOH (3:1)	CBA/Ca/Ola/Hsd female mice (4)	EC_3 >50% w/v (>12,500 μg/cm^2)	RIFM (2005e)
2-(4-Methylphenoxy)ethanol	LLNA	1, 5, 10, 20, or 40% in acetone:olive oil (4:1)	Female CBA/J Hsd mice (5)	EC_3 >30% (7500 μg/cm^2)	RIFM (2002b)
2-Methyl-4-phenylpentanol	LLNA	7.5, 15, or 30% in DEP:EtOH (3:1)	Female CBA/J mice (5)	EC_3 >30% (7500 μg/cm^2)	RIFM (2004d)
Phenethyl alcohol	LLNA	2.5, 5, 10, 25, or 50% in DEP:EtOH (3:1)	CBA/Ca/Ola/Hsd female mice (4)	EC_3 >50% (12,500 μg/cm^2)	RIFM (2004e)
β, β-3-Trimethyl benzenepropanol	LLNA	3, 10, or 30% in acetone: olive oil (4:1)	CBA/Ca/Ola/Hsd female mice (4)	EC_3 >30% (7500 μg/cm^2)	RIFM (2002c)
β, β,3-Trimethyl benzenepropanol	LLNA	3%, 10% or 30% in 4:1 acetone:olive oil	CBA/Ca Mice (4)	SI >3 at 30%	RIFM, 2002d
β, β,3-Trimethyl-benzenepropanol	LLNA	3, 10, or 30% in olive oil	CBA/Ca/Ola/Hsd male mice (4)	SI < 3 at all doses; not considered a sensitizer at any dose	RIFM (2002c)
β, β,3-Trimethyl-benzenepropanol	LLNA	3, 10, or 30% in acetone:olive oil (4:1)	CBA/CA female mice (4)	SI > 3 at 30%; considered a potential sensitizer	RIFM (2002d)
Secondary alcohols					
α-Isobutylphenethyl alcohol	LLNA	1, 5, 10, 20, 40% in acetone:olive oil (4:1)	Female CBA/J mice (5)	EC_3 >30% (7500 μg/cm^2)	RIFM (2003b)

Table 10-1a
Phototoxicity in humans.

Material	Method	Concentration	Energy	Subjects	Results	References
Primary alcohols						
β -Methoxy benzeneethanol	HRIPT	15% in petrolatum	1680 μwatts/cm^2 for 15 min at 15 inches	Humans (20)	0/20	RIFM (1979e)
2-Phenoxyethanol	HRIPT	10% in mineral oil (0.3 mL)	15.6–17.4 J/cm^2	Humans (30)	0/30	RIFM (1987j)

Table 10-1b
Phototoxicity in animals.

Material	Test system	Concentration	Energy	Results	References
Primary alcohols					
2,2-Dimethyl-3-phenylpropanol	Pirbright guinea pigs (15)	10% in peanut oil open application daily for 14 days	NR (UVA for 30 seconds at 30 cm)	0/15	RIFM (1982d)
2,2-Dimethyl-3-phenylpropanol	Hartley–Dunkin guinea pigs (20)	10% in peanut oil open application daily for 14 days	NR (UVA for 30 seconds at 30 cm)	Inconclusive (irritation resulted from vehicle)	RIFM (1982e)
β, β,3-Trimethyl-benzenepropanol	Pirbright guinea pigs (10/sex/dose)	5% in 80% ethanol	Wavelength of 370–450 nm at a distance of 30 cm for a period of 30 seconds	Not Phototoxic	RIFM (1985h)

Table 10-2a
Photosensitization in humans.

Material	Method	Concentration	Energy	Subjects	Results (frequency)	References
Primary alcohols						
Benzyl alcohol	Photopatch test	5% in petrolatum	NR	Humans (425)	0/425	Nagareda et al. (1992)
Benzyl alcohol	Diagnostic Photopatch test	5% in petrolatum on patients with photosensitivity dermatitis with actinic reticuloid syndrome	NR	Humans (50)	1/50 (2%)	Addo et al. (1982)
Benzyl alcohol	Diagnostic Photopatch test	5% in petrolatum on patients with contact sensitivity	NR	Humans (669)	1/669 (0.2%)	Katoh et al. (1995)
Benzyl alcohol	Diagnostic Photopatch test	5% in petrolatum on patients with contact dermatitis	NR	Humans (398)	0/398	Sugai (1996)
Benzyl alcohol	Diagnostic Photopatch test	5% in petrolatum on patients with contact dermatitis	NR	Humans (479)	0/479	Nagareda et al. (1996)
β-Methoxy benzeneethanol	HRIPT	15% in petrolatum	1680 μwatts/cm^2 for 15 min at 15 inches	Humans (20)	0/20	RIFM (1979e)
2-Phenoxyethanol	HRIPT	10% in mineral oil (0.3 mL)	15.6–17.4 J/cm^2	Humans (30)	0/30	RIFM (1987j)

Table 10-2b
Photosensitization in animals.

Material	Method	Concentration	Energy	Subjects	Results	References
Primary alcohols						
2,2-Dimethyl-3-phenylpropanol	Maximization	Induction: 20% in peanut oil (topical); Challenge 20% in peanut oil followed by same radiation	NR (UVA for 30 s at 30 cm)	Pirbright guinea pigs (20)	0/20	RIFM (1981g)
β,β-3-Trimethyl-benzenepropanol	Photosensitization	5% in 80% ethanol	wavelength of 370–450 nm at a distance of 30 cm for a period of 30 seconds	Pirbright guinea pigs (20)	0/20	RIFM (1985i)

Table 11
Summary of UV spectra data.

Material	UV Spectra Range of Absorption (nm)
Primary Aryl Alky Alcohol	
Benzyl alcohol	Peaked at 200–210 and at 240–250 Returned to baseline at 280
p-Isopropylbenzyl alcohol	Peaked at 201 and at 218 Returned to baseline at 285 (with minor absorption 255–275)
2-Methyl-4-phenylpentanol	Peaked at 200–210 Returned to baseline at 220
3-Methyl-5-phenylpentanol	Peaked at 209 Returned to baseline at 280 (with minor absorption 260–270)
Phenethyl alcohol	Peaked at 207 Returned to baseline at 280 (with minor absorption 250–260)
Secondary aryl alkyl alcohol	
2-Methyl-4-phenyl-2-butanol	Peaked at 208 Returned to baseline at 280 (with minor absorption 250–270)

AAA fragrance ingredients should not induce sensitization. However, for those individuals who are already sensitized, there is a possibility that an elicitation reaction may occur because the relationship between the no effect level for induction and the no effect level for elicitation is not known for this group of materials.

- On the basis of limited UVA or UVB light and review of existing phototoxicity and photosensitization data, the AAA fragrance ingredients would not be expected to elicit phototoxicity or photosensitization under the current recommended conditions of use in consumer products.
- To calculate the margin of safety (MOS), the lowest NOAEL of 10 mg/kg body weight/day is used (from 90-day dietary studies on β-methylphenethyl alcohol and α-isobutylphenethyl alcohol) along with daily systemic uptakes of 0.09 and 0.01 mg/kg body weight/day, respectively (100% dermal absorption is assumed as worst case). The MOS is > 100 *for these two materials*. If we do not adjust for dermal absorption, and assume 100% is absorbed as a worst case scenario, and use the highest daily systemic uptake (0.320 mg/kg body weight/day for phenethyl alcohol), then MOS would be 31 *for the group*. If a margin of safety of 100 were used, the maximum allowable exposure would be 0.1 mg/kg body weight/day.

Conflict of Interest

This research was supported by the Research Institute for Fragrance Materials, an independent research institute that is funded by the manufacturers of fragrances and consumer products containing fragrances. The authors are all members of the Expert Panel for Fragrance Materials, an independent group of experts who evaluate the safety of fragrance materials.

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