Food and Chemical Toxicology 50 (2012) S269–S313

Contents lists available at SciVerse ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Review

A toxicological and dermatological assessment of aryl alkyl alcohol simple acid ester derivatives when used as fragrance ingredients ☆

The RIFM Expert Panel
D. Belsito [a], D. Bickers [a], M. Bruze [b], P. Calow [c], M.L. Dagli [d], A.D. Fryer [e], H. Greim [f], Y. Miyachi [g], J.H. Saurat [h], I.G. Sipes [i]

[a] Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Ave., New York, NY 10032, USA
[b] Department of Occupational and Environmental Dermatology, Skane University Hospital, Malmo, Lund University, S-205 02 Malmo, Sweden
[c] University of Nebraska, Science and Public Policy, Office of Research and Economic Development, 230 Whittier Research Center, Lincoln, NE 68583-0857, USA
[d] University of Sao Paulo, School of Veterinary Medicine and Animal Science, Department of Pathology, Av. Prof. Dr. Orlando Marques de Paiva 87, Sao Paulo 05508-900, Brazil
[e] Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA
[f] Technical University of Munich, Institute for Toxicology and Environmental Hygiene, Hohenbachernstrasse 15–17, Freising-D-85354 Weihenstephan, Germany
[g] Department of Dermatology, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan
[h] Swiss Centre for Human Applied Toxicology, University Medical Center, University of Geneva, Rue Michel Servat, 1211 Geneve 4 CH, Switzerland
[i] Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ 85724-5050, USA

ARTICLE INFO

Article history:
Available online 9 March 2012

Keywords:
Review
Safety
Fragrance ingredients
Aryl alkyl alcohol
Simple acid ester

ABSTRACT

The aryl alkyl alcohol simple acid ester derivatives (AAASAE) group of fragrance ingredients was critically evaluated for safety following a complete literature search of the pertinent data. For high end users, calculated maximum skin exposures vary widely from 0.01% to 4.17%. AAASAE exhibit a common route of primary metabolism by carboxylesterases resulting in the formation of the simple acid and an aryl alkyl alcohol. They have low acute toxicity. No significant toxicity was observed in repeat-dose toxicity tests. There was no evidence of carcinogenicity of benzyl alcohol when it was administered in the feed; gavage studies resulted in pancreatic carcinogenesis due to the corn oil vehicle. The AAASAE are not mutagenic in bacterial systems or *in vitro* in mammalian cells, and have little to no *in vivo* genotoxicity. Reproductive and developmental toxicity data show no indication of adverse effects on reproductive function and NOELs for maternal and developmental toxicity are far in excess of current exposure levels. The AAASAE are generally not irritating or sensitizing at the current levels of exposure. The Panel is of the opinion that there are no safety concerns regarding the AAASAE at the current levels of use and exposure.

Contents

☆ All correspondence should be addressed to: A.M. Api, Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ 07677, USA. Tel.: +1 201 689 8089; fax: +1 201 689 8090. E-mail address: aapi@rifm.org.

0278-6915/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.fct.2012.02.091

1. Introduction

In 2010 complete literature searches were conducted on the aryl alkyl alcohol simple acid esters (AAASAE) fragrance ingredients. This document provides a risk assessment of these materials as fragrance ingredients and is a critical evaluation of the pertinent data. The scientific evaluation focuses on dermal exposure, which is considered to be the primary route for fragrance materials. Where relevant, toxicity, metabolism and biological fate data from other exposures have been considered.

The current format includes a group summary evaluation paper and individual fragrance material reviews on discrete chemicals. 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 comprehensive summary of all published reports including complete bibliographies (McGinty et al., in press-a, in press-b, in press-c, in press-d, in press-e, in press-f, in press-g, in press-h, in press-i, in press-j, in press-k, in press-l, in press-m, in press-n, in press-o, in press-p, in press-q, in press-r, in press-s, in press-t, in press-u, in press-v, in press-w, in press-x, in press-y, in press-z, in press-aa, in press-bb, in press-cc, in press-dd, in press-ee, in press-ff, in press-gg, in press-hh, in press-ii, in press-jj, in press-kk, in press-ll, in press-mm, in press-nn).

2. Chemical identity, regulatory status, and exposure

This report provides a safety assessment of aryl alkyl alcohol simple acid esters (AAASAE) for their use as fragrance ingredients. The AAASAE fragrance ingredients are blended with other fragrance ingredients that may or may not be AAASAE derivatives for use 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 report summarizes available animal and human toxicology data, for different routes of exposure, and integrates this information to evaluate the potential for human health effects associated with the use of AAASAE fragrance ingredients. The AAASAE risk evaluation focuses on dermal exposure, which is considered to be a primary route of exposure through which consumers may be exposed to fragrance materials. When available, toxicity, metabolism and kinetic data from other routes of exposure such as inhalation, which is another important route of exposure for fragrances, have also been discussed.

The AAASAE report also represents an evaluation of relevant data selected from a large bibliography of studies and reports on the individual chemicals. The selected data from published and unpublished reports were deemed appropriate 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 available toxicology data are summarized in Tables 1–10.

In 2001, 2002, and 2003 the International Joint FAO/WHO Expert Committee on Food Additives (JECFA) conducted and published Safety Evaluations of Certain Food Additive Safety and Contaminants that included Cinnamyl Alcohol and Related Substances (JECFA, 2001), 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). These publications, which include the toxicology for the AAASAE fragrance ingredients α-methylbenzyl acetate; α-methylbenzyl propionate; benzyl acetate; benzyl acetoacetate; benzyl butyrate; benzyl formate; benzyl isobutyrate; benzyl propionate; anisyl acetate; anisyl butyrate; anisyl formate; anisyl propionate; phenethyl acetate; phenethyl butyrate; phenethyl formate; phenethyl isobutyrate; phenethyl propionate; and 2-phenoxyethyl isobutyrate, were judged by the WHO Expert Committee not to present a human health safety concern at the current estimated levels of human exposure.

In the United States (US) the regulatory status of some fragrance ingredient substances (*p*-anisyl acetate; anisyl butyrate; anisyl formate; anisyl propionate; benzyl acetate; benzyl acetoacetate; benzyl butyrate; benzyl formate; benzyl isobutyrate; benzyl propionate; 1,1-dimethyl-2-phenylethyl butyrate; 1,1-dimethyl-2-phenylethyl formate; α-methylbenzyl acetate; α-methylbenzyl isobutyrate; α-methylbenzyl propionate; 2-methyl-4-phenyl-2-butyl acetate; phenethyl acetate; phenethyl butyrate; phenethyl isobutyrate; phenethyl formate; phenethyl propionate; 2-phenoxyethyl isobutyrate; 3-phenylpropyl acetate; piperonyl acetate) have been approved by the Food and Drug Administration (FDA) as synthetic flavoring substances and food adjuvants in accordance with 21 CFR 172.515. The Flavor and Extract Manufacturers Association (FEMA) member companies have reviewed some of the AAASAE fragrance ingredients and acknowledged them to be Generally Recognized as Safe (GRAS) for use as flavor ingredients. These include: *p*-anisyl acetate; anisyl butyrate; anisyl formate; anisyl propionate; benzyl acetate; benzyl acetoacetate; benzyl butyrate; benzyl formate; benzyl isobutyrate; benzyl propionate; 1,1-dimethyl-2-phenylethyl butyrate; 1,1-dimethyl-2-phenylethyl formate; α-methylbenzyl acetate; α-methylbenzyl isobutyrate; α-methylbenzyl propionate; 2-methyl-4-phenyl-2-butyl acetate; phenethyl acetate; phenethyl butyrate; phenethyl isobutyrate; phenethyl formate; phenethyl propionate; 2-phenoxyethyl isobutyrate; 3-phenylpropyl acetate; piperonyl acetate. The exposure, toxicity and safety of some of the AAASAE fragrance ingredients described in this assessment have also been summarized in FEMA GRAS assessments for benzyl derivatives (Adams et al., 2005a), hydroxyl- and alkoxy-substituted benzyl derivatives (Adams et al., 2005b) and aromatic substituted secondary alcohols, ketones and related esters (Adams et al., 2007). In addition benzyl acetate, a high production volume (HPV) chemical, was included in a robust summary and test plan for "Benzyl Derivatives", prepared by the Flavor and Fragrance High Production Volume Consortia (FFHPVC, 2001).

2.1. Rationale for grouping the aryl alkyl alcohol simple acid esters

The AAASAE are a structurally diverse class of fragrance ingredients in which the common structural element is a carboxylic acid ester group (–COOR). Many of the AAASAE fragrances are derived from AAA fragrance ingredients that were discussed in the preceding safety assessment and illustrated in Tables 1–3 of the Introductory comments.

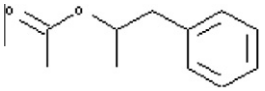
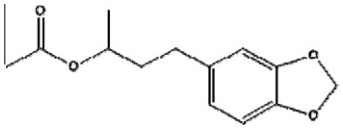
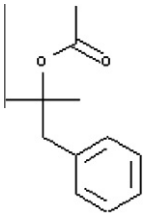
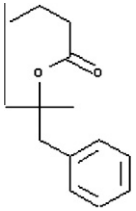
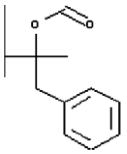
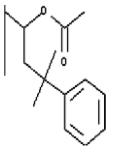
The AAASAE fragrance ingredients are prepared by reacting an aryl alkyl alcohol with a simple (chain of 1–4 carbons) carboxylic acid, such as formic, acetic, propionic, butyric, and isobutyric and carbonic to generate formate, acetate, propionate, butyrate, isobutyrate and carbonate esters. The alkyl portion of the aryl alkyl alcohol may be either linear or branched. The linear aryl alkyl alcohols include benzyl alcohol, phenylethyl alcohol, phenyl propyl alcohol, and phenoxyethyl alcohol. The phenyl ring of the linear benzyl alcohols may either be unsubstituted or substituted with the following groups: para-methyl, para-methoxy, para-isopropyl, ortho, para-dimethyl and meta, para-piperonyl. Similarly the linear phenonoxy ethyl alcohol ring is generally unsubstituted, but in one case substituted with a para-methyl. The phenyl ring of the other linear aryl alkyl alcohols, phenyl ethyl alcohol and 3-phenyl propyl alcohol is not substituted. The branched AAASAE secondary aryl alkyl alcohols include 1-methyl benzyl alcohol; 3-phenyl-3-buteneol or 1,3-dimethyl-3-phenylbutanol and the tertiary AAASAE aryl alkyls alcohols include 1,1-dimethyl-2-phenylethanol; 2-methyl-4-phenyl-2-butanol and 1-phenyl-3-methyl-3-pentanol. The phenyl ring of the aryl alkyl tertiary alcohols is not substituted.

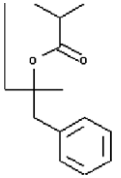
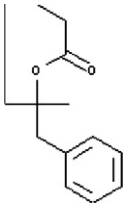
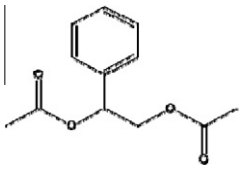
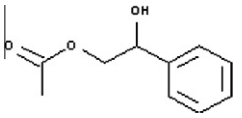
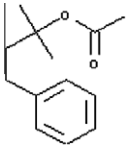
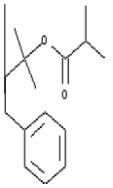
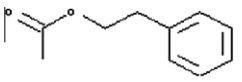
The primary path of metabolism for all of the AAASAE fragrance ingredients is hydrolysis in the gut and or liver to generate the corresponding Aryl Alkyl Alcohol, many of which are also fragrance ingredients, and a simple carboxylic acid (formic acid, acetic acid, propionic acid, butyric acid, isobutyric acid and carbonic acid). The formation of toxic or bioaccumulative metabolites has not been reported. The simple carboxylic acid AAASAE metabolite is either excreted directly or conjugated and excreted. As will be discussed in more detail in Section 3, published metabolic studies have demonstrated that some of the AAASAE fragrance ingredients are either hydrolyzed in the gastrointestinal tract and absorbed or rapidly absorbed as the parent compound and then hydrolyzed primarily in the liver by carboxylesterases to the corresponding aryl alkyl alcohol and simple carboxylic acids. The simple acids are readily excreted directly or as conjugates. Branching of the side chain can alter aryl alkyl alcohol metabolism. Primary linear aryl alkyl alcohols are either excreted directly, or oxidized to aryl carboxylic acid metabolites that are quickly conjugated with glycine or glucuronide and quickly eliminated mainly through the urine. The aryl branched alkyl secondary and tertiary alcohols may be conjugated and excreted directly but reversible oxidation of aryl branched alkyl secondary alcohols to ketones followed by further oxidation before conjugation and excretion may also occur to a lesser extent. No *in vivo* studies are available for AASAE fragrance ingredients derived from branched tertiary aryl alcohols, but there is *in vitro* study evidence that these types of compounds may not be metabolized and are excreted unchanged.

Table 1 provides a list of the aryl alkyl alcohol simple acid esters that are evaluated in this report along with their chemical abstract service (CAS) numbers, synonyms, structural formulas, physicochemical properties (calculated log K_{ow}, vapor pressure, water solubility), annual worldwide production, and dermal systemic exposure data for these compounds. The physicochemical properties of the AAA fragrance ingredients were summarized in the preceding risk assessment and are also relevant for the AAASAE compounds. Esterification of the AAA results in increases in lipophilicity that increases with carbon chain length. Accordingly, this is demonstrated by the incremental increase in log K_{ow} for benzyl alcohol (CAS No. 100-51-6), log K_{ow} 1.08 following esterification with a series of C1–C4 carboxylic acid and for benzyl formate (CAS No. 104-57-4), log K_{ow} 1.53; benzyl acetate (CAS No. 140-11-4), log K_{ow} 2.08; benzyl propionate (CAS No. 122-63-4), log K_{ow} 2.57; and benzyl isobutyrate (CAS No. 103-28-6), log K_{ow} 2.99.

Tables 2–10 summarize the available toxicology data. Considering that the parent compounds tested in the different systems are hydrolysed to form the alcohol and the acid, it can be concluded

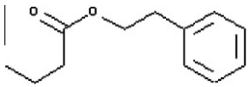
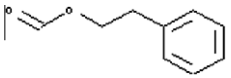
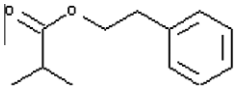
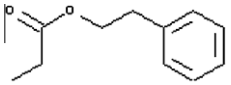
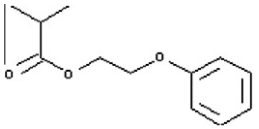
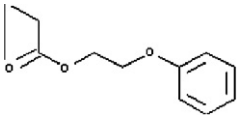
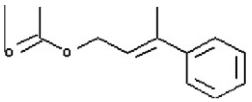
Table 1
Aryl alkyl alcohol simple acid esters.

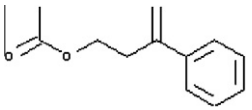
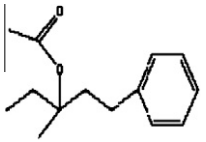
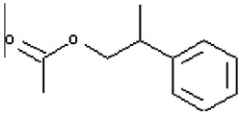
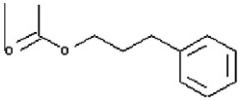
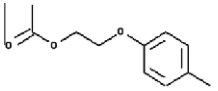
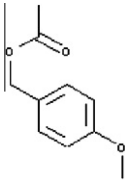
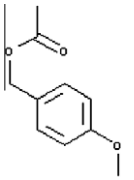
Material	Synonyms	Structure	Worldwide metric tons (annual)[a]	Dermal systemic exposure in cosmetic products[b,c] (mg/kg/day)	Maximum skin level[d,e] (%)
2-Acetoxy-1-phenyl propane[g] $C_{11}H_{14}O_2$ CAS No. 2114-33-2 Log K_{ow} 2.99[h] Molecular weight: 178.23 Vapor pressure: 0.0428 mm Hg at 25 °C[h] Water solubility: 157.2 mg/l 25 °C[h]	• Benzeneethanol, α-methyl-, acetate • Methyl benzyl carbinyl acetate • α-Methylphenethyl acetate • 1-Methyl-2-phenylethyl acetate • 1-Phenyl-2-propyl acetate		0	0	0
1,3-Benzodioxole-5-propanol, α-methyl-, 5-acetate $C_{13}H_{16}O_4$ CAS No. 68844-96-2 Log K_{ow} 3.54[h] Molecular weight: 236.27 Vapor pressure: 0.000169 mm Hg at 25 °C[h] Water solubility: 26.55 mg/L[h]	• 1,3-Benzodioxole-5-propanol, α-methyl-, acetate		<0.01	0.0005[f]	0.02%[f]
1,1-Dimethyl-2-phenylethyl acetate $C_{12}H_{16}O_2$ CAS No. 151-05-3 Log K_{ow} 3.44 at 30 °C Molecular weight: 192.26 Vapor pressure: 0.0223 mm Hg at 25 °C[h] Water solubility: 54.93 mg/l 25 °C[h]	• Benzeneethanol, α,α-dimethyl-, acetate • Benzyl dimethyl carbinyl acetate • 2-Benzyl-2-propyl acetate • Dimethylbenzyl carbinyl acetate • DMBCA1-Phenyl-2-methyl-2-propyl acetate • α,α-Dimethylphenyl acetate		100–1000	0.05	1.12%
1,1-Dimethyl-2-phenylethyl butyrate $C_{14}H_{20}O_2$ CAS No. 10094-34-5 Log K_{ow} 4.43 at 35 °C Molecular weight: 220.31 Vapor pressure: 0.00257 mm Hg at 25 °C[h] Water solubility: 5.701 mg/l 25 °C[h]	• Benzyl dimethyl carbinyl butyrate • 2-Benzyl-2-propyl butyrate • Butanoic acid, 1,1-dimethyl-2-phenethyl ester • Dimethylbenzyl carbinyl butyrate DMBC butyrate 2-Methyl-1-phenyl-2-propyl butyrate • α,α-Dimethylphenethyl butyrate		100–1000	0.04	1.59%
1,1-Dimethyl-2-phenylethyl formate $C_{11}H_{14}O_2$ CAS No. 10058-43-2 Log K_{ow} 2.9[h] Molecular weight: 178.23 Vapor pressure: 0.0531 mm Hg at 25 °C[h] Water solubility: 189 mg/l 25 °C[h]	• Benzeneethanol, α,α-dimethyl-, formate • Benzyl dimethyl carbinyl formate • 2-Benzyl-2-propyl formate • Dimethyl benzyl carbinyl formate • DMBC formate α,α-Dimethylphenethyl formate		< 0.01	0.0005[f]	0.02%[f]
1,3-Dimethyl-3-phenylbutyl acetate $C_{14}H_{20}O_2$ CAS No. 68083-58-9 Log K_{ow} 4.35[h] Molecular weight: 220.12 Vapor pressure: 0.0053 mm Hg at 25 °C[h] Water solubility: 6.587 mg/l 25 °C[h]	• Benzenepropanol,α,γ,γ-trimethyl-, acetate • 4-Methyl-4-phenyl-2-pentyl acetate		1–10	0.025	0.19%

1,1-Dimethyl-2-phenylethyl isobutyrate $C_{14}H_{20}O_2$ CAS No. 59354-71-1 LogK_{ow}4.35[h] Molecular weight: 220.12 Vapor pressure: 0.0053 mm Hg at 25 °C[h] Water solubility: 6.587 mg/l 25 °C[h]	• 1,1-Dimethyl-2-phenylethyl 2-methylpropanoate • Propanoic acid, 2-methyl-, 1,1-dimethyl-2-phenyl-ethyl ester		0.1–1.0	0.0005[f]	0.02%[f]
1,1-Dimethyl-2-phenylethyl propionate $C_{13}H_{18}O_2$ CAS No. 67785-77-7 LogK_{ow}3.93[h] Molecular weight: 206.29 Vapor pressure: 0.00743 mm Hg at 25 °C[h] Water solubility: 17.74 mg/l 25 °C[h]	• Benzeneethanol, α,α-dimethyl-, propanoate • Dimethylbenzylcarbinyl propionate • a,a-Dimethylphenethyl propionate • α,α-Dimethylphenylethyl propionate		0.1–1.0	0.04	0.27%
1,2-Ethanediol, 1-phenyl-, 1,2-diacetate $C_{12}H_{14}O_4$ CAS No. 6270-03-7 LogK_{ow}2.04[h] Molecular weight: 222.24 Vapor pressure: 0.00806 mm Hg at 25 °C[h] Water solubility: 607.4 mg/L[h]	•1,2-Ethanediol, 1-phenyl-, diacetate		< 0.01	0.0005[f]	0.02%[f]
2-Hydroxy-2-phenylethyl acetate $C_{10}H_{12}O_3$ CAS No. 10522-41-5 LogK_{ow} 1.03 Molecular weight: 180.03 Vapor pressure: 0.00026 mm Hg at 25 °C[h] Water solubility: 23290 mg/l 25 °C[h]	• 2-Acetoxy-1-phenylethanol • 1,2-Ethanediol,1-phenyl-, 2-acetate • beta.-Hydroxyphenethyl acetate		0.01–0.1	0.0005[f]	0.02%[f]
2-Methyl-4-phenyl-2-butyl acetate $C_{13}H_{18}O_2$ CAS No. 103-07-1 LogK_{ow}3.93[h] Molecular weight: 206.29 Vapor pressure: 0.00743 mm Hg at 25 °C[h] Water solubility: 17.74 mg/l 25 °C[h]	• Benzenepropanol,α,α-dimethyl-, acetate • Dimethylphenylethylcarbinyl acetate • 1,1-Dimethyl-3-phenylpropan-1-yl acetate • 1,1-Dimethyl-3-phenylpropyl acetate • D.M.P.E.C. acetate		1–10	0.02	0.08%
2-Methyl-4-phenyl-2-butyl isobutyrate[g] $C_{15}H_{22}O_2$ CAS No. 10031-71-7 LogK_{ow} 4.84[h] Molecular weight: 234.34 Vapor pressure: 0.00187 mm Hg at 25 °C[h] Water solubility: 2.109 mg/l 25 °C[h]	• Dimethyl phenethyl carbinyl isobutyrate • 1,1-Dimethyl-3-phenylpropyl isobutyrate • 1,1-Dimethyl-3-phenylpropyl 2-methylpropanoate • D.M.P.E.C. isobutyrate • D.M.P.E.C. 2-methylpropanoate • 2-Methyl-4-phenyl-2-butyl 2-methylpropanoate • Phenylethyl dimethyl carbinyl isobutyrate • Propanoic acid, 2-methyl-,1,1-dimethyl-3-phenyl-propyl ester		0	0	0
Phenethyl acetate $C_{10}H_{12}O_2$ CAS No. 103-45-7 LogK_{ow}2.57 at 25C Molecular weight: 164.2 Vapor pressure: 0.0683 mm Hg25 °C[h] Water solubility: 710.8 mg/l 25 °C[h]	• Acetic acid, 2-phenylethyl ester • Benzylcarbinyl acetate • Methylbenzylacetate • 2-Phenylethyl acetate • beta-Phenylethyl acetate • Phenylethyl ethanoate • Phenylethyl acetate		100–1000	0.02	1.44%

(*continued on next page*)

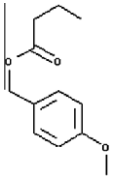
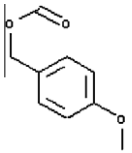
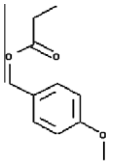
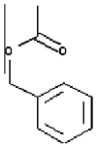
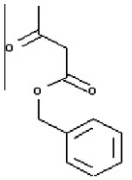
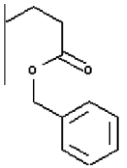
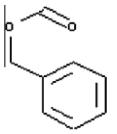
Table 1 (*continued*)

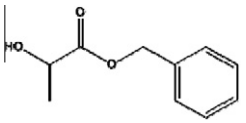
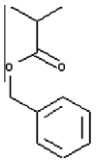
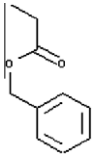
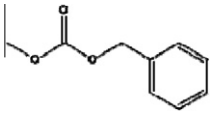
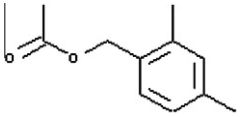
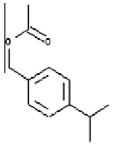
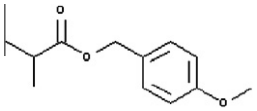
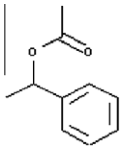
Material	Synonyms	Structure	Worldwide metric tons (annual)[a]	Dermal systemic exposure in cosmetic products[b,c] (mg/kg/day)	Maximum skin level[d,e] (%)
Phenethyl butyrate $C_{12}H_{16}O_2$ CAS No. 103-52-6 LogK_{ow}3.55[h] Molecular weight: 192.26 Vapor pressure: 0.00859 mm Hg at 25 °C[h] Water solubility: 44.15 mg/l at 25 °C[h]	• Benzylcarbinyl butyrate • Butanoic acid, 2-phenylethyl ester • 2-Phenylethyl butanoate • 2-Phenylethyl butyrate		0.1–1	0.002	0.01
Phenethyl formate $C_9H_{10}O_2$ CAS No. 104-62-1 LogK_{ow}2.02[h] Molecular weight: 150.18 Vapor pressure: 0.15 mm Hg at 25 °C[h]0 Water solubility: 1413 mg/l 25 °C[h]	• Benzylcarbinyl formate • Formic acid, phenylethyl ester • 2-Phenylethyl formate • 2-Phenylethyl methanoate		1–10	0.004	0.07
Phenethyl isobutyrate $C_{12}H_{16}O_2$ CAS No. 103-48-0 LogK_{ow} 3.5 at 35 °C Molecular weight: 192.26 Vapor pressure: 0.0272 mm Hg at 25 °C[h] Water solubility: 51.02 mg/l 25 °C[h]	• Benzylcarbinyl isobutyrate • Benzylcarbinyl 2-methylpropanoate • Phenethyl 2-methylpropanoate • 2-Phenylethyl isobutyrate • 2-Phenylethyl 2-methylpropanoate • Propanoic acid, 2-methyl-,2-phenylethyl ester		10–100	0.02	0.59
Phenethyl propionate $C_{11}H_{14}O_2$ CAS No. 122-70-3 LogK_{ow}3.06[h] Molecular weight: 178.23 Vapor pressure: 0.0514 mm Hg at 25 °C[h] Water solubility: 136 mg/l 25 °C[h]	• Benzylcarbinyl propionate • 2-Phenylethyl propanoate • 2-Phenylethyl propionate • Propanoic acid, 2-phenylethyl ester		0.1–1.0	0.002	0.01
2-Phenoxyethyl isobutyrate $C_{12}H_{16}O_3$ CAS No. 103-60-6 LogK_{ow}3.2 at 24 °C Molecular weight: 208.26 Vapor pressure: 0.00526 mm Hg at 25 °C[h] Water solubility: 105.7 mg/l 25 °C[h]	• Ethylene glycol monophenyl ether isobutyrate • Phenirat • Phenoxyethyl isobutyrate • 2-Phenoxyethyl 2-methylpropanoate • Phenylcellosolve isobutyrate • Propanoic acid, 2-methyl-,2-phenoxyethyl ester		100–1000	0.08	1.95%
2-Phenoxyethyl propionate $C_{11}H_{14}O_3$ CAS No. 23495-12-7 LogK_{ow} 2.6[h] Molecular weight: 194.23 Vapor pressure: 0.00737 mm Hg at 25 °C[h] Water solubility: 283.6 mg/l 25 °C[h]	• Ethanol, 2-phenoxy-, propanoate • Ethylene glycol monophenyl ether, propionate		1–10	0.003	0.05
3-Phenyl-2-butenyl acetate[g] $C_{12}H_{14}O_2$ CAS No. 20883-16-3 LogK_{ow} 3.4[h] Molecular weight: 190.42 Vapor pressure: 0.00941 mm Hg at 25 °C[h] Water solubility: 61.75 mg/l 25 °C[h]	• 2-Buten-1-ol, 3-phenyl-, acetate • 3-Phenylbut-2-en-1-yl acetate		0	0	0

3-Phenyl-3-buten-1-yl acetate $C_{12}H_{14}O_2$ CAS No. 7306-12-9 LogK_{ow} 3.47[h] Molecular weight: 190.24 Vapor pressure: 0.0133 mm Hg at 25 °C[h] Water solubility: 52.91 mg/l 25 °C[h]	• AnismalBenzenepropanol, γ-methylene-, acetate • 3-Phenylbut-3-en-1-yl acetate		<0.01	0.0005[f]	0.02%[f]
1-Phenyl-3-methyl-3-pentyl acetate $C_{14}H_{20}O_2$ CAS No. 72007-81-9 LogK_{ow}4.43[h] Molecular weight: 220.31 Vapor pressure: 0.00257 mm Hg at 25 °C[h] Water solubility: 5.701 mg/l 25 °C[h]	• Benzenepropanol,α-ethyl-α-methyl-, acetate • 1-Ethyl-1-methyl-3-phenylpropyl acetate • Phenylethyl methyl ethyl carbinyl acetate		<0.01	0.0005[f]	0.02%[f]
2-Phenylpropyl acetate $C_{11}H_{14}O_2$ CAS No. 10402-52-5 LogK_{ow}2.99[h] Molecular weight: 178.23 Vapor pressure: 0.0428 mm Hg at 25 °C[h] Water solubility: 157.2 mg/l 25 °C[h]	• Benzeneethanol,beta.-methyl-, acetate • Hydratropic acetate; • alpha-Methylphenylethyl acetate;Hydratropyl acetate		<0.01	0.0005[f]	0.02%[f]
3-Phenylpropyl acetate $C_{11}H_{14}O_2$ CAS No. 122-72-5 Log K_{OW}:3.06[h] Molecular weight: 178.23 Vapor pressure: 0.0243 mm Hg at 25 °C[h] Water solubility: 136 mg/l 25 °C[h]	• Benzenepropanol, acetate • Hydrocinnamyl acetate • Phenylpropyl acetate • beta-Phenylpropyl acetate		1–10	0.002	0.10%
2-(p-Tolyloxy) ethyl acetate $C_{11}H_{14}O_3$ CAS No. 6807-11-0 Log K_{OW}:2.65[h] Molecular weight: 194.3 Vapor pressure: 0.00645 mm Hg at 25 °C[h] Water solubility: 253.9 mg/l 25 °C[h]	• Ethanol, 2-(4-methylphenoxy)-, acetate • 2-(4-Methylphenoxy) ethyl acetate		<0.01	0.0005[f]	0.02%[f]
Benzylic alcohol					
p-Anisyl acetate $C_{10}H_{12}O_3$ CAS No. 104-21-2 LogK_{ow} 2.16[h] Molecular weight: 180.2 Vapor pressure: 0.00258 mm Hg at 25 °C[h] Water solubility: 782.9 mg/l 25 °C[h]	• acetic acid, 4-methoxybenzyl ester • Benzenemethanol, 4-methoxy-, acetate • Benzyl alcohol, p-methoxy-, acetate • Cassie ketone • 1-Methoxy-4-acetoxymethylbenzene • 4-Methoxybenzyl acetate • p-Methoxybenzyl acetate		10–100	0.03	0.50%
Anisyl acetate (isomer unspecified) $C_{10}H_{12}O_3$ CAS No. 1331-83-5 LogK_{ow}2.16[h] Molecular weight: 180.03 Vapor pressure: 0.00258 mm Hg at 25 °C[h] Water solubility: 782.9 mg/l 25 °C[h]	• Benzenemethanol, ar-methoxy-, acetate • 4-Methoxyphenyl acetate		1–10	0.02	0.29%

(*continued on next page*)

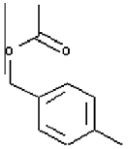
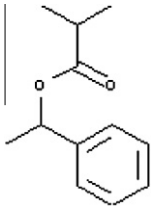
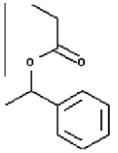
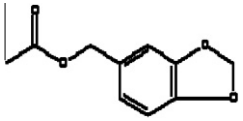
Table 1 (*continued*)

Material	Synonyms	Structure	Worldwide metric tons (annual)[a]	Dermal systemic exposure in cosmetic products[b,c] (mg/kg/day)	Maximum skin level[d,e] (%)
Anisyl butyrate [g] $C_{12}H_{16}O_3$ CAS No. 6963-56-0 Log K_{ow} 3.14[h] Molecular weight: 208.26 Vapor pressure: 0.00223 mm Hg at 25 °C[h] Water solubility: 81.94 mg/l 25 °C[h]	• Anisyl *n*-butyrate Butanoic acid, (4-methoxy-phenyl) methyl ester • 4-Methoxybenzyl butyrate • p-Methoxybenzyl butyrate		0	0	0
Anisyl formate $C_9H_{10}O_3$ CAS No. 122-91-8 Log K_{ow} 1.61[h] Molecular weight: 166.18 Vapor pressure: 0.0462 mm Hg at 25 °C[h] Water solubility: 2679 mg/l 25 °C[h]	• Anisyl methanoate • Benzenemethanol, 4-methoxy-, formate • 4-Methoxybenzyl formate • p-Methoxybenzyl formate • p-Methoxybenzyl methanoate		1–10	0.009	0.02%
Anisyl propionate $C_{11}H_{14}O_3$ CAS No. 7549-33-9 Log K_{ow} 2.65[h] Molecular weight: 194.23 Vapor pressure: 0.00645 mm Hg at 25 °C[h] Water solubility: 253.9 mg/l at 25 °C[h]	• Benzenemethanol, 4-methoxy-, propanoate • 4-Methoxybenzyl propionate • p-Methoxybenzyl propionate		0.01–0.1	0.0005[f]	0.02%[f]
Benzyl acetate $C_9H_{10}O_2$ CAS No. 140-11-4 Log K_{ow} 2.08[h] Molecular weight: 150.18 Vapor pressure: 0.187 mm Hg at 25 °C[h] Water solubility: 1605 mg/L (mean) at 20 °C[h]	• Acetic acid, benzyl ester • Acetic acid, phenylmethyl ester • Benteine • Benzyl ethanoate • Methyl benzeneacetate • Methyl phenylethanoate • Methyl α-toluate • Phenylmethyl acetate		>1000	0.12	4.17%
Benzyl acetoacetate [g] $C_{11}H_{12}O_3$ CAS No. 5396-89-4 Log K_{ow} 1.01[h] Molecular weight: 192.21 Vapor pressure: 0.00231 mm Hg at 25 °C[h] Water solubility: 6531 mg/L[h]	• Benzyl acetylacetate • Benzyl beta-ketobutyrate • Benzyl 3-oxobutanoate • Butanoic acid, 3-oxo-, phenylmethyl ester		0	0	0
Benzyl butyrate $C_{11}H_{14}O_2$ CAS No. 103-37-7 Log K_{ow} 3.06[h] Molecular weight: 178.23 Vapor pressure: 0.0488 mm Hg at 25 °C[h] Water solubility: 136 mg/l 25 °C[h]	• Benzyl butanoate • Butanoic acid, phenylmethyl ester		1–10	0.002	0.06
Benzyl formate $C_8H_8O_2$ CAS No. 104-57-4 Log K_{ow} 1.53[h] Molecular weight: 136.15 Vapor pressure: 0.31 mm Hg at 25 °C[h] Water solubility: 4257 mg/l 25 °C[h]	• Benzyl methanoate • Formic acid, phenylmethyl ester		1–10	0.005	0.06

Benzyl 2-hydroxypropionate $C_{10}H_{12}O_3$ CAS No. 2051-96-9 LogK_{ow}1.03[h] Molecular weight: 180.2 Vapor pressure: 0.00026 mm Hg at 25 °C[h] Water solubility: 23290 mg/L[h]	• Benzyl 2-hydroxypropanoate • Benzyl lactate • Phenylmethyl 2-hydroxypropanoate • Propanoic acid, 2-hydroxy-, phenylmethyl ester		<0.01	0.0005[f]	0.02%[f]
Benzyl isobutyrate $C_{11}H_{14}O_2$ CAS No. 103-28-6 LogK_{ow} 2.99[h] Molecular weight: 178.23 Vapor pressure: 0.0428 mm Hg at 25 °C[h] Water solubility: 157.2 mg/l 25 °C[h]	• Benzyl 2-methylpropanoate • Propanoic acid, 2-methyl-, phenylmethyl ester		1–10	0.02	0.16
Benzyl propionate $C_{10}H_{12}O_2$ CAS No. 122-63-4 LogK_{ow} 2.57[h] Molecular weight: 164.2 Vapor pressure: 0.131 mm Hg at 25 °C[h] Water solubility: 416.4 mg/l 25 °C[h]	• Benzyl propanoate • Propanoic acid, phenylmethyl ester		10–100	.01	0.46
Carbonic acid, methyl phenylmethyl ester $C_9H_{10}O_3$ CAS No. 13326-10-8	• Benzyl methyl carbonate		<0.01	0.0005[f]	0.02%[f]
2,4-Dimethylbenzyl acetate $C_{11}H_{14}O_2$ CAS No. 62346-96-7 LogK_{ow} 3.18[h] Molecular weight: 178.23 Vapor pressure: 0.0198 mm Hg at 25 °C[h] Water solubility: 109 mg/l 25 °C[h]	• Benzenemethanol, 2,4-dimethyl-, acetate • Trifurol Acetate		0.1–1	0.02	0.04%
p-Isopropylbenzyl acetate $C_{12}H_{16}O_2$ CAS No. 59230-57-8 LogK_{ow} 3.54[h] Molecular weight: 192.26 Vapor pressure: 0.0158 mm Hg at 25 °C[h] Water solubility: 45.68 mg/l 25 °C[h]	• Benzenemethanol, 4-(1-methylethyl)-, acetate • Cuminyl acetate • 4-Isopropylbenzyl acetate		0.1–1	0.001	0.01%
(4-Methoxyphenyl) methyl isobutyrate $C_{12}H_{16}O_3$ CAS No. 71172-26-4 LogK_{ow} 3.07[h] Molecular weight: 208.57 Vapor pressure: 0.0046 mm Hg at 25 °C[h] Water solubility: 94.68 mg/l 25 °C[h]	• Propanoic acid, 2-methyl-, (4-methoxyphenyl) methyl ester		<0.01	0.0005[f]	0.02%[f]
α-Methylbenzyl acetate $C_{10}H_{12}O_2$ CAS No. 93-92-5 LogK_{ow} 2.5[h] Molecular weight: 164.2 Vapor pressure: 0.112 mm Hg at 25 °C[h] Water solubility: 481.1 mg/l 25 °C[h]	• Benzenemethanol, α-methyl-, acetate • Gardenol • Methylphenylcarbinyl acetate • α-Phenylethyl acetate • 1-Phenylethyl acetate • sec-Phenylethyl acetate • Phenyl methyl carbinyl acetate • Styralyl acetate		100–1000	0.03	1.20%

(*continued on next page*)

Table 1 (*continued*)

Material	Synonyms	Structure	Worldwide metric tons (annual)[a]	Dermal systemic exposure in cosmetic products[b,c] (mg/kg/day)	Maximum skin level[d,e] (%)
4-Methylbenzyl acetate $C_{10}H_{12}O_2$ CAS No. 2216-45-7 Log K_{ow} 2.63[h] Molecular weight: 164.2 Vapor pressure: 0.0624 mm Hg at 25 °C[h] Water solubility: 539.8 mg/l 25 °C[h]	• p-Acetoxymethyltoluene • Benzenemethanol, 4-methyl-, acetatep-Methylbenzyl acetate • p-Tolubenzyl acetate • p-Xylyl acetate		0.1–1	0.01	0.15%
α-Methylbenzyl isobutyrate $C_{12}H_{16}O_2$ CAS No. 7775-39-5 Log K_{ow} 3.41[h] Molecular weight: 192.26 Vapor pressure: 0.0294 mm Hg at 25 °C[h] Water solubility: 58.95 mg/L[h]	• α-Methylbenzyl 2-methylpropanoate • Methyl phenylcarbinyl isobutyrate • 1-Phenyl-1-ethyl isobutyrate • 1-Phenylethyl 2-methylpropanoate • 1-Phenyl-1-ethyl 2-methylpropanoate • Propanoic acid, 2-methyl-, 1-phenylethyl ester • Styralyl isobutyrate		0.1–1	0.0005[f]	0.02%[f]
α-Methylbenzyl propionate $C_{11}H_{14}O_2$ CAS No. 120-45-6 Log K_{ow} 2.99[h] Molecular weight: 178.23 Vapor pressure: 0.0428 mm Hg at 25 °C[h] Water solubility: 157.2 mg/l 25 °C[h]	• Benzenemethanol, α-methyl-, propanoate • Methylphenylcarbinyl propionate • 1-Phenylethyl propionate • Styralyl propionate		1–10	0.02	0.10
Piperonyl acetate $C_{10}H_{10}O_4$ CAS No. 326-61-4 Log K_{ow} 2.14[h] Molecular weight: 194.19 Vapor pressure: 0.00169 mm Hg at 25 °C[h] Water solubility: 692.8 mg/l 25 °C[h]	• 1,3-Benzodioxole-5-methanol, acetate • 1,3-Benzodioxol-5-ylmethyl acetate • Heliotropyl acetate • 3,4-Methylenedioxybenzyl acetate		0.1–1	0.02	0.08

[a] 2008 Volume of use survey (IFRA, 2008c).
[b] Based on a 60-kg adult.
[c] Cadby et al. (2002), Ford et al. (2000).
[d] Upper 97.5 percentile levels of the fragrance ingredient in the fragrance mixture used in these products.
[e] 2008 Use level survey (IFRA, 2008a,b).
[f] Exposure was not reported. For the high end users of the AAASAE containing products, a default value of 0.02% is generally assumed as the maximum daily skin exposure and the dermal systemic exposure is estimated to be 0.0005 mg/kg/day.
[g] The following CAS No.s are not used as fragrance materials, but are considered structurally related.
[h] Physical properties have been calculated.

Table 2-1
Skin absorption data on benzyl acetate.

In vivo			In vitro		
Monkey		Rat	Human	Rat	
Occluded	Non-Occluded	Occluded	Occluded	Occluded	Non-Occluded
	34.6%[d]	>95%[e]	1. 3%[f]	49. 8%[i]	53%[j]
17.3%[b]			5.5.%[g]	34. 3%[g]	49.3[k]
78.7%[c]			17.8%[h]	55.8%[h]	50%[l]
					4.2%[m]
					45.9%[n]
					50%[o]
					55.8%[p]
				47.52%[q]	47.52%[r]

[b] In moisturizing lotion; occluded with plastic wrap.
[c] In moisturizing lotion; occluded with glass chamber.
[d] In a moisturizing lotion.
[e] Neat or 50% in ethanol; occluded with tape; at 24 hours.
[f] At 72 hours.
[g] At 24 hourss; occluded with teflon caps.
[h] At 72 hours; occluded with teflon caps.
[i] Neat or 50% in ethanol; at 48 hours.
[j] Neat at 3 hours; 50% in ethanol at 1 hour.
[k] Neat at 48 hours.
[l] 50% in ethanol at 48 hours.
[m] Neat at 6 hours.
[n] Neat at 48 hours.
[o] Neat at 48 hours.
[p] Neat at 72 hours.
[q] Neat at 48 hours; occluded with parafilm.
[r] Neat at 48 hours.

that the test result apply to both the parent compound and the resulting metabolites. Contained within Tables 2-10 are additional toxicology data for esters (2-acetoxy-1-phenyl propane; 2-methyl-4-phenyl-2-butyl isobutyrate; 3-phenyl-2-butenyl acetate; anisyl butyrate; and benzyl acetoacetate) that are not used in fragrances but are structurally related to the AAASAE fragrance ingredients. These materials are not being reviewed because there was no reported use of these materials as fragrance ingredients (IFRA, 2008a,b,c). However, any safety data on these materials, if available, will appear in the data tables.

2.2. Occurrence and use

The AAASAE are generally synthetic compounds that may be used both as fragrance ingredients and flavoring agents in food products. The annual worldwide production of the individual AAASAE fragrance and flavoring ingredients varies from less than 0.01 to greater than 1000 metric tons. The worldwide production of 2-phenoxyethyl isobutyrate; phenylethyl acetate;1,1-dimethyl-2-phenylethyl acetate; 1,1-dimethyl-2-phenylethyl butyrate; α-methylbenzyl acetate; and benzyl acetate is 100 to >1000 metric tons per year. The remaining AAASAE compounds' volumes of production can be found in Table 1.

Benzyl acetate is a naturally occurring compound with highest quantities found in cloves and chamomile (VCF, 2010). Benzyl acetate, whose annual worldwide production exceeds 1000 metric

Table 2-2
Acute dermal toxicity studies.

Material	Species	Number per dose group	LD_{50}[a] (mg/kg) (95% Confidence interval)	References
2-Acetoxy-1-phenylpropane[b]	Rabbit	10	>5000	RIFM (1978a)
1,1-Dimethyl-2-phenylethyl acetate	Rabbit	1 or 3 (5 total)	>3000 mg/kg	RIFM (1971a)
1,1-Dimethyl-2-phenylethyl butyrate	Rabbit	10	>5000	RIFM (1977b)
1,1-Dimethyl-2-phenylethyl formate	Rat (performed under EEC Directive test No. 402, GLP)[a]	10 (5/sex)	>2000	RIFM (1989a)
1,1-Dimethyl-2-phenylethyl propionate	Rabbit	10	>5000	RIFM (1977b)
1,3-Dimethyl-3-phenylbutyl acetate	Rabbit (performed under 16 CFR 1500.3)[a]	10	>2000	RIFM (1979a)
2-Methyl-4-phenyl-2-butyl acetate	Rabbit	4	>5000	RIFM (1975a)
Phenethyl acetate	Rabbit	3	<10,000	RIFM (1970a)
Phenethyl acetate	Rabbit	3	6210 (3900–9900 mg/kg)	RIFM (1970a)
Phenethyl butyrate	Rabbit	4	>5000 (>5 ml/kg)	RIFM (1974b)
Phenethyl formate	Rabbit	4 (2/sex)	>5000 (>5 ml/kg)	RIFM (1973a)
Phenethyl isobutyrate	Rabbit	6	>5000	RIFM (1971b)
Phenethyl propionate	Rabbit	10	>5000	RIFM (1973a)
Phenethyl propionate[c]	Rabbit	4	1200	Beroza et al. (1975)
1-Phenyl-3-methyl-3-pentyl acetate	Rabbit	10	>5000	RIFM (1976a)
2-Phenoxyethyl isobutyrate	Rabbit	10	>5000	RIFM (1973a)
2-Phenoxyethyl propionate	Rabbit	4 (2/sex)	>5000 (>5 ml/kg)	RIFM (1973a)
3-Phenyl-3-buten-1-yl acetate	Rat	NR	>5000	RIFM (1981a)
2-Phenylpropyl acetate	Rabbit	10	>5000	RIFM (1975b)
3-Phenylpropyl acetate	Rabbit	10	>5000	RIFM (1973a)
Benzylic alcohols				
p-Anisyl acetate	Rabbit	6	>5000	RIFM (1971c)
Anisyl butyrate[b]	Rabbit	10	>5000	RIFM (1976a)
Anisyl formate	Rabbit	4	>5700 (>5 ml/kg)	RIFM (1975a)
Anisyl propionate	Rabbit	10	>5000	RIFM (1974c)
Benzyl acetate	Rabbit	3	>5000	RIFM (1972a)
Benzyl butyrate	Rabbit	5	>5000	RIFM (1973a)
Benzyl formate	Rabbit	3	<5000	RIFM (1971b)
Benzyl isobutyrate	Rabbit	4 (2/sex)	>5000	RIFM (1971d)
Benzyl propionate	Rabbit	5	>5000	RIFM (1973a)
2,4-Dimethylbenzyl acetate	Guinea pig	10	>5000	RIFM (1982a)
Ethyl phenyl carbonyl acetate	Rabbit	10	>5000	RIFM (1982a)
p-Isopropylbenzyl acetate	Rabbit	10	>5000	RIFM (1978a)
α-Methylbenzyl acetate	Rabbit	12	>8200 (>8 ml/kg)	RIFM (1971e)
4-Methylbenzyl acetate	Rabbit	10 (MF)	>5000	RIFM (1981b)
α-Methylbenzyl propionate	Rabbit	4 (2/sex)	>5000	RIFM (1973a)
Piperonyl acetate	Rabbit	10	>5000	RIFM (1973a)

[a] For the purpose of comparison some units may have been changed from the reported units in the original study.
[b] 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.
[c] This study was performed with a mixture of phenethyl propionate and eugenol at a ratio of 7:3.

Table 2-3
Acute oral toxicity studies.

Material	Species	Number per dose group	LD_{50}[a] (mg/kg) (95% Confidence interval)	References
2-Acetoxy-1-phenyl propane[b]	Rat	10	>5000	RIFM (1978a)
1,1-Dimethyl-2-phenylethyl acetate	Rat	10	3300 (2600–4100 mg/kg)	RIFM (1971f)
1,1-Dimethyl-2-phenylethyl butyrate	Rat	10	>5000	RIFM (1977b)
1,1-Dimethyl-2-phenylethyl formate	Rat	10	>2000	RIFM (1990b)
1,1-Dimethyl-2-phenylethyl propionate	Rat	10	>5000	RIFM (1977b)
1,3-Dimethyl-3-phenylbutyl acetate	Rat (performed under 16 CFR 1500.3)[a]	10	>5000	RIFM (1979b)
1,3-Dimethyl-3-phenylbutyl acetate	Rat	10	9000	RIFM (1984a)
2-Methyl-4-phenyl-2-butyl acetate	Mouse	10	4850	RIFM (1975a)
Phenethyl acetate[c]	Guinea pig	6	3700	Zaitsev and Rakhmanina (1974)
Phenethyl acetate	Rat	10	>5000	RIFM (1973a)
Phenethyl acetate[c]	Rat	6	3700	Zaitsev and Rakhmanina (1974)
Phenethyl acetate[c]	Mouse	6	3700	Zaitsev and Rakhmanina (1974)
Phenethyl acetate[d]	Mouse	6	2400	RIFM (1980a)
Phenethyl butyrate	Rat	10	4600 (4.6 ml/kg) (4200–5000 mg/kg)	RIFM (1974b)
Phenethyl formate	Rat	10	3200 (3.2 ml/kg) (2800–3700 mg/kg)	RIFM (1973c)
Phenethyl formate	Mouse	6	2300 (2.3 ml/kg) (1900–2700 mg/kg)	RIFM (1980b)
Phenethyl isobutyrate	Rat	10	>5000	RIFM (1971g)
Phenethyl propionate	Rat	10	4000 (2600–5400 mg/kg)	RIFM (1973b)
Phenethyl propionate[f]	Rat	4	4000 (2000–6800 mg/kg)	Beroza et al. (1975)
2-Phenoxyethyl isobutyrate	Rat	10	>5000	RIFM (1973b)
2-Phenoxyethyl isobutyrate	Mouse	2 or 6	>2000 and <5000	RIFM (1979c)
2-Phenoxyethyl propionate	Rat	10	4400 (4.4 ml/kg) (4100–4800 mg/kg)	RIFM (1973c)
3-Phenyl-3-buten-1-yl acetate	Rat	10	>2900 and <5000 (M) >1700 and <2900 (F)	RIFM (1981c)
1-Phenyl-3-methyl-3-pentyl acetate	Rat	10	>5000	RIFM (1976a)
2-Phenylpropyl acetate	Rat	10	4300 (3500–5100 mg/kg)	RIFM (1975b)
3-Phenylpropyl acetate	Rat	10	4700 (3800–5600 mg/kg)	RIFM (1973b)
Benzylic alcohols				
p-Anisyl acetate[e]	Rat	5	2300 (1800–2700 mg/kg)	RIFM (1971c)
Anisyl butyrate[b]	Rat	10	3400 (3000–3800 mg/kg)	RIFM (1976a)
Anisyl formate	Rat	10	1770 (1.55 ml/kg) (1200–2000 mg/kg)	RIFM (1975a)
Anisyl propionate	Rat	10	3300	RIFM (1974c)
Benzyl acetate	Rabbit	12	2600	Graham and Kuizenga (1945)
Benzyl acetate	Rat	NR	2500	Nishimura et al. (1994)
Benzyl acetate	Rat	10 (5/sex)	>2000 and <4000	NTP (1986)
Benzyl acetate	Rat	10 (5F, 5M)	2500	Bar and Griepentrog (1967)
Benzyl acetate	Rat	10 (5F, 5M)	2500 (2000–3000 mg/kg)	Jenner et al. (1964)
Benzyl acetate	Rat	30	3700	Graham and Kuizenga (1945)
Benzyl acetate	Mouse	10 (5/sex)	>2000 and <4000	NTP (1986)
Benzyl butyrate	Rat	10	1900 (1100–2600 mg/kg)	RIFM (1973b)
Benzyl butyrate	Rat	NR	2300	Bar and Griepentrog (1967)
Benzyl butyrate	Rat	10 (5F, 5M)	2300 (1900–2800 mg/kg)	Jenner et al. (1964)
Benzyl formate	Rat	10 (5F, 5M)	<5000	RIFM (1971g)
Benzyl 2-hydroxypropionate	Rat	5/sex	>2000	Clary et al. (1998)
Benzyl isobutyrate	Rat	10	2850	RIFM (1971d)
Benzyl propionate	Rat	10	3300 (3000–3600 mg/kg)	RIFM (1973b)
Carbonic acid, methyl phenylmethyl ester	Rat	4	>1600 and <5000	RIFM (1984b)
Carbonic acid, methyl phenylmethyl ester	Rat	10 (5/sex)	2400 (2100–2700 mg/kg)	RIFM (1984b)
2,4-Dimethylbenzyl acetate	Mouse	10	>5000	RIFM (1982a)
Ethyl phenyl carbonyl acetate	Rat	10	>5000	RIFM (1982a)
p-Isopropylbenzyl acetate	Rat	10	1500 (1000–2200 mg/kg)	RIFM (1978a)
α-Methylbenzyl acetate	Rat	10	>5000	RIFM (1971h)
4-Methylbenzyl acetate	Rat	10 (M)	~5000	RIFM (1981b)
α-Methylbenzyl propionate	Rat	10 (5F, 5M)	5200 (3900–6900 mg/kg)	RIFM (1973c)
Piperonyl acetate	Rat	10	2100 (1800–2400 mg/kg)	RIFM (1973b)

[a] For the purpose of comparison some units may have been changed from the reported units in the original study.
[b] 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.
[c] Twenty to forty-five percent solution in sunflower oil.
[d] Twenty percent solution in ground nut oil.
[e] Fifty percent solution in corn oil.
[f] This study was performed with a mixture of phenethyl propionate and eugenol at a ratio of 7:3.

tons, is extensively used as a fragrance ingredient in soap, detergents, creams, lotions, perfumes and as a solvent in lacquers, resins, polishes and printing inks.

There are 46 materials belonging to this group (see Table 1); as mentioned, 5 are structurally related but not used as fragrance materials (2-acetoxy-1-phenyl propane; 2-methyl-4-phenyl-2-butyl isobutyrate; 3-phenyl-2-butenyl acetate; anisyl butyrate; and benzyl acetoacetate). Since the industry has reported that these materials are not being used as fragrance materials (IFRA, 2008a,b,c), they are not discussed further. Any toxicological data available for these materials will be included within Tables 2–10.

Table 3-1
Oral repeat dose toxicity studies.

Material	Route and duration	Dose	Species (No., No./sex)	Results	References
Phenethyl acetate	Gavage 20-week	73 mg/kg/day (2% of the LD_{50}, 3670 mg/kg/day)	Rats (12M)	LOAEL 73 mg/kg/day Significant increase in cholinesterase activity; no changes in aldolase activity, ASP or ALT, availability of serum thiols, or protein levels in the blood	Zaitsev and Rakhmanina (1974)
Benzylic alcohols					
Benzyl acetate	Diet 28-day	20,000; 35,000; or 50,000 ppm in diet (2000, 3500, or 5000 mg/kg/day)[a]	Rats	LOAEL – 2000 mg/kg/day (histopathic lesions in brain, skeletal muscle, liver and kidney)	Abdo and Wenk (1995)
Benzyl acetate	Diet 28-day	20000, 35000, or 50000 ppm in diet (2000, 3500, or 5000 mg/kg/day)[a]	Rats (30M)	LOEL – 3500 mg/kg/day (decreased food consumption, body weight, and absolute brain weight; neurobehavioral effects; convulstions; neuronal necrosis; astrocyte reactivity)	Abdo et al. (1998)
Benzyl acetate	Diet 12-week	18.7 ppm in diet (in composite with five other compounds) (374 mg/kg/day)[a]	Rats 24 (12/sex)	No effects at 374 mg/kg/day (normal growth, hemoglobin, urine sugar and albumin, liver and kidney organ weights)	RIFM (1957)
Benzyl acetate	Diet 13-week (GLP compliant)	3130, 6250, 12,500, 2500 or 50,000 ppm in diet (230, 460, 900, 1750, or 3900 mg/kg/day (M) 240, 480, 930, 1870, or 4500 mg/kg/day (F))[a]	Rats 20 (10/sex)	NOEL – 900 (M) and 480 (F) LOEL – 1750 (M) and 930 (F) Based on decreased body weight gain in males and neurological endpoints in males and females 18/20M and F receiving highest dose diet	NTP (1993)
Benzyl acetate	Diet 13-week (GLP compliant)	3130, 6250, 12500, 2500 or 50000 ppm in diet (425, 1000, 2000, 3700, or 7900 mg/kg (M); 650, 1280, 2980, 4300, or 9400 mg/kg/day (F))[a]	Mice 20 (10/sex)	LOAEL – 425 (M) and 630 (F) mg/kg/day (decreased body weight; consumption rate; necrosis of the brain and tremors observed at higher doses)	NTP (1993)
Benzyl acetate	Diet 4-month	0.9% in diet (with 5% corn oil) (450 mg/kg/day)[a] after two 30-mg/kg ip injections of azaserine (initiator)	Rats (4–5M)	No observed effects – 450 mg/kg/day	Longnecker et al. (1986)
Benzyl acetate	Diet 6- to 12-month	0.4% or 0.8% (200–400 mg/kg/day)[a] in diet after two 30-mg/kg ip injections of azaserine (initiator)	Rats (25M)	LOAEL – 0.4% (dose-dependent increase in the diameter of acidophilic acinoar cell foci in the pancreas; decrease in number of foci per cm^3 at 0.8%; no effect on growth of basophilc foci)	Longnecker et al. (1990)
Benzyl acetate	Diet 1-year	0.4% or 0.8% in diet (200–400 mg/kg/day)[a] (with 5% corn oil) after two 30-mg/kg ip injections of azaserine (initiator)	Rats (20M)	LOAEL – 0.4% (premature death from chronic renal disease in rats with azaserine; more severe disease in rats given benzyl acetate in diet; survival time and incidence of pancreatic carcinoma decreased with benzyl acetate)	Longnecker et al. (1990)
Benzyl acetate	Gavage 14-day	250, 500, 1000, 2000 or 4000 mg/kg/day in corn oil	Rats 10 (5/sex)	NOEL – 1000 mg/kg/day LOEL – 2000 mg/kg/day (mortality)	NTP (1986)[b], Abdo et al. (1985)
Benzyl acetate	Gavage 14-day	125, 250, 500, 1000, or 2000 mg/kg/day in corn oil	Mice 10 (5/sex)	NOEL – 1000 (M) and 2000 (F) mg/kg/day LOEL – 2000 (M) mg/kg/day (mortality)	NTP (1986)[b]; Abdo et al. (1985)
Benzyl acetate	Gavage 13-week	62.5, 125, 250, 500, or 1000 mg/kg/day in corn oil	Rats 20 (10/sex)	LOEL – 1000 mg/kg/day NOAEL – 500 mg/kg/day (M, based on decreased body weight and neurological endpoints) NOAEL – 250 mg/kg/day (F, based on neurological endpoints) (mortality – 2/10M and 1/10F receiving 1000 mg/kg/day on day 86; ataxia, trembling, sluggishness, decreased body weight)	NTP (1986)[b]; Abdo et al. (1985)
Benzyl acetate	Gavage 13-week	62.5, 125, 250, 1000 mg/kg/day in corn oil (M); 125, 250, 500, 1000, 2000 mg/kg/day in corn oil (F)	Mice 20 (10/sex)	LOEL – 2000 mg/kg/day (mortality – 7/10F in 2000 mg/kg/day group died; trembling, inactivity, labored breathing, decreased body temperature)	NTP (1986)[b]; Abdo et al. (1985)
Benzyl acetate	Gavage 4-month	500 mg/kg/day by gavage in tricaprylin after one 30-mg/kg ip injection of azaserine (initiator)	Rats (4–5M)	No observed effect – 500 mg/kg/day	Longnecker et al. (1986)
Benzyl butyrate	Diet 12-week	21 mg/kg/day in diet (as part of a blend with five other aromatic esters)	Rats 24 (12/sex)	No observed effects (growth, food intake or body weight, urinary or hematology measures or liver and kidney weights)	RIFM (1957)
α-Methylbenzyl acetate	gavage 2-week	50 or 150 mg/kg/day in corn oil	Rats (5/sex)	NOAEL 50 mg/kg/day LOAEL 150 mg/kg/day (increased number of cells in urine of male rats; no change in consumption, relative organ weights or in haematological or serum analyses)	Gaunt et al. (1974)

(*continued on next page*)

Table 3-1 (*continued*)

Material	Route and duration	Dose	Species (No., No./sex)	Results	References
α-Methylbenzyl acetate	Gavage 6-week	50 or 150 mg/kg/day in corn oil	Rats (5/sex)	NOAEL 15 mg/kg/day (increased number of cells in urine of male rats; no change in consumption, relative organ weights or in hematological or serum analyses)	Gaunt et al. (1974)
α-Methylbenzyl acetate	Gavage 13-week	15, 50 or 150 mg/kg/day in corn oil	Rats 30 (5/sex)	NOAEL 15 mg/kg/day LOAEL 50 mg/kg/day (mean intake of food for males increased; increased mean relative liver and kidney weight)	Gaunt et al. (1974)

[a] Units in parentheses have been converted from the original reported units.
[b] Due to the confounding effect of the corn oil vehicle on the incidence of pancreatic acinar cell adenomas in rats, and questions about the use of the gavage route of administration, NTP repeated the 2-year bioassays with benzyl acetate in rats and mice using the dietary route of exposure (NTP, 1993).

Table 3-2
Dermal repeat dose toxicity studies.

Material	Route and duration	Dose	Species (No., No./sex)	Results	References
2-Phenoxyethyl isobutyrate	Dermal 2-week	66, 190, 700, or 1000 mg/kg/day in DEP	Rats 10 (5/sex)	NOAEL 1000 mg/kg/day irritation was observed at test site and was evident as erythema and desquamation at a slightly greater severity than observed with controls	RIFM (1994a)
2-Phenoxyethyl isobutyrate	Dermal 13-week	100, 300, or 1000 mg/kg/day in DEP	Rats 24 (12/sex)	NOAEL 1000 mg/kg/day	Api and Ford (1993), RIFM (1990c); Api (2004)

2.3. Estimated consumer exposure

Exposure data have been provided by the fragrance industry. Potential consumer exposure to fragrance ingredients occurs through the dermal and inhalation routes of exposure. Worst-case scenario calculations indicate that depositions on the surface of the skin following use of cosmetics represents the major route of exposure to fragrance materials when conservative estimates for evaporation, rinsing and other forms of product removal are employed (Cadby et al., 2002). 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 method is volume of use. The total worldwide volume of use for fragrance materials in the AAASAE group ranges from <0.01 to >1000 metric tons per year (IFRA, 2008c). The reported volume is for the fragrance ingredient as used in fragrance compounds (mixtures) in all 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 provide 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 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 the fragrance industry from examination of several thousand commercial formulations. The upper 97.5 percentile concentration is calculated from the data obtained. This upper 97.5 percentile concentration is then used 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 conservative; it is unlikely that a consumer will consistently use a number of different consumer products which are all perfumed with the upper 97.5 percentile level of the fragrance ingredient from a fine fragrance type product (Cadby et al., 2002; Ford et al., 2000). The total consumer exposures to fragrance ingredients range from 0.001 mg/kg body weight/day to 0.12 mg/kg body weight/day for the AAASAE fragrance ingredients in high end users of cosmetic products containing these materials (see Table 1) (IFRA, 2008a,b).

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, 2008a,b). The maximum skin exposure levels of the AAASAE compounds that form part of the formulae of fine fragrances vary widely and have been reported to range from 0.01% to 4.17%. The maximum skin exposure for AAASAE's in fine fragrance products are listed in Table 1 (IFRA, 2008a,b).

Exposure data for thirteen fragrance materials: 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate; 1,1-dimethyl-2-phenylethyl formate; 1,1-dimethyl-2-phenylethyl isobutyrate; 2-hydroxy-2-phenylethyl acetate; 3-phenyl-3-buten-1-yl acetate; 1-phenyl-3-methyl-3-pentyl acetate; 2-phenylpropyl acetate; 2-(*p*-tolyloxy) ethyl acetate; anisyl propionate; benzyl 2-hydroxypropionate; carbonic acid, methyl phenylmethyl ester; (4-methoxyphenyl) methyl isobutyrate; α-methylbenzyl isobutyrate; and ethyl phenyl

Table 4-1
Genotoxicity in bacteria.

Material	Test	Bacterial strain	Concentration	Results	References
1,1-Dimethyl-2-phenylethyl butyrate	Ames (performed under OECD test guideline 471)	*Salmonella typhimurium* TA98, TA100, TA102, TA 1535, or TA1537 ± S9	Up to 5000 μg/plate	Negative	RIFM (2001a)
1,1-Dimethyl-2-phenylethyl formate	Ames (performed under OECD test guideline 471)	*Salmonella typhimurium* TA98, TA100, TA1535, or TA1537 ± S9	Up to 1000 μg/plate	Negative	RIFM (1989b)
Phenethyl acetate	Ames (performed under OECD test guideline 471)	*Salmonella typhimurium* TA98, TA100, TA102, TA 1535, or TA1537 ± S9	Up to 5000 μg/plate	Negative	RIFM (2000a)
Phenethyl acetate	Ames (performed under OECD test guideline 471)	*Salmonella typhimurium* TA98, TA100, TA102, TA1535, or TA1537 ± S9	up to 3330 μg/plate	Negative	RIFM (2002a)
Phenethyl acetate	Ames	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, or TA1538 ± S9	0.0025–0.1 μl/plate (2.5–100 μg/plate)[a]	Negative	RIFM (1980c)
Phenethyl formate	Ames	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, or TA1538 ± S9	Up to 5 μl/plate (5000 μg/plate)[a]	Negative	RIFM (1980d)
Phenethyl isobutyrate	Ames (performed under OECD test guideline 471)	*Salmonella typhimurium* TA98, TA100, TA102, TA 1535, or TA1537 ± S9	Up to 5000 μg/plate + S9 Up to 1500 μg/plate − S9	Negative	RIFM (2001b)
2-Phenoxyethyl isobutyrate	Ames	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, or TA1538 ± S9	Up to 3600 μg/plate	Negative	Wild et al. (1983)
2-Phenoxyethyl isobutyrate	Ames	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, or TA1538 ± S9	up to 10 μl/plate (10,000 μg/plate)[a]	Negative	RIFM (1980e)
Benzylic alcohols					
p-Anisyl acetate	Ames (performed under OECD test guideline 471)	*Salmonella typhimurium* TA98, TA100, TA102, TA 1535, or TA1537 ± S9	Up to 5000 μg/plate	Negative	RIFM (2000b)
p-Anisyl acetate	Ames	*Salmonella typhimurium* TA98, TA100, TA102, TA1535, or TA1537 ± S9	19.5 up to 5000 μg/plate	Negative	RIFM (2003)
Benzyl acetate	Ames	*Salmonella typhimurium* TA100	50 mg/plate (50,000 μg/plate)[a]	Negative	Yoo (1986)
Benzyl acetate	Ames	*Salmonella typhimurium* TA98, TA100, TA1535, or TA1537 ± S9	Up to 10 mg/plate (10,000 μg/plate)[a]	Negative	Mortelmans et al. (1986)
Benzyl acetate	Ames	*Salmonella typhimurium* TA98, TA100, TA1535, or TA 1537 ± S9	10 mg/plate (10,000 μg/plate0[a]	Negative	Tennant et al. (1987)
Benzyl acetate	Ames	*Salmonella typhimurium* TA98, TA100, TA1535, or TA1537 ± S9	0.033 to 10 mg/plate (33–10,000 μg/plate][a]	Negative	NTP (1986)
Benzyl acetate	Ames	*Salmonella typhimurium* TA98 and TA100 ± S9	5, 50, or 500 μg/plate	Negative	Schunk et al. (1986)
Benzyl acetate	Ames (GLP compliant)	*Salmonella typhimurium* TA98, TA100, TA1535, or TA1537 ± S9	0.033–10 mg/plate (33–10,000 μg/plate)[a]	Negative	NTP (1993)
Benzyl acetate	Ames	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, or TA1538 ± S9	0.03 to 30 μmol/plate (0.0045–4.5 μg/plate)[a]	Negative	Florin et al. (1980)
Benzyl acetate	Ames	*Salmonella typhimurium* TA98, TA100, TA1535, or TA1537 ± S9	0.3, 3, or 30 μmol/plate 90.045, 0.45, or 4.5 μg/plate)[a]	Negative	Florin et al. (1980)
Benzyl acetate	Ames	*Salmonella typhimurium* TA98 or TA100 ± S9	Up to 0.3 μmol/plate (0.045 μg/plate)[a]	Negative	Rogan et al. (1986)
Benzyl acetate	Umu test	*Salmonella typhimurium* TA1535/pSK1002 ± S9 umu	Up to 5 mg/mL (5000 μg/mL)[a]	Negative	Yasunaga et al. (2004)
Benzyl acetate	Rec assay	*Bacillus subtilis* H17 rec+ and M45 rec−	20 μl/disk	Positive (M45 rec− only)	Yoo (1985), Yoo (1986)
Benzyl acetate	Rec assay	*Bacillus subtilis* H17 rec+ and M45 rec−	21 μg/disk	Negative	Oda et al. (1978)
Benzyl acetate	Microscreen assay	*Escherichia coli* WP2(λ) trpE, uvrA ± S9	6.25 μg/well	Positive	Rossman et al. (1991)
Benzyl acetate	SOS repair test	*Escherichia coli* PQ37	0–50 μg/assay	Negative	Kevekordes et al. (1999)
Benzyl acetate	DNA damage activity	*Escherichia coli* WP2 uvrA	0.25–2.0 mg/plate (250–2000 μg/plate)[a]	Negative	Yoo (1985); Yoo (1986)
Benzyl formate	DNA damage activity	*Escherichia coli* WP2 uvrA	0.5–4.0 mg/plate (500–4000 μg/plate)[a]	Negative	Yoo (1986)
Benzyl formate	Rec assay	*Bacillus subtilis* H17 rec+ and M45 rec−	20 μl/disk	Positive (M45 rec− only)	Yoo (1986)
Benzyl propionate	Rec assay	*Bacillus subtilis* H17 rec+ and M45 rec−	21 μg/disk	Negative	Oda et al. (1978)
Piperonyl acetate	Ames	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, or TA1538 ± S9	Up to 3600 μg/plate	Negative	Wild et al. (1983)
Piperonyl acetate	Ames	*Salmonella typhimurium* TA98, TA100, TA1535, or TA1537 ± S9	Up to 3333 μg/plate	Negative	Mortelmans et al. (1986)

Ames = reverse mutation.
[a] Units in parentheses have been converted from the original reported units.

carbonyl acetate, have not been reported. A default value of 0.02% is used to calculate the maximum daily exposure on the skin which is 0.0005 mg/kg bw 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.

Table 4-2
Genotoxicity in mammalian cells.

Material	Test system	Species/test system	Concentration	Results	References
Benzylic alcohols					
Benzyl acetate	Sister chromatid exchange	Chinese hamster ovary cells	5000 μg/mL	Negative	Tennant et al. (1987)
Benzyl acetate	Sister chromatid exchange (GLP compliant)	Chinese hamster ovary cells (CHO-B1) ± S9	0.05–0.5 mg/mL (50–500 μg/mL][a] (−S9); 0.5 to 5 mg/mL (500–5000 μg/mL)[a] (+S9)	Negative	Galloway et al. (1987); NTP (1993)
Benzyl acetate	Chromosome abberration	Chinese hamster ovary cells	5000 μg/mL	Negative	Tennant et al. (1987)
Benzyl acetate	Chromosome abberration	Chinese hamster lung fibroblast cll line (CHL/IU) ± S9	0.15–2.4 mg/mL (150–2400 μg/mL)[a]	Negative	Matsuoka et al. (1996)
Benzyl acetate	Chromosome abberration (GLP compliant)	Chinese hamster ovary cells (CHO-B1) ± S9	0.16–1.6 mg/mL (160–1600 μg/mL)[a] (−S9); 0.5–5 mg/mL (500–5000 μg/mL)[a] (+S9)	Negative	Galloway et al. (1987), NTP (1993)
Benzyl acetate	Micronucleus test	Human lymphocytes ± S9	Up to 500 μmol/L (75.09 μg/mL)	Negative	Kevekordes et al. (2001)
Benzyl acetate	Micronucleus test	Human Hep G2 cells	Up to 500 μmol/L (75.09 μg/mL)[a]	Negative	Kevekordes et al. (2001)
Benzyl acetate	Forward mutation assay	Human TK6 lymphoblasts ± S9	1.5 mg/mL (1500 μg/mL)[a]	Negative without activation Positive with activation	Caspary et al. (1988)
Benzyl acetate	Forward mutation assay	Mouse L5178Y ± TK lymphoma cells	1 mg/mL (1000 μg/mL)[a]	Positive without activation	McGregor et al. (1988)
Benzyl acetate	Forward mutation assay	Mouse L5178Y ± TK lymphoma cells ± S9	0.7 mg/mL (700 μg/mL)[a]	Negative	Tennant et al. (1987)
Benzyl acetate	Forward mutation assay	Mouse L5178Y ± TK lymphoma cells ± S9	5 mg/mL (5000 μg/mL)[a]	Negative without activation Equivocal with activation	Honma et al. (1999)
Benzyl acetate	Forward mutation assay	Mouse L5178Y ± TK lymphoma cells ± S9	0.5 mg/mL (500 μg/mL)[a]	Negative without activation Positive with activation	Caspary et al. (1988)
Benzyl acetate	Forward mutation assay (GLP compliant)	Mouse L5178Y ± TK lymphoma cells ± S9	0.50–1.25 μl/mL (+S9); 0.25–1.00 μl/mL (−S9)	Negative without activation Positive with activation	NTP (1986), NTP (1993)
Benzyl acetate	Forward mutation assay (GLP compliant)	Mouse L5178Y ± TK lymphoma cells ± S9	700–1500 μg/mL (−S9)	Equivocal without activation	NTP (1993)
Benzyl acetate	Forward mutation assay	Mouse L5178Y ± TK lymphoma cells ± S9	NR	Positive without activation Negative with activation	Rudd et al. (1983)

[a] Units in parentheses have been converted from the original reported units.

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

In vivo metabolism of carboxylic acid esters proceeds in all animals to generate the corresponding alcohols and carboxylic acids. In addition to total or partial hydrolysis in the gastrointestinal tract, aromatic carboxylic esters are also known to be hydrolyzed through the catalytic activity of carboxylesterases that are found primarily in the hepatocytes (Heymann, 1980). Published metabolic studies have also demonstrated that some of the AAASAE fragrance ingredients are either hydrolyzed in the gastrointestinal tract and absorbed or rapidly absorbed as the parent compound and then hydrolyzed primarily in the liver by carboxylesterases to the corresponding aryl alkyl alcohol and simple carboxylic acid metabolites. General AAASAE metabolic pathways are described below and illustrated in Fig. 1, for the benzyl esters that are derived from the primary AAA benzyl alcohol, and in Fig. 2, for the α-methyl benzyl esters that are derived from the secondary AAA α-methyl benzyl alcohol.

The simple carboxylic acid metabolites (i.e., formic, acetic, propionic, butyric, isobutyric, and carbonic acids) are either readily excreted directly or conjugated with glycine or glucuronide and then excreted. Although phenyl ring substituents (e.g., methyl, dimethyl, isopropyl, methoxy, or piperonyl) may also be metabolized, generally the aryl ring substituents do not affect either the

Table 4-3
Genotoxicity in mice and rats.

Material	Test system	Mouse strain	Dose	Results	References
2-Phenoxyethyl isobutyrate	Micronucleus assay	Mouse NMRI bone marrow	IP (4 per dose) 625, 1250, or 1875 mg/kg in olive oil; 30 h after dose	Negative	Wild et al. (1983)
Benzylic alcohols					
Benzyl acetate	Sister chromatid exchange (GLP compliant)	Mouse BC6F31 bone marrow	IP (5 per dose) 325–1700 mg/kg	Negative	NTP (1993)
Benzyl acetate	Chromosomal aberrations (GLP compliant)	Mouse BC6F31 bone marrow	IP (5 per dose) 325–1700 mg/kg	Negative	NTP (1993)
Benzyl acetate	Micronucleus assay (GLP compliant)	Mouse BC6F31 Peripheral blood	13-week diet (7–9MF) 3130, 6250, 12500, 25,000, 50,000 ppm (470, 938, 1875, 3750, 7500 mg/kg/day)	Negative	NTP (1993), Witt et al. (2000)
Benzyl acetate	Micronucleus assay (GLP compliant)	Mouse BC6F31 bone marrow	IP (5 per dose) 312, 625, 1250 mg/kg	Negative	NTP (1993), Shelby et al. (1993)
Benzyl acetate	Unscheduled DNA synthesis	Rat Fischer 344 pancreatic cells	Gavage (M) 1000 mg/kg at 2, 12 and 24 h	Negative	Steinmetz and Mirsalis (1984)
Benzyl acetate	Unscheduled DNA synthesis	Rat Fischer 344 hepatocytes	Gavage (3M per dose) 50, 200 and 500 mg/kg at 2 and 12 h	Negative	Mirsalis et al. (1989)
Benzyl acetate	Replicative DNA synthesis	Mouse BC63F1 hepatocytes	Gavage (4–5M per dose) 800 and 1600 mg/kg at 24, 39 and 48 h	Negative at 24 h Positive at 1600 mg/kg at 39 and 48 h	Miyagawa et al. (1995), Yoshikawa (1996)
Benzyl acetate	Alkaline DNA elution analysis	Rat Fischer 344 pancreatic cells	IP (1M per dose) 150, 500, 1500 mg/kg at 1 h	Negative	Longnecker et al. (1990)
Benzyl acetate	Comet assay	Rat Wistar	Gavage (4M) 1200 mg/kg at 3, 8, and 24 h	Positive (stomach, colon, kidney, bladder, lung and liver) Negative (brain, bone marrow)	Sasaki et al. (2000), Sekihashi et al. (2002)
Benzyl acetate	Comet assay	Mouse ddY	Gavage (4M) 1600 mg/kg at 3, 8, and 24 h	Positive (stomach, colon, kidney, bladder, and brain) Negative (liver, bone marrow)	Sasaki et al. (2000), Sekihashi et al. (2002)
Piperonyl acetate	Micronucleus assay	Mouse NMRI bone marrow	IP (4 per dose) 388, 680 or 970 mg/kg in olive oil; 30 h after dose	Negative	Wild et al. (1983)

primary hydrolysis and or carboxylesterase metabolism or the subsequent oxidative degradation and excretion of the primary AAASAE acid and alkyl aryl alcohol metabolites. Rather, branching of the alkyl aryl alcohol has a more pronounced effect.

The metabolism of linear primary aryl alkyl alcohols, such as benzyl alcohol, phenethyl alcohol (and phenyl propyl alcohol by analogy), and the branched secondary aryl alkyl alcohols (e.g., 1-methyl benzyl alcohol) have been evaluated and peer reviewed (JECFA, 2001, 2002a,b,c, 2003). These published studies confirm that the primary linear and secondary branched aryl alkyl alcohols may either be conjugated and excreted directly or oxidized before being conjugated and excreted. One study found that 3-phenylpropyl acetate was not hydrolysed *in vitro* by partially purified human plasma arylesterase (Augustinsson and Ekedahl, 1962). Tertiary AAASAE alkyl aryl alcohol metabolism data are currently limited to two *in vitro* studies (RIFM, 1972a; Grundschober, 1977). These studies indicate that the highly branched aryl alkyl esters are not readily metabolized. If aryl alkyl tertiary alcohols are generated, it would be expected that they would be metabolically resistant to oxidation (Williams, 1959),

It has been reported that linear aryl alkyl primary alcohol such as the benzyl (JECFA, 2002b), phenyl ethyl (JECFA, 2003), phenyl *n*-propyl (JECFA, 2001), and phenoxy ethyl (JECFA, 2003) alcohols are rapidly oxidized to an aryl alkyl carboxylic acid that is then conjugated with glycine or glucuronide and excreted in the urine (Adams et al., 2005a,b, 2007). It is also reported that the benzyl alcohol metabolites are likely to be further oxidized to their corresponding benzoic acid and excreted as the glycine conjugate (Snapper et al., 1925). At high doses, the formation of the glycine conjugate is limited; when glycine is depleted, free benzoic acid may sequester acetyl coenzyme A or be excreted unchanged or as the glucuronic acid conjugate. Oxidation of the benzyl alcohol may be accompanied by oxidation of alkyl side chain as well.

It has also been reported, that branched secondary aryl alkyl alcohols metabolites are generally conjugated and excreted. However, secondary alcohols may also be further oxidized to ketones (JECFA, 2002a). The ketone oxidation is reversible and the secondary alcohol and ketone metabolites are interchangeable. The interconvertable secondary alcohol ketone metabolite if comprised of an even number carbon chain length may undergo oxidative cleavage to yield a phenyl acetic acid type metabolite that is conjugated with glycine and excreted. Alternatively, if the aryl secondary alkyl alcohol chain of the ketone is comprised of an odd carbon chain length, oxidative cleavage would yield a benzoic acid type metabolite that would also be conjugated with glycine and excreted. As already noted, if generated, the tertiary aryl alcohol metabolite would not be expected to be oxidized and would therefore be eliminated directly or conjugated and then excreted.

The metabolism of benzyl acetate has been very well studied, and there is also some information for phenethyl acetate and piperonyl acetate. No information regarding metabolism of the other aryl alkyl linear congeners was reported, but presumably their metabolism should be similar to that of the benzyl acetate.

After a single oral dose, benzyl acetate has also been shown in humans to be rapidly hydrolyzed to benzyl alcohol and acetate; benzyl alcohol is oxidized to benzoic acid and excreted as hippuric acid after conjugation with glycine (Snapper et al., 1925). Benzoic acid was used for many years as a liver function test in humans

Table 5-1
Carcinogenicity and tumor promotion.

Material	Method	Dose	Species (No. per group)	Results	References
Phenethyl acetate	IP injection; study duration 20 weeks	1200 or 6000 mg/kg in tricaprylin 3×/week for 8 weeks	Mice (20F)	NOAEL 1200 mg/kg decreased mean tumor values; no other neoplasms; vehicle toxic first week; mortality observed: 7/20 at 1200 mg/kg and 3/20 at 6000 mg/kg	Stoner et al. (1973)
Benzylic alcohols					
Benzyl acetate	Gavage 2-year	250 or 500 mg/kg/day in corn oil	Rats 100 (50/sex)	NOEL – 500 mg/kg/day (F) LOEL – 500 mg/kg/day (M) (increased incidence of acinar cell adenomas of exocrine pancreas in males; trend observed but not significant at 250 mg/kg/day) NOTE – statistical significance confounded by shelf placement, data not used by author; corn oil may also be confounder	NTP (1986)[b]; Abdo et al. (1985), Young (1989)
Benzyl acetate	Gavage 2-year	500 or 1000 mg/kg/day in corn oil	Mice 100 (50/sex)	LOAEL – 500 mg/kg/day (M) LOEL – 1000 mg/kg/day (F) (increased incidence of heptatocelluar adenomas and squamous cell neoplasms of forestomach)	NTP (1986)[b]; Abdo et al. (1985)
Benzyl acetate	Diet 2-year (GLP compliant)	3000, 6000, 12,000 ppm in diet (130, 260, or 510 mg/kg/day (M); 145, 290, or 575 mg/kg/day (F))	Rats 120 (60/sex)	NOEL – 260 mg/kg/day LOEL – 510 and 575 mg/kg/day (decreased body weight and decreased feed consumption (M); no neoplasms, lesions, or hematology or clinical chemistry changes)	NTP (1993)
Benzyl acetate	Diet 2-year (GLP compliant)	330, 1000, 3000 ppm in diet (35, 110, or 345 mg/kg/day (M); 40, 130, 375 mg/kg/day (F))	Mice 120 (60/sex)	NOAEL – 345 and 375 mg/kg/day (decreased body weight; dose related increase in nasal lesions)	NTP (1993)
Benzyl acetate	Diet 2-year	0.8% in diet (400 mg/kg/day)[a] (with 5% corn oil)	Rats (25M)	LOEL – 400 mg/kg/day (lesions showing anaplastic changes and desmoplasia which denote progression to carcinoma; no adverse effecto on growth or survival)	Longnecker et al. (1990)

[a] Units in parantheses have been converted from the original reported units.
[b] Due to the confounding effect of the corn oil vehicle on the incidence of pancreatic acinar cell adenomas in rats, and questions about the use of the gavage route of administration, NTP repeated the 2-year bioassays with benzyl acetate in rats and mice using the dietary route of exposure (NTP, 1993).

Table 5-2
Reproductive toxicity.

Material	Method	Dose	Species (No. per group)	Results	References
Benzylic alcohols					
Benzyl acetate	Gavage GD6–GD15 (study based on OECD guidelines)	10, 100, 500, or 1000 mg/kg/day	Rats (6–7F)	Maternal NOAEL – 500 mg/kg/day based on weight gain) Fetal NOAEL – 100 mg/kg/day (based on weight and internal organ malformations)	Ishiguro et al. (1993)

by measuring the urinary excretion of hippuric acid after administration by oral (6 g) or intravenous (1.5–2.0 g) routes (Stein et al., 1954; Armstrong et al., 1955, as cited in World Health Organization, 1996). The rate of excretion of hippuric acid in urine was studied in a person who received an oral dose of 4.2 mg/kg or 0.16 mg/kg bodyweight benzoic acid. The concentration of hippuric acid was maximal 0.5–1 h after dosing, and excretion was complete within 4 h with the high dose and completely excreted 0.5–1 h for the low dose (Akira et al., 1994; Baba et al., 1995, both cited in World Health Organization, 1996).

In a study conducted to determine the pathway by which benzyl acetate is metabolized to benzyl mercapturic acid in the rat, male F344 rats received by gavage 500 mg/kg benzyl acetate in corn oil with or without inhibitors of alcohol dehydrogenase or an inhibitor of sulfotransferases. Treatment with the inhibitors independently did not affect the rate or route of excretion. The authors determined that the formation of benzyl mercapturic acid involves the formation of benzyl sulfate as an obligatory intermediate and that, therefore, it is unlikely that the formation of benzyl mercapturic acid from benzyl acetate is associated with the formation of reactive metabolites of toxicological significance (Chidgey et al., 1986).

In a study on the absorption and distribution of topically applied benzyl acetate in rats, it was determined that after absorption through the skin, benzyl acetate is first hydrolyzed to benzyl alcohol, the majority of which is oxidized to benzoic acid before undergoing conjugation to hippuric acid or glucuronide (Chidgey et al., 1987; Caldwell et al., 1987). This observation resembles those seen after oral administration of benzyl acetate (see Snapper et al., 1925, above; Chidgey and Caldwell, 1986). Benzyl mercapturic acid

Table 6-1
Skin irritation in humans.

Material	Method	Concentration	Subjects	Results	References
2-Acetoxy-1-phenyl propane[a]	Max (pre-test)	6% in petrolatum	25 (MF)	No irritation	RIFM (1977c)
1,1-Dimethyl-2-phenylethyl acetate	Irritation 48 h Occluded	20% in petrolatum	28 (MF)	No irritation	Fujii et al. (1972)
1,1-Dimethyl-2-phenylethyl acetate	Irritation 48 h Occluded	2% in ointment	30 (MF)	No irritation	Fujii et al. (1972)
1,1-Dimethyl-2-phenylethyl acetate	Irritation	4% in petrolatum	25	Mild irritation	RIFM (1971i)
1,1-Dimethyl-2-phenylethyl acetate	HRIPT (induction)	1.25% in EtOH	42 (7M, 35F)	Slight to no irritation	RIFM (1964a)
1,1-Dimethyl-2-phenylethyl acetate	Patch test	0.05–0.5% in non-irritant cream base or EtOH	80	No irritation	Takenaka et al. (1968)
1,1-Dimethyl-2-phenylethyl butyrate	Max (pre-test)	10% in petrolatum	25 (M)	No irritation	RIFM (1977c)
1,1-Dimethyl-2-phenylethyl formate	Max (pre-test)	4% in petrolatum	24 (M)	No irritation	RIFM (1985e)
1,3-Dimethyl-3-phenylbutyl acetate	HRIPT (induction)	20% in petrolatum	50 (MF)	No irritation	RIFM (1979d)
1,1-Dimethyl-2-phenylethyl propionate	Max (pre-test)	10% in petrolatum	28 (M)	No irritation	RIFM (1977d)
2-Methyl-4-phenyl-2-butyl acetate	Max (pre-test)	4% in petrolatum	5 (MF)	No irritation	RIFM (1975c)
Phenethyl acetate	Irritation 24 h occluded	100%	20 (MF)	No irritation	Katz (1946)
Phenethyl acetate	HRIPT (induction)	2.5% in EtOH	39 (33F, 6M)	No irritation	RIFM (1964b)
Phenethyl acetate	Patch test	0.05–0.5% in non-irritant cream base or EtOH	117	7/117	Takenaka et al. (1968)
Phenethyl butyrate	Max (pre-test)	8% in petrolatum	25 (MF)	No irritation	RIFM (1977c)
Phenethyl butyrate	Max (pre-test)	8% in petrolatum	10 (MF)	Minimal irritation (1/10)	RIFM (1974d)
Phenethyl formate	Max (pre-test)	6% in petrolatum	5 (M)	No irritation	RIFM (1972b)
Phenethyl isobutyrate	Max (pre-test)	2% in petrolatum	5 (M)	No irritation	RIFM (1971i)
Phenethyl propionate	Max (pre-test)	8% in petrolatum	5 (M)	No irritation	RIFM (1973d)
2-Phenoxyethyl isobutyrate	HRIPT (induction)	0.5% in EtOH	38 (31F, 7M)	No irritation	RIFM (1965a)
2-Phenoxyethyl isobutyrate	Max (pre-test)	4% in petrolatum	5 (M)	No irritation	RIFM (1973d)
2-Phenoxyethyl propionate	Max (pre-test)	10% in petrolatum	5 (M)	No irritation	RIFM (1973d)
3-Phenyl-2-butenyl acetate[a]	HRIPT (induction)	5% in EtOH	49 (47F, 2M)	No irritation	RIFM (1974e)
3-Phenyl-2-butenyl acetate[a]	HRIPT (induction)	1% in EtOH	48 (33F, 15M)	No irritation	RIFM (1974f)
3-Phenyl-3-buten-1-yl acetate	HRIPT (induction)	5% in EtOH	49 (47F, 2M)	No irritation	RIFM (1974f)
3-Phenyl-3-buten-1-yl acetate	HRIPT (induction)	1.2% in EtOH	54 (MF)	Slight irritation 3/54	RIFM (1981d)
3-Phenyl-3-buten-1-yl acetate	HRIPT (induction)	1% in EtOH	48 (33F, 15M)	No irritation	RIFM (1974e)
1-Phenyl-3-methyl-3-pentyl acetate	Max (pre-test)	10% in petrolatum	27 (M)	No irritation	RIFM (1976b)
2-Phenylpropyl acetate	HRIPT (induction)	2.5% in EtOH	43 (24F, 19M)	No irritation	RIFM (1973g)
2-Phenylpropyl acetate	Max (pre-test)	12% in petrolatum	5 (MF)	No irritation	RIFM (1975c)
3-Phenylpropyl acetate	Max (pre-test)	8% in petrolatum	5 (M)	No irritation	RIFM (1973d)
Benzylic alcohols					
p-Anisyl acetate	Irritation (24 h)	20% in petrolatum	10	No irritation	Smith et al. (2000)
p-Anisyl acetate	Max (pre-test)	10% in petrolatum	5 (MF)	No irritation	RIFM (1975c)
p-Anisyl acetate	Max (pre-test)	4% in petrolatum	5 (MF)	No irritation	RIFM (1975c)
p-Anisyl acetate	Max (pre-test)	4% in petrolatum	5 (M)	No irritation	RIFM (1973d)
p-Anisyl acetate	Max (pre-test)	4% in petrolatum	5 (M)	No irritation	RIFM (1973d)
p-Anisyl acetate	Max (pre-test)	4% in petrolatum	5 (M)	No irritation	RIFM (1971i)
Anisyl butyrate[a]	Max (pre-test)	8% in petrolatum	25 (MF)	No irritation	RIFM (1975c)
Anisyl butyrate[a]	Max (pre-test)	8% in petrolatum	25 (MF)	No irritation	RIFM (1975c)
Anisyl formate	Max (pre-test)	4% in petrolatum	22 (M)	No irritation	RIFM (1975d)
Anisyl propionate	Max (pre-test)	4% in petrolatum	22 (M)	No irritation	RIFM (1974g)
Benzyl acetate	HRIPT (induction)	18.7% in EtOH	35 (18F, 17M)	No irritation	RIFM (1975e)
Benzyl acetate	HRIPT (induction)	8% in EtOH:DEP (3:1)	106	Mild to no irritation 2/106	RIFM (1988a)
Benzyl acetate	HRIPT (induction)	8% in EtOH:DEP (3:1)	34 (34F, 0M)	Mild to no irritation 2/34	RIFM (1988b)
Benzyl acetate	HRIPT (induction)	8% in EtOH:DEP (3:1)	27 (23F, 4M)	No irritation	RIFM (1988c)
Benzyl acetate	HRIPT (induction)	8% in EtOH:DEP (3:1)	38 (25F, 13M)	Mild to no irritation 4/38	RIFM (1988d)
Benzyl acetate	HRIPT (induction)	7.5% in EtOH	35	No irritation	RIFM (1975f)
Benzyl acetate	HRIPT (induction)	7.5% in petrolatum	39	No irritation	RIFM (1975g)
Benzyl acetate	HRIPT (induction)	3% in EtOH	42 (31F, 11M)	No irritation	RIFM (1975h)
Benzyl acetate	HRIPT (induction)	3% in petrolatum	44 (32F, 12M)	No irritation	RIFM (1975i)
Benzyl acetate	48 h semi-occluded Patch test	32% in acetone	50 (0F, 50M)	No irritation	Motoyoshi et al. (1979)
Benzyl acetate	Closed 48 h Patch test	20% in petrolatum or Unguentum Hydrophilicum	28 (MF)	No irritation	Fujii et al. (1972)
Benzyl acetate	Patch test	5% (vehicle not reported)	48	1/48	Ishihara et al. (1981)

(*continued on next page*)

Table 6-1 (*continued*)

Material	Method	Concentration	Subjects	Results	References
Benzyl acetate	Patch test	5% (vehicle not reported)	101	1/101	Nishimura et al. (1984)
Benzyl acetate	Patch test	5% (vehicle not reported)	122	1/122	Itoh et al. (1986)
Benzyl acetate	Patch test	5% (vehicle not reported)	115	1/115	Itoh et al. (1988)
Benzyl acetate	Patch test	5% in petrolatum	12	No irritation	Haba et al. (1993)
Benzyl acetate	Patch test	5% and 1% in petrolatum	100 at both doses	0/100 at 5%; 1/100 at 1%	Frosch et al. (1995)
Benzyl acetate	Closed 24–72 h Patch test	2% in Unguentum Simplex or Unguentum Hydrophilicum	30 (MF)	No irritation	Fujii et al. (1972)
Benzyl acetate	Patch test	0.05–0.5% in non-irritant cream base or EtOH	77	No irritation	Takenaka et al. (1968)
Benzyl acetate	Patch test	0.12% in 1% soap	50	No irritation	RIFM (1961)
Benzyl butyrate	Irritation (24 h occluded)	100%	13 (MF)	Mild to no irritation 1/13	Katz (1946)
Benzyl butyrate	Max (pre-test)	4% in petrolatum	5 (M)	No irritation	RIFM (1973d)
Benzyl formate	Irritation (24 h occluded)	100%	24 (MF)	Mild to no irritation 1/24	Katz (1946)
Benzyl formate	Max (pre-test)	10% in petrolatum	5 (M)	No irritation	RIFM (1971i)
Benzyl isobutyrate	Max (pre-test)	4% in petrolatum	10 (M)	No irritation	RIFM (1971i)
Benzyl propionate	Max (pre-test)	4% in petrolatum	5 (M)	No irritation	RIFM (1973d)
Benzyl propionate	Patch test	20% in petrolatum	34	No irritation	Fujii et al. (1972)
Benzyl propionate	Patch test	2% in petrolatum	30	No irritation	Fujii et al. (1972)
2,4-Dimethylbenzyl acetate	HRIPT (induction)	2.5% in EtOH	44 (37F, 7M)	No irritation	RIFM (1965b)
2,4-Dimethylbenzyl acetate	Max (pre-test)	3% in petrolatum	21 (MF)	No irritation	RIFM (1981e)
Ethyl phenyl carbonyl acetate	Max (pre-test)	4% in petrolatum	27 (MF)	No irritation	RIFM (1982b)
p-Isopropylbenzyl acetate	Max (pre-test)	12% in petrolatum	25 (MF)	No irritation	RIFM (1978b)
p-Isopropylbenzyl acetate	48-h Closed Patch test	12% in petrolatum	25	No irritation	RIFM (1978b)
α-Methylbenzyl acetate	Max (pre-test)	4% in petrolatum	5 (M)	No irritation	RIFM (1970b)
α-Methylbenzyl acetate	Patch test	0.05–0.5% in non-irritant cream base or EtOH	188	4/188	Takenaka et al. (1968)
α-Methylbenzyl acetate	Patch test	1 or 20% in petrolatum or ointment	30	0/30	Fujii et al. (1972)
4-Methylbenzyl acetate	Max (pre-test)	5% in petrolatum	25 (MF)	No irritation	RIFM (1981e)
4-Methylbenzyl acetate	Patch test	0.05–0.5% in non-irritant cream base or EtOH	265	1/265	Takenaka et al. (1968)
α-Methylbenzyl propionate	Max (pre-test)	10% in petrolatum	5 (M)	No irritation	RIFM (1973d)
α-Methylbenzyl propionate	Patch test	0.05–0.5% in non-irritant cream base or EtOH	188	11/188	Takenaka et al. (1968)
α-Methylbenzyl propionate	48-h Closed Patch test	1 or 20% in petrolatum or ointment	30	0/30	Fujii et al. (1972)
Piperonyl acetate	HRIPT (induction)	5% in EtOH	37	No irritation	RIFM (1964e)
Piperonyl acetate	Max (pre-test)	8% in petrolatum	5 (M)	No irritation	RIFM (1973d)

[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.

arises from the glutathione conjugation of the intermediate metabolite benzyl sulfate, a pathway not expected to involve a reactive species of toxicological significance (Caldwell et al., 1987). Esterase activity is particularly high in the skin, explaining the observation that after topical application of benzyl acetate to rat skin *in vitro*, there is a rapid and complete hydrolysis to benzyl alcohol (97%) with further oxidation to benzoic acid (3%) (Garnett et al., 1994). In mammals, phenethyl acetate has been reported to be hydrolyzed to acetic acid and phenethyl alcohol (Sandmeyer and Kirwin, 1981). Phenethyl alcohol is further oxidized to phenylacetaldehyde and to phenylacetic acid, which in humans is excreted in the urine in its conjugated form as phenylacetyl glutamine (Stein et al., 1954 as cited in Sandmeyer and Kirwin, 1981; James and Smith, 1973 as cited in JECFA, 2003). The health effects for 2-phenethyl alcohol, the metabolite of phenethyl acetate, including teratogenicity, genotoxicity, acute toxicity, irritation, and repeat dose toxicity have been described elsewhere (JECFA, 2003; USEPA, 1985).

Piperonyl acetate and piperonyl isobutyrate, in an aqueous suspension, were administered by gavage to male rabbits at 100 mg/kg bodyweight (Wright and Holder, 1980). The two metabolites identified in the urine extracts were piperonylic acid and piperonyl alcohol, and represented 70% and 11% of the ingested dose after three days. An estimated 83% of the piperonyl acetate and 15% of the piperonyl isobutyrate was hydrolyzed and excreted either as free or conjugated (with glycine) piperonylic acid within 72 h. Less than 1% of piperonyl alcohol was excreted.

Investigation of the metabolism of anisyl alcohol (the aryl alkyl alcohol metabolite of anisyl acetate, anisyl formate, or anisyl propionate) by rat intestinal microflora was studied by analyzing rat caecal extract. The presence of anisic acid was observed in the extract after 46 h indicating that *O*-demethylation of the methoxy group on the phenyl ring was not observed (Scheline, 1972 as cited in JECFA, 2002a).

It is presumed, based on extensive reports with benzyl acetate, that the hydrolysis of 1-methyl benzyl acetate and propionate yields *1*-methyl benzyl alcohol and the corresponding aliphatic carboxylic acids. In earlier studies with rabbits, *1*-methyl benzyl alcohol (the aryl alkyl alcohol metabolite of *1*-methyl benzyl acetate) was reported to be absorbed after oral administration, metabolized, and excreted as polar metabolites within 24 h (Smith et al., 1954 as cited in JECFA, 2002a). Presumably the methyl group on the alkyl group of this secondary aryl alcohol did not interfere with hydrolysis, oxidation or conjugation that would change the expected excreted metabolites. Oxidation of *1*-methyl benzyl alcohol to acetophenone and reversible reduction back to 1-methyl benzyl alcohol has been reported in rat hepatocytes (Hopkins et al., 1972; Maylin et al., 1973 as cited in JECFA, 2002a). As observed in various animal species, the ketone undergoes *omega*-oxidation and subsequent oxidative decarboxylation to yield benzoic acid and is excreted as hippuric acid; the alcohol is conjugated mainly with glucuronic acid and excreted (Culp and McMahon, 1968; Callaghan et al., 1973; Sullivan

Table 6-2
Skin irritation in animals.

Material	Method	Concentration	Species	Results	References
2-Acetoxy-1-phenylpropane[a]	Irritation (LD_{50})	100%	Rabbits (10)	Slight irritation	RIFM (1978a)
1,1-Dimethyl-2-phenylethyl acetate	Primary irritation 4 h semi-occluded (performed under Annex V, EEC Directive 79/831)	50%	Rabbits (3)	Very slight (3/3) erythema (clear by day 7); very slight (2/3) edema (clear by day 2)	RIFM (1984c)
1,1-Dimethyl-2-phenylethyl acetate	Primary irritation 4 h semi-occluded (performed under Annex V, EEC Directive 79/831)	100%	Rabbits (6)	Very slight (6/6) erythema (5/6 clear by day 7); very slight (3/6) edema (all clear by day 7)	RIFM (1985a)
1,1-Dimethyl-2-phenylethyl acetate	Irritation (LD_{50})	100%	Rabbits (3)	Moderate erythema; normal by end of test period	RIFM (1971a)
1,1-Dimethyl-2-phenylethyl butyrate	Irritation (LD_{50})	100%	Rabbits (10)	Moderate (8/10) to slight (2/10) redness; moderate (5/10) to slight (5/10) edema	RIFM (1977b)
1,1-Dimethyl-2-phenylethyl formate	Primary irritation 4 h semi-occluded (performed under EEC Directive 84/449/EEC)	100%	Rabbits (4)	Well defined to slight erythema to day 3 (4/4); slight erythema at day 7 (1/4). Slight edema at day 7 (1/4).	RIFM (1989c)
1,1-Dimethyl-2-phenylethyl formate	Max (pre-test) (performed under EEC Directive L251)	100%, 50%, 25%, 12.5% in EtOH (topical)	Guinea pigs (4)	No irritation	RIFM (1990d)
1,1-Dimethyl-2-phenylethyl formate	Max (pre-test) (performed under EEC Directive L251)	50%, 25%, 10%, 5%, 1% in liquid paraffin (intradermal)	Guinea pigs (1)	Irritation at >10%	RIFM (1990d)
1,3-Dimethyl-3-phenylbutyl acetate	Primary irritation (Draize) (performed according to 16 CFR 1500.3)	100%	Rabbits (6)	Very slight to Slight erythema (4/6) at 72 h Very Slight to Slight edema (2/6) at 72 h	RIFM (1979e)
1,3-Dimethyl-3-phenylbutyl acetate	Irritation (Buehler)	5% in petrolatum	Guinea pigs (20)	No irritation	RIFM (1984d)
1,3-Dimethyl-3-phenylbutyl acetate	Irritation (LD_{50}) (performed according to 16 CFR 1500.3)	100%	Rabbits (10)	Very slight to well defined erythema (10/10)	RIFM (1979a)
1,1-Dimethyl-2-phenylethyl propionate	Irritation (LD_{50})	100%	Rabbits (10)	Slight or moderate erythema (5/10); Slight (8/10) and moderate (1/10) edema	
2-Methyl-4-phenyl-2-butyl acetate	Irritation (LD_{50})	100%	Rabbits (4)	Erythema observed at 24 h	RIFM (1975a)
Phenethyl acetate	Primary irritation 4 h semi-occluded	100%	Rabbits (8)	Marginal irritant reaction at 4 h, clear 72 h later	RIFM (1979f)
Phenethyl acetate	Irritation (LD_{50})	10 and 15 g/kg	Rabbits (3)	Slight erythema (clear within 6 h)	RIFM (1970a)
Phenethyl acetate	Irritation (LD_{50})	6.5, 10, 15 g/kg	Rabbits (3)	Slight erythema (rapidly subsided after removal of compound)	RIFM (1970a)
Phenethyl butyrate	Irritation (LD_{50})	100%	Rabbits (4)	Mild erythema (clearing after 24 h)	RIFM (1974b)
Phenethyl formate	Irritation (LD_{50})	100%	Rabbits (4/dose)	No irritation	RIFM (1973a)
Phenethyl formate	Primary irritation 4 h semi-occluded	100%	Rabbits (8)	Slight to very slight erythema on day 1 (8/8), day 2 (4/8), and day 3 (1/8). Fairly distinct to very slight edema day 1 (3/8) to day 3 (2/8). Cracking (3/8) and scaling (1/8) on day 3. No day 7 data	RIFM (1979g)
Phenethyl isobutyrate	Irritation (LD_{50})	100%	Rabbits (6)	No irritation	RIFM (1971b)
Phenethyl propionate	Irritation (LD_{50})	100%	Rabbits (10)	No irritation	RIFM (1973b)
Phenethyl propionate	Primary irritation	70% in Eugenol[b]	Rabbits (6)	Irritation observed; primary irritation score is 1.2	Beroza et al. (1975)
2-Phenoxyethyl isobutyrate	Primary irritation 4 h semi-occluded	100%	Rabbits (8)	Slight to very slight erythema at 4 h (6/8) to day 3 (2/8). Slight to very slight edema at 4 h (6/8) to day 3 (1/8). No day 7 data	RIFM (1979h)
2-Phenoxyethyl isobutyrate	Irritation (LD_{50})	100%	Rabbits (10)	Moderate to slight irritation	RIFM (1973b)
2-Phenoxyethyl isobutyrate	Irritation (13-week repeat dose study)	100, 300, 1000 mg/kg/day semi-occluded in DEP	Rats (24)	Well defined erythema was occasionally seen in all dose groups; desquamation was seen in all dose groups including controls	Api (2004), RIFM (1990c), Api and Ford (1993)
2-Phenoxyethyl isobutyrate	Irritation (2-week repeat dose study)	66, 190, 700, 1000 mg/kg/day semi-occluded in DEP	Rats 10 (5/sex)	Slight to well defined erythema and mild desquamation	RIFM (1994a)
2-Phenoxyethyl propionate	Irritation (LD_{50})	100%	Rabbits (4/dose)	No irritation	RIFM (1973a)
3-Phenyl-2-butenyl acetate[a]	Primary irritation 24 h occluded	5% in EtOH	Rabbits (3)	No irritation	RIFM (1974h)

(*continued on next page*)

Table 6-2 (*continued*)

Material	Method	Concentration	Species	Results	References
3-Phenyl-3-buten-1-yl acetate	Primary irritation 24 h occluded	5% in EtOH	Rabbits (3)	No irritation	RIFM (1974g)
3-Phenyl-3-buten-1-yl acetate	Primary irritation 24 h occluded	1% in EtOH	Rabbits (3)	No irritation	RIFM (1974i)
3-Phenyl-3-buten-1-yl acetate	Primary irritation 24 h occluded 1×/week for 3 weeks	2.4, 1.2, 0.6 or 0.3% in EtOH	Guinea Pigs (4)	No irritation	RIFM (1981f)
1-Phenyl-3-methyl-3-pentyl acetate	Irritation (LD_{50})	100%	Rabbits (10)	Moderate (8/10) to slight (2/10) erythema; moderate (5/10) to slight (5/10) edema	RIFM (1976a)
2-Phenylpropyl acetate	Primary Irritation 24 h occluded; 2^{nd} patch 48 h	2.5% in EtOH	Rabbits (3)	No irritation	RIFM (1973e)
2-Phenylpropyl acetate	Irritation (LD_{50})	100%	Rabbits (10)	Moderate (1/10) to slight (3/10) erythema; slight (1/10) edema	RIFM (1975b)
3-Phenylpropyl acetate	Irritation (LD_{50})	100%	Rabbits (10)	No irritation	RIFM (1973b)
Benzylic alcohols					
p-Anisyl acetate	Irritation (LD_{50})	5 ml/kg (concentration NR)	Rabbits (10)	Well defined to moderate erythema (10/10); slight to severe edema (5/10)	RIFM (1971)
Anisyl acetate (isomer unspecified)	Primary irritation (phototoxicity control)	50%, 30% or 10% in acetone	Guinea pigs (5)	No irritation	RIFM (1993)
Anisyl butyrate[a]	Irritation (LD_{50})	100%	Rabbits (10)	Moderate to slight irritation	RIFM (1976a)
Benzyl acetate	Primary irritation 4 h semi-occluded (performed under EEC methods)	100%	Rabbits (3)	Very slight to well defined irritation. Clear by day 4 or 8	RIFM (1994b)
Benzyl acetate	Primary irritation 4 h semi-occluded (performed under Annex V, EEC Directive 79/831)	100%	Rabbits (3)	Well-defined erythema and mild edema	RIFM (1984c)
Benzyl acetate	Primary irritation 4 h semi-occluded (performed under Annex V, EEC Directive 79/831)	100%	Rabbits (4)	Slight to well-defined erythema. Clear by day 7 with slight desquamation (1/4)	RIFM (1985a)
Benzyl acetate	Primary irritation 6 h occluded	100%, 50%, 25%, 10%, 5%, 2.5%, 1.25%, 0.625% in EtOH	Guinea pigs (16)	Moderate to severe erythema at all concentrations. Necrosis at 50% and 100%	RIFM (1986)
Benzyl acetate	Primary irritation 6 h occluded	100%, 50%, 25%, 10%, 5%, 2.5%, 1%, 0.5% in DEP	Guinea pigs (16)	No irritation	RIFM (1986)
Benzyl acetate	Primary irritation 24 h occluded	100%	Miniature swine (6)	No irritation	Motoyoshi et al. (1979)
Benzyl acetate	Primary irritation 24 h occluded	100%	Rabbits (6)	Moderate irritation	Motoyoshi et al. (1979)
Benzyl acetate	Primary irritation 24 h occluded	100%	Rabbits (9)	No irritation	RIFM (1977a)
Benzyl acetate	Primary irritation 24 h occluded	100%	Guinea pigs (6)	No irritation	Motoyoshi et al. (1979)
Benzyl acetate	Primary irritation 24 h occluded	100%	Rats (6)	No irritation	Motoyoshi et al. (1979)
Benzyl acetate	Irritation 24 h occluded	18.7% in EtOH	Rabbits (3)	No irritation	RIFM (1975j)
Benzyl acetate	Irritation 24 h occluded	7.5% in EtOH	Rabbits (3)	No irritation	RIFM (1975k)
Benzyl acetate	Irritation 24 h occluded	7.5% in petrolatum	Rabbits (3)	No irritation	RIFM (1975l)
Benzyl acetate	Primary irritation 24 h occluded	3% in EtOH	Rabbits (3)	No irritation	RIFM (1975m)
Benzyl acetate	Irritation 24 h occluded	3% in petrolatum	Rabbits (3)	No irritation	RIFM (1975n)
Benzyl acetate	Primary irritation 48 h occluded	30, 10 or 3% in petrolatum	Guinea pigs (10)	Faint erythema	RIFM (1985b)
Benzyl acetate	Range Finding (Max test)	100%, 50%, 25%, 10%, 5%, 2.5% or 1.25% in saline (0.1 ml intradermal injection)	Guinea pigs (2 per dose)	Irritation observed at each concentration	RIFM (1985c)
Benzyl acetate	Max (pre-test)	100, 30, 10, or 3%	Guinea pigs (5)	No irritation	RIFM (1985d)
Benzyl butyrate	Irritation (LD_{50})	100%	Rabbits (10)	No irritation	RIFM (1973b)
Benzyl formate	Irritation	20% in solvent (0.1 mL topical)	Guinea pigs (4)	No irritation	Sharp (1978)
Benzyl formate	Irritation	0.25% in solvent (0.1 mL injection)	Guinea pigs (4)	Slight irritation with no edema	Sharp (1978)
Benzyl isobutyrate	Irritation (LD_{50})	100%	Rabbits (8)	Erythema (8/8) that cleared by day 8; edema (4/8) that cleared by day 6	RIFM (1971d)
Benzyl propionate	Irritation (LD_{50})	100%	Rabbits (5)	Moderate erythema (1/5)	RIFM (1973b)

Table 6-2 (*continued*)

Material	Method	Concentration	Species	Results	References
Carbonic acid, methyl phenylmethyl ester	Range finding	0.05%, 0.1%, 0.5%, 2.0%, 10.0%, 25.0% and 50.0% in EtOH	Guinea pigs (20)	Weak irritation; 1.0% was selected as dose for induction; challenge doses were 0.1% and 1.0%.	RIFM (1987a)
2,4-Dimethylbenzyl acetate	Irritation (LD_{50})	100%	Guinea pigs (10)	Slight erythema (9/10) and edema (6/10) on day 1 (clear by day 7)	RIFM (1982a)
Ethyl phenyl carbonyl acetate	Irritation (LD_{50})	100%	Rabbits (10)	Well defined erythema (7/10) and moderate edema (1/10) at 24 h; Clear by day 14	RIFM (1982a)
p-Isopropylbenzyl acetate	Irritation (LD_{50})	100%	Rabbits (10)	Moderate (3/10) to slight (7/10) erythema and moderate (1/10) to slight (5/10) edema on day 1	RIFM (1978a)
α-Methylbenzyl acetate	Primary irritation	100%	Rabbits (6)	No irritation	RIFM (1971h)
α-Methylbenzyl acetate	Irritation (LD_{50})	100%	Rabbits (12)	Very slight (2/12) erythema on day 1; no edema	RIFM (1971e)
4-Methylbenzyl acetate	Irritation (LD_{50})	100%	Rabbits (10)	Very slight (1/10) erythema and slight (1/10) to very slight (4/10) edema on day 1 (clear by day 7).	RIFM (1981b)
α-Methylbenzyl propionate	Irritation (LD_{50})	100%	Rabbits (4/dose)	Mild (1/4) erythema on day 1	RIFM (1973a)
Piperonyl acetate	Irritation (LD_{50})	100%	Rabbits (10)	Slight erythema and edema (1/10)	RIFM (1973b)

[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.
[b] This study was performed with a mixture of phenethyl propionate and eugenol at a ratio of 7:3.

et al., 1976; El Masry et al., 1956; Kiese and Lenk, 1974 – all as cited in JECFA, 2002a).

No published *in vivo* metabolism studies were identified for the AAASAE fragrance ingredients derived from branched aryl alkyl tertiary alcohols. In an *in vitro* study in which 1, 1-dimethyl-2-phenylethyl acetate was incubated with intestinal mucosal preparation from the small intestines of a pig, hydrolysis to acetic acid and 1,1-dimethyl-2- phenylethyl tertiary alcohol was not observed. The majority of other esters in the same study (isoamyl acetate; 1, 3-dimethylbutyl acetate; ethyl acetate; benzyl tiglate; allyl tiglate) all hydrolyzed within 2 h. In another experiment, after incubation with pig liver homogenate for 2 h, only 20% of the 1,1-dimethyl-2-phenylethyl acetate was hydrolyzed. It was thus concluded that this compound may not be readily hydrolyzed in the gastrointestinal tract and is minimally hydrolyzed in the liver by carboxylesterases (RIFM, 1974a).

4. Toxicokinetics

In vivo laboratory animal oral and dermal AAASAE fragrance ingredients exposure studies are more readily available than those from respiratory, intraperitoneal injection and intravenous routes of exposure. The oral and dermal exposure data confirm that the benzyl esters are rapidly absorbed through the gut, hydrolyzed and metabolized mostly in the liver, and excreted in the urine primarily as glycine- and to a lesser extent glucuronide-conjugate of benzoic acid derivatives (Davison, 1971; Abdo et al., 1985; Temellini et al., 1993).

4.1. Dermal exposure skin absorption data on benzyl acetate

4.1.1. In vivo studies

Few tracer studies have been performed with this group of esters to determine their toxicokinetic pathway in mammalian species. One study with benzyl acetate applied to the skin of F344 rats was identified. After 24 h of pure benzyl acetate dermal administration to male F344 rats at doses of 100, 250, or 500 mg/kg bodyweight, 28–48% of the dose was recovered at the application site and 26–46% was absorbed and excreted in the urine. Approximately 95% of the absorbed dose was excreted, mostly as hippuric acid, during the first 24 h of treatment. After 48 and 72 h, additional amounts of 2% and 1% were recovered in the urine. Less than 3% of the administered dose was found in the feces and 2% in the animal tissues after 72 h. The absorbed dose was not affected by the applied concentration, area of application or use of ethanol as a vehicle. Other urinary metabolites included benzoyl glucuronide, benzoic acid, and benzyl-mercapturic acid; benzoyl glucuronide accounted for a minor proportion of the metabolites. Glucuronide derivatives levels increased more at 500 mg/kg than at 250 mg/kg (Chidgey et al., 1987).

The absorption of radioactive 2-phenoxyethyl isobutyrate in diethylphthalate was studied in Sprague–Dawley rats following topical application of 0, 0.5, 5 or 50% in diethyl phthalate (0, 10, 100, and 1000 mg/kg) under semi-occlusive dressing for 6 h (Api, 2004; Api and Ford, 1993; RIFM, 1990a). After 6 h, removal of the patches and washing of the skin in the area of application removed 61–69% of the applied dose. The amounts remaining in the skin were related to dose with 0.4, 7, and 17 mg/kg at the low, mid and high doses respectively. After 72 h, 20–35% of the radioactivity was still bound to the skin. Less than 1% of the dose was excreted in the feces. After 6 h, elimination of 1, 2, and 3% of the low, mid and high applied dose was almost exclusively via the urine and after 72 h, 18, 19 and 19% of the applied doses were in the urine.

Radioactive benzyl acetate was applied for 6 h to the skin of male F344 rats at doses of 100, 250, or 500 mg/kg to areas of 6.25, 12 or 18 cm^2 (Caldwell et al., 1987; Chidgey et al., 1987) or as a 50% v/v ethanol solution. Absorption was affected by concentration of the applied dose but not by dose size, area of application or ethanol vehicle. After 6 h, approximately 28–48% of the dose was recovered from the application site, mostly on the dressings. Approximately 28–46% was absorbed and excreted in the urine within 24 h; 1% was found in the feces. Doubling the concentration on the skin led to an approximate doubling of the amount absorbed per cm^2 of skin. Hippuric acid was the major metabolite (>95%) with smaller amounts of benzoyl glucuronide, benzoic acid and benzyl mercapturic acid (1–2% each).

Bronaugh et al. (1990) measured the skin absorption of [7-^{14}C] benzyl acetate in 4 female rhesus monkeys. The test material in a

Table 7
Mucous membrane (eye) irritation studies in rabbits.

Material	Method (Vol., %, No. animals)	Results	References
1,1-Dimethyl-2-phenylethyl acetate	0.1 mL of 100% (n = 6)	No irritation	RIFM (1980f)
1,1-Dimethyl-2-phenylethyl acetate	0.1 mL of 1.25% in EtOH (n = 3)	Severe (3/3) conjunctival irritation; decreased to diffuse vessel injection and slight chemosis by 7th day	RIFM (1963a)
1,1-Dimethyl-2-phenylethyl acetate	0.1 mL of 0.125% in EtOH (n = 3)	Severe (1/3) to moderate (2/3) conjunctival irritation (all clear by day 4)	RIFM (1964c)
1,1-Dimethyl-2-phenylethyl butyrate	0.1 ml of 100% (n = 4) (performed under OECD test guideline 405)	Slight irritation (4/4) was observed as redness and edema of the conjunctiva 1 h after application, eyes clear by 48 h. All effects were reversible within 72 h	RIFM (2000c)
1,1-Dimethyl-2-phenethyl formate	0.1 mL of 100% (n = 4) (performed under EEC Directive 84/449/EEC)	Mild (1/4) to slight (3/4) conjunctival irritation (clear by day 2) and moderate (2/4) inflammation of iris (clear by day 1)	RIFM (1989d)
1,3-Dimethyl-3-phenylbutyl acetate	0.1 mL of 100% (n = 6) (performed under 16 CFR 1500.42)	2/6 animals had positive conjunctival scores (clear by day 3); no irritation to cornea or iris	RIFM (1979i)
1,3-Dimethyl-3-phenylbutyl acetate	0.1 mL of 5% in petrolatum (n = 6)	No irritation	RIFM (1984e)
Phenethyl acetate	0.1 ml of 2.5% in EtOH (n = 3)	Moderate to severe conjunctival irritation in all (corneal opacity and iris congestion)	RIFM (1965c)
Phenethyl isobutyrate	0.1 mL of 100% (n = 4) (performed under OECD test guideline 405)	Slight conjunctive irritation (4/4) was observed 1 h after application. All effects were reversible within 48 h	RIFM (2001c)
Phenethyl propionate	0.1 mL of 70% (n = 6)[b]	Slight irritation on day 1; clear by day 3	Beroza et al. (1975)
3-Phenyl-2-butenyl acetate[a]	0.1 mL of 5% in EtOH (n = 3)	Moderate conjunctive irritation (2/3) with corneal and iris involvement (did not clear by day 7)	RIFM (1974j)
3-Phenyl-3-buten-1-yl acetate	0.1 mL of 5% in EtOH (n = 3)	Mild to moderate conjunctive irritation (3/3) (2/3 did not clear by day 7) with moderate corneal opacity (1/3)	RIFM (1974k)
3-Phenyl-3-buten-1-yl acetate	0.1 mL of 1% in EtOH (n = 3)	Mild to moderate conjunctive irritation (3/3) (2/3 did not clear by day 7) with moderate corneal opacity (1/3)	RIFM (1974l)
2-Phenylpropyl acetate	0.1 mL of 2.5% in EtOH (n = 3)	Mild (3/3) conjunctive irritation (clear by day 4)	RIFM (1973f)
Benzylic alcohols			
p-Anisyl acetate	0.1 ml of 100% (n = 4) (performed under OECD test guideline 405)	Slight to moderate conjunctive irritation (4/4) was observed 1 h after application. All effects were reversible within 48 h	RIFM (2000d)
Benzyl acetate	0.1 mL of 100% (n = 6)	No irritation	RIFM (1977a)
Benzyl acetate	0.1 mL of 100% (n = 3) (performed under EEC methods)	Conjunctival irritation (temporary)	RIFM (1994b)
Benzyl acetate	0.1 mL of 18.7% in EtOH (n = 3)	Conjunctival and corneal irritation effects (1/3), clear by day 10	RIFM (1975o)
Benzyl acetate	0.1 mL of 7.5% in petrolatum (n = 3)	No irritation	RIFM (1975p)
Benzyl acetate	0.1 mL of 7.5% in EtOH (n = 3)	Irritation effects (conjunctival and corneal)	RIFM (1975q)
Benzyl acetate	0.1 mL of 3% in petrolatum (n = 3)	No irritation	RIFM (1975r)
Benzyl acetate	0.1 mL of 3% in EtOH (n = 3)	Irritation effects (conjunctival and corneal), clear by day 10	RIFM (1975s)
Benzyl acetoacetate[a]	0.1 mL of 0.5% in EtOH (n = 3)	Definite (3/3) conjunctival irritation (clear by day 7)	RIFM (1964d)
Benzyl formate	0.1 ml of 100% (n = 4) (performed under OECD test guideline 405)	Slight to Moderate irritation (4/4) involving the conjunctiva and cornea (clear by day 7)	RIFM (2000d)
2,4-Dimethylbenzyl acetate	0.1 ml of 2.5% in EtOH (n = 3)	Definite conjunctival irritation (clear by day 7)	RIFM (1965d)
α-Methylbenzyl acetate	100% (n = 6)	No irritation	RIFM (1971h)
Piperonyl acetate	0.1 mL of 5% in EtOH (n = 3)	Severe (3/3) conjunctival irritation on day 1 with slight (3/3) conjunctival irritation on day 7	RIFM (1963b)

[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.
[b] This study was performed with a mixture of phenethyl propionate and eugenol at a ratio of 7:3.

moisturizing lotion was applied at a concentration of 4 μg/cm^2 to a 1 cm^2 area of abdominal skin for 24 h. When the application site was occluded with either plastic wrap or a glass chamber, the absorption of benzyl acetate was 17.3 ± 2.7% and 78.7 ± 7.5%, respectively. When the site was not occluded, the absorption was 34.6 ± 9.4%.

Neat [methylene-^{14}C] benzyl acetate or as a 50% concentration in ethanol was applied to the occluded skin (5–18 cm^2) of male Fischer 344 rats for 6 h at doses of 100, 250 and 500 mg/kg. At 6 h, 28–48% of the dose was recovered from the application site. At 24 h, more than 95% of the absorbed radioactivity was detected in the urine. Ethanol had no effect on the absorption of benzyl acetate. The recovery of benzyl acetate at 72 h was 77–88% (Hotchkiss et al., 1990a).

In an effort to compare the structure–activity relationships relative to skin absorption, data on absorption for 24 fragrances was collected with the aim of correlating the extent of absorption with the structure and physical/chemical properties of the compound (Hotchkiss et al., 1992a,b,c; Hotchkiss, 1998). Optimal absorption through human skin is observed when the octanol–water partition co-efficient, log K_{ow}, is within the range 1.3–2.0. In an interspecies comparison the effect of occlusion on the percutaneous absorption through rat and human skin *in vitro* was studied. For 2-phenoxyethyl isobutyrate, 41% and 46% of the dose applied to rats was absorbed after 72 h with unoccluded and occluded applications respectively. In humans only 5% of the dose was absorbed regardless of application. For benzyl acetate, 58 and 59% of the applied dose was absorbed in the rat after 72 h of unoccluded or occluded

Table 8–1a
Skin sensitization in humans.

Material	Method	Concentration	Subjects	Results	References
2-Acetoxy-1-phenyl propane[b]	Maximization	6% in petrolatum (4140 μg/cm^2)	25 (MF)	0/25	RIFM (1977c)
1,1-Dimethyl-2-phenylethyl acetate	HRIPT	1.25% in EtOH (1477 μg/cm^2)	42 (35F, 7M)	0/42	RIFM (1964a)
1,1-Dimethyl-2-phenylethyl acetate	Maximization	10% in petrolatum (6900 μg/cm^2)	25 (MF)	0/25	RIFM (1970b, 1971i)
1,1-Dimethyl-2-phenylethyl butyrate	Maximization	10% in petrolatum (6900 μg/cm^2)	25 (MF)	0/25	RIFM (1975c)
1,1,-Dimethyl-2-phenylethyl formate	Maximization	4% in petrolatum (2760 μg/cm^2)	24 (MF)	1/24[a]	RIFM (1985e)
1,3-Dimethyl-3-phenylbutyl acetate	HRIPT	20% in petrolatum	50 (MF)	0/50	RIFM (1979d)
1,1-Dimethyl-2-phenylethyl propionate	Maximization	10% in petrolatum (6900 μg/cm^2)	28 (M)	0/28	RIFM (1977d)
2-Methyl-4-phenyl-2-butyl acetate	Maximization	4% in petrolatum (2760 μg/cm^2)	25 (MF)	0/25	RIFM (1975c)
Phenethyl acetate	HRIPT	2.5% in EtOH (1938 μg/cm^2)	39 (33F, 6M)	0/39	RIFM (1964b)
Phenethyl acetate	Maximization	10% in petrolatum (6900 μg/cm^2)	20 (M)	0/20	RIFM (1970b)
Phenethyl butyrate	Maximization	8% in petrolatum (5520 μg/cm^2)	25 (MF)	0/25	RIFM (1977c)
Phenethyl butyrate	Maximization	8% in petrolatum (5520 μg/cm^2)	10 (MF)	0/10	RIFM (1974d)
Phenethyl formate	Maximization	6% in petrolatum (4140 μg/cm^2)	25 (M)	0/25	RIFM (1972b)
Phenethyl isobutyrate	Maximization	2% in petrolatum (1380 μg/cm^2)	25 (M)	0/25	RIFM (1971i)
Phenethyl propionate	Maximization	8% in petrolatum (5520 μg/cm^2)	25 (M)	0/25	RIFM (1973d)
2-Phenoxyethyl isobutyrate	Maximization	4% in petrolatum (2760 μg/cm^2)	25 (M)	0/25	RIFM (1973d)
2-Phenoxyethyl isobutyrate	HRIPT	0.5% in EtOH (388 μg/cm^2)	38 (31F, 7M)	0/38	RIFM (1965a)
2-Phenoxyethyl propionate	Maximization	10% in petrolatum (6900 μg/cm^2)	25 (M)	0/25	RIFM (1973d)
3-Phenyl-2-butenyl acetate[b]	HRIPT	5% in EtOH (5905 μg/cm^2)	49 (47F, 2M)	0/49	RIFM (1974e)
3-Phenyl-2-butenyl acetate[b]	HRIPT	1% in EtOH (1181 μg/cm^2)	48 (33F, 15M)	0/48	RIFM (1974f)
3-Phenyl-3-buten-1-yl acetate	HRIPT	5% in EtOH (3876 μg/cm^2)	49 (47F, 2M)	0/49	RIFM (1974f)
3-Phenyl-3-buten-1-yl acetate	HRIPT	1% in EtOH (775 μg/cm^2)	48 (33F, 15M)	0/48	RIFM (1974e)
3-Phenyl-3-buten-1-yl acetate	HRIPT	1.2% in EtOH (1286 μg/cm^2)	47 (MF)	0/47	RIFM (1981d)
1-Phenyl-3-methyl-3-pentyl acetate	Maximization	10% in petrolatum (6900 μg/cm^2)	27 (M)	0/27	RIFM (1976b)
2-Phenylpropyl acetate	Maximization	12% in petrolatum (8280 μg/cm^2)	25 (MF)	0/25	RIFM (1975c)
2-Phenylpropyl acetate	HRIPT	2.5% in EtOH (1938 μg/cm^2)	43 (24F, 19M)	0/43	RIFM (1973g)
3-Phenylpropyl acetate	Maximization	8% in petrolatum (5520 μg/cm^2)	25 (M)	0/25	RIFM (1973d)
Benzylic alcohols					
p-Anisyl acetate	Maximization	10% in petrolatum (6900 μg/cm^2)	25 (MF)	0/25	RIFM (1975c)
p-Anisyl acetate	Maximization	4% in petrolatum (2760 μg/cm^2)	25 (MF)	0/25	RIFM (1975c)
p-Anisyl acetate	Maximization	4% in petrolatum (2760 μg/cm^2)	25 (MF)	0/25	RIFM (1973d)
p-Anisyl acetate	Maximization	4% in petrolatum (2760 μg/cm^2)	25 (MF)	2/25[a]	RIFM (1973d)
p-Anisyl acetate	Maximization	4% in petrolatum (2760 μg/cm^2)	25 (M)	1/25[a]	RIFM (1971i)
Anisyl butyrate[b]	Maximization	8% in petrolatum (5520 μg/cm^2)	25 (MF)	0/25	RIFM (1975c)
Anisyl butyrate[b]	Maximization	8% in petrolatum (5520 μg/cm^2)	25 (MF)	4/25[a]	RIFM (1975c)
Anisyl formate	Maximization	4% in petrolatum (2760 μg/cm^2)	22 (M)	0/22	RIFM (1975d)
Anisyl propionate	Maximization	4% in petrolatum (2760 μg/cm^2)	22 (M)	0/22	RIFM (1974g)
Benzyl acetate	HRIPT	18.7% in EtOH (14496 μg/cm^2)	35 (18F, 17M)	0/35	RIFM (1975e)
Benzyl acetate	HRIPT	8% in EtOH/DEP (3721 μg/cm^2)	65 (55F, 10M)	0/65	RIFM (1987b)
Benzyl acetate	HRIPT	8% in EtOH/DEP (3721 μg/cm^2)	106 (87F, 21M)	0/106	RIFM (1988a)
Benzyl acetate	HRIPT	8% in EtOH/DEP (3721 μg/cm^2)	34 (34F, 0M)	0/34	RIFM (1988b)
Benzyl acetate	HRIPT	8% in EtOH/DEP (3721 μg/cm^2)	27 (23F, 4M)	0/27	RIFM (1988c)
Benzyl acetate	HRIPT	8% in EtOH/DEP (3721 μg/cm^2)	38 (25F, 13M)	1/38[a]	RIFM (1988d)
Benzyl acetate	HRIPT	7.5% in EtOH (5814 μg/cm^2)	35 (24F, 11M)	0/35	RIFM (1975g)
Benzyl acetate	HRIPT	7.5% in petrolatum (5814 μg/cm^2)	39 (29F, 10M)	0/39	RIFM (1975f)
Benzyl acetate	HRIPT	3% in EtOH (2326 μg/cm^2)	42 (31F, 11M)	0/42	RIFM (1975h)
Benzyl acetate	HRIPT	3% in petrolatum (2326 μg/cm^2)	44 (32F, 12M)	0/44	RIFM (1975i)
Benzyl acetate	Maximization	5% in EtOH	25 (MF)	0/25	Greif (1967)
Benzyl butyrate	Maximization	4% in petrolatum (2760 μg/cm^2)	25 (M)	0/25	RIFM (1973d)
Benzyl formate	Maximization	10% in petrolatum (6900 μg/cm^2)	25 (M)	0/25	RIFM (1971i)
Benzyl isobutyrate	Maximization	4% in petrolatum (2760 μg/cm^2)	25 (M)	0/25	RIFM (1971i)
Benzyl propionate	Maximization	4% in petrolatum (2760 μg/cm^2)	25 (M)	0/25	RIFM (1973d)
2,4-Dimethylbenzyl acetate	HRIPT	2.5% in EtOH (1938 μg/cm^2)	44 (37F, 7M)	0/44	RIFM (1965b)
2,4-Dimethylbenzyl acetate	Maximization	3% in petrolatum (2070 μg/cm^2)	21 (MF)	0/21	RIFM (1981e)
Ethyl phenyl carbinyl acetate	Maximization	4% in petrolatum (2760 μg/cm^2)	27 (MF)	0/27	RIFM (1982b)
p-Isopropylbenzyl acetate	Maximization	12% in petrolatum (8280 μg/cm^2)	25 (MF)	0/25	RIFM (1978b)
α-Methylbenzyl acetate	Maximization	4% in petrolatum (2760 μg/cm^2)	25 (M)	0/25	RIFM (1970b)
4-Methylbenzyl acetate	Maximization	5% in petrolatum (3450 μg/cm^2)	25 (MF)	0/25	RIFM (1981e)
α-Methylbenzyl propionate	Maximization	10% in petrolatum (6900 μg/cm^2)	25 (M)	0/25	RIFM (1973d)
Piperonyl acetate	HRIPT	5% in EtOH (3876 μg/cm^2)	37	0/37	RIFM (1964e)
Piperonyl acetate	Maximization	8% in petrolatum (5520 μg/cm^2)	25 (M)	0/25	RIFM (1973d)

[a] Sensitization type reaction was likely related to the adjacent testing of a known dermal sensitizer, which was tested in the same panel of subjects.
[b] 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.

application. In humans, 12% of the dose was absorbed regardless of applications. The author concluded that compared to rats, smaller amounts of these two chemicals are absorbed in humans, and in humans, occlusion did not significantly enhance the absorption of these two chemicals. Benzyl acetate absorption in the rat at 48 h is a fixed proportion of the applied dose up to a rate of 33 mg/cm^2; increasing dose decreases the absorption efficiency to only 7% at 331 mg/cm^2. Esterase activity is particularly high in the skin, explaining the observation that after topical application of benzyl acetate to rat skin *in vitro*, there is a rapid and complete hydrolysis to benzyl alcohol (97%) with further oxidation to benzoic acid (3%). In human skin, benzyl acetate is also hydrolyzed (99% of the absorbed dose) with 1% of the absorbed dose recovered as the parent compound (Garnett, 1992).

Table 8–1b
Diagnostic patch tests.

Material	Concentration	Subjects	Results (frequency)	References
1,1-Dimethyl-2-phenylethyl acetate	5% in petrolatum	European dermatological patients	3/1855 (0.2%)	Frosch et al. (2002)
1,1-Dimethyl-2-phenylethyl acetate	5% or 1% in petrolatum	European dermatological patients	1/313 (0.3%) at 5%; 0/313 (0%) at 1%	Frosch et al. (1995)
1,1-Dimethyl-2-phenylethyl acetate	0.2% in EtOH or petrolatum	Patients with dermatoses	0/80 (0%)	Fujii et al. (1972)
1,3-Dimethyl-3-phenylethyl acetate	5% in petrolatum	Patients with various kinds of eczema	0/50 (0%)	RIFM (1984f)
Benzylic alcohols				
Benzyl acetate	5% in petrolatum	Cosmetic dermatitis patients	3/155 (1.9%)	Itoh (1982)
Benzyl acetate	5% in petrolatum	Perfume sensitive patients	2/20 (10%)	Larsen (1977)
Benzyl acetate	5% in petrolatum	Japanese dermatitis and eczema patients (1977–1978)	5/126 (4.0%)	Ishihara et al. (1979)
Benzyl acetate	5% in petrolatum	Japanese dermatitis and eczema patients (1978–1986)	8/756 (1.1%)	Itoh et al. (1988)
Benzyl acetate	5% in petrolatum	Japanese Dermatitis and eczema patients (1990–1991)	1/103 (1%)	Haba et al. (1993)
Benzyl acetate	5% in petrolatum	Japanese dermatitis and eczema patients (1978–1980)	7/362 (1.9%)	Ishihara et al. (1981)
Benzyl acetate	5% in petrolatum	Japanese dermatitis and eczema patients (1978–1985)	8/660 (1.2%)	Itoh et al. (1986)
Benzyl acetate	5% in petrolatum	Japanese dermatitis and eczema patients (1978–1982)	7/522 (1.3%)	Nishimura et al. (1984)
Benzyl acetate	5% or 1% in petrolatum, isopropyl myristate, DEP	European dermatological patients	0/100 (0%) at 5 % 1/100 (1%) at 1%	Frosch et al. (1995)
Benzyl acetate	2% in petrolatum	Japanese dermatitis and eczema patients (1977–1978)	2/126 (1.6%)	Ishihara et al. (1979)
Benzyl acetate	1% in petrolatum	Japanese dermatitis and eczema patients (1977–1978)	1/126 (0.8%)	Ishihara et al. (1979)
Benzyl acetate	0.4% in EtOH or non-irritant cream base	Dermatitis patients	0/77 (0%)	Fujii et al. (1972)
Benzyl propionate	5% in petrolatum	Contact dermatitis patients	0/38 (0%)	Ishihara (1977)
α-Methylbenzyl acetate	5% in petrolatum	Contact dermatitis patients	0/56 (0%)	Ishihara (1977)
α-Methylbenzyl acetate	0.5% in 99% EtOH or non-irritant cream base	Patients with dermatoses	0/89 (0%)	Fujii et al. (1972)
α-Methylbenzyl acetate	0.25% in oil of helianthi	Patients sensitized to perfume composition type F	1/10 (10%)	Novak (1974)

4.1.2. In vitro skin absorption studies

4.1.2.1. Human skin. The penetration of benzyl acetate and benzyl propionate through human epidermis was measured using cadaver abdominal skin. The amount of absorption 72 h after application was 1.3 ± 0.2%. for benzyl acetate and 0.39 ± 0.04% for benzyl propionate (Jimbo, 1983).

Benzyl acetate (0.2–18.1 mg/cm^2) was applied to human skin using flow-through diffusion cells. The absorption over 72 h ranged from approximately 0.3–38% and was unaffected when the skin was occluded with a Teflon cap. Approximately 3–64% and 4–23% remained on the skin surface and within the skin, respectively (Hotchkiss et al., 1992a).

Neat [methylene-^{14}C] benzyl acetate (10 μl) was applied to full-thickness human skin (0.32 cm^2) of surgical patients. The skin was then occluded using Teflon caps. Penetration of benzyl acetate reached 5.5 ± 0.1% and 17.8 ± 3.3% at 24 h and 72 h, respectively (Garnett et al., 1994).

4.1.2.2. Skin from experimental animals. Hotchkiss et al. (1989a, 1990a) measured the absorption of a 50% solution of [methylene-^{14}C] benzyl acetate in ethanol or the neat material after application to skin (0.32 cm^2) from male Fischer 344 rats. Penetration of benzyl acetate began 1 h after application and peaked at 49.8 ± 3.2% at 48 h. There was no significant difference in absorption at 48 h when benzyl acetate was diluted in ethanol although at 12 h there was an increase of 8.5%.

The absorption of neat benzyl acetate into the skin of rats was 18% at 3 min and peaked at 53% at 3 h. Benzyl acetate in ethanol was absorbed into the skin more rapidly (31% at 3 min; 53% at 1 h). Penetration of benzyl acetate through the skin began within 1 h and peaked after 48 h at 49.3 ± 2% and 50.0 ± 1% for neat and diluted test material, respectively. Swabbing the skin surface at 6 h after application did not affect the absorption of benzyl acetate. The data showed evidence that there is a delay in partitioning of benzyl acetate from the skin into the systemic circulation and that this reservoir might be considered during its safety evaluation (Hotchkiss et al., 1989b).

In another absorption study using rat skin with neat [methylene-^{14}C] benzyl acetate or a 10, 20, 50, 80 or 90% concentration in ethanol, the absorption of neat benzyl acetate through exposed skin was 4.2 ± 0.53% and 45.87 ± 1% at 6 h and 48 h, respectively. Ethanol had no significant effect on absorption at 48 h although the initial rate of absorption was increased in the 80–90% samples. The absorption at occluded sites was up to 10% greater than at exposed sites at all concentrations (Hotchkiss et al., 1988; Hotchkiss et al., 1990b).

A volume of 10 μl of ^{14}C benzyl acetate was applied to exposed skin (0.32 cm^2) from male Fischer 344 rats. In an *in vitro* skin diffusion apparatus study, approximately 35 and 50% of the dose was recovered in the receptor fluid at 24 and 48 h, respectively (Garnett et al., 1989).

Neat [methylene-^{14}C] benzyl acetate (10 μl) was applied and occluded to skin (0.32 cm^2) from male Fischer 344 rats in a flow-through system. Penetration of benzyl acetate reached 34.3 ± 3.9% and 55.8 ± 5.0% at 24 and 72 h, respectively. The rate of benzyl acetate absorption peaked at 8 h at 0.6 ± 0.1 mg/cm^2/h and then declined to 0.3 ± 0.0 and 0.1 ± 0.0 mg/cm^2/h at 24 and 72 h, respectively. The total recovery of benzyl acetate was

Table 8–2a
Skin sensitization in animals.

Material	Method	Induction	Challenge	Species	Results	References
1,1-Dimethyl-2-phenylethyl acetate	Open epicutaneous test	100%, 30%, 10%, 3%, 1%, or 0.3% in vehicle (open topical, 21 days)	4% in vehicle (topical)	Guinea pig (6–8)	No sensitization	Klecak (1979), Klecak (1985)
1,1-Dimethyl-2-phenylethyl formate	Maximization (performed under EEC Directive L251)	10% in liquid paraffin and 20% in FCA (0.1 ml intradermal injection); 100% (topical 48-h on day 7)	100% or 50% in EtOH (topical 24 h on day 21)	Guinea pigs (20)	1/20 when challenged with 100%; no sensitization with 50%	RIFM (1990d)
1,3-Dimethyl-3-phenylbutyl acetate	Modified Buehler	5% in petrolatum (topical)	5% in petrolatum (topical)	Guinea pig (20)	No sensitization	RIFM (1984d)
Phenethyl acetate	Open epicutaneous test	100%, 30%, 10%, 3%, 1%, or 0.3% in vehicle (open topical, daily, 21 days)	10% in vehicle (topical)	Guinea pig (6–8)	No sensitization	Klecak (1979), Klecak (1985)
Phenethyl propionate	Open epicutaneous test	100%, 30%, 10%, 3%, 1%, or 0.3% in vehicle (open topical, daily, 21 days)	8% in vehicle (topical)	Guinea pig (6–8)	No sensitization	Klecak (1979), Klecak (1985)
3-Phenyl-3-buten-1-yl acetate	Modified Buehler	1.2% in EtOH (topical 6 h/3×/week)	1.2% in EtOH (topical)	Guinea pig (15)	No sensitization	RIFM (1981f)
3-Phenylpropyl acetate	Open epicutaneous test	100%, 30%, 10%, 3%, 1%, or 0.3% in vehicle (open topical, 21 days)	8% in vehicle (topical, days 21 & 35)	Guinea pig (6–8)	No sensitization	Klecak (1979), Klecak (1985)
Benzylic alcohols						
Anisyl acetate (isomer unspecified)	Maximization	10% in FCA (0.1 ml intradermal injection on day 1; 0.2 ml topical 48-h patch on day 7)	20% in acetone (0.02 ml topical for 3 days)	Guinea pig (6)	No sensitization	RIFM (1997b)
Benzyl acetate	Maximization	10% in vehicle (topical, 3×/week, 2 weeks, 48-h patch)	10% in vehicle (topical, 1×/week, 2 weeks, 48-h patch)	Guinea pig	No sensitization	Ishihara et al. (1986)
Benzyl acetate	Maximization	10% in FCA or saline (0.1 mL intradermal injection, 2/week, 2 weeks) followed by 30% in petrolatum (topical 48-h closed patch)	10, 3, and 1% in petrolatum on day 19 (topical, 24-h closed patch)	Guinea pig (20)	Weak sensitization (clear by day 7)	RIFM (1985c)
Benzyl acetate	Open epicutaneous test	100%, 30%, 10%, or 3% in EtOH (topical, 5×/week for 4 weeks)	100%, 30%, 10%, or 3% in EtOH (topical, 1× per week for two weeks)	Guinea pig (6/dose)	No sensitization	RIFM (1985d)
Benzyl acetate	Open epicutaneous test	100%, 30%, 10%, 3%, 1%, or 0.3% in vehicle (open topical, daily, 21 days)	8%, vehicle not specified (topical, 1×/week, 2 weeks)	Guinea pig (6–8)	No sensitization	Klecak (1979); Klecak (1985)
Benzyl acetate	Closed epicutaneous test (DHS)	10% in petrolatum (topical 3×/week, 2 weeks, 48-h or 72-h)	10, 3, or 1% in petrolatum (topical 48-h patch)	Guinea pig (20)	No sensitization	RIFM (1985b)
Benzyl acetate	Closed epicutaneous test	100% (topical 6-h, 1/week, 3-weeks)	100%, 30% or 10% in DEP (topical 6-h)	Guinea pig (20)	No sensitization	RIFM (1986)
Benzyl acetate	FCAT	10% in FCA (injections, 3×, 0.1 mL)	10% in EtOH (topical)	Guinea pigs (10)	No sensitization	RIFM (1985d)
Benzyl formate	Modified Draize	0.625% in solvent (4 injections)	0.25% (0.1 mL injection) and 20% (0.1 mL topical application)	Guinea pig (10)	No sensitization	Sharp (1978)
Benzyl formate	Open epicutaneous test	100%, 30%, 10%, 3%, 1%, or 0.3% in vehicle (open topical, 21 days)	10% in vehicle (topical, on days 21 & 35)	Guinea pig (6–8)	No sensitization	Klecak (1979), Klecak (1985)
Benzyl propionate	Open epicutaneous test	100%, 30%, 10%, 3%, 1%, or 0.3% in vehicle (open topical, 21 days)	4% in EtOH (topical 1/week, 2 weeks)	Guinea pig (6–8)	No sensitization	Klecak (1985)
Carbonic acid, methyl phenylmethyl ester	Delayed contact hypersensitivity	1% in EtOH (0.4 mL topical)	0.1% or 1% (0.4 mL topical)	Guinea pig (20)	No sensitization	RIFM (1987a)

96.8 ± 1.9% from the receptor fluid, skin, swab, diffusion cell and cap combined, with 20.6 ± 0.3% coming from the skin alone (Garnett et al., 1994).

In a study to determine the effect of different solvents on benzyl acetate absorption, a volume of 5 µl of [methylene-^{14}C] benzyl acetate either neat or diluted in ethanol, 2-phenylethanol or dimethylsulfoxide was applied to skin from male Fischer 344 rats. The skin was either left exposed or occluded with parafilm. The absorption of neat benzyl acetate was 47–52% at the final measurement. All 3 solvents enhanced the absorption of benzyl acetate at 48 h. Ethanol increased the absorption at concentrations greater than 50% and 2-phenylethanol increased absorption up to 10%

Table 8–2b
Murine local lymph node assay (LLNA).

Material	Method	Dose	Species (No./group)	Results	References
Primary alcohols					
2-Phenoxyethyl isobutyrate	LLNA (performed under OECD test guideline 406)	0.1%, 1%, 10%, and 100% in EtOH:water (7:3)	CBA/Ca Mice (4)	Not sensitizing; no concentration tested resulted in stimulation index (SI) > 3	RIFM (2002b)

Table 9-1
Phototoxicity in humans.

Material	Method	Concentration	Energy	Subjects	Results	References
1,3-Dimethyl-3-phenylbutyl acetate	HRIPT	20% in petrolatum	365 nm for 15 min at a distance of approximately 15 in.	Human (20)	No phototoxicity	RIFM (1979d)

Table 9-2
Phototoxicity in animals.

Material	Method	Concentration	Energy	Subjects	Results	References
1,3-Dimethyl-3-phenylbutyl acetate	Phototoxicity	5% in petrolatum	UV-light exposure (320 nm) for 30 s at a distance of 30 cm	Guinea pigs (15)	No phototoxicity	RIFM (1984g)
1,3-Dimethyl-3-phenylbutyl acetate	Phototoxicity	5% in petrolatum	UV-light exposure (320 nm) for 30 s at a distance of 30 cm	Guinea pigs (10)	No phototoxicity	RIFM (1984h)
Benzylic alcohols						
Anisyl acetate (isomer unspecified)	Phototoxicity	50%, 30%, or 10% in acetone with UVA for 60 min	UVA at about 13 J/cm^2 for 60 minutes	Guinea pigs (5)	No phototoxicity	RIFM (1993)
Benzyl acetate	Phototoxicity (performed under CTFA guidelines)	10% or 3% in EtOH ± 2% DMSO	UV light at 320–400 nm 1×10^4 ergs/cm^2/s and 20 J/cm^2	Guinea pigs (10)	Slight (4/10) at 10%, clear by 48 h No reactions at 3%	RIFM (1983)

Table 10-1
Photosensitization in humans.

Material	Method	Concentration	Energy	Subjects	Results	References
1,3-Dimethyl-3-phenylbutyl acetate	HRIPT	20% in petrolatum	365 nm for 15 min at a distance of approximately 15 in.	Human (20)	No photosensitization	RIFM (1979d)

Table 10-2
Photosensitization in animals.

Material	Method	Concentration	Energy	Subjects	Results	References
1,3-Dimethyl-3-phenylbutyl acetate	*In vivo* photosensitization	5% in petrolatum	UV-light exposure (320 nm) for 30 s at a distance of 30 cm	Guinea pigs (15)	No photosensitization	RIFM (1984g)

more than ethanol solutions at 48 h. Dimethylsulfoxide increased absorption at all time points (Hotchkiss et al., 1989a).

The skin of guinea pigs was exposed to 50% concentration of benzyl acetate, benzyl butyrate and phenethyl acetate for 2 h. Rhodamine B was used as the agent to measure penetration of the materials. There was noticeable absorption of benzyl butyrate into the epithelium, while benzyl acetate and phenethyl acetate had slight absorption. Benzyl acetate, benzyl butyrate and phenethyl acetate had slight absorption into the hair follicle, and no absorption into the subcutis. Benzyl acetate and benzyl butyrate were slightly absorbed into the corium while phenethyl acetate was not absorbed into the corium (Meyer, 1965).

In vitro studies in human skin showed that absorption of 2-phenoxyethyl isobutyrate was much lower than that for rodent skin in vivo. The amount absorbed was 5% of the applied dose after 72 h. Occlusion has no impact on absorption (Hotchkiss, 1998).

4.2. Oral exposure

AAASAE hydrolysis is expected to occur prior to absorption through the gastrointestinal tract as evidenced by *in vitro* experiments with structurally related benzyl esters (e.g., benzyl acetate, benzyl phenyl acetate) in simulated intestinal fluid containing pancreatin (Leegwater and van Straten, 1974). After absorption, the aryl alkyl alcohol simple acid ester derivatives undergo rapid *in vivo* hydrolysis by esterases, primarily in the liver, to their corresponding alcohols and carboxylic acids. These benzyl alcohol derivatives are the quickly oxidized to benzoic acid and conjugated with

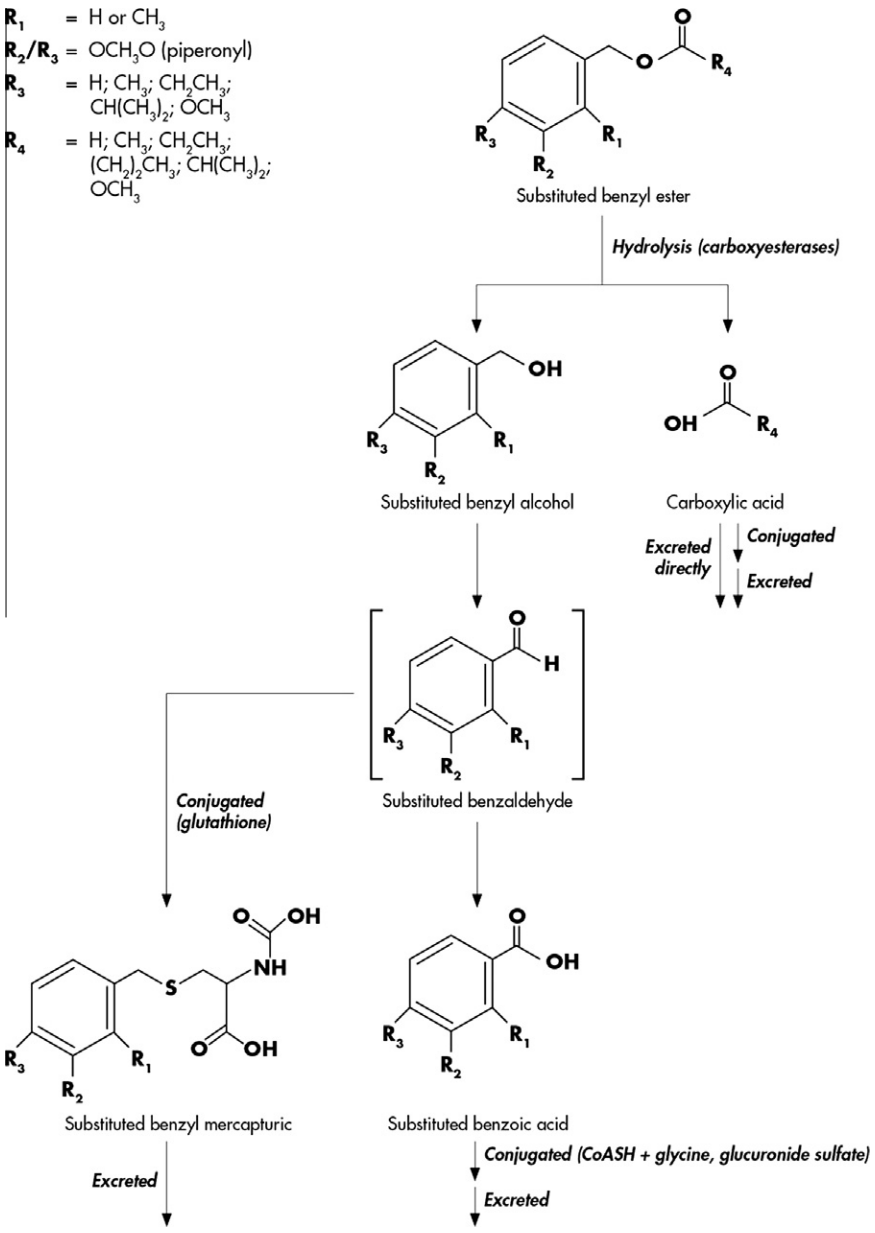


Fig. 1. Metabolism of substituted benzyl esters.

glycine and excreted as hippuric acid (Snapper et al., 1925). Aromatic ring substitution is anticipated to have little influence on the principal pathway of metabolism. Several pharmacokinetic studies after oral exposure have been performed with these ester derivatives.

Yuan et al. (1995) conducted a toxicokinetic study comparing groups of 6 F344/N rats or 12 B6C3F1 mice administered benzyl acetate in corn oil by gavage (500 or 1000 mg/kg, respectively) for 7 days, with groups of 10 rats or mice exposed to benzyl acetate in food (648 or 900 mg/kg, respectively) for 7 days. No plasma benzyl acetate or benzyl alcohol was observed. This was thought to be due to rapid hydrolysis. Peak plasma levels of benzoic acid and hippuric acid (glycine conjugate of benzoic acid) were reached within 3 h of gavage. Plasma concentrations of benzoic acid on day 7 were analyzed with a dosed feed model. The model treats a dosed feed study as a series of consecutive gavage studies with variable doses repeated at small time intervals such as 0.5 h. Animals were allowed to acclimatize to benzyl acetate feed formulation for 7 days before the blood sample collections were started. Furthermore, to avoid the possible alteration of feeding behavior by the blood sampling procedure, each animal was sampled only once. Much lower concentrations of plasma benzoic acid were found after administration by diet, 40-fold less in rats and 300-fold less in mice, than by gavage, but similar plasma levels of hippuric acid were observed. The authors concluded that benzyl acetate is rapidly hydrolyzed to benzyl alcohol, which is then rapidly oxidized to benzoic acid. The bolus gavage administration effectively saturated the benzoic acid elimination pathway via glycine conjugation to hippuric acid while the dosed feed administration did not (Yuan et al., 1995). At high doses, the formation of the glycine conjugate is limited; when glycine is depleted, free benzoic acid may sequester acetyl coenzyme A or be excreted unchanged or as the glucuronic acid conjugate.

Radiolabeled benzyl acetate in a single oral dose was given to different aged F344/N rats (5 or 500 mg/kg body weight) or C57BI/6 N mice (10 mg/kg body weight). Approximately 80% of the radioactivity was recovered in the urine for rats of all ages with the major urinary metabolite being hippuric acid and minor

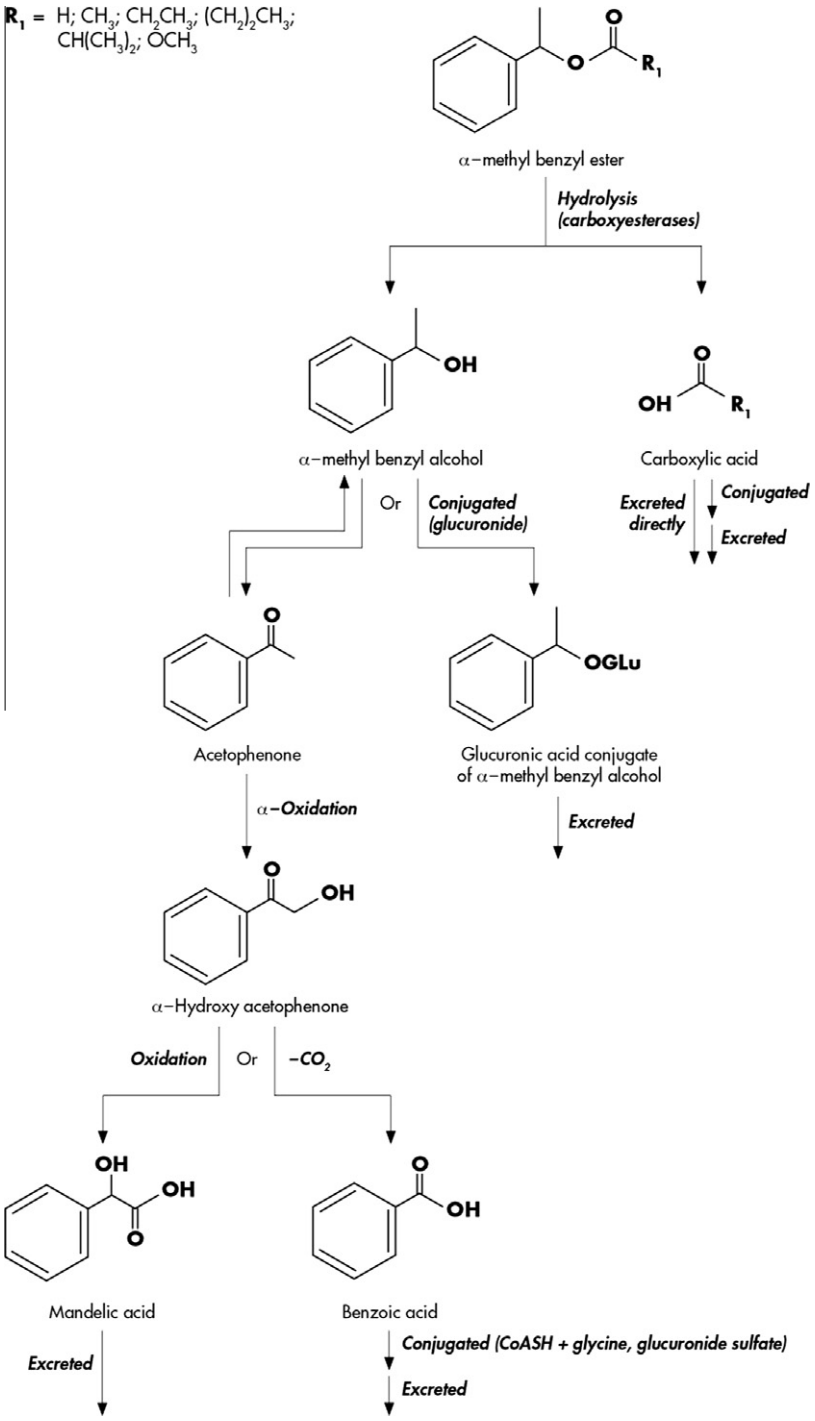


Fig. 2. Metabolism of substituted alpha-methyl benzyl esters.

metabolite as benzyl-mercapturic acid. Rats of all ages eliminated approximately 83% of the dose in the urine and feces in 4 days with the major urinary metabolite being hippuric acid and minor metabolite being benzyl mercapturic acid. Older rats eliminated slightly less in the feces. Mice eliminated more than 98% of the dose in 2 h, 93–95% of it as hippuric acid in the urine. The formation of hippuric acid was not affected by age, but aging did affect the minor routes of metabolism and excretion (McMahon et al., 1989a,b).

Radiolabeled benzyl acetate in was administered by gavage to F344 rats at doses of 5, 250, or 500 mg/kg bodyweight ($n = 3$). Within 24 h, 70–89% of the dose was excreted in the urine and 4% was detected in the feces after 72 h. No further elimination of radiolabeled benzyl acetate and its metabolites was measured after 3 days and negligible residues were found in tissues. Unconjugated benzoic acid was the major plasma metabolite at 500 mg/kg bodyweight and hippuric acid (the glycine conjugate of benzoic acid) predominated in plasma at 5 mg/kg. Hippuric acid was the major urinary metabolite. With increasing dose, the portion of the glucuronic acid conjugate of benzoic acid increased, interpreted by the authors as a limited capacity for glycine conjugation (Chidgey and Caldwell, 1986).

Radiolabeled benzyl acetate was administered by gavage to 50 male rats at 5–500 mg/kg bodyweight and 50 male mice at

10–1000 mg/kg bodyweight for five days per week for a period of two weeks. Urine and feces were collected for 24 h after dosing; carbon dioxide was collected at 2, 4, 5, and 24 h after each dose; and blood, liver, muscle, adipose, skin, lung, kidney, and stomach were collected in order to determine the pattern of metabolites in respective tissues. Benzyl acetate was rapidly absorbed through the gastrointestinal tract and within 24 h, approximately 90% of the total dose was recovered as hippuric acid in the urine and 0.3–1.3% was recovered as hippuric acid in the feces. No radioactivity was detected in any tissue after 24 hours. Repeat dosing did not affect the clearance of benzyl acetate. Approximately 71% of the total dose was recovered in the urine and feces when 5 mg/kg was administered; when 500 mg/kg was administered approximately 92% was recovered (Abdo et al., 1985).

The metabolism of 4-methylbenzyl acetate is presumed to be hydrolyzed to the carbinol and acetic acid as the first step. After oral administration of methylbenzyl acetate to rabbits, 28% of the dose was oxidized to benzoic acid and excreted as hippuric acid, while 50% was recovered as the glucuronic acid conjugate (El Masry et al., 1956; Williams, 1959). There was some evidence of oxidation and demethylation, as mandelic and hippuric acids were found in the urine.

1-Methyl benzyl alcohol (the aryl alkyl secondary alcohol metabolite of 1-methyl benzyl acetate and propionate) was administered to rabbits by gavage at a dose of 460 mg/kg bodyweight. Approximately 50% of the dose was excreted as the glucuronic acid conjugate in the urine within 24 h; other urinary metabolites included hippuric acid (30%), and mandelic acid (1–2%). Acetophenone had the same metabolic fate (Smith et al., 1954 as cited in JECFA, 2002a). Likewise, after a single dose of 244 mg/kg 1-methyl benzyl alcohol to Chinchilla rabbits by gavage, approximately 28% of the dose was excreted in the urine as hippuric acid within 24 h (El Masry et al., 1956 as cited in JECFA, 2002a). When dogs were given a single oral dose of 500 mg/kg 1-methyl benzyl ketone, approximately 35 and 20% of the glucuronic conjugate and hippuric acid were excreted in the urine and the remainder was excreted unchanged (Quick, 1928 as cited in JECFA, 2002a). When interchanged to the acetophenone from the alcohol, acetophenone undergoes *omega*-oxidation and subsequent stereo selective reduction of the ketone and oxidation of the terminal alcohol to yield mandelic acid or simple oxidation of the terminal alcohol to yield the corresponding ketoacid which can then undergo oxidative decarboxylation to yield benzoic acid that is excreted as hippuric acid (JECFA, 2002a).

4.3. Respiratory exposure

Very little information was available regarding toxicokinetics following inhalation exposures. Benzyl acetate is absorbed through the lungs of rats (Silver, 1992; RIFM, 1997a) and mice (RIFM, 1977a; Buchbauer et al., 1993) following inhalation. Phenethyl propionate, as part of a mixture with eugenol in a ratio of 7:3, is absorbed through the lungs of rats (Beroza et al., 1975) following inhalation. Phenethyl acetate is absorbed through the lungs of mice (Buchbauer et al., 1993) following inhalation. Some of these materials have relatively low vapor pressure and are quite volatile.

4.4. Other routes of exposure

Male F344/N rats and male B6C3F1 mice were treated intravenously with radioactive benzyl acetate at 5 and 10 mg/kg, respectively. Elimination of benzyl acetate as carbon dioxide or volatile substances was minimal and analysis of tissues of animals sacrificed 24 h after administration showed no radioactivity indicating that elimination was complete by this time (Abdo et al., 1985).

After a single subcutaneous dose of 500–1400 mg/kg 2-methyl benzyl ketone to rabbits, the major urinary metabolites were still the glucuronic acid conjugate (35%) and hippuric acid (24%) (Thierfelder and Daiber, 1923 as cited in JECFA, 2002a).

5. Toxicological studies

5.1. Acute toxicity

Acute dermal toxicity studies are available for 32 AAASAE fragrance ingredients Table 2-2). Dermal LD_{50} values exceeded 5000 mg/kg bodyweight for 29 of these materials. At the highest doses tested, 1,3-dimethylphenylbutyl acetate and 1,1-dimethyl-2-phenylethyl formate had LD_{50} values above 2000 mg/kg; 1,1-dimethyl-2-phenylethyl acetate had an LD_{50} value above 3000 mg/kg; benzyl formate had an LD_{50} value of 2000 mg/kg.

Oral LD_{50} values have been tested for thirty-five of the simple acid ester derivatives used in fragrances (Table 2-2). The majority of LD_{50} values ranged from 2000 to 5000 mg/kg; seven materials had reported LD_{50} values which exceeded 5000 mg/kg. Anisyl formate, benzyl butyrate and *p*-isopropylbenzyl acetate had LD_{50} values ranging from 1500 mg/kg, the lowest LD_{50} reported for these esters, to 1900 mg/kg.

Acute inhalation toxicology studies were available for 3 of the AAASAE derivatives. Ten SD rats were kept in an inhalation chamber and exposed for 1 h to aerosolized undiluted test material (a 7:3 mixture of phenethyl propionate:eugenol). Investigators calculated the dose to be 5 mg/L, and observed no effects on the rats (Beroza et al., 1975). An acute inhalation toxicity study was performed with benzyl acetate. Rats were exposed for 4 h to a vapor of benzyl acetate at 0.766 mg/L. This was the maximum attainable concentration of vapor at ambient temperature. Under the conditions of this study the LC_{Lo} for benzyl acetate as vapor is in excess of 0.766 mg/L (RIFM, 1997a). Five rats/sex/group were exposed nose-only for 4 h to benzyl 2-hydroxypropionate. The target concentration was 5000 mg/m_3, or the highest vapor concentration obtainable using a compressed air nebulizer. Investigators observed irregular breathing patterns and wet nares and fur. On gross necropsy, 2 females were found to have rusty-brown colored lungs. LC_{50} was >2420 mg/m^3 (Clary et al., 1998).

5.2. Repeat-dose studies

Benzyl acetate was identified as the material with the most AAASAE repeat dose data. A summary of the repeat dose oral and dermal studies can be found in Tables 3-1 and 3-2.

5.2.1. Oral studies

The National Toxicology Program (NTP) investigated the toxicology and carcinogenicity of benzyl acetate administered in corn oil by gavage to F344/N rats and B6C3F1 mice in 14-day, 13-week, and 2-year studies (NTP, 1986); however, because of the confounding effect of corn oil on the incidence of pancreatic acinar cell adenomas in rats and because of questions about the use of the gavage route of administration, NTP repeated the 13-week and 2-year studies with this chemical in these two rodent species using a dietary route of administration instead (NTP, 1993). Observations included in these NTP studies were survival, body weight, clinical signs, food intake, hematology, clinical chemistry, necropsy, histopathology and pancreatic enzyme assay.

5.2.1.1. 14-Day. Groups of B63F/N mice (n = 10) were dosed with 0, 125, 250, 1000, or 2000 mg/kg/day benzyl acetate in corn oil for 14 days. All mice receiving the high dose had died by day three of the study. In the 2000 mg/kg/day group, roughening of the mucosa of the stomach in the cardiac region was reported for 2/5

males and all of the females, and 1/5 females in the 1000 mg/kg/day group (NTP, 1986).

5.2.1.2. 28-Day. Groups of male F344 rats were fed diets containing 0, 2000, 3500, or 5000 mg/kg bodyweight/day (0, 20,000, 35,000, or 50,000 ppm) benzyl acetate for 28 days. Another group of rats fed 5000 mg/kg bodyweight/day benzyl acetate had their diet supplemented with 2700 mg/kg/bodyweight/day glycine to determine if glycine depletion contributed to the toxicity induced in an earlier study by large doses (3000–4000 mg/kg) of benzyl acetate. Observations included mortality, body weight, clinical signs, and gross and microscopic pathology. The addition of glycine to the diet reduced mortality in the high dose group from 100% to 10% and alleviated the dose-related bodyweight loss and neurobehavioral signs (ataxia or convulsions). The authors concluded that providing adequate levels of glycine protected the rats against the toxicity of benzyl acetate which is normally detoxified by conjugation with glycine (Abdo and Wenk, 1995).

5.2.1.3. 13-Week. Groups of 10 F344/N rats of each sex received 0, 62.5, 125, 250, 500, or 1000 mg/kg/day benzyl acetate in corn oil by gavage 5 days a week for 13 weeks (NTP, 1986). The 1000 mg/kg/day groups of females and males and 500 mg/kg/day females showed ataxia, trembling and slow reactions. Males in the 1000 mg/kg/day group showed a 21% depression in mean body weight. The NOAEL for this study was 500 mg/kg/day for males based on decreased body weight and neurological endpoints and 250 mg/kg/day for females based on neurological endpoints (NTP, 1986).

In the subsequent study, groups of 10 F344/N rats of each sex were fed diets containing 0, 230, 460, 900, 1750 or 3900 mg/kg bodyweight/day for males and 0, 240, 480, 930, 1870, or 4500 mg/kg for females benzyl acetate for 13-weeks (NTP, 1993). The mean body weight and body weight gain were decreased for the 1750 and 3900 mg/kg/day males and 4500 mg/kg/day females. The major clinical findings were tremors and ataxia in the high dosed male rats. Chemical-related lesions occurred in the brain, kidney, tongue, and skeletal muscles of the thigh in the high dose groups. Significant chemical-related findings included decreases in plasma cholesterol levels and an increase in volume, surface, and numerical densities of hepatic peroxisomes in female rats. This effect was observed in the 1000 mg/kg/day group of rats receiving benzyl acetate by gavage in the previous gavage study (NTP, 1986). The brain was the organ the most affected and showed hippocampal necrosis with a higher incidence and greater severity in males than in females, at the highest dose. The NOAEL for this study was 900 mg/kg/day based on decreased bodyweight gain in the males and females at the next highest dose (NTP, 1993).

Groups of ten B6C3F1 mice of each sex were fed diets containing 0, 425, 1000, 2000, 3700 or 7900 mg/kg/day for males and 0, 650, 1280, 2980, 4300, or 9400 mg/kg/day for females of benzyl acetate for 13-weeks (NTP, 1993). Mean body weight gains and final mean bodyweights of all exposed male and female mice were significantly lower than controls; mean bodyweight gains decreased with increased in exposure level. Feed consumption by 425 mg/kg/day males and all exposed females was significantly lower than the controls. Necrosis of the brain occurred in the highest dose mice. The major clinical findings were tremors in female mice dosed in the feed at 2980, 4300, or 9400 mg/kg/day; these findings occurred in the rats and mice given benzyl acetate or benzyl alcohol by gavage (NTP, 1986). A NOAEL was not observed in this study; the LOAEL for this study is 425 mg/kg/day for males and 650 g/kg/day for females based on decreased bodyweight and feed consumption.

Groups of twelve rats of each sex were maintained on a diet containing a mixture of six esters, including benzyl butyrate, at an average daily intake of 0 or 126 mg/kg bodyweight/day. Observations included survival, behavior, body weight, appearance, food intake, efficiency of food utilization, urinalysis, blood hemoglobin levels, necropsy and liver and kidney weights. The treated group exhibited normal body weight gain, food consumption, efficiency of food utilization, appearance and behavior. Hematology and urine measures showed no significant changes. Liver and kidney weights were normal (RIFM, 1957).

Groups of 15 rats of each sex received *alpha*-methyl benzyl acetate by gavage 7 days per week for 13-weeks at doses of 0, 15, 50 or 150 mg/kg bodyweight/day (Gaunt et al., 1974). Body weight, food consumption, hematology, urine parameters, and organ weights were measured and tissues were collected for histological examination. Mean intake of male rats given 150 mg/kg/day were slightly but significantly elevated. There were no dose-related effects in the result of the hematology examinations. The relative liver and kidney weights were increased in male rats given 50 or 150 mg/kg/day, and there were increased cells in the urine at the higher dose. No histopathological alterations were observed; hence the NOAEL was 15 mg/kg/day based on increased liver and kidney weights (Gaunt et al., 1974).

In a subchronic exposure to 73 mg/kg/day phenethyl acetate (20% of the LD_{50} reported in this study) to rats ($n = 12$) for 4 months, several blood enzyme levels and activities were measured. An increase in blood serum levels and activity of alanine aminotransferase were observed along with decreased serum cholinesterase activity and serum protein levels (Zaitsev and Rakhmanina, 1974).

5.2.1.4. 2-Year. Dietary levels of 0, 1000, 1750, or 2500 mg/kg bodyweight/day benzyl acetate were fed to groups of male F344/N rats for 103 weeks (Abdo et al., 1998; NTP, 1986). Survival, body weight, clinical signs, food intake, hematological parameters, clinical chemistry parameters and pancreatic enzyme activity were measured, and necropsy (gross and microscopic) was performed. Neuronal necrosis was seen in groups receiving 1750 and 2500 mg/kg/day. When the 2500 mg/kg/day group was fed supplemental glycine, mortality and signs of toxicity were significantly reduced (Abdo et al., 1998). The NOAEL for the study was 1000 mg/kg/day based on neurological endpoints (Abdo et al., 1998; NTP, 1986).

Groups of 60 male and female F344/N rats were fed diets resulting in an average daily consumption level of 0, 130, 260, 510 mg/kg/day (males) and 0, 145, 290, 575 mg/kg/day (females) for 2 years (NTP, 1993). Observations included survival, body weight, clinical signs, food intake, hematology, clinical chemistry, necropsy, histopathology and pancreatic enzyme assay. High dose males and all exposed females had lower mean body weights than controls. No biologically significant changes in hematology or clinical chemistry parameters were found that could be attributed to benzyl acetate administration. There were no increased incidences of neoplasms or non-neoplastic lesions in male or female rats. The NOAEL for males was 260 mg/kg/day based on lower body weight at higher doses; the NOAEL was not identified for females and would be at a level less than 145/mg/kg/day based on decreased body weights (NTP, 1993).

Groups of 60 male and female B6C3F1 mice were fed benzyl acetate in the diet at concentrations of 0, 35, 110, or 345 mg/kg/day for males and 0, 40, 130, or 375 for females (NTP, 1993). Observations included survival, body weight, clinical signs, food intake, hematology, clinical chemistry, necropsy, histopathology and pancreatic enzyme assay. The high dose female mice showed a statistically significant increase in survival. In the 2 year NTP study (1993) with mice, benzyl acetate administration in the food of female and male mice was associated with a dose related increase in the incidence or severity of non-neoplastic nasal lesions (i.e.,

mucosal atrophy and degeneration, cystic hyperplasia of the submucosal gland, and luminal exudates and pigmentation of the mucosal epithelium). NTP (1993) stated that although the nose was not the deposition site for benzyl acetate, nasal tissue could have been exposed directly to high concentrations of the chemical or its degradation products. The results of chemical recovery studies showed that approximately 10% of the benzyl acetate in the feed was lost during storage and that with the relatively high vapor pressure of benzyl acetate (5 mm Hg at 73 °C) and the housing of mice in polycarbonate cages with polyester cage filters, benzyl acetate vapors were likely to have concentrated in the cage air. The incidence of hepatocellular adenomas and carcinomas as well as forestomach squamous cell papillomas and carcinomas is discussed below in the carcinogenicity section. There were no biologically significant changes in hematology or clinical chemistry parameters. The NOAEL for this study was 345 and 375 mg/kg/day; no LOAEL was identified (NTP, 1993).

5.2.2. Dermal studies

5.2.2.1. 2-Week. Sprague–Dawley rats were dosed for two weeks with 0, 66, 190, 700 or 1000 mg/kg/day 2-phenoxyethyl isobutryate. Observations included mortality, clinical signs and skin reactions, food and water intake and body weight. Urinalysis, hematology, clinical chemistry screening, necropsy and histology were performed. Irritation at the test site was observed at all dose levels over 0 mg/kg body weight/day. This reaction was evident as erythema and desquamation at slightly greater severity than seen in the diethyl phthalate control group. Epidermal thickening, hyperkeratosis and or localized parkeratosis were evident histologically. The LOAEL was 66 mg/kg bw/day (RIFM, 1994a).

5.2.2.2. 13-Week. A dermal 13-week study was conducted in groups of 12 Sprague–Dawley rats of each sex (Api and Ford, 1993; Api, 2004; RIFM, 1990c). The rats were dosed daily with 0, 100, 300, or 1000 mg/kg/day 2-phenoxyisobutyrate under occlusion for 6 h per day at a constant volume of 2 mL/kg. During week 13, urine and blood samples were collected for urinalysis, hematology, and clinical chemistry screens. No adverse effects were seen at any dose level. The NOAEL was 1000 mg/kg/day.

5.2.3. Inhalation studies

Inhalation of 1.3 mg/L of benzyl acetate by mice for 7–13 h resulted in irritation of the respiratory passages (RIFM, 1977a) as determined by measurement of respiratory rate using a whole body plethysmograph. Further acute inhalation experiments determined that exposure to 189 or 324 μg/L of benzyl acetate resulted in a minimal respiratory rate depression that disappeared immediately after the exposure period. Inhalation of 722 μg/L of benzyl alcohol resulted in a mild effect measured by a 27% decrease in breathing rate within the first 20 seconds of exposure that returned to 90% of normal for the rest of the experiment (RIFM, 1977a).

In the 2 year NTP study (1993) with mice, benzyl acetate administration in the food of female and male mice was associated with a dose related increase in the incidence or severity of non-neoplastic nasal lesions (i.e., mucosal atrophy and degeneration, cystic hyperplasia of the submucosal gland, and luminal exudates and pigmentation of the mucosal epithelium). NTP (1993) stated that although the nose was not the deposition site for benzyl acetate, nasal tissue could have been exposed directly to high concentrations of the chemical or its degradation products. The results of chemical recovery studies showed that approximately 10% of the benzyl acetate in the feed was lost during storage and that with the relatively high vapor pressure of benzyl acetate (5 mm Hg at 73 °C) and the housing of mice in polycarbonate cages with polyester cage filters, benzyl acetate vapors were likely to have concentrated in the cage air.

6. Genotoxicity

Studies evaluating genotoxicity have been performed with eleven of the aryl alkyl alcohol simple acid esters; again benzyl acetate has the most robust set of experiments. The results of these tests are summarized in Tables 4-1, 4-2 and 4-3.

6.1. Bacterial studies

Eleven AAASAE fragrance ingredients have been studied in bacterial systems using the Ames test with *Salmonella typhimurium* (Ames et al., 1975), the rec assay with *Bacillus subtilis*, or SOS repair or DNA damage activity tests with *Escherichia coli*, 1,1-dimethyl-2-phenylethyl butyrate; 1,1-dimethyl-2-phenylethyl formate; phenethyl acetate; phenethyl formate; 2-phenoxyethyl isobutyrate; *p*-anisyl acetate; benzyl acetate and piperonyl acetate were inactive in Salmonella typhimuruium including strains TA98, TA100, TA102, TA1535, TA1537, or TA1538 (see details of studies in Table 4-1). The assays were performed with these derivatives with a concentration range up to cytotoxic concentrations, both in the presence and absence of metabolic activation (S9 fraction) obtained from livers of Arochlor- or methylcholanthrene-induced rats or hamsters. Benzylic alcohol esters including benzyl acetate, benzyl formate and benzyl propionate tested with Bacillus subtilis negative results with the H17 rec+ assay and benzyl acetate and benzyl formate gave positive results with the M45 rec- assay. Benzyl acetate gave positive results in a single microscreen assay with *Escherichia coli*.

6.2. Studies on mammalian cells

Studies in mammalian cell systems showed negative genotoxic results for the only AAASAE tested, benzyl acetate (Table 4-2). Benzyl acetate at concentrations ranging from 0.05 to 5 mg/mL [50–5000 μg/mL] did not induce chromosome aberrations or sister chromatid exchange in Chinese hamster ovary cells or lung fibroblast cells with or without metabolic activation (S9 fraction). Benzyl acetate produced four negative responses, two positive responses and one equivocal response in the L5178Y ± TK mouse lymphoma cell mutation assay system without metabolic activation. Conversely, benzyl acetate produced two positive, two negative and one equivocal response with metabolic activation in this system. Forward mutation assays with benzyl acetate and Human TK6 lymphoblast cells followed the trend, with a negative response without activation and positive response with activation. Micronucleus test results with benzyl acetate were negative with both human lymphocytes with and without activation and human HepG2 liver cells.

6.3. Mouse and rat studies

2-Phenoxyethyl isobutyrate, benzyl acetate and piperonyl acetate were (Table 4-3) the only AAASAEs that have been tested for *in vivo* genotoxic potential.

No evidence of genotoxic/mutagenic activity in the micronucleus assay was reported after measuring polychromatic and normochromatic erythrocytes extracted from the bone marrow of NMRI treated with a single intraperitoneal injection of 2-phenoxyethyl isobutyrate (625, 1250 or 1875 mg/kg) or piperonyl acetate (388, 680, or 970 mg/kg); negative results were also reported with the bone marrow of BC63F1 mice treated with a single or 3-day intraperitoneal injection of benzyl acetate ranging from 312 to 1250 mg/kg. Likewise, peripheral blood from BC63F1 mice

consuming a diet ranging from 470 to 7500 mg/kg bodyweight/day showed no evidence of genotoxic/mutagenic activity in the micronucleus assay. The bone marrow of BC63F1 mice treated with an intraperitoneal dose of benzyl acetate had negative results for both sister chromatid exchange and chromosomal aberrations.

Unscheduled DNA synthesis in hepatocytes from Fischer 344 rats receiving a single dose of benzyl acetate by gavage at 50, 200, or 500 mg/kg did not change; the replicative DNA synthesis of hepatocytes from BC63F1 mice receiving 800 or 1600 mg/kg benzyl acetate was negative at 24-h and positive effects at 39- and -hours after dosing. Both the alkaline elution assay and unscheduled DNA synthesis assay of pancreatic cells from Fischer 344 rats receiving either intraperitoneal injection or gavage treatment did not change with treatment. The comet assay of the stomach, colon, kidney, bladder and brain was positive for both rats and mice receiving 1200 or 1600 mg/kg orally and the liver and bone marrow showed negative results.

7. Carcinogenicity

7.1. Carcinogenesis bioassays

Carcinogenicity and tumor promotion studies are summarized in Table 5-1.

The carcinogenicity of benzyl acetate in corn oil administered by gavage to F344/N rats and B6C3F1 mice was investigated in 2 year studies (NTP, 1986). However, because of the confounding effect of corn oil on the incidence of pancreatic acinar cell adenomas in rats and because of questions about the use of the gavage route of administration, NTP repeated the 2-year bioassays with benzyl acetate in these two rodent species using the dietary route of exposure (NTP, 1993). In both studies, observations included survival, body weight, clinical signs, food intake, hematology, clinical chemistry, necropsy, histopathology and pancreatic enzyme assay.

There was "*no evidence of carcinogenic activity* of benzyl acetate in male or female mice." The NTP concluded that "the differences in response were due to the different methods of administrations and the resulting metabolites" (see discussion above in toxicokinetic section.).

Doses used in the NTP (1993) 2-year feed studies for rats were 0, 130, 260, or 510 mg/kg/day in males and 0, 145, 290, or 575 mg/kg/day for females. NTP concluded that "no increased incidences of neoplasms or non-neoplastic lesions could be associated with benzyl acetate administration in the feed of in male or female rats.

In the earlier (1986) study, male rats administered benzyl acetate in corn oil by gavage at doses of 250 or 500 mg/kg had significantly increased incidences of exocrine pancreatic acinar cell adenoma and hyperplasia; however this effect did not occur in females" (Abdo et al., 1985; NTP, 1986). These contrasting results were probably due to the use of corn oil as a vehicle in the earlier study. The administration of high levels of fat to experimental animals has been shown to enhance the development of spontaneous and chemical-induced neoplasms. Other studies suggest that the use of a corn oil vehicle may have been a contributing factor in the increased incidences of pancreatic adenomas in benzyl acetate doses in male rats. A review of data from several NTP studies indicated the incidences of pancreatic hyperplasia and adenomas in corn oil vehicle control rats were significantly higher than those occurring in untreated controls (Haseman et al., 1984). Longnecker et al. (1986) observed that corn oil given by gavage or in the diet in the presence or absence of benzyl acetate to azaserine-treated Lewis rats enhanced development (number and size) of pancreatic acinar cell foci. The increased incidence of hepatocellular neoplasms and squamous cell neoplasms of the forestomach serving as evidence for the NTP (1986) regarding carcinogenicity was revoked. NTP (1993) concluded that "under the conditions of these 2-year feed studies there was *no evidence of carcinogenic activity* of benzyl acetate in male or female rats; however, rats may have tolerated higher doses."

Doses used in the NTP (1993) 2-year feed studies for mice were 0, 35, 110, or 345 mg/kg/day for males and 0, 40, 130, or 375 for females. Benzyl acetate administration in the feed of female and male mice was associated with increased incidences of nasal lesions, which consisted of atrophy and degeneration of the nasal epithelium and luminal exudates and pigmentation of the nasal mucosal epithelium. NTP (1993) stated that although the nose was not the deposition site for benzyl acetate, nasal tissue could have been exposed directly to high concentrations of the chemical or it's degradation products. The results of chemical recovery studies showed that approximately 10% of the benzyl acetate in the feed was lost during storage and that with the relatively high vapor pressure of benzyl acetate (5 mm Hg at 73 °C) and the housing of mice in polycarbonate cages with polyester cage filters, a build in benzyl acetate concentration was likely to have occurred in the cage air. NTP concluded that "administration of benzyl acetate in the feed for 2 years did not increase the incidence of neoplasms in male or female mice" (NTP, 1986).

Administration of benzyl acetate (1000 mg/kg) in corn oil by gavage for 2 years significantly increased the incidences of hepatocellular adenomas and marginally increased the incidences of squamous cell neoplasms of the forestomach in male and female mice. This effect did not occur at the lowest dose (500 mg/kg) used in the gavage study. These contrasting results might be due in part simply to differences in the size of the administered dose. In the gavage studies, the animals were temporarily exposed to large concentrations of benzyl acetate, whereas animals in the feed studies received their daily dose over 24 h. In addition, in a toxicokinetic study conducted at NEIHS by Yuan et al. (1995) it was reported that after gavage administration of benzyl acetate corn oil at 500 mg/kg (rats) and 1000 (mice), high benzoic acid plasma concentrations were observed. In contrast much lower benzoic acid plasma concentrations were found after dosed feed administration at about 615 mg/kg/day for rats and about 850 mg/kg/day for mice. Although the daily doses of benzyl acetate were comparable, bolus gavage administration effectively saturated the benzoic acid elimination pathway while dosed feed administration did not. The pharmacokinetic studies demonstrated that blood levels of the major metabolite of benzyl acetate, benzoic acid, were up to 300 times greater after gavage administration than after administration in the feed.

In a 4-month study, no pancreatic tumor effects were reported in male F344 or Lewis rats administered 500 mg/kg/day benzyl acetate by gavage or fed 0.9% in the diet (approximately 450 mg/kg/day) (Longnecker et al., 1986).

7.2. Tumor initiation and promotion studies

Benzyl acetate has been evaluated for its potential to promote pancreatic carcinogenesis in the male F344 rats. Rats were treated twice with 30 mg/kg of azaserine, a pancreatic carcinogen, at 16 and 23 days of age, then fed benzyl acetate approximately 400 mg/kg bodyweight/day for a period of 6 months (experiment 1) or one year (experiment 2) along with a control group fed benzyl acetate without the preliminary azaserine treatment (experiment 3). Body weight and food consumption were measured, necropsy performed, and pancreas weight and presence of acinar foci recorded. In experiment 1, in benzyl acetate-fed rats, the pancreas had fewer lesions per cm^3; however, the mean diameter and the volume percentage foci were significantly greater than in controls. The animals treated in experiment 2 did not survive treatment as a

result of azaserine-induced nephrotoxicity. In experiment 3, animals given benzyl acetate had a marginal statistically significant increase in the incidence of pancreatic carcinoma *in situ*. The authors concluded that benzyl acetate was a weak promoter, but not an initiator of pancreatic carcinogenesis in the rat (Longnecker et al., 1990).

Intraperitoneal injection of 50 mg/kg or 250 mg/kg 2-phenethyl acetate in tricaprylin was administered to groups of A/He female mice ($n = 20$ per group) three times weekly for 8 weeks (total dose of 1200 or 6000 mg/kg). Observations included survival, body weight, and gross and microscopic examination for abnormalities at necropsy. One mouse at the lower dose, and none at the higher dose, had a lung tumor. This frequency was significantly lower than that of the tricaprylin vehicle alone (Stoner et al., 1973).

8. Reproductive toxicity

In a developmental toxicity study based on OECD guidelines, benzyl acetate in olive oil was administered to pregnant rats by gavage daily from the 6th day of gestation (GD6) to GD15 (see Table 5-2). Doses of 10, 100, 500, or 1000 mg/kg bodyweight/day were administered to 6 or 7 rat dams per dose. Maternal observations included body weight, food intake, survival and reproductive parameters; fetal observations included viability, sex, body weight, and morphological parameters. No statistically significant changes in maternal body weight or food consumption were reported. At term, dams were sacrificed and examined to ascertain intrauterine death, external, internal and skeletal malformations of the fetuses. There were no remarkable differences among the groups in the values for the number of corpora lutea, implantation sites, viable fetuses, resorptions, sex ratio and body weight of live fetuses. Morphological findings in fetuses of dams administered 1000 mg/kg/day included significant decreases in the body weight increases in number of fetuses with internal and skeletal variations, internal malformations (e.g., dilation of the renal pelvis) and skeletal malformations (e.g., wavy ribs, vertebra body shape) and decreased degree of ossification in the vertebrae and sternebrea. The male fetuses from the 10 mg/kg and 100 mg/kg groups weighed slightly more than fetuses from the control group. The difference was not statistical. The high dose (1000 mg/kg) resulted in no effects on pregnant rats (maternal NOAEL), but reduced growth in the fetuses (fetal NOAEL 500 mg/kg day) and was associated with fetal abnormalities (Ishiguro et al., 1993).

The RIFM Expert Panel and the Reproductive Adjunct Group of the RIFM Expert Panel reviewed the Ishiguro et al. (1993) results and concluded that the minor fetal anomalies observed at the highest dose level were most likely developmental delay. An increased fetal body weight may indicate an adverse effect. For example, chemicals which induce maternal diabetes mellitus may increase fetal weight. Early embryocidal effects leading to a reduced litter size may secondarily increase fetal weight. The Panel members and the Reproductive Adjunct Group concluded that the increased fetal body weight observed in the 100 and 10 mg/kg groups was biologically insignificant and that no additional reproductive or developmental toxicity studies are needed. They concluded that the maternal NOAEL was 500 mg/kg based on weight gain and the fetal NOAEL is 100 based on weight and internal organ malformations.

As part of the NTP testing program, sperm morphology and vaginal cytology examinations were conducted on male and female rats and mice from the benzyl acetate 13-week study (NTP, 1993). Benzyl acetate in the diet of rats had no effect on epididymis weight, caudal epididymis weight, testis weight, sperm motility, sperm density, percent of abnormal sperm or vaginal cytology. In mice, benzyl acetate in the feed had no effect on any of the parameters measured; however, the mean length of the estrous cycle of mice at the high dose (9400 mg/kg/day) was significantly greater than that of the control group; however, this effect was associated with a significant decrease in body weight (Gaworski et al., 1998; NTP, 1993).

9. Irritation

9.1. Human studies

Thirty-one AAASAE fragrances have been evaluated for skin irritation in approximately 2320 male and female volunteers (Table 6-1). Six materials had at least one study that reported mild skin irritation in at least one volunteer. Benzyl acetate in several different vehicles (i.e., acetone, ethanol, ethanol: diethyl phalate, petrolatum, non-irritant cream base and soap) was tested on 1133 subjects in 20 studies with concentrations raging from 0.12% to 18.7%. Twelve of these studies produced no irritation in the subjects tested and eight of the studies produced mild to no irritation among a small number of subjects. Other compounds which produced equivocal results were 1,1-dimethyl-2-phenylethyl acetate; phenethyl acetate; 3-phenyl-3-buten-1-yl acetate; benzyl butyrate; benzyl formate; 4-methylbenzyl propionate; and α-methylbenzyl propionate producing reactions ranging from mild to no irritation in a small number of subjects. The overwhelming lack of irritation for these materials and the few equivocal results indicate that this group of compounds does not produce skin irritation in humans.

9.2. Animals studies

9.2.1. Skin irritation

Irritation reactions for 31 AAASAE fragrances were tested on guinea pigs, rabbits, rats and miniature swine with a range of reactions from severe to none (Table 6-2). Irritation studies on animals included observations from acute dermal toxicity tests, primary irritation tests and preliminary irritation tests to find the dose range for maximization tests with guinea pigs.

Seven materials were tested on guinea pigs for primary irritation or for irritation prior to a maximization test or a Buehler test. 1,3-Dimethyl-3-phenyl butyl acetate and anisyl acetate produced no irritation reactions in separate studies.

1,1-Dimethyl-2-phenylethyl formate produced both moderate irritation and no irritation and benzyl acetate produced both slight irritation and no irritation in separate studies. Carbonic acid, methyl phenylmethyl ester also produced slight irritation when applied to guinea pigs. Benzyl formate produced no irritation at a concentration of 20%, and slight irritation at a concentration of 0.25%. 3-Phenyl-3-buten-1-yl acetate produced slight patchy erythema at 2.4% and at 0.6%.

2-Phenoxy isobutyrate in diethyl phthalate was applied to rats at concentrations of 66, 190, 700, 1000 mg/kg/day for 2 weeks and slight to severe irritation was observed at all dose levels.

Of this ester group, benzyl acetate was applied dermally in 18 studies ranging in concentrations of 1.25% to 100% and resulted in no irritation in 16 of the 18 studies. In the study slight irritation was observed after intradermal injection.

Twelve other fragrances had studies that reported no irritation, but six of these yielded other study results that varied from slight irritation (phenethyl formate; phenethyl propionate; and benzyl formate), to moderate irritation (1,3-dimethyl-3-phenylbutyl acetate and 1,1-dimethylphenethyl formate), to severe irritation (2-phenoxyisobutyrate) resulting in equivocal results. Slight to no irritation was reported from tests on guinea pigs with benzyl acetate and benzyl formate; to moderate irritation was reported for 1,1-dimethylphenethyl formate; no irritation was reported for

anisyl acetate and 1,3-dimethyl-3-phenylbutylacetate; and slight irritation for methyl phenylmethyl carbonic acid ester.

Irritation was measured for 26 compounds as a part of an LD_{50} test on rabbits. No irritation was reported for the ester fragrances that included phenethyl formate; phenethyl isobutyrate; 2-phenoxyethyl propionate; benzyl butyrate; ethyl phenyl carbonyl acetate and α-methylbenzyl acetate. The other fragrances had varying reactions from slight to mild to moderate irritation; there were no severely irritating compounds. Primary irritation was measured with twelve compounds, and all reported slight to mild irritation except 1,1-dimethyl-2-phenylethyl formate, which yielded a slight to well-defined moderate erythema in rabbits.

9.2.2. Mucous membrane (eye) irritation in rabbits

The potential for fifteen of these compounds to induce eye irritation has been evaluated by the Draize rabbit eye irritation test (see Table 7). No irritation as well as temporary conjunctival and corneal irritation effects have been reported with benzyl acetate at concentrations ranging from 3% to 100%. Transient moderate irritation has been reported for 70% phenethyl propionate in a mixture with eugenol (7:3, respectively), transient slight to moderate irritation has been reported for both 100% benzyl formate and 100% *p*-anisyl acetate, and moderate to severe eye irritation has been reported for 2.5% phenethyl acetate, 5% piperonyl acetate and 2.5% 2,4-dimethylbenzyl acetate. 3-Phenyl-3-buten-1-yl acetate at 1% produced moderate conjunctival irritation with corneal opacity which was not clear by day 7. Equivocal reports from no irritation (at 100%) to severe irritation (at 0.125% and 1.25%) have been reported for 1,1-dimethyl-2-phenylethyl acetate.

10. Skin sensitization

10.1. Human studies

Table 8–1a lists AAASAE fragrance ingredients that have been evaluated for the potential to induce and or elicit sensitization.

10.1.1. Induction of human sensitization

Induction of dermal sensitization was measured by standard human repeat-insult patch tests and maximization tests in approximately 2175 male and female volunteers for 32 of the esters in this group (Table 8–1a). There was no evidence of sensitization with 29 compounds. Three compounds exhibited sensitization potential: 1,1-dimethylphenethyl formate (1/24 study participants), *p*-anisyl acetate (1/25 and 2/25 study participants) and benzyl acetate (1/38 study participants). The reactions observed to these materials were likely related to the adjacent testing of a known dermal sensitizer, in the same panel of individuals (RIFM, 1985e, 1971i, 1973d, 1988d). All of these compounds exhibited a lack of sensitization in comparative tests; hence this result is equivocal.

10.1.2. Elicitation of human sensitization

No elicitation studies were available for these simple acid ester derivatives.

10.1.3. Diagnostic patch-tests

Diagnostic patch-tests on patients have been reported for four of the AAASAE derivatives used as fragrances (8–1b). In a multicenter study of 48 fragrances, there was one positive reaction to diagnostic patch testing in 313 European dermatology patients with 5% of 1,1-dimethyl-2-phenylethyl acetate (Frosch et al., 1995). In a follow up study there were three positive reactions to 1,1-dimethyl-2-phenethyl acetate in 1855 patients (Frosch et al., 2002). In a series of studies of Japanese dermatitis and eczema patients, patients had a positive reaction to 5% benzyl acetate at frequencies ranging from 1.1% to 4% (Ishihara et al., 1979; Ishihara et al., 1981; Nishimura et al., 1984; Itoh et al., 1986, 1988; Haba et al., 1993). In patch tests with benzyl acetate (5% in petrolatum) 2/20 perfume sensitive patients and 3/155 patients with cosmetic dermatitis had positive reactions (Larsen, 1977; Itoh, 1982). When α-methyl benzylacetate (0.25% in oil of helianthi) was patch tested on perfume sensitive patients, 1/10 had positive reactions (Novak, 1974).

Diagnostic patch tests on individual patients have also been reported for a number of the AAASAE derivatives. The details of these studies can be found in the FMRs (McGinty et al., in press-a, in press-b, in press-c, in press-d, in press-e, in press-f, in press-g, in press-h, in press-i, in press-j, in press-k, in press-l, in press-m, in press-n, in press-o, in press-p, in press-q, in press-r, in press-s, in press-t, in press-u, in press-v, in press-w, in press-x, in press-y, in press-z, in press-aa, in press-bb, in press-cc, in press-dd, in press-ee, in press-ff, in press-gg, in press-hh, in press-ii, in press-jj, in press-kk, in press-ll, in press-mm, in press-nn).

10.2. Animal studies

AAASAE fragrance ingredients were evaluated for sensitization in guinea pigs with twelve compounds using various test methods including the Magnusson–Kligman maximization test, the Buehler delayed hypersensitivity test, the Freund complete adjuvant test, and a modified Draize test (Table 8–2a). Among the twelve compounds tested, 1,1-dimethyl-2-phenylethyl formate tested positive in 1/20 guinea pigs when the challenge dose was 100% and 0/20 when the challenge dose was 50% (RIFM, 1990d) and only one of the eight benzyl acetate studies tested positive for weak sensitization that cleared by day seven (RIFM, 1985c).

Sensitization was evaluated using the murine local lymph node assay conducted with 2-phenoxyethyl isobutyrate (Table 8–2b). Sensitization was not indicated; none of the concentrations tested (0.1, 1, 10 or 100%) resulted in a stimulation index greater than 3 (RIFM, 2002b).

11. Phototoxicity and photosensitization

Three compounds were assessed for phototoxicity, one of which was also tested for photosensitization. The studies are summarized in Tables 9-1, 9-2, 10-1 and 10-2.

11.1. Phototoxicity

11.1.1. Phototoxicity in humans

Phototoxicity was evaluated during the induction phase of an associated photosensitization study, which was part of larger repeated insult patch test study (RIFM, 1979d). A subset of 20 male and female volunteers were selected from the original group of 50 volunteers and treated simultaneously on the opposite arms with a 0.2 g sample of 20% 1,-3-dimethyl-3-phenylbutyl acetate in petrolatum. After UVA irradiation was repeated at the application site on days 1, 4, 7 and 9. No phototoxic effects were observed.

11.1.2. Phototoxicity in animals

1,3-Dimethyl-3-phenylbutyl acetate (5%) in petrolatum was applied to the backs of guinea pigs (10) every day for two weeks, followed by UVA irradiation (30 s, at a distance of 30 cm). The dosage of ray-treatment was below the threshold of erythema (320 nm). There were no skin reactions during the two weeks, and it was concluded that 1,3-dimethyl-3-phenylbutyl acetate caused no phototoxic effect in guinea pigs (RIFM, 1984h,g).

Female guinea pigs received 50, 30 or 10% anisyl acetate in acetone in a 1.5 cm^2 area. The site was irradiated with UVA (13 J/cm^2)

Table 11
Summary of UV spectra data.

Material	UV spectra Range of absorption (nm)
1,1-Dimethyl-2-phenylethyl acetate	Peaked at 209–211P Returned to baseline at 230
1,1-Dimethyl-2-phenylethyl butyrate	Peaked at 205–210 Returned to baseline at 230
1,3-Dimethyl-3-phenylbutyl acetate	Peaked at 200–210 Returned to baseline at 230
2-Methyl-4-phenyl-2-butyl acetate	Peaked at 208–211 Returned to baseline at 235
Phenethyl acetate	Peaked at 208–210 Returned to baseline at 225
Phenethyl butyrate	Peaked at 200–210 Returned to baseline at 230
Phenethyl formate	Peaked at 200–210 Returned to baseline at 220 (with minor absorption 250–260)
Phenethyl isobutyrate	Peaked at 201 and at 219 Returned to baseline at 280 (with minor absorption 250–280)
Phenethyl propionate	Peaked at 200–210 Returned to baseline at 330
2-Phenoxyethyl isobutyrate	Peaked at 200 and at 220 Returned to baseline at 250 (with minor absorption 250–280)
2-Phenoxyethyl propionate	Peaked at 210–220 Returned to baseline at 230 (with minor absorption 260–280)
3-Phenylpropyl acetate	Peaked at 250 Returned to baseline at 280
p-Anisyl acetate	Peaked at 200 and at 230 Returned to baseline at 290 (with minor absorption 270–280)
Anisyl acetate (isomer unspecified)	Peaked at 220–230 Returned to baseline at 240 (with minor absorption 270–280)
Anisyl formate	Peaked at 220–230 Returned to baseline at 240 (with minor absorption 270–280)
Benzyl acetate	Peaked at 207 Returned to baseline at 225
Benzyl butyrate	Peaked at 200–220 Returned to baseline at 230 (with minor absorption 250–260)
Benzyl formate	Peaked at 200–220 Returned to baseline at 240 (with minor absorption 250–260)
Benzyl isobutyrate	Peaked at 200–210 Returned to baseline at 230 (with minor absorption 250–260)
Benzyl propionate	Peaked at 200–220 Returned to baseline at 230 (with minor absorption 250–260)
2,4-Dimethylbenzyl acetate	Peaked at 200 and at 220 Returned to baseline at 240
p-Isopropylbenzyl acetate	Peaked at 210–220 Returned to baseline at 240 (with minor absorption 250–270)
α-Methylbenzyl acetate	Peaked at 200–210 Returned to baseline at 230 (with minor absorption 250–260)
4-Methylbenzyl acetate	Peaked at 210–220 Returned to baseline at 240 (with minor absorption 260–270)
α-Methylbenzyl propionate	Peaked at 200–210 Returned to baseline at 230 (with minor absorption 250–260)
Piperonyl acetate	Peaked at 200–210 Returned to baseline at 250 (with minor absorption 290–300)

No phototoxicity was observed at this dose under these conditions (RIFM, 1993).

Four guinea pigs received either 10 or 3% benzyl acetate in ethanol with 2% DMSO in a 2 cm^2 area. Thirty minutes after application, UVA irradiation was administered (20 J/cm^2) At the 10% dose, 4/10 guinea pigs demonstrated slight irritation, both with and without irradiation, which cleared by 48 h. Under the test conditions used, no phototoxic potential of the test material could be found (RIFM, 1983).

11.2. Photosensitization

11.2.1. Photosensitization in humans

In the challenge phase of the aforementioned repeat insult patch test, two weeks after the last induction patch, a challenge application was made to the same site as well as to a virgin site on the same arm and irradiation was repeated. Reactions to challenge were scored at 24, 48 and 72 h after patch application. No photosensitization reactions were observed (RIFM, 1979d).

11.2.2. Photosensitization in animals

In a follow up to a phototoxicity study, treated guinea pigs received a dermal application of 5% 1,3-dimethyl-3-phenyl butyl acetate in petrolatum on the back then were exposed to UVA irradiation. After a break of 21 days, the animals again received a challenge application of 5% test substance and a similar light treatment. The animals showed no skin irritation on the treated areas, nor was there an evidence of a photosensitizing effect (RIFM, 1984g).

11.3. UV spectra

UV spectra have been obtained for 26 AAASAE fragrance ingredients. Most 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, AAASAE fragrance ingredients would not be expected to elicit phototoxicity or photosensitization under the current conditions of use as a fragrance ingredient.

12. Conclusion

The AAASAE fragrance ingredients are a diverse group of structures that have similar metabolic and toxicity profiles. *In vivo* metabolic studies have shown that AAASAE fragrance ingredients are readily absorbed by the gastrointestinal tract and the lung. They also undergo percutaneous absorption. These compounds exhibit a common route of primary metabolism by carboxylesterases resulting in the formation of the simple acid and an aryl alkyl alcohol. Alcohol metabolites are either conjugated and excreted or oxidized further and then conjugated and excreted without the formation of toxic or bioaccumulative metabolites. More specifically, they undergo primary metabolism in the liver by esterases or by esterases in the skin yielding benzoic acid which is conjugated primarily with glycine, and to a lesser extent, glucuronide, depending on dose and material. Excretion is primarily in the urine as hippuric acid (the glycine conjugate of benzoic acid) with very little material detected in the feces or the expired air.

The available data indicate that there are no safety concerns regarding the use of AAASAE fragrance ingredients under the presently declared levels of exposure. Use of these fragrance ingredients at levels beyond the higher maximum dermal levels or higher systemic exposure levels requires re-evaluation by the Panel. Since all the short term and repeated dose studies revealed a low toxicity, this conclusion applies to the AAASAE group of fragrance ingredients including their metabolites. This conclusion is based on the following observations and rationale regarding both AAASAE hazard and estimated exposures:

- Benzyl acetate is absorbed through the skin, with considerable species variation. Results of *in vivo* studies in monkeys and rats showed that 17% and greater than 95% of the applied dose was absorbed, respectively when occlusion methods were similar. When occlusion was by glass chamber, absorption in monkeys rose to 79%. In *in vitro* studies, only 18% was absorbed in human skin, while 56% was absorbed in rat skin. In *in vivo* skin absorption studies in rats approximately 20% of 2-phenoxyethyl isobutyrate and 5% of methylbenzyl acetate was absorbed.
- The AAASAE have low order of acute toxicity, with dermal LD_{50} values in rabbits reported to be greater than 2000 mg/kg body weight and oral LD_{50} values generally greater than 1000 mg/kg body weight.
- No significant toxicity was observed in repeat-dose toxicity tests using doses many times greater than occur under current conditions of use as fragrances. For AAASAE fragrance ingredients tested oral NOAEL's of 260 and less than 145 mg/kg bodyweight/day for male and female rats, respectively, in a 2 year dietary study were established. This was based on reduced body weight at higher doses in males and at all doses in females. A dermal NOAEL in rats of >1000 mg/kg bodyweight/day is based on a study with 2-phenoxyisobutyrate.
- Eleven AAASAE fragrance ingredients were evaluated for genotoxicity. These materials were not mutagenic in bacterial systems, had no to equivocal *in vitro* mutagenicity and clastogenicity in mammalian cells, and had little to no *in vivo* genotoxicity. A weight of evidence evaluation of genotoxicity studies and the metabolism and detoxification of these materials indicate that they would have no genotoxic potential under the current conditions of use as fragrances.
- There was no evidence of carcinogenic activity of benzyl acetate in rats or mice administered benzyl acetate by feed (NTP, 1993). Benzyl acetate in corn oil administered by gavage did result in pancreatic carcinogenesis due to the corn oil vehicle (NTP, 1986). Due to the confounding effect of the corn oil vehicle on the incidence of pancreatic acinar cell adenomas in rats, and questions about the use of the gavage route of administration, NTP repeated the 2-year bioassays with benzyl acetate in rats and mice using the dietary route of exposure (NTP, 1993). A review of several NTP studies indicated the incidences of pancreatic hyperplasia and adenomas in corn oil vehicle control rats were significantly higher than those in untreated controls (Haseman et al., 1984). Benzyl acetate may have weak promoting potential, but is not an initiator in the rat (Longnecker et al., 1990).
- Reproductive and developmental toxicity data are limited, but the reported data on benzyl acetate show no indication of a relevant adverse effect on reproductive function. NOELs for maternal and developmental toxicity (1000 mg/kg body weight/day and 500 mg/kg body weight/day, respectively) are far in excess of current human exposure levels and therefore should raise no safety concern.
- Animal and human dermatological studies show that the AAASAE fragrance ingredients are generally not irritating or sensitizing at currently reported maximum levels used in consumer products and in fine fragrances. Likewise, the potential for eye irritation, under the present conditions of use, is minimal.
- Based on the UV spectra for these materials and the lack of absorption in the UVA and UVB range (>290 nm) these materials are not expected to be phototoxic. This is supported by data obtained on 3 compounds (1,3-dimethyl-3-phenylethyl acetate; anisyl acetate and benzyl acetate) that were evaluated and found not to cause phototoxicity or photosensitivity. Therefore, AAASAE fragrance ingredients would not be expected to elicit phototoxicity or photosensitization under the current conditions of use as a fragrance ingredient.
- To calculate margin of safety, the lowest NOAEL of 15 mg/kg body weight/day (from 13-week gavage study of α-methylbenzyl alcohol in rats) is used as a representative worst case scenario for the group. Using the fragrance material in this group with the highest estimated daily exposure (0.12 mg/kg body weight/day for benzyl acetate) again, as a representative worst case scenario, and assuming 100% dermal absorption, the margin of safety (MOS) is calculated to be 125. If a MOS of 100 is used, the maximum allowable exposure is calculated to be 0.15 mg/kg body weight/day.
- Margin of safety calculations based on dermal absorption have been calculated using dermal absorption data for rats and humans (see Table 2-1, Section 4.1) to estimate internal dose, and then converted to mg/m^2 based on the FDA's human equivalent dose (Reagan-Shaw et al., 2007). *In vitro* skin absorption of neat benzyl acetate under occlusion in rats and humans was 34.3% and 5.5% at 24 h, respectively. Therefore, the lowest NOAEL from the rat 13-week gavage study is 30.6 mg/m^2 (or 15 mg/kg body weight × 34% × 6 (the K_m factor for rats)) and the highest systemic exposure for the group is 0.244 mg/m^2 (or 0.12 mg/kg body weight × 5.5% × 37 (the K_m factor for humans)). MOS is calculated to be 125.

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.

Acknowledgements

The Panel wishes to express its sincere appreciation to Dr. A.E. Rogers for her help and guidance in the preparation of this manuscript.

References

Abdo, K.M., Huff, J.E., Haseman, J.K., Boorman, G.A., Eustis, S.L., Matthews, H.B., Burka, L.T., Prejean, J.D., Thompson, R.B., 1985. Benzyl acetate carcinogenicity, metabolism, and disposition in Fischer 344 rats and B6C3F1 mice. Toxicology 37 (1–2), 159–170.

Abdo, K.M., Wenk, M.L., 1995. Requirement for adequate glycine for the detoxification of benzyl acetate and maintenance of its detoxification pathways. Toxicologist 15 (1), 19.

Abdo, K.M., Wenk, M.L., Harry, G.J., Mahler, J., Goehl, T.J., Irwin, R.D., 1998. Glycine modulates the toxicity of benzyl acetate in F344 rats. Toxicologic Pathology 26 (3), 395–402.

Adams, T.B., Cohen, S.M., Doull, J., Feron, V.J., Goodman, J.I., Marnett, L.J., Munro, I.C., Portoghese, P.S., Smith, R.L., Waddell, W.J., Wagner, B.M., 2005a. The FEMA GRAS assessment of benzyl derivatives used as flavor ingredients. Food and Chemical Toxicology 43, 1207–1240.

Adams, T.B., Cohen, S.M., Doull, J., Feron, F.J., Goodman, J.I., Marnett, L.J., Munro, I.C., Portoghese, P.S., Smith, R.L., Waddell, W.J., Wagner, B.M., 2005b. The FEMA GRAS assessment of hydroxyl- and alkoxyl substituted benzyl derivatives used as flavor ingredients. Food and Chemical Toxicology 43, 1241–1271.

Adams, T.B., McGowen, M.M., Williams, M.C., Cohen, S.M., Doull, J., Feron, V.J., Goodman, J.I., Marnett, L.J., Munro, I.C., Portoghese, P.S., Smith, R.L., Waddell, W.J., 2007. The FEMA GRAS assessment of aromatic substituted secondary alcohols, ketones, and related esters used as flavor ingredients. Food and Chemical Toxicology 45, 171–201.

Akira, K., Farrant, R.D., Lindon, J.C., Caddick, S.T., Nicholls, A.W., Nicholson, J.K., 1994. High-field deuterium nuclear magnetic resonance spectroscopic monitoring of the phamracokinetics of selectively deuterated benzoic acid in man. Analytical Biochemistry 221, 297–302 (as cited in World Health Organization, 1996).

Ames, B.N., McCann, J., Yamasaki, E., 1975. Methods for detecting carcinogens and mutagens with the *Salmonella*/mammalian-microsome mutagenicity test. Mutation Research 31, 347–363.

Api, A.M., 2004. Evaluation of the dermal subchronic toxicity of phenoxyethyl isobutyrate in the rat. Food and Chemical Toxicology 42 (2), 307–311.

Api, A.M., Ford, R.A., 1993. Safety investigation of 2-phenoxyethyl isobutyrate by dermal exposure. Toxicologist 13 (1), 54.

Armstrong, B.E., Chao, F.C., Parker, V.J., Wall, P.E., 1955. Endogenous formation of hippuric acid. Proceeding of the Society for Experimental Biology and Medicine 90, 675–679 (as cited in World Health Organization, 1996).

Augustinsson, K.B., Ekedahl, G., 1962. On the specificity of arylesterases. Acta Chemica Scandinavica 16 (Part 1), 240–241.

Baba, S., Akira, K., Suzuki, H., Imachi, M., 1995. Use nuclear magnetic resonance spectroscopy and selective ^{13}C-labeling of pharmacokinetic research in man: detection of benzoic acid conversion to hippuric acid. Biological and Pharmaceutical Bulletin 18, 643–647 (as cited in World Health Organization, 1996).

Bar, V.F., Griepentrog, F., 1967. Die Situation in der gesundheitlichen Beurteilung der Aromatisierungsmittel fur Lebensmittel (where we stand concerning the evaluation of flavoring substances from the viewpoint of health). Medizinische Ernahrung 8, 244–251.

Beroza, M., Inscoe, M.N., Schwartz, J., Keplinger, M.L., Mastri, C.W., 1975. Acute toxicity studies with insect attractants. Toxicology and Applied Pharmacology 31 (3), 421–429.

Bronaugh, R.L., Wester, R.C., Bucks, D., Maibach, H.I., Sarason, R., 1990. *In vivo* percutaneous absorption of fragrance ingredients in rhesus monkeys and humans. Food and Chemical Toxicology 28 (5), 369–373.

Buchbauer, G., Jirovetz, L., Jager, W., Plank, C., Dietrich, H., 1993. Fragrance compounds and essential oils with sedative effects upon inhalation. Journal of Pharmaceutical Science 82 (6), 660–664.

Cadby, P.A., Troy, W.R., Vey, M.G.H., 2002. Consumer exposure to fragrance ingredients: providing estimates for safety evaluation. Regulatory Toxicology and Pharmacology 36, 246–252.

Caldwell, J., Kennedy, J.F., Chidgey, M.A.J., 1987. Absorption and disposition of topically-applied methylene-carbon-14 benzyl acetate in the rat. In: Pharmacology and the Skin, vol. 1. Skin Pharmacokinetics, pp. 209–213.

Callaghan, P., Borge, P.A., Elsden, J., Hopkins, R.P., 1973. Dehydrogenation of methylphenylcarbinol by soluble preparations of rat liver. Biochemical Society Transactions 1, 421–423 (as cited in JECFA, 2002a).

Caspary, W.J., Langerbach, R., Penman, B.W., Crespi, C., Myhr, B.C., Mitchell, A.D., 1988. The mutagenic activity of selected compounds at the TK locus: Rodent vs. human cells. Mutation Research 196 (1), 61–81.

Chidgey, M.A.J., Caldwell, J., 1986. Studies on benzyl acetate I. Effect of dose size and vehicle on the plasma pharmacokinetics and metabolism of [methylene-(14)C] benzyl acetate in the rat. Food and Chemical Toxicology 24 (12), 1257–1265.

Chidgey, M.A.J., Kennedy, J.F., Caldwell, J., 1986. Studies on benzyl acetate II. Use of specific metabolic inhibitors to define the pathway leading to the formation of benzylmercapturic acid in the rat. Food and Chemical Toxicology 24 (12), 1267–1272.

Chidgey, M.A.J., Kennedy, J.F., Caldwell, J., 1987. Studies on benzyl acetate. III. The percutaneous absorption and disposition of [methylene-(14)C] benzyl acetate in the rat. Food and Chemical Toxicology 25 (7), 521–525.

Clary, J.J., Feron, V.J., Van Velthuijsen, J.A., 1998. Safety assessment of lactate esters. Regulatory Toxicology and Pharmacology 27 (2), 88–97.

Culp, H.W., McMahon, R.E., 1968. The partial purification and properties of a reduced triphophopyriudine nucleotide-dependent reductase from rabbit kidney cortex. Journal of Biological Chemistry 243, 848–852 (as cited in JECFA, 2002a).

Davison, C., 1971. Salicylate metabolism in man. Journal of Pharmacology and Experimental Therapeutics 179, 249–268 (as cited in JECFA, 2002a).

ElMasry, A.M., Smith, J.N., Willeams, R.T., 1956. Studies in detoxication 69. The metabolism of alkylbenzenes: *n*-propyulbenzene and *n*-butylbenzene with further observations on ethyl benzene. Biochemical Journal 64, 50–57 (as cited in JECFA 2002a).

FFHPVC (The Favor and Fragrance High Production Volume Consortia), 2001. Test plan for benzyl derivatives.

Florin, I., Rutberg, L., Curvall, M., Enzell, C.R., 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames test. Toxicology 18 (3), 219–232.

Ford, R.A., Domeyer, B., Easterday, O., Maier, K., Middleton, J., 2000. Criteria for development of a database for safety evaluation of fragrance materials. Regulatory Toxicology and Pharmacology 31, 166–181.

Frosch, P.J., Pilz, B., Andersen, K.E., Burrows, D., Camarasa, J.G., Dooms-Goossens, A., Ducombs, G., Fuchs, T., Hannuksela, M., Lachapelle, J.M., Lahti, A., Maibach, H.I., Menne, T., Rycroft, R.J.G., Shaw, S., Wahlberg, J.E., White, I.R., Wilkinson, J.D., 1995. Patch testing with fragrances: results of a multicenter study of the European Environmental and Contact Dermatitis Research Group with 48 frequently used constituents of perfumes. Contact Dermatitis 33 (5), 333–342.

Frosch, P.J., Johansen, J.D., Menne, T., Pirker, C., Rastogi, S.C., Andersen, K.E., Bruze, M., Goossens, A., Lepoittevin, J.P., White, I.R., 2002. Further important sensitizers in patients sensitive to fragrances. I. Reactivity to 14 frequently used chemicals. Contact Dermatitis 47 (2), 78–85.

Fujii, T., Furukawa, S., Suzuki, S., 1972. Studies on compounded perfumes for toilet goods. On the non-irritative compounded perfumes for soaps. Yukugaku 21 (12), 904–908.

Galloway, S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B., Zeiger, E., 1987. Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. Environmental and Molecular Mutagenesis 10 (Suppl. 10), 1–175.

Garnett, A., 1992. Doctorial dissertation: investigation of the in vitro percutaneous absorption and skin metabolism of benzyl acetate and related compounds. Unpublished Thesis submitted for the degree of Doctor of Philosophy in the University of London, RIFM Report Number 412.

Garnett, A., Hotchkiss, S.A., Caldwell, J., 1989. In vitro dermal absorption and metabolism of benzyl acetate, IUTOX Poster Presentation, Brighton, UK.

Garnett, A., Hotchkiss, S.A.M., Caldwell, J., 1994. Percutaneous absorption of benzyl acetate through rat skin *in vitro* 3. A comparison with human skin. Food and Chemical Toxicology 32 (11), 1061–1065.

Gaunt, I.F., Mason, P.L., Hardy, J., Lansdown, A.B.G., Gangolli, S.D., 1974. Short-term toxicity of methylphenylcarbinyl acetate in rats. Food and Chemical Toxicology 12, 185–194.

Gaworski, C.L., Dozier, M.M., Heck, J.D., Gerhart, J.M., Rajendran, N., David, R.M., Brennecke, L.H., Morrissey, R., 1998. Toxicologic evaluation of flavor ingredients added to cigarette tobacco: 13-week inhalation exposures in rats. Inhalation Toxicology 10 (4), 357–381.

Graham, B.E., Kuizenga, M.H., 1945. Toxicity studies on benzyl benzoate and related benzyl compounds. Journal Pharmacology Experimental Therapeutics 84 (4), 358–362.

Greif, N., 1967. Cutaneous safety of fragrance material as measured by the maximization test. American Perfumer and Cosmetics 82, 54–57.

Grundschober, F., 1977. Toxicological assessment of flavouring esters. Toxicology 8, 387–390.

Haba, Y., Itoh, M., Morita, C., Tsuyuki, S., 1993. Results of patch tests on cosmetic ingredients conducted in 1990 and 1991. Hifu [Skin Research] 35 (Suppl. 16), 65–74.

Haseman, J.K., Huff, J., Boorman, G.A., 1984. Use of historical control data in carcinogenicity studies in rodents. Toxicologic Pathology 12 (2), 126–135.

Heymann, E., 1980. Carboxylesterases and amidases. In: Jakoby, W.B. (Ed.), Enzymatic Basis Detoxification, vol. 2(16). Academic Press, Inc., New York, pp. 291–323.

Honma, M., Hayashi, M., Shimada, H., Tanaka, N., Wakuri, S., Awogi, T., Yamamoto, K.I., Kodani, N.U., Nishi, Y., Nakadate, M., Sofuni, T., 1999. Evaluation of the mouse lymphoma TK assay (microwell method) as an alternative to the *in vitro* chromosomal aberration test. Mutagenesis 14 (1), 5–22.

Hopkins, R.P., Borge, P.A., Callaghan, P., 1972. Dehydrogenation of dl-methylphenylcarbinol in the rat. Biochemical Journal 127, 26–27 (as cited in JECFA 2002a).

Hotchkiss, S.A.M., 1998. Absorption of fragrance ingredients using *in vitro* models with human skin. In Fragrances: Beneficial and Adverse Effects, 125–135.

Hotchkiss, S.A., Fraser, S., Caldwell, J., Miller, J.M., 1988. The percutaneous absorption of benzyl acetate through rat skin *in vitro*. In: Presented at ISSX-88 Mtg., Kobe, Japan.

Hotchkiss, S.A., Fraser, S., Miller, J.M., Caldwell, J., 1989a. Percutaneous absorption of topically applied benzyl acetate *in vitro* effect of vehicle on skin penetration. Human Toxicology 8 (1), 71–72.

Hotchkiss, S.A., Rose, S., Caldwell, J., 1989b. Evidence for the existence of a cutaneous reservoir for benzyl acetate, IUTOX Poster Presentation, Brighton, UK.

Hotchkiss, S.A., Chidgey, M.A.J., Rose, S., Caldwell, J., 1990a. Percutaneous absorption of benzyl acetate through rat skin *in vitro* 1. Validation of an *in vitro* model against *in vivo* data. Food and Chemical Toxicology 28 (6), 443–447.

Hotchkiss, S.A., Fraser, S., Chidgey, M.A.J., Caldwell, J., 1990b. An *in vitro* skin diffusion technique for the prediction of *in vivo* absorption; a case study with benzyl acetate. In: Prediction of Percutan: Penetration-Methods, Measurements Modelling, pp. 123–128.

Hotchkiss, S.A.M., Hewitt, P., Mint, A., Garnett, A., Caldwell, J., 1992a. Percutaneous absorption of fragrance chemicals through human skin *in vitro*. Toxicology Letters Suppl. 1, 173.

Hotchkiss, S.A.M., Miller, J.M., Caldwell, J., 1992b. Percutaneous absorption of benzyl acetate through rat skin *in vitro* 2. Effect of vehicle and occlusion. Food and Chemical Toxicology 30 (2), 145–153.

Hotchkiss, S.A.M., Nasseri-Sina, P., Garnett, A., Caldwell, J., 1992c. *In vitro* metabolism of benzyl acetate and benzoic acid in cultured human keratinocytes and full thickness human skin. ISSX International Meeting, 2, p. 158.

IFRA (International Fragrance Association), 2008a. Use Level Survey, September, 2008.

IFRA (International Fragrance Association), 2008b. Use Level Survey, November, 2008.

IFRA (International Fragrance Association), 2008c. Volume of Use Survey, MONTH 2008.

Ishiguro, S., Miyamoto, A., Obi, T., Nishio, A., 1993. Teratological studies on benzyl acetate in pregnant rats. Bulletin Faculty Agriculture Kagoshima University 43, 25–31.

Ishihara, M., 1977. Problems of closed patch tests with ingredients of cosmetic products. Journal Japanese Cosmetic Science Society 1, 87–102.

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

Ishihara, M., Itoh, M., Hosono, K., Nishimura, M., 1981. Some problems with patch tests using fragrance materials. Skin Research 23 (6), 808–817.

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

Itoh, M., 1982. Sensitization potency of some phenolic compounds – with special emphasis on the relationship between chemical structure and allergenicity. Journal of Dermatology 9 (3), 223–233.

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

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

James, M.O., Smith, R.L., 1973. Conjugation of pheylacetic acid in phenylketourics. European Journal of Clinical Pharmacology 5, 243–246 (as cited in JECFA, 2003).

JECFA, 2001. Safety evaluation of certain food additives and contaminants: cinnamyl alcohol and related substances. In: Prepared by the fifty-fifth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), WHO Food Additives Series 46, International Programme on Chemical Safety (IPCF), Geneva.

JECFA, 2002a. Safety evaluation of certain food additives and contaminants: aromatic substituted secondary alcohols, ketones, and related esters. In: Prepared by the fifty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), WHO Food Additives Series 48, International Programme on Chemical Safety (IPCF), Geneva.

JECFA, 2002b. Safety evaluation of certain food additives and contaminants: benzyl derivatives. In: Prepared by the fifty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), WHO Food Additives Series 48, International Programme on Chemical Safety (IPCF), Geneva.

JECFA, 2002c. Safety evaluation of certain food additives and contaminants: hydroxy- and alkoxy-substituted benzyl derivatives. In: Prepared by the fifty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), WHO Food Additives Series 48, International Programme on Chemical Safety (IPCF), Geneva.

JECFA, 2003. Safety evaluation of certain food additives and contaminants: phenethyl alcohol, aldehyde, acid and related acetals and esters and related substances. In: Prepared by the fifty-ninth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), WHO Food Additives Series 50, International Programme on Chemical Safety (IPCF), Geneva.

Jenner, P.M., Hagan, E.C., Taylor, J.M., Cook, E., Fitzhugh, O.G., 1964. Food flavorings and compounds of related structure I. Acute oral toxicity. Food and Cosmetics Toxicology 2, 327–343.

Jimbo, Y., 1983. Penetration of fragrance compounds through human epidermis. Journal of Dermatology 10 (3), 229–239.

Katz, A.E., 1946. Dermal irritating properties of essential oils and aromatic chemicals. Spice Mill 69, 46–47, 50–51.

Kevekordes, S., Mersch-Sundermann, V., Burghaus, C.M., Spielberger, J., Schmeiser, H.H., Arlt, V.M., Dunkelberg, H., 1999. SOS induction of selected naturally occurring substances in *Escherichia coli* (SOS chromotest). Mutation Research 445 (1), 81–91.

Kevekordes, S., Spielberger, J., Burghaus, C.M., Birkenkamp, P., Zietz, B., Paufler, P., Diez, M., Bolten, C., Dunkelberg, H., 2001. Micronucleus formation in human lymphocytes and in the metabolically competent human hepatoma cell line Hep G2: results with 15 naturally occurring substances. Anticancer Research 21 (1A), 461–470.

Kiese, M., Lenk, W., 1974. Hydroacetophenone: urinary metaoblites of ethylbenzene and acetophenone in the rabbit. Xenobiotica 4, 337–343 (as cited in JECFA, 2002a).

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

Klecak, G., 1985. The Freund's complete adjuvant test and the open epicutaneous test. In: Current Problems in Dermatology, vol. 14, pp. 152–171.

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

Leegwater, D.C., van Straten, S., 1974. In vitro study on the hydrolysis of eight carboxylic esters by intestinal and liver enzymes. Private communication to FEMA. Utrechtseweg 48 Zeist.

Longnecker, D.S., Roebuck, B.D., Curphey, T.J., Lhoste, E., Coon, C.I., Macmillan, D.L., 1986. Effects of corn oil and benzyl acetate on number and size of azaserine-induced foci in the pancreas of LEW and F344 rats. Environmental Health Perspectives 68, 197–201.

Longnecker, D.S., Roebuck, B.D., Curphey, T.J., MacMillan, D.L., 1990. Evaluation of promotion of pancreatic carcinogenesis in rats by benzyl acetate. Food and Chemical Toxicology 28 (10), 665–668.

Matsuoka, A., Yamakage, K., Kusakabe, H., Wakuri, S., Asakura, M., Noguchi, T., Sugiyama, T., Shimada, H., Nakayama, S., Kasahara, Y., Takahashi, Y., Miura, K.F., Hatanaka, M., Ishidate, J., Morita, T., Watanabe, K., Hara, M., Odawara, K., Tanaka, N., Hayashi, M., Sofuni, T., 1996. Re-evaluation of chromosomal aberration induction on nine mouse lymphoma assay 'unique positive' NTP carcinogens. Mutation Research 369 (3–4), 243–252.

Maylin, G.A., Cooper, M.J., Anders, M.W., 1973. Effect of phenobarbital treatment on the stereochemistry of the in vitro metabolism of ethyl benzene. Journal of Medicinal Chemistry 16, 606–610 (as cited in JECFA 2002a).

McGinty, D.M., Letizia, C.S., Api, A.M., in press-a. Fragrance material review on 1,3-benzodioxole-5-propanol, α-methyl-, 5-acetate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.049.

McGinty, D.M., Letizia, C.S., Api, A.M., in press-b. Fragrance material review on 1,1-dimethyl-2-phenylethyl acetate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.053.

McGinty, D.M., Letizia, C.S., Api, A.M., in press-c. Fragrance material review on 1,1-dimethyl-2-phenylethyl butyrate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.076.

McGinty, D.M., Letizia, C.S., Api, A.M., in press-d. Fragrance material review on 1,1-dimethyl-2-phenylethyl formate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.055.

McGinty, D.M., Letizia, C.S., Api, A.M., in press-e. Fragrance material review on 1,3-dimethyl-3-phenylbutyl acetate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.045.

McGinty, D.M., Letizia, C.S., Api, A.M., in press-f. Fragrance material review on 1,1-dimethyl-2-phenylethyl isobutyrate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.054.

McGinty, D.M., Letizia, C.S., Api, A.M., in press-g. Fragrance material review on 1,1-dimethyl-2-phenylethyl propionate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.047.

McGinty, D.M., Letizia, C.S., Api, A.M., in press-h. Fragrance material review on 1,2-ethanediol, 1-phenyl-, 1,2-diacetate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.048.

McGinty, D.M., Letizia, C.S., Api, A.M., in press-i. Fragrance material review on 2-hydroxy-2-phenylethyl acetate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.078.

McGinty, D.M., Letizia, C.S., Api, A.M., in press-j. Fragrance material review on 2-methyl-4-phenyl-2-butyl acetate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.075.

McGinty, D.M., Letizia, C.S., Api, A.M., in press-k. Fragrance material review on phenethyl acetate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.089.

McGinty, D.M., Letizia, C.S., Api, A.M., in press-l. Fragrance material review on phenethyl butyrate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.061.

McGinty, D.M., Letizia, C.S., Api, A.M., in press-m. Fragrance material review on phenethyl formate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.067.

McGinty, D.M., Letizia, C.S., Api, A.M., in press-n. Fragrance material review on phenethyl isobutyrate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.065.

McGinty, D.M., Letizia, C.S., Api, A.M., in press-o. Fragrance material review on phenethyl propionate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.068.

McGinty, D.M., Letizia, C.S., Api, A.M., in press-p. Fragrance material review on 2-phenoxyethyl isobutyrate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.079.

McGinty, D.M., Letizia, C.S., Api, A.M., in press-q. Fragrance material review on 2-phenoxyethyl propionate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.093.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-r. Fragrance material review on 3-phenyl-3-buten-1-yl acetate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.081.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-s. Fragrance material review on 1-phenyl-3-methyl-3-pentyl acetate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.046.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-t. Fragrance material review on 2-phenylpropyl acetate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.095.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-u. Fragrance material review on 3-phenylpropyl acetate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.080.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-v. Fragrance material review on 2-(*p*-tolyloxy)ethyl acetate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.087.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-w. Fragrance material review on *p*-anisyl acetate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.094.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-x. Fragrance material review on anisyl acetate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.083.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-y. Fragrance material review on anisyl formate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.084.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-z. Fragrance material review on anisyl propionate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.051.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-aa. Fragrance material review on benzyl acetate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.057.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-bb. Fragrance material review on benzyl butyrate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.063.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-cc. Fragrance material review on benzyl formate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.062.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-dd. Fragrance material review on benzyl 2-hydroxypropionate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.050.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-ee. Fragrance material review on benzyl isobutyrate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.066.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-ff. Fragrance material review on benzyl propionate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.088.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-gg. Fragrance material review on 2,4-dimethylbenzyl acetate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.077.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-hh. Fragrance material review on *p*-isopropylbenzyl acetate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.060.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-ii. Fragrance material review on (4-methoxyphenyl)methyl isobutyrate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.052.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-jj. Fragrance material review on α-methylbenzyl acetate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.059.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-kk. Fragrance material review on 4-methylbenzyl acetate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.085.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-ll. Fragrance material review on α-methylbenzyl isobutyrate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.058.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-mm. Fragrance material review on α-methylbenzyl propionate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.064.
McGinty, D.M., Letizia, C.S., Api, A.M., in press-nn. Fragrance material review on piperonyl acetate. Food and Chemical Toxicology. http://dx.doi.org/10.1016/j.fct.2012.02.056.
McGregor, D.B., Brown, A., Cattanach, P., Edwards, I., McBride, D., Riach, C., Caspary, W.J., 1988. Responses of the L5178Y TK+/TK-mouse lymphoma cell forward mutation assay: III. 72 Coded chemicals. Environmental and Molecular Mutagenesis 12 (2), 85–153.
McMahon, T.F., Diliberto, J.J., Birnbaum, L.S., 1989a. Age related changes in disposition of benzyl acetate (BA): a model compound for glycine conjugation. Toxicologist 9 (1), 88.
McMahon, T.F., Diliberto, J.J., Birnbaum, L.S., 1989b. Age-related changes in the disposition of benzyl acetate: a model compound for glycine conjugation. Drug Metabolism and Disposition 17 (5), 506–512.
Meyer, F., 1965. Penetrating agents. Patent M49750IVa/30h, 7/20/61, British, 1,001,949.
Mirsalis, J.C., Tyson, C.K., Steinmetz, K.L., Loh, E.K., Hamilton, C.M., Bakke, J.P., Spalding, J.W., 1989. Measurement of unscheduled DNA synthesis and S-phase synthesis in rodent hepatocytes following *in vivo* treatment: testing of 24 compounds. Environmental and Molecular Mutagenesis 14 (3), 155–164.
Miyagawa, M., Takasawa, H., Sugiyama, A., Inoue, Y., Murata, T., Uno, Y., Yoshikawa, K., 1995. The *in vivo in vitro* replicative DNA synthesis (RDS) test with hepatocytes prepared from male B6C3F1 mice as an early prediction assay for putative nongenotoxic (Ames-negative) mouse hepatocarcinogens. Mutation Research 343 (1), 157–183.
Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B., Zeiger, E., 1986. Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. Environmental Mutagenesis 8 (7), 1–119.
Motoyoshi, K., Toyoshima, Y., Sato, M., Yoshimura, M., 1979. Comparative studies on the irritancy of oils and synthetic perfumes to the skin of rabbit, guinea pig, rat, miniature swine and man. Cosmetics and Toiletries 94 (8), 41–48.
Nishimura, M., Ishihara, M., Itoh, M., Hosono, K., Kantoh, H., 1984. Results of patch tests on cosmetic ingredients conducted between 1979 and 1982. Skin Research 26 (4), 945–954.
Nishimura, H., Saito, S., Kishida, F., Matsuo, M., 1994. Analysis of acute toxicity (LD50-value) of organic chemicals to mammals by solubility parameter (delta). 1. Acute oral toxicity to rats. Sangyo Igaku 36 (5), 314–323 (Japanese Journal Industrial Health).
Novak, M., 1974. Contact sensitization to perfume composition components in antiphlogistic ointment. Czechoslavak. Dermatology 49 (6), 375–378.
NTP, 1986. Toxicology and carcinogenesis studies of benzyl acetate in F344/N rats and B6CF1 mice (gavage studies). NTP-TR-250; PB-86-2506. National Toxicology Program.
NTP, 1993. Toxicology and carcinogenesis studies of benzyl acetate in F344 rats and B6C3F1 mice (feed studies). NTP-TR-431; NIH Publication No. 92-3162. National Toxicology Program.
Oda, Y., Hamano, Y., Inoue, K., Yamamoto, H., Niihara, T., Kunita, N., 1978. Mutagenicity of food flavours in bacteria (1st Report). Osaka-furitsu Koshu Eisei Kenkyu Hokoku Shokuhin Eisei Hen, 9, pp. 177-181.
Quick, A.J., 1928. Quantitative studies of beta-oxidation. II. The metabolism of phenylvaleric acid, phenyl-*alpha*,*beta*-pentenic acid, phenyl-*beta*-*gamma*-pentenic acid, mandelic acid, phenyl-*beta*-hydroxypropionic acid and acetophenone in dogs. Journal of Biological Chemistry 80, 515–526 (as cited in JECFA, 2002a).
Reagan-Shaw, S., Nihal, M., Ahmad, N., 2007. Dose translation from animal to human studies revisited. FASEB Journal 22, 659–661.
RIFM (Research Institute for Fragrance Materials, Inc.), 1957. Toxicological screening of ethyl benzoate, isobutyl benzoate, benzyl acetate, benzyl butyrate, and ethyl methylphenylglycidate in rats. Class V. Aromatic esters. Unpublished report from Trubek Laboratories Inc., RIFM Report Number 29140, June 5. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1961. Sensitization and irritation studies. Unpublished report from Givaudan Corporation. RIFM Report Number 14581, March 24. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1963a. Eye irritation study with alpha, *alpha*-dimethylphenethyl acetate in rabbits. Unpublished report from International Flavors and Fragrances. RIFM Report Number 50699, October 31. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1963b. Eye irritation study with piperonyl acetate in rabbits. Unpublished report from International Flavors and Fragrances. RIFM Report Number 54787, September 23. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1964a. Repeated insult patch test with alpha, alpha-dimethyl phenethyl acetate. Unpublished report from International Flavors and Fragrances. RIFM Report Number 50698, April 28. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1964b. Repeated insult patch test of phenylethylacetate on human subjects. Unpublished report from International Flavors and Fragrances. RIFM Report Number 12619. November 19. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1964c. Eye irritation study with alpha, alpha-dimethylphenethyl acetate in rabbits. Unpublished report from International Flavors and Fragrances. RIFM Report Number 50700, March 10. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1964d. Irritation of benzyl acetoacetate when instilled into rabbits' eyes. Unpublished report from International Flavors and Fragrances. RIFM Report Number 48806. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1964e. Repeated insult patch test with piperonyl acetate in humans. Unpublished report from International Flavors and Fragrances. RIFM Report Number 54786, April 2. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1965a. Repeated insult patch test with 2-phenoxyethyl isobutyrate (phenoxy ethyl isobutyrate) in humans. Unpublished report from International Flavors and Fragrances. RIFM Report Number 54722, January 4. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1965b. Repeated insult patch test with 2,4-dimethylbenzyl acetate. Unpublished report from International Flavors and Fragrances. RIFM Report Number 52418, May 14. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1965c. Eye irritation study of phenethylacetate in rabbits. Unpublished report from International Flavors and Fragrances. RIFM Report Number 12618. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1965d. Eye irritation study with 2,4-dimethylbenzyl acetate in rabbits. Unpublished report from International Flavors and Fragrances. RIFM Report Number 52419, December 31. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1970a. Acute dermal toxicity study in rabbits. RIFM Report Number 2735, September 14. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1970b. The contact sensitizing potential of fragrance materials in humans. RIFM Report Number 1760, June 1. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1971a. Acute dermal toxicity study in rabbits. RIFM Report Number 2729, March 24. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1971b. Acute dermal toxicity study in rabbits. RIFM Report Number 2031, November 14. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1971c. Acute oral and dermal toxicity studies in rabbits. RIFM Report Number 2110, August 25. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1971d. Acute oral and dermal toxicity studies. RIFM Report Number 2710, June 28. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1971e. Acute dermal toxicity of *alpha*-methylbenzyl acetate in rabbits. RIFM Report Number 2736, March 19. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1971f. Acute oral toxicity study in rats. RIFM Report Number 2728, March 24. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1971g. Acute oral toxicity in rats. RIFM Report Number 2030, November 14. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1971h. Report on *alpha*-Methylbenzyl acetate. Unpublished report from KG Laboratories, Inc. RIFM Report Number 2737, March 1. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1971i. Appraisal of sensitizing powers by maximization testing in humans. RIFM Report Number 1805, September 27. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1972a. Acute toxicity studies in mice, rats and rabbits. RIFM Report Number 2536, November 1. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1972b. The contact-sensitization potential of fragrance materials by maximization testing in humans. RIFM, Report Number 1804, November 22. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1973a. Acute dermal toxicity study in rabbits. RIFM Report Number 2026, February 16. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1973b. Acute toxicity studies on rats and rabbits. RIFM Report Number 2021, July 05. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1973c. Acute oral toxicity reports on rats. RIFM Report Number 2014, January 17. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1973d. Report on human maximization studies. RIFM Report Number 1802, May 9. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1973e. Skin irritation study with 2-phenylpropyl acetate in rabbits. Unpublished report from International Flavors and Fragrances. RIFM Report Number 51932, June 21. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1973f. Eye irritation study with 2-phenylpropyl acetate in rabbits. Unpublished report from International Flavors and Fragrances. RIFM Report Number 51931, June 26. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1973g. Repeated insult patch test with 2-phenylpropyl acetate. Unpublished report from International Flavors and Fragrances. RIFM Report Number 51930, September 27. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1974a. In vitro study on the hydrolysis of eight carboxylic esters by intestinal and liver enzymes. Unpublished report from Naarden Inc. RIFM Report Number 8217, August 1. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1974b. Acute toxicity study in rats and rabbits. RIFM Report Number 2025, July 17. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1974c. Acute oral and dermal toxicity studies. RIFM Report Number 2028, April 2. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1974d. Determination of potential hazards of fragrance materials by dermal contact. RIFM Report Number 34368, October 10. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1974e. Repeated insult patch test with 3-phenyl-2-butenyl acetate. Unpublished report from International Flavors and Fragrances, Inc. RIFM Report Number 47212/48658, November 22. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1974f. Repeated insult patch test with 3-phenyl-3-buten-1-yl acetate. Unpublished report from International Flavors and Fragrances. RIFM Number 47213/48659, November 21. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1974g. Report on human maximization studies. RIFM Report Number 1801, May 20. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1974h. Irritation study of 3-phenyl-2-butenyl acetate in rabbits. Unpublished report from International Flavors and Fragrances. RIFM Report Number 47214/48662, August 20. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1974i. Skin irritation study with 3-phenyl-3-buten-1-yl acetate in rabbits. RIFM Report Number 48663, August 20. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1974j. Eye irritation study of 3-phenyl-2-butenyl acetate in rabbits. Unpublished report from IFF Incorporated. RIFM Report Number 47215, August 8. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1974k. Eye irritation study with 3-phenyl-3-buten-1-yl acetate in rabbits. Unpublished report from International Flavors and Fragrances. RIFM Report Number 48660, September 3. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1974l. Eye irritation study with 3-phenyl-3-buten-1-yl acetate in rabbits. Unpublished report from International Flavors and Fragrances. RIFM Report Number 48661, August 21. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1975a. Acute toxicity studies in rats, mice, and rabbits. RIFM Report Number 2024, May 19. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1975b. Acute toxicity studies on rats, rabbits and guinea pigs. RIFM Report Number 2020, June 25. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1975c. Report on human maximization studies. RIFM Report Number 1799, May 15. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1975d. Report on human maximization studies. RIFM Report Number 1798, January 31. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1975e. Repeated insult patch test of benzyl acetate in human subjects. Unpublished report from International Flavors and Fragrances. RIFM Report Number 24179, June 18. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1975f. Repeated insult patch test of benzyl acetate in humans subjects. Unpublished report from International Flavors and Fragrances. June 18. RIFM Report Number 24178, June 18. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1975g. Repeated insult patch test of benzyl acetate on human subjects. Unpublished report from International Flavors and Fragrances. RIFM Report Number 24177, June 17. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1975h. Repeated insult patch test of benzyl acetate in human subjects. Unpublished report from International Flavors and Fragrances. RIFM Report Number 24175, June 16. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1975i. Repeated insult patch test of benzyl acetate in human subjects. Unpublished report from International Flavors and Fragrances. RIFM Report Number 24176, June 18. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1975j. Sensitization study of benzyl acetate in rabbits. Unpublished report from International Flavors and Fragrances. RIFM Report Number 24189, March 28. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1975k. Sensitization study of benzylacetate in rabbits. Unpublished report from International Flavors and Fragrances. RIFM Report Number 24187, March 21. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1975l. Sensitization study of benzyl acetate of rabbits. Unpublished report from International Flavors and Fragrances. RIFM Report Number 24188, March 11. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1975m. Sensitization study on benzyl acetate in rabbits. Unpublished report from International Flavors and Fragrances. RIFM Report Number 24185, March 20. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1975n. Sensitization study on benzyl acetate in rabbits. Unpublished report from International Flavors and Fragrances, March 7. RIFM Report Number 24186 RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1975o. Acute eye irritation study of benzyl acetate in rabbits. Unpublished report from International Flavors and Fragrances. RIFM Report Number 24184, April 2. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1975p. Acute eye irritation study of benzyl acetate in rabbits. RIFM Report Number 24183, March 10. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1975q. Acute eye irritation study of benzyl acetate in rabbits. Unpublished report from International Flavors and Fragrances. RIFM Report Number 24182, April 2. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1975r. Acute eye irritation study of benzyl acetate in rabbits. Unpublished report from International Flavors and Fragrances. RIFM Report Number 24181, March 11. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1975s. Acute eye irritation study of benzyl acetate in rabbits. Unpublished report from International Flavors and Fragrances. RIFM Report Number 24180, April 2. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1976a. Acute toxicity studies in rats, mice, rabbits and guinea pigs. RIFM Report Number 2019, January 5. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1976b. Report on human maximization studies. RIFM Report Number 1796, January 26. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1977a. Doctoral dissertation: the comparative respiratory irritation potential of fourteen fragrance raw materials. RIFM Report Number 9011. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1977b. Acute toxicity study in rats, rabbits and guinea pigs. RIFM Report Number 1695, October 18. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1977c. Report on human maximization studies. RIFM Report Number 1702, February 15. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1977d. Report on human maximization studies. RIFM Report Number 1691. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1978a. Acute toxicity studies in rats, mice, rabbits, and guinea pigs. RIFM Report Number 1699, September 30. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1978b. Report on human maximization studies, 1 November. RIFM Report Number 1787, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1979a. Test for acute dermal toxicity of 1,3-dimethyl-3-phenylbutyl acetate in rabbits. Unpublished report from Firmenich Inc. RIFM Report Number 41857, September 19. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1979b. Test for oral toxicity of 1,3-dimethyl-3-phenylbutyl acetate in rats. Unpublished report from Firmenich Inc. RIFM Report Number 41856, September 19. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1979c. Acute oral range-finding toxicity test with 2-phenoxyethyl isobutyrate in mice. Unpublished report from Quest International. RIFM Report Number 46678, September 7. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1979d. Repeated insult patch test/photosensitization study of 1,3-dimethyl-3-phenylbutyl acetate in human subjects. Unpublished report from Firmenich Inc. RIFM Report Number 41860, September 26. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1979e. Test for primary dermal irritation study of 1,3-dimethyl-3-phenylbutyl acetate in rabbits. Unpublished report from Firmenich Inc. RIFM Report Number 41858, September 19. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1979f. Rabbit covered patch skin irritation test with phenethyl acetate. Unpublished report from Quest International. RIFM Report Number 46692, November 20. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1979g. Rabbit covered patch skin irritation test with phenethyl formate. Unpublished report from Quest International. RIFM Report Number 46696, November 20. RIFM, Research Institute for Fragrance Materials, Inc., Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1979h. Rabbit covered patch skin irritation test with 2-phenoxyethyl isobutyrate. Unpublished report from Quest International. RIFM Report Number 46677, October 1. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1979i. Test for eye irritation of 1,3-dimethyl-3-phenylbutyl acetate in rabbits. Unpublished report from Firmenich Incorporated. RIFM Report Number 41859, September 19. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1980a. Acute oral toxicity (LD50) test with phenethyl acetate in mice. Unpublished report from Quest International. RIFM Report Number 46690, February 27. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1980b. Acute oral toxicity (LD50) test with phenethyl formate in mice. Unpublished report from Quest International. RIFM Report Number 46694, February 27. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1980c. Ames metabolic activation test to assess the potential mutagenic effect of phenethyl acetate. Unpublished report from Quest International, 5 February. RIFM Report Number 46691, February 5. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1980d. Ames metabolic activation test to assess the potential mutagenic effect of phenethyl formate. Unpublished report from Quest International. RIFM Report Number 46695, February 6. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1980e. Ames metabolic activation test to assess the potential mutagenic effect of 2-phenoxyethyl isobutyrate. Unpublished report from Quest International. RIFM Report Number 46679, January 25. RIFM, Woodcliff Lake, NJ, USA..
RIFM (Research Institute for Fragrance Materials, Inc.), 1980f. Primary ocular irritation study of alpha, alpha-dimethyl phenethyl acetate in rabbits. Unpublished report from International Flavors and Fragrances. RIFM Report Number 50701, June 9. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1981a. Acute dermal toxicity study of 3-phenyl-3-buten-1-yl acetate in rats. Unpublished report from International Flavors and Fragrances. RIFM Report Number 47741, March 16. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1981b. Acute toxicity studies. RIFM Report Number 1806, August 31. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1981c. Acute oral toxicity study with 3-phenyl-3-buten-1-yl acetate in rats. Unpublished report from International Flavors and Fragrances. RIFM Report Number 47740, March 16. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1981d. Repeated insult patch test of 6,7-dihyrdo-1,1,2,3,3-pentamethyl-4(5H)-indanone in human subjects. Unpublished report from International Flavors and Fragrances. RIFM Report Number 19905, November 6. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1981e. Report on human maximization studies. RIFM Report Number 1792, November 23. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1981f. Delayed contact hypersensitivity study of 3-phenyl-3-buten-1-yl acetate in guinea pigs. Unpublished report from International Flavors and Fragrances. RIFM Report Number 47742, April 1. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1982a. Acute toxicity studies. RIFM Report Number 1689, February 22. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1982b. Report on human maximization studies. RIFM Report Number 1643, May 20. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1983. Determination of phototoxicity of benzyl acetate in guinea pigs. Unpublished report from Givaudan-Roure Corporation. RIFM Report Number 33519, May 24. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1984a. 1,3-Dimethyl-3-phenylbutyl acetate: acute oral toxicity in rats. Unpublished report from Dragoco Gerberding and Co. GmbH. RIFM Report Number 39244, date. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1984b. Acute oral toxicity study in rats with carbonic acid, methyl phenylmethyl ester. Unpublished report from International Flavors and Fragrances. RIFM Report Number 48819, December 31. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1984c. Primary irritation test in rabbits. RIFM Report Number 1795, June 1. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1984d. 1,3-Dimethyl-3-phenylbutyl acetate: delayed contact hypersensitivity modified by E.V. Buehler. Unpublished report from Dragoco Gerberding and Co. GmbH, Date. RIFM Report Number 39241. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1984e. Draize animal mucus membrane irritation test of 1,3-dimethyl-3-phenylbutyl acetate. Unpublished report from Dragoco Gerberding and Co. GmbH, Date. RIFM Report Number 39240. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1984f. Epicutaneous patch test of 1,3-dimethyl-3-phenylbutyl acetate on humans. Unpublished report from Dragoco Gerberding and Co. GmbH, May 15. RIFM Report Number 39239. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1984g. 1,3-Dimethyl-3-phenylbutyl acetate: experimental investigation on photosensitizing effect in guinea-pigs modified by Vinson and Borselli. Unpublished report from Dragoco Gerberding and Co. GmbH, May. RIFM Report Number 39242. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1984h. 1,3-Dimethyl-3-phenylbutyl acetate: experimental investigation on phototoxic effect in guinea-pigs. Unpublished report from Dragoco Gerberding and Co. GmbH, Date. RIFM Report Number 39243, April. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1985a. Primary irritation test in rabbits. RIFM Report Number 3099, June 1. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1985b. Closed epicutaneous test of methyl-2-octynoate, methyl-2-nonynoate, benzyl acetate, trans, trans-2, 4-hexadienal, 2-hexylidene cyclopentanone, hexen-2-al, trans-2-hexenal diethyl acetal and isoeugenol in guinea pigs. RIFM Report Number 4474, October 25. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1985c. Guinea pig maximization test. RIFM Report Number 4899, November 4. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1985d. Open and closed epicutaneous and maximization tests of fragrance materials in guinea pigs. Unpublished report from Givaudan Corporation. RIFM Report Number 6068, November 12. RIFM, Woodcliff Lake, NJ, USA.
RIFM (Research Institute for Fragrance Materials, Inc.), 1985e. Report on human maximization studies. RIFM Report Number 1919, January 7. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1986. Delayed contact hypersensitivity study of benzyl acetate in guinea pigs. RIFM Report Number 4513, December 9. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1987a. Delayed contact hypersensitivity in guinea pigs with carbonic acid, methyl phenylmethyl ester. Unpublished report from International Flavors and Fragrances. RIFM Report Number 48818, October 12. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1987b. Report on human repeated insult patch test. RIFM Report Number 7973, July 20. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1988a. Repeated insult patch test in human subjects. Unpublished report from RIFM. RIFM Report Number 8881, December 16. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1988b. Repeated insult patch test in human subjects. RIFM Report Number 27673, February 8. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1988c. Repeated insult patch test in human subjects. RIFM Report Number 27674, October 2. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1988d. Repeated insult patch test in human subjects. RIFM Report Number 27675, March 17. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1989a. Acute dermal toxicity study of *alpha,alpha*-dimethylphenethyl formate in the rat. Unpublished report from Firmenich Inc. RIFM Report Number 41297, October 6. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1989b. Bacterial reverse mutation assay with *alpha, alpha*-dimethylphenethyl formate. Unpublished report from Firmenich Inc. RIFM Report Number 41301, October 18. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1989c. Acute dermal irritation study of *alpha, alpha*-dimethylphenethyl formate in rabbits. Unpublished report from Firmenich Inc. RIFM Report Number 41298, September 14. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1989d. Eye irritation study of *alpha,alpha*-dimethylphenethyl formate in rabbits. Unpublished report from Firmenich Inc. RIFM Report Number 41299, October 13. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1990a. The absorption, distribution and elimination of 2-[(14) C]-phenoxyethyl isobutyrate following topical administration to rats. RIFM Report Number 23241, June. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1990b. Acute oral toxicity study with *alpha,alpha*-dimethylphenethyl formate in the rat. Unpublished report from Firmenich Inc. RIFM Report Number 41296, January 3. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1990c. 13-Week dermal toxicity study of 2-phenoxyethyl isobutyrate in rats, Date. RIFM Report Number 23239, date. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1990d. Sensitization test with *alpha,alpha*-dimethylphenethyl formate in the guinea pig: Magnusson and Kligman maximization method. Unpublished report from Firmenich Incorporated. RIFM Report Number 41300, September 6. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1993. Primary skin irritation study and phototoxicity study in guinea pigs of anisyl acetate. Unpublished report from Takasago International Corp. RIFM Report Number 31611, December 9. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1994a. 2-Week dermal dose range finding study of diphenyl ether, beta-naphthyl methyl ether, *p*-methylanisol and 2-phenoxyethyl isobutyrate in rats. RIFM Report Number 23238, April 5. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1994b. Ocular and dermal studies on benzyl acetate, *alpha*-hexylcinnamaldehyde, decanal, lauric aldehyde, *alpha*-amylcinnamaldehyde and octanal in rabbits. Unpublished report from Bush Boake Allen Ltd. RIFM Report Number 23201, August 19. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1997a. Benzyl acetate-Acute inhalation toxicity in rats 4-h exposure. Unpublished report from Haarmann and Reimer GmbH, Date. RIFM Report Number 35546, May 8. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 1997b. Delayed contact hypersensitivity study in guinea pigs of anisyl acetate. Unpublished report from Takasago International Corp. RIFM Report Number 31604, December 9. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000a. Mutagenicity study of phenethyl acetate in the Salmonella typhimurium/mammalian microsome reverse mutation assay (Ames-test). Unpublished report from Haarman & Reimer GmbH. RIFM Report Number 57617, December 18. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000b. Mutagenicity study of para-anisyl acetate in the Salmonella typhimurium/mammalian microsome reverse mutation assay (Ames-test). Unpublished report from Haarman & Reimer GmbH. RIFM Report Number 57681, July 17. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000c. alpha,alpha-Dimethylphenethyl butyrate: acute eye irritation/corrosion study in the rabbit. Unpublished report from Haarman & Reimer GmbH. RIFM Report Number 57606. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2000d. Benzyl formate: acute eye irritation/corrosion study in the rabbit. Unpublished report from Haarman & Reimer GmbH. RIFM Report Number 52920. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2001a. Mutagenicity study of *a,a*-dimethylphenethyl butyrate in a Salmonella typhimurium/mammalian microsome reverse mutation assay (Ames test). Unpublished report from Haarman & Reimer GmbH. RIFM Report Number 57607, January 19. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2001b. Mutagenicity study of phenethyl isobutyrate in the Salmonella typhimurium/mammalian microsome reverse mutation assay (Ames-test). Unpublished report from Haarman & Reimer GmbH. RIFM Report Number 57723, April 17. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2001c. Phenethyl isobutyrate: acute eye irritation/corrosion study in the rabbit. Unpublished report from Haarman & Reimer GmbH. RIFM Report Number 57722, March 21. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2002a. Evaluation of the mutagenic activity of phenethyl acetate in the Salmonella typhimurium reverse mutation assay. Unpublished report from Givaudan. RIFM Report Number 43053, October 31. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2002b. 2-Phenoxyethyl isobutyrate: local lymph node assay (LLNA) in mice. Unpublished report from Givaudan. RIFM Report Number 57200, October 21. RIFM, Woodcliff Lake, NJ, USA.

RIFM (Research Institute for Fragrance Materials, Inc.), 2003. *p*-Anisyl acetate: reverse mutation in Salmonella typhimurium. Unpublished report from Givaudan. RIFM Report Number 43807, December 11. RIFM, Woodcliff Lake, NJ, USA.

Rogan, E.G., Cavalieri, E.L., Walker, B.A., Balasubramanian, R., Wislocki, P.G., Roth, R.W., Saugier, R.K., 1986. Mutagenicity of benzylic acetates, sulfates and bromides of polycyclic aromatic hydrocarbons. Chemical Biology International Report 58 (3), 253–275.

Rossman, T.G., Molina, M., Meyer, L., Boone, P., Klein, C.B., Wang, Z., Li, F., Lin, W.C., Kinney, P.L., 1991. Performance of 133 compounds in the lambda prophage induction endpoint of the micro screen assay and a comparison with *S. typhimurium* mutagenicity and rodent carcinogenicity assays. Mutation Research 260, 349–367.

Rudd, C.J., Mitchell, A.D., Spalding, J., 1983. L5178Y Mouse lymphoma cell mutagenesis assay of coded chemicals incorporating analyses of the colony size distributions. Environmental Mutagenesis 5 (3), 419.

Sandmeyer, E.E., Kirwin, C.J., 1981. Esters, . third ed.. In: Clayton, G.D., Clayton, F.E. (Eds.), Patty's Industrial hygiene and toxicology third ed., vol. IIa New York Interscience Publishers, p. 2281.

Sasaki, Y.F., Sekihashi, K., Izumiyama, F., Nishidate, E., Saga, A., Ishida, K., Tsuda, S., 2000. The Comet assay with multiple mouse organs: comparison of comet assay results and carcinogenicity with 208 chemicals selected from the IARC monographs and US NTP carcinogenicity database. Critical Reviews in Toxicology 30 (6), 629–799.

Scheline, R.R., 1972. The metabolism of some aromatic aldehydes and alcohols by the rat intestinal microflora. Xenobiotica 2, 227–236 (as cited by JECFA, 2002a).

Schunk, H.H., Shibamoto, T., Tan, H.K., Wei, C.-I., 1986. Biological and chemical studies on photochemical products obtained from eugenol, benzyl acetate and benzyl benzoate. Flavors and fragrances: A world perspective. In: Proceedings of the 10th International Congress of Essential Oils, Fragrances and Flavors, pp. 1045–1068.

Sekihashi, K., Yamamoto, A., Matsumura, Y., Ueno, S., Watanabe-Akanuma, M., Kassie, F., Knasmuller, S., Tsuda, S., Sasaki, Y.F., 2002. Comparative investigation of multiple organs of mice and rats in the comet assay. Mutation Research 517 (1–2), 53–75.

Sharp, D.W., 1978. The sensitization potential of some perfume ingredients tested using a modified Draize procedure. Toxicology 9 (3), 261–271.

Shelby, M.D., Erexson, G.L., Hook, G.L., Tice, R.R., 1993. Evaluation of a three-exposure mouse bone marrow micronucleus protocol: results with 49 chemicals. Environmental and Molecular Mutagenesis 21 (2), 160–179.

Silver, W.L., 1992. Neural and pharmacological basis for nasal irritation. In: Annals of the New York Academy of Sciences, vol. 641, pp. 152–163.

Smith, J.N., Smithies, R.H., Williams, R.T., 1954. Studies in detoxication. 56. The metabolism of alkylbenzenes: stereochemical aspects of the biological hydroxylation of ethylbenzene to methylphenylcarbinol. Biochemical Journal 56, 320–324 (as cited by JECFA, 2002a).

Smith, J.S., Macina, O.T., Sussman, N.B., Karol, M.H., Maibach, H.I., 2000. Experimental validation of a structure–activity relationship model of skin irritation by esters. Quantitative Structure–Activity Relationships 19 (5), 467–474.

Snapper, J., Gruenbaum, A., Sturkop, S., 1925. Uber die Spaltung und die Oxydation von Benzylalkohol und Benzylestern im Menschlichen Organismus [About the fission and oxidation of benzyl alcohol and benzyl esters in the human organism]. Biochemistry Zeitschrift 155, 163–173.

Stein, W.H., Paladini, A.C., Hirs, C.H., Moore, S., 1954. A phenylacetylglutamine as a constituent of normal human urine (Letter to the Editor). Journal of Chemical Society of Perkin Transactions 76, 2848–2849 (as cited in JECFA, 2003).

Steinmetz, K.L., Mirsalis, J.C., 1984. Measurement of DNA repair in primary cultures of rat pancreatic cells following *in vivo* treatment. Environmental Mutagenesis 6 (3), 446.

Stoner, G.D., Shimkin, M.B., Kniazeff, A.J., Weisburger, J.H., Weisburger, E.K., Go, G.B., 1973. Test for carcinogenicity of food additives and chemotherapeutic agents by the pulmonary tumor response in strain A mice. Cancer Research 33 (12), 3069–3085.

Sullivan, H.R., Miller, W.M., McMahon, R.E., 1976. Reaction pathways of *in vivo* stereoselective conversion of ethylbenzene to (−)-mandelic acid. Xenobiotica 6, 49–54 (as cited by JECFA 2002a).

Takenaka, T., Hasegawa, E., Takenaka, U., Saito, F., Odaka, T., 1968. Fundamental studies of safe compound perfumes for cosmetics. Part 1. The primary irritation of compound materials to the skin. Preprint of Scientific Papers, The Fifth Congress of International Federation of Societies of Cosmetic Chemists, May 12–17, Tokyo, pp. 313–329.

Temellini, A., Mogavero, S., Giulianotti, P.C., Pietrabissa, A., Mosca, F., Pacifici, G.M., 1993. Conjugation of benzoic acid with glycine in human liver and kidney: a study on the interindividual variability. In: Fifth North American ISSX Meeting, Tucson, AZ, USA, vol. 4, p. 250 (as cited in JECFA, 2002a).

Tennant, R.W., Margolin, B.H., Shelby, M.D., Zeiger, E., Haseman, J.K., Spalding, J., Caspary, W., Resnick, M., Stasiewicz, S., Anderson, B., Minor, R., 1987. Prediction of chemical carcinogenicity in rodents from *in vitro* genetic toxicity assays. Science 236, 933–941.

Thierfelder, H., Daiber, K., 1923. Behavior of aliphatic-aromatic ketones in the animal body. Zeitschrift fur Physiologische Chemie 130, 380–396 (as cited in JECFA, 2002a).

USEPA, 1985. Chemical hazard information profile. 20 Phenylethanol and 2-phenylethyl acetate. Draft Report. US Environmental Protection Agency, 17 May 1985.

VCF (Volatile Compounds in Food): database. In: Nijssen, L.M., Ingen-Visscher, C.A., van Donders, J.J.H. (Eds.), Version 11.1.1 – TNO Quality of Life, Zeist, The Netherlands, pp. 1963–2010.

World Health Organization, 1996. Benzyl acetate, benzyl alcohol, benzaldehyde and benzoic acid and its salts. WHO Food Additives Series 37, pp. 31–79.

Wild, D., King, M.T., Gocke, E., Eckhardt, K., 1983. Study of artificial flavouring substances for mutagenicity in the Salmonella/microsome, basic and micronucleus tests. Food and Chemical Toxicology 21 (6), 707–719.

Williams, R., 1959. Detoxication mechanisms: the metabolism and detoxication of drugs, toxic substances, and other organic compounds, second ed. Chapman & Hall, London, pp. 67–69.

Witt, K.L., Knapton, A., Wehr, C.M., Hook, G.J., Mirsalis, J., Shelby, M.D., Macgregor, J.T., 2000. Micronucleated erythrocyte frequency in peripheral blood of B6C3F1 mice from short-term, prechronic, and chronic studies of the NTP carcinogenesis bioassay program. Environmental and Molecular Mutagenesis 36 (3), 163–194.

Wright, D.J., Holder, G.M., 1980. The metabolism of some food additives related to piperonal in the rabbit. Xenobiotica 10 (4), 265–270.

Yasunaga, K., Kiyonari, A., Oikawa, T., Abe, N., Yoshikawa, K., 2004. Evaluation of the Salmonella umu test with 83 NTP chemicals. Environmental and Molecular Mutagenesis 44 (4), 329–345.

Yoo, Y.S., 1985. Mutagenic and antimutagenic activities of flavoring agents used in foodstuffs. Journal Osaka City Medical Center 34 (3–4), 267–288.

Yoo, Y.S., 1986. Mutagenic and antimutagenic activities of flavoring agents used in foodstuffs. Osaka-shi Igakkai Zasshi [Journal Osaka City Medical Center] 34 (3–4), 267–288.

Yoshikawa, K., 1996. Anomalous nonidentity between Salmonella genotoxicants and rodent carcinogens: nongenotoxic carcinogens and genotoxic noncarcinogens. Environmental Health Perspectives 104 (1), 40–46.

Young, S.S., 1989. What is the proper experimental unit for long-term rodent studies? An examination of the NTP benzyl acetate study. Toxicology 54, 233–239.

Yuan, J.H., Goehl, T.J., Abdo, K., Clark, J., Espinosa, O., Bugge, C., Garcia, D., 1995. Effects of gavage versus dosed feed administration on the toxicokinetics of benzyl acetate in rats and mice. Food and Chemical Toxicology 33 (2), 151–158.

Zaitsev, A.N., Rakhmanina, N.L., 1974. Toxic properties of phenylethanol and cinnamic alcohol derivatives. Voprosy Pitaniya 6, 48–53.