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Review

A toxicologic and dermatologic assessment of related esters and alcohols of cinnamic acid and cinnamyl alcohol when used as fragrance ingredients ☆

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Abstract

An evaluation and review of a structurally related group of fragrance materials.

Keywords: Safety; Review; Fragrance; Esters; Alcohols; Cinnamic

Contents

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1. Introduction

This report summarizes scientific data relevant to the risk assessment of related esters and alcohols of cinnamic acid and cinnamyl alcohol (see Table 1). These substances are all used as fragrance ingredients. This report uses data from animals and humans by various routes of exposure, but emphasizes the risk assessment for the use of related esters and alcohols of cinnamic acid and cinnamyl alcohol as fragrance ingredients. 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. This assessment, therefore, addresses the use of the material as a fragrance ingredient.

The current format includes a group summary evaluation paper and individual Fragrance Materials 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 protocols that conform with current guidelines, quality of the data, statistical significance and appropriate exposure. These are identified in tabular form in the group summary. The Fragrance Material Reviews (available online at www.rifm.org) contain a comprehensive summary of published and non-published reports including complete bibliographies.

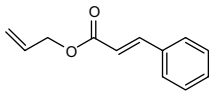
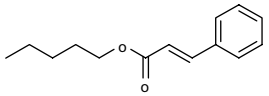
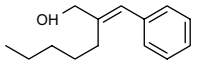
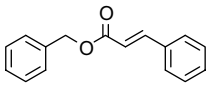
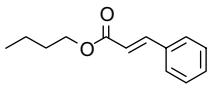
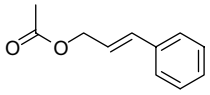
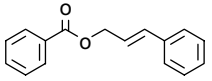
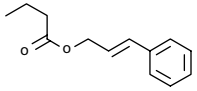
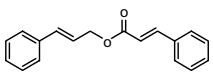
2. Chemical identity and exposure (Table 1)

In the United States, the regulatory status of these materials includes approval of 21 substances (21 CFR 172.515) by the Food and Drug Administration (FDA) and 20 materials by the Flavor and Extract Manufacturers' Association (FEMA, 1965) as Generally Recognized as Safe (GRAS) as flavor ingredients [Numbers 2022, 2063, 2064, 2065, 2142, 2192, 2193, 2293, 2296, 2297, 2298, 2299, 2300, 2301, 2302, 2430, 2641, 2698, 2863, 2939]. Twenty one of these materials were also included in the Council of Europe's list of substances [Numbers 79, 208, 216, 235, 279, 323, 325, 326, 327, 328, 329, 331, 332, 333, 335, 336, 352, 414, 454, 496, 743] which may be used in foodstuffs (Council of Europe, 2000). Finally, the International Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2000) has evaluated 19 of these materials and found them to have no safety concerns based on current levels of intake as food flavors.

Seven of the 23 substances have been reported as common components of food occurring mainly in a wide variety of fruits, vegetables, herbs and spices in varying concentrations. For example, concentrations of 2800–51,000 ppm cinnamyl acetate in cinnamon (*Cinnamomum zeylanicum* Blume and other *Cinnamomum* species), and trace-278,000 ppm methyl cinnamate in basil (*Ocimum basilicum* varieties) have been reported (TNO, 2006). Quantitative natural occurrence data have been reported for methyl cinnamate and ethyl cinnamate, and indicate that intake of these substances is predominately from food (i.e., consumption ratio >1) (Stofberg and Grundschober, 1987).

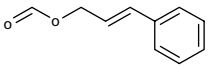
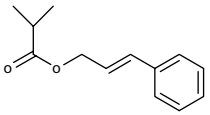
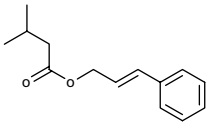
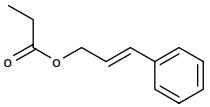
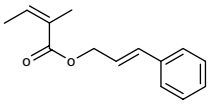
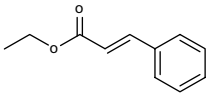
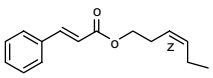
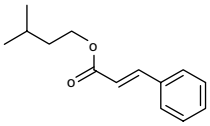
Data from a survey conducted in the year 2004 indicate that the annual worldwide use of benzyl cinnamate, cinnamyl acetate and methyl cinnamate is between 10 and 100 metric tons (see Table 1) and the annual worldwide

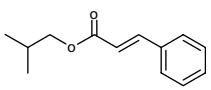
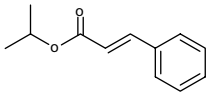
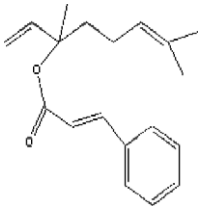
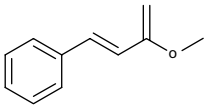
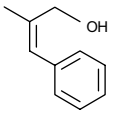
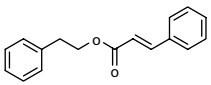
Table 1
Material identification and summary of volume of use and dermal exposure

Material	Synonyms	Structure	Annual worldwide (metric tons)[a]	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin Level[b]
Allyl cinnamate CAS# 1866-31-5 Molecular weight: 188.23 Log K_{ow} (calculated): 3.2	• Allyl β-phenylacrylate • Allyl 3-phenyl-2-propenoate • 2-Propenoic acid, 3-phenyl-, 2-propenyl ester • Propenyl cinnamate • 2-Propen-1-yl 3-phenyl-2-propenoate • Vinyl carbinyl cinnamate		<0.1	0.0127	0.10%
Amyl cinnamate CAS# 3487-99-8 Molecular weight: 218.3 Log K_{ow} (calculated): 4.32	• Pentyl cinnamate • Pentyl 3-phenyl-2-propenoate • 2-Propenoic acid, 3-phenyl-, pentyl ester		<0.1	0.0127	0.10%
***alpha*-Amylcinnamyl alcohol** CAS# 101-85-9 Molecular weight: 204.31 Log K_{ow} (calculated): 4.35	• α-Amylcinnamic alcohol • 2-Amyl-3-phenyl-2-propen-1-ol • 2-Benzylideneheptanol • 1-Heptanol, 2-(phenylmethylene)- • α-Pentylcinnamyl alcohol		0.1–1	0.0038	0.04%
Benzyl cinnamate CAS# 103-41-3 Molecular weight: 238.29 Log K_{ow} (calculated): 4.06	• Benzyl β-phenylacrylate • Benzyl 3-phenylpropenoate • Cinnamein • 2-Propenoic acid, 3-phenyl-, phenylmethyl ester		10–100	0.0022	0.89%
Butyl cinnamate CAS# 538-65-8 Molecular weight: 204.27 Log K_{ow} (calculated): 3.83	• *n*-Butyl cinnamate • Butyl β-phenylacrylate • *n*-Butyl phenylacrylate • Butyl 3-phenylpropenoate • 2-Propenoic acid, 3-phenyl-, butyl ester		<0.1	0.0127	0.10%
Cinnamyl acetate CAS# 103-54-8 Molecular weight: 176.22 Log K_{ow} (calculated): 2.85	• 3-Phenylallyl acetate • 3-Phenyl-2-propen-1-yl acetate • 2-Propen-1-ol, 3-phenyl-, acetate		10–100	0.0115	0.62%
Cinnamyl benzoate CAS# 5320-75-2 Molecular weight: 238.29 Log K_{ow} (calculated): 4.3	• 3-Phenyl-2-propen-1-yl benzoate • 2-Propen-1-ol, 3-phenyl-, benzoate		<0.1	0.0127	0.10%
Cinnamyl butyrate CAS# 103-61-7 Molecular weight: 204.27 Log K_{ow} (calculated): 3.83	• Butanoic acid, 3-phenyl-2-propenyl ester • 3-Phenylallyl butyrate • 3-Phenyl-2-propen-1-yl butanoate		<0.1	0.0025	0.02%
Cinnamyl cinnamate CAS# 122-69-0 Molecular weight: 264.33 Log K_{ow} (calculated): 4.83	• Phenylallyl cinnamate • 3-Phenylallyl cinnamate • 3-Phenyl-2-propen-1-yl 3-phenylpropenoate • 2-Propenoic acid, 3-phenyl-, 3-phenyl-2-propenyl-ester		0.1–1	0.0061	0.24%

(*continued on next page*)

Table 1 (*continued*)

Material	Synonyms	Structure	Annual worldwide (metric tons)[a]	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin Level[b]
Cinnamyl formate CAS# 104-65-4 Molecular weight: 162.19 Log K_{ow} (calculated): 2.3	• 3-Phenylallyl formate • 3-Phenyl-2-propen-1-yl formate • 2-Propen-1-ol, 3-phenyl-, formate		0.1–1	0.0010	0.01%
Cinnamyl isobutyrate CAS# 103-59-3 Molecular weight: 204.27 Log K_{ow} (calculated): 3.76	• Cinnamyl 2-methylpropanoate • 3-Phenyl-2-propen-1-yl isobutyrate • 3-Phenyl-2-propen-1-yl 2-methylpropanoate • Propanoic acid, 2-methyl-, 3-phenyl-2-propenyl ester		0.1–1	0.0005	0.02%
Cinnamyl isovalerate CAS# 140-27-2 Molecular weight: 218.39 Log K_{ow} (calculated): 4.25	• Butanoic acid, 3-methyl-, 3-phenyl-2-propenyl ester • Cinnamyl 3-methylbutanoate • 3-Phenylallyl isovalerate • 3-Phenylallyl 3-methylbutanoate • 3-Phenyl-2-propen-1-yl 3-methylbutanoate		<0.1	0.0008	0.002%
Cinnamyl propionate CAS# 103-56-0 Molecular weight: 190.24 Log K_{ow} (calculated): 3.34	• 3-Phenylallyl propionate • 3-Phenyl-2-propenyl propanoate • 3-Phenyl-2-propen-1-yl propionate • 2-Propen-1-ol, 3-phenyl-, propanoate		0.1–1	0.0023	0.02%
Cinnamyl tiglate CAS# 61792-12-9 Molecular weight: 216.28 Log K_{ow} (calculated): 4.16	• 2-Butenoic acid, 2-methyl-, 3-phenyl-2-propenyl-ester, (2E)- • Cinnamyl *trans*-2-methyl-2-butenoate • Cinnamyl 2-methylcrotonate • Cinnamyl α-methylcrotonate		<0.1	0.0003	0.002%
Ethyl cinnamate CAS# 103-36-6 Molecular weight: 176.22 Log K_{ow} (calculated): 2.85	• Ethyl phenylacrylate • Ethyl 3-phenylpropenoate • 2-Propenoic acid, 3-phenyl-, ethyl ester		1–10	0.0003	0.13%
***cis*-3-Hexenyl cinnamate** CAS# 68133-75-5 Molecular weight: 230.07 Log K_{ow} (calculated): 4.6	• (Z)-3-Hexenyl cinnamate • 2-Propenoic acid, 3-phenyl-, (3Z)-3-hexenyl ester • 2-Propenoic acid, 3-phenyl-, 3-hexenyl ester, (?,Z)-		<0.1	0.0178	0.08%
Isoamyl cinnamate CAS# 7779-65-9 Molecular weight: 218.3 Log K_{ow} (calculated): 4.25	• Amyl(iso) cinnamate • Isoamyl β-phenylacrylate • Isopentyl cinnamate • Isopentyl β-phenylacrylate • Isopentyl 3-phenylpropenoate • 2-Propenoic acid, 3-phenyl-, 3-methylbutyl ester		0.1–1	0.0029	0.05%

Isobutyl cinnamate CAS# 122-67-8 Molecular weight: 204.27 Log K_{ow} (calculated): 3.76	• Isobutyl β-phenylacrylate • Isobutyl 3-phenylpropenoate • Labdanol • 2-Methylpropyl cinnamate • 2-Methylpropyl β-phenylacrylate • 2-Methylpropyl 3-phenylpropenoate • 2-Propenoic acid, 3-phenyl-, 2-methylpropyl ester		0.1–1	0.0127	0.10%
Isopropyl cinnamate CAS# 7780-06-5 Molecular weight: 190.24 Log K_{ow} (calculated): 3.27	• Isopropyl 3-phenylpropenoate • 1-Methylethyl 3-phenylpropenoate • 2-Propenoic acid, 3-phenyl-, 1-methylethyl ester		0.1–1	0.0008	0.01%
Linalyl cinnamate CAS# 78-37-5 Molecular weight: 284.4 Log K_{ow} (calculated): 6.37	• Cinnamic acid, linalyl ester • 3,7-Dimethyl-1,6-octadien-3-yl cinnamate • 3,7-Dimethyl-1,6-octadien-3-yl β-phenylacrylate • 3,7-Dimethyl-1,6-octadien-3-yl 3-phenylpropenoate • Linalyl 3-phenylpropenoate • 2-Propenoic acid, 3-phenyl-, 1-ethenyl-1,5-dimethyl-4-hexenyl ester		0.1–1	0.0268	0.42%
Methyl cinnamate CAS# 103-26-4 Molecular weight: 162.19 Log K_{ow} (calculated): 2.36	• Methyl 3-phenylpropenoate • 2-Propenoic acid, 3-phenyl-, methyl ester		10–100	0.0054	0.31%
α-Methylcinnamic alcohol CAS# 1504-55-8 Molecular weight: 148.21 Log K_{ow} (calculated): 2.39	• Cinnamyl alcohol, α-methyl- • Methylcinnamic alcohol • α-Methylcinnamyl alcohol • 3-Phenyl-2-methyl-2-propen-1-ol		0.1–1	0.0051	0.01%
Phenethyl cinnamate CAS# 103-53-7 Molecular weight: 252.32 Log K_{ow} (calculated): 4.56	• Benzylcarbinyl cinnamate • β-Phenethyl β-phenylacrylate • Phenylethyl cinnamate • 2-Phenylethyl cinnamate • 2-Phenylethyl 3-phenylpropenoate • 2-Propenoic acid, 3-phenyl-, 2-phenylethyl ester		1–10	0.0196	0.22%

[a] 2004 IFRA volume of use survey.

[b] The maximum skin levels are based on the assumption that the fragrance mixture is used at 20% in a consumer product (IFRA Use Level Survey).

use of ethyl cinnamate and phenethyl cinnamate is between 1 and 10 metric tons and the annual worldwide use of the other cinnamyl materials range from <0.1 to 1 metric ton (Table 1).

The most recent total annual volume and exposure data for these compounds in fine fragrances, personal care products, and household products comes from a 2004 survey. Data from this survey indicates that the annual worldwide use of these materials ranges from a high of approximately 27 metric tons for methyl cinnamate to a low of 0.001 metric tons for cinnamyl benzoate and *cis*-3-hexenyl cinnamate with a majority of the materials being used at less than one metric ton (see Table 1).

2.1. Estimated consumer exposure

The availability of fragrance ingredients for potential exposure by consumers is estimated in two ways (see Table 1). One is for estimating potential percutaneous absorption from the entire body due to the use of many different fragranced products. The other is for estimating potential dermal exposure due to the use of products, such as fine fragrances, that usually contain higher concentrations and are used on smaller localized skin sites. Thus potential systemic exposure to linalyl cinnamate from ten types of cosmetic products (body lotion, face cream, eau de toilette, fragrance cream, anti-perspirant, shampoo, bath products, shower gel, toilet soap and hair spray) using an average 97.5 percentile concentration of 1.05% is calculated as 0.0268 mg/kg body weight/day (IFRA, 2001). The calculated exposures for the other cinnamyl materials range from 0.0003 mg/kg body weight/day for cinnamyl tiglate to 0.0196 mg/kg body weight/day for phenethyl cinnamate (IFRA, 2001) (see Table 1). For consideration of potential sensitization, the exposure is calculated as a per cent concentration used on the skin. Thus exposure to linalyl cinnamate used in fine fragrance products is reported as 0.42% based on the use of 20% of the fragrance mixture containing the fragrance material in the fine fragrance consumer product (IFRA, 2001). The comparable exposures for the other cinnamyl materials range from 0.002% for cinnamyl tiglate to 0.89% for benzyl cinnamate (IFRA, 2001) (see Table 1). Exposure data are provided by the fragrance industry. An explanation of how the data are obtained and how exposure is determined has been reported by Cadby et al. (2002) and Ford et al. (2000).

3. Biological data

3.1. Absorption, distribution and metabolism

3.1.1. Percutaneous absorption

There are no absorption studies on these cinnamyl materials. However, there are limited data on the absorption of cinnamyl alcohol, cinnamaldehyde and cinnamic acid through the skin. The data that exist suggest that there is significant absorption through the skin. A conservative estimate from in vitro studies on human skin is that 61% cinnamic acid, 52% cinnamaldehyde and 66% cinnamyl alcohol are absorbed through the skin (Bickers et al., 2005).

3.1.2. Pharmacokinetics

Cinnamyl alcohol, cinnamaldehyde and cinnamic acid have all been shown to be rapidly absorbed from the gut, metabolized and excreted primarily in the urine and, to a minor extent, in the feces. Results of studies beginning in 1909 indicate that cinnamyl derivatives are absorbed, metabolized and excreted as polar metabolites within 24 h. Recent studies in laboratory animals on the effects of dose, species, sex, and mode of administration on the absorption, metabolism and excretion of cinnamyl alcohol, cinnamaldehyde and cinnamic acid are discussed in detail in Bickers et al. (2005). After oral or intraperitoneal administration to rats and mice, 76–77%, 69–98% and 73–94% [^{14}C] of the dose of cinnamyl alcohol, cinnamaldehyde and cinnamic acid, respectively, were recovered in the urine and feces within 24 h (Bickers et al., 2005). In human subjects, plasma was cleared of cinnamic acid within 20 minutes after a single intravenous dose; 100% of a dose of cinnamaldehyde was recovered as metabolites in the urine within 8 h (Bickers et al., 2005).

In rats, 1.5 mmol/kg body weight dose of methyl cinnamate was rapidly and almost completely (95%) absorbed from the gut after oral administration. Methyl cinnamate was hydrolyzed to some extent in the stomach (approximately 9% of the administered methyl cinnamate was detected in the stomach of the rat as cinnamic acid) and approximately 40% of the administered ester was detected in the lower part of the gut as cinnamic acid. The rates of absorption for cinnamic acid and methyl cinnamate from the gut was similar. No ester was detected in the peripheral blood of dosed rabbits or rats. Only traces were detected in portal and heart blood samples taken from dosed rats, indicating that almost complete hydrolysis of methyl cinnamate occurred upon or during absorption from the gut (Fahelbum and James, 1977).

3.1.3. Metabolism

These substances are simple aromatic compounds and they participate in common routes of absorption, distribution, and metabolic detoxication, and exhibit similar toxicological endpoints. The members of this group are expected to be hydrolyzed to yield the component alcohol, aldehyde, or acid. If the product is an alcohol or aldehyde, it is oxidized to yield the corresponding 3-phenylpropenoic acid or a 3-phenylpropanoic acid derivative which undergoes further side-chain β-oxidation and cleavage to yield mainly the corresponding benzoic acid derivatives (Williams, 1959). The benzoic acid derivatives are conjugated with glycine and/or glucuronic acid and excreted primarily in the urine (Snapper et al., 1940). To a minor extent, the presence of *o*-alkyl- and *o*-alkoxy-ring substituents may lead to alternative metabolic pathways (Solheim and

Scheline, 1973; Solheim and Scheline, 1976; Samuelsen et al., 1986).

In general, esters containing an aromatic ring system are expected to be hydrolyzed in vivo. Hydrolysis is catalyzed by classes of enzymes recognized as carboxylesterases or esterases (Heymann, 1980), the most important of which are the A-esterases. In mammals, A-esterases occur in most tissues throughout the body (Anders, 1989; Heymann,

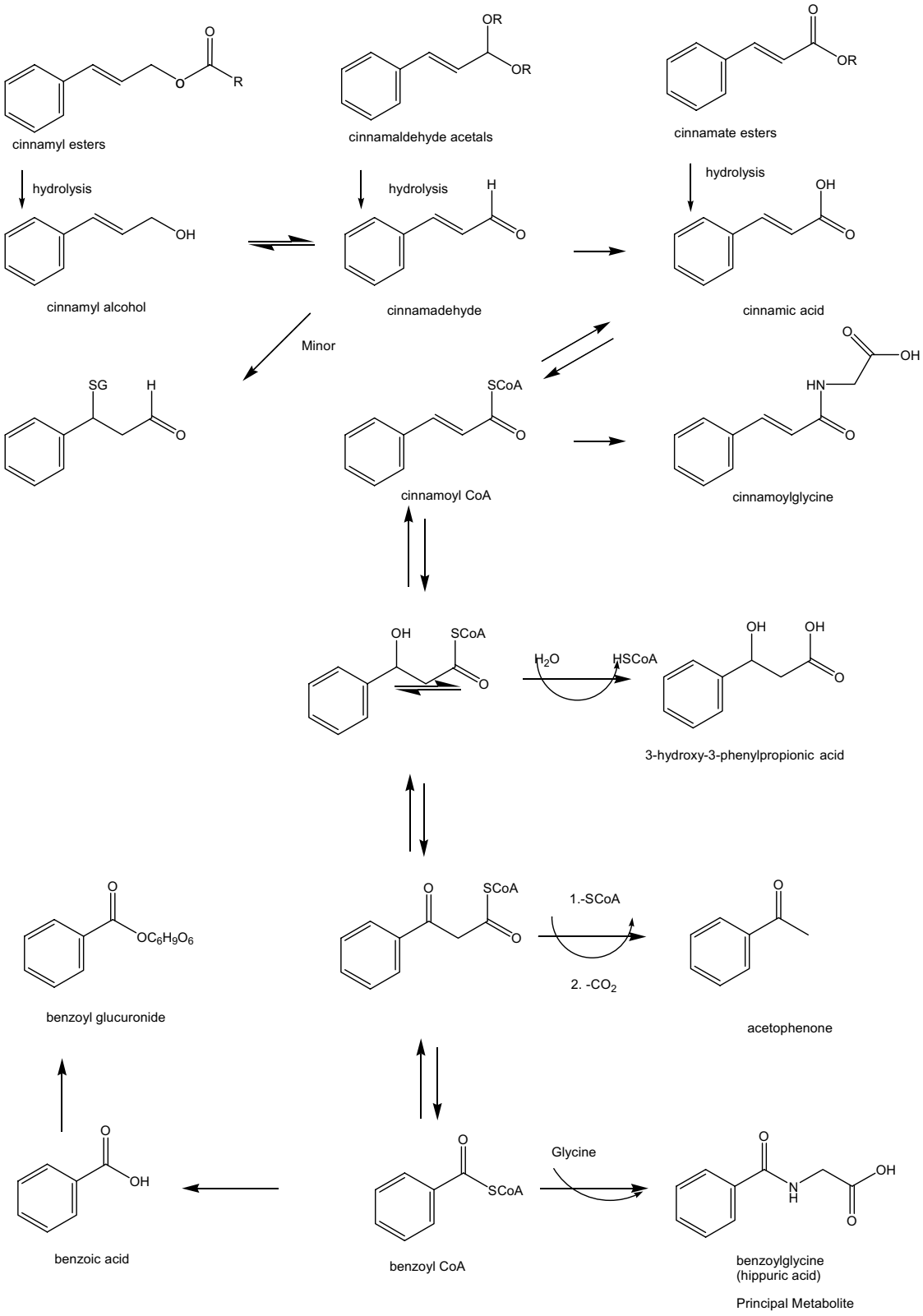


Fig. 1. Metabolism of cinnamyl derivatives.

1980) but predominate in the hepatocytes (Heymann, 1980).

Esters of cinnamic acid and structurally related aromatic esters have been shown to hydrolyze rapidly to the component acid and alcohol. Oral administration of methyl cinnamate (50 mg/kg body weight) resulted in the urinary excretion, after 24 h, of hippuric acid (66%) and benzoylglucuronide (5%). This distribution of metabolites, nearly identical to that for cinnamic acid, indicates that rapid hydrolysis of the ester in vivo precedes metabolism of the acid (Fahelbum and James, 1977). Ethyl cinnamate administered subcutaneously to a cat produced cinnamic acid metabolites that were excreted in the urine (Dakin, 1909). Eighty percent hydrolysis was measured when benzyl cinnamate was incubated with simulated intestinal fluid (pH 7.5; pancreatin) at 37° for 2 h (Grundschober, 1977).

The aromatic primary alcohols used as flavoring substances or formed by the hydrolysis of esters and acetals are readily oxidized to a cinnamic acid derivative (see Fig. 1). Human NAD^+ dependent alcohol dehydrogenase (ADH) catalyzes oxidation of primary alcohols to aldehydes (Pietruszko et al., 1973). Aromatic alcohols have been reported to be excellent substrates for ADH (Sund and Theorell, 1963). The aldehydes that are formed are

Table 2A
Acute toxicity oral studies

Material	Species	No. animals/dose group	LD_{50}[a]	References
Allyl cinnamate	Rat	10 (5/sex)	1.52 g/kg body weight (95% C.I. 0.79–1.29 g/kg body weight)	Jenner et al. (1964)
α-Amylcinnamyl acetate[b]	Rat	10	>5.0 g/kg body weight	RIFM (1974a)
α-Amylcinnamyl alcohol	Rat	10	4.0 g/kg body weight (95% C.I. 3.08–5.20 g/kg body weight)	RIFM (1973a)
Benzyl cinnamate	Rat	10 (5/sex)	3.28 g/kg body weight (95% C.I. 2.62–4.10 g/kg body weight)	RIFM (1972a)
Benzyl cinnamate	Rat	10 (5/sex)	5.53 g/kg body weight (95% C.I. 3.10–7.74 g/kg body weight)	Jenner et al. (1964)
Benzyl cinnamate	Guinea pig	Not specified	3.760 g/kg body weight (95% C.I. 2.340–6.055 g/kg body weight)	Jenner et al. (1964)
Butyl cinnamate	Rat	10	>5.0 g/kg body weight	RIFM (1977a)
Cinnamyl acetate	Rat	10	3.3 g/kg body weight (95% C.I. 2.9–3.7 g/kg body weight)	RIFM (1972b)
Cinnamyl benzoate	Rat	10	4.0 g/kg body weight (95% C.I. 3.56–4.44 g/kg body weight)	RIFM (1975a)
Cinnamyl butyrate	Rat	10	>5.0 g/kg body weight	RIFM (1976a)
Cinnamyl cinnamate	Rat	10	4.2 g/kg body weight	RIFM (1974b)
Cinnamyl formate	Rat	10	2.9 g/kg body weight (95% C.I. 2.38–3.54 g/kg body weight)	RIFM (1973b)
Cinnamyl isobutyrate	Rat	10	>5.0 g/kg body weight	RIFM (1977a)
Cinnamyl isovalerate	Rat	10	≥5.0 g/kg body weight	RIFM (1973c)
Cinnamyl propionate	Rat	10	3.4 g/kg body weight (95% C.I. 3.2–3.6 g/kg body weight)	RIFM (1973d)
Cinnamyl tiglate	Rat	10	>5.0 g/kg body weight	RIFM (1975b)
Ethyl cinnamate	Guinea pig	6	4.0 g/kg body weight	Zaitsev and Rakhmanina (1974)
Ethyl cinnamate	Rat	6	4.0 g/kg body weight	Zaitsev and Rakhmanina (1974)
Ethyl cinnamate	Mouse	6	4.0 g/kg body weight	Zaitsev and Rakhmanina (1974)
Ethyl cinnamate	Rat	Not reported	1.52 g/kg body weight	Bar and Griepentrog (1967)
Isoamyl cinnamate	Rat	10	>5.0 g/kg body weight	RIFM (1974a)
Isobutyl cinnamate	Rat	10	>5.0 g/kg body weight	RIFM (1975b)
Isopropyl cinnamate	Rat	10	>5.0 g/kg body weight	RIFM (1982a)
Isopropyl cinnamate	Guinea pig	10	2.7 g/kg body weight	Draize et al. (1948)
Linalyl cinnamate	Rat	10 (5/sex)	9.96 g/kg body weight (95% C.I. 8.23–12.05 g/kg body weight)	Jenner et al. (1964)
Linalyl cinnamate	Mouse	10	>39.04 g/kg body weight	RIFM (1967)
Methyl cinnamate	Rat	5 male and female	2.61 g/kg body weight (95% C.I. 2.00–3.41 g/kg body weight)	RIFM (1971a)
α-Methylcinnamic alcohol	Rat	10	2.4 g/kg body weight (95% C.I. 1.9–3.0 g/kg body weight)	RIFM (1974c)
Phenethyl cinnamate	Rat	10	~5.0 g/kg body weight	RIFM (1975a)
Phenethyl cinnamate	Mouse	10	>5.0 g/kg body weight	RIFM (1975b)
Propyl cinnamate[b]	Guinea pig	10	3 g/kg body weight	Draize et al. (1948)
Propyl cinnamate[b]	mouse	10	7 g/kg body weight	Draize et al. (1948)

[a] Units have been converted to make easier comparisons; original units are in the Fragrance Material Reviews.
[b] α-Amylcinnamyl acetate and propyl cinnamate are not materials that are being reviewed, but they are included in this table because they are structurally related.

Table 2B
Acute toxicity dermal studies

Material	Species	No. animals/dose group	LD_{50}[a]	References
Allyl cinnamate	Rabbit	4	<5.0 g/kg body weight	RIFM (1975b)
α-Amylcinnamyl acetate[b]	Rabbit	10	>5.0 g/kg body weight	RIFM (1974a)
α-Amylcinamyl alcohol	Rabbit	6	>5.0 g/kg body weight	RIFM (1973a)
Benzyl cinnamate	Rabbit	4	>3.0 g/kg body weight	RIFM (1972a)
Butyl cinnamate	Rabbit	10	>5.0 g/kg body weight	RIFM (1977a)
Cinnamyl acetate	Rabbit	10	>5.0 g/kg body weight	RIFM (1972b)
Cinnamyl benzoate	Rabbit	10	>5.0 g/kg body weight	RIFM (1975a)
Cinnamyl butyrate	Rabbit	4	>5.0 g/kg body weight	RIFM (1976a)
Cinnamyl cinnamate	Rabbit	10	>5.0 g/kg body weight	RIFM (1974b)
Cinnamyl formate	Rabbit	6	>5.0 g/kg body weight	RIFM (1973b)
Cinnamyl isobutyrate	Rabbit	10	>5.0 g/kg body weight	RIFM (1977a)
Cinnamyl isovalerate	Rabbit	10	>5.0 g/kg body weight	RIFM (1973c)
Cinnamyl propionate	Rabbit	10	>5.0 g/kg body weight	RIFM (1973d)
Cinnamyl tiglate	Rabbit	4	>5.0 g/kg body weight	RIFM (1975b)
Ethyl cinnamate	Rabbit	10	>5.0 g/kg body weight	RIFM (1973e)
Isoamyl cinnamate	Rabbit	7	>5.0 g/kg body weight	RIFM (1974a)
Isobutyl cinnamate	Rabbit	4	>5.0 g/kg body weight	RIFM (1975b)
Isopropyl cinnamate	Rabbit	10	>5.0 g/kg body weight	RIFM (1982a)
Isopropyl cinnamate	Rabbit	Not specified	>10 g/kg body weight	Draize et al. (1948)
Linalyl cinnamate	Rabbit	10	>5.0 g/kg body weight	RIFM (1973b)
Methyl cinnamate	Rabbit	4 (male and female)	>5.0 g/kg body weight	RIFM (1971a)
α-Methylcinnamic alcohol	Rabbit	4	>5.0 g/kg body weight	RIFM (1974c)
Phenethyl cinnamate	Rabbit	10	>5.0 g/kg body weight	RIFM (1975a)
Phenethyl cinnamate	Rabbit	4	>5.0 g/kg body weight	RIFM (1975b)

[a] Units have been converted to make easier comparisons; original units are in the Fragrance Material Reviews.
[b] α-Amylcinnamyl acetate is not one of the materials being reviewed, but it is included in this table because it is structurally related.

Table 2C
Acute toxicity miscellaneous studies

Material	Route	Species	No. animals/dose group	LD_{50}	References
Cinnamyl acetate	Intraperitoneal	Mouse	Not specified	1.2 g/kg body weight	Powers et al. (1961)

further metabolized by aldehyde dehydrogenase to yield the acid (Feldman and Weiner, 1972). The urinary metabolites of cinnamyl alcohol are mainly those derived from metabolism of cinnamic acid.

In animals, aromatic carboxylic acids, such as cinnamic acid, that enter the cell are converted to acyl CoA esters (Nutley et al., 1994). Cinnamoyl CoA either conjugates with glycine, a reaction catalyzed by *N*-acyl transferase, or undergoes β-oxidation eventually leading to the formation of benzoyl CoA. The reactions, which form benzoic acid from cinnamic acid, are reversible, but the equilibrium favors formation of the benzoic acid CoA ester (Nutley et al., 1994). Benzoyl CoA is in turn conjugated with glycine, yielding hippuric acid, or the CoA thioester is hydrolyzed to yield free benzoic acid which is then excreted (Nutley et al., 1994). CoA thioesters of carboxylic acids are obligatory intermediates in amino acid conjugation reactions (Hutt and Caldwell, 1990). Regardless of dose or species, the β-oxidation pathway is the predominant pathway of metabolic detoxication of cinnamic acid in animals.

The position and size of the substituents play a role in the metabolism of cinnamyl derivatives. Cinnamyl derivatives containing α-methyl substituents are extensively metabolized via β-oxidation and cleavage to yield mainly the corresponding hippuric acid derivative. A benzoic acid metabolite was isolated from the urine of dogs given α-methylcinnamic acid (Kay and Raper, 1924). Larger substituents located at the α- or β-position to some extent inhibit β-oxidation (Kassahun et al., 1991; Deuel, 1957), in which case there may be direct conjugation of the carboxylic acid with glucuronic acid followed by excretion. While α-methylcinnamic acid undergoes oxidation to benzoic acid, α-ethyl- and α-propylcinnamic acids are excreted unchanged (Carter, 1941). α-Ethylcinnamic alcohol administered orally to rabbits resulted in the urinary excretion of α-ethylcinnamic acid, in addition to small amounts of benzoic acid (Fischer and Bielig, 1940).

4. Toxicological studies

4.1. Acute toxicity (Tables 2A–2C)

Twenty one cinnamyl materials have been evaluated for acute toxicity (see Tables 2A–2C). Dermal LD_{50} values in rabbits exceeded 5000 mg/kg body weight for 20 of these materials; benzyl cinnamate was non-toxic at 3000 mg/kg body weight which was the highest dose tested. Oral

Table 3
Subchronic toxicity

Material	Method	Concentration	Species	Results	References
Benzyl cinnamate	Oral 19-week study	50 & 500 mg/kg body weight/day	Rats (5/sex/dose)	NOEL 500 mg/kg body weight/day	Hagan et al. (1967)
Benzyl cinnamate	Oral 19-week study	50 & 500 mg/kg body weight/day	10 rats (5/sex/dose)	NOEL 500 mg/kg body weight/day	FDA (1954)
Cinnamyl benzoate	Oral 14-day study	~750, 1500 and 3000 mg/kg body weight/day	24 male albino rats (6/dose)	No deaths and no gross abnormalities were reported; significantly depressed growth, food intake and food efficiency were noted	RIFM (1958b)
Cinnamyl cinnamate (as part of a mixture containing 5 cinnamic flavoring agents)	Oral 12-week study	~3 mg/kg body weight/day cinnamyl cinnamate (tested in a mixture containing 5 cinnamic flavoring agents)	24 rats (12/sex)	Depressed growth; food utilization significantly decreased in both sexes	RIFM (1958a)
Ethyl cinnamate	Oral 12-week study	~3 mg/kg body weight/day ethyl cinnamate (tested in a mixture containing 5 cinnamic flavoring agents)	24 rats (12/sex)	Depressed growth; food utilization significantly decreased in both sexes	RIFM (1958a)
Isopropyl cinnamate	Dermal 90-day study	500, 1000, 2000 and 4000 mg/kg body weight/day	Rabbits (no further details reported)	NOAEL 1000 mg/kg body weight/day	Draize et al. (1948)
Linalyl cinnamate	Oral 17 week study	50, 125 & 500 mg/kg body weight/day	rats (10/sex/dose)	NOEL 500 mg/kg body weight/day	Hagan et al. (1967)
Propyl cinnamate[a]	Dermal 90-day study	500, 1000, 2000 and 4000 mg/kg body weight/day	Rabbits (no further details reported)	Inanition; moderate atrophy of testis; inconsistent slight bone marrow hyperplasia (no further details reported)	Draize et al. (1948)
Methyl cinnamate	12-week study	~3 mg/kg body weight/day methyl cinnamate (tested in a mixture containing 5 cinnamic flavoring agents)	24 rats (12/sex)	Depressed growth; food utilization significantly decreased in both sexes	RIFM (1958a)

[a] Propyl cinnamate is not one of the materials being reviewed, but is included in this table because it is structurally related.

LD_{50} values have been reported for 21 materials and were in the range from 1520 mg/kg body weight for allyl cinnamate to 39,040 mg/kg for linalyl cinnamate with a majority of the materials in the 2500–5000 mg/kg body weight range. An intraperitoneal LD_{50} value of 1200 mg/kg body weight was reported for cinnamyl acetate.

4.2. Subchronic toxicity (Table 3)

Toxicological studies have been reported for benzyl cinnamate, cinnamyl benzoate, cinnamyl cinnamate, ethyl cinnamate, isopropyl cinnamate, linalyl cinnamate, and methyl cinnamate. Results of these studies are summarized in Table 3 and are described below.

4.2.1. Dermal studies

Isopropyl cinnamate applied daily to rabbit's skin for 90 days at dose levels of 0.5, 1.0, 2.0 and 4.0 ml/kg body weight [~ equivalent to 500, 1000, 2000 and 4000 mg/kg body weight] produced moderate chronic dermatitis; at the two highest dose levels, atrophy of the testes, hyperplasia of the bone marrow, slight inanition and severe skin irritation were also observed. The 90-day LD_{50} was reported to exceed 4000 mg/kg body weight. The No-Observed-Adverse-Effect Level (NOAEL) was concluded to be 1000 mg/kg body weight. (Draize et al., 1948). A related material, propyl cinnamate, also tested in the same manner, produced mild irritation, moderate atrophy of the testes, slight but inconsistent bone marrow hyperplasia and minimal splenitis; the 90-day LD_{50} was reported to be 2000 mg/kg body weight (Draize et al., 1948).

4.2.2. Oral studies

Osborne–Mendel rats received a dietary admixture containing linalyl cinnamate at dose levels of 0, 1000, 2500 or 10000 ppm [~ equivalent to 0, 50, 125 and 500 mg/kg body weight/day] for 17 weeks. There were no deaths and no adverse clinical signs were observed. There were no effects on growth or hematology, and no macroscopic or microscopic changes in the tissues were observed. The No-Observed-Effect Level (NOEL) was concluded to be 500 mg/kg body weight/day (Hagan et al., 1967).

Table 4
Mutagenicity and genotoxicity bacterial studies

Material	Test system in vitro	Species	Dose[a]	Results	References
Allyl cinnamate	Ames with and without S9 activation	*Salmonella typhimurium* TA1535, TA100, TA1537, TA1538 and TA98	Doses up to 3600 μg/plate	Negative	Wild et al. (1983)
α-Amylcinnamyl alcohol	Ames with and without S9 activation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	Doses up to 3600 μg/plate	Negative	Wild et al. (1983)
Benzyl cinnamate	Modified Ames (spot test) with and without S9 activation	*S. typhimurium* TA98, TA100, TA1535, TA1537	715 μg/plate	Sample precipitated (questionable results)	Florin et al. (1980)
Benzyl cinnamate	Rec assay	*Bacillus subtilis* H17(rec+) & M45(rec−)	1000 μg/plate	Negative	Yoo (1986)
Cinnamyl acetate	Ames with and without S9 activation	*S. typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102	Doses up to 5000 μg/plate	Negative	RIFM (2003a)
Ethyl cinnamate	Ames with and without S9 activation	*S. typhimurium* TA92, TA1535, TA100, TA1537, TA94, TA98	Doses up to 5000 μg/plate	Negative	Ishidate et al. (1984)
Ethyl cinnamate	Rec assay	*B. subtilis* H17(rec+) & M45(rec−)	20 μg/plate	Negative	Oda et al. (1978)
Isoamyl cinnamate	Ames assay with and without S9 activation	*S. typhimurium* TA98 & TA100 with/without activation and TA97, TA1535	Not reported	Negative	Zeiger and Margolin (2000)
Linalyl cinnamate	Ames assay with and without S9 activation	*S. typhimurium* TA98, TA100, TA102, TA1535, with/without S9 activation	Doses up to 5000 μg/plate	Negative	RIFM (2003b)
Methyl cinnamate	Rec assay	*B. subtilis* H17(rec+) & M45(rec-)	20 μg/plate	Negative	Oda et al. (1978)
α-Methyl cinnamic alcohol	Ames assay	*S. typhimurium* TA98,TA100, TA102, TA1535 and TA1537	Doses up to 5000 μg/plate	Weakly mutagenic	RIFM (1997a)

[a] Units have been converted to make easier comparisons; original units are in the Fragrance Material Reviews.

In another study, Osborne–Mendel rats received a dietary admixture containing benzyl cinnamate at dose levels of 0, 1000, or 10000 ppm [∼ equivalent to 0, 50 and 500 mg/kg body weight/day] for 19 weeks. There were no deaths and no adverse clinical signs were observed. There were no effects on growth or hematology and no macroscopic or microscopic changes in the tissues were observed. The NOEL was concluded to be 500 mg/kg body weight/day (FDA, 1954; Hagan et al., 1967).

A mixture of 897 ppm cinnamaldehyde and 25 ppm each of methyl cinnamate, ethyl cinnamate, cinnamyl cinnamate and α-methylcinnamaldehyde was added to the diet of rats for 12 weeks at levels calculated to result in average daily intakes of 103 mg/kg body weight for cinnamaldehyde and 3 mg/kg body weight for the other components. A slight retardation of growth was observed only in the females. Measurements of hematology, clinical chemistry, and urinalysis at weeks 6 and 12 showed no significant differences between test and control groups. Histopathology revealed no dose-related lesions. Food utilization was significantly decreased in both males and females. Depressed growth was observed in male rats which was not considered to be statistically significant, however, it may have been biologically relevant (RIFM, 1958a).

Male albino rats received a dietary admixture for 14 days containing cinnamyl benzoate at dose levels of 0.5% (∼750 mg/kg body weight/day), 1.0% (∼1500 mg/kg/day) and 2.0% (3000 mg/kg body weight/day). Behavior and appearance were normal and gross observations at necropsy were normal. Significantly depressed growth rates, food intake and efficiency of food utilization were observed at all dose levels due in part to poor palatability of the diet (RIFM, 1958b).

4.3. Chronic toxicity

There are no long term studies on these materials; however, since the members of this group may be hydrolyzed to yield the component alcohol, aldehyde, or acid, chronic studies for cinnamaldehyde provide a basis for the estimation of the toxic potential of the group.

The National Toxicology Program (NTP, 2003) has conducted a 2-year feeding assay with trans-cinnamaldehyde in rats and mice. In rats, they identified a No-Observed-Adverse-Effect-Level (NOAEL) as 200 mg/kg body weight/day; in mice the NOAEL was identified as 550 mg/kg body weight/day.

4.4. Mutagenicity and genotoxicity

Studies evaluating mutagenicity/genotoxicity have been performed on eight cinnamyl materials in this group. The results of these tests are summarized in Tables 4–6 and are described below.

4.4.1. Bacterial studies (Table 4)

Five cinnamyl materials were tested in bacterial assays using *Salmonella typhimurium,* and/or *Bacillus subtilis.*

Allyl cinnamate, α-amylcinnamyl alcohol, benzyl cinnamate, ethyl cinnamate, isoamyl cinnamate and linalyl cinnamate were inactive in *Salmonella typhimurium*, including strains TA92, TA94, TA98, TA100, TA1535, TA1537, and TA1538. The assays were performed at concentrations ranging up to the level of cytotoxicity, both in the absence and presence of metabolic activation (S9 fraction) obtained from the livers of Aroclor 1254- or methylcholanthrene-induced Sprague–Dawley rats or

Table 5
Mutagenicity and genotoxicity insect studies

Material	Test system in vitro	Test object	Concentration	Results	References
Allyl cinnamate	Basc test	*Drosophila melanogaster.* Berlin K (wild type) and Basc	1 mM	Negative	Wild et al. (1983)
α-Amylcinnamyl alcohol	Basc test	*Drosophila melanogaster* Berlin K (wild type) and Basc	45 mM	Negative	Wild et al. (1983)

Table 6
Mutagenicity and genotoxicity mammalian studies

Material	Test system in vitro	Test object	Concentration	Results	References
Allyl cinnamate	Bone marrow micronucleus assay	Male and female NMRI mice	94–282 mg/kg body weight	Negative	Wild et al. (1983)
α-Amylcinnamyl alcohol	Bone marrow micronucleus assay	Male and female NMRI mice	204–510 mg/kg body weight	Negative	Wild et al. (1983)
Cinnamyl acetate	Sister chromatid exchange	Chinese hamster ovary cells (CHO-K1)	1.0–100 μM	Negative (highest dose tested was toxic)	Sasaki et al. (1989)
Ethyl cinnamate	Sister chromatid exchange	Chinese hamster ovary cells (CHO-K1)	1.0, 3.3 and 10 μM	Negative (highest dose tested was toxic)	Sasaki et al. (1989)
Ethyl cinnamate	Chromosomal aberration	Chinese hamster fibroblast cell line	0.063 mg/ml (tested at three doses, only maximum dose reported)	Equivocal increases in chromosome aberrations and polyploidization effects were observed	Ishidate et al. (1984)
Methyl cinnamate	Sister chromatid exchange	Chinese hamster ovary cells (CHO-K1)	1.0, 3.3, 10 and 33.3 μM	Negative (highest dose tested was toxic)	Sasaki et al. (1989)
α-Methyl cinnamic alcohol	L5178Y TK+/− assay	Mouse L5178Y TK+/− cells	600 nl/ml	No effects	RIFM (1998)

Syrian hamsters (Wild et al., 1983; Florin et al., 1980; Ishidate et al., 1984; RIFM, 2003; Zeiger and Margolin, 2000).

Benzyl cinnamate, ethyl cinnamate and methyl cinnamate gave negative results in the Rec assay in *Bacillus subtilis* (Oda et al., 1978; Yoo, 1986).

4.4.2. Insect studies (Table 5)

No significant increases in sex-linked recessive lethal (SRL) mutations were observed with 1 mM allyl cinnamate or with 45 mM α-Amylcinnamyl alcohol in a Basc test using *Drosophila melanogaster* Berlin K and Basc strains (Wild et al., 1983).

4.4.3. Mammalian cell systems (Table 6)

Sister chromatid exchange (SCE) were not observed in Chinese hamster ovary (CHO) cells treated with cinnamyl acetate at doses of 1.0–100 μM or with ethyl cinnamate at doses of 3.3 and 10 μM, or with methyl cinnamate at doses of 3.3, 10 and 33.3 μM (Sasaki et al., 1989). Ethyl cinnamate produced equivocal increases in chromosome aberrations in a Chinese hamster fibroblast cell line without metabolic activation; polyploidization effects were also observed (Ishidate et al., 1984).

4.4.4. In vivo studies

In a micronucleus assay, groups of male and female mice received a single ip injection of allyl cinnmate or amylcinnamyl alcohol at dose levels of 94, 188 or 282 mg/kg body weight (allyl cinnamate), or 204, 357 or 510 mg/kg body weight (amylcinnamyl alcohol). At 30 h, the mice were sacrificed, the bone marrow extracted and polychromatic and normochromatic erythrocytes were scored for the presence of micronuclei. No evidence of genotoxic activity was produced (Wild et al., 1983).

Both in vitro tests in mammalian cells and in vivo studies in rats and mice have been carried out with cinnamyl alcohol, cinnamaldehyde and cinnamic acid. After an in depth review of all available data on these three materials, Bickers et al. (2005) concluded that based on a weight of evidence evaluation of all genotoxicity and mutagenicity studies as well as the metabolism and detoxification of these three materials, that they would have no significant genotoxic potential under their current conditions of use.

4.5. Carcinogenicity

There are no definitive long term studies that directly evaluate the carcinogenicity of these cinnamyl ester or alcohol derivatives. However, cinnamaldehyde has been evaluated by the National Toxicology Program (NTP, 2003) in a 2-year assay feeding microencapsulated cinnamaldehyde to rats and mice at dose levels of 50, 100 or 200 mg/kg body weight/day and 125, 270 and 550 mg/kg body weight/day, respectively. There was no evidence of carcinogenic activity (or other lesions) in rats or mice. Also, no significant carcinogenic effects (Wiseman et al., 1987) were produced by cinnamaldehyde when it was evaluated for

Table 7
Skin irritation humans

Material	Method	Concentration	Subjects	Results	References
Allyl cinnamate	Maximization pre-test. 48-h closed patch test	4% in petrolatum	22 male volunteers	irritant reactions observed in 20/22	RIFM (1975c)
Allyl cinnamate	48-h patch test	0.10%, 0.25%, 0.50% and 4% in petrolatum	11 male volunteers	No irritant reactions at 0.1% 5 irritant reactions at 0.25% 9 irritant reactions at 0.50% 10 irritant reactions at 4%	RIFM (1975c)
α-Amylcinnamyl acetate[a]	Maximization pre-test. 48-h closed patch test	8% in petrolatum	5 male and female volunteers	No irritation	RIFM (1975d)
α-Amylcinnamyl alcohol	Induction phase of an HRIPT	3% concentration in 3:1 diethyl phthalate: ethanol	105 male and female volunteers	No irritation	RIFM (2004a)
α-Amylcinnamyl alcohol	Maximization pre-test. 48-h closed patch test	8% in petrolatum	5 male volunteers	No irritation	RIFM (1973d)
Benzyl cinnamate	Induction phase of an HRIPT	4% in ethanol:diethyl phthalate (1:3)	101 male and female volunteers	No irritation	RIFM (2005a)
Benzyl cinnamate	Maximization pre-test. 48-h closed patch test	8% in petrolatum	5 male volunteers	No irritation	RIFM (1972c)
Benzyl cinnamate	Maximization pre-test. 48-h closed patch test	8% in petrolatum	5 male and female volunteers	No irritation	RIFM (1975d)
Butyl cinnamate	Maximization pre-test. 48-h closed patch test	4% in petrolatum	25 male and female volunteers	No irritation	RIFM (1977b)
Cinnamyl acetate	Maximization pre-test. 48-h closed patch test	5% in petrolatum	5 male volunteers	No irritation	RIFM (1972c)
Cinnamyl acetate	48-h semi-occluded patch test	32% in acetone	50 male volunteers	Irritation observed in 10–40% of subjects (no further details reported)	Motoyoshi et al. (1979)
Cinnamyl benzoate	Maximization pre-test. 48-h closed patch test	5% in petrolatum	5 male and female volunteers	No irritation	RIFM (1975d)
Cinnamyl butyrate	Maximization pre-test. 48-h closed patch test	4% in petrolatum	29 male volunteers	No irritation	RIFM (1976b)
Cinnamyl cinnamate	Maximization pre-test. 48-h closed patch test	4% in petrolatum	5 male and female volunteers	No irritation	RIFM (1974d)
Cinnamyl formate	Maximization pre-test. 48-h closed patch test	4% in petrolatum	5 male volunteers	No irritation	RIFM (1973d)
Cinnamyl isobutyrate	Maximization pre-test. 48-h closed patch test	4% in petrolatum	31 male volunteers	No irritation	RIFM (1977c)
Cinnamyl isovalerate	Maximization pre-test. 48-h closed patch test	2% in petrolatum	5 male volunteers	No irritation	RIFM (1973d)
Cinnamyl propionate	Maximization pre-test. 48-h closed patch test	4% in petrolatum	5 male volunteers	No irritation	RIFM (1973d)
Cinnamyl tiglate	Maximization pre-test. 48-h closed patch test	4% in petrolatum	24 male volunteers	No irritation	RIFM (1975c)
Ethyl cinnamate	Maximization pre-test. 48-h closed patch test	4% in petrolatum	5 male volunteers	No irritation	RIFM (1973d)
Ethyl cinnamate	24-h closed patch test	100%	22 male and female volunteers	1/22 irritant reactions	Katz (1946)
Isoamyl cinnamate	Maximization pre-test. 48-h closed patch test	8% in petrolatum	5 male and female volunteers	No irritation	RIFM (1974d)
Isobutyl cinnamate	Maximization pre-test. 48-h closed patch test	8% in petrolatum	29 male volunteers	No irritation	RIFM (1975c)
Isopropyl cinnamate	Maximization pre-test. 48-h closed patch test	6% in petrolatum	28 male and female volunteers	No irritation	RIFM (1982b)
Linalyl cinnamate	Maximization pre-test. 48-h closed patch test	8% in petrolatum	5 male volunteers	No irritation	RIFM (1973d)

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Table 7 (*continued*)

Material	Method	Concentration	Subjects	Results	References
Methyl cinnamate	Maximization pre-test. 48-h closed patch test	10% in petrolatum	5 male and female volunteers	No irritation	RIFM (1975d)
α-Methylcinnamic alcohol	Maximization pre-test. 48-h closed patch test	2% in petrolatum	5 male and female volunteers	No irritation	RIFM (1974d)
Phenethyl cinnamate	Maximization pre-test. 48-h closed patch test	2% in petrolatum	5 male and female volunteers	No irritation	RIFM (1975d)
Phenethyl cinnamate	Maximization pre-test. 48-h closed patch test	2% in petrolatum	5 male and female volunteers	No irritation	RIFM (1975d)

[a] α-Amylcinnamyl acetate is not one of the materials being reviewed, but it is included in this table because it is structurally related.

hepatocarcinogenic potential in 44 B6C3F1 mice that had received intraperitoneal injections once a week for 4 weeks (total cumulative dose, 0.0006 g). While hemangiosarcomas were observed in three treated animals in this study, they were also observed in two control animals and the authors concluded that no significant carcinogenic effects were produced by cinnamaldehyde.

In addition, both cinnamyl alcohol (total cumulative intraperitoneal doses were 1.4 and 7.0 g/kg body weight) and cinnamaldehyde (total cumulative intraperitoneal doses, 0.8 and 4.0 g/kg body weight) did not induce primary lung tumors in female A/He mice under the conditions of the test (Stoner et al., 1973).

4.6. Reproductive and developmental toxicity

There are no reproductive studies on these cinnamyl materials. However in a review of cinnamyl alcohol, cinnamaldehyde and cinnamic acid, Bickers et al. (2005) reported on developmental toxicity studies conducted in rats and mice on cinnamyl alcohol, cinnamaldehyde and cinnamic acid that showed that these materials do not possess any significant potential for developmental effects under current conditions of use as fragrance ingredients.

4.7. Skin irritation

4.7.1. Human studies (Table 7)

Twenty-one cinnamyl materials were evaluated for skin irritation in 537 male and female volunteers. Allyl cinnamate produced irritation in a majority of its' test subjects (which was thought to be caused by its allyl component) at dose levels ranging from 0.25% to 4% in petrolatum. Irritation was not observed with the other cinnamyl materials tested at dose levels up to 10%. Mild irritation was observed with 32% cinnamyl acetate (see Table 7).

4.7.2. Animal studies (Table 8)

Fifteen materials that were tested for skin irritation at 100% in rabbits produced reactions that ranged from non-irritating to very slight irritation to moderate irritation. Linalyl cinnamate was also tested at 5% in rabbits and produced slight irritation. Benzyl cinnamate(3%), cinnamyl acetate(100%) and methyl cinnamate(3%) were also tested for irritation in guinea pigs and/or miniature swine and produced minimal irritation (see Table 8).

4.8. Mucous membrane (eye) irritation (Table 9)

Undiluted linalyl cinnamate and 5% linalyl cinnamate produced very slight to well-defined irritation to the rabbit eye which cleared by 24 h; undiluted methyl cinnamate produced no irritation to the rabbit eye (see Table 9).

4.9. Skin sensitization

4.9.1. Human studies (Table 10)

Bickers et al. (2005) reported that cinnamyl alcohol and cinnamaldehyde were sensitizers in humans, with NOELs of approximately 4% for the alcohol. More recent studies (RIFM, 2004d,e) show that the NOEL is 2.5% (3000 μg/cm^2) for the alcohol and 0.5% (591 μg/cm^2) for the aldehyde. Dermal sensitization was not observed for 21 cinnamyl esters and alcohols that were tested in maximization tests at concentrations ranging from 2% (1380 μg/cm^2) to 10% (6900 μg/cm^2) in 608 volunteers (see Table 10). In a modified Draize test, which was considered to be a non-standard test in which the induction consisted of continuous 48 h occluded patches and the challenge consisted of a 72 h occluded patch application, 8% (2481 μg/cm^2) α-amylcinnamyl alcohol produced one reaction in 78 volunteers when tested in an alcohol vehicle but not when tested in petrolatum. However, in a standard repeated insult patch test, 3% (3543 μg/cm^2)α-amylcinnamyl alcohol did not produce sensitization when tested in 105 volunteers. When 4% (4720 μg/cm^2) benzyl cinnamate was tested in a standard repeated insult patch test in 101 volunteers, it also did not produce sensitization. It is likely that their slow hydrolysis does not produce sensitizing levels of cinnamaldehyde.

However, as a result of recent studies and this review, IFRA (2007) has established Standards on α-amylcinnamyl alcohol and benzyl cinnmate using a Quantitative Risk Assessment (QRA) for dermal sensitization (see the individual Fragrance Material Reviews on these materials for more information).

Table 8
Skin irritation animals

Material	Method	Concentration	Species	Results	References
Allyl cinnamate	Irritation evaluated during an associated LD_{50} study	100%	4 rabbits	No irritation was observed	RIFM (1975b)
α-Amylcinnamyl acetate[a]	Irritation evaluated during an associated LD_{50} study	100%	10 rabbits	Slight to moderate irritation	RIFM (1974a)
Benzyl cinnamate	Irritation evaluated during an associated LD_{50} study	100%	4 rabbits	Moderate irritation which cleared by 48 h	RIFM (1972a)
Benzyl cinnamate	Preliminary irritation screen for an open epicutaneous test	A range of concentrations (vehicle not specified)	6–8 guinea pigs	3% = minimal irritating concentration (defined as lowest concentration producing mild erythema in at least 25% of animals)	Klecak et al. (1977)
Benzyl cinnamate	Induction phase of open epicutaneous test	A range of concentrations (vehicle not specified)	6–8 guinea pigs	3% = minimal irritating concentration	Klecak et al. (1977)
Butyl cinnamate	Irritation evaluated during an associated LD_{50} study	100%	10 rabbits	Mild to moderate irritation	RIFM (1977a)
Cinnamyl acetate	A 48-h closed patch test	100%	6 miniature swine	No irritation was observed	Motoyoshi et al. (1979)
Cinnamyl acetate	A 24-h open application to clipped dorsal skin; 30 minutes after reading, cinnamyl acetate was applied again. A 2nd set of readings and applications was made 48 h later. After 72-h reading, Evans blue was injected intravenously	100%	6 guinea pigs	Mild irritation	Motoyoshi et al. (1979)
Cinnamyl acetate	A 24-h open application to clipped dorsal skin; 30 minutes after reading, cinnamyl acetate was applied again. A 2nd set of readings and applications was made 48 h later. After 72-h reading, Evans blue was injected intravenously	100%	6 rabbits	Moderate irritation	Motoyoshi et al. (1979)
Cinnamyl benzoate	Irritation evaluated during an associated LD_{50} study	100%	10 rabbits	Slight to moderate irritation	RIFM (1975a)
Cinnamyl butyrate	Irritation evaluated during an associated LD_{50} study	100%	4 rabbits	Irritation lasting 24 h was observed	RIFM (1976a)
Cinnamyl isobutyrate	Irritation evaluated during an associated LD_{50} study	100%	10 rabbits	Mild to moderate irritation	RIFM (1977a)
Cinnamyl propionate	Irritation evaluated during an associated LD_{50} study	100%	10 rabbits	Slight to moderate irritation	RIFM (1973d)
Cinnamyl tiglate	Irritation evaluated during an associated LD_{50} study	100%	4 rabbits	No irritation	RIFM (1975b)
Isoamyl cinnamate	Irritation evaluated during an associated LD_{50} study	100%	7 rabbits	Slight irritation in one animal	RIFM (1974a)
Isobutyl cinnamate	Irritation evaluated during an associated LD_{50} study	100%	4 rabbits	Mild irritation lasting 24 h	RIFM (1975b)
Isopropyl cinnamate	Irritation evaluated during an associated LD_{50} study	100%	10 rabbits	Very slight to well-defined irritation	RIFM (1982a)
Linalyl cinnamate	Irritation evaluated during an associated LD_{50} study	100%	10 rabbits	Slight to moderate irritation	RIFM (1973b)
Linalyl cinnamate	Single application to intact or abraded skin	100%	3 rabbits	Very slight irritation	RIFM (1967)
Linalyl cinnamate	Single application to intact or abraded skin	5% in diethyl phthalate	3 rabbits	Very slight irritation	RIFM (1967)

(*continued on next page*)

Table 8 (*continued*)

Material	Method	Concentration	Species	Results	References
Methyl cinnamate	Irritation evaluated during an associated LD_{50} study	100%	6 rabbits	No irritation	RIFM (1971a)
Methyl cinnamate	Preliminary irritation screen for an open epicutaneous test	A range of concentrations (vehicle not specified)	6–8 guinea pigs	30% = minimal irritating concentration	Klecak et al. (1977)
Methyl cinnamate	Induction phase of open epicutaneous test	A range of concentrations (vehicle not specified)	6–8 guinea pigs	3% = minimal irritating concentration	Klecak et al. (1977)
α-Methylcinnamic alcohol	Intradermal pre-screen test for a maximization test	1%, 5%, 10% and 25% concentration w/v in arachis oil BP	4 guinea pigs	5% = highest concentration that caused a mild to moderate skin irritation	RIFM (1997b)
α-Methylcinnamic alcohol	A 48-h occluded patch test	100%, and 25%, 50%, and 75% v/v in arachis oil BP	2 guinea pigs	Very slight erythema was observed in 1/2 at 25%, 75% and 100%	RIFM (1997b)
α-Methylcinnamic alcohol	A 24-h occluded patch test	100%, and 25%, 50%, and 75% v/v in arachis oil BP	2 guinea pigs	No irritation observed at any dose level	RIFM (1997b)
α-Methylcinnamic alcohol	Irritation evaluated during an associated LD_{50} study	100%	4 rabbits	Mild irritation	RIFM (1974c)
Phenethyl cinnamate	Irritation evaluated during an associated LD_{50} study	100%	10 rabbits	Slight irritation	RIFM (1975a)
Phenethyl cinnamate	Irritation evaluated during an associated LD_{50} study	100%	4 rabbits	No irritation	RIFM (1975b)

[a] α-Amylcinnamyl acetate is not one of the materials being reviewed, but it is included in this table because it is structurally related.

4.9.2. Animal studies (Table 11)

Weak sensitization effects were observed with cinnamyl cinnamate in a modified Freund's Complete Adjuvant test at 3% and 10%. Sensitization was also observed with benzyl cinnamate (6 studies) and methyl cinnamate (4 studies) when they were tested in several studies using various test methods. Ethyl cinnamate did not produce sensitization at 4% in an open epicutaneous test (see Table 11).

4.10. Phototoxicity and photoallergy

4.10.1. Phototoxicity (Table 12)

UV spectra have been obtained on 19 cinnamyl esters and alcohols. All 19 peaked within a 245–278 nm range and all showed minute absorption in 290–320 nm region (see Table 12). In addition, 1% cinnamaldehyde and 20% cinnamic acid were evaluated for phototoxicity and photoallergy in guinea pigs and showed no potential for phototoxic or photoallergic activity (Bickers et al., 2005). Based on these data, it is not expected that the cinnamyl ester and alcohol derivatives would have a potential to produce phototoxic or photoallergic effects.

4.11. Environmental data

In addition to a human health assessment, environmental assessment of fragrance materials is performed according to a standard framework (Salvito et al., 2002). This screens chemicals in the RIFM/FEMA Database for their potential to present a hazard to the aquatic environment by considering their removal in wastewater treatment, minimal dilution in the mixing zone, and the application of a large uncertainty factor to ecotoxicological endpoints determined using quantitative structure-activity relationships. This screening, based on conservative assumptions, identifies priority materials that may require further study to quantitatively assess potential environmental risks. None of the materials in the Substituted Cinnamyl Alcohols and Esters of Cinnamic Acid and Alcohol group was identified as priority material for risk assessment refinement.

Table 9
Mucous membrane (eye) irritation

Material	Species	Concentration	Vehicle	Results	References
α-Amylcinnamyl alcohol	3 rabbits	1.25%	Not specified	Mild conjunctival irritation in 3/3 which cleared by day 7	RIFM (1964)
Linalyl cinnamate	3 rabbits	100%	N/A	Very slight to well-defined irritation in 3/3	RIFM (1967)
Linalyl cinnamate	3 rabbits	5%	Diethyl phthalate	Very slight to well-defined irritation in 3/3	RIFM (1967)
Methyl cinnamate	Rabbits	100%	N/A	No irritation	RIFM (1971b)
Methyl cinnamate	Rabbits	15%	Not specified	No irritation	RIFM (1971b)
Methyl cinnamate	6 Rabbits	100%	N/A	No irritation	RIFM (1971a)

Table 10
Skin sensitization humans

Material	Method	Concentration	Subjects	Results	References
Allyl cinnamate	MAX	4% (2760 μg/cm^2) in petrolatum	22 male volunteers	No reactions	RIFM (1975c)
α-Amylcinnamyl acetate[a]	MAX	8% (5520 μg/cm^2) in petrolatum	25 male and female volunteers	No reactions	RIFM (1975d)
α-Amylcinnamyl alcohol	HRIPT	3% (3543 μg/cm^2) in 3:1 diethyl phthalate:ethanol	31 male and 74 female volunteers	No reactions	RIFM (2004a)
α-Amylcinnamyl alcohol	MAX	8% (5520 μg/cm^2) in petrolatum	25 male volunteers	No reactions	RIFM (1973d)
α-Amylcinnamyl alcohol	Modified Draize	8% in petrolatum 8% in ethyl alcohol	78 volunteers	No (0/78) reactions with 8% in petrolatum 1/78 reactions with 8% in ethyl alcohol	Marzulli and Maibach (1980)
Benzyl cinnamate	HRIPT	4% (4720 μg/cm^2) in 1:3 ethanol: diethyl phthalate	25 male and 76 female volunteers	No reactions	RIFM (2005a)
Benzyl cinnamate	MAX	8% (5520 μg/cm^2) in petrolatum	25 male volunteers	No reactions	RIFM (1972c)
Benzyl cinnamate	MAX	8% (5520 μg/cm^2) in petrolatum	25 male and female volunteers	No reactions	RIFM (1975d)
Butyl cinnamate	MAX	4% (2760 μg/cm^2) in petrolatum	25 male and female volunteers	No reactions	RIFM (1977b)
Cinnamyl acetate	MAX	5% (3450 μg/cm^2) in petrolatum	25 male volunteers	No reactions	RIFM (1972c)
Cinnamyl benzoate	MAX	5% (3450 μg/cm^2) in petrolatum	25 male and female volunteers	No reactions	RIFM (1975d)
Cinnamyl butyrate	MAX	4% (2760 μg/cm^2) in petrolatum	29 male volunteers	No reactions	RIFM (1976b)
Cinnamyl cinnamate	MAX	4% (2760 μg/cm^2) in petrolatum	25 male and female volunteers	No reactions	RIFM (1974d)
Cinnamyl formate	MAX	4% (2760 μg/cm^2) in petrolatum	25 male volunteers	No reactions	RIFM (1973d)
Cinnamyl isobutyrate	MAX	4% (2760 μg/cm^2) in petrolatum	31 male volunteers	No reactions	RIFM (1977c)
Cinnamyl isovalerate	MAX	2% (1380 μg/cm^2) in petrolatum	25 male volunteers	No reactions	RIFM (1973d)
Cinnamyl propionate	MAX	4% (2760 μg/cm^2) in petrolatum	25 male volunteers	No reactions	RIFM (1973d)
Cinnamyl tiglate	MAX	4% (2760 μg/cm^2) in petrolatum	24 male volunteers	1 questionable reaction which was negative at re-test 5 months later	RIFM (1975c)
Ethyl cinnamate	MAX	4% (2760 μg/cm^2) in petrolatum	25 male volunteers	No reactions	RIFM (1973d)
Isoamyl cinnamate	MAX	8% (5520 μg/cm^2) in petrolatum	25 male and female volunteers	No reactions	RIFM (1974d)
Isobutyl cinnamate	MAX	8% (5520 μg/cm^2) in petrolatum	24 male volunteers	No reactions	RIFM (1975c)
Isopropyl cinnamate	MAX	6% (4140 μg/cm^2) in petrolatum	28 male and female volunteers	No reactions	RIFM (1982b)
Linalyl cinnamate	MAX	8% (5520 μg/cm^2) in petrolatum	25 male volunteers	No reactions	RIFM (1973d)
Methyl cinnamate	MAX	2% (1380 μg/cm^2) in petrolatum	25 male volunteers	No reactions	RIFM (1970a)
Methyl cinnamate	MAX	10% (6900 μg/cm^2) in petrolatum	25 male and female volunteers	No reactions	RIFM (1975d)
α-Methylcinnamic alcohol	MAX	2% (1380 μg/cm^2) in petrolatum	25 male and female volunteers	No reactions	RIFM (1974d)
Phenethyl cinnamate	MAX	2% (1380 μg/cm^2) in petrolatum	25 male and female volunteers	No reactions	RIFM (1975d)
Phenethyl cinnamate	MAX	2% (1380 μg/cm^2) in petrolatum	25 male and female volunteers	No reactions	RIFM (1975d)

[a] α-Amylcinnamyl acetate is not one of the materials being reviewed, but it is included in this table because it is structurally related.

However, there are environmental data in the RIFM/FEMA Database for materials within the Substituted Alcohols and Esters of Cinnamic Acid and Cinnamic Alcohol group. These include biodegradation and acute invertebrate studies. Data are available for four materials. Values for ready biodegradation (minimum 28-day studies) for the 3 materials tested range from 50% to 106%; the acute invertebrate toxicities range from 2.8 to 13 mg/L (48 h Geometric Mean EC_0/EC_{100} and 96 h LC_{50}, respectively).

The Substituted Cinnamyl Alcohols and Esters of Cinnamic Acid and Cinnamic Alcohol, as used in fragrance compounds, present a negligible environmental risk as indicated by applying the RIFM framework (Salvito et al., 2002) and reviewing the available environmental data.

5. Summary

1. Based on data from cinnamyl alcohol, cinnamaldehyde and cinnamic acid, these cinnamyl materials are anticipated to be significantly absorbed through the skin.
2. Cinnamyl ester and alcohol derivatives are anticipated to be extensively hydrolyzed by tissue esterases. The cinnamyl alcohol, aldehyde or ester formed all

Table 11
Sensitization animals

Material	Method	Concentration	Species	Results	References
α-Amylcinnamyl alcohol	Open Epicutaneous Test	8% (vehicle not specified by material)	male & female guinea pigs	No reactions (no further data reported)	Klecak (1979, 1985)
α-Amylcinnamyl alcohol	Local Lymph Node Assay	1%, 2.5%, 5%, 10% & 25% in 1:3 ethanol:diethyl phthalate	4 female CBA/Ca/Ola/Hsd mice per group	Negative EC_3 > 25% (6250 μg/cm^2)	RIFM (2004b)
α-Amylcinnamyl alcohol	Local Lymph Node Assay	7.5%, 15% & 30% in 1:3 diethyl phthalate:ethanol	5 female CBA/J f mice per group	Negative EC_3 > 30% (7500 μg/cm^2)	RIFM (2004c)
Benzyl cinnamate	Maximization test	A subirritant concentration in petrolatum	Male & female outbred Himalayan guinea pigs	Sensitization was observed (no further data reported)	Klecak et al. (1977)
Benzyl cinnamate	Freund's Complete Adjuvant Test	A subirritant concentration in petrolatum	Male & female outbred Himalayan guinea pigs	Sensitization was observed (no further data reported)	Klecak et al. (1977)
Benzyl cinnamate	Open Epicutaneous Test	0.3% & 3.0% (vehicle not specified)	Male & female outbred Himalayan guinea pigs	Sensitization was observed (no further data reported)	Klecak et al. (1977)
Benzyl cinnamate	Open Epicutaneous Test	3.0% (vehicle not specified)	6–8 guinea pigs	No reactions (no further data reported)	Klecak (1979)
Benzyl cinnamate	Modified Draize test	0.1% in saline	Male & female outbred Himalayan guinea pigs	Sensitization was observed (no further data reported)	Klecak et al. (1977)
Benzyl cinnamate	Modified Freund's Complete Adjuvant Test	3% and 10% in acetone	10 female Pirbright guinea pigs	1/10 reactions plus 3 questionable reactions at 10% 1/10 reactions plus 2 questionable reactions at 3%	Hausen and Wollenweber (1988) Hausen et al. (1995)
Benzyl cinnamate	Local Lymph Node Assay	2.5%, 5%, 10%, 25% & 50% in 1:3 ethanol: diethyl phthalate	4 female CBA/Ca mice	EC_3 = 18.44% (4610 μg/cm^2)	RIFM (2005b)
Cinnamyl cinnamate	Modified Freund's complete adjuvant test	3% & 10% in acetone	Guinea pigs	Weak sensitization was observed at both concentrations (no further details given)	Hausen et al. (1992) Hausen et al. (1995)
Ethyl cinnamate	Open epicutaneous test	4% (vehicle not specified)	6–8 guinea pigs	No reactions	Klecak (1979) Klecak (1985)
Methyl cinnamate	Maximization test	a subirritant concentration in petrolatum	Male & female outbred Himalayan guinea pigs	Sensitization effects were observed (no further details given)	Klecak et al. (1977)
Methyl cinnamate	Freund's complete adjuvant test	a subirritant concentration in petrolatum	Male & female outbred Himalayan guinea pigs	Sensitization effects were observed (no further details given)	Klecak et al. (1977)
Methyl cinnamate	Modified Freund's complete adjuvant test	10% in acetone	guinea pigs	No reactions (no further details given)	Hausen et al. (1992) Hausen et al. (1995)
Methyl cinnamate	Open epicutaneous test	30% (vehicle not specified)	Male & female outbred Himalayan guinea pigs	Sensitization effects were observed (no further details given)	Klecak et al. (1977)
Methyl cinnamate	Open epicutaneous test	2.0% (vehicle not specified)	6–8 guinea pigs	No reactions (no further details given)	Klecak (1979)
Methyl cinnamate	Open epicutaneous test	10% (vehicle not specified)	6–8 guinea pigs	No reactions (no further details given)	Klecak (1985)
Methyl cinnamate	Intradermal sensitization test	0.1% in 5% ethyl alcohol in distilled water	Male albino guinea pigs	No reactions	RIFM (1971b)
Methyl cinnamate	Modified Draize test	0.1% in saline	Male & female outbred Himalayan guinea pigs	Sensitization effects were observed (no further details given)	Klecak et al. (1977)
α-Methyl cinnamic alcohol	Maximization test	75% test material v/v in arachis oil BP	Dunkin Hartley albino guinea pigs	No reactions	RIFM (1997b)

Table 12
Summary of UV Spectra Data for Cinnamyl Esters and Substituted Alcohols

Material	UV Spectra Range of Absorption (nm)
Allyl cinnamate	peaked at 245–278 minor absorption in 290–320 nm range
α-Amylcinnamyl alcohol	peaked at 245–278 minor absorption in 290–320 nm range
Benzyl cinnamate	peaked at 245–278 minor absorption in 290–320 nm range
Cinnamyl acetate	peaked at 245–278 minor absorption in 290–320 nm range
Cinnamyl benzoate	peaked at 245–278 minor absorption in 290–320 nm range
Cinnamyl butyrate	peaked at 245–278 minor absorption in 290–320 nm range
Cinnamyl cinnamate	peaked at 245–278 minor absorption in 290–320 nm range
Cinnamyl formate	peaked at 245–278 minor absorption in 290–320 nm range
Cinnamyl isobutyrate	peaked at 245–278 minor absorption in 290–320 nm range
Cinnamyl isovalerate	peaked at 245–278 minor absorption in 290–320 nm range
Cinnamyl propionate	peaked at 245–278 minor absorption in 290–320 nm range
Ethyl cinnamate	peaked at 245–278 minor absorption in 290–320 nm range
Isoamyl cinnamate	peaked at 245–278 minor absorption in 290–320 nm range
Isobutyl cinnamate	peaked at 245–278 minor absorption in 290–320 nm range
Linalyl cinnamate	peaked at 245–278 minor absorption in 290–320 nm range
Methyl cinnamate	peaked at 245–278 minor absorption in 290–320 nm range
Phenethyl cinnamate	peaked at 245–278 minor absorption in 290–320 nm range

follow the same metabolic pathway in that the alcohol is transformed into the aldehyde, which is metabolized to the acid. The final major urinary metabolite is hippuric acid.

3. Based on acute toxicity data, these cinnamyl materials can be considered to range from practically nontoxic to moderately toxic.
4. Based on a subchronic dermal study, the NOAEL for isopropyl cinnamate is 1000 mg/kg body weight/day. Based on oral studies, the NOELs for benzyl cinnamate and linalyl cinnamate are 500 mg/kg body weight/day. Based on the results of oral chronic studies (2 years) available for trans-cinnamaldehyde, NOAELs for it and related materials have been identified as 200 mg/kg body weight/day in rats and 550 mg/kg/body weight per day in mice. All of these NOAELs greatly exceed the expected dose absorbed from dermal exposure in humans from the use of these compounds as fragrance ingredients. Such exposures are estimated at 0.0003–0.0268 mg/kg body weight/day.
5. Based on a weight of evidence evaluation of the available mutagenicity and genotoxicity data on these cinnamyl materials, as well as the metabolism and detoxification of cinnamyl alcohol, cinnamaldehyde and cinnamic acid, it can be concluded that this group of fragrance materials has no significant genotoxic potential under the current conditions of use as fragrance ingredients.
6. Oral chronic studies (2 years) with trans-cinnamaldehyde in rats and mice produced no evidence of carcinogenic activity.
7. Based on the available data on developmental toxicity studies on cinnamyl alcohol, cinnamaldehyde and cinnamic acid, it is not expected that these cinnamyl materials possess any significant potential for developmental effects under the current conditions of use as fragrance ingredients.
8. Based on human studies, these cinnamyl materials are not considered to be primary irritants under the recommended current conditions of use as fragrance ingredients with the exception of allyl cinnamate which produced irritation due to its allyl component.
9. Although slight to well-defined eye irritation was observed in animals with linalyl cinnamate, these cinnamyl materials are not considered to be eye irritants in humans under the recommended current conditions of use as fragrance ingredients.
10. Weak sensitization reactions were observed in animals, but no reactions were observed in human studies. While, IFRA (2007) has established Standards on α-amylcinnamyl alcohol and benzyl cinnamate using a Quantitative Risk Assessment (QRA) for dermal sensitization (see the individual fragrance material reviews on α-amylcinnamyl alcohol and benzyl cinnamate for more information); the weight of evidence supports the conclusion that these cinnamyl materials present no significant risk of sensitization under the recommended current conditions of use as fragrance ingredients.
11. Based on UV spectra and phototoxicity and photoallergy studies with cinnamaldehyde and cinnamic acid, it is not expected that these materials would produce phototoxic or photoallergic effects.

6. Conclusion

After a review of all available data on the related esters and alcohols of cinnamic acid and cinnamyl alcohol and on the parent materials, cinnamyl alcohol, cinnamaldehyde and cinnamic acid, the Panel has determined that there

are unlikely to be safety concerns regarding these materials under the present conditions of use and exposure for the following reasons:

- In acute studies, these materials have a low to moderate order of oral toxicity (LD50 values of 1.5–39 g/kg body weight), and a low order of dermal toxicity based on dermal LD50 values that exceeded 3–5 g/kg body weight.
- Dermal and oral subchronic NOAELs greatly exceed the expected dose absorbed in humans from their use as fragrance ingredients.
- While there are no long-term studies on these materials, a 2-year oral chronic study with trans-cinnamaldehyde provides a basis for the estimation of toxic potential for these materials; NOAELs from this study also greatly exceed the expected dose absorbed in humans from their use as fragrance ingredients.
- These materials have no significant potential to produce genotoxic effects in vivo based on a weight of evidence evaluation of all mutagenicity and genotoxicity data.
- These materials are expected to be extensively hydrolyzed by tissue esterases and the alcohols and acids that are formed are expected to undergo further oxidation, conjugation and excretion. The metabolic fate of the parent materials, cinnamyl alcohol, cinnamaldehyde and cinnamic acid are well known and toxic or persistent metabolites are not formed from their metabolism.
- In Human Dermatological Studies: Allyl cinnamate has a potential to produce irritation; with the remaining cinnamyl materials, no irritation was observed at dose levels up to 10%.
- These materials pose no significant risk of sensitization based on studies with 22 materials.
- Phototoxicity and photoallergic effects have not been evaluated in humans for these materials; however, 1% cinnamaldehyde and 20% cinnamic acid did not produce phototoxicity or photoallergy. It is not expected that these materials would have a potential to produce phototoxicity or photoallergy.
- These materials are used at low levels of exposure relative to doses that elicit adverse effects in laboratory animals via systemic exposure. The estimated dermal systemic exposure is greatest for linalyl cinnamate (0.03 mg/kg body weight/day). If one looks at the NOAEL in mice for cinnamaldehyde (550 mg/kg body weight/day), the margin of safety for systemic exposure based on this NOAEL is 18, 333 times the maximum daily exposure for linalyl cinnamate.

Conflicts of interest statement

D. Belsito, D. Bickers, M. Bruze, P. Calow, H. Greim, J.M. Hanifin, A.E. Rogers and J.H. Saurat are members of the Expert Panel of the Research Institute for Fragrance Materials, an independent group of experts who evaluate the safety of fragrance materials that is supported by the manufacturers of fragrances and consumer products containing fragrances. I.G. Sipes and H. Tagami are employees of the Research Institute for Fragrance Materials, an independent research institute supported by the manufacturers of fragrances and consumer products containing fragrances. 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.

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