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Food and Chemical Toxicology 43 (2005) 799–836
www.elsevier.com/locate/foodchemtox

Review

A toxicologic and dermatologic assessment of cinnamyl alcohol, cinnamaldehyde and cinnamic acid when used as fragrance ingredients ☆

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Received 10 January 2004; accepted 24 September 2004

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0278-6915/$ - see front matter
doi:10.1016/j.fct.2004.09.013

1. Chemical identity and exposure (Tables 1 and 2, Fig. 1)

This report summarizes scientific data relevant to the assessment of cinnamyl alcohol, cinnamaldehyde and cinnamic acid (see Fig. 1 and Table 1). These substances are all used as fragrance and flavor ingredients. This report uses data from animals and humans by different routes of exposure, but emphasizes the risk assessment for use of cinnamyl alcohol, cinnamaldehyde and cinnamic acid 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 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 currency of protocols, quality of the data, statistical significance and appropriate exposure. These are identified in tabular form in the group summary. The Fragrance Material Reviews contain a comprehensive summary of published reports including complete bibliographies.

Cinnamyl compounds are a fundamental part of plant biochemistry. *trans*-Cinnamic acid is ubiquitous in the plant kingdom and is required for lignin formation in plants. It is derived from the action of L-phenylalanine ammonia lyase upon L-phenylalanine, forming ammonia and cinnamic acid (Goodwin and Mercer, 1972; JECFA, 2000). Cinnamic acid is also converted to *p*-hydroxy cinnamic acid (*p*-coumaric acid) by plants. *p*-Coumaric acid is one of the more important precursors of lignins as it can be converted to polyphenolic alcohols which readily polymerize to form lignin (Goodwin and Mercer, 1972; JECFA, 2000).

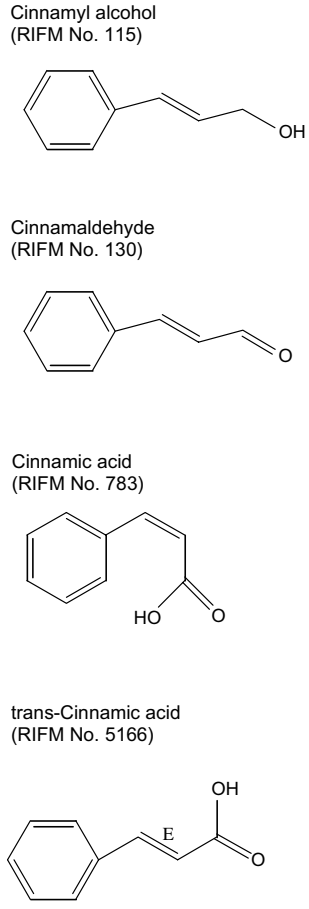

Fig. 1. Structures of cinnamyl alcohol, cinnamaldehyde and cinnamic acid.

In the United States, the regulatory status of these three materials includes approval (21 CFR 172.515 and 21 CFR 182.60) by the Food and Drug Administration (FDA) and Generally Recognized as Safe (GRAS) as flavor ingredients [Numbers 2294, 2286, 2288] by the Flavor and Extract Manufacturers' Association (FEMA, 1965). All three of these materials were also in-

Table 1
Cinnamyl materials included in this summary

Compound	CAS number	Synonyms
Cinnamic acid	621-82-9	Benzylideneacetic acid Cinnamylic acid 3-Phenylacrylic acid 3-Phenylpropenoic acid 2-Propenoic acid, 3-phenyl-
trans-Cinnamic acid	140-10-3	*trans*-3-Phenylacrylic acid (E)-3-Phenyl-2-propenoic acid 2-Propenoic acid, 3-phenyl-, (E)-
Cinnamaldehyde	104-55-2	Cinnamal Cinnamic aldehyde Phenylacrolein 3-Phenylpropenal 3-Phenyl-2-propen-1-al 2-Propenal, 3-phenyl-
Cinnamyl alcohol	104-54-1	Cinnamic alcohol 3-Phenyl-2-propen-1-ol 2-Propen-1-ol, 3-phenyl- Styryl carbinol Zimtalcohol

cluded in the Council of Europe's list of substances [Numbers 65, 102, 22] 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 these three materials and found them to have no safety concerns based on current levels of intake as food flavors. Because of their potential for allergenicity, the European Union has placed both cinnamaldehyde and cinnamyl alcohol on the list of fragrance materials that must be labeled on consumer products (7th Amendment to Council Directive 76/768/EEC). Cinnamaldehyde is a High Production Volume (HPV) material and as such has been included in a Robust Summary and Test Plan for "Cinnamyl Derivatives" which has been prepared by the Flavor and Fragrance High Production Volume Consortia. Cinnamaldehyde is also registered under the International Council of Chemical Associations (ICCA) HPV Initiative and FEMA has recently published a GRAS assessment of 56 cinnamyl materials used as flavoring ingredients (Adams et al., 2004).

All three substances have been reported as common components of food occurring mainly in a wide variety of fruits, vegetables, and spices in varying concentrations. For example, concentrations of 750,000 ppm cinnamaldehyde in cinnamon (*Cinnamomum zeylanicum* Blume) and 3000–7900 ppm cinnamyl alcohol in cinnamon (*Cinnamomum zeylanicum* Blume and other *Cinnamomum* species) have been reported (TNO, 1994).

Data from a survey conducted in the year 2001 indicate that the annual worldwide use of cinnamic acid is between 1 and 10 metric tons (see Table 2) and the annual worldwide use of cinnamaldehyde and cinnamyl alcohol is between 100 and 1000 metric tons for each material (Table 2).

Estimated consumer exposure (Table 2). The availability of fragrance ingredients for potential exposure by consumers is estimated in two ways (see Table 2). 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 cinnamaldehyde from 10 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 0.099% is calculated as 0.0026 mg/kg/day (IFRA, 2001). The calculated exposures for cinnamic acid and cinnamyl alcohol are 0.0005 mg/kg/day and 0.0416 mg/kg/day, respectively (IFRA, 2001) (see Table 2). For consideration of potential sensitization the exposure is calculated as a percent concentration used on the skin. Thus exposure to cinnamaldehyde used in fine fragrance products is reported as 0.05% based on the use of 20% of the fragrance mixture in the fine fragrance consumer product (IFRA, 2001). The comparable exposures for cinnamic acid and cinnamyl alcohol are 0.01% and 0.4%, respectively (IFRA, 2001) (see Table 2). Exposure

Table 2
Cinnamic acid, cinnamaldehyde and cinnamyl alcohol summary of volume of use and dermal exposure

Material	RIFM number	Annual Worldwide[a] (metric tons)	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin level[b] (%)
Cinnamic acid	783	1–10	0.0005	0.01
Cinnamaldehyde	130	100–1000	0.0026	0.05
Cinnamyl alcohol	115	100–1000	0.0416	0.4

[a] 2000 Volume of Use Survey.
[b] The maximum skin level for cinnamic acid is based on the assumption that the fragrance mixture is used at 20% in a consumer product (2001 IFRA Use Level Survey). The maximum skin levels for cinnamaldehyde and cinnamyl alcohol are based on IFRA standards of 0.05% and 0.4%, respectively (IFRA, 2003, 2004).

data are provided by the fragrance industry. An explanation of how the data are obtained and how exposure was determined has been reported by Cadby et al. (2002) and Ford et al. (2000).

2. Biological data

2.1. Absorption, distribution and metabolism

2.1.1. Percutaneous absorption (Table 3)

Cinnamyl alcohol, cinnamaldehyde and cinnamic acid are all partially absorbed through the skin with a greater degree of absorption occurring under occluded conditions. In vivo (monkey) skin percutaneous absorption was greatest with cinnamic acid. Using a vehicle (acetone) and longer exposure time significantly increased the absorption of cinnamic alcohol and cinnamaldehyde in in vitro human skin experiments (these results are described below).

2.1.1.1. In vivo percutaneous absorption. In in vivo dermal application studies, approximately 25% and 75% cinnamyl alcohol and 39% and 84% cinnamic acid (non-occluded and occluded, respectively) were absorbed through the skin of rhesus monkeys within a five day period following application of the materials in an acetone vehicle to a clipped area of abdominal skin (Bronaugh et al., 1985).

2.1.1.2. In vitro percutaneous absorption. Using a skin absorption model system with human skin for cinnamaldehyde (Hotchkiss, 1998) or a diffusion cell technique for cinnamyl alcohol and cinnamic acid (Bronaugh et al., 1985) with excised human abdominal skin, it was reported that 34% and 66% cinnamyl alcohol, 24% and 52% cinnamaldehyde and 18% and 61% cinnamic acid (non-occluded and occluded, respectively) were absorbed by 72 h.

The in vitro human skin absorption and metabolism of neat cinnamyl alcohol and cinnamaldehyde under occluded conditions were also measured over a 24-h period.

A total of 1.9 ± 0.2% of the initial applied dose of cinnamyl alcohol penetrated the skin as either parent cinnamyl alcohol (1.3%) or metabolite, cinnamic acid (0.6%). The majority of cinnamyl alcohol (55.2%) remained unabsorbed on the surface of the skin; approximately 3.9% of the initial applied dose of cinnamyl alcohol converted to cinnamaldehyde, which remained unabsorbed; no cinnamic acid metabolite was observed on the skin surface. Within the skin, a total of 3.5 ± 0.2% of the initial cinnamyl alcohol was found as either cinnamyl alcohol (3.1 ± 0.1%) or cinnamic acid (0.4 ± 0.2%) (Smith et al., 2000).

Approximately 9% (9.4 ± 1.6%) of the applied dose of cinnamaldehyde penetrated the skin as cinnamaldehyde (2.6%), or one of its metabolites, cinnamyl alcohol (2.4%) or cinnamic acid (4.4%). The majority of cinnamaldehyde (55.3% of the total dose) was unabsorbed and remained on the surface of the skin; approximately 10.6% of the initial dose of cinnamaldehyde converted to cinnamic acid which also remained on the skin surface. Within the skin, a total of 6.6 ± 2.8% of the initial cinnamaldehyde dose was found as either cinnamaldehyde (2.9 ± 1.0%), cinnamyl alcohol (0.4 ± 0.2%), or cinnamic acid (3.3 ± 1.7%) (Smith et al., 2000). Using a skin absorption model system with excised rat skin, 37% and 56% cinnamyl alcohol, 34% and 42% cinnamaldehyde and 9% and 7% cinnamic acid (non-occluded and occluded, respectively) have been reported to be absorbed within 48–72 h (Hotchkiss, 1998).

2.1.2. Pharmacokinetics

These three substances participate in common routes of absorption, distribution and metabolic detoxication and exhibit similar toxicological endpoints. Cinnamyl alcohol, cinnamaldehyde and cinnamic acid have all

Table 3
Summary of percutaneous absorption data

Material	In vivo		In vitro			
	Monkey (acetone vehicle)		Human		Rat (48–72 h; vehicle unspecified)	
	Non-occluded	Occluded	Non-occluded (%)	Occluded (%)	Non-occluded (%)	Occluded (%)
Cinnamic acid	39%[a]	84%[a]	18[b]	61[b]	9[c]	7[c]
Cinnamic alcohol	25%[a]	75%[a]	34[b]	66[b] 1.9[d]	37[c]	56[c]
Cinnamaldehyde	ND	ND	24[e]	52[e] 9[d]	34[f]	42[f]

ND—no data.
[a] Absorption for 96 h (Bronaugh et al., 1985).
[b] Abdominal skin, vehicle was acetone, absorption for 72 h (Bronaugh et al., 1985).
[c] Absorption for 48 h (Hotchkiss, 1998).
[d] Breast and abdominal skin, neat material, absorption for 24 h (Smith et al., 2000).
[e] Vehicle unspecified, absorption for 72 h (Hotchkiss, 1998).
[f] Absorption for 72 h (Hotchkiss, 1998).

been shown to be rapidly absorbed from the gut, metabolized and excreted primarily in the urine and to a minor extent, in the feces (JECFA, 2000).

Following an oral dose of 2.5 mmol/kg bodyweight cinnamyl alcohol given to rats, 71% of radioactivity [^{14}C] was excreted in the urine, and 6% in the feces within 24 h; at 72 h, 82% and 9% were excreted in the urine and feces, respectively. When the same dose was administered by intraperitoneal injection to mice, 71% was recovered in the urine and 5% in the feces within 24 h, increasing to 78% in the urine and 13% in the feces at 72 h (Nutley, 1990).

Sixty-two percent (62%) of an oral dose of 2.5 mmol/kg/bodyweight cinnamaldehyde given to rats was excreted in the urine, and 16% in the feces within 24 h; this increased to 68% and 24% at 72 h. When the same dose was administered by intraperitoneal injection to mice, 54% was recovered in the urine and 15% in the feces within 24 h increasing to 63% and 26% at 72 h (Nutley, 1990). The total percentage of radioactivity [^{14}C] recovered from both the urine and feces 24 h after intraperitoneal administration of 2 or 250 mg [^{14}C]cinnamaldehyde/kg/bodyweight was 89% and 86% in male rats and 90% and 79% in female rats, respectively (Peters, 1993; Peters and Caldwell, 1994). After oral administration of 250 mg/kg bodyweight to male rats, 98% of the dose was recovered in urine and feces. Recoveries after 24 h in mice were all more than 85% of the dose. The similar percentages of the dose recovered after both intraperitoneal and oral administration indicate that absorption from the intestinal tract is complete (Peters, 1993; Peters and Caldwell, 1994). Absorption also appears to be rapid and complete in humans. The elimination of cinnamaldehyde by two adult volunteers, who had received a single oral dose of 0.7 mg/kg, was rapid with 100% recovered in the urine within 8 h (Peters, 1993).

Eighty-two percent (82%) of an oral dose of 2.5 mmol/kg/bodyweight cinnamic acid given to rats was excreted in the urine within 24 h, and 0.9% in the feces. When the same dose was administered by intraperitoneal injection to mice, 90% was recovered in the urine within 24 h, and 4% in the feces (Nutley, 1990). When doses of 0.5 μmol–2.5 mmol/kg cinnamic acid were given orally to rats or by intraperitoneal injection to mice, greater than 85% was recovered in the urine, with 5% in the feces within 3 days (Caldwell and Nutley, 1986). In another study, twenty-four (24) h after rats were given oral doses of 0.0005–2.5 mmol [^{14}C]cinnamic acid/kg, 73–88% of the radioactivity was recovered in the urine. After 3 days, only trace amounts of radioactivity were present in the carcasses, indicating that cinnamic acid was readily and quantitatively excreted at all dose levels (Nutley et al., 1994). Comparable results were obtained in the mouse following intraperitoneal administration of cinnamic acid. The 24-h urine collection accounted for 78–93% of the dose (Nutley et al., 1994).

Humans also clear systemically available cinnamic acid quickly. Eleven adult human volunteers received single intravenous doses of cinnamic acid, equivalent to 5 mg/kg bodyweight. Plasma was cleared of cinnamic acid within 20 min (Quarto di Palo and Bertolini, 1961).

2.1.3. Metabolism (Fig. 2)

Cinnamyl alcohol, cinnamaldehyde, and cinnamic acid undergo extensive metabolism. The alcohol is rapidly converted to the aldehyde via alcohol dehydrogenase to cinnamaldehyde, which, in turn, is converted to cinnamic acid. Thus, cinnamic acid is the major intermediate metabolite for both chemicals. The major urinary metabolites for all three chemicals are glycine or glucuronic acid conjugates of benzoic acid, which forms as a result of β-oxidation of cinnamic acid. Glycine and glucuronic acid conjugates of cinnamic acid are formed in small amounts. A minor percentage of cinnamaldehyde undergoes conjugation with glutathione to form mercapturic acid derivatives. Other minor metabolites have been identified (JECFA, 2000) (see Fig. 2).

Aromatic acids, such as cinnamic acid are converted to acyl CoA esters (Nutley et al., 1994). CoA thioesters of carboxylic acids are obligatory intermediates in amino acid conjugation reactions (Hutt and Caldwell, 1990; JECFA, 2000). 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; JECFA, 2000). 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; JECFA, 2000). Regardless of dose or species, the β-oxidation pathway is the predominant pathway of metabolic detoxication of cinnamic acid in animals.

Six dose levels in the range of 0.0005–2.5 mmol/kg (≈0.08–400 mg/kg bodyweight) [^{14}C]- or [^{14}C/$^{5}H_2$]-cinnamic acid were administered orally to male rats or by intraperitoneal injection to male mice. In both species, 84–101% was recovered within 72 h with the majority (73–93%) recovered from the urine within 24 h. The metabolites identified at all dose levels included hippuric acid, benzoyl glucuronide, 3-hydroxy-3-phenyl-propionic acid, benzoic acid, and unchanged cinnamic acid. The major metabolite was hippuric acid at all dose levels (44–77%). At the highest dose given, (2.5 mmol/kg/bodyweight) the percentage of hippuric acid decreased while the percentages of benzoyl glucuronide and benzoic acid increased. Increased formation of benzoyl glucuronide (0.5–5%) and free benzoic acid (0.4–2%) at dose levels above 0.5 mmol/kg/bodyweight provide evidence that saturation of the glycine conjugation pathway occurs at these higher dose levels. The fact that

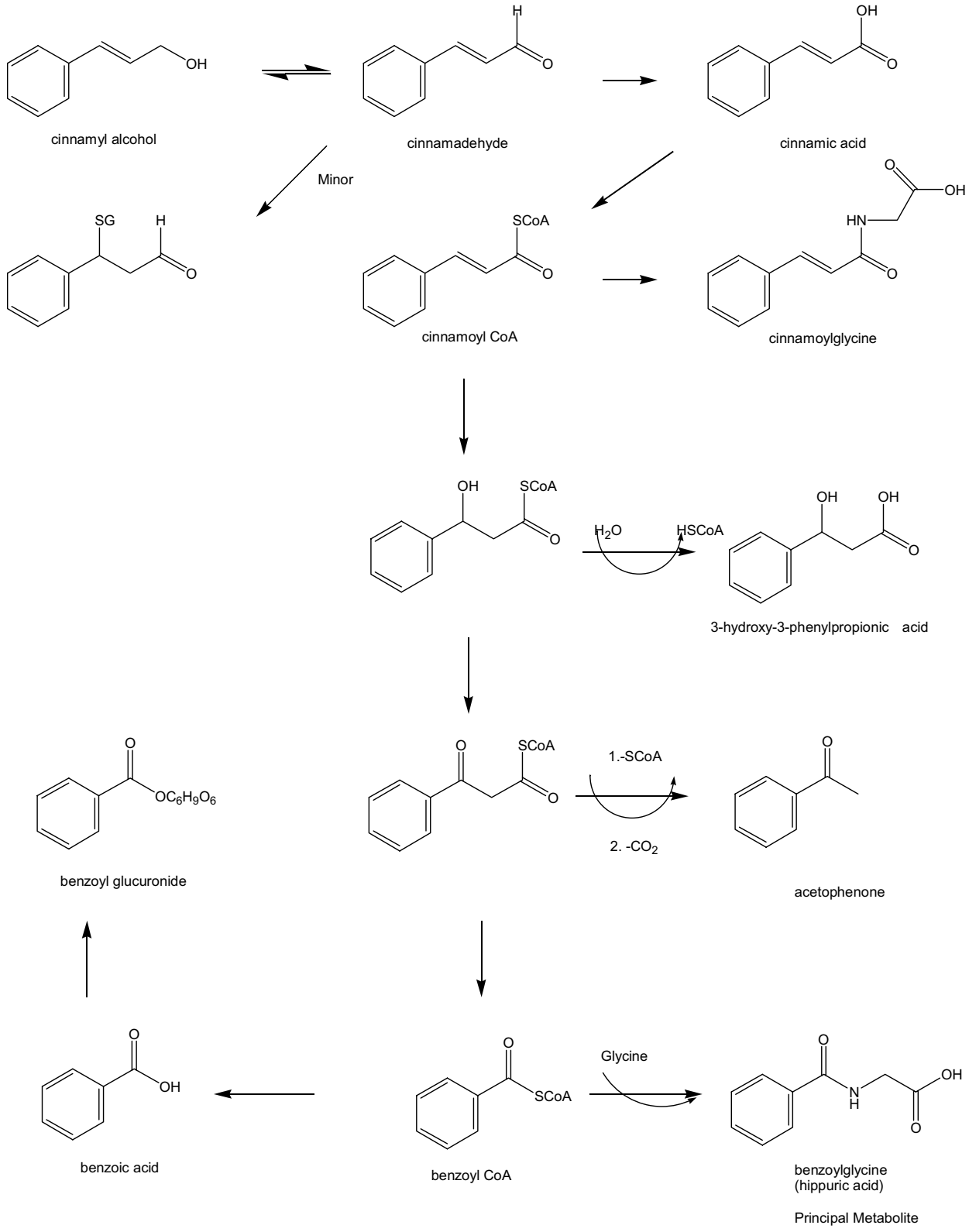

Fig. 2. Metabolism of cinnamyl alcohol, cinnamaldehyde and cinnamic acid (JECFA, 2000).

3-hydroxy-3-phenyl-propionic acid was only slightly changed over the dose range (0.2–0.9%) supports the conclusion that the β-oxidation pathway is not capacity-limited up to 2.5 mmol/kg bodyweight cinnamic acid in the male rat (Nutley et al., 1994; JECFA, 2000). The increasing role of glucuronic acid conjugation relative to glycine

conjugation as dose size increases is a general trend observed in the metabolism of carboxylic acids (Caldwell et al., 1980).

In mice, glycine conjugation of cinnamic acid competes with the β-oxidation pathway, but only at low dose levels. As dose levels increase from 0.0005 to 2.5 mmol/kg/bodyweight, urinary hippuric acid increases from 44% to 67%, while cinnamoylglycine levels decrease from 29% to 2.4%. These results suggest that glycine *N*-acetyl transferase has high affinity but low capacity for cinnamic acid compared to benzoic acid. At the highest dose (2.5 mmol/kg bodyweight), an increase in excreted free benzoic acid (0.8–8.6%) suggests that glycine conjugation of benzoyl CoA is also capacity limited in mice. At all dose levels, the mouse excretes a small proportion of benzoyl glucuronide, which suggests that this conjugation reaction is of minimal importance in this species (Nutley et al., 1994; JECFA, 2000).

Humans metabolize cinnamic acid in a manner similar to rodents. Ninety (90) minutes after dosing 11 adults with 5 mg/kg bodyweight cinnamic acid, urinalysis revealed hippuric acid, cinnamoylglucuronide, and benzoylglucuronide as the major metabolites, present in a ratio of 74:24.5:1.5, respectively (Quarto di Palo and Bertolini, 1961).

In both rats and mice the major urinary metabolite of orally administered cinnamaldehyde (doses of 2 and 250 mg/kg) is hippuric acid. It represents 71–87% of the dose, depending on the particular study (Peters, 1993; Peters and Caldwell, 1994; Sapienza et al., 1993). Small amounts of other metabolites include 3-hydroxy-3-phenylpropionic acid (0.4–4%), benzoic acid (0.4–3%), and benzoyl glucuronide (0.8–7.0%). The glycine conjugate of cinnamic acid was formed to a considerable extent only in the mouse (4–13%). Repeated daily dosing with large doses of cinnamaldehyde (500 mg/kg) saturates the glycine pathway such that benzoic acid becomes the major urinary metabolite. Apart from the expected metabolites of cinnamaldehyde (i.e. cinnamic acid derivatives), mercapturic acids derived from the direct conjugation of cinnamaldehyde with glutathione were identified in the urine of rats and mice. These represented 6–15% of the administered dose of cinnamaldehyde. For example, 15% of an oral gavage dose of 250 mg/kg cinnamaldehyde to rats was excreted in the urine as two mercapturic acids: *N*-acetyl-*S*-(1-phenyl-3-hydroxypropyl)cysteine and *N*-acetyl-*S*-(1-phenyl-2-carboxyethyl)cysteine, in a ratio of four to one (Delbressine et al., 1981). Taken together, the results of these and other studies, demonstrate that in rats and mice the excretion pattern and metabolic profile of cinnamaldehyde are not systemically affected by gender, route of administration or dose (at least up to 250 mg/kg).

The profile of urinary metabolites of cinnamaldehyde in humans is similar to that observed in rats and mice. Ninety three percent (93%) of a 0.7 mg/kg oral dose of cinnamaldehyde given to two adult volunteers was recovered in 0–8 h in the urine as the glycine conjugate of benzoic acid (hippuric acid), accompanied by small amounts of 3-hydroxy-3-phenylpropionic acid (1.2% and 1.5%) and benzoic acid (1.1% and 1.3%). Two further metabolites were also detected in the urine, *N*-acetyl-*S*-(1-phenyl-3-hydroxypropyl)cysteine and *N*-acetyl-*S*-(1-phenyl-2-carboxy-ethyl)cysteine (Peters, 1993; Peters and Caldwell, 1994).

The urinary metabolic profile of cinnamyl alcohol follows that of cinnamic acid and cinnamaldehyde. In rats, fifty-two percent (52%) of an oral dose of cinnamyl alcohol (335 mg/kg) was recovered in 24 h in the urine as the glycine conjugate of benzoic acid (hippuric acid). Ten minor metabolites cumulatively accounted for about 10% of the dose (Nutley, 1990). In another study, approximately 9% of an oral dose of cinnamyl alcohol (125 mg/kg) administered to rats by gavage was excreted in the urine as *N*-acetyl-*S*-(1-phenyl-3-hydroxypropyl)cysteine (Delbressine et al., 1981). When cinnamyl alcohol was administered to mice by intraperitoneal injection, hippuric acid was the major urinary metabolite (Nutley, 1990).

Although metabolic studies with cinnamyl alcohol in humans have not been reported, it is expected that the human metabolic profile for this material would be similar to that observed in rats.

3. Toxicological studies

3.1. Acute toxicity (Table 4a and b)

Cinnamyl alcohol, cinnamaldehyde and cinnamic acid have all been evaluated for acute toxicity (see Table 4a and b). Dermal LD_{50} values in rabbits exceeded 5000 mg/kg for cinnamyl alcohol and cinnamic acid; the dermal LD_{50} value in rabbits for cinnamaldehyde exceeded 1000 mg/kg for a well-defined, pure commercial sample. Oral LD_{50} values for cinnamyl alcohol and cinnamic acid in the rat have been reported as 2000 mg/kg and 3570 mg/kg, respectively. Oral LD_{50} values for cinnamaldehyde in rats and guinea pigs have been reported as 2220 mg/kg and 1160 mg/kg, respectively. Intraperitoneal studies with cinnamaldehyde in mice show that it is more toxic by that route of exposure with an LD_{50} value of 460 mg/kg.

3.2. Subchronic toxicity (Table 5a)

Toxicological studies have been reported for cinnamaldehyde. Results of these studies are summarized in Table 5a and are described below.

Male and female F344/N rats were fed diets containing 4100, 8200, 16,500 or 33,000 ppm microencapsulated *trans*-cinnamaldehyde (equivalent to average daily doses of approximately 275, 625, 1300 or 4000 mg *trans*-cinnamaldehyde/kg bodyweight to males and 300, 570, 1090

Table 4
Acute toxicity

Material	Species	No. of animals/dose group	LD_{50}[a]	References
(a) Oral studies				
Cinnamaldehyde	Rat	10 (5/sex)	2200 mg/kg bodyweight (95% CI 1900–2600 mg/kg bodyweight)	Jenner et al. (1964)
Cinnamaldehyde	Guinea pig	Not specified	1200 mg/kg bodyweight (95% CI 1000–1400 mg/kg bodyweight)	Jenner et al. (1964)
Cinnamic acid	Rat	10	3570 mg/kg bodyweight (95% CI 3070–4140 mg/kg bodyweight)	RIFM (1976a)
Cinnamyl alcohol	Rat	10 (except 20 at 1600 mg/kg)	2000 mg/kg bodyweight (95% CI 1700–2300 mg/kg bodyweight)	RIFM (1973a)
(b) Dermal studies				
Cinnamaldehyde	Rabbit	4	619 mg/kg bodyweight (441–882 mg/kg bodyweight)	RIFM (1973b)
Cinnamaldehyde	Rabbit	2–4	1260 mg/kg bodyweight (945–1680 mg/kg bodyweight)	RIFM (1986a)
Cinnamaldehyde	Rabbit	10 (5/sex)	>1000 mg/kg bodyweight	RIFM (1997)
Cinnamaldehyde	Rabbit	10 (5/sex)	>1000 mg/kg bodyweight	RIFM (1994)
Cinnamic acid	Rabbit	4	>5000 mg/kg bodyweight	RIFM (1976a)
Cinnamyl alcohol	Rabbit	5	>5000 mg/kg bodyweight	RIFM (1973a)

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

or 3100 mg/kg bodyweight to females) for 14 weeks. All rats survived to the end of the study. Feed consumption was decreased in all treated animals, possibly due to poor palatability. Mean body weights of all exposed groups of males and of females in the two highest dose levels were significantly decreased. Early in the study, increases in serum bile concentration in the 4100 ppm or greater males and 8200 ppm or greater females was observed but the number of dose groups affected ameliorated and only the animals in the highest dose group had increased serum concentrations by the end of the study. Akaline phosphatase activity demonstrated dose-related decreases that ameliorated with time but this may have reflected decreases in feed intake and loss of the intestinal contribution to serum alkaline phosphatase activity. Thus, the increased bile acid concentration may suggest a cholestasis but also could suggest a hepatic effect. However, no histopathological lesions in the liver were observed. Gross lesions observed at necropsy included multifocal to diffuse white nodules of the forestomach mucosa in males and females at the three highest dose levels. Increased incidences of nonneoplastic lesions of the forestomach included squamous epithelial hyperplasia in males and females at the three highest dose levels and chronic active inflammation in males at the highest dose level and in females at the two highest dose levels (Johnson et al., 1998; NTP, 2004).

In a similar study, male and female $B6C3F_1$ mice were fed diets containing 4100, 8200, 16,500 or 33,000 ppm microencapsulated *trans*-cinnamaldehyde (equivalent to average daily doses of approximately 650, 1320, 2550 or 5475 mg/kg bodyweight to males and 625, 1380, 2680 or 5200 mg/kg bodyweight to females) for 14 weeks. Palatability of the dosed feed was a problem at the two highest doses. Mean body weights of males and females in the three highest dose levels were significantly less than those of controls. Feed consumption in mice at the two highest dose levels was decreased during weeks 1 and 2. There were deaths of 5 and 8 males at the 2550 and 5475 mg/kg doses, respectively. The incidences of squamous epithelial hyperplasia and hyperkeratosis of the forestomach mucosa in females at the highest dose level were significantly increased, and olfactory epithelial degeneration of the nasal cavity occurred in both males and females in the two highest dose levels (Johnson et al., 1998; NTP, 2004).

In Osborne-Mendel rats (10/sex/dose) maintained on a diet containing, 1000, 2500 or 10,000 ppm (approximately equivalent to 50, 125 or 500 mg/kg bodyweight/day) cinnamaldehyde for a total of 16 weeks, there were no significant differences from controls in growth, hematology, or histopathology at the two lowest dose levels; a slight hepatic cellular swelling and a slight hyperkeratosis of squamous epithelium of the forestomach was noted in rats at the highest dose level (Hagan et al., 1967). In a similar study, no adverse toxic effects and no effects on growth, general clinical observations, feed intake volumes, hematology, urinalysis, or histopathology were observed in rats (5/sex/dose) maintained on a diet containing cinnamaldehyde at levels calculated to result in the approximate daily intake of 58, 114 or 227 mg/kg bodyweight for a total of 12 weeks (RIFM, 1958a; Adams et al., 2004).

The results of a subchronic study by Devaraj et al. (1992) differ from those just summarized above. In this study, rats were fed 1.25 or 2.5 mg/kg bodyweight/day cinnamaldehyde in the diet for 24 weeks. At the high dose, bodyweight was significantly decreased, while hepatic cytochrome P450 activities, cytochrome P450 content, and liver weight and liver protein content were

Table 5
Subchronic toxicity (Panel a) and chronic toxicity (Panel b)

Material	Method	Dose[a]	Species	Results	References
(a) Subchronic					
Cinnamaldehyde	Oral 14-week study	275, 625, 1300 and 4000 mg/kg bodyweight/day (males); 300, 570, 1090, and 3100 mg/kg bodyweight/day (females); microencapsulated *trans*-cinnamaldehyde in feed	20 rats (10/sex/dose)	Feed consumption decreased in all treated animals; mean body weights decreased at all doses in males and in two highest doses in females; serum bile acid concentration increased in all doses in males and in the three highest doses in females (however, by end of study only the highest dose had increased serum concentration); forestomach nodules and squamous epithelial hyperplasia in males and females at the three highest doses; chronic active inflammation of forestomach in males at the highest dose and in females at the two highest doses	Johnson et al. (1998), NTP (2004)
Cinnamaldehyde	Oral 14-week study	650, 1320, 2550 and 5475 mg/kg bodyweight/day (males); 625, 1380, 2680 and 5200 mg/kg bodyweight/day (females); microencapsulated *trans*-cinnamaldehyde in feed	20 mice (10/sex/dose)	Mean body weights significantly decreased in males and females at three highest doses; 50% and 80% mortality in males at 2550 and 5475 mg/kg dose levels, respectively; squamous epithelial hyperplasia and hyperkeratosis of forestomach in females at highest dose; olfactory epithelial degeneration of nasal cavity in males and females at the two highest doses	Johnson et al. (1998), NTP (2004)
Cinnamaldehyde	Oral 12-week study	58, 114 and 227 mg/kg bodyweight/day in the diet	10 rats (5/sex/dose)	Traces of albumin were observed in male urine (this was attributed to the presence of sperm). No other statistically significant differences were observed	RIFM (1958a)
Cinnamaldehyde	Oral 12-week study	103 mg/kg bodyweight/day as part of a mix of five cinnamyl materials added to the feed	24 rats (12/sex)	Food utilization significantly decreased in both sexes; moderate growth retardation in males but this was not considered statistically significant	RIFM (1958b)
Cinnamaldehyde	Oral 16-week study	50, 125 and 500 mg/kg bodyweight/day in the diet	20 rats (10/sex/dose)	Slight hepatic cellular swelling and a slight hyperkeratosis of the stomach at the highest dose level	Hagan et al. (1967)

Table 5 (*continued*)

Material	Method	Dose[a]	Species	Results	References
Cinnamaldehyde	Oral 24-week study	1.25 and 2.5 mg/kg bodyweight in feed	20 male rats (10/dose)	At the highest dose group, four deaths were observed. In addition to decreased bodyweights, increased relative liver weights and increased cytochrome P450 activity and content were observed.	Devaraj et al. (1992)
(b) Chronic					
Cinnamaldehyde	Oral 2-year study	50, 100 and 200 mg/kg bodyweight/day microencapsulated *trans*-cinnamaldehyde in feed	100 rats (50/sex/dose)	NOAEL 200 mg/kg bodyweight/day	NTP (2004)
Cinnamaldehyde	Oral 2-year study	125, 270 and 550 mg/kg bodyweight/day microencapsulated *trans*-cinnamaldehyde in feed	100 mice (50/sex/dose)	NOAEL 550 mg/kg bodyweight/day	NTP (2004)

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

significantly increased. These results are difficult to interpret because 4 of the 10 animals in the high dose group died. Based on the reported acute LD_{50} and the results of other subchronic and chronic feeding studies (see above) cinnamaldehyde-induced mortality would not be expected at a dose of 2.5 mg/kg.

3.3. Chronic toxicity (Table 5b)

Male and female F344/N rats were fed diets containing 1000, 2100 or 4100 ppm microencapsulated *trans*-cinnamaldehyde (equivalent to average daily doses of approximately 50, 100 or 200 mg/kg) for 2 years (NTP, 2004). There were no clinical findings related to *trans*-cinnamaldehyde exposure. Survival of males at the 200 mg/kg dose was greater than that of controls. Survival of other exposed groups was similar to that of the controls. Mean body weights of males and females at the 200 mg/kg dose were generally less than those of the controls throughout the study. At the beginning and end of this study, feed consumption was reduced in both males and females at this dose as well as in males at the 100 mg/kg dose. A No-Observed-Adverse-Effect-Level (NOAEL) was identified as 200 mg/kg bodyweight per day. Under the conditions of this 2-year feed study, there was no evidence of carcinogenic activity of *trans*-cinnamaldehyde in male or female F344/N rats exposed to 50, 100 or 200 mg/kg/day. In addition, no neoplastic lesions could be attributed to chronic *trans*-cinnamaldehyde exposure. (see Table 5b).

Male and female $B6C3F_1$ mice were fed diets containing 1000, 2100 or 4100 ppm microencapsulated *trans*-cinnamaldehyde (equivalent to average daily doses of approximately 125, 270 or 550 mg/kg) for 2 years (NTP, 2004). There were no clinical findings related to *trans*-cinnamaldehyde exposure. Survival of males in the 270 mg/kg group was less than that of the controls. Survival of other exposed groups was similar to that of the controls. The mean body weights of 270 mg/kg and 550 mg/kg males and females were generally less than those of the controls throughout the study, and mean body weights of males at 125 mg/kg were less after week 74. A No-Observed-Adverse-Effect-Level (NOAEL) was identified as 550 mg/kg bodyweight per day. Under the conditions of this 2-year feed study, there was no evidence of carcinogenic activity (or other lesions) of *trans*-cinnamaldehyde in male or female $B6C3F_1$ mice exposed to 125, 270 or 550 mg/kg (see Table 5B).

3.4. Mutagenicity and genotoxicity

Numerous studies evaluating the mutagenicity/genotoxicity of cinnamyl alcohol, cinnamaldehyde and cinnamic acid have been reported. Results of those studies that provide sufficient detail for evaluation are summarized in Tables 6–8 and are described below.

Table 6
Mutagenicity and genotoxicity bacterial studies[a]

Material	Test system in vitro	Species	Dose[b]	Results	References
Cinnamaldehyde	Ames with and without S9 activation	*S. typhimurium* TA92, TA1535, TA100, TA1537, TA94, TA98	Doses up to 500 μg/plate (tested at 6 doses, only the dose with maximum number of revertant colonies was reported	Positive at 100 μg/plate in strain TA100 without S9	Ishidate et al. (1984)
Cinnamaldehyde	Ames with and without S9 activation	*S. typhimurium* TA98 and TA100	0.05–500 μg/plate	Negative	Kasamaki et al. (1982)
Cinnamaldehyde	Ames with and without S9 activation	*S. typhimurium* TA100, TA1535, TA98, TA1537	Four to six doses up to 10,000 μg/plate	Negative	Prival et al. (1982)
Cinnamaldehyde	Ames with and without S9 activation	*S. typhimurium* TA98, TA100, TA1535 and TA1537	2.3–185 μg/ml	Negative	Kim et al. (1997)
Cinnamaldehyde	Ames without S9 activation; modified Ames (preincubation method) with S9	*S. typhimurium* TA100, TA1535, TA98, TA1537, TA1538	60 μg/plate 120 μg/plate 300 μg/plate 600 μg/plate	Negative at 60, 120 and 300 μg/plate Lethal at 600 μg/plate	Sekizawa and Shibamoto (1982)
Cinnamaldehyde	Ames and modified Ames (liquid preincubation method) with and without rat or hamster S9 activation	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100	Ames = 500 μg/plate (max non-toxic dose); modified Ames = 50 μg/plate (max non-toxic dose)	Negative	Lijinsky and Andrews (1980)
Cinnamaldehyde	Modified Ames (preincubation method) with and without S9 activation	*S. typhimurium* TA100	13.2–660.8 μg/plate	Negative	Neudecker et al. (1983)
Cinnamaldehyde	Modified Ames (liquid preincubation method)	*S. typhimurium* TA104	105.7 μg/plate (max non-toxic dose)	Negative	Marnett et al. (1985)
Cinnamaldehyde	Modified Ames (preincubation method) with and without rat and mouse S9 activation	*S. typhimurium* TA100, TA102, TA104	25–300 μg/plate	Weakly positive in strain TA100 with mouse S9 only	Dillon et al. (1992, 1998)
Cinnamaldehyde	Modified Ames (preincubation method) with and without rat and hamster S9 activation	*S. typhimurium* TA97, TA98, TA100, TA1535, TA1537	1–100 μg/plate	Negative	Mortelmans et al. (1986)
Cinnamaldehyde	Modified Ames (120-min preincubation method) with and without S9 activation	*S. typhimurium* TA97, TA98, TA100	1000 μg/ml	Negative	Azizan and Blevins (1995)
Cinnamaldehyde	Modified Ames (60-min preincubation method) with S9 activation	*S. typhimurium* TA100	1000 μg/ml	Negative	Azizan and Blevins (1995)
Cinnamaldehyde	Modified Ames(spot test) with and without S9 activation	*S. typhimurium* TA98, TA100, TA1535, TA1537	396 μg/plate	Sample precipitated (questionable results)	Florin et al. (1980)
Cinnamaldehyde	Modified Ames (glucose in the media and preincubation for 3 days at 37 °C)	*S. typhimurium* TA1537	0.5 μg/plate	Negative	Podger and Grigg (1986)
Cinnamaldehyde	Modified Ames (histidine replaced with tryptophan) with and without S9 activation	*E. coli* WP2 uvrA trp-	60 μg/plate 120 μg/plate 300 μg/plate 600 μg/plate	Negative at 60 μg/plate, 120 μg/plate and 300 μg/plate Lethal at 600 μg/plate	Sekizawa and Shibamoto (1982)
Cinnamaldehyde	Mutagenicity assay	*E. coli* WP2 uvrA	100–800 μg/plate	Negative	Yoo (1986)
Cinnamaldehyde	Rec assay	*B. subtilis* H17(rec+) and M45(rec−)	21 μg	Negative	Oda et al. (1979)
Cinnamaldehyde	Rec assay with and without S9 activation	*B. subtilis* H17(rec+) and M45(rec−)	1050–10,500 μg/disk	Positive with and without S9	Kuroda et al. (1984b)

Table 6 (*continued*)

Material	Test system in vitro	Species	Dose[b]	Results	References
Cinnamaldehyde	Rec assay without S9 activation	*B. subtilis* H17(rec+) and M45(rec−)	200 mg	Positive	Sekizawa and Shibamoto (1982)
Cinnamaldehyde	Rec assay	*B. subtilis* H17(rec+) and M45(rec−)	10,500 μg/plate (max dose tested)	Positive	Yoo (1986)
Cinnamic acid	Ames and modified Ames (liquid preincubation method) with and without rat and hamster S9 activation	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100	Ames = 1000 μg/plate (max non-toxic dose); modified Ames = 1000 μg/plate (max non-toxic dose)	Negative	Lijinsky and Andrews (1980)
Cinnamic acid	Rec assay	*B. subtilis* H17(rec+) and M45(rec−)	25 μg/disk	Negative	Oda et al. (1979)
Cinnamic acid	Rec assay	*B. subtilis* H17(rec+) and M45(rec−)	2000 μg/disk (max dose tested)	Negative	Yoo (1986)
Cinnamyl alcohol	Ames without S9 activation; modified Ames (preincubation method) with S9	*S. typhimurium* TA100, TA1535, TA98, TA1537, TA1538	250 μg/plate 750 μg/plate 1500 μg/plate 3000 μg/plate	Negative at 250, 750 and 1500 μg/plate; lethal at 3000 μg/plate (both with and without S9)	Sekizawa and Shibamoto (1982)
Cinnamyl alcohol	Modified Ames (liquid suspension test system) with and without S9	*S. typhimurium* TA100	A range of five concentrations from 10.4–10,400 μg/2 ml incubation volume	Negative	Eder et al. (1980, 1982a,b), Lutz et al. (1980)
Cinnamyl alcohol	Modified Ames (histidine replaced with tryptophan) with and without S9 activation	*E. coli* WP2 uvrA trp-	250 μg/plate 750 μg/plate 1500 μg/plate 3000 μg/plate	Negative at 250, 750 and 1500 mg/plate Lethal at 3000 mg/plate	Sekizawa and Shibamoto (1982)
Cinnamyl alcohol	Mutagenicity assay	*E. coli* WP2 uvrA	500–4000 μg/plate	Negative	Yoo (1986)
Cinnamyl alcohol	Rec assay	*B. subtilis* H17(rec+) and M45(rec−)	21 μg	Negative	Oda et al. (1979)
Cinnamyl alcohol	Rec assay	*B. subtilis* H17(rec+) and M45(rec−)	10,400 mg (max dose tested)	Positive	Yoo (1986)
Cinnamyl alcohol	Rec assay without S9 activation	*B. subtilis* H17(rec+) and M45(rec−)	1000 μg/plate	Positive	Sekizawa and Shibamoto (1982)

[a] Studies where the dose levels were not reported are not included in this table.
[b] Units have been converted to make easier comparisons; original units are in the Fragrance Material Reviews.

Table 7
Mutagenicity and genotoxicity insect studies

Material	Test system in vitro	Test object	Dose	Results	References
Cinnamaldehyde	Sex linked recessive lethal mutation test in meiotic and postmeiotic germ cell stages	*Drosophila melanogaster* Canton-S males	800 ppm by feeding; 20,000 ppm by injection	No effect at 800 ppm; positive at 20,000 ppm	Woodruff et al. (1985)
Cinnamaldehyde	Reciprocal translocation test	*D. melanogaster* Canton-S males	20,000 ppm by injection	Negative	Woodruff et al. (1985)

Studies that did not report the concentration/dose of the test material are not included in this safety assessment but are provided in the Fragrance Material Reviews of the individual fragrance materials.

3.4.1. Bacterial studies (Table 6)

Cinnamyl alcohol (*trans*- and unspecified stereochemistry), cinnamaldehyde (*trans*- and unspecified stereochemistry), and cinnamic acid were inactive in *Salmonella typhimurium*, including strains TA92, TA94, TA97, TA98, TA102, TA104, 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) (Azizan and Blevins, 1995; Dillon et al., 1992, 1998; Eder et al., 1980, 1982a,b, 1991; Florin et al., 1980; Ishidate et al., 1984; Kasamaki et al., 1982; Kato et al., 1989; Lijinsky and Andrews, 1980; Lutz et al., 1982; Marnett et al., 1985; Neudecker et al., 1983; Prival et al., 1982; Sasaki and Endo, 1978; Sekizawa and Shibamoto, 1982).

Some weakly positive to positive results were reported for cinnamaldehyde in *S. typhimurium* strain TA100 using the pre-incubation method (Ishidate et al., 1984; Dillon et al., 1992, 1998). However, the majority of similar studies in strain TA100, including a recent study using a prolonged pre-incubation time (120 min), and others using the standard plate incorporation method, did not find any evidence of mutagenicity in strain TA100 at doses up to 10,000 μg/plate (Sasaki and Endo, 1978; Lijinsky and Andrews, 1980; Eder et al., 1982a,b, 1991; Kasamaki et al., 1982; Lutz et al., 1982; Prival et al., 1982; Sekizawa and Shibamoto, 1982; Neudecker et al., 1983; Kato et al., 1989; Azizan and Blevins, 1995).

Mutation assays in *Escherichia coli* strains WP2 *uvrA*, PQ37, and Sd-4-73, including several using the pre-incubation method, were negative for cinnamyl alcohol, cinnamaldehyde and cinnamic acid (Eder et al., 1991, 1993; Kato et al., 1989; Kuroda et al., 1984a; Sekizawa and Shibamoto, 1982; Yoo, 1986).

In the Rec assay in *Bacillus subtilis*, overall positive results were reported for cinnamyl alcohol and cinnamaldehyde, whereas cinnamic acid had negative results in all tests using this assay (Oda et al., 1979; Sekizawa and Shibamoto, 1982; Kuroda et al., 1984a,b; Yoo, 1986).

3.4.2. Insect studies (Table 7)

An increase in the frequency of sex-linked recessive lethal mutations was reported when *Drosophila melanogaster* was injected with 20,000 ppm cinnamaldehyde. However, no increase in the frequency of mutations occurred when *D. melanogaster* were fed 800 ppm cinnamaldehyde for three days. Reciprocal translocations were not observed in either assay (Woodruff et al., 1985).

3.4.3. Mammalian studies (Table 8)

Tests for the induction of sister chromatid exchange (SCE) in Chinese hamster ovary (CHO) cells exposed to cinnamaldehyde produced negative results at low concentrations and weakly positive results at concentrations approaching cytotoxic levels, suggesting only weak SCE activity (Galloway et al., 1987; Sasaki et al., 1987; JECFA, 2000). Cinnamaldehyde was reported to induce chromosome aberrations at low concentrations (i.e., <15 μg/ml) in Chinese hamster fibroblasts and B241 cells tested with and without metabolic activation (Ishidate et al., 1984; Kasamaki et al., 1982, 1987; Kasamaki and Urasawa, 1983, 1985; JECFA, 2000). However, higher concentrations (i.e., up to 100 μg/ml) were negative in CHO cells, both with and without metabolic activation (Galloway et al., 1987; JECFA, 2000). In addition, chromosome aberrations were not detected in human diploid HAIN-55 fibroblast cells (Kasamaki et al., 1987).

Transformation assays showed mixed activity for cinnamaldehyde, with positive results obtained at near-cytotoxic concentrations or after multiple generations of growth in Clone A31-1-13 of mice BALB/c-3T3 and Chinese hamster B241 cells, and with negative results obtained in human HAIN-55 cells (Matthews et al., 1993; Kasamaki and Urasawa, 1983, 1985; Kasamaki et al., 1986, 1987; JECFA, 2000). Subcutaneous injection of these transformed cells into nude mice led to the formation of nodules at the site of injection and neoplastic growth in the spleen (Kasamaki et al., 1986, 1987). Negative results were obtained with cinnamaldehyde in the mutation assay in Chinese hamster V79 cells (Fiorio and Bronzetti, 1994), while a weakly positive increase in the incidence of micronucleated Hep-G2 cells was reported by Sanyal et al. (1997) and JECFA (2000).

In mammalian test systems, there was no evidence of an increase in unscheduled DNA synthesis in

Table 8
Mutagenicity and genotoxicity mammalian studies

Material	Test system	Test object	Concentration/dose[a]	Results[a]	References
Cinnamaldehyde	Sister chromatid exchange test with and without S9 activation	Chinese hamster ovary cells	A range of concentrations	Weakly positive. Sister chromatid exchanges were induced at 250–690 μM with S9 and at 2.5–51 μM without S9	Galloway et al. (1987)
Cinnamaldehyde	Sister chromatid exchange test without metabolic activation	Chinese hamster ovary cells	3.3–33 μM	Negative	Sasaki et al. (1987)
Cinnamaldehyde	Chromosome aberration assay without metabolic activation, 24 and 48 h harvest times	Chinese hamster CHL fibroblast cells	Concentrations up to 113 μM	Positive	Ishidate et al. (1984)
Cinnamaldehyde	Chromosome aberration assay with and without S9 activation	Chinese hamster B241 cells	2–20 nM; 10 nM was the highest concentration without visible cytotoxicity	Positive (for structural and numerical aberrations)	Kasamaki et al. (1982, 1987), Kasamaki and Urasawa (1983, 1985)
Cinnamaldehyde	Chromosome aberration assay with and without S9 activation	Chinese hamster ovary cells	A range of concentrations	Negative. Chromosome aberrations were not induced at 380–750 μM with S9 or 45–134 μM without S9	Galloway et al. (1987)
Cinnamaldehyde	Chromosome aberration assay	Human fibroblast HAIN-55 cells	40 nM	Negative	Kasamaki et al. (1987)
Cinnamaldehyde	Transformation assay	Clone A31-1-13 of mice BALB/c-3T3 cells	No concentrations given	Positive. Evaluated as active in the transformation assay	Matthews et al. (1993)
Cinnamaldehyde	Cell transformation assay (to observe changes in saturation density, plating efficiency and colony forming efficiency)	Chinese hamster B241 cells	10 nM	Positive (for saturation density and colony forming efficiency)	Kasamaki et al. (1986, 1987), Kasamaki and Urasawa (1983, 1985)
Cinnamaldehyde	Cell transformation assay (to observe changes in saturation density, plating efficiency and colony forming efficiency)	Human fibroblast HAIN-55 cells	40 nM	Negative	Kasamaki et al. (1986, 1987)
Cinnamaldehyde	Assay of induction of HGPRT-mutants	Chinese hamster V79 ovary cells	100 μM	Negative	Fiorio and Bronzetti (1994)
Cinnamaldehyde	Micronucleus assay	Human hepatoma Hep-G2 cells	0.37–3.78 μM	Weak positive	Sanyal et al. (1997)

Cinnamaldehyde	UDS assay	Male Fischer-344 rats	50–1000 mg/kg bodyweight	Negative	Mirsalis et al. (1989)
Cinnamaldehyde	Bone marrow micronucleus assay. Test materials were given IP once or in multiples (4–5) with 24 h between injections. Mice were sacrificed at 18, 24, 30, 48 or 72 h after dosing	Eight-week-old male ddY mice	62.5–500 mg/kg bodyweight	Negative	Hayashi et al. (1984, 1988)
Cinnamaldehyde	Micronucleus assay	Random-bred male albino Sprague–Dawley rats	550 mg/kg bodyweight; 1100 mg/kg bodyweight; 1650 mg/kg bodyweight	Positive. Significantly increased frequency of micro- and binucleated hepatocytes and a statistically significant increase of nuclear anomalies in the forestomach mucosa at 1100 mg/kg (highest dose tested was toxic)	Martelli et al. (1993), Mereto et al. (1994)
Cinnamaldehyde	Micronucleus assay	Random-bred male Swiss mice	850 mg/kg bodyweight; 1700 mg/kg bodyweight; 2550 mg/kg bodyweight	Positive. Significantly increased frequency of micronucleated hepatocytes at doses of 850 and 1700 mg/kg bodyweight (highest dose tested was toxic)	Martelli et al. (1993), Mereto et al. (1994)
Cinnamaldehyde	DNA fragmentation/alkaline elution assay	Male albino Sprague–Dawley rats	1100 mg/kg bodyweight	Negative	Mereto et al. (1994)
Cinnamaldehyde	Solt/Farber assay, to investigate the induction of hyperplastic foci of the liver. Initiated with *N*-nitrosodiethylamine (200 mg/kg ip)	Random-bred male albino Sprague–Dawley rats	500 mg/kg bodyweight for 14 successive days	Positive. Significant increase in mean diameter and area of GGT-positive liver foci as compared to control animals. Relative liver weight significantly increased	Mereto et al. (1994)

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

hepatocytes when rats were administered 1000 mg cinnamaldehyde/kg/bodyweight by oral gavage (Mirsalis et al., 1989; JECFA, 2000). In a micronucleus assay, there were no increases in micronucleated polychromatic erythrocytes when mice were administered up to 500 mg/kg bodyweight by intraperitoneal injection (Hayashi et al., 1984, 1988).

In a larger scale micronucleus assay using male albino Sprague–Dawley rats and male Swiss mice (Martelli et al., 1993; Mereto et al., 1994), the frequencies of micronucleated cells in the bone marrow and liver, plus the frequency of nuclear anomalies in forestomach mucosa in the same animal were investigated. The frequency of micronuclei in polychromatic erythrocytes was not increased when rats or mice were given up to 1100 mg/kg bodyweight or 1700 mg/kg bodyweight, respectively, of cinnamaldehyde by oral gavage. However, a dose-dependent increase of micronucleated hepatocytes was observed in both rats (1100 mg/kg bodyweight) and mice (850 and 1700 mg/kg bodyweight). No increase in forestomach micronuclei was observed at a dose level of 550 mg/kg bodyweight in the rat. There was no evidence of a significant increase in nuclear anomalies of the forestomach mucosa in mice, although a moderate yet statistically significant increase was observed in rats at a dose of 1100 mg/kg bodyweight. No cinnamaldehyde associated DNA fragmentation was observed in the rat hepatocytes or gastric mucosa cells (Martelli et al., 1993; Mereto et al., 1994). The induction of micronuclei in hepatocytes and forestomach mucosal cells most likely relates to the method of dosing with cinnamaldehyde. Positive findings were detected in these tissues following gavage administration of large bolus doses of the reactive aldehyde with high exposure to the stomach and liver. These same doses did not cause an increased frequency of micronuclei in erythrocytes presumably because of the first pass extraction and metabolism of cinnamaldehyde by intestinal and hepatic tissue. Induction of micronuclei was dose-dependent and demonstrated a threshold. At highly exaggerated doses cinnamaldehyde would affect cellular defense mechanisms (i.e. glutathione), which could explain the threshold phenomenon and dose dependency that were observed. The authors (Mereto et al., 1994) acknowledged these facts and concluded that the data did not justify classification of cinnamaldehyde as clastogenic for gastric mucosa.

3.5. Carcinogenicity (Table 9)

As stated previously in the NTP chronic bioassay, there was no evidence of carcinogenic activity (or other lesions) of *trans*-cinnamaldehyde in rats or mice. Two additional studies that focused on the ability of cinnamyl alcohol and cinnamaldehyde to induce tumors were conducted. Cinnamyl alcohol and cinnamaldehyde were examined for their ability to induce primary lung tumors in female A/He mice. Animals received intraperitoneal injections of cinnamyl alcohol or cinnamaldehyde

Table 9
Carcinogenicity

Material	Method	Dose	Species	Results	References
Cinnamaldehyde	Oral 2-year study	50, 100 and 200 mg/kg bodyweight/day microencapsulated *trans*-cinnamaldehyde in feed	100 rats (50/sex/dose)	No evidence of carcinogenic activity	NTP (2004)
Cinnamaldehyde	Oral 2-year study	125, 270 and 550 mg/kg bodyweight/day microencapsulated *trans*-cinnamaldehyde in feed	100 mice (50/sex/dose)	No evidence of carcinogenic activity	NTP (2004)
Cinnamaldehyde	Cinnamaldehyde in tricaprylin was given to mice via intraperitoneal injections, three times weekly for 8 weeks	800 and 4000 mg/kg bodyweight	60 A/He mice (15/sex/dose)	No carcinogenic effects were observed	Stoner et al. (1973)
Cinnamaldehyde	Cinnamaldehyde in trioctanoin was given to mice via intraperitoneal injections, once a week for 4 weeks	4.8 μmol	44 B6C3F1 mice	No significant carcinogenic effects were produced by cinnamaldehyde	Wiseman et al. (1987)
Cinnamyl alcohol	Cinnamyl alcohol in tricaprylin was given to mice via intraperitoneal injections, three times weekly for 8 weeks	1400 and 7000 mg/kg bodyweight	60 A/He mice (15/sex/dose)	No carcinogenic effects were observed	Stoner et al. (1973)

three times weekly for 8 weeks. They were sacrificed 24 weeks after the first injection. The total cumulative doses were 1.4 and 7.0 g/kg (cinnamyl alcohol) and 0.8 and 4.0 g/kg (cinnamaldehyde). Both cinnamyl alcohol and cinnamaldehyde were negative for pulmonary tumor response under the conditions of the test (Stoner et al., 1973).

Hepatocarcinogenic potential for cinnamaldehyde was evaluated in 44 B6C3F1 mice that received intraperitoneal injections of cinnamaldehyde once a week for 4 weeks. The total cumulative dose of cinnamaldehyde was 4.8 μmol (0.0006 g). Hemangiosarcomas were observed in 3 mice, 2 in the liver and 1 in the spleen, (in control animals, two mice had hemangiosarcomas, one in the liver and 1 in the spleen and one mouse had a s.c. fibromyosarcoma). The authors concluded that no significant carcinogenic effects were produced by cinnamaldehyde (Wiseman et al., 1987).

3.6. Reproductive and developmental toxicity

While there are no fertility studies on cinnamyl alcohol, cinnamaldehyde or cinnamic acid, there are several developmental studies.

Groups of 14–15 female rats were orally administered either 0, 5.35 or 53.5 mg/kg bodyweight cinnamyl alcohol once daily for the entire course of pregnancy. On day 20 of gestation, 6–9 rats from each group were sacrificed and the fetuses removed for examination. The remaining animals delivered normally on days 22–23 of gestation. Measurements of offspring bodyweight, size, survival number and general development at birth and at one month following birth revealed no significant differences between test and control animals (Zaitsev and Maganova, 1975).

Female rats were administered 5, 25 or 250 mg/kg/day cinnamaldehyde by gavage in olive oil on days 7–17 of gestation. Fetal abnormalities observed were not dose related and occurred in the mid- and high-dose groups, doses which also showed maternal toxicity as indicated by a decrease in maternal weight gain. Decrease in weight gain was greatest at the mid-dose (Mantovani et al., 1989).

In a short-term developmental toxicity assay, 49 CD-1 female mice were administered 1200 mg/kg cinnamaldehyde by gavage on gestation days 6–13. Cinnamaldehyde had no effect on maternal survival or bodyweight; all viable litters survived and weight gain was within normal parameters for all pups (Hardin et al., 1987).

Groups of 14–15 female rats were orally administered either 0, 5 or 50 mg/kg bodyweight cinnamic acid once daily for the entire course of pregnancy. On day 20 of gestation, 6–9 rats from each group were sacrificed and the fetuses removed for examination. The remaining animals delivered normally on days 22–23 of gestation. Measurements of offspring bodyweight, size, survival number and general development at birth and at one month following birth revealed no significant differences between test and control animals (Zaitsev and Maganova, 1975).

Cinnamic acid was evaluated for potential estrogenic activity in a standardized estrogen receptor (ER) competitive binding assay using uteri from ovariectomized rats. Cinnamic acid did not bind to the ER and was considered inactive (Blair et al., 2000).

3.7. Skin irritation

3.7.1. Human studies (Table 10)

Cinnamyl alcohol, cinnamaldehyde and cinnamic acid were evaluated for skin irritation in humans. Cinnamyl alcohol at concentrations up to 10% produced no irritation in 605 male and female volunteers. Cinnamaldehyde produced no irritation in 171 volunteers at concentrations of 0.125–1.25%, but did produce irritation in 10/63 volunteers at 3% and severe irritation in five (5/5) volunteers at 8%. Cinnamic acid produced no irritation in 25 volunteers when tested at 4% (see Table 10).

3.7.2. Animal studies (Table 11)

Reactions to cinnamyl alcohol ranged from slight to moderate when applied as the neat material to the skin of rabbits. Slight irritation was observed in guinea pigs with 10% cinnamyl alcohol after one application and with 3% cinnamyl alcohol after 21 daily applications. Cinnamaldehyde produced mild irritation in mice and guinea pigs at concentrations of 3–5% and was non-irritating to rabbits at 1%; severe irritation in rabbits was observed with undiluted cinnamaldehyde. Concentrations of cinnamic acid above 10–15% produced only slight irritation when applied to skin of rabbits, guinea pigs or mice (see Table 11).

3.8. Mucous membrane (eye) irritation (Table 12)

Cinnamaldehyde and cinnamic acid were evaluated for mucous membrane irritation. Cinnamaldehyde produced mild to severe irritation in the rabbit eye at doses of 0.125% and higher. Cinnamic acid at dose levels up to 10 mg/ml (1%) was non-irritating to rabbit or guinea pig eyes (see Table 12).

3.9. Skin sensitization

3.9.1. Human studies (Table 13)

3.9.1.1. Induction. All three materials were evaluated for the potential to induce sensitization. For details of individual studies, see Table 13 and the corresponding Fragrance Material Reviews. Cinnamyl alcohol and cinnamaldehyde both have a potential to induce sensitization in humans with cinnamaldehyde having a stronger

Table 10
Skin irritation: humans

Material	Method	Concentration	Subjects	Results	References
Cinnamaldehyde	Maximization pre-test. 48-h closed patch test	8% in petrolatum	5 male volunteers	Severe irritation in 5/5 subjects	RIFM (1973c)
Cinnamaldehyde	Maximization pre-test. 48-h closed patch test	3% in butylene glycol	5 male and female volunteers	No reactions	RIFM (1974a)
Cinnamaldehyde	Irritation evaluated during the induction phase of a Human Repeated Insult Patch Test	3% cinnamaldehyde in 3:1 DEP:EtOH with 0.5% α-tocopherol	28 male and female volunteers	2/28 reactions	RIFM (2003b)
Cinnamaldehyde	Irritation evaluated during the induction phase of a Human Repeated Insult Patch Test	3% cinnamaldehyde in 3:1 EtOH:DEP with 0.5% α-tocopherol	30 male and female volunteers	8/30 reactions	RIFM (2003b)
Cinnamaldehyde	Irritation evaluated during the induction phase of a Human Repeated Insult Patch Test	0.125% in ethanol	41 male and female volunteers	No reactions	RIFM (1964b)
Cinnamaldehyde	Irritation evaluated during the induction phase of a Human Repeated Insult Patch Test	0.5% in ethanol	38 male and female volunteers	No reactions	RIFM (1965)
Cinnamaldehyde	Irritation evaluated during the induction phase of a Human Repeated Insult Patch Test	0.5% cinnamaldehyde in 3:1 DEP:EtOH with 0.5% α-tocopherol	22 male and female volunteers	No reactions	RIFM (2002a)
Cinnamaldehyde	Irritation evaluated during the induction phase of a Human Repeated Insult Patch Test	0.5% cinnamaldehyde in 3:1 EtOH:DEP with 0.5% α-tocopherol	19 male and female volunteers	No reactions	RIFM (2002b)
Cinnamaldehyde	Irritation evaluated during the induction phase of a Human Repeated Insult Patch Test	1.0% in alcohol SDA 39C	41 male and female volunteers	No reactions	RIFM (1973d)
Cinnamaldehyde	Irritation evaluated during the induction phase of a Human Repeated Insult Patch Test	1.25% in ethanol	10 male and female volunteers	No reactions	RIFM (1964a)
Cinnamic acid	Maximization pre-test. 48-h closed patch test	4% in petrolatum	25 male volunteers	No reactions	RIFM (1976b)

Cinnamyl alcohol	Maximization pre-test. 48-h closed patch test	10% in petrolatum	182 subjects in 7 test panels	No reactions	RIFM (1977b, 1975, 1976c, 1977a)
Cinnamyl alcohol	Maximization pre-test. 48-h closed patch test	10% in hydrophilic ointment	25 male and female volunteers	No reactions	RIFM (1976c)
Cinnamyl alcohol	Maximization pre-test. 48-h closed patch test	10% in DEP	284 subjects in 11 test panels	No reactions	RIFM (1979a, 1980, 1981, 1982)
Cinnamyl alcohol	Irritation evaluated during the induction phase of a Human Repeated Insult Patch Test	4% in 3:1 DEP:EtOH	54 male and female volunteers	No reactions	RIFM (2001a, 2002c)
Cinnamyl alcohol	Irritation evaluated during the induction phase of a Human Repeated Insult Patch Test	4% in 3:1 EtOH:DEP	55 male and female volunteers	No reactions	RIFM (2001b, 2002d)

potential then cinnamyl alcohol. Cinnamic acid has been reported not to induce sensitization in humans.

A total of 23 human maximization tests with cinnamyl alcohol were carried out. Twenty-one maximization tests using 21 different test panels were conducted with 10% cinnamyl alcohol on 527 male and female volunteers; an additional two maximization tests using two different test panels were conducted with 4% cinnamyl alcohol on 49 volunteers. Nineteen different samples of cinnamyl alcohol prepared by different manufacturing methods were used in these tests. Sensitization reactions were observed with 10% cinnamyl alcohol in 79 subjects from 19 test panels, while no sensitization reactions were observed at 4%. In two additional tests performed under exaggerated conditions (nine 48 h occluded induction applications followed 2 weeks later by two consecutive 48 h occluded challenge applications) 4% cinnamyl alcohol (with ethanol as a vehicle) produced 5/180 reactions; no reactions occurred in these same subjects to 4% cinnamyl alcohol with petrolatum as a vehicle when tested under the same conditions. The Human Repeated Insult Patch Test (HRIPT) data show that a 4% solution of cinnamyl alcohol, when applied in a vehicle of ethanol/diethyl phthalate (EtOH/DEP), caused three reactions in a total of 109 subjects. Upon rechallenge using a 24-h occluded patch, a 24-h semi-occluded patch and 5-day repeated open application test, reactivity was observed only under occlusive patch conditions. No skin reactivity was observed under semi-occlusive patch conditions or under open exaggerated rub-in conditions. Thus, those individuals who were sensitized to 4% cinnamic alcohol in the HRIPT, did not elicit a reaction under repeated open application conditions.

Cinnamaldehyde was evaluated for sensitization in two maximization tests and nine repeated insult patch tests using 12 different test panels at concentrations of 0.125–3% on a total of 451 male and female volunteers. Sensitization reactions were observed in 29 volunteers at concentrations of 1% and higher. No sensitization reactions were observed at concentrations of 0.125–0.5% in a standard study.

Quenching studies with cinnamaldehyde and eugenol or cinnamaldehyde and limonene were repeated in human repeated insult patch tests and were not verified.

Cinnamic acid was evaluated for sensitization in a maximization test. No sensitization reactions were observed in 25 healthy, male volunteers when tested with 4% cinnamic acid.

3.9.1.2. Elicitation. Experimental provocation studies were conducted to investigate the significance of the cinnamaldehyde concentration in deodorants for elicitation of allergic contact dermatitis in persons with prior hypersensitivity to cinnamaldehyde. Dermatitis patients with prior reactivity to cinnamaldehyde used a deodorant containing 0.032% cinnamaldehyde, twice daily for

Table 11
Skin irritation: animals

Material	Method	Concentration	Species	Results	References
Cinnamaldehyde	Irritation evaluated during an associated LD_{50} study	100%	10 rabbits	Severe erythema, severe eschar and very slight to severe edema was observed	RIFM (1997)
Cinnamaldehyde	Irritation evaluated during an associated LD_{50} study	100%	2–4 rabbits	Severe erythema, severe eschar and severe edema was observed	RIFM (1986a)
Cinnamaldehyde	Irritation evaluated during an associated LD_{50} study	100%	10 rabbits	Moderate to severe erythema and slight to moderate edema was observed	RIFM (1994)
Cinnamaldehyde	Primary irritancy phase of a phototoxicity/photoallergy study	0.05%, 0.1%, 0.5%, 1%, 3% and 5% in 3:1 DEP:EtOH	Albino hairless guinea pigs	No irritation observed at 0.05–1%. Slight irritation observed at 3% and 5%	RIFM (2003a)
Cinnamaldehyde	Open applications were made to the ear and ear thickness measured	5%, 10%, 15% and 20% (vehicle not specified)	5 mice	Irritation was observed at all dose levels	Thorne et al. (1991)
Cinnamaldehyde	Preliminary irritation screen for a modified Draize sensitization study (intradermal injection)	0.25% (ICC) (vehicle not specified)	4 inbred Hartley strain albino guinea pigs	Slight but perceptible irritation	Sharp (1978)
Cinnamaldehyde	Preliminary irritation screen for a modified Draize sensitization study (Topical)	20% (ACC) (vehicle not specified)	4 inbred Hartley strain albino guinea pigs	No irritation was observed	Sharp (1978)
Cinnamaldehyde	Preliminary irritation screen for an open epicutaneous test (OET)	A range of concentrations (vehicle not specified)	6–8 male and female Himalayan white spotted guinea pigs	3% = minimal irritating concentration (defined as lowest concentration producing mild erythema in at least 25% of animals)	Klecak et al. (1977)
Cinnamaldehyde	Evaluation performed as induction phase of an open epicutaneous test (OET)	A range of concentrations (vehicle not specified)	6–8 male and female Himalayan white spotted guinea pigs	3% = minimal irritating concentration	Klecak et al. (1977)
Cinnamaldehyde	24-h occluded patch test	100%	9 New Zealand albino rabbits	Severe irritation was observed (primary irritation index = 4.0)	Troy (1977)
Cinnamaldehyde	24-h occluded patch test	2, 4, 8, 15 and 30 mg/ml in 96% ethanol	3 guinea pigs	Irritation observed at 15 and 30 mg/ml	Weibel et al. (1989)

Cinnamaldehyde	4-h semi-occluded patch test	100%	4 New Zealand white albino rabbits	Avg. erythema score = 2.0; avg. edema score = 1.7	RIFM (1988)
Cinnamaldehyde	24-h occluded patch test	1% in alcohol SDA 39C	3 albino rabbits	No irritation was observed	RIFM (1972a)
Cinnamaldehyde	Open applications were made to the back, abdomen and flank	5% in absolute ethanol	5 female Hartley guinea pigs	Erythema was observed	Lahti and Maibach (1984)
Cinnamic acid	Irritation evaluated during an associated LD_{50} study	100%	4 rabbits	Slight erythema	RIFM (1976a)
Cinnamic acid	Primary irritancy phase of a phototoxicity/photoallergy study	0.1%, 1%, 10% and 20% in 3:1 DEP:EtOH	Albino hairless guinea pigs	Irritation was not observed at any dose level	RIFM (2003a)
Cinnamyl alcohol	Preliminary irritation screen for a modified Draize sensitization study (injection)	0.1% (ICC) (vehicle not specified)	4 inbred Hartley strain albino guinea pigs	Slight but perceptible irritation	Sharp (1978)
Cinnamyl alcohol	Preliminary irritation screen for a modified Draize sensitization study (topical)	10% (ACC) (vehicle not specified)	4 inbred Hartley strain albino guinea pigs	No irritation was observed	Sharp (1978)
Cinnamyl alcohol	Preliminary irritation screen for a Freund's Complete Adjuvant Test	1–100% (vehicle ethanol); four dose levels	4 female Himalayan white spotted guinea pigs	30% = maximal non-irritating concentration (defined as highest dose not causing macroscopic reactions in any animal)	RIFM (1986c)
Cinnamyl alcohol	Preliminary irritation screen for a Freund's Complete Adjuvant Test	100% (30% (in ethanol); 10% (in ethanol); 3% (in ethanol))	4 female Himalayan white spotted guinea pigs	100% = maximal non-irritating concentration (defined as highest dose not causing macroscopic reactions in any animal)	RIFM (1985a)
Cinnamyl alcohol	Preliminary irritation screen for an open epicutaneous test	A range of concentrations (vehicle not specified)	6–8 male and female Himalayan white spotted guinea pigs	10% = minimal irritating concentration (defined as lowest concentration producing mild erythema in at least 25% of animals)	Klecak et al. (1977)
Cinnamyl alcohol	Evaluation performed as induction phase of open epicutaneous test	A range of concentrations (vehicle not specified)	6–8 male and female Himalayan white spotted guinea pigs	3% = minimal irritating concentration	Klecak et al. (1977)
Cinnamyl alcohol	4-h semi-occluded patch test	100%	3 New Zealand white albino rabbits	No irritation	RIFM (1984)
Cinnamyl alcohol	4-h semi-occluded patch test	100%	4 New Zealand white albino rabbits	No irritation	RIFM (1985b)
Cinnamyl alcohol	Irritation evaluated during an associated LD_{50} study	100%	5 rabbits	Slight to moderate irritation at 5000 mg/kg; moderate irritation at 2500 mg/kg	RIFM (1973a)

Table 12
Mucous membrane (eye) irritation

Material	Concentration	Vehicle	Species	Results	References
Cinnamic acid	0.1–1%	Distilled water	Rabbit	No irritation	Das et al. (1976)
Cinnamic acid	0.1–1%	Distilled water	Guinea pig	No irritation	Das et al. (1976)
Cinnamaldehyde	1.25%	alcohol SDA 39C	Rabbit	Intense irritation	RIFM (1963)
Cinnamaldehyde	1.0%	alcohol SDA 39C	Rabbit	Mild irritation	RIFM (1972b)
Cinnamaldehyde	0.125%	alcohol SDA 39C	Rabbit	Irritation	RIFM (1964c)
Cinnamaldehyde	100	NA	Rabbit	Irritation	Troy (1977)

two weeks. If no reactions were observed at the end of two weeks, the concentration of cinnamaldehyde in the deodorant was increased to 0.1% during the third and fourth weeks and increased again to 0.32% during the 5th and 6th weeks. In the first study, 8/8 patients reacted to the deodorant containing cinnamaldehyde (2 at the low-dose, 4 at the mid-dose and 2 at the high-dose). In a second study using the same protocol, deodorants containing 0.01%, 0.032% or 0.1% cinnamaldehyde were tested in 9 patients with prior hypersensitivity to cinnamaldehyde. In these studies, which simulated occlusive conditions, 1/9 reacted to the deodorant containing the low dose of cinnamaldehyde, 4/9 reacted to the deodorant containing the mid-dose and 3/9 reacted to the deodorant containing the high-dose of cinnamaldehyde (Bruze, 2000; Bruze et al., 2003). Therefore, if a person is already sensitized to cinnamaldehyde, there is a small risk of developing clinical allergic reactions to concentrations as low as 0.01% in a deodorant-type product.

Human repeated insult patch tests show that the no-effect-level for cinnamaldehyde for the induction of sensitization is 0.5%. For this assessment, the no-effect-level for induction of sensitization to cinnamaldehyde was selected rather than the concentrations eliciting sensitization.

3.9.2. Animal studies (Table 14)

Cinnamyl alcohol was evaluated for sensitization in 24 studies in guinea pigs or mice using various test methods such as the Magnusson–Kligman maximization test, Buehler Delayed Hypersensitivity test, Modified Draize Test, Freund's Complete Adjuvant Test, Closed Epicutaneous test or the Open Epicutaneous Test at concentrations ranging from 1% up to 100%. Sensitization was observed at all dose levels over 1% (see Table 14).

Forty-two sensitization tests were conducted with cinnamaldehyde in guinea pigs or mice including Magnusson–Kligman maximization tests, Modified Draize tests, Buehler Delayed Hypersensitivity tests, Maguire tests, Freund's Complete Adjuvant Test, Closed Epicutaneous Test, Open Epicutaneous Test, Cumulative Contact Enhancement Test and the Local Lymph Node Proliferation Assay, at concentrations from 0.1% to 40% in various vehicles. Sensitization was generally observed at all dose levels and in almost every study (see Table 14).

Cross-reactions in guinea pigs that were induced with cinnamaldehyde and then challenged or cross-challenged with cinnamyl alcohol have also been reported (Basketter, 1992; RIFM, 1978).

Cinnamic acid was tested in seven guinea pig sensitization tests including a Buehler delayed hypersensitivity test, a guinea pig maximization test, a Freund's Complete Adjuvant Test, and a Closed Epicutaneous Test. No reactions were observed in four studies at concentrations up to 10%; weak to moderate sensitization was observed in two studies at concentrations of 10%. In a guinea pig ear thickness study, 1% cinnamic acid produced sensitization; however, no sensitization was observed when 15% cinnamic acid was tested in a mouse ear thickness study (see Table 14).

3.10. Phototoxicity and photoallergy

UV spectra have been obtained for all three materials in this evaluation. Cinnamaldehyde and cinnamic acid both absorb UVB light (290–320 nm), cinnamaldehyde peaking at 287 nm and returning to baseline at 330 nm, and cinnamic acid peaking at 273 nm and returning to baseline at 315 nm. Cinnamyl alcohol does not absorb light at >295 nm; from 275–295, only slight absorption (approximately 0.2 AU) was observed. Based on these data and the fact that cinnamaldehyde and cinnamic acid show no phototoxic or photoallergic potential, we do not expect cinnamyl alcohol to show any phototoxic or photoallergic activity.

3.10.1. Phototoxicity

3.10.1.1. In vivo studies. Phototoxicity was investigated as part of a photoallergy study (RIFM, 2003a). Groups of male hairless guinea pigs received dermal applications of cinnamaldehyde (0.1% and 1%), cinnamic acid (2% and 20%) or 8-methoxypsoralen (0.01% and 0.1%). Test materials were applied to 25 mm Hilltop chambers and placed on the dorsal skin of the animals along the midline for a 2-h period. The skin sites were then irradiated with solar-simulated UVR for approximately 2.25 h. Clinical observations were made four times on the first day (before administration, during and immediately after UVR exposure and 4 h after completion of UVR exposure) and then once daily on days two through four. A single topical application of the positive control,

Table 13
Skin sensitization: humans

Material	Method	Concentration	Subjects	Results	References
Cinnamaldehyde	MAX	2% in petrolatum	25 male volunteers	11/25 reactions	RIFM (1973c)
Cinnamaldehyde	MAX	3% in butylene glycol	25 male and female volunteers	3/25 reactions	RIFM (1974a)
Cinnamaldehyde	HRIPT	0.5% in 3:1 DEP:EtOH	94 male and female volunteers	No reactions	RIFM (2004)
Cinnamaldehyde	HRIPT	3% in 3:1 DEP:EtOH with 0.5% α-tocopherol	28 male and female volunteers	4/28 reactions	RIFM (2003b)
Cinnamaldehyde	HRIPT	3% in 3:1 EtOH:DEP with 0.5% α-tocopherol	Male and female volunteers	Study aborted during induction phase due to the number of irritant reactions	RIFM (2003b)
Cinnamaldehyde	HRIPT	0.125% in ethanol	41 male and female volunteers	No reactions	RIFM (1964a)
Cinnamaldehyde	HRIPT	0.5% in ethanol	38 male and female volunteers	No reactions	RIFM (1965)
Cinnamaldehyde	HRIPT	0.5% in 3:1 DEP:EtOH with 0.5% α-tocopherol	22 male and female volunteers	No reactions	RIFM (2002a)
Cinnamaldehyde	HRIPT	0.5% in 3:1 EtOH:DEP with 0.5% α-tocopherol	19 male and female volunteers	No reactions	RIFM (2002b)
Cinnamaldehyde	HRIPT	1.0% in alcohol SDA 39C	41 male and female volunteers	5/41 reactions	RIFM (1973d)
Cinnamaldehyde	HRIPT	1.0% in ethanol 1.0% in petrolatum	108 male and female volunteers	1/55 reactions with ethanol as vehicle; no reactions with petrolatum as vehicle	Marzulli and Maibach (1976, 1980)
Cinnamaldehyde	HRIPT	1.25% in ethanol	10 male and female volunteers	5/10 reactions	RIFM (1964b)
Cinnamic acid	MAX	4% in petrolatum	25 male volunteers	No reactions	RIFM (1976b)
Cinnamyl alcohol	MAX	4% in petrolatum	24 adult volunteers	1 irritation reaction in 24 Japanese Americans	RIFM (1979b)
Cinnamyl alcohol	MAX	4%	25 adult volunteers	No reactions	Greif (1967)
Cinnamyl alcohol	MAX	10% in petrolatum	25 male and female volunteers	3/25	RIFM (1975)
Cinnamyl alcohol	MAX	10% hydrophilic ointment	25 male and female volunteers	2/25	RIFM (1976d)
Cinnamyl alcohol	MAX	10% in petrolatum	33 male volunteers	10/33 plus 3 questionable and 2 irritant reactions	RIFM (1977b)
Cinnamyl alcohol	MAX	10% in petrolatum	24 male volunteers	1/24	RIFM (1977b)
Cinnamyl alcohol	MAX	10% in petrolatum	25 male and female volunteers	5/25	RIFM (1977a)
Cinnamyl alcohol	MAX	10% in DEP	22 male and female volunteers	2/22	RIFM (1981)
Cinnamyl alcohol	MAX	10% in DEP	23 male and female volunteers	2/23	RIFM (1981)
Cinnamyl alcohol	MAX	10% in petrolatum	11 female volunteers	1/11	RIFM (1976b)
Cinnamyl alcohol	MAX	10% in petrolatum	25 male and female volunteers	7/25	RIFM (1976c)

Table 13 (*continued*)

Material	Method	Concentration	Subjects	Results	References
Cinnamyl alcohol	MAX	10% in petrolatum	25 male and female volunteers	9/25	RIFM (1976c)
Cinnamyl alcohol	MAX	10% in petrolatum	25 male and female volunteers	3/25	RIFM (1977a)
Cinnamyl alcohol	MAX	10% in petrolatum	25 male and female volunteers	5/25	RIFM (1976c)
Cinnamyl alcohol	MAX	10% in DEP	22 male and female volunteers	2/22 plus 1 questionable reaction	RIFM (1980)
Cinnamyl alcohol	MAX	10% in DEP	35 male and female volunteers	0/35 sensitization reactions; 7 irritation reactions and 1 hyper-irritation reaction	RIFM (1980)
Cinnamyl alcohol	MAX	10% in DEP	28 male and female volunteers	6/28	RIFM (1980)
Cinnamyl alcohol	MAX	10% in DEP	24 male and female volunteers	No reactions	RIFM (1980)
Cinnamyl alcohol	MAX	10% in DEP	28 male and female volunteers	1/28	RIFM (1980)
Cinnamyl alcohol	MAX	10% in DEP	26 male and female volunteers	6/26	RIFM (1979a)
Cinnamyl alcohol	MAX	10% in DEP	28 male and female volunteers	4/28	RIFM (1982)
Cinnamyl alcohol	MAX	10% in DEP	27 male and female volunteers	4/27 questionable para-allergic reactions. Three of these subjects were re-challenged and 2/3 reacted	RIFM (1982)
Cinnamyl alcohol	MAX	10% in DEP	21 male and female volunteers	1/21 questionable reactions	RIFM (1980)
Cinnamyl alcohol	HRIPT	4% in 3:1 DEP:EtOH	54 male and female volunteers	2/54	RIFM (2001a, 2002c)
Cinnamyl alcohol	HRIPT	4% in 3:1 EtOH:DEP	55 male and female volunteers	1/55	RIFM (2001b, 2002d)
Cinnamyl alcohol	Modified MAX	4% in ethanol and 4% in petrolatum	25–30 male volunteers	1 reaction (25–30 subjects) with ethanol as vehicle; no reactions with petrolatum as vehicle	Jordan and King (1977)
Cinnamyl alcohol	Modified Draize	4% in ethanol and 4% in petrolatum	150 male and female volunteers	4/150 reactions with ethanol as vehicle; no reactions with petrolatum as vehicle	Jordan and King (1977)

Table 14
Skin sensitization: animals

Material	Method	Concentration	Species	Results	References
Cinnamaldehyde	Buehler delayed hypersensitivity test	5% in petrolatum	8 guinea pigs	2/8 cross-reactions were observed when animals were challenged with cinnamic alcohol	RIFM (1978)
Cinnamaldehyde	Buehler delayed hypersensitivity test	0.1–1.0% in acetone	10 guinea pigs	Sensitization effects were observed at all doses	Buehler and Ritz (1985), Basketter and Gerberick (1996)
Cinnamaldehyde	Modified Draize test	0.1% in saline	Male and female outbred Himalayan guinea pigs	Sensitization effects were observed at all doses	Klecak et al. (1977)
Cinnamaldehyde	Modified Draize test	0.25% (injection challenge concentration); 20% (application challenge concentration)	10 inbred Hartley strain albino guinea pigs	Sensitization reactions were observed after the test was repeated twice	Sharp (1978)
Cinnamaldehyde	Landsteiner–Draize test	2.0% in petrolatum	Hartley strain male guinea pigs	2/20 reactions	Prince and Prince (1977)
Cinnamaldehyde	Modified Landsteiner–Draize test	2.0% in petrolatum	Hartley strain male guinea pigs	4/20 reactions	Prince and Prince (1977)
Cinnamaldehyde	Maximization test	A subirritant concentration in petrolatum	Male and female outbred Himalayan guinea pigs	Sensitization effects were observed	Klecak et al. (1977)
Cinnamaldehyde	Magnusson–Kligman maximization test	3.0% in petrolatum	Outbred albino female Dunkin–Hartley guinea pigs	4/5 reactions with induction concentrations of 0.03% (intradermal) and 0.3% (topical); 5/5 reactions at all other dose levels	Andersen et al. (1995)
Cinnamaldehyde	Magnusson–Kligman maximization test	2.0% in petrolatum	Hartley strain male guinea pigs	16/20 reactions	Prince and Prince (1977)
Cinnamaldehyde	Magnusson–Kligman maximization test	1.0% (vehicle not specified)	10 male albino guinea pigs	10/10 reactions; cross-reactions with cinnamyl alcohol and with α and β methylcinnamaldehyde were also observed	Senma et al. (1978)
Cinnamaldehyde	Magnusson–Kligman maximization test	8 mg/ml in ethanol	Albino female guinea pigs (Ssc:AL)	17/20 reactions; 15/20 cross-reactions were observed when animals were challenged with cinnamyl alcohol; 7/20 cross-reactions when animals were challenged with cinnamic acid	Weibel et al. (1989)

Table 14 (*continued*)

Material	Method	Concentration	Species	Results	References
Cinnamaldehyde	Guinea pig maximization test	3.0% (vehicle not reported)	Guinea pigs	Strong sensitization effects were produced (no further details given)	Ishihara et al. (1986)
Cinnamaldehyde	Guinea pig maximization test	0.75% in 70:30 acetone/PEG 400	Dunkin–Hartley albino guinea pigs	100% of the animals were sensitized	Basketter and Scholes (1992)
Cinnamaldehyde	Guinea pig maximization test. To evaluate cross-sensitization, animals were also cross-challenged with *trans*-cinnamyl alcohol and *cis*-cinnamyl alcohol	0.75% 2 samples of cinnamaldehyde were tested (vehicle not reported)	Dunkin–Hartley guinea pigs	9/10 and 10/10 reactions; 4/10 and 5/10 cross-reactions were observed when animals were challenged with 40% *trans*-cinnamyl alcohol; 3/10 and 2/10 cross-reactions were observed when animals were challenged with 40% *cis*-cinnamyl alcohol	Basketter (1992)
Cinnamaldehyde	Guinea pig maximization test. To evaluate cross-sensitization, animals were cross-challenged with cinnamyl alcohol	0.75% cinnamaldehyde	Dunkin–Hartley guinea pigs	No cross-sensitization reactions were produced in animals induced with cinnamyl alcohol (0/10)	Basketter (1992)
Cinnamaldehyde	Maguire test	2.0% in petrolatum	Hartley strain male guinea pigs	20/20 reactions	Prince and Prince (1977)
Cinnamaldehyde	Modified Maguire test	2.0% in petrolatum	Hartley strain male guinea pigs	15/20 reactions	Prince and Prince (1977)
Cinnamaldehyde	Modified Maguire hypersensitivity test	2.0% in petrolatum	8 male Hartley guinea pigs	6/6 sensitization reactions; 2 deaths were noted but the cause of death was not specified	RIFM (1974b)
Cinnamaldehyde	Open epicutaneous test (OET)	0.3–3.0% (vehicle not specified)	6–8 guinea pigs	Sensitization effects were observed	Klecak (1979), Klecak et al. (1977)
Cinnamaldehyde	Closed epicutaneous test (CET)	0.5% (vehicle not reported)	Guinea pigs	3/5 reactions	Ishihara et al. (1986)
Cinnamaldehyde	Freund's complete adjuvant test (FCAT)	A subirritant concentration in petrolatum	Male and female outbred Himalayan guinea pigs	Sensitization effects were observed	Klecak et al. (1977)
Cinnamaldehyde	Cumulative contact enhancement test (CCET)	0.2%, 1.0% and 5.0% in ethanol	Male Hartley albino guinea pigs	Sensitization effects were observed at all doses	Tsuchiya et al. (1982), Tsuchiya et al. (1985)
Cinnamaldehyde	Cumulative contact enhancement test (CCET)	0.5%, 1.0% and 5.0% in ethanol	Female Hartley albino guinea pigs	Calculated sensitization indices were 20%, 70% and 90% for the test concentrations 0.5%, 1.0% and 5.0% respectively	Kern and Kiplinger (2000)

Cinnamaldehyde	Cumulative contact enhancement test (CCET)	5.0%. The vehicles were: (1) ethanol; (2) low viscosity liquid paraffin (L-liq-p); (3) high viscosity liquid paraffin (H-liq-p)	Guinea pigs	Ethanol induction: 0/10—Ethanol challenge; 4/10—L-liq-p challenge; 0/10—H-liq-p challenge; L-liq-p induction: 3/10—Ethanol challenge; 9/10—L-liq-p challenge; 2/10—H-liq-p challenge; H-liq-p induction: 1/10—Ethanol challenge; 7/10—L-liq-p challenge; 4/10—H-liq-p induction	Tsuchiya et al. (1985)
Cinnamaldehyde	Guinea pig sensitization study using the AP2 test method	3.0% in ethanol	10 female Hartley albino guinea pigs	Sensitization effects were observed	Kashima et al. (1993)
Cinnamaldehyde	Sensitization evaluated during a photoallergy study; six 2-h induction applications followed 10 days later by a 2-h occluded challenge application	1% in 3:1 DEP:EtOH	5 male hairless guinea pigs	Sensitization was not observed	RIFM (2003a)
Cinnamaldehyde	Optimization test	0.1% in a mixture of Freund's complete adjuvant and saline (1:1)—intradermal challenge; 3.0% in petrolatum—epidermal challenge	20 male and female Pirbright white strain guinea pigs	20/20 reactions after intradermal challenge; 19/20 reactions after epidermal challenge	Maurer et al. (1980)
Cinnamaldehyde	Local lymph node proliferation assay (LLNA)	1.0% in ethanol	5 female Hartley albino guinea pigs	Lymph node cell proliferation was stimulated	Kashima et al. (1996)
Cinnamaldehyde	LLNA	0.7% in liquid paraffin/ intradermal injections; 1.0% in ethanol/patch applications	Female Hartley albino guinea pigs	Sensitization effects were observed	Kashima et al. (1994)
Cinnamaldehyde	LLNA	0.5%, 1.0%, 2.0% and 5.0% in dimethyl acetamide: acetone:ethanol (4:4:3)	Dunkin–Hartley Pirbright guinea pigs	Lymph node cell proliferation was stimulated at all dose levels	Maurer and Kimber (1991)
Cinnamaldehyde	LLNA	5.0–25% in acetone:olive oil (4:1)	Young adult Balb/c mice	No increase in IL-6 production was observed	Dearman et al. (1994)
Cinnamaldehyde	LLNA	5.0% vehicle was either acetone:olive oil or dimethyl formamide	Young adult Balb/c and CBA/Ca mice	Positive effects: [^{3}H]-TdR incorporation was 13.27 cpm. Mean lymph node weight was 2.9 mg. Frequency of pyronin-positive cells was 6.3%	Kimber and Weisenberger (1989)
Cinnamaldehyde	LLNA	0.5–2.0% vehicle was acetone:olive oil (4:1) or dimethylformamide	Young adult CBA/ Ca strain mice	Lymph node cell proliferation was stimulated at all dose levels	Maurer and Kimber (1991)

Table 14 (*continued*)

Material	Method	Concentration	Species	Results	References
Cinnamaldehyde	LLNA	10% in 70% ethanol (topical dose)3 μg/ml [~equivalent to 3 mg/ml] in ethanol (in vitro dose); 25% in acetone:olive oil (4:1)	Female Balb/c mice	Sensitization effects were observed	Mori et al. (1992), Hatao et al. (1995)
Cinnamaldehyde	LLNA	25% in acetone:olive oil	15–25 Balb/c mice	Sensitization effects were observed based on a weak increase in local lymph node cell proliferation but IL-6 production was not increased	Dearman et al. (1993)
Cinnamaldehyde	LLNA	1%, 5% and 25% in dimethylformamide	CBA/Ca mice	Sensitization effects were observed	Montelius et al. (1994)
Cinnamaldehyde	LLNA	5%, 10% and 25% in acetone/olive oil (4:1)	CBA/Ca mice	Sensitization effects were observed	Basketter and Scholes (1992)
Cinnamaldehyde	LLNA	0.5%, 1%, 2.5%, 5%, and 10% in acetone/olive oil	CBA/Ca mice	Sensitization effects were observed	Basketter et al. (2001)
Cinnamaldehyde	LLNA	1.0–25% in seven different vehicles	CBA/Ca mice	Sensitization effects were observed	Wright et al. (2001)
Cinnamaldehyde	LLNA	0.1–10% in 3:1 EtOH:DEP with and without the addition of antioxidants	CBA/Ca mice	Sensitization effects were observed both with and without the addition of antioxidants in both air exposed and fresh material	RIFM (2003c), Lalko (2002)
Cinnamaldehyde	Mouse ear swelling assay	10% in ethanol	10–15 female CF-1 mice	30% of the mice were sensitized	Gad et al. (1986a), Gad et al. (1986b)
Cinnamaldehyde	Mouse ear swelling assay	10%, 20%, 40% (vehicle not reported)	Male Balb/cBy mice	Sensitization effects were observed at all doses; ~5%—predicted SD_{50} (induction dose to sensitize half of the animals)	Thorne et al. (1991)
Cinnamic acid	Beuhler skin sensitization test	10% (vehicle not reported)	Guinea pigs	No reactions	Basketter and Gerberick (1996)
Cinnamic acid	Buehler delayed hypersensitivity test	10% in acetone	10 guinea pigs	No reactions	Buehler and Ritz (1985)
Cinnamic acid	Magnusson–Kligman maximization test. To evaluate cross-sensitization, animals were also challenged with cinnamic aldehyde and cinnamyl alcohol	9 mg/ml in ethanol; 120 mg/ml in ethanol; 200 mg/ml in dimethylisosorbide	20 female albino Ssc:AL guinea pigs	9 mg/ml, No reactions (0/20) and no cross-reactions when challenged with cinnamic aldehyde and cinnamyl alcohol; 120 mg/ml, 1/20 reactions; no cross-reactions when challenged with cinnamic aldehyde and cinnamyl alcohol; 200 mg/ml; No reactions (0/20); 7/20 cross-reactions when challenged with cinnamic aldehyde; no cross-reactions when challenged with cinnamyl alcohol	Weibel et al. (1989)

Cinnamic acid	Closed epicutaneous test (CET)	1% in acetone	5 guinea pigs	No reactions	Ishihara et al. (1986)
Cinnamic acid	Modified Freund's Complete Adjuvant test (FCAT)	10% in acetone	Guinea pigs	Weak to moderate sensitization	Hausen et al. (1992), Hausen et al. (1995)
Cinnamic acid	Sensitization evaluated during a photoallergy study; six 2-h induction applications followed 10 days later by a 2-h occluded challenge application	20% in 3:1 DEP:EtOH	5 male hairless guinea pigs	Sensitization was not observed	RIFM (2003a)
Cinnamic acid	Open applications were made to both sides of the earlobes and ear thickness measured	15% in absolute ethanol	10 female Hartley guinea pigs	Sensitization was observed	Lahti and Maibach (1985)
Cinnamic acid	Open applications were made to both sides of the earlobes and ear thickness measured	1%, 5% and 15% in absolute ethanol	15 female Hartley guinea pigs (5/dose)	Sensitization was observed at all dose levels	Lahti and Maibach (1984)
Cinnamic acid	Open applications were made to the back, abdomen and flank	15% in absolute ethanol	5 female Hartley guinea pigs	No sensitization was observed	Lahti and Maibach (1984)
Cinnamic acid	Open applications were made to the right earlobes	15% in absolute ethanol	2 female Hartley guinea pigs	Sensitization was observed	Lahti and Maibach (1984)
Cinnamic acid	Mouse ear swelling assay	15% in acetone:oil (1:1)	10 female Balb/c mice	No reactions	Maisey and Miller (1986)
Cinnamyl alcohol	Buehler delayed hypersensitivity test	1%, 3% and 10% in acetone	10 guinea pigs/group	No reactions at 1%; 1/10 reactions at 3%; 2/10 reactions at 10%	Buehler and Ritz (1985)
Cinnamyl alcohol	Buehler delayed hypersensitivity test	10% (vehicle not reported)	Guinea pigs	50% of the animals were sensitized	Basketter and Gerberick (1996)
Cinnamyl alcohol	Buehler delayed hypersensitivity test	5% in petrolatum	10 guinea pigs	No reactions	RIFM (1978)
Cinnamyl alcohol	Modified Draize test	0.1% (injection challenge concentration); 10% (application challenge concentration)vehicle not reported	10 inbred Hartley strain albino guinea pigs	No reactions	Sharp (1978)
Cinnamyl alcohol	Modified Draize test	0.1% in saline	Male and female outbred Himalayan guinea pigs	No reactions	Klecak et al. (1977)
Cinnamyl alcohol	Modified Draize test	Dose and vehicle were not reported	Guinea pigs	No reactions	Johnson and Goodwin (1985)
Cinnamyl alcohol	Maximization test	a subirritant concentration in petrolatum	Male and female outbred Himalayan guinea pigs	Sensitization effects were observed	Klecak et al. (1977)

Table 14 (*continued*)

Material	Method	Concentration	Species	Results	References
Cinnamyl alcohol	Magnusson–Kligman maximization test	40% in acetone/PEG	10 albino Dunkin–Hartley guinea pigs	Sensitization was observed	RIFM (1986b)
Cinnamyl alcohol	Magnusson–Kligman maximization test. To evaluate cross-sensitization, animals were also cross-challenged with related materials	1% (vehicle not specified)	10 male albino guinea pigs	No reactions. No cross-reactions with related materials	Senma et al. (1978)
Cinnamyl alcohol	Magnusson–Kligman maximization test. To evaluate cross-sensitization, animals were cross-challenged with cinnamaldehyde and cinnamic acid	8 mg/ml in ethanol	Albino female guinea pigs (Ssc:AL)	1/20 reactions; no cross-reactions were observed when animals were cross-challenged with cinnamaldehyde or cinnamic acid	Weibel et al. (1989)
Cinnamyl alcohol	Magnusson–Kligman maximization test; to evaluate cross-sensitization, animals were cross-challenged with cinnamaldehyde and cinnamic acid	120 mg/ml in ethanol	Albino female guinea pigs (Ssc:AL)	9/19 reactions; 15/20 cross-reactions observed when animals were cross-challenged with cinnamaldehyde. No cross-reactions were observed with cinnamic acid	Weibel et al. (1989)
Cinnamyl alcohol	Guinea pig maximization test	40% *cis*-cinnamyl alcohol and 40% *trans*-cinnamyl alcohol (vehicle not reported)	Dunkin–Hartley guinea pigs	Cross-reactions were observed with both *cis*- and *trans*-cinnamyl alcohol	Basketter (1992)
Cinnamyl alcohol	Guinea pig maximization test	10% (vehicle not reported)	Guinea pigs	Strong sensitization effects were produced	Ishihara et al. (1986)
Cinnamyl alcohol	Guinea pig maximization test; to evaluate cross-sensitization, animals were cross-challenged with cinnamaldehyde	40% *trans*-cinnamic alcohol (vehicle not reported)	Dunkin–Hartley guinea pigs	2/10 questionable reactions were observed. No cross-reactions were observed with cinnamaldehyde	Basketter (1992)

Cinnamyl alcohol	Guinea pig maximization test; to evaluate cross-sensitization, animals were cross-challenged with cinnamaldehyde	40% *cis*-cinnamic alcohol (vehicle not reported)	Dunkin–Hartley guinea pigs	1/10 questionable reactions were observed. No cross-reactions were observed with cinnamaldehyde	Basketter (1992)
Cinnamyl alcohol	Open epicutaneous test (OET)	100%	Male and female outbred Himalayan guinea pigs	No reactions	Klecak et al. (1977)
Cinnamyl alcohol	OET	4% (vehicle not specified)	6–8 guinea pigs	No reactions	Klecak (1979)
Cinnamyl alcohol	Closed epicutaneous test (CET)	10% in acetone	Guinea pigs	2/6 reactions	Ishihara et al. (1986)
Cinnamyl alcohol	Modified Freund's Complete Adjuvant test (FCAT)	30% in ethanol	Male and female outbred Himalayan white spotted guinea pigs	3/19 reactions after first challenge. No reactions after second challenge	RIFM (1986c)
Cinnamyl alcohol	FCAT	100%	Female outbred Himalayan white spotted guinea pigs	2/20 reactions after first challenge; 1/20 reactions after second challenge	RIFM (1985a)
Cinnamyl alcohol	FCAT	A subirritant concentration in petrolatum	Male and female outbred Himalayan guinea pigs	Sensitization effects were observed	Klecak et al. (1977)
Cinnamyl alcohol	FCAT	3% and 10% in acetone	Guinea pigs	weak sensitization was observed at both concentrations	Hausen et al. (1992), Hausen et al. (1995)

8-methoxypsoralen, produced skin reactions indicative of cutaneous phototoxicity. Cinnamaldehyde at concentrations as high as 1% and cinnamic acid as high as 20%, did not cause skin changes indicative of phototoxicity.

Phototoxicity was not observed in guinea pigs after application of 1000 µg cinnamic acid to a 2.5 cm^2 area on the back followed by UV irradiation for 45 min (Pathak and Fitzpatrick, 1959a,b).

3.10.1.2. In vitro studies. Cinnamyl alcohol was evaluated for phototoxicity in three different assays; a photohemolysis assay with red blood cells, an assay using the photosensitized oxidation of histidine and in a yeast assay using *Candida utilis*. Phototoxic effects were observed in the photohemolysis assay and in the yeast assay. Cinnamyl alcohol does not absorb light at >295 nm; from 275–295, only slight absorption (approximately 0.2 AU) was observed. Based on this information and the fact that cinnamaldehyde and cinnamic acid showed no phototoxic or photoallergic potential, we believe these studies are not predictive for the in vivo situation. Ten in vitro phototoxicity assays were conducted with cinnamaldehyde including a Skin^2 PI assay using the Skin cutaneous model, a photohemolysis assay, a Neutral Red Uptake growth inhibition assay, and yeast assays using *C. utilis* or *Saccharomyces cerevisiae*. Phototoxicity was observed in the Neutral Red Uptake assay and yeast assay using *C. utilis*, but was not observed in the other assays.

3.10.2. Photoallergy

3.10.2.1. Human studies. There were no photoallergic effects observed when Hashimoto et al. (1990) evaluated cinnamyl alcohol at 2% in petrolatum in 242 dermatitis patients or when Schauder and Ippen (1997) evaluated 1% cinnamyl alcohol in 41 dermatitis patients. No photoallergic reactions were observed when Hashimoto et al. (1990) evaluated cinnamaldehyde at 1% in petrolatum in 248 dermatitis patients; however Schauder and Ippen (1997) reported that 1% cinnamaldehyde produced two reactions in 41 dermatitis patients. No reactions were observed in 121 cosmetic dermatitis patients when cinnamaldehyde was evaluated by Nagareda et al. (1992) for photoallergic potential. Using open and closed photopatch studies, Addo et al. (1982) reported that cinnamaldehyde produced photoallergic effects in two patients with polymorphic light eruption and in one patient with contact dermatitis.

3.10.2.2. Animal studies. A photoallergy study in groups of male hairless guinea pigs was conducted (RIFM, 2003a). During the induction period, a nuchal area of skin approximately 2.5 cm^2 was defined by intradermal injections with a formulation of sterile water and Freund's complete adjuvant (FCA), (1:1 v/v) then tape stripped. One 25 mm Hilltop chamber containing 1%

cinnamaldehyde, 20% cinnamic acid or 3% 3,3′,4′,5′-tetrachlorosalicylanilide (TSCA) was applied to the nuchal area for a 2-h period. The skin sites were then irradiated with solar-simulated UVR for approximately 2.25 h. This process (with the exception of the FCA injections) was repeated on days 3, 5, 8, 10 and 12 of the induction phase of the study. The animals were observed immediately before administration and/or UVR exposure for general skin appearance and overt signs of toxicity, and the test sites were examined daily for irritation, infection and/or sloughing. Following a 10-day rest period, the animals were challenged with cinnamaldehyde (0.1% and 1%), cinnamic acid (2% and 20%) or TSCA (0.1% and 0.3%). The test material was applied to 25 mm Hilltop chambers which were then placed on the dorsal skin of the animals along the midline for a two-hour period. The skin sites were then irradiated with solar-simulated UVR for approximately 2.25 h. The animals were observed 4 h following administration and/or UVR exposure for general skin appearance and overt signs of toxicity, and then once daily for the next three days. The FCA sites were examined daily for irritation, infection and/or sloughing. Cinnamaldehyde at concentrations as high as 1%, and cinnamic acid as high as 20%, did not cause skin changes indicative of photoallergy.

4. Summary

1. The available information on percutaneous absorption suggest that there is significant absorption of cinnamyl alcohol, cinnamaldehyde and cinnamic acid through the skin. For humans, only data from in vitro studies are available. Based on these data, the conservative estimate is that greater than 50% of the applied doses of these three materials is absorbed through the skin under occluded conditions.
2. Cinnamyl alcohol, cinnamaldehyde and cinnamic acid are rapidly absorbed, metabolized, and excreted in the urine. They all follow the same metabolic pathway in that the alcohol is transformed into the aldehyde, which is metabolized to the acid. The final metabolite is hippuric acid, which is the principal metabolite being excreted in the urine (see Fig. 2). The qualitative pattern of metabolism of cinnamaldehyde and cinnamic acid in humans is similar to that seen in laboratory species; and it is anticipated that this would also be broadly true for the metabolic fate of cinnamyl alcohol.
3. Based on acute toxicity data, cinnamyl alcohol and cinnamic acid are not acutely toxic by the dermal route of exposure while cinnamaldehyde has a low order of toxicity by the dermal route.
4. 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 bodyweight per day in rats and 550 mg/kg bodyweight per day in mice. These NOAELs greatly exceed the expected dose absorbed from dermal exposure to humans from the use of these compounds as fragrance ingredients. Such exposures are estimated at 0.0416 mg/kg/day for cinnamyl alcohol 0.0026 mg/kg/day for cinnamaldehyde; and 0.0005 mg/kg/day for cinnamic acid.
5. Based on a weight of evidence evaluation of the available mutagenicity and genotoxicity data on cinnamyl alcohol, cinnamaldehyde and cinnamic acid, as well as metabolism and detoxification, it can be concluded that these three materials have no significant genotoxic potential under the current conditions of use as fragrance ingredients.
6. Based on the available data on developmental toxicity studies on cinnamyl alcohol, cinnamaldehyde and cinnamic acid, these materials do not possess any significant potential for developmental effects under the current conditions of use as fragrance ingredients.
7. Based on human studies, cinnamyl alcohol and cinnamic acid are not considered to be primary irritants in humans under the recommended current conditions of use as fragrance ingredients; cinnamaldehyde up to concentrations of 1.25% is not considered to be a primary irritant but it is an irritant at concentrations of 3% or more.
8. Data on cinnamaldehyde suggest that these three cinnamyl materials have the potential to be primary eye irritants in humans under the recommended current conditions of use as fragrance ingredients.
9. Cinnamyl alcohol is a human sensitizer and the NOEL in humans for induction of sensitization is in the region of 4%. This has resulted in an IFRA Standard limiting the use of this material to 0.4% (IFRA Standard, 2003). Cinnamaldehyde is a sensitizer in humans, with a NOEL for induction of sensitization in humans at 0.5%; quenching studies with cinnamaldehyde were not verified. This has resulted in an IFRA Standard limiting the use of this material to 0.05% (RIFM, 2004). Cinnamic acid has not been shown to be a sensitizer in humans.
10. Cinnamaldehyde and cinnamic acid both absorb UVB light (290–320 nm), cinnamaldehyde peaking at 287 nm and returning to baseline at 330 nm, and cinnamic acid peaking at 273 nm and returning to baseline at 315 nm. Since cinnamaldehyde and cinnamic acid absorb in the UV range of 290–400 nm, and there are no definitive human studies avail-

able, the phototoxic and photoallergic potential of these two materials was investigated. Neither cinnamaldehyde nor cinnamic acid, at concentrations up to 1% and 20% respectively, produced skin changes indicative of phototoxicity or photoallergy in guinea pigs. While in vitro phototoxicity studies with cinnamyl alcohol produced positive effects, it is not expected that cinnamyl alcohol would produce phototoxic effects in humans as cinnamyl alcohol does not absorb light at >295 nm; from 275–295, only slight absorption (approximately 0.2 AU) was observed. Based on these data and the fact that cinnamaldehyde and cinnamic acid show no phototoxic or photoallergic potential, we do not expect cinnamyl alcohol to show any phototoxic or photoallergic activity under the current conditions of use as a fragrance ingredient.

5. Conclusion

The Panel has determined that there are no safety concerns regarding the materials in this group under the present declared levels of use and exposure for the following reasons:

- In acute studies, cinnamyl alcohol, cinnamaldehyde and cinnamic acid have a low order of toxicity by the oral and dermal route of exposure.
- Chronic tests reveal a NOAEL of 200 mg/kg/day in rats and 550 mg/kg/day in mice after 2 years of dietary administered *trans*-cinnamaldehyde.
- Based on a weight of evidence evaluation of all available mutagenicity and genotoxicity studies, it has been determined that these materials have no significant potential to produce genotoxic effects in vivo.
- The metabolic fate of cinnamyl alcohol, cinnamaldehyde and cinnamic acid is well known in that the alcohol is transformed to the aldehyde which is further metabolized to the acid. Toxic or persistent metabolites are not formed.
- In human dermatological studies:
  No irritation was observed with cinnamyl alcohol or cinnamic acid and the NOEL for irritation caused by cinnamaldehyde is 1.25%.
  The NOEL for sensitization caused by cinnamyl alcohol has been determined to be in the region of 4%; this has resulted in an IFRA standard limiting the use of this material to 0.4%. The NOEL for sensitization caused by cinnamaldehyde has been established at 0.5%; this has resulted in an IFRA standard limiting the use of this material to 0.05%. Quenching studies with cinnamaldehyde were not verified in humans. Cinnamic acid is non-sensitizing. For this assessment, the sensitization no-effect level for cinnamaldehyde and cinnamyl alcohol were based on the induction of sensitization.
  Phototoxic and photoallergic effects have not been evaluated in humans, but concentrations as high as 1% cinnamaldehyde and 20% cinnamic acid did not produce skin changes indicative of phototoxicity or photoallergy in guinea pigs.
- These materials are used at low levels of exposure relative to doses that elicit adverse effects in laboratory animals via systemic exposure. The estimate for maximum systemic exposure by humans using cosmetic products is 0.0416 mg/kg for cinnamyl alcohol, 0.0026 mg/kg for cinnamaldehyde and 0.0005 mg/kg/day for cinnamic acid. Using the most conservative in vitro human percutaneous absorption data (highest percent absorbed under occluded conditions) of approximately 66% for cinnamyl alcohol, 52% for cinnamaldehyde and 61% for cinnamic acid, the conservative estimate for systemic exposure by humans using cosmetic products is 0.0275 mg/kg/day for cinnamyl alcohol (66% of 0.0416 mg/kg/day); 0.0014 mg/kg/day for cinnamaldehyde (52% of 0.0026 mg/kg/day) and 0.0003 mg/kg/day for cinnamic acid (61% of 0.0005 mg/kg/day).

Based on the above considerations, and using the NOAEL of 200 mg/kg from the oral chronic study in rats with *trans*-cinnamaldehyde, a margin of safety for systemic exposure of humans to cinnamyl alcohol, cinnamaldehyde and cinnamic acid in cosmetic products may be calculated as: more than 7000 times the maximum daily exposure for cinnamyl alcohol (200 mg/kg/day ÷ 0.0275 mg/kg/day = 7272); more than 142,000 times the maximum daily exposure for cinnamaldehyde (200 mg/kg/day ÷ 0.0014 mg/kg/day = 142,857); more than 666,000 times the maximum daily exposure for cinnamic acid (200 mg/kg/day÷0.0003 mg/kg/day = 666, 666).

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