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Review

A toxicologic and dermatologic assessment of cinnamyl phenylpropyl materials when used as fragrance ingredients ☆

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ABSTRACT

The cinnamyl phenylpropyl fragrance ingredients are a diverse group of chemical structures that have similar metabolic and toxicity profiles. A toxicological and dermatological review of these fragrance ingredients is presented. The common characteristic structural element of cinnamyl phenylpropyl materials is an aryl substituted primary alcohol/aldehyde/ester. For high end users, calculated maximum dermal exposures vary from 0.14% to 0.72%; systemic exposures vary from 0.0002 to 0.0280 mg/kg/day. Human dermatological studies show that these materials are not generally irritants or sensitizers at lower exposures from consumer products. Reactions (0.9%) in fragrance sensitive patients were observed with 3-phenyl-1-propanol at 5% in petrolatum. The cinnamyl phenylpropyl materials had low acute toxicity and no significant toxicity in repeat dose oral or dermal toxicity studies. No mutagenic or genotoxic activity in bacteria and mammalian cell line assays was observed. The cinnamyl phenylpropyl alcohol materials participate in the same beta oxidation pathways as their parent cinnamic acid derivatives, including common routes of absorption, distribution, and metabolic detoxification, and exhibit similar toxicological endpoints. Based on the review of available data, it is concluded that these materials would not present a safety concern at current levels of use as fragrance ingredients.

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1. Introduction

In 2006 a comprehensive literature search was conducted on the cinnamyl phenylpropyl group of fragrance materials and an update was conducted in 2009. The present group is comprised of 3 materials (3-phenyl-1-propanol, 3-phenylpropyl cinnamate, and 3-phenylpropyl isobutyrate). This document provides a risk assessment of these materials as fragrance ingredients and is a critical evaluation of the pertinent data. The scientific evaluation focuses on dermal exposure, which is considered to be the primary route for fragrance materials. Where relevant, toxicity, metabolism and biological fate data from other exposures have been considered. As fragrance ingredients these agents are used in cosmetics, fine fragrances, shampoos, toilet soaps and other toiletries as well as in non-cosmetic products such as household cleaners and detergents. This report uses data obtained from animals by various routes, but emphasizes the risk assessment for use of cinnamyl phenylpropyl materials as fragrance ingredients.

The current format includes a group summary evaluation paper and individual Fragrance Material Reviews on discrete chemicals. The group summary is an evaluation of relevant data selected from the large bibliography of studies and reports on the individual chemicals. The selected data were deemed to be relevant based on the currency of protocols, quality of the data, statistical significance and appropriate exposure. These are identified in tabular form in the group summary. Details that are provided in the tables are not always discussed in the text of the group summary. The Fragrance Material Reviews contain a comprehensive summary of all published reports including complete bibliographies (Bhatia et al., 2011a,b,c).

2. Chemical Identity, regulatory status and exposure (Table 1)

This report summarizes chemical and toxicological data relevant to the risk assessment of the use of cinnamyl phenyl materials as fragrance ingredients.

In United States, all three of these cinnamyl phenylpropyl materials have been approved for use as flavors by the Food and Drug Administration (FDA) in accordance with (21 CFR 172.515). The Flavor and Extract Manufacturers' Association (FEMA, 1965, 1979) has approved these substances as Generally Recognized as Safe (GRAS) as flavor ingredients [Numbers 2885, 2893, 2894]. These materials were also included in the Council of Europe's list of substances which may be used in foodstuffs, granted B – information required [Numbers 303, 338 (hydrolysis studies) and 80 (28 day oral studies)] (COE, 2000). These three materials have been included on the indicative non-exhaustive list (INEL) and on Japan's Industrial Safety and Health Law list.

Finally all the cinnamyl phenylpropyl materials assessed in this group summary have been evaluated by the International Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2000), which concluded that none of the materials present a safety concern at current estimated levels of intake as flavoring agents [Numbers 636, 640, 672].

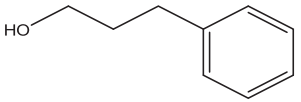
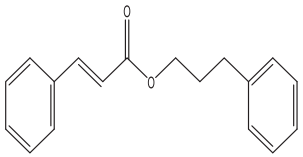
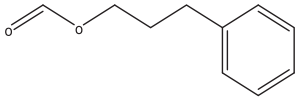
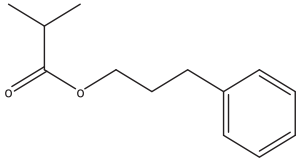
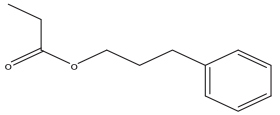
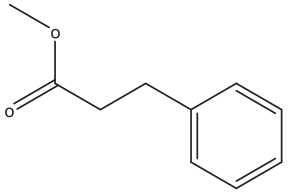
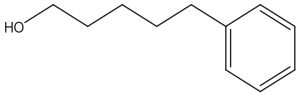
Table 1 provides a list of the cinnamyl phenyl propyl fragrance ingredients that are evaluated in this report along with their Chemical Abstract Service registration numbers (CAS), synonyms, structural formulas, annual world wide production, and estimated dermal system, exposure data for these compounds. Tables 2–8 summarize the available toxicology data.

2.1. Rationale for grouping cinnamyl phenyl propyl together

The common characteristic structural element of cinnamyl phenylpropyl materials is an aryl substituted primary alcohol/aldehyde/ester. The present group is comprised of 3 substances which include one aromatic alcohol (3-phenyl-1-propanol) and two aromatic esters (3-Phenylpropyl cinnamate and 3-phenylpropyl isobutyrate). They are simple aromatic compounds with saturated propyl or unsaturated propenyl side chain containing a primary oxygenated functional group (5-phenylpentanol bearing substituents) which have little toxic potential. 3-Phenyl-1-propyl derivatives participate in the same *beta*-oxidation pathways as do its parent cinnamic acid derivatives. As the data base for these cinnamyl phenyl propyl materials are limited, additional data on toxicokinetics, metabolism and systemic toxicity of the structurally related cinnamaldehyde, cinnamyl alcohol and cinnamic acid from an evaluation by Bickers et al. (2005) are used.

There are three materials belonging to this group (see Table 1). Tables 2–8 summarize the available toxicology data. Also contained within Tables 2–8 are additional toxicology data for three esters (3-phenylpropyl propionate, 3-phenylpropyl formate, and methyl 3-phenylpropionate) and one alcohol (5-phenylpentanol) that are not used in fragrances but are structurally related to the cinnamyl phenylpropyl materials that are used as fragrance ingredients. Although these materials are not being reviewed because there was no reported use of these materials as fragrance ingredients (IFRA, 2008), safety data on these materials, if available, will appear in the data tables.

Table 1
Material identity, summary of volume use and dermal exposure.

Material	Synonyms	Structure	Worldwide metric tons[a]	Dermal systemic exposure in cosmetic products (mg/kg/day)[b]	Maximum skin level[c]
3-Phenyl-1-propanol CAS# 122-97-4 Molecular weight: 136.19 Log K_{ow} (calculated): 2.06 Water solubility: 6969 mg/L[g] Vapor pressure: 0.00848 mm Hg @ 25 °C[g]	• Benzenepropanol • Benzylethyl alcohol • Dihydrocinnamyl alcohol • Hydrocinnamyl alcohol • Phenethyl carbinol • Phenylpropyl alcohol • 3-Phenylpropyl alcohol		100–1000	0.0204[d]	0.72[d]
3-Phenylpropyl cinnamate CAS# 122-68-9 Molecular weight: 266.34 Log K_{ow} (calculated): 5.05 Water solubility: 0.9383 mg/L[g] Vapor pressure: 7.09e-006 mm Hg @ 25 °C[g]	• Cinnamic acid, 3-phenylpropyl ester • Hydrocinnamyl cinnamate • β-Phenylpropyl cinnamate • 3-Phenylpropyl β-phenylacrylate • 3-Phenylpropyl 3-phenylpropenoate • 2-Propenoic acid, 3-phenyl-, 3-phenylpropyl ester		0.1–1	0.0280[e]	0.14[e]
3-Phenylpropyl formate[f] CAS# 104-64-3 Molecular weight: 164.2 Log K_{ow} (calculated): 2.52 Water solubility: 465 mg/L[g] Vapor pressure: 0.0272 mm Hg @ 25 °C[g]	• Benzenepropanol, formate • Hydrocinnamyl formate • Phenylpropyl formate • β-Phenylpropyl formate		0	0	0
3-Phenylpropyl isobutyrate CAS# 103-58-2 Molecular weight: 206.29 Log K_{ow} (calculated): 3.97 Water solubility: 16.47 mg/L [g] Vapor pressure:0.0068 mm Hg @ 25 °C [g]	• Hydrocinnamyl isobutyrate • Hydrocinnamyl 2-methylpropanoate • β-Phenylpropyl 2-methylpropanoate • 3-Phenylpropyl 2-methylpropanoate • Propanoic acid, 2-methyl-, 3-phenylpropyl ester		<0.1	0.0002[e]	0.02[e]
3-Phenylpropyl propionate[f] CAS# 122-74-7 Molecular weight: 192.26 Log K_{ow} (calculated): 3.55 Water solubility: 44.15 mg/L [g] Vapor pressure: 0.00859 mm Hg @ 25 °C [g]	• Benzenepropanol, propanoate • Hydrocinnamyl propionate • 3-Phenylpropyl propanoate • Phenylpropyl propionate • β-Phenylpropyl propionate		0	0	0
Methyl 3-phenylpropionate[f] CAS# 103-25-3 Molecular weight: 164.2 Log K_{ow} (calculated): 2.57 Water solubility: 683.4 mg/L [g] Vapor pressure: 0.0501 mm Hg @ 25 °C [g]	• Benzenepropanoic acid, methyl ester • Methyl dihydrocinnamate • Methyl hydrocinnamate		0	0	0
5-Phenylpentanol[f] CAS# 10521-91-2 Molecular weight: 164.25 Log K_{ow} (calculated): 3.04 Water solubility: 536.7 mg/L [g] Vapor pressure: 0.000445 mm Hg @ 25° [g]	• Benzenepentanol • Phenylamyl alcohol • 5-Phenylpentan-1-ol		0	0	0

[a] 2008 Volume of use survey (IFRA, 2008).
[b] Based on a 60 kg adult.
[c] Upper 97.5 percentile levels of the fragrance ingredient in the fragrance mixture used in these products.
[d] 2004 Use level survey (IFRA, 2004).
[e] 2002 Use level survey (IFRA, 2002).
[f] This material is not one of the compounds being reviewed as it is not used in fragrances but it is included because it is structurally related.
[g] Physical properties were calculated using Epi Suite (EPA, 2010).

Table 2A
Oral toxicity.

Material	Species	Number per dose group	LD_{50} g/kg body weight[a]	References
Methyl 3-phenylpropionate[b]	Rat	10	4.20 (95% C.I. 3.10–5.70 weight)	RIFM (1981a)
3-Phenyl-1-propanol	Rat	10	2.30 (95% C.I. 1.50–3.10 g/kg body weight)	RIFM (1976a)
3-Phenyl-1-propanol	Rat	10	2.25 (95% C.I. 1.68–3.00 g/kg body weight)	RIFM (1971a)
3-Phenylpropyl cinnamate	Rat	10	>5	RIFM (1972a)
3-Phenylpropyl formate[b]	Rat	10	4.09 (95% C.I. 3.49–4.78 g/kg body weight)	RIFM (1975a)
3-Phenylpropyl isobutyrate	Rat	10	>5	RIFM (1975a)
3-Phenylpropyl propionate[b]	Rat	10	>5	RIFM (1977a)

[a] Units have been converted to make easier comparisons; original units are in the Fragrance Material Reviews.
[b] This material is not one of the compounds being reviewed as it is not used in fragrances but it is included because it is structurally related.

Table 2B
Dermal toxicity study.

Material	Species	No. animals/dose group	LD50 g/kg body weight[a]	References
Methyl 3-phenylpropionate[b]	Rabbit	9	>5	RIFM (1981a)
3-Phenyl-1-propanol	Rabbit	6	~5	RIFM (1976a)
3-Phenyl-1-propanol	Rabbit	6	<5	RIFM (1971a)
3-Phenylpropyl cinnamate	Rabbit	6	>5	RIFM (1972a)
3-Phenylpropyl formate[b]	Rabbit	4	>5	RIFM (1975a)
3-Phenylpropyl isobutyrate	Rabbit	4	>5	RIFM (1975a)
3-Phenylpropyl propionate[b]	Rabbit	10	>5	RIFM (1977a)

[a] Units have been converted to make easier comparisons; original units are in the Fragrance Material Reviews.
[b] This material is not one of the compounds being reviewed as it is not used in fragrances but it is included because it is structurally related.

Table 3
Bacterial test systems – mutagenicity studies.

Material	Test System *in vitro*	Species	Dose[a]	Results	References
3-Phenyl-1-propanol	Ames with and without S9 activation	*Salmonella typhimurium* TA98, T100, TA102, TA1535 and TA 1537	15–5000 μg/plate in DMSO	Negative	RIFM (2002)

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

Table 4
Irritation studies in humans.

Material	Method	Concentration	Subjects	Results	References
Methyl-3-phenylpropionate[a]	Maximization pre-test. 48-h closed patch test	8% in petrolatum	25 male and female volunteers	No irritation	RIFM (1981b)
3-Phenyl-1-propanol	Maximization pre-test. 48-h closed patch test	8% in petrolatum	25 male and female volunteers	No irritation	RIFM (1976b)
3-Phenyl-1-propanol	Induction phase of an HRIPT	4% in petrolatum	50 male and female volunteers	No irritation	RIFM (1971b)
3-Phenylpropyl cinnamate	Maximization pre-test. 48-h closed patch test	4% in petrolatum	5 male volunteers	No irritation	RIFM (1972b)
3-Phenylpropyl formate[a]	Maximization pre-test. 48-h closed patch test	8% in petrolatum	5 male volunteers	No irritation	RIFM (1975c)
3-Phenylpropyl isobutyrate	Maximization pre-test. 48-h closed patch test	8% in petrolatum	24 male volunteers	No irritation	RIFM (1975b)
3-Phenylpropyl propionate[a]	Maximization pre-test. 48-h closed patch test	8% in petrolatum	5 volunteers (unspecified sex)	No irritation	RIFM (1977c)
3-Phenylpropyl propionate[a]	Maximization pre-test. 48-h closed patch test	8% in petrolatum	25 male and female volunteers	No irritation	RIFM (1977c)
3-Phenylpropyl propionate[a]	Maximization pre-test. 48-h closed patch test	8% in petrolatum	29 male volunteers	No irritation	RIFM (1977b)

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

2.2. Occurrence and use

Two (3-phenyl-1-propanol and 3-phenylpropyl cinnamate) of the cinnamyl phenylpropyl materials have been reported to occur in nature. They are naturally present in foods such as fruits, fruit juices, cheese and grains. Examples include: 3-phenyl-1-propanol in jackfruit (*Artocarpus* species), crowberry (*Empetrum nigrum* coll.), loquat (*Eriobotrya japonica* Lindl.), malt, matsutake (*Tricholoma matsutake*), mushroom, raspberry, blackberry, boysenberry, strawberry (Fragaria species), syzygium species, tapereba, caja fruit (*Spondias lutea* L.), wine, 0.05 mg/kg in cloudberry (*Rubus chamaemorus* L.) in juice, 0.3–0.8 mg/kg in guava and feyoa, 0.002–0.2 mg/kg in honey, <0.01 mg/kg in passiflora species, 0.0002 mg/kg in sapodilla fruit (*Achras sapota* L.), trace – 0.01 mg/kg in vaccinium species (VCF, 2010). 3-Phenylpropyl cinnamate is found in Asian styrax which is a balsam obtained from trees of the genus *Liquidambar* (Fernandez et al., 2005). Furthermore, 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 (Goodwin and Mercer, 1972).

2.3. Estimated consumer exposure

Exposure data have been provided by the fragrance industry. Potential consumer exposure to fragrance materials occurs through the dermal and inhalation routes of exposure. Worst-case scenario calculations indicate that depositions on the surface of the skin following use of cosmetics represents the major route of

Table 5
Irritation studies in animals.

Material	Method	Concentration[a]	Species	Results	References
Methyl-3-phenylpropionate[b]	Irritation evaluated during an associated LD_{50} study	Undiluted	9 Rabbits	Slight to moderate irritation	RIFM (1981a)
3-Phenyl-1-propanol	Irritation evaluated during an associated LD_{50} study	Undiluted	6 Rabbits	Moderate to severe irritation	RIFM (1971a)
3-Phenyl-1-propanol	A 24-h occluded patch test (Draize scoring)	Undiluted	6 Rabbits	Moderate irritation	RIFM (1971a)
3-Phenyl-1-propanol	Irritation evaluated during an associated LD_{50} study (2.5 & 5 g/kg)	Undiluted	6 Rabbits	Moderate at 2.5 and moderate to severe at 5 g/kg	RIFM (1976a)
3-Phenylpropyl cinnamate	Irritation evaluated during an associated LD_{50} study	Undiluted	6 Rabbits	Mild irritation in one rabbit	RIFM (1972a)
3-Phenylpropyl formate[b]	Irritation evaluated during an associated LD_{50} study	Undiluted	4 Rabbits	Mild irritation lasting 24-h	RIFM (1975a)
3-Phenylpropyl Isobutyrate	Irritation evaluated during an associated LD_{50} study	Undiluted	4 Rabbits	Mild irritation	RIFM (1975a)
3-Phenylpropyl propionate[b]	Irritation evaluated during an associated LD_{50} study	Undiluted	10 Rabbits	Mild to moderate irritation	RIFM (1977a)

[a] Units have been converted to make easier comparisons; original units are in the Fragrance Material Reviews.
[b] This material is not one of the compounds being reviewed as it is not used in fragrances but it is included because it is structurally related.

Table 6
Sensitization studies in humans.

Material	Method	Concentration	Subjects	Results	References
Methyl-3-phenylpropionate[a]	MAX	8% (5520 μg/cm^2) in petrolatum	25 male and female volunteers	1 questionable reaction which was negative at re-test approximately 7 days later	RIFM (1981b)
3-Phenyl-1-propanol	HRIPT	4% (4724 μg/cm^2) in petrolatum	50 male and female volunteers	No reactions	RIFM (1971b)
3-Phenyl-1-propanol	MAX	8% (5520 μg/cm^2) in petrolatum	25 male and female volunteers	No reactions	RIFM (1976b)
3-Phenylpropyl cinnamate	MAX	4% (2760 μg/cm^2) in petrolatum	25 male volunteers	No reactions	RIFM (1972b)
3-Phenylpropyl formate[a]	MAX	8% (5520 μg/cm^2) in petrolatum	24 male volunteers	No reactions	RIFM (1975c)
3-Phenylpropyl Isobutyrate	MAX	8% (5520 μg/cm^2) in petrolatum	25 male and female volunteers	No reactions	RIFM (1975b)
3-Phenylpropyl propionate[a]	MAX	8% (5520 μg/cm^2) in petrolatum	25 male volunteers	1/25 reactions – thought to be a cross reaction to other materials in the test group	RIFM (1977c)

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

Table 7
Elicitation studies in humans.

Material	Method	Concentration	Subjects	Results	References
3-Phenyl-1-propanol	Patch test	5% in petrolatum	218 fragrance sensitive male and female volunteers	0.9% of 218 patients tested were positive	Larsen et al. (2002)
3-Phenyl-1-propanol	Patch test	5% in a base cream or 99% ethanol – not specified	82 male and female volunteers	No reactions	Takenaka et al. (1986)

Table 8
Summary of UV spectra data.

Material	UV Spectra absorption (nm)
3-Phenyl-1-propanol	Peaked at 245–278 minor absorption in 290–320 range
3-Phenylpropyl cinnamate	Peaked at 245–278 minor absorption in 290–320 range
3-Phenylpropyl isobutyrate	Peaked at 245–278 minor absorption in 290–320 range

exposure to fragrance ingredients when conservative estimates for evaporation, rinsing and other forms of product removal are employed (Cadby et al., 2002). Therefore, the dermal route was the major route in assessing the safety of these compounds.

The fragrance industry has developed three types of approaches to estimate potential exposure for consumers to fragrance materials. All three types of exposure are summarized in Table 1. The first is volume of use. The total worldwide volume of use for 3-phenyl-1-propanol is 100–1000 tons; for 3-phenylpropyl cinnamate is 0.1–1 metric tons and for 3-phenylpropyl isobutyrate is less than 0.1 metric tons per year (IFRA, 2008). The reported volume is for the fragrance ingredient as used in fragrance compounds (mixtures) in all finished consumer product categories. The volume of use is determined by IFRA approximately every four years through a comprehensive survey of IFRA and RIFM member companies. As such the volume of use data from this survey provides volume of use of fragrance ingredients for the majority of the fragrance industry.

The second method estimates the potential percutaneous (total skin exposure) absorption from the entire body based on the use of

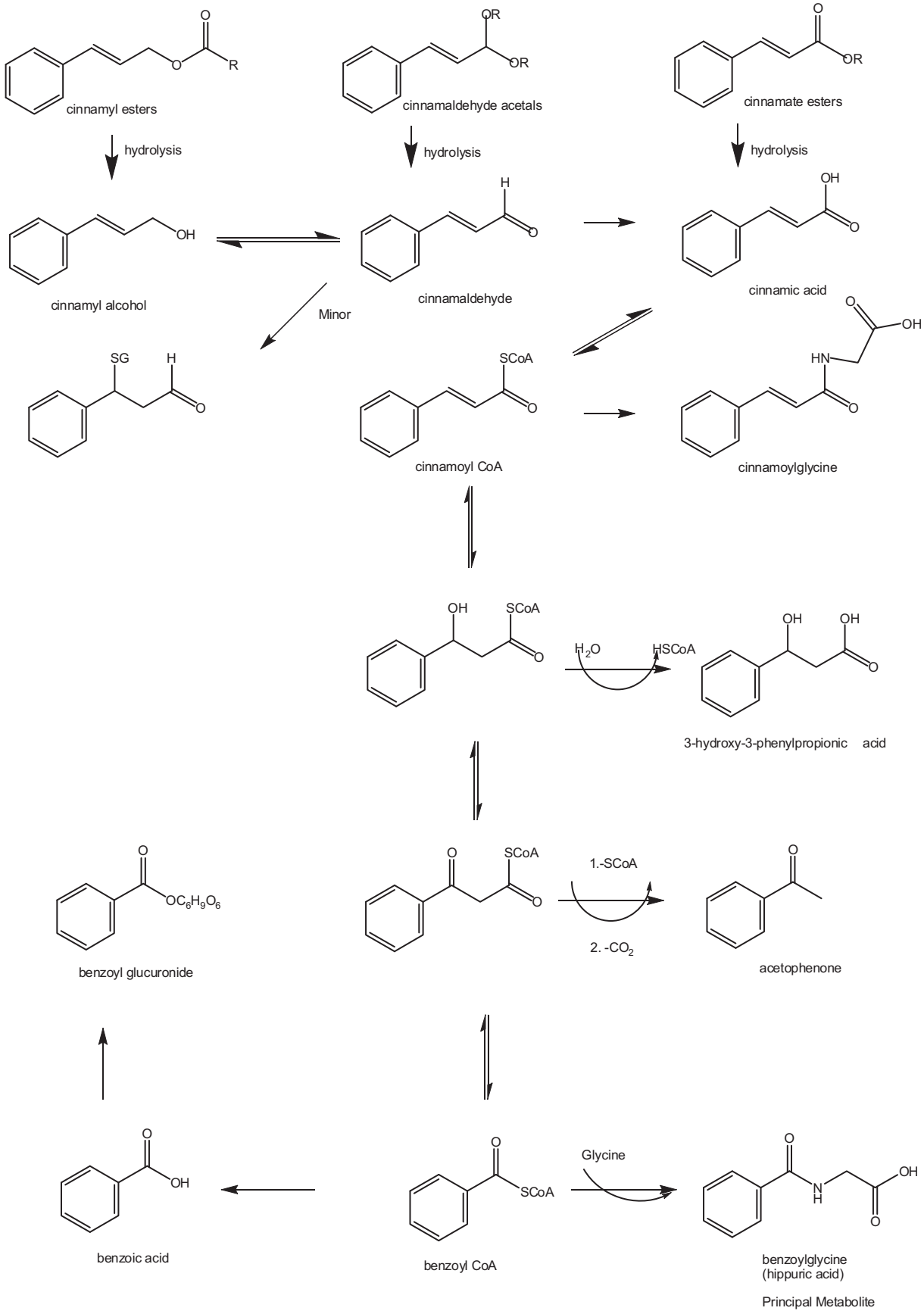


Fig. 1. Metabolism of cinnamyl derivatives.

multiple consumer personal care products containing the same fragrance ingredient. The dermal systemic exposure in cosmetic products is calculated based on the concentrations in ten types of the most frequently used personal care and cosmetic products (antiperspirant, bath products, body lotion, eau de toilette, face cream, fragrance cream, hair spray, shampoo, shower gel, and toilet soap). The concentration of the fragrance ingredient in fine fragrances is obtained from examination of several thousand commercial formulations. The upper 97.5 percentile concentration is calculated from the data obtained. This upper 97.5 percentile concentration is then used for all 10 consumer products. These concentrations are multiplied by the amount of product applied, the number of applications per day for each product type, and a "retention factor" (ranging from 0.001 to 1.0) to account for the length of time a product may remain on the skin and/or likelihood of the fragrance ingredient being removed by washing. The resultant calculation represents the total consumer exposure (mg/kg/day) (Cadby et al., 2002; Ford et al., 2000). In view of all of the above assumptions, the total calculated consumer exposure is conservative; it is unlikely that a consumer will consistently use a number of different consumer products which are all perfumed with the upper 97.5 percentile level of the fragrance ingredient from a fine fragrance type of product (Cadby et al., 2002; Ford et al., 2000). The total consumer exposures to fragrance ingredients range from 0.0002 to 0.0280 mg/kg/body weight (bw)/day for the cinnamyl phenyl propyl fragrance ingredients in high-end users of cosmetic products containing these materials (see Table 1) (IFRA, 2004).

The third method provides maximum skin levels. For consideration of potential sensitization, the exposure is calculated as the percent concentration of the fragrance ingredient applied to the skin based on the use of 20% of the fragrance mixture in the fine fragrance consumer product (IFRA, 2008). The maximum skin exposure levels of the cinnamyl phenylpropyl compounds that form part of the formulae of fine fragrances vary widely and have been report to range from 0.14% to 0.72%. The maximum skin exposure for cinnamyl phenylpropyl compounds in fine fragrance products are listed in Table 1 (IFRA, 2004, 2002).

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

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

3. Metabolism (Fig. 1)

The cinnamyl phenylpropyl alcohol materials participate in the same beta oxidation pathways as their parent cinnamic acid derivatives.

These substances are simple aromatic compounds and they participate in common routes of absorption, distribution, and metabolic detoxification, and exhibit similar toxicological endpoints. The ester members of this group are expected to be hydrolyzed by carboxylesterases or esterases to their component acid and alcohol. The alcohol and aldehyde members of this group are expected to be oxidized to yield the corresponding 3-phenylpropenoic acid or a 3-phenylpropanoic acid derivative which undergoes further side-chain beta–oxidation and cleavage to yield mainly the corresponding benzoic acid derivatives (Williams, 1959). The benzoic acid derivatives are conjugated and excreted in the urine (Snapper et al., 1940). To a minor extent, the presence of o-alkyl- and o-alkoxy-ring substituents may lead to alternative metabolic pathways (Solheim and Scheline, 1973, 1976; Samuelsen et al., 1986). In general, esters containing an aromatic ring system are expected to be hydrolyzed in vivo. Hydrolysis is catalyzed by classes of enzymes recognized as carboxylesterases or esterases (Heymann, 1980), the most important of which are the A-esterases. In mammals, A-esterases occur in most tissues throughout the body (Anders, 1989; Heymann, 1980) but predominate in the hepatocytes (Heymann, 1980). Esters of cinnamic acid and structurally related aromatic esters have been shown to hydrolyze rapidly to the component acid and alcohol. Oral administration of methyl cinnamate (50 mg/kg body weight) resulted in the urinary excretion, after 24 h, of hippuric acid (66%) and benzoylglucuronide (5%). This distribution of metabolites, nearly identical to that for cinnamic acid, indicates that rapid hydrolysis of the ester in vivo precedes metabolism of the acid (Fahelbum and James, 1977). Ethyl cinnamate administered subcutaneously to a cat produced cinnamic acid metabolites that were excreted in the urine (Dakin, 1909). Eighty percent hydrolysis was measured when benzyl cinnamate was incubated with simulated intestinal fluid (pH 7.5; pancreatin) at 37 °C for 2 h (Grundschober, 1977). The aromatic primary alcohols used as flavoring substances or formed by the hydrolysis of esters and acetals are readily oxidized to a cinnamic acid derivative (see Fig. 1). Human NAD^+ dependent alcohol dehydrogenase (ADH) catalyzes oxidation of primary alcohols to aldehydes (Pietruszko et al., 1973). Aromatic alcohols have been reported to be excellent substrates for ADH (Sund and Theorell, 1963). The aldehydes that are formed are further metabolized by aldehyde dehydrogenase to yield the acid (Feldman and Weiner, 1972). The urinary metabolites of cinnamyl alcohol are mainly those derived from metabolism of cinnamic acid.

In animals, aromatic carboxylic acids, such as cinnamic acid, are converted to acyl CoA esters (Nutley et al., 1994). Cinnamoyl CoA either conjugates with glycine, a reaction catalyzed by *N*-acetyl transferase, or undergoes beta-oxidation eventually leading to the formation of benzoyl CoA. Benzoyl CoA is in turn conjugated with glycine, yielding hippuric acid, or the CoA thioester is hydrolyzed to yield free benzoic acid which is then excreted (Nutley et al., 1994). CoA thioesters of carboxylic acids are obligatory intermediates in amino acid conjugation reactions (Hutt and Caldwell, 1990). Regardless of dose or species, the beta-oxidation pathway is the predominant pathway of metabolic detoxication of cinnamic acid in animals. The position and size of the substituents play a role in the metabolism of cinnamyl derivatives. Cinnamyl derivatives containing alpha-methyl substituents are extensively metabolized via beta-oxidation and cleavage to yield mainly the corresponding hippuric acid derivative. A benzoic acid metabolite was isolated from the urine of dogs given alpha-methylcinnamic acid (Kay and Raper, 1924). Larger substituents located at the alpha or beta-position to some extent inhibit beta oxidation (Kassahun et al., 1991; Deuel, 1957), in which case there may be direct conjugation of the carboxylic acid with glucuronic acid followed by excretion. While alpha-methylcinnamic acid undergoes oxidation to benzoic acid, alpha-ethyl- and alpha-propylcinnamic acids are excreted unchanged (Carter, 1941). alpha-Ethylcinnamic alcohol administered orally to rabbits resulted in the urinary excretion of alpha-ethylcinnamic acid, in addition to small amounts of benzoic acid (Fischer and Bielig, 1940). 3-Phenyl-1-propyl derivatives participate in the same beta oxidation pathways as do cinnamic acid derivatives. Like cinnamic acid, 3-phenyl-1-propanol is oxidized to the corresponding acid which as the CoA ester undergoes beta

oxidation and dehydration to yield the corresponding cinnamyl CoA derivative. When ring deuterated 3-phenylpropionic acid was administered orally to a human as a single dose (57 mg), deuterobenzoic acid corresponding to 110% of the dose was isolated from the alkaline hydrolyzed urine collected within 100 minutes of dosing (Pollitt, 1974). These data demonstrate that 3-phenylpropionic acid and cinnamic acid are rapidly oxidized to benzoic acid metabolites, and excreted in the urine (HPV, 2001).

4. Toxicokinetics

4.1. Dermal route of exposure

An *in vitro* percutaneous absorption study of 3-phenyl-1-propanol across human skin was conducted by Diez-Salez et al. (1993) using a diffusion cell. 3-Phenyl-1-propanol (5.0 mg/ml, working concentration) was dissolved in buffer solution at a concentration equivalent to approximately 75% of its solubility in that medium. The mean permeability coefficient [Kp ± SD ($\times 10^3$, (cm/h)] which is a measure of the rate of penetration into the skin for 3-phenyl-1-propanol was reported to be 52.35 ± 4.98 Kp[cm/hour] and the flow value was 1.18 ± 0.11 J[mg/h]. 3-Phenyl-1-propanol was significantly absorbed (Copovi et al., 1997).

Similar experiments were carried out using Wistar rat skin (aged 20–25 days) with 3-phenyl-1-propanol at 75% saturation concentration. The permeability coefficient of 3-phenyl-1-propanol was 60.07 ± 3.52 cm/h. When saturated solution was used, the effective concentration in the donor compartment was equal to the solubility value. The permeability coefficient of 3-phenyl-1-propanol was 88.97 ± 17.94 cm/h. When the duration of the experiment was increased to 32-h, the permeability coefficient of 3-phenyl-1-propanol was 130.22 ± 23.56 cm/h. 3-Phenyl-1-propanol was significantly absorbed (Lopez et al., 1998).

4.2. Oral route of exposure

No studies in humans or laboratory animals via the oral route are available for the cinnamyl phenylpropyl materials, however, cinnamyl alcohol, cinnamaldehyde and cinnamic acid have all been shown to be rapidly absorbed from the gut, metabolized and excreted primarily in the urine and to a minor extent, in the feces (JECFA, 2000).

Results of studies beginning in 1909 indicate that cinnamyl derivatives are absorbed, metabolized and excreted as polar metabolites within 24 h. Recent studies in laboratory animals on the effects of dose, species, sex, and mode of administration on the absorption, metabolism and excretion of cinnamyl alcohol, cinnamaldehyde and cinnamic acid are discussed in detail in Bickers et al. (2005). After oral or intraperitoneal administration to rats and mice, 76–77%, 69–98% and 73–94% of the [^{14}C] dose of cinnamyl alcohol, cinnamaldehyde and cinnamic acid, respectively, were recovered in the urine and feces within 24 h (Caldwell and Nutley, 1986; Nutley, 1990; Peters, 1993; Peters and Caldwell, 1994). In human subjects, plasma was cleared of cinnamic acid within 20 min after a single intravenous dose; 100% of a dose of cinnamaldehyde was recovered as metabolites in the urine within 8 h (Quarto di Palo and Bertolini, 1961).

4.3. Respiratory route of exposure

No studies in humans or laboratory animals are available for the cinnamyl phenylpropyl materials or their parent materials cinnamyl alcohol, cinnamaldehyde and cinnamic acid.

5. Toxicological studies

5.1. Acute toxicity (Tables 2A–B)

All the three cinnamyl phenylpropyl materials have been evaluated for acute toxicity (see Tables 2A–B). Dermal LD_{50} values in rabbits exceeded 5.0 g/kg body weight for two (3-phenylpropyl isobutyrate and 3-phenylpropyl cinnamate) of the three materials tested. While the dermal LD_{50} of 3-phenyl-1-propanol in rabbits was >2.5 ml/kg body weight and <5 ml/kg body weight based on 4/6 deaths and equal to 5.0 g/kg/bodyweight based on 3/6 deaths. Oral LD50 values ranged from a low of 2.25 g/kg body weight to a high of >5.0 g/kg body weight for all the three materials tested.

5.2. Repeated dose toxicity

There are no repeated dose toxicity studies on cinnamyl phenyl propyl materials However, since these materials may be hydrolyzed to yield cinnamic acid, alcohol or aldehyde, subchronic and chronic studies of the latter compounds provide a basis for estimating the toxic potential of the phenylpropyl compounds.

Male and female F344/N rats were fed diets containing 4100, 8200, 16,500 or 33,000 ppm microencapsulated *trans*-cinnamaldehyde (~275, 625, 1300 or 4000 mg *trans*-cinnamaldehyde/kg body weight/day to males and 300, 570, 1090 or 3100 mg/kg body weight/day 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. Alkaline 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. No histopathological lesions in the liver were observed. Gross lesions observed at necropsy included multifocal to diffuse white nodules of the forestomach mucosa at the three highest dose levels. The NOAEL was identified as 4100 ppm (~275 mg/kg body weight/day) and was selected as the top dose for the 2-year chronic study (Johnson et al., 1998; NTP, 2003; Hooth et al., 2004).

In a similar study, B6C3F_1 mice were fed diets containing 4100, 8200, 16,500 or 33,000 ppm microencapsulated *trans*-cinnamaldehyde (~650, 1320, 2550 or 5475 mg/kg body weight/day to males and 625, 1380, 2680 or 5200 mg/kg body weight/day to females) for 14 weeks. Mean body weights in the three highest dose levels and feed consumption at the two highest doses had significantly decreased. Deaths occurred at 2550 and 5475 mg/kg/day doses. 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 at the two highest dose levels. The NOAEL (~650 mg/kg bodyweight/day) was identified as 4100 ppm and was selected as the top dose for the 2-year chronic study (Johnson et al., 1998; NTP, 2003; Hooth et al., 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 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 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, 1958).

5.3. Chronic toxicity

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

Male and female F344/N rats were fed diets containing 1000, 2100 or 4100 ppm microencapsulated *trans*-cinnamaldehyde (~50, 100 or 200 mg/kg bodyweight per day) for 2 years (NTP, 2003). 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. The NOAEL was identified as 200 mg/kg bodyweight per day. 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.

Male and female $B6C3F_1$ mice were fed diets containing 1000, 2100 or 4100 ppm microencapsulated *trans*-cinnamaldehyde (~125, 270 or 550 mg/kg) for 2 years (NTP, 2003). 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. The NOAEL was identified as 550 mg/kg/bodyweight per day.

5.4. Mutagenicity and genotoxicity

5.4.1. Bacterial studies (Table 4)

In Ames studies with and without S9 activation using *S. typhimurium* strains TA98, T100, TA102, TA1535 and TA1537, 3-phenyl-1-propanol at 15–5000 μg/plate in DMSO, was negative in the presence of S9 mix the test material was bacteriotoxic towards strain TA102 at 5000 μg/plate. At the dose levels tested, the test material did not induce a significant increase in the mutation frequency of the tester strains in the presence and absence of a metabolic activation system (RIFM, 2002).

5.4.2. Mammalian studies

In addition to a negative Ames test conducted on 3-phenyl-1-propanol, in-vivo and in-vitro tests in mice and rats have been carried out with the parent compound cinnamaldehyde, cinnamyl alcohol and cinnamic acid. These tests included:

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). 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). 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).

Negative results were obtained with cinnamaldehyde in a 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).

In mammalian test systems, there was no evidence of an increase in unscheduled DNA synthesis in hepatocytes when rats were administered 1000 mg cinnamaldehyde/kg/bodyweight by oral gavage (Mirsalis et al., 1989). 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 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. The authors (Mereto et al., 1994) acknowledged that positive finding was due to the gavage administration of large bolus doses of the reactive aldehyde with high exposure to the stomach and liver and they concluded that the data did not justify classification of cinnamaldehyde as clastogenic for gastric mucosa.

After an in depth review of all available data which included studies summarized above and based on a weight of evidence evaluation of all genotoxicity studies of the parent compounds cinnamaldehyde cinnamyl alcohol and cinnamic acid, it has been determined that the cinnamyl phenyl propyl materials would have no significant potential to produce genotoxic effects under their current conditions of use as fragrance ingredients.

5.5. Carcinogenicity

There are no definitive long term studies that directly evaluate the carcinogenicity of cinnamyl propyl compounds. However, carcinogenicity studies conducted with cinnamaldehyde and cinnamyl alcohol provide a basis for the estimation of the carcinogenic potential of the group.

trans-Cinnamaldehyde has been evaluated by the National Toxicology Program (NTP, 2003) in a 2-year assay feeding microencapsulated cinnamaldehyde to rats and mice at dose levels of 50, 100 or 200 mg/kg body weight/day and 125, 270 and 550 mg/kg body weight/day, respectively. Under the conditions of this 2-year assay, the NTP concluded that there was no evidence of carcinogenic activity of *trans*-cinnamaldehyde in rats or mice. No significant carcinogenic effects (Wiseman et al., 1987) were produced by cinnamaldehyde when it was evaluated for hepatocarcinogenic potential in B6C3F1 mice that had received intraperitoneal injections of cinnamaldehyde once a week for 4 weeks (total cumulative dose 0.0006 g). While hemangiosarcomas were observed in three treated mice in this study, they were also observed in two control animals. Therefore, the authors concluded that no significant carcinogenic effects were produced by cinnamaldehyde in this model. In addition, both cinnamyl alcohol (total cumulative intraperitoneal doses were 1.4 and 7.0 g/kg body weight) and cinnamaldehyde (total cumulative intraperitoneal doses 0.8 and 4.0 g/kg) did

not induce primary lung tumors in female A/He mice under the conditions of the test (Stoner et al., 1973).

5.6. Reproductive toxicity

There are no reproductive studies on cinnamyl phenyl propyl materials. However, the developmental toxicity studies conducted in rats and mice on cinnamyl alcohol, cinnamaldehyde and cinnamic acid that showed that these materials do not possess any significant potential for developmental effects under current conditions of use as fragrance ingredients (Zaitsev and Maganova, 1975; Hardin et al., 1987; Mantovani et al., 1989).

Groups of 14–15 female rats were orally administered 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 at 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 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).

5.7. Skin irritation

5.7.1. Human studies (Table 4)

Tests of the majority of the cinnamyl phenyl propyl materials did not result in any irritation. In the induction phase of a Human Repeated Insult Patch Test (HRIPT), no irritation was observed to 3-phenyl-1-propanol at 4% in petrolatum (RIFM, 1971b). Likewise, in a 24-h pre-test for a human maximization test, no irritation was noted for 3-phenylpropyl cinnamate at 4% and 3-phenylpropyl isobutyrate at 8% in petrolatum (RIFM, 1975b, 1976b).

5.7.2. Animal studies (Table 5)

Mild to moderate irritation was observed with 3-phenylpropyl isobutyrate and 3-phenylpropyl cinnamate in a dermal LD50 study in rabbits (RIFM, 1972a, 1975a). Moderate to severe irritation was observed with 3-phenyl-1-propanol in a dermal LD50 study and in a 24-h occluded test in rabbits (RIFM, 1976a, 1971a).

5.8. Mucous membrane (eye) irritation

No data are available on these materials.

5.9. Skin sensitization

5.9.1. Human studies (Tables 6 and 7)

The cinnamyl phenylpropyl materials did not produce any sensitization reactions. 3-Phenyl-1-propanol and 3-phenylpropyl isobutyrate both tested at 8% in petrolatum in human maximization tests did not result in any sensitization (RIFM 1975b, 1976b). Likewise in a HRIPT, 3-phenyl-1-propanol at 4% in petrolatum did not produce any sensitization (RIFM, 1971b).

Elicitation studies with dermatitis patients have been reported on one cinnamyl phenyl propyl material. In a multicenter study, 218 fragrance sensitive patients were patch tested with various fragrance materials. Reactions (0.9%) were observed with 3-phenyl-1-propanol at 5% in petrolatum (Larsen et al., 2002). No reactions were observed to 3-phenyl-1-propanol in a base cream or 99% ethanol in 82 patients (Takenaka et al., 1986).

5.10. Phototoxicity and photoallergy (Table 8)

UV spectra have been obtained for 3 materials (3-phenyl-1-propanol; 3-phenylpropyl cinnamate; 3-phenylpropyl isobutyrate). They all absorbed UV light peaking in the UVC range (<290 nm; peaking in the range of 245–278 nm) with very minor absorption in UVB light (290–320 nm). In general, they did not significantly absorb UVB light (290–320; see Table 8). In addition, 1% cinnamaldehyde and 20% cinnamic acid were evaluated for phototoxicity and photoallergy in guinea pigs and showed no potential for phototoxic or photoallergic activity (RIFM, 2003). 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). Based on these data, it is not expected that the cinnamyl phenylpropyl materials would have the potential to elicit phototoxic or photoallergic effects.

6. Conclusion

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 phenyl propyl materials have a low order of toxicity by the oral and dermal routes 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 the available mutagenicity and genotoxicity studies on conducted on the parent compounds cinnamaldehyde, cinnamyl alcohol and cinnamic acid, it has been determined that the cinnamyl phenyl propyl materials have no significant potential to produce genotoxic effects.
- The cinnamyl phenyl propyl materials follow the same metabolic pathway as its parent compounds. The metabolic fate of cinnamyl alcohol, cinnamaldehyde and cinnamic acid is well known in that the alcohol is converted to the aldehyde which is further metabolized to the acid. Toxic or persistent metabolites are not formed.
- While, IFRA (IFRA, 2007) has established standards on cinnamaldehyde and cinnamyl alcohol using a Quantitative Risk Assessment (QRA) for dermal sensitization; no sensitization was observed with 3-phenyl-1-propanol or 3-phenylpropyl cinnamate or 3-phenylpropyl isobutyrate or in the other structurally related compounds tested. The weight of evidence supports the conclusion that the cinnamyl phenyl propyl materials present no significant risk of sensitization under the recommended

current conditions of use as fragrance ingredients. However, for those individuals who are already sensitized, there is a possibility that an elicitation reaction may occur.

- Phototoxic and photoallergic effects have not been evaluated in humans, but based on the UV spectra data and phototoxicity and photoallergy studies conducted with its parent materials cinnamaldehyde and cinnamic acid (Bickers et al., 2005), cinnamyl phenyl propyl materials are not expected to show any phototoxic or photoallergic activity under the current conditions of use as a fragrance material.
- 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 0.0280 mg/kg for 3-phenylpropyl cinnamate and 0.0204 mg/kg for 3-phenyl-1-propanol based on the most conservative estimate of 100% dermal absorption
- Based on the above maximum exposure considerations, and using the NOAEL of 200 mg/kg per day from the oral chronic study in rats with *trans*-cinnamaldehyde, the margin of safety for systemic exposure of humans to 3-phenylpropyl cinnamate and 3-phenyl-1-propanol when used as fragrance ingredients exceeds 7000 times the maximum daily exposure for 3-phenylpropyl cinnamate (200 mg/kg/day ÷ 0.0280 mg/kg/day = 7143); 9000 times the maximum daily exposure for 3-phenyl-1-propanol (200 mg/kg/day ÷ 0.0204 mg/kg/day = 9804).

Conflict of Interest

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

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