PERGAMON

Food and Chemical Toxicology 41 (2003) 919–942

Food and Chemical Toxicology

www.elsevier.com/locate/foodchemtox

A toxicologic and dermatologic assessment of linalool and related esters when used as fragrance ingredients☆

The RIFM Expert Panel

D. Bickers[a], P. Calow[b], H. Greim[c], J.M. Hanifin[d], A.E. Rogers[e], J.H. Saurat[f], I.G. Sipes[g], R.L. Smith[h], H. Tagami[i]

[a]*College of Physicians and Surgeons of Columbia University, Department of Dermatology, 161 Fort Washington Avenue, New York, NY 10032, USA*
[b]*The University of Sheffield, Department of Animal and Plant Sciences, Alfred Denny Building, Western Bank, Sheffield S10 2TN, UK*
[c]*Institute of Toxicology and Environmental Hygiene, Technical University of Munich, Hohenbachernstrasse 15-17, D-85354 Freising, Germany*
[d]*Oregon Health Sciences University, Dept. of Dermatology L468, 3181 SW Sam Jackson Park Road, Portland, Oregon 97201-3098, USA*
[e]*Boston University School of Medicine, Department of Pathology and Laboratory Medicine, 80 E. Concord Street, Boston, MA 02118-2394, USA*
[f]*University Hospital Geneva, Department of Dermatology, CH-1211 Geneva 14, Switzerland*
[g]*University of Arizona, Health Sciences Center, College of Pharmacy, 1703 East Mable Street, Tucson, AZ 85721, USA*
[h]*Imperial College of Science, Technology & Medicine, Division of Biomedical Sciences/Molecular Toxicology Section, Alexander Fleming Building, South Kensington, London SW7 2AZ, UK*
[i]*Tohoku University School of Medicine, 1-1 Seiryo-machi, Aoba-ku Sendai 980, Japan*

Contents

☆ All correspondence should be addressed to A.M. Api, RIFM, 50 Tice Blvd, Woodcliff Lake, NJ 07677, USA. Tel.: +1-201-689-8089; fax: +1-201-689-8090.
E-mail address: amapi@rifm.org (A.M. Api).

0278-6915/03/$ - see front matter
doi:10.1016/S0278-6915(03)00016-4

1. Chemical identity and exposure

This report summarizes scientific data relevant to the assessment of the unsaturated tertiary alcohol, linalool, and ten related substances (see Fig. 1 and Table 1). These substances are used as fragrance and in some cases flavor 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 all published reports including complete bibliographies.

The linalyl esters were included in this report because they would be expected to be converted by hydrolysis, to the principle substance, linalool, both in the gastrointestinal tract and by tissue hydrolases after absorption.

In the United States, the regulatory status of these 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 2635, 2636, 2638, 2639, 2640, 2641, 2642, 2643, 2645, 2646, 3501] by the Flavor and Extract Manufacturers Association (FEMA, 1965, 1977). These materials were also included in the Council of Europe's list of substances [Numbers 61, 203, 276, 298, 318, 329, 347, 411, 449, 654, 655] which may be used in foodstuffs (Council of Europe, 1992). Finally, the international Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1999) has evaluated most of these materials (all except phenylacetate), and found them to have no safety concerns based on current levels of intake as food flavors.

Nine of the eleven substances have been reported as common components of food occurring mainly in a wide variety of fruits, fruit peels, fruit juices, vegetables, and spices in varying concentrations. For example, concentrations of 15,100–227,200 ppm linalool in laurel (Laurus nobilis L.), 492,000–733,000 ppm linalool in coriander seed, and 1,900–776,000 ppm linalyl acetate in clary sage have been reported (TNO, 1994). The annual worldwide use of linalool and linalyl acetate in fragrances is >1000 metric tons (see Table 2). The annual worldwide use of the other linalyl esters range from a low of <0.1 metric tons for linalyl hexanoate to a high of 10 metric tons for linalyl cinnamate (see Table 2). This report uses relevant data available by different routes of exposure, but emphasizes the assessment for use of linalool and linalyl esters as fragrance ingredients.

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 sensitization 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 linalool from ten types of cosmetic products (body lotion, face cream, eau de toilette, fragrance cream, anti-perspirant, shampoo, bath products, shower gel, toilet soap and hair spray) using an average 97.5 percentile concentration of 12.7% is calculated as 0.324 mg/kg/day (IFRA, 1998). The calculated exposures for the

linalyl esters range from 0.026 mg/kg/day for linalyl isovalerate to 0.331 mg/kg/day for linalyl acetate (IFRA, 1998) (see Table 2). For consideration of potential sensitization the exposure is calculated as a percent concentration used on the skin. Thus exposure to linalool used in fine fragrance products is reported as 4.3% based on the use of 20% of the fragrance mixture in the fine fragrance consumer product (IFRA, 1998). The comparable exposures for the linalyl esters range from 0.4% for linalyl isovalerate to 4.6% for linalyl acetate (IFRA, 1998) (see Table 2). Exposure 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

There are no definitive percutaneous absorption studies on any of the substances in this summary. Therefore, for this assessment, the conservative assumption of 100% absorption is taken.

2.1.2. Pharmacokinetics

2.1.2.1. Dermal studies. Blood levels of linalool and linalyl acetate were followed for 90 min after the use of a massage oil which contained lavender oil and peanut oil in a 2:98 ratio. The lavender oil contained approximately 25% linalool and approximately 30% linalyl

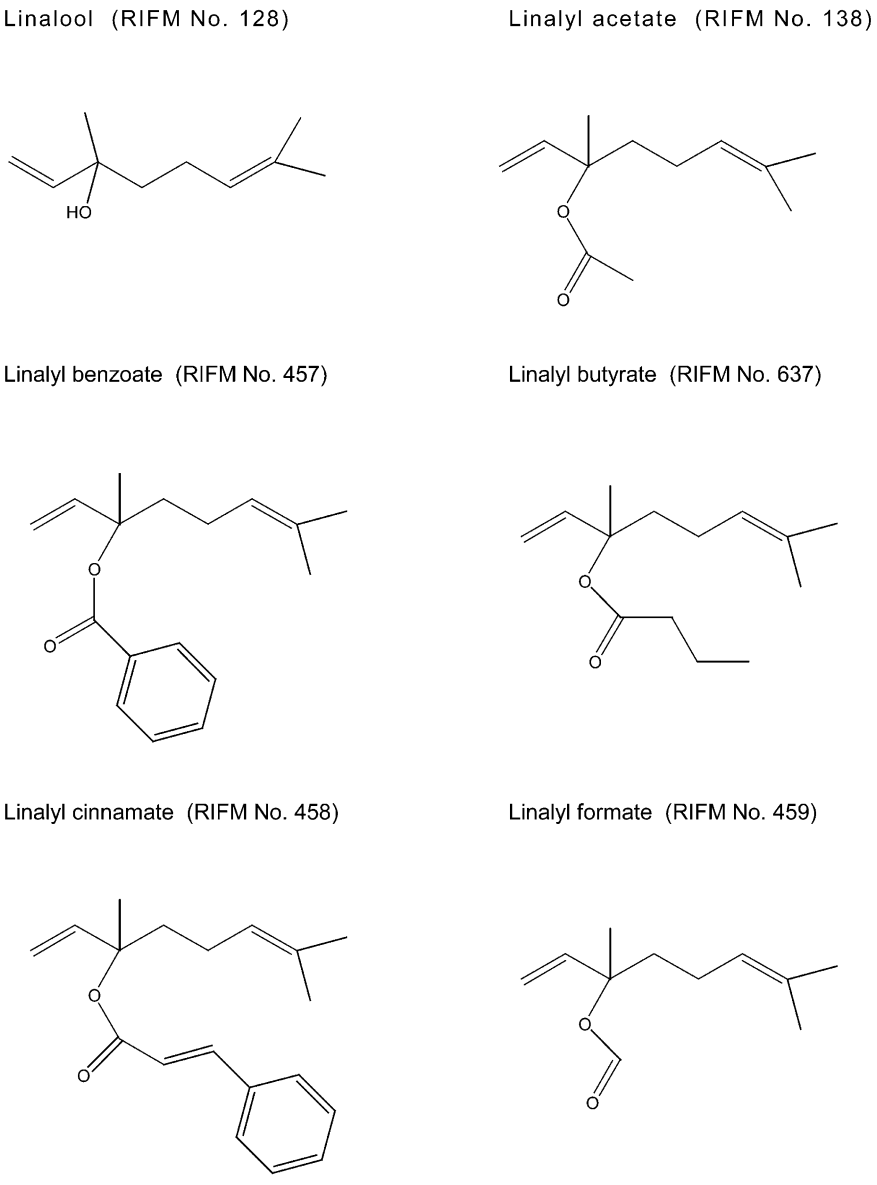
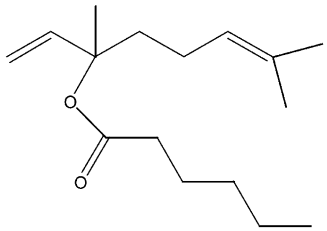
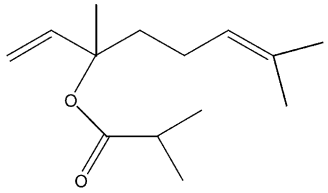


Fig. 1. Linalool and related esters.

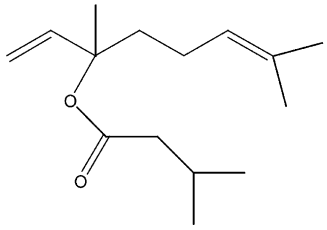
Linalyl hexanoate (RIFM No. 5114)



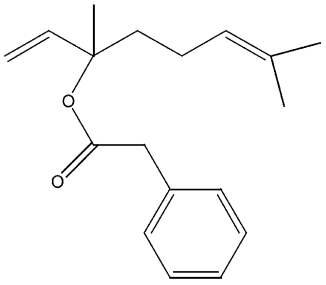
Linalyl isobutyrate (RIFM No. 508)



Linalyl isovalerate (RIFM No. 638)



Linalyl phenylacetate (RIFM No. 550)



Linalyl propionate (RIFM No. 433)

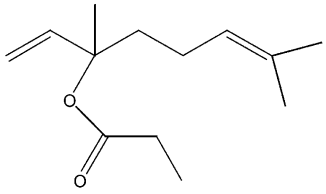


Fig. 1 (*continued*).

acetate. A 1500 mg sample of the lavender oil was gently massaged for 10 min into a 376 cm^2 area on the abdomen of a 60 kilogram male volunteer. Trace amounts of both linalool and linalyl acetate were detected in the blood 5 min after the massage. Peak plasma concentrations were reached by 19 minutes with a mean plasma concentration of 100 ng/ml for linalool and 121 ng/ml for linalyl acetate. Most of the linalool and linalyl acetate had disappeared from the blood in 90 min with biological half lives of approximately 14 min for both linalool and linalyl acetate (Jager et al., 1992).

2.1.2.2. Inhalation studies. After a 1-h inhalation exposure to 5 mg/l linalool, serum linalool levels in mice were 7–9 ng/ml, and after a 1-h inhalation exposure to 5 mg/l linalyl acetate, serum linalyl acetate levels were 1–2 ng/ml and serum linalool levels were 4-5 ng/ml (Jirovetz et al., 1991). In separate experiments, groups of 4 mice were exposed to an atmosphere containing 5 mg/l linalool or 5 mg/l linalyl acetate or 5 mg/l lavender oil (which contained 37.3% linalool and 41.6% linalyl acetate). After a 1-h exposure to linalool, the serum linalool levels were 8 ng/ml; after linalyl acetate inhalation, the serum linalool levels were 4 ng/ml and the serum linalyl acetate levels were 1 ng/ml; after lavender oil inhalation, the serum linalool levels were 3 ng/ml and the serum linalyl acetate levels were 11 ng/ml (Buchbauer et al., 1991; Jirovetz et al., 1990). The addition of β-glucuronidase to these one hour samples resulted in an increase of serum linalool to 12 ng/ml after linalool inhalation; to 6 ng/ml after linalyl acetate inhalation; and to 4 ng/ml after lavender oil inhalation.

Serum linalool levels after a one hour exposure to linalool or linalyl acetate were 7–9 ng/ml and 4–5 ng/ml,

Table 1
Material identity

Compound	CAS number	Synonyms
Linalool	78-70-6	2,6-Dimethyl-2,7-octadien-6-ol 3,7-Dimethyl-1,6-octadien-3-ol Licareol Linalol
Linalyl acetate	115-95-7	Bergamol 3,7-Dimethyl-1,6-octadien-3-yl acetate
Linalyl benzoate	126-64-7	3,7-Dimethyl-1,6-octadien-3-yl benzoate
Linalyl butyrate	78-36-4	Butanoic acid, 1-ethenyl-1,5-dimethyl-4-hexenyl ester 3,7-Dimethyl-1,6-octadien-3-yl butanoate 3,7-Dimethyl-1,6-octadien-3-yl butyrate Linalool butanoate
Linalyl cinnamate	78-37-5	Cinnamic acid, linalyl ester 3,7-Dimethyl-1,6-octadien-3-yl cinnamate 3,7-Dimethyl-1,6-octadien-3-yl β-phenylacrylate 3,7-Dimethyl-1,6-octadien-3-yl 3-phenylpropenoate Linalyl 3-phenylpropenoate 2-Propenoic acid, 3-phenyl-, 1-ethenyl-1,5-dimethyl-4-hexenyl ester
Linalyl formate	115-99-1	3,7-Dimethyl-1,6-octadien-3-yl formate
Linalyl hexanoate	7779-23-9	3,7-Dimethyl-1,6-octadien-3-yl hexanoate 1,5-Dimethyl-1-vinyl hex-4-enyl hexanoate Hexanoic acid, 1-ethenyl-1,5-dimethyl-4-hexenyl ester Linalyl caproate Linalyl capronate
Linalyl isobutyrate	78-35-3	3,7-Dimethyl-1,6-octadien-3-yl isobutanoate 3,7-Dimethyl-1,6-octadien-3-yl 2 methylpropanoate 1,5-Dimethyl-1-vinyl-4-hexenyl isobutyrate Isobutyric acid, 1,5-dimethyl-1-vinyl-4-hexenyl ester Linalool 2-methylpropanoate Propanoic acid, 2-methyl-, 1-ethenyl-1,5-dimethyl-4-hexenyl ester
Linalyl isovalerate	1118-27-0	3,7-Dimethyl-1,6-octadien-3-yl isovalerate 3,7-Dimethyl-1,6-octadien-3-yl 3-methylbutanoate Isovaleric acid, 3,7-dimethyl-1,6-octadien-3-yl ester Linalyl isopentanoate Linalyl isovalerianate Linalyl 3-methylbutanoate
Linalyl phenylacetate	7143-69-3	Benzeneacetic acid, 1-ethenyl-1,5-dimethyl-4-hexenyl ester 3,7-Dimethyl-1,6-octadien-3-yl phenylacetate Linalyl α-toluate
Linalyl propionate	144-39-8	3,7-Dimethyl-1,6-octadien-3-yl propanoate 3,7-Dimethyl-1,6-octadien-3-yl propionate Linalool propanoate

Table 2
Volume of use and dermal exposure

Material	RIFM number	Worldwide[a] metric tons	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin level[b,c]
Linalool	128	>1000	0.32	4.30%
Linalyl acetate	138	>1000	0.33	4.60%
Linalyl benzoate	457	<0.1	0.1	1.50%
Linalyl butyrate	637	0.1–1	0.03	0.46%
Linalyl cinnamate	458	0.1–1	0.03	0.42%
Linalyl formate	459	1–10	0.03	0.48%
Linalyl hexanoate	5114	<0.1	0.03	0.46%
Linalyl isobutyrate	508	1–10	0.03	0.48%
Linalyl isovalerate	638	<0.1	0.03	0.40%
Linalyl phenylacetate	550	0.1–1	0.03	0.46%
Linalyl propionate	433	1–10	0.05	0.82%

[a] 1995/1996 Volume of use survey.
[b] Skin levels were based on the assumption that the fragrance mixture is used at 20% in a consumer product.
[c] 1998/1999 IFRA Use level survey.

respectively. Serum linalyl acetate levels were 1–2 ng/ml after a 1 h exposure to linalyl acetate.

2.1.3. Metabolism

In general, esters are hydrolyzed to their corresponding alcohol and carboxylic acid. Hydrolysis is catalyzed by carboxylesterases or esterases (Satoh, 1987; JECFA, 1999), the most important of which are the so called β-esterases which occur in most tissues, but particularly the liver. In mammals, these enzymes occur in most tissues throughout the body (Anders, 1989; Satoh, 1987; JECFA, 1999) but predominate in the hepatocytes (Satoh, 1987; JECFA, 1999). Linalyl esters are expected to be hydrolyzed in humans to yield linalool and the corresponding carboxylic acid.

Tertiary alcohols such as linalool are metabolized primarily through conjugation with glucuronic acid and are excreted in the urine and to a lesser extent feces (Williams, 1959; Ventura et al., 1985; Parke et al., 1974; Eder et al., 1982a; JECFA, 1999). Alkyl or alkenyl substituents may undergo oxidation to form polar metabolites that may also be excreted free or in the conjugated form. Oxidation is mediated by cytochrome P-450 dependant mono-oxygenases (Chadha and Madyastha, 1984; JECFA, 1999).

The carboxylic acids formed by hydrolysis of the linalyl esters included in this summary are all known to be easily and rapidly metabolized. The linear saturated carboxylic acids are metabolized normally as fatty acids that undergo β-oxidation. Successive two-carbon units are removed from the carbonyl end with production from even numbered-carbon acids of acetyl CoA and from odd numbered-carbon acids of acetyl CoA and propionyl CoA. Acetyl CoA enters the citric acid cycle directly, or it reacts with propionyl CoA to form succinyl CoA, which also enters the citric acid cycle (Voet and Voet, 1990; JECFA, 1999). The branched-chain carboxylic acids from linalyl isovalerate and isobutyrate are similarly oxidized, but the end product is acetone. The carboxylic acids from linalyl benzoate and phenylacetate are conjugated and excreted. The cinnamic acid from linalyl cinnamate is conjugated and excreted, or metabolized to benzoic acid.

The metabolic fate of linalool has been studied in mammals (see Fig. 2). In rats, the majority (55%) of an orally administered ^{14}C-labelled dose of 500 mg/kg linalool was excreted in the urine as the glucuronic acid conjugate, while 23% of the dose was excreted in expired air, and 15% was excreted in the feces within 72 h of dose administration. Only 3% was detected in tissues after 72 h, with 0.5% in the liver, 0.6% in the gut, 0.8% in the skin and 1.2% in the skeletal muscle (Parke et al., 1974; JECFA, 1999). In a separate study, metabolites isolated from rat urine after daily oral administration of 800 mg/kg linalool for 20 days were 8-hydroxylinalool and 8-carboxylinalool. Cytochrome

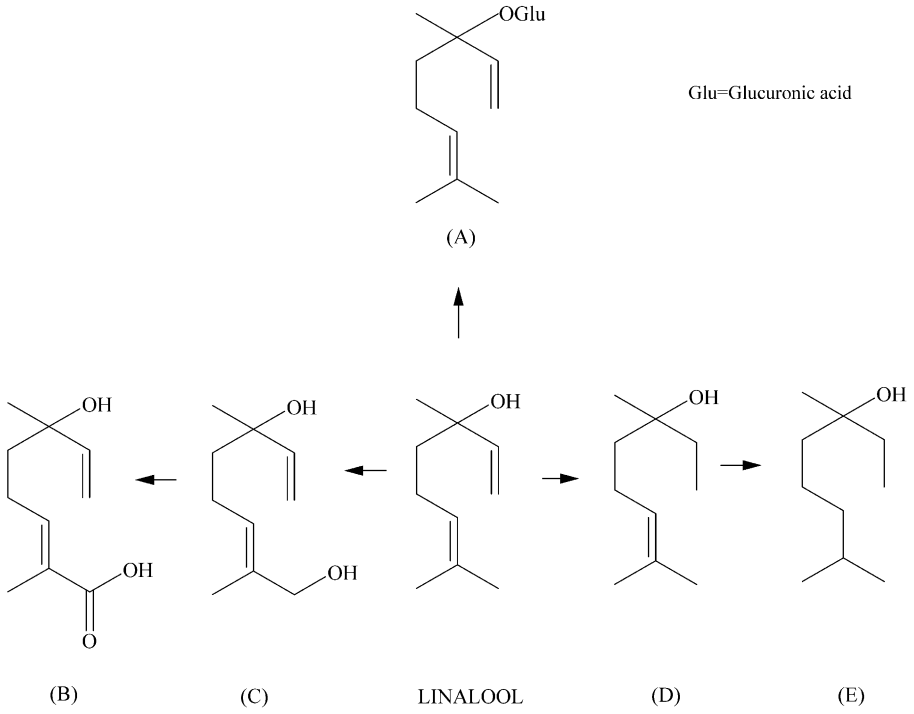


Fig. 2. Metabolism of linalool in mammals. These metabolites have been identified in the urine of rats after treatment with linalool by the oral route (JECFA, 1999). The major metabolite (A) was the glucuronic acid conjugate identified after a single dose. Metabolite B (8-carboxylinalool) and metabolite C (8-hydroxylinalool) were identified after treatment for 20 days. Metabolite D (dihydrolinalool) and metabolite E (tetrahydrolinalool) were identified after a single dose.

P-450 concentration in hepatic microsomes prepared from these rats was increased approximately 50% after three days, but the activity decreased to control values after six days (Chadha and Madyastha, 1984; JECFA, 1999). In addition, the concentration of cytochrome b_5 increased by 20% after three days of dosing but returned to control values after 6 days.

Incubation of linalool with rat hepatic microsomes results in the rapid oxidation of linalool by cytochrome P-450 (FEMA, 1998a; 1998b). Similarly, pulmonary microsomes obtained from rats pretreated with β-naphthoflavone convert linalool to 8-hydroxy linalool (Chadha and Madyastha, 1984). Linalool and its P-450 derived metabolites are converted to glucuronide conjugate by rat liver homogenates (FEMA, 1998a; 1998b).

In neutral gastric juice, linalyl acetate is slowly ($t_{1/2}=121$ min) hydrolyzed to a mixture of linalool and the ring-closed form, α-terpineol (see Fig. 3). In acidic artificial gastric juice, linalyl acetate is rapidly hydrolyzed ($t_{1/2}<5$ min) to yield linalool which rapidly rearranges into α-terpineol (FEMA, 1998a; 1998b; JECFA, 1999). Linalyl acetate was slowly hydrolyzed ($t_{1/2}=153$–198 min) in intestinal fluid with or without pancreatin. Linalyl acetate also hydrolyzed in homogenates of rat intestinal mucosa, blood, and liver, but at rates much slower than in acidic gastric juice (rate constant for hydrolysis $k=0.01$ to 0.0055 min^{-1} vs. >5 min^{-1} in gastric juice). Based on these observations it is concluded that linalyl acetate hydrolyzes in gastric juice to yield linalool which, to some extent, is rapidly ring-closed to yield α-terpineol (FEMA, 1998a; 1998b; JECFA, 1999). The other linalyl esters are also expected to be readily hydrolyzed to linalool and their corresponding carboxylic acids. Both linalool and α-terpineol may then be either conjugated and excreted or oxidized to more polar excretable metabolites (JECFA, 1999). Linalool was partly conjugated to glucuronic acid in mice exposed to an atmosphere containing 5 mg/l linalool (Jirovetz et al., 1990).

Biliary excretion of conjugated linalool was determined in male rats that received a single intraperitoneal dose of 20 mg linalool. More than 25% of the dose appeared exclusively in the form of polar conjugates in the bile within 6–11 h, principally in the first 4 h; no free linalool was detected (Parke et al., 1974).

3. Toxicological studies

3.1. Acute toxicity

Linalool and the linalyl esters have been evaluated for acute toxicity (see Tables 3A–3C). Rodent oral LD_{50} values have been reported for linalool and all of the linalyl esters. These range from 2200 mg/kg to 48,800 mg/kg. Dermal LD_{50} values in rabbits exceeding 5000 mg/kg have been reported for linalool and nine of the linalyl esters (data not available for linalyl hexanoate). Intraperitoneal LD_{50} values in mice and rats range from 200 mg/kg to 2864 mg/kg for linalool and linalyl acetate. In mice, subcutaneous and intramuscular LD_{50} values for linalool are 1470 mg/kg and 8000 mg/kg, respectively.

3.2. Subchronic toxicity

3.2.1. Dermal studies

The results of short-term and long-term studies with linalool and the linalyl esters are summarized in Table 4 and described below.

Linalool was applied to the skin of Wistar rats at dose levels of 125, 250, 500, 1000, 2000 or 4000 mg/kg/day for 29 consecutive days as a range-finding study for a 90-day study. Significant toxic signs observed were lethargy, ataxia and piloerection. Moderate to severe erythema was observed at all dose levels. Moderate eschar formation, with bleeding, scabbing, and cracked and peeling skin was also observed at all dose levels. Toxic signs and dermal irritation were dose-related. At necropsy, all animals were observed to have abnormalities in the treated skin area including redness, flaking, scaling and edema. Gross abnormalities of the liver,

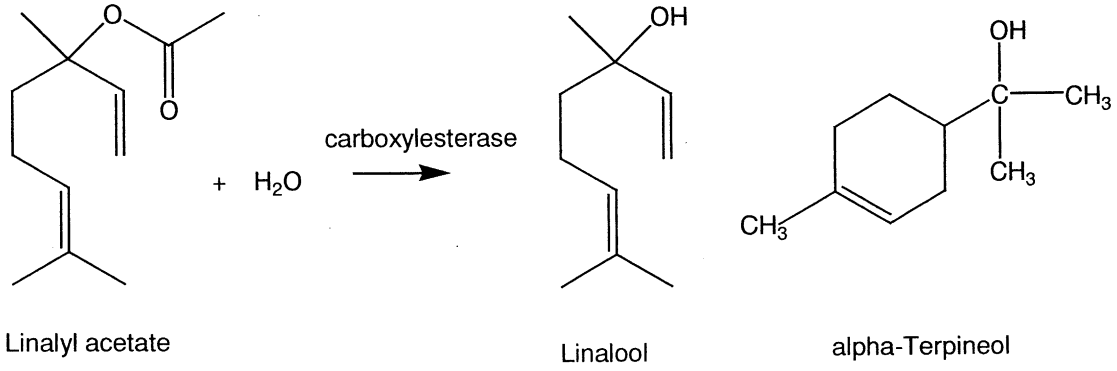


Fig. 3. Hydrolysis of linalyl acetate. In neutral gastric juice, linalyl acetate is slowly hydrolyzed to a mixture of linalool and alpha-terpineol. In acidic artificial gastric juice, linalyl acetate is rapidly hydrolyzed to yield linalool which rapidly rearranges into alpha-terpineol.

Table 3A
Acute oral toxicity studies

Material	Species	No. animals/ dose group	LD_{50}[a]	References
Linalool	Rats	10 (5/sex)	2790 mg/kg (95% C.I. 2440–3180 mg/kg)	Jenner et al., 1964
Linalool	Mice	10 male & female	3920 mg/kg±300 mg/kg	RIFM, 1967a
Linalool	Mice	8 (4/sex)	3500 mg/kg	RIFM, 1992
Linalool	Mice	8 (4/sex)	2200 mg/kg (10% aqueous emulsion in gum arabic)	RIFM, 1992
Linalyl acetate	Rats	Not specified	10,000 mg/kg/bodyweight (30% aqueous emulsion in gum tragacanth)	RIFM, 1969
Linalyl acetate	Rats	10 (5/sex)	14,550 mg/kg (C.I. 12,300–17,170 mg/kg)	Jenner et al., 1964
Linalyl acetate	Mice	Not specified	13,360 mg/kg (95% C.I. 11,920–15,000 mg/kg	Jenner et al., 1964
Linalyl acetate	Mice	5 (males only)	13,540 mg/kg±900 mg/kg	RIFM, 1967a
Linalyl benzoate	Rats	10	>5000 mg/kg	RIFM, 1973a
Linalyl benzoate	Mice	5 (males only)	9400 mg/kg±390 mg/kg	RIFM, 1967a
Linalyl butyrate	Rats	10	>5000 mg/kg	RIFM, 1975a
Linalyl butyrate	Mice	5 (males only)	>8900 mg/kg	RIFM, 1967a
Linalyl cinnamate	Rats	10 (5/sex)	9960 mg/kg (C.I. 8230–12,050 mg/kg)	Jenner et al., 1964
Linalyl cinnamate	Mice	10	>39,040 mg/kg	RIFM, 1967a
Linalyl formate	Rats	10	>5000 mg/kg	RIFM, 1973b
Linalyl formate	Mice	5 (males only)	5490 mg/kg±730 mg/kg	RIFM, 1967a
Linalyl hexanoate	Mice	10 male & female	37,870 mg/kg±1940 mg/kg	RIFM, 1967b
Linalyl isobutyrate	Rats	10 (5/sex)	>36,300 mg/kg	Jenner et al., 1964
Linalyl isobutyrate	Mice	not specified	15,100 mg/kg (95% C.I. 12,330–18,500 mg/kg)	Jenner et al., 1964
Linalyl isobutyrate	Mice	5 (males only)	>17,700 mg/kg	RIFM, 1967a
Linalyl isovalerate	Rats	10	>5000 mg/kg	Jenner et al., 1964
Linalyl isovalerate	Mice	10	25,170 mg/kg±2650 mg/kg	RIFM, 1967a
Linalyl octanoate[b]	Mice	10 male & female	48,850 mg/kg±860 mg/kg	RIFM, 1967b
Linalyl phenylacetate	Rats	10	>5000 mg/kg	RIFM, 1974a
Linalyl phenylacetate	Mice	10	15,480 mg/kg±1930 mg/kg	RIFM, 1967a
Linalyl propionate	Rats	10	>5000 mg/kg	RIFM, 1973a
Linalyl propionate	Mice	5 (males only)	13,870 mg/kg±1790 mg/kg	RIFM, 1967a

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

Table 3B
Acute dermal toxicity studies

Material	Species	No. animals/ dose group	LD_{50}[a]	References
Linalool	Rabbits	3	5610 mg/kg (95% C.I. 3580–8370 mg/kg)	RIFM, 1970a
Linalyl acetate	Rabbits	3	>5000 mg/kg	RIFM, 1972
Linalyl benzoate	Rabbits	10	>5000 mg/kg	RIFM, 1973a
Linalyl butyrate	Rabbits	4	>5000 mg/kg	RIFM, 1975a
Linalyl cinnamate	Rabbits	10	>5000 mg/kg	RIFM, 1973a
Linalyl formate	Rabbits	10	>5000 mg/kg	RIFM, 1973b
Linalyl isobutyrate	Rabbits	10	>5000 mg/kg	RIFM, 1974a
Linalyl isovalerate	Rabbits	10	>5000 mg/kg	RIFM, 1975b
Linalyl phenylacetate	Rabbits	10	>5000 mg/kg	RIFM, 1974a
Linalyl propionate	Rabbits	10	>5000 mg/kg	RIFM, 1973a

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

kidneys and intestines were observed. Epithelial hyperplasia of the skin was observed upon histopathological evaluation. Histopathology revealed very slight to slight changes in the liver and kidneys but no relationship to treatment was detected. Based upon these results, the dose levels selected for the 90-day study were 250, 1000 and 4000 mg/kg (RIFM, 1979).

Linalool was administered once daily in doses of 250, 1000 or 4000 mg/kg/day for 13 weeks to the clipped and shaved back of male and female Sprague Dawley rats (20/sex/dose). Nine females and 2 males died at the highest dose level, and these deaths were attributed to treatment. Sporadic and transient lethargy was observed at the two lower dose levels; extreme lethargy was observed in females at the highest dose level. Slight erythema was observed in all groups which cleared after 3 weeks at the lowest dose and after 6 weeks at the mid-dose level but persisted to week 13 at the highest dose.

Table 3C
Acute miscellaneous toxicity studies

Material	Route	Species	No. animals/ dose group	LD_{50}[a]	References
Linalool	sc	Mice	5	1470 mg/kg ± 140 mg/kg	Nozawa, 1952
Linalool	ip	Rats	Unknown	307 mg/kg (95% C.I. 233–405 mg/kg) in isotonic sodium chloride with Tween 80	Atanassova-Shopova et al., 1973
Linalool	ip	Rats	5/sex	687 mg/kg (95% C.I. 513–920 mg/kg)	RIFM, 1984a
Linalool	ip	Mice	Unknown	340 mg/kg (95% C.I. 267–510 mg/kg) in isotonic sodium chloride with Tween 80	Atanassova-Shopova et al., 1973
Linalool	ip	Mice	10 male	459 mg/kg (297–782 mg/kg)	Elisabetsky et al., 1995
Linalool	ip	Mice	8 (4/sex)	200 mg/kg as an emulsion in 0.5% HV carboxymethyl cellulose & 0.4% Tween 80	RIFM, 1992
Linalool	ip	Mice	8 (4/sex)	1200 mg/kg in peanut oil	RIFM, 1992
Linalool	im	Mice	10	8000 mg/kg	Northover and Verghese, 1962
Linalyl acetate	ip	Mice	Not specified	800 mg/kg bodyweight (30% aqueous emulsion in gum tragacanth)	RIFM, 1969
Linalyl acetate	ip	Rats	10 (5/sex)	2864 mg/kg (95% C.I. 2414–3399 mg/kg)	RIFM, 1986b

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

Body weights in high-dose males and in mid-dose females were depressed. Increased liver weights were observed in males and females at the high dose. Increased kidney weights were also observed in females at the highest dose level. Slight to moderate epithelial hyperplasia of the skin was observed in all animals at the highest dose level. No histopathologic abnormalities were observed in animals in the liver, adrenals, brain, heart, kidneys, liver, thyroids, mesenteric lymph node, spinal cord, testes, ovaries, spleen, urinary bladder, sternal bone marrow, pituitaries or sciatic nerve as compared to control animals. Hematology, clinical chemistry and urinalysis findings were normal. The percutaneous exposure of linalool in the rat for 90 days produced no changes at the lowest dose, 250 mg/kg, except for transient erythema and depressed activity. At 1000 mg/kg it produced decreased weight gain, decreased activity and erythema (RIFM, 1980).

3.2.2. Oral studies

In a study to assess general toxicity in an immunotoxicity assay, no adverse effects were reported when female B6C3F1 mice were given 94, 188 or 375 mg/kg linalool via stomach tube for five days (Gaworski et al., 1994; Vollmuth et al., 1989). In a 90-day study, a 50/50 mixture of 50 mg linalool and 50 mg citronellol was added to the diet of rats at levels calculated to result in an average daily intake of 100 mg/kg of both linalool and citronellol combined. A slight retardation of growth was observed only in the males. Measurements of hematology, clinical chemistry and urinalysis at weeks 6 and 12 showed no significant differences between test and control groups. Histopathology revealed no dose-related lesions. The authors concluded that the slight retardation of growth observed in the males was biologically insignificant (RIFM, 1958a).

In a similar study, a mixture of linalyl isobutyrate, linalyl acetate and geranyl acetate was added to the diet of rats for 12 weeks at a total dose level of 100 mg/kg calculated to result in average daily intakes of 27.4 mg/kg, 24.2 mg/kg or 48.4 mg/kg, respectively. A slight retardation of growth was observed only in the females. Measurements of hematology, clinical chemistry, and urinalysis at weeks 6 and 12 showed no significant differences between test and control groups. Histopathology revealed no dose-related lesions. The slight retardation of growth observed in the females was associated with depressed food intake levels and depressed efficiency of food utilization, which may be attributed to poor palatability (RIFM, 1958b).

In 2 separate studies, Osborne-Mendel rats (10/sex/dose) received a dietary admixture containing linalyl cinnamate or linalyl isobutyrate at dose levels of 0, 1000, 2500 or 10,000 ppm for 17–18 weeks. These levels were calculated to provide estimated daily intakes of 0, 50, 125 or 500 mg/kg/bodyweight/day. Body weight, hematology, and gross pathology were performed on all test animals, and a detailed microscopic examination was performed on 6 or 8 animals in the high dose group only. There were no deaths and no adverse clinical signs were observed. There were no effects on growth or hematology and no macroscopic or microscopic changes in the tissues (Hagan et al., 1967).

The acid products that are formed upon hydrolysis of linalyl esters are without significant toxicity. Most of these acids are endogenous molecules. Benzoic acid, which is formed from hydrolysis of linalyl benzoate, has been shown to have a chronic NOAEL of 1% (approximately equivalent to 500 mg/kg/day) in the diet of rats (Kieckebush and Lang, 1960) and has a JECFA ADI of 0-5 mg/kg bodyweight (JECFA, 1997). While cinnamic acid, which is formed from linalyl cinnamate, has not been directly studied in long term tests, cinnamaldehyde, which is readily converted to cinnamic acid, has been shown to have a NOAEL of 1.25% (approxi-

Table 4
Oral and dermal subchronic toxicity studies

Material	Method	Dose[a]	Species	Results	References
Linalool	Dermal 29-day range finding study conducted to determine dose levels for a 90 day study	125, 250, 500, 1000, 2000 & 4000 mg/kg/day	Wistar albino rats (2/sex/dose)	One female in the 4000 mg/kg group died on day 26 and one male in the 250 mg/kg dose group died on day 7. Decreased body weight gain in males & females and elevated glucose & cholesterol mean values were observed at the highest dose level only. Dermal irritation and the following toxic signs were observed at all dose levels and were dose related: lethargy, ataxia, piloerection &, discomfort were observed. Moderate to severe erythema and slight to moderate edema were also observed. Bleeding, scabbing & moderate eschar were noted in 1 or more animals at each dose level. Alkaline phosphatase values were elevated in a dose related manner. Slight to moderate epithelial hyperplasia of the treated skin was observed at histopathology. Very slight to slight changes in the liver & kidney were also observed at histopathology but were not considered to be treatment related.	RIFM, 1979
Linalool	Dermal 13-week study	4000 mg/kg/day	40 male and female Sprague Dawley rats (20/sex)	11 deaths (9 female & 2 males); food consumption and body weight depressed in males; liver weight increased in both males & females; increased kidney weight in females; slight to moderate epithelial hyperplasia; slight erythema; depressed activity; lethargy in females	RIFM, 1980
Linalool	Dermal 13-week study	1000 mg/kg/day	40 male and female Sprague Dawley rats (20/sex)	1 female died but this death was not considered to be treatment related; Body weight depressed in females; Slight erythema was observed which cleared after 6 weeks; depressed activity was also observed	RIFM, 1980
Linalool	Dermal 13-week study	250 mg/kg/day	40 male and female Sprague Dawley rats (20/sex)	2 females died but these deaths were not considered to be treatment related; mean testes weight depressed but this was not considered to be treatment related; Slight erythema was observed which cleared after 3 weeks; depressed activity was also observed	RIFM, 1980
Linalool	Oral (food) 90-day study	100 mg/kg (the test material was a mixture of 2 flavoring materials; 50 mg/kg linalool and 50 mg/kg citronellol)	20 male and female rats (10/sex)	Food intake and weight gain were significantly depressed in males; however, since the EFUs were not significantly altered, this was attributed to poor palatability	RIFM, 1958a
Linalyl acetate	Oral (food) 90-day study	100 mg/kg (the test material was a mixture of 3 flavoring materials; 24.2 mg/kg linalyl acetate, 27.5 mg/kg linalyl isobutyrate and 48.4 mg/kg geranyl acetate)	20 male and female rats (10/sex)	Food intake and weight gain slightly depressed in females	RIFM, 1958b
Linalyl cinnamate	Oral (food) 17-week study	50, 125 & 500 mg/kg/day	Male and female Osborne-Mendel rats (10/sex/dose)	No effects	Hagan et al., 1967
Linalyl isobutyrate	Oral (food) 18-week study	50, 125 & 500 mg/kg/day	Male and female Osborne-Mendel rats (10/sex/dose)	No effects	Hagan et al., 1967
Linalyl isobutyrate	Oral (food) 90-day study	100 mg/kg (the test material was a mixture of 3 flavoring materials; 24.2 mg/kg linalyl acetate, 27.4 mg/kg linalyl isobutyrate and 48.4 mg/kg geranyl acetate)	20 male and female rats (10/sex)	Food intake and weight gain slightly depressed in females	RIFM, 1958b

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

mately 625 mg/kg/day) in a 13-week dietary study in mice (Johnson et al., 1998) and a NOAEL of 0.25% (approximately 125 mg/kg/day) in a 16-week dietary study in rats (Hagan et al., 1967). Phenylacetic acid which is formed from linalyl phenylacetate has also not been directly studied, however, phenylethyl alcohol, which is converted to phenylacetic acid, has been shown to have a NOAEL of 500 mg/kg/day in a 13 week dermal study in rats (Owston et al., 1981).

3.3. Mutagenicity and genotoxicity

Mutagenic and genotoxic testing has been performed on linalyl acetate and linalool. The results of these tests are summarized in Tables 5 and 6 and described below.

3.3.1. Bacterial studies

Linalool was inactive in *Salmonella typhimurium* strains TA92, TA94, TA98, TA100, TA1535, TA1537 and TA1538 with and without S9 metabolic activation (Eder et al., 1980; Eder et al., 1982a; Eder et al., 1982b; Heck et al., 1989; Ishidate et al., 1984; Lutz et al., 1980; RIFM, 1983a; Rockwell and Raw, 1979). Doses up to 25,000 μg/plate linalyl acetate were inactive in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA 1538 with and without S9 metabolic activation (Heck et al., 1989). When incubated with *Escherichia coli* strain WP2 uvrA (trp$^-$), doses of 0.125–1.0 mg/plate (approximately equivalent to 125–1000 μg/plate) linalool had no effect (Yoo, 1986).

The urinary metabolites of linalool were assayed for mutagenicity. The 24-h urine of two Sprague Dawley rats, following administration of 0.5 ml linalool by gavage, was incubated with *S. typhimurium* strains TA98 and TA100. Assays were conducted with the following samples: aliquot of 24-h urine (with and without metabolic activation), ether extract of 24-h urine (with and without metabolic activation), and aqueous phase of 24-h urine ether extract (with and without metabolic activation). Urine incubated with β-glucuronidase was also tested. All tests for mutagenicity were negative (Rockwell and Raw, 1979).

When incubated with *Bacillus subtilis* strains H17 (rec$^+$) and M45 (rec$^-$), linalool was negative at 17 μg/disk and linalyl acetate was negative at 18 μg/disk (Oda et al., 1979). However, Kuroda et al. (1984) reported that linalool produced questionable effects in *B. subtilis* strains H17 (rec$^+$) and M45 (rec$^-$) at the higher doses of 0.63–10 μl/disk (approximately equivalent to 630–10,000 μg/disk). Yoo (1986) reported positive effects at the high dose of 10 μl/disk (approximately equivalent to 10,000 μg/disk) linalool in *B. subtilis* strains H17 (rec$^+$) and M45 (rec$^-$).

Table 5
Mutagenicity and genotoxicity bacterial studies

Material	Test system in vitro	Species	Concentration[a]	Results	References
Linalool	Ames, (modified liquid suspension) with and without S9 activation	*S. typhimurium* TA100	10–3000 μg per 2 ml incubation volume	Negative	Eder et al., 1980; 1982a; 1982b; Lutz et al., 1980
Linalool	Ames with and without S9 activation	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100	5–10,000 μg/plate	Negative	RIFM, 1983a; Heck et al., 1989
Linalool	Ames with and without S9 activation	*S. typhimurium* TA92, TA1535, TA100, TA1537, TA94, TA98	Doses up to 1000 μg/plate	Negative	Ishidate et al., 1984
Linalool	Ames with and without S9 activation	*S. typhimurium* TA100, TA98	50–100,000 μg/plate	Negative	Rockwell and Raw, 1979
Linalool (0.5 ml undiluted linalool administered to rats by gavage, urine collected for a 24 hour period)	Ames with and without β-glucuronidase	*S. typhimurium* TA100, TA98	50–300 μl of 24 h direct urine samples	Negative	Rockwell and Raw, 1979
Linalool (0.5 ml undiluted linalool administered to rats by gavage, urine collected for a 24 hour period)	Ames with S9 activation	*S. typhimurium* TA100, TA98	ether extraction of 24 h urine samples (dose not specified)	Negative	Rockwell and Raw, 1979
Linalool (0.5 ml undiluted linalool administered to rats by gavage, urine collected for a 24 hour period)	Ames with and without β-glucuronidase	*S. typhimurium* TA100, TA98	50–300 μl of aqueous fraction of the ether extractions of 24 h urine samples	Negative	Rockwell and Raw, 1979
Linalool	Ames assay	*E. coli*	125–1000 μg/plate	Negative	Yoo, 1986
Linalool	Rec-assay, spore plate method	*B. subtilis* M45 (rec-) & H17 (rec+)	630–10,000 μg/disk	Questionable effects observed	Kuroda et al., 1984
Linalool	Rec-assay	*B. subtilis* M45 (rec-) & H17 (rec+)	17 μg/disk	Negative	Oda et al., 1979
Linalool	Rec-assay	*B. subtilis* M45 (rec-) & H17 (rec+)	10,000 μg/disk	Positive	Yoo, 1986
Linalyl acetate	Ames with and without S9 activation	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100	100–25,000 μg/plate	Negative	RIFM, 1987; Heck et al., 1989
Linalyl acetate	Rec-assay	*B. subtilis* M45 (rec-) & H17 (rec+)	18 μg/disk	Negative	Oda et al., 1979

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

Table 6
Mutagenicity and genotoxicity mammalian studies

Material	Test system in vitro	Test object	Concentration[a]	Results	References
Linalool	Micronucleus test	Swiss CD-1 mice (5/sex/dose)	500, 1000 or 1500 mg/kg	Negative	RIFM, 2001
Linalool	Chromosome aberration	Chinese hamster ovary cells	5–150 μg/ml	Negative	Sasaki et al., 1989
Linalool	Chromosome aberration with and without S9 activation	Chinese hamster ovary cells	16.7–500 μg/ml	Negative	RIFM, 1983b
Linalool	Chromosome aberration	Chinese hamster fibroblasts	250 μg/ml (sample tested at 3 doses; only maximum dose reported)	Negative	Ishidate et al., 1984
Linalool	Unscheduled DNA synthesis (UDS) assay	Rat hepatocytes	Tested at 8 dose levels ranging from 0.1–500 μg/ml Evaluated at 5 dose levels ranging from 0.5–50 μg/ml	Negative	RIFM, 1986a; Heck et al., 1989
Linalool	Mouse lymphoma forward mutation assay (MYL) with and without S 9 activation	Mouse lymphoma L5178Y TK$^{+/-}$	3.9–300 μg/ml	Negative without activation Weakly positive with activation at doses of 200 nl/ml and above; 150 nl/ml was the highest inactive dose	RIFM, 1982; Heck et al., 1989
Linalool	Mouse lymphoma forward mutation assay (MYL) with and without S9 activation (for this experiment, osmolarity was controlled and the pH kept at 7.0)	Mouse lymphoma L5178Y TK$^{+/-}$	12.5–274 μg/ml	Negative	RIFM, 1994
Linalyl acetate	Chromosome aberration assay	Human lymphocytes	33–180 μg/ml	Negative	RIFM, 2000
Linalyl acetate	Unscheduled DNA synthesis (UDS) assay	Rat hepatocytes	Doses up to 300 μg/ml	Negative	Heck et al., 1989

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

3.3.2. Mammalian studies

Linalool did not induce chromosomal aberrations when incubated with Chinese hamster fibroblast cells at concentrations up to 0.25 mg/ml (approximately equivalent to 250 μg/ml) (Ishidate et al., 1984) or with Chinese hamster ovary (CHO-WBI) cells at concentrations up to 300 nl/ml (approximately equivalent to 300 μg/ml) (RIFM, 1983b). Linalool did not enhance the number of sister chromatid exchanges that were induced with mitomycin C in Chinese hamster ovary (CHO K-1) cells when tested at 33.3–1000 μM (approximately equivalent to 5–150 μg/ml) (Sasaki et al., 1989).

Induction of unscheduled DNA synthesis (UDS) in rat hepatocytes was not observed at concentrations up to 50 nl/ml (approximately equivalent to 50 μg/ml) linalool (Heck et al., 1989; RIFM, 1986a) and 300 nl/ml (approximately equivalent to 300 μg/ml) linalyl acetate (Heck et al., 1989).

No effects were seen with linalool in the absence of metabolic activation in the L5178Y/TK$^{\pm}$ mouse lymphoma assay at concentrations of 3.9–300 nl/ml (approximately equivalent to 3.9–300 μg/ml). Weak positive effects were observed in the presence of metabolic activation at doses of 200 nl/ml (approximately equivalent to 200 μg/ml) and above. The highest inactive dose was 150 nl/ml (approximately equivalent to 150 μg/ml) (Heck et al., 1989; RIFM, 1982a). Linalool was tested in a second mouse lymphoma assay (RIFM, 1994) using a current protocol in which osmolality was controlled and the pH maintained at or above 7.0. Doses up to 200 μg/ml (with activation) and up to 224 μg/ml (without activation) did not induce a mutant frequency that exceeded the minimum criterion for a positive response and were evaluated as negative under conditions of the test.

3.3.3. Interpretation of results

In 19 separate in vitro tests on the mutagenicity and genotoxicity of linalool and linalyl acetate, 16 were negative, one was positive, one was weakly positive and one was questionable. The positive result and the questionable result observed with the rec-assays are of questionable relevance for the evaluation of genotoxicity of linalool. The rec-assay with *B. subtilis* used in both investigations detects DNA damage, which may be induced by genotoxicity but also by nonspecific cytotoxicity of a test compound (Kuroda et al., 1984; Yoo, 1986). In contrast, no evidence of DNA damage was observed in the rat hepatocyte UDS assay (Heck et al., 1989). The authors of the mouse lymphoma assay (Heck et al., 1989), which gave a weak positive result for linalool, emphasized that positive results in this assay are commonly observed for polar substances in the presence of S9 and may be associated with changes in physiologic

culture conditions (pH and osmolality). When a second mouse lymphoma study was conducted which took into account cytotoxicity, osmolality and pH, the results were negative (RIFM, 1994).

3.4. Carcinogenicity

3.4.1. Dermal studies

To determine co-carcinogenic activity, female ICR/Ha mice were given dermal applications of linalyl acetate alone or with simultaneous applications of 1 or 5 μg benzo-a-pyrene (BaP). No carcinogenic activity was observed when linalyl acetate was administered alone; no co-carcinogenic activity was observed when it was administered with 1 μg BaP. Weak co-carcinogenic activity was observed when linalyl acetate was administered with 5 μg BaP (Van Duuren et al., 1971).

Using a two-stage mouse skin carcinogenesis model, modulation of 9,10-dimethyl-1,2-benzanthracene (DMBA) initiation by 10% linalool was studied. An average number of 10.4 papillomas per mouse were observed in mice treated with linalool as compared with an average number of 15 papillomas for the acetone control (Gould et al., 1987). In another study, linalool (20% in acetone) elicited a weak tumor promoting response in strain 101 mice when tested with DMBA (Roe and Field, 1965).

3.4.2. Oral studies

Chemopreventive activity was evaluated with 1% linalool using the DMBA induced rat mammary carcinogenesis model. Linalool did not significantly reduce the total number of tumors observed when compared to controls or significantly extend the tumor latency period (Gould et al., 1990; Russin et al., 1989).

When the capacity of linalool to inhibit large bowel and duodenal tumor formation was tested using azoxymethane-induced neoplasia in rats, linalool produced a modest decrease in adenocarcinomas of the duodenum but the decrease was not statistically significant (Wattenberg, 1991).

3.4.3. Intraperitoneal studies

Linalool and linalyl acetate were examined for their ability to induce primary lung tumors in female A/He mice. Animals received intraperitoneal injections of linalool or linalyl acetate 3 times weekly for 8 weeks and were sacrificed 24 weeks after the first injection. Dose levels were set at the maximum tolerated dose (MTD) and at 0.2×MTD. The total cumulative doses were 600 and 3000 mg/kg for linalool and 4800 and 24000 mg/kg for linalyl acetate. No significant differences from controls were observed; linalool and linalyl acetate were negative for pulmonary tumor response under the conditions of the test (Stoner et al., 1973).

The results of the above studies are summarized in Table 7.

3.5. Reproductive toxicity

While there appear to be no reproductive or developmental studies on linalool itself, several investigations have been conducted on coriander oil, in which linalool is the major constituent, accounting for, in some cases, 90% of the composition.

A coriander oil that contained 72.9% linalool and 22.3% of other identified terpenes[1] was administered to female rats via gavage, once daily, at dose levels of 250, 500 or 1000 mg/kg/day from 7 days prior to cohabitation through gestation, delivery and a 4-day lactation/postparturition period.

Excess salivation was observed in all dose groups and was statistically significantly increased in the mid- and high-dose groups. Significant inhibition of average maternal body weight gain before mating occurred at the highest dose level and a significant number of animals in this group had urine stained abdominal fur. Statistically significant increases in body weight gains occurred during gestation in the low- and high-dose groups and statistically significant increases in absolute and relative feed consumption occurred at all 3 dose levels; the mid-dose group had increased body weight also, but it was not statistically significant. A marked decrease (~16.3% as compared to controls) in delivered live litter size, indicative of in utero deaths, and a statistically significant increase in pup mortality on day 1, with associated observations of pup morbidity were observed at the highest dose level. These effects were not seen at the mid- and low-dose levels. Since the adverse effects on reproductive performance and/or pup development occurred only at a dose level that also elicited statistically significant maternal toxicity, it was concluded that coriander oil at dose levels that do not evoke maternal adverse effects, does not affect the reproductive performance of female rats or development of their offspring (RIFM, 1989).

The same type of coriander oil as above was also tested in a 28-day subchronic study in rats. Coriander oil was administered by gavage to male and female rats at dose levels of 160, 400 and 1000 mg/kg/bodyweight/day. Macroscopic examinations were made of all major organs and microscopic examinations were conducted on all major organs in the high-dose group and on selected organs in the low- and mid-dose group. Increases in absolute and relative liver weights were

[1] Composition as %: linalool (72.9); camphor (4.6); para-cymene (4.0); α-pinene (3.9); γ-terpinene (3.6); limonene (2.7); geranyl acetate (1.2); myrcene (0.9); α-terpineol (0.8); camphene (0.6); unknowns (4.8). These terpenes are either open-chain or cyclic hydrocarbons or oxygenated hydrocarbons. Because of their close structural similarity, in which there are no structural alerts for toxicity, one might anticipate that they would share common features in terms of their metabolism and toxicology).

Table 7
Carcinogenicity studies

Material	Method	Dose[a]	Species	Results	References
Linalool	A single application of DMBA was made to clipped dorsal skin followed by a 3 week rest period, after which linalool was applied once a week for 33 weeks	20% in acetone	Inbred strain 101 mice	A weak tumor promoting response was elicited	Roe and Field, 1965
Linalool	Modulation of DMBA initiation was studied using a two-stage mouse skin carcinogenesis model. These preliminary data are from 15 wks post DMBA treatment. Linalool applied from 3 days before to 3 days after DMBA treatment.	10% in acetone	Mice (strain not specified)	Average number of papillomas per mouse was 10.4 for linalool and 15.0 for the acetone control	Gould et al., 1987
Linalool	Mice received intraperitoneal in injections of linalool in tricaprylin 3 times weekly for 8 weeks. Twenty-four weeks after the first injection, animals were sacrificed.	Cumulative dose of 600 and 3000 mg/kg	Mice	No significant difference in the incidence of lung tumors was observed as compared to controls.	Stoner et al., 1973
Linalool	Chemopreventive activity was evaluated in a DMBA-induced rat mammary carcinogenesis model. Rats were fed a diet containing 1% linalool for 20 weeks. Two weeks after the initiation of the dietary regimen, each animal was administered a single dose of 65 mg/kg DMBA in 0.5 ml sesame oil by gastric intubation.	1% (w/w) in feed	Rat	No significant reduction in the total number of tumors was observed when compared to controls. No significant extension to the tumor latency period was observed.	Gould et al., 1990; Russin et al., 1989
Linalool	The ability to inhibit azoxymethane (AOM) induced neoplasia of the large bowel and duodenum was studied in rats. Each animal was given subcutaneous doses of 15 mg/kg bodyweight AOM twice weekly for 3 weeks. Three days following the final dose, each animal was fed a diet containing 5 mg/kg linalool for 22 weeks.	5 mg/kg of feed	Rat	A modest, but statistically insignificant, decrease in adenocarcinomas of the duodenum was observed tumor formation in the large bowel was not inhibited	Wattenberg, 1991
Linalyl acetate	Linalyl acetate applied to clipped backs three times a week for duration of study (460 days) Linalyl acetate was tested alone or with simultaneous applications of 1 μg or 5 μg Benzo-a-Pyrene (BaP)	3 mg linalyl acetate in 0.1 ml acetone	20 Female ICR/Ha mice/group	No carcinogenic effects observed when linalyl acetate was tested alone or with 1 μg BaP weak co-carcinogenic activity observed when linalyl acetate was administered with 5 μg BaP	Van Duuren et al., 1971
Linalyl acetate	Mice received intraperitoneal injections of linalyl acetate in tricaprylin 3 times weekly for 8 weeks. Twenty-four weeks after the first injection, animals were sacrificed	Cumulative dose of 4800 and 24,000 mg/kg	Mice	No significant difference in the incidence of lung tumors was observed as compared to controls	Stoner et al., 1973

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

observed in mid- and high-dose male and females and an increase in absolute liver weight was also observed in low-dose females. Degenerative lesions were noted in the renal cortex in the high-dose males and a high incidence of slight periportal hepatocellular cytoplasmic vacuolization in the liver was observed in the high-dose females. Similar lesions were also noted in the low- and mid-dose females, but at a lower incidence. Based on these effects, the NOEL was determined to be 160 mg/kg/day for males and less than 160 mg/kg/day for females. However, the reproductive organs were examined macroscopically in all three dose groups and microscopically in the high-dose group and no adverse effects were found even at the highest dose level, 1000 mg/kg/day.

There have been several studies attempting to evaluate a number of natural products, including coriander seeds, as potential antifertility agents. It is doubtful whether such studies are relevant to the safety assessment of coriander oil and its main constituent, linalool, but nevertheless the findings are summarized here. The findings are of doubtful relevance partly because the material tested consisted of aqueous boiled extracts of coriander seeds, and was of unknown composition and because there are no observations on possible maternal toxicity of the administered material. This coriander seed extract (linalool content unknown) was administered orally to female rats at dose levels of 250 and 500 mg/kg/body weight from day-1 to day-5 of pregnancy. Dose-dependent significant anti-implantation effects were observed. The mean percent loss of implantation/rat in the control group, the low-dose group and in the high-dose group were 1.42, 48.8 and 75%, respectively. Progesterone levels in this study were observed to be lowered in the early stage of pregnancy as compared to control values but no significant change was observed in the late stages (Al-Said et al., 1987). In another study, mild abortifacient activities were observed in female rats who received 500 mg/kg/body weight coriander seed extract (linalool content unknown) orally from day-8 to day-12 of pregnancy. However, no effects were observed when a second group of female rats were dosed orally with a coriander seed extract at a dose level of 500 mg/kg/body weight from day-12 to day-20 of pregnancy (Al-Said et al., 1987). Coriander seed extract (linalool content unknown) also had an effect on the estrus cycle in rats significantly increasing the duration of the diestrous phase but not significantly prolonging the length of the estrous cycle (Al-Said et al., 1987).

An extract of coriander (type of extract and linalool content unknown) had no effect on fertility in female Swiss mice when 0.05–0.2 ml (approximately equivalent to 50–200 mg) was injected subcutaneously twice a day for five days (Matsui et al., 1967).

Cilantro, which is an extract of the coriander plant (linalool content unknown), diluted in cell growth media did not exhibit estradiol or progesterone binding activities in intact human breast cancer cell lines (Zava et al., 1998).

3.6. Skin irritation

3.6.1. Human studies

Linalool and nine of the linalyl esters were evaluated for skin irritation in humans (data were not available for linalyl hexanoate). Approximately 380 healthy, male and female volunteers were tested. No irritation was observed with 20% linalool or with any of the linalyl esters at dose levels up to 32%. Mild irritation was observed with 32% linalool (see Table 8).

3.6.2. Animal studies

Undiluted linalool was slightly to severely irritating to guinea pigs and rabbits; no irritation was observed with a 10% concentration. Reactions to undiluted linalyl acetate ranged from slight to severe in guinea pigs and rabbits; a 5% concentration was slightly irritating to rabbits. Eight of the other nine linalyl esters that were tested for irritation in rabbits at 100% produced reactions that ranged from very slight to moderate (data were not available for linalyl hexanoate). These 8 linalyl esters were also tested at a concentration of 5% in rabbits and very slight irritation, which generally cleared by 72 h, was observed (see Table 9).

3.7. Mucous membrane (eye) irritation

Undiluted linalool was a moderate eye irritant; doses of linalool from 3–30% were slightly irritating to non-irritating. At concentrations comparable to use levels for linalool and linalyl acetate there were no observations of eye irritation in rabbits. The nine linalyl esters (data were not available for linalyl hexanoate) that were evaluated for eye irritation were very slightly to slightly irritating at concentrations up to 100% (see Table 10).

3.8. Skin sensitization

3.8.1. Human studies

For details of individual studies, see Table 11. No sensitization reactions were observed in the human maximization test when linalool was tested at 8 or 20% in 50 volunteers, from two different test panels. Five maximization tests using 5 different test panels were conducted with 10% linalyl acetate on 131 volunteers. Sensitization reactions were observed in 3 subjects from 2 test panels. Both samples of linalyl acetate that produced reactions were re-tested or purified and then re-tested; upon re-test, no sensitization reactions were produced. A 12% concentration and a 20% concentration of linalyl acetate were also tested and produced no reactions in two test panels consisting of 25 subjects each. Dermal sensitization was not observed for the

Table 8
Skin irritation studies in humans

Material	Method	Concentration	Subjects	Results	References
Linalool	Primary irritation test. A 48-hour closed patch test	20% in petrolatum or unguentum hydrophilicum	28 healthy male and female volunteers	No reactions	Fujii et al., 1972
Linalool	Primary irritation test. A 24-72 hour closed patch test	2% in unguentum simplex or in unguentum hydrophilicum	30 healthy male and female volunteers	No reactions	Fujii et al., 1972
Linalool	A 48-hour semi-occluded patch test	32% in acetone	50 male volunteers	Mild irritation	Motoyoshi et al., 1979
Linalyl acetate	Primary irritation test. A 48-hour closed patch test	20% in petrolatum or unguentum hydrophilicum	40 healthy male and female volunteers	No reactions	Fujii et al., 1972
Linalyl acetate	Primary irritation test. A 24-72 hour closed patch test	2% in unguentum simplex or in unguentum hydrophilicum	30 healthy male and female volunteers	No reactions	Fujii et al., 1972
Linalyl acetate	A 48-hour semi-occluded patch test	32% in acetone	50 male volunteers	No reactions	Motoyoshi et al., 1979
Linalyl acetate	Maximization pre-test. A 48-hour closed patch test	10% in petrolatum	22 male volunteers	No reactions	RIFM, 1974b
Linalyl acetate	Maximization pre-test. A 48-hour closed patch test	10% in petrolatum	26 male volunteers	No reactions	RIFM, 1974b
Linalyl acetate	Maximization pre-test. A 48-hour closed patch test	10% in petrolatum	27 male and female volunteers	No reactions	RIFM, 1982
Linalyl acetate	Maximization pre-test. A 48-hour closed patch test	10% in petrolatum	26 male and female volunteers	No reactions	RIFM, 1982
Linalyl acetate	Maximization pre-test. A 48-hour closed patch test	10% in petrolatum	30 male and female volunteers	No reactions	RIFM, 1982
Linalyl acetate	Maximization pre-test. A 48-hour closed patch test	20% in petrolatum	5 volunteers	No reactions	RIFM, 1975c
Linalyl acetate	Primary irritation test. A 24-hour closed patch test	5% in petrolatum	25 male and female volunteers	No reactions	RIFM, 1997a
Linalyl benzoate	Maximization pre-test. A 48-hour closed patch test	8% in petrolatum	5 male volunteers	No reactions	RIFM, 1973c
Linalyl butyrate	Maximization pre-test. A 48-hour closed patch test	8% in petrolatum	25 male volunteers	No reactions	RIFM, 1975d
Linalyl cinnamate	Maximization pre-test. A 48-hour closed patch test	8% in petrolatum	5 male volunteers	No reactions	RIFM, 1973c
Linalyl formate	Maximization pre-test. A 48-hour closed patch test	10% in petrolatum	5 male volunteers	No reactions	RIFM, 1973c
Linalyl isobutyrate	Maximization pre-test. A 48-hour closed patch test	8% in petrolatum	5 volunteers	No reactions	RIFM, 1974c
Linalyl isovalerate	Maximization pre-test. A 48-hour closed patch test	20% in petrolatum	5 volunteers	No reactions	RIFM, 1975c
Linalyl phenylacetate	Maximization pre-test. A 48-hour closed patch test	4% in petrolatum	5 volunteers	No reactions	RIFM, 1974c
Linalyl propionate	Maximization pre-test. A 48-hour closed patch test	8% in petrolatum	5 male volunteers	No reactions	RIFM, 1973c

other linalyl esters that were tested in maximization tests at concentrations ranging from 4 to 20% in 200 volunteers. There have been a few cases of positive patch tests on dermatological patients but with no consistent pattern (Letizia et al., 2003a,b).

3.8.2. Animal studies

No sensitization was observed with linalool in guinea pig sensitization studies at concentrations up to 20%. With linalyl acetate at a concentration of 10%, weak to moderate sensitization effects were observed in guinea pig sensitization studies. Linalyl acetate was non-sensitizing when tested at 5% in these same guinea pig sensitization studies. No sensitization reactions were observed with linalyl isobutyrate and linalyl propionate (data were not available for the other linalyl esters) when tested at 8% in open epicutaneous tests in guinea pigs (see Table 12).

3.9. Photoirritation and photoallergy

UV spectra have been obtained for linalool and all of the esters. Linalyl cinnamate was the only material which absorbed UVB light (290–320 nm), peaking at 275 nm and returning to baseline at 316 nm. The other linalyl esters (acetate, benzoate, butyrate, formate, hexanoate, isobutyrate, isovalerate, phenylacetate and propionate) did not absorb UV light in the 290–400 nm range, and therefore would have no potential to elicit photoirritation or photoallergy.

There are no photoirritation data for linalyl cinnamate. However, cinnamic acid has been tested for photoirritation (Pathak and Fitzpatrick, 1959; RIFM, 2002) and photoallergy (RIFM, 2002) in the guinea pig and has shown no activity. In addition, the potential human exposure to linalyl cinnamate is low since the volume of use is less than one metric ton and the maximum skin level is 0.4%.

4. Summary

1. There are no definitive percutaneous absorption studies on any of the substances in this summary. Therefore, for this assessment, the conservative assumption of 100% absorption is taken.

Table 9
Skin irritation studies in animals

Material	Method	Concentration	Species	Results	References
Linalool	A 48-h closed patch test	100%	6 Pitman-Moore improved strain miniature swine	No irritation was observed	Motoyoshi et al., 1979
Linalool	A 24-h open application to clipped dorsal skin; 30 min after reading, linalool was applied again. A 2nd set of readings and applications was made 48 h later. After the 72-h reading, Evans blue was injected intravenously.	100%	6 male Hartley guinea pigs	Moderate irritation	Motoyoshi et al., 1979
Linalool	Preliminary irritation screen for a modified Draize sensitization study. To determine the injection challenge concentration (ICC); guinea pigs were given intradermal injections of linalool over a range of concentrations.	0.05% (ICC) (Vehicle not specified)	4 inbred Hartley strain albino guinea pigs	Slight but perceptible irritation	Sharp, 1978
Linalool	Preliminary irritation screen for a modified Draize sensitization study. To determine the application challenge concentration (ACC); guinea pigs received open applications of linalool at a range of concentrations.	10% (ACC) (Vehicle not specified)	4 inbred Hartley strain albino guinea pigs	No irritation was observed	Sharp, 1978
Linalool	Irritation evaluated during an associated LD_{50} study	100%	9 Albino rabbits	Slight to moderate irritation	RIFM, 1970a
Linalool	A 4-hour semi-occluded patch test	100%	3 Albino rabbits	Avg. erythema score = 1.9; Avg. edema score = 1.4 (not considered to be an irritant per Annex V of EEC Directive 79/831)	RIFM, 1984b
Linalool	A 4-h semi-occluded patch test	100%	4 Female New Zealand albino rabbits	Avg. erythema score = 2.0; Avg. edema score = 1.4	RIFM, 1985
Linalool	A 4-h semi-occluded patch test	100%	4 Female New Zealand White rabbits	(not considered to be an irritant per Annex V of EEC Directive 79/831)	RIFM, 1986c
Linalool	A 4-h semi-occluded patch test	50% in diethyl phthalate	4 Female New Zealand White rabbits	Avg. erythema score = 0.6; Avg. edema score = 0 (not considered to be an irritant per Annex V of EEC Directive 79/831)	RIFM, 1986c
Linalool	Single application to intact or abraded skin	100%	3 Rabbits	Very slight to well defined irritation	RIFM, 1967a
Linalool	Single application to intact or abraded skin	5% in diethyl phthalate	3 Rabbits	Very slight irritation	RIFM, 1967a
Linalool	A 24-h open application to clipped dorsal skin; 30 min after reading, linalool was applied again. A 2nd set of readings and applications was made 48 hours later. After the 72-hour reading, Evans blue was injected intravenously.	100%	6 albino Angora rabbits	Severe irritation	Motoyoshi et al., 1979
Linalool	A 24-h closed patch test	100%	6 New Zealand White rabbits	Very slight irritation	RIFM, 1992
Linalool	A 24-h closed patch test	30% in peanut oil	6 New Zealand White rabbits	Very slight irritation	RIFM, 1992
Linalool	A 24-h closed patch test	10% in peanut oil	6 New Zealand White rabbits	No irritation was observed	RIFM, 1992
Linalool	A 24-h closed patch test	3% in peanut oil	6 New Zealand White rabbits	No irritation was observed	RIFM, 1992
Linalool	A 24-h closed patch test	100%	9 female New Zealand rabbits	No irritation was observed	Troy, 1977
Linalyl acetate	A 48-h closed patch test	100%	6 Pitman-Moore Improved strain miniature swine	No irritation was observed	Motoyoshi et al., 1979
Linalyl acetate	A 24-h open application to clipped dorsal skin; 30 min after reading, linalool was applied again. A 2nd set of readings and applications was made 48 h later. After the 72-h reading, Evans blue was injected intravenously.	100%	6 male Hartley guinea pigs	Moderate irritation	Motoyoshi et al., 1979

(*continued on next page*)

Table 9 (*continued*)

Material	Method	Concentration	Species	Results	References
Linalyl acetate	A 4-h semi-occluded patch test	100%	3 albino rabbits	Avg erythema score = 1.9; Avg edema score = 1.8 (not considered to be an irritant per Annex V of EEC Directive 79/831)	RIFM, 1984b
Linalyl acetate	A 4-h semi-occluded patch test	100%	4 female albino rabbits	Avg erythema score = 1.9; Avg edema score = 1.0 (not considered to be an irritant per Annex V of EEC Directive 79/831)	RIFM, 1985
Linalyl acetate	A 24-h open application to clipped dorsal skin; 30 min after reading, linalool was applied again. A 2nd set of readings and applications was made 48 h later. After the 72-h reading, Evans blue was injected intravenously.	100%	6 albino Angora rabbits	Severe irritation	Motoyoshi et al., 1979
Linalyl acetate	Single application to intact or abraded skin	100%	3 rabbits	Slight irritation	RIFM, 1967b
Linalyl acetate	Single application to intact or abraded skin	5% in diethyl phthalate	3 rabbits	Slight irritation	RIFM, 1967b
Linalyl acetate	Dermal application to backs for 1, 5 and 15 min	100%	Rabbits (number not specified)	Slight to severe irritation	RIFM, 1969
Linalyl acetate	Dermal application to backs for 20 hours	100%	rabbits (number not specified)	Mild to severe irritation	RIFM, 1969
Linalyl acetate	Dermal application to the ear for 20 h	100%	rabbits (number not specified)	Very severe irritation	RIFM, 1969
Linalyl acetate	A 24-h closed patch test	100%	9 New Zealand female rabbits	Minimal irritation	Troy, 1977
Linalyl benzoate	Irritation evaluated during an associated LD_{50} study	100%	10 rabbits	Slight to moderate irritation	RIFM, 1973a
Linalyl benzoate	Single application to intact or abraded skin	100%	3 rabbits	Very slight to well defined irritation	RIFM, 1967b
Linalyl benzoate	Single application to intact or abraded skin	5% in diethyl phthalate	3 rabbits	Very slight irritation	RIFM, 1967b
Linalyl butyrate	Irritation evaluated during an associated LD_{50} study	100%	4 rabbits	No irritation was observed	RIFM, 1975a
Linalyl butyrate	Single application to intact or abraded skin	100%	3 rabbits	Very slight to well defined irritation	RIFM, 1967b
Linalyl butyrate	Single application to intact or abraded skin	5% in diethyl phthalate	3 rabbits	Very slight irritation	RIFM, 1967b
Linalyl cinnamate	Irritation evaluated during an associated LD_{50} study	100%	10 rabbits	Slight to moderate irritation	RIFM, 1973a
Linalyl cinnamate	Single application to intact or abraded skin	100%	3 rabbits	Very slight irritation	RIFM, 1967a
Linalyl cinnamate	Single application to intact or abraded skin	5% in diethyl phthalate	3 rabbits	Very slight irritation	RIFM, 1967a
Linalyl formate	Single application to intact or abraded skin	100%	3 rabbits	Very slight irritation	RIFM, 1967b
Linalyl formate	Single application to intact or abraded skin	5% in diethyl phthalate	3 rabbits	Very slight irritation	RIFM, 1967b
Linalyl isobutyrate	Irritation evaluated during an associated LD_{50} study	100%	10 rabbits	Slight to moderate irritation	RIFM, 1974a
Linalyl isobutyrate	Single application to intact or abraded skin	100%	3 rabbits	Very slight to well defined irritation	RIFM, 1967b
Linalyl isobutyrate	Single application to intact or abraded skin	5% in diethyl phthalate	3 rabbits	Very slight irritation	RIFM, 1967b
Linalyl isovalerate	Irritation evaluated during an associated LD_{50} study	100%	10 rabbits	Slight to moderate irritation	RIFM, 1975b
Linalyl isovalerate	Single application to intact or abraded skin	100%	3 rabbits	Very slight to well defined irritation	RIFM, 1967a
Linalyl isovalerate	Single application to intact or abraded skin	5% in diethyl phthalate	3 rabbits	Very slight irritation	RIFM, 1967a
Linalyl phenylacetate	Irritation evaluated during an associated LD_{50} study	100%	10 rabbits	No irritation was observed	RIFM, 1974a
Linalyl phenylacetate	Single application to intact or abraded skin	100%	3 rabbits	Very slight to well defined irritation	RIFM, 1967a
Linalyl phenylacetate	Single application to intact or abraded skin	5% in diethyl phthalate	3 rabbits	No irritation was observed	RIFM, 1967a
Linalyl propionate	Irritation evaluated during an associated LD_{50} study	100%	10 rabbits	Slight to moderate irritation	RIFM, 1973a
Linalyl propionate	Single application to intact or abraded skin	100%	3 rabbits	Very slight to well defined irritation	RIFM, 1967b
Linalyl propionate	Single application to intact or abraded skin	5% in diethyl phthalate	3 rabbits	Very slight irritation	RIFM, 1967b

Table 10
Mucous membrane (eye) irritation studies

Material	Concentration	Results	References
Linalool	100%	Irritation	Troy, 1977
Linalool	100%	Slight to moderate irritation	RIFM, 1967a
Linalool	5% in diethyl phthalate	Very slight irritation	RIFM, 1967a
Linalool	100%	Moderate irritation	RIFM, 1992
Linalool	30% in peanut oil	Slight irritation	RIFM, 1992
Linalool	10% in peanut oil	Very slight irritation	RIFM, 1992
Linalool	3% in peanut oil	No irritation	RIFM, 1992
Linalyl acetate	100%	No irritation	RIFM, 1969
Linalyl acetate	100%	No irritation	Troy, 1977
Linalyl acetate	100%	Very slight irritation	RIFM, 1967b
Linalyl acetate	5% in diethyl phthalate	No irritation	RIFM, 1967b
Linalyl benzoate	100%	Very slight irritation	RIFM, 1967b
Linalyl benzoate	5% in diethyl phthalate	Very slight irritation	RIFM, 1967b
Linalyl butyrate	100%	Very slight irritation	RIFM, 1967b
Linalyl butyrate	5% in diethyl phthalate	Very slight irritation	RIFM, 1967b
Linalyl cinnamate	100%	Very slight to well defined irritation	RIFM, 1967a
Linalyl cinnamate	5% in diethyl phthalate	Very slight to well defined irritation	RIFM, 1967a
Linalyl formate	100%	Very slight irritation	RIFM, 1967b
Linalyl formate	5% in diethyl phthalate	Very slight irritation	RIFM, 1967b
Linalyl isobutyrate	100%	Very slight irritation	RIFM, 1967b
Linalyl isobutyrate	5% in diethyl phthalate	Very slight irritation	RIFM, 1967b
Linalyl isovalerate	100%	Very slight to well defined irritation	RIFM, 1967a
Linalyl isovalerate	5% in diethyl phthalate	Very slight irritation	RIFM, 1967a
Linalyl phenylacetate	100%	Very slight to well defined irritation	RIFM, 1967a
Linalyl phenylacetate	5% in diethyl phthalate	Very slight irritation	RIFM, 1967a
Linalyl propionate	100%	Very slight irritation	RIFM, 1967b
Linalyl propionate	5% in diethyl phthalate	Very slight irritation	RIFM, 1967b

Table 11
Skin sensitization studies in humans

Material	Method	Concentration	Subjects	Results	References
Linalool	Max	20% in petrolatum	25 male volunteers	No reactions	RIFM, 1970b
Linalool	Max	8% (vehicle not reported)	25 volunteers	No reactions	Greif, 1967
Linalyl acetate Sample # 74-10-98	Max	10% in petrolatum	22 male volunteers	2/22 reactions	RIFM, 1974b
Linalyl acetate Sample # 74-10-98 was retested	Max	10% in petrolatum	26 male volunteers	No reactions	RIFM, 1974b
Linalyl acetate A new sample (81-10-8517-R) was tested	Max	10% in petrolatum	27 male and female volunteers	No reactions	RIFM, 1982
Linalyl acetate Another new sample (82-10-49666R) was tested	Max	10% in petrolatum	26 male and female volunteers	1/26 reactions	RIFM, 1982
Linalyl acetate Sample # 82-10-49666R was treated with sodium carbonate, then retested	Max	10% in petrolatum	30 male and female volunteers	No reactions	RIFM, 1982
Linalyl acetate Sample # 74-20-98R(2)	Max	20% in petrolatum	25 male and female volunteers	No reactions	RIFM, 1975c
Linalyl acetate	Max	12% (vehicle not reported)	25 volunteers	No reactions	Greif, 1967
Linalyl benzoate	Max	8% in petrolatum	25 male volunteers	No reactions	RIFM, 1973c
Linalyl butyrate	Max	8% in petrolatum	25 male volunteers	No reactions	RIFM, 1975d
Linalyl cinnamate	Max	8% in petrolatum	25 male volunteers	No reactions	RIFM, 1973c
Linalyl formate	Max	10% in petrolatum	25 male volunteers	No reactions	RIFM, 1973c
Linalyl isobutyrate	Max	8% in petrolatum	25 male and female volunteers	No reactions	RIFM, 1974c
Linalyl isovalerate	Max	20% in petrolatum	25 male and female volunteers	No reactions	RIFM, 1975c
Linalyl phenylacetate	Max	4% in petrolatum	25 male and female volunteers	No reactions	RIFM, 1974c
Linalyl propionate	Max	8% in petrolatum	25 male volunteers	No reactions	RIFM, 1973c

Table 12
Skin sensitization studies in animals

Material	Method	Concentration	Species	Results	References
Linalool	Modified Draize test	0.05% (injection challenge concentration) 10% (application challenge concentration) (vehicle not specified)	10 male and female inbred Hartley strain guinea pigs	No reactions	Sharp, 1978
Linalool	Open epicutaneous test (OET)	20% (vehicle not specified)	6–8 guinea pigs	No reactions	Klecak, 1979
Linalool	Guinea pig maximization test	10% (vehicle not specified)	guinea pigs	No reactions	Ishihara, et al., 1986
Linalyl acetate	Guinea pig maximization test	10% (vehicle not specified)	guinea pigs	Moderate sensitization effects were produced (no further details given)	Ishihara, et al., 1986
Linalyl acetate	Guinea pig maximization test	20% in acetone 10% in acetone 5% in acetone	Female albino Hartley-Dunkin guinea pigs	4/10 reactions at 20% 2/10 reactions at 10% No reactions at 5%	RIFM, 1997b
Linalyl acetate	Guinea pig sensitization test	10% in acetone 5% in acetone	guinea pigs	No reactions	RIFM, 1969
Linalyl isobutyrate	Open epicutaneous test (OET)	8% (vehicle not specified)	6–8 guinea pigs	No reactions	Klecak, 1979
Linalyl propionate	Open epicutaneous test (OET)	8% (vehicle not specified)	6–8 guinea pigs	No reactions	Klecak, 1979

2. The acute oral and dermal toxicity of linalool and the linalyl esters is very low. Parenteral (i.p., i.m. and s.c.) administrations of linalool and i.p. administration of linalyl acetate yield LD_{50}'s of 200–8000 mg/kg.
3. Based on the results of a number of subchronic studies available for linalool, linalyl acetate, linalyl cinnamate and linalyl isobutyrate as well as the available data on the carboxylic acids derived from the hydrolysis of the linalyl esters, it is concluded that these materials have dermal and oral NOAELs of 50 mg/kg/day or greater. These NOAELs greatly exceed the dermal exposure to humans from their use as fragrance ingredients. Such exposures are estimated at 0.3 mg/kg/day for linalool and linalyl acetate and less than 0.1 mg/kg/day for the other linalyl esters, even with the assumption of 100% dermal absorption.
4. Based on a weight of evidence evaluation of the available mutagenicity and genotoxicity data on linalool and linalyl acetate, as well as the similar metabolism and detoxification of the other related esters and the lack of structural alerts for genotoxicity, it is concluded that linalool and the related esters have no significant genotoxic potential under the recommended current conditions of use as fragrance ingredients.
5. There are no long-term studies that evaluated directly the carcinogenicity of linalool. However, based on the conclusion of no significant genotoxic potential, weak, if any, tumor promoting activity, the high NOAELs observed in subchronic studies, the information on metabolism and detoxification and the lack of structural alerts for carcinogenicity, it is considered reasonable to conclude that linalool and the related esters have no significant potential for carcinogenicity under the recommended current conditions of use as fragrance ingredients.
6. A review of the reproductive data available from studies carried out in the rat and mouse given coriander oil, in which linalool was the major component, and of data derived from a 28-day toxicity study in the rat, which included an evaluation of the reproductive organs, indicated that coriander oil, and by implication, its major constituent, linalool, do not affect reproductive performance or subsequent growth and survival of the offspring except at dose levels which cause significant maternal toxicity. No other developmental toxicity studies have been conducted.
7. Although slight to severe irritation was observed in animals, from tests on human volunteers, it can be concluded that linalool and the linalyl esters are unlikely to be primary irritants in humans under the recommended current conditions of use as fragrance ingredients.
8. Although slight eye irritation was observed in animals with linalool and the linalyl esters at higher concentrations, they are not considered to be eye irritants in humans under the recommended current conditions of use as fragrance ingredients.
9. Although some sensitization reactions were observed with linalyl acetate, when the samples that produced sensitization were re-tested or purified and then retested, no sensitization was

observed. In addition, higher concentrations of linalyl acetate did not produce sensitization reactions. The weight of evidence supports the conclusion that linalool and its esters present no significant risk of sensitization under the recommended current conditions of use as fragrance ingredients.

10. Based on the available evidence it can be concluded that neither linalool nor its esters included in this summary would have potential for photoirritation or photoallergy.

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:

- Linalool and the linalyl esters have a low order of acute toxicity.
- No significant toxicity was observed in subchronic tests; it is concluded that these materials have dermal and oral NOAELS of 50 mg/kg/day or greater.
- Based on a critical review of all available mutagenicity and genotoxicity studies, it has been determined that these materials are negative in short-term tests and therefore would have no significant potential to produce genotoxic effects.
- The metabolic fate of linalool and the linalyl esters is either known or assumed from analogies with structurally related substances that indicate no production of toxic or persistent metabolites and the structural analogies indicate no concern.
- Human dermatological studies show that these materials are not irritating, phototoxic or sensitizing.
- These materials are used at low levels of exposure relative to doses that elicit adverse effects. The estimate for maximum systemic exposure by humans using cosmetic products is 0.3 mg/kg/day for linalool and linalyl acetate and 0.1 mg/kg/day or lower for the other linalyl esters (see Table 2). Using the NOAELs (50 mg/kg/day or greater) and the maximum exposure estimates and assuming 100% absorption, a margin of safety for the exposure of humans to linalool and the linalyl esters may conservatively be calculated as 167 times the maximum daily exposure for linalool and linalyl acetate (50 mg/kg/day ÷ 0.3 mg/kg/day for linalool or linalyl acetate = 167) and 500 times the maximum daily exposure for the other individual linalyl esters (50 mg/kg/day ÷ 0.1 mg/kg/day for the other individual linalyl esters = 500).

References

Al-Said, M.S., Al-Khamis, K.I., Islam, M.W., Parmar, N.S., Tariq, M., Ageel, A.M., 1987. Post-coital antifertility activity of the seeds of *Coriandrum Sativum* in rats. Journal of Ethnopharmacology 21, 165–173.

Anders, M.W., 1989. Biotransformation and bioactivation of xenobiotics by the kidney. In: Hutson, D.H., Caldwell, J., Paulson, G.D. (Eds.), Intermediary Xenobiotic Metabolism in Animals. Taylor and Francis, New York, pp. 81–97.

Atanassova-Shopova, S., Roussinov, K.S., Boycheva, I., 1973. On certain central neurotropic effects of lavender essential oil II. Communication: Studies on the effects of linalool and of terpinenol. Izv. Inst. Fiziol., Sof. (Bulletin of the Institute of Physiology) 15, 149–156.

Buchbauer, G., Jirovetz, L., Jager, W., Dietrich, H., Plank, C., Karamat, E., 1991. Aromatherapy: Evidence for sedative effects of the essential oil of lavender after inhalation. Zeitschrift fur Naturforschung C Biosciences 46, 1067–1072.

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

Chadha, A., Madyastha, K.M., 1984. Metabolism of geraniol and linalool in the rat and effects on liver and lung microsomal enzymes. Xenobiotica 14, 365–374.

Council of Europe, 1992. Partial Agreement in the Social and Public Health Field. Flavouring Substances and Natural Sources of Flavourings. Volume 1, Chemically-defined flavouring substances. Pages 62, 210, 225, 244, 255, 270, 317, 325, 380, 385, 400. Numbers 61, 203, 276, 298, 318, 329, 347, 411, 449, 654, 655. Editeur Maisonneuve S.A., Strasbourg.

Eder, E., Neudecker, T., Lutz, D., Henschler, D., 1980. Mutagenic potential of allyl and allylic compounds. Structure–activity relationship as determined by alkylating and direct in-vitro mutagenic properties. Biochemical Pharmacology 29, 993–998.

Eder, E., Henschler, D., Neudecker, T., 1982a. Mutagenic properties of allylic and α,β-unsaturated compounds: considerations of alkylating mechanisms. Xenobiotica 12, 831–848.

Eder, E., Neudecker, T., Lutz, D., Henschler, D., 1982b. Correlation of alkylating and mutagenic activities of allyl and allylic compounds: standard alkylation test vs kinetic investigation. Chemico-Biological Interactions 38, 303–315.

Elisabetsky, E., Coelho De Souza, G.P., Dos Santos, M.A.C., Siquieira, I.R., Amador, T.A., 1995. Sedative properties of linalool. Fitoterapia 66, 407–414.

FEMA (Flavor and Extract Manufacturers Association), 1965. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 3. Gras Substances. Food Technology 19, 151–197.

FEMA (Flavor and Extract Manufacturers Association), 1977. Recent progress in the consideration of flavoring ingredients under the Food Additives Amendment. 10. GRAS substances. Food Technology 31, 65–74.

FEMA (Flavor and Extract Manufacturers Association), 1998a. Draft report on the metabolism of linalool in rat tissue and intestinal homogenates. Unpublished report.

FEMA (Flavor and Extract Manufacturers Association), 1998b. Draft report on the metabolism of linalyl acetate in rat tissue and intestinal homogenates. Unpublished report.

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

Gaworski, C.K., Vollmuth, T.A., Dozier, M.M., Heck, J.D., Dunn, L.T., Ratajczak, H.V., Thomas, P.T., 1994. An immunotoxicity assessment of food flavouring ingredients. Food and Chemical Toxicology 32, 409–415.

Gould, M.N., Maltzman, T.H., Tanner, M.A., Boston, J.L., Hurt, L.M., Elson, C.E., 1987. Anticarcinogenic effects of terpenoids in orange peel oil. Proceedings of the 78th Annual Meeting of the American Association for Cancer Research 28, 153.

Gould, M.N., Wacker, W.D., Maltzman, T.H., 1990. Chemoprevention and chemotherapy of mammary tumors by monoterpenoids. Progress in Clinical and Biological Research: Mutagens and Carcinogens in the Diet. 347, 255–268.

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

Hagan, E.C., Hansen, W.H., Fitzhugh, O.G., Jenner, P.M., Jones, W.I., Taylor, J.M., Long, E.L., Nelson, A.A., Brouwer, J.B., 1967. Food flavourings and compounds of related structure II. Subacute and chronic toxicity. Food and Cosmetics Toxicology 5, 141–157.

Heck, J.D., Vollmuth, T.A., Cifone, M.A., Jagannath, D.R., Myhr, B., Curren, R.D., 1989. An evaluation of food flavoring ingredients in a genetic toxicity screening battery. The Toxicologist 9, 257.

IFRA (International Fragrance Association), 1998. 1995/1996 Volume of Use Survey.

Ishidate Jr., M., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., Matsuoka, A., 1984. Primary mutagenicity screening of food additives currently used in Japan. Food and Chemical Toxicology 22, 623–636.

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

Jager, W., Buchbauer, G., Jirovetz, L., Fritzer, M., 1992. Percutaneous absorption of lavender oil from a massage oil. Journal of the Society of Cosmetic Chemists 43, 49–54.

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

Jirovetz, L., Buchbauer, G., Jager, W., Raverdino, V., Nikiforov, A., 1990. Determination of lavender oil fragrance compounds in blood samples. Fresenius' Journal of Analytical Chemistry 338, 922–923.

Jirovetz, L., Jager, W., Buchbauer, G., Nikiforov, A., Raverdino, V., 1991. Investigations of animal blood samples after fragrance drug inhalation by gas chromatography/mass spectrometry with chemical ionization and selected ion monitoring. Biological Mass Spectrometry 20, 801–803.

Johnson, J.D., Reichelderfer, D.L., Ryan, M.J., Toft II, J.D., Yarrington, J.T., Graves, S.W., Hejtmancik, M.R., Bucher, J., 1998. Microencapsulated trans-cinnamaldehyde subchronic dosed-feed study using F344 rats and B6C3F1 mice. The Toxicologist 42, 56.

JECFA (Joint Expert Committee on Food Additives), 1997. Evaluation of Certain Food Additives and Contaminants. Forty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series, No. 868.

JECFA (Joint Expert Committee on Food Additives), 1999. Safety evaluation of certain food additives. Who Food Additives Series: 42. Prepared by the Fifty-first meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). World Health Organization, Geneva.

Kieckebusch, W., Lang, K., 1960. The tolerability of benzoic acid in chronic feeding experiments. Arzneimittel-Forschung 10, 1001–1003.

Klecak, G., 1979 The open epicutaneous test (OET), a predictive test procedure in the guinea pig for the estimation of allergenic properties of simple chemical compounds, their mixtures and of finished cosmetic preparations. International Federation Societies Cosmetic Chemists 9/18/79.

Kuroda, K., Tanaka, S., Yu, Y.S., Ishibashi, T., 1984. Rec-assay of food additives. Nippon Kosnu Eisei Zasshi 31, 277–281.

Letizia, C.S., Cocchiara, J., Lalko, J., Api, A.M., 2003a. Fragrance material review on linalool. Food and Chemical Toxicology, 41, PII:S0278-6915(03)00015-2.

Letizia, C.S., Cocchiara, J., Lalko, J., Api, A.M., 2003b. Fragrance material review on linalyl acetate. Food and Chemical Toxicology, 41, PII:S0278-6915(03)00014-0.

Lutz, D., Neudecker, T., Eder, E., 1980. Mutagenic effects of allylic alcohols and their corresponding aldehydes. Archives of Pharmacology 311 (suppl), R25.

Matsui, A.S., Rogers, J., Woo, Y.-K., Cutting, W.C., 1967. Effects of some natural products on fertility in mice. Medicina Pharmacologia Experimentalis 16, 414–424.

Motoyoshi, K., Toyoshima, Y., Sato, M., Yoshimura, M., 1979. Comparative studies on the irritancy of oils and synthetic perfumes to the skin of rabbit, guinea pig, rat, miniature swine and man. Cosmetics and Toiletries 94, 41–48.

Northover, B.J., Verghese, J., 1962. The pharmacology of certain terpene alcohols and oxides. Journal of Scientific and Industrial Research 21C, 342–345.

Nozawa, Y., 1952. A report on studies of anthelmintic actions of principles of volatile oils III. Toxicity for mice and the efficacy against pig ascaria and earthworm muscles. Sapporo Igaku Zasshi 3, 73–77.

Oda, Y., Hamono, Y., Inoue, K., Yamamoto, H., Niihara, T., Kunita, N., 1979. Mutagenicity of food flavors in bacteria. Shokuhin Eisei Hen 9, 177–181.

Owston, E., Lough, R., Opdyke, D.L., 1981. A 90-day study of phenylethyl alcohol in the rat. Food and Cosmetics Toxicology 19, 713–715.

Parke, D.V., Rahman, K.H.M.Q., Walker, R., 1974. Effect of linalool on hepatic drug-metabolizing enzymes in the rat. Biochemical Society Transactions 2, 615–618.

Pathak, M.A., Fitzpatrick, T.B., 1959. Relationship of molecular configuration to the activity of furocoumarins which increase the cutaneous responses following long wave ultraviolet radiation. Journal of Investigative Dermatology 32, Part 2, 255–262.

RIFM (Research Institute for Fragrance Materials, Inc.), 1958a. Toxicological screening of citronellol and linalool in rats. Class VI. Unpublished report from Trubek Laboratories, Inc. Project No. 73800, 11 August. Report number 29150. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1958b. Toxicological screening of linalyl acetate, linalyl isobutyrate and geranyl acetate in rats. Class VIII. Unpublished report from Trubek Laboratories, Inc. Report number 29144. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1967a. Acute toxicity, eye and skin irritation test of fragrance materials. Unpublished report from Hoffmann-LaRoche, 20 September. Report number 30642. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1967b. Acute toxicity, eye and skin irritation test of fragrance materials. Unpublished report from Hoffmann-LaRoche, 20 August. Report number 30645. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1969. Acute toxicity, irritation, and sensitization studies on linalyl acetate. Unpublished report from BASF, 29 July. Report number 4418. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1970a. Acute dermal toxicity study in rabbits. RIFM report number 2735, September 14. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1970b. The contact sensitizing potential of fragrance materials in humans. RIFM report number 1760, October 7. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1972. Acute toxicity studies in rats and rabbits. RIFM report number 2536, September 20 and November 1. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1973a. Acute toxicity studies in rats and rabbits. RIFM report number 2021, May 14 and 18. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1973b. Acute oral and dermal toxicity studies. RIFM report number 2033, March 6. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1973c. Report on human maximization studies. RIFM report number 1802, August 12 and October 9 and 10. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.)., 1974a. Acute toxicity studies. RIFM report number 1778, January 23 and August 22. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1974b. Report on human maximization studies. RIFM report number 1801, May 31 and August 19. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1974c. Report on human maximization studies. RIFM report number 1779, June 6 and August 12. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1975a. Acute toxicity studies in rats, mice, and rabbits. RIFM report number 2024, January 30. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1975b. Acute toxicity studies on rats, rabbits and guinea pigs. RIFM report number 2020, April 10. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1975c. Report on human maximization studies. RIFM report number 1799, April 9 and October 24. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1975d. Report on human maximization studies. RIFM report number 1798, May 6. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1979. Twenty-nine day percutaneous toxicity range finding study with linalool in rats. RIFM report number 32943, May 22. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1980. Ninety day subacute dermal toxicity with linalool in rats. RIFM report number 4001, April 4. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1982a. Mutagenicity evaluation of linalool in the mouse lymphoma forward mutation assay. Report from Lorillard Tobacco Company, 31 August, cited in Heck et al., 1989. Report number 35826. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1982b. Report on human maximization studies. RIFM report number 1643, April 27 and 30 and September 14. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1983a. Mutagenicity evaluation of linalool in the Ames *Salmonella*/microsome plate test. Unpublished report from Lorillard Tobacco Company, 20 July. Report number 35823. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1983b. Mutagenicity evaluation of linalool in an in vitro cytogenetic assay measuring chromosome aberration frequencies in Chinese hamster ovary (CHO) cells. Unpublished report from Lorillard Tobacco Company, 7 October. Report number 35824. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1984a. A 14-Day single dose subacute toxicity study in the rat. Unpublished report from Lorillard Tobacco Company, 12 January. Report number 36660. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1984b. Acute dermal irritation study in rabbits. RIFM report number 1795, June 1. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1985. Acute dermal irritation study in rabbits. RIFM report number 3099, June 1. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1986a. Unscheduled DNA synthesis in rat primary hepatocytes. Report from Lorillard Tobacco Company, 5 May, cited in Heck et al., 1989. Report number 35825. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1986b. A 14-day single dose subacute toxicity study. Unpublished report from Lorillard Tobacco Company, 17 July. Report number 36498. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1986c. Acute dermal irritation study in rabbits. RIFM report number 5664, June 1. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1987. Mutagenicity evaluation of lynalyl acetate in the Ames Salmonella/microsome reverse mutation assay. Unpublished report from Lorillard Tobacco Company. 30 January. Report number 36497. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1989. Reproductive and developmental toxicity screening test of coriander oil administered orally via gavage to Crl:CD™ (SD)BR female rats. Unpublished report from Lorillard Tobacco Company, 12 April. Report number 36124. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1992. Linalool and dehydolinalool. Acute toxicity and local tolerance. Submission to EPA by Rhone-Poulenc Inc., 11 September. Report number 23272. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1994. Mutagenicity test on linalool in the L5178Y TK$^{\pm}$ mouse lymphoma forward mutation assay with a confirmatory assay. Unpublished report from Lorillard Tobacco Company, 3 March. Report number 35827. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1997a. Human patch test of linalyl acetate. Unpublished report from Takasago International Corporation, 9 December. Report number 31609. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1997b. Delayed contact hypersensitivity study of linalyl acetate in guinea pigs. Unpublished report from Takasago International Corporation, 9 December. Report number 31606. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2000. Evaluation of the ability of linalylacetate to induce chromosome aberrations in cultured peripheral human lymphocytes. Unpublished report from Hoffmann-LaRoche, 22 June. Report number 38576. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2001. Micronucleus test in bone marrow cells of the mouse with linalool. Unpublished report from Hoffmann-LaRoche, 18 November. Report number 38577. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2003. Topical photoallergy screening test of cinnamaldehyde and cinnamic acid in male albino hairless guinea pigs. RIFM report number 41273. (RIFM, Woodcliff Lake, NJ, USA).

Rockwell, P., Raw, I., 1979. A mutagenic screening of various herbs, spices, and food additives. Nutrition and Cancer 1, 10–15.

Roe, F.J.C., Field, W.E.H., 1965. Chronic toxicity of essential oils and certain other products of natural origin. Food and Cosmetics Toxicology 3, 311–324.

Russin, W.A., Hoesly, J.D., Elson, C.E., Tanner, M.A., Gould, M.N., 1989. Inhibition of rat mammary carcinogenesis by monoterpenoids. Carcinogenesis 10, 2161–2164.

Sasaki, Y.F., Imanishi, H., Phta, T., Shirasu, Y., 1989. Modifying effects of components of plant essence on the induction of sister-chromatid exchanges in cultured Chinese hamster ovary cells. Mutation Research 226, 103–110.

Satoh, T., 1987. Role of carboxylesterases in xenobiotic metabolism. In: Hodgson, E., Bend, J.R., Philpot, R.P. (Eds.), Reviews in Biochemical Toxicology. vol. 8. Elsevier, New York, pp. 155–181.

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

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

TNO, 1994. Volatile Components in Food-Qualitative and Quantitative Data. Supplement 5 to the 6th Ed. In: Maarse, H., Visscher, C.A., Willemsens, L.C., Nijssen, L.M., Boelens, M.H. TNO Nutrition and Food Research Center, Zeist, The Netherlands.

Troy, W.R., 1977. Doctoral Dissertation: The comparative respiratory irritation potential of fourteen fragrance raw materials. Private communication to RIFM. Report number 9011.

Van Duuren, B.L., Blazej, T., Goldschmidt, B.M., Katz, C., Melchionne, S., Sivak, A., 1971. Cocarcinogenesis studies on mouse skin and inhibition of tumor induction. Journal of the National Cancer Institute 46, 1039–1044.

Voet, D., Voet, J.G., 1990. Biochemistry. John Wiley & Sons, New York.

Vollmuth, T.A., Heck, J.D., Ratajczak, H.V., Thomas, P.T., 1989. Immunotoxicity assessment of flavoring ingredients using a rapid and economical screen. The Toxicologist 9, 206.

Wattenberg, L.W., 1991. Inhibition of azoxymethane-induced neoplasia of the large bowel by 3-hydroxy-3,7,11-trimethyl-1,6,10-dodecatriene (nerolidol). Carcinogenesis 12, 151–152.

Williams, R.T., 1959. Detoxification Mechanisms. The Metabolism and Detoxication of Drugs, Toxic Substances, and Other Organic Compounds, 2nd Edn. Chapman and Hall Ltd, London. pp. 67–69.

Yoo, Y.S., 1986. Mutagenic and antimutagenic activities of flavoring agents used in foodstuffs. Journal of Osaka Shiritso Daigaku Igaku Zasshi 34, 267–288.

Zava, D.T., Dollbaum, C.M., Blen, M., 1998. Estrogen and progestin bioactivity of foods, herbs, and spices. Proceedings of the Society for Experimental Biology and Medicine 217, 369–378.