SUMMARY OF DATA FOR CHEMICAL SELECTION

LINALOOL

CAS NO. 78-70-6

BASIS OF NOMINATION TO THE CSWG

The nomination of linalool to the CSWG is based on high production volume, widespread human exposure, and an unknown potential for adverse health effects from long-term administration. Linalool came to the attention of the CSPG because of information supplied by the Food and Drug Administration (FDA) from a review of "GRAS" substances used as spices and food additives. According to the FDA data, linalool is found in 63 different spices. It is also a common flavoring in beverages and foods and has widespread use in cosmetics. North American consumption in the flavor and fragrance industry alone has been estimated to be 2.2 million lbs. Occupational exposure to linalool in the United States is significant, estimated to be nearly 250,000 workers in 106 industries. Linalool is found in herbs, other plants, and in household and pet products, helping to account for its widespread occurrence in the environment. Although virtually every person in the United States has some degree of exposure to linalool, no studies in humans or experimental animals were found that address or identify the chronic effects of linalool.

SELECTION STATUS

ACTION BY CSWG: 7/16/97

Studies requested:

- Metabolism studies
- Mechanistic studies to include examination of the role of α_{2u}-globulin in transport
- Carcinogenicity
- *In vitro* cytogenetic analysis
- *In vivo* micronucleus assay

Priority: High

Rationale/Remarks:

- High production levels
  Widespread exposure as an ingredient in natural products and as an environmental pollutant
- Lack of chronic toxicity data
- Test in parallel with citronellol

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

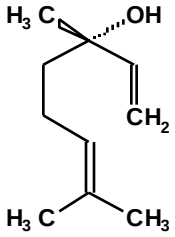
Dr. Dan Benz, Center for Food Safety and Applied Nutrition (CFSAN), Food and Drug Administration (FDA), and Dr. Ed Matthews (formerly with CFSAN), provided information on linalool from FDA's Priority-Based Assessment of Food Additives (PAFA) database. Ms. Joellen Putnam, Scientific Project Manager, Flavor and Extract Manufacturers' Association (FEMA) provided a copy of the FEMA monograph on linalool.

Linalool
78-70-6

CHEMICAL IDENTIFICATION

CAS Registry Number:	78-70-6
Chemical Abstracts Service Name:	1,6-Octadien-3-ol, 3,7-dimethyl- (8CI,9CI)
Synonyms and Trade Names:	Allo-ocimenol; 2,6-dimethyl-2,7-octadien-6-ol; 2,6- dimethylocta-2,7-dien-6-ol; 3,7-dimethyl-1,6-octadien-3-ol; 3,7-dimethylocta-1,6-dien-3-ol; linalol; β-linalool; linalyl alcohol
Structural Class:	Acyclic, unsaturated, monoterpenoid tertiary, allylicalcohol

Structure, Molecular Formula and Molecular Weight:



$C_{10}H_{18}O$ Mol. wt.: 154.25

Chemical and Physical Properties: (from Clark (1988) and Lide (1995), unless otherwise noted)

Description:	Mobile, clear, colorless liquid
Boiling Point:	198-199%C
Refractive index:	1.4615 at 20%C
Flash Point:	~76%C (TCC)
Density:	0.865-0.870 g/cm^3 at 15%C; 0.8622 g/cm^3 at 20%C
Solubility:	Insoluble in water (<1% at 20%C); soluble in ethanol, diethyl phthalate, benzyl benzoate, most aliphatic and aromatic esters, mineral oil, and chlorinated solvents

Technical Products and Impurities: Linalool is available in several grades (purity): 925 (94-96%); Special (96-97.5%); Coeur (97.5-99%); Extra (99%); Pure, FCC (99.5%); and Supra, FCC (99.7%) (Millenium Specialty Chemicals, 1995a,b,c,d,e, 1997).

EXPOSURE INFORMATION

Production and Producers: Linalool is listed in the EPA's TSCA Inventory (NLM, 1997a).

In the 1950s, nearly all linalool used in perfumery was isolated from essential oils, particularly from rosewood oil. Currently, this method is used only in countries where oils with a high linalool content are available and where the importation of linalool is restricted. Since linalool is an important intermediate in the manufacture of vitamin E, several large-scale processes have been developed for its production. Preferred starting materials and/or intermediates are the pinenes and 2-methyl-2-hepten-6-one. Most perfumery grade linalool is synthetic (Bauer *et al*., 1988).

Linalool can be obtained naturally by fractional distillation and subsequent rectification from oils of the following: Cajenne rosewood, Brazil rosewood, Mexican linaloe, Shiu, and coriander seeds (NLM, 1997b). It can also be produced synthetically by one of several methods. In the first method, α-pinene from turpentine oil is selectively hydrogenated to *cis*-pinane, which is oxidized with oxygen in the presence of a radical initiator to give a mixture of ca. 75% *cis*- and 25% *trans*-pinane hydroperoxide. The mixture is reduced to the corresponding pinanols with sodium bisulfite or a catalyst. The pinanols are separated by fractional distillation and are pyrolyzed to linalool. In the second method, pyrolysis of _-pinene yields myrcene. Addition of hydrogen chloride to myrcene results in a mixture of geranyl, neryl, and linalyl chlorides. Reaction of this mixture with acetic acid-sodium acetate in the presence of copper(I) chloride gives linalyl acetate; linalool is obtained after saponification. In the third method, 2-methyl-2-hepten-6-one is converted into linalool in excellent yield by base-catalyzed ethynylation with acetylene to dehydrolinalool. This is followed by selective hydrogenation of the triple bond to a double bond in the presence of a palladium-carbon catalyst (Bauer *et al*., 1988).

Pure linalool possesses a fresh, clean, mild, light floral odor with a slight citrus impression. The products produced by each synthetic process display slight odor variations, inherent to that process. For most purposes, the prime grades from each source are interchangeable. Less pure grades may show enough variation from the true note to render them usable only in specific applications. Because of the concentrations used, the variations in odor usually are more critical in fragrances than in flavors. The small amount of natural linalool available is produced from Bois de Rose oils from Brazil and Paraguay and Ho-leaf oil from Taiwan and China. Natural linalool is now considered a specialty (Clark, 1988).

Linalool and its esters are distributed in a large number of essential oils from trace to major amounts. Its early production was accomplished in 1875 by isolation from Cayenne Bois de Rose oil from French Guiana. Subsequent production shifted to Brazil (Bois de Rose oil) and Mexico (Linaloe oil) and more recently from Ho-leaf and Ho-wood oil (Taiwan, China, and Japan). Availability of natural linalool has remained fairly constant since 1925. The volume of supply of natural product, however, has been dwarfed by the supply of synthetic product. The demand for linalool cannot be met by the production of natural oils (Clark, 1988).

Consumption in 1988 of synthetic linalool in the flavor and fragrance industry was estimated at 8 million lbs. worldwide; North American consumption was estimated at 2.2 million lbs. Because synthetic linalool is a by-product of vitamin production, manufacturers of vitamins A and E convert intermediate feedstocks into linalool and other products in order to maintain their plants at optimum capacity. The major sources of synthetic linalool are Fritzsche (BASF), Givaudan (Hoffmann-LaRoche), Glidco (SCM), and Kuraray. These manufacturers can be divided into two groups: (1) producers with in- house capacity to convert intermediates into vitamins, such as BASF and Hoffmann-LaRoche; and (2) producers who sell linalool or downstream products to the flavor and fragrance industry and to vitamin producers, such as Glidco and Kuraray (Clark, 1988).

Use Pattern: Because of its structure, linalool can be regarded as a basic material for a very large range of other terpenoids. It can be converted to terpineol, geraniol, and citral, and used in the preparation of citronellol, the ionones, vitamin A, farnesol, and sesquiterpenes. To the perfumer, linalool and its esters represent a source of fragrances which no other material can provide. A good grade of linalool has a soft sweetness quite different from its isomeric primary alcohols, geraniol and citronellol. Having a lower boiling point than these alcohols, it serves as a natural and desirable top note in perfumes (Bedoukian, 1985).

Linalool is used in large quantities in soap and detergent products, and has been found to be stable and nondiscoloring. Its mellow character and fresh odor are of value in giving a natural character to perfumes based on synthetic aromatics. These properties extend the use of linalool to a wide range of floral and nonfloral fragrances (Bedoukian, 1985; Bauer *et al.*, 1988).

Although world fragrance sales have lagged in some areas in recent years, the growing trend to liquid versus solid detergents will contribute significantly to the steady growth of linalool. In 1984 the ratio of solid to liquid detergent was 4:1, and it was expected to reach 1:1 by 1990. As liquid detergents contain twice the amount of fragrance, they will be important outlets for aroma chemicals (Clark, 1988).

Linalool and many of its esters have been identified as constituents of the flavors of many fruits and as natural components of many essential oils used in flavorings, mainly of the citrus type. Numerous natural and artificial flavorings for alcoholic and nonalcoholic beverages, hard and soft candies, chewing gum, ice creams, gelatin puddings, condiment relishes, meat products, and baked goods contain various amounts of linalool and its esters. The GRAS list of flavoring ingredients published in 1965 lists linalool and nine of its common esters (Bedoukian, 1985; FEMA, 1997).

Linalool has also been registered for use in 10 pesticidal products, all in pet care products. The formulations include: dips (3.0%), sprays (0.925-1.0%) [for animals, homes, and carpets], shampoos (3.7%), foggers (1.0%), an emulsifiable concentrate (37.0%), and a technical product (92.5%) (US Environmental Protection Agency, 1997).

Human Exposure: There is potential for widespread, low-level exposures to linalool in general and consumer populations resulting from its presence as a flavoring agent in foods, as a fragrance material, and as a component of pet care products. The National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 245,476 workers in 106 industries, including 109,311 female employees, were potentially exposed to linalool in the workplace. The NOES database does not contain information on the frequency, level, or duration of exposure to workers of any chemical listed therein (NLM, 1997a).

Environmental Occurrence: Linalool is found widely in nature as a constituent of essential oils. Table 1 presents the linalool content of several essential oils (Clark, 1988).

Linalool's production and use in perfume, as a synthetic flavoring agent, top note, and modifier in citrus and carbonated beverages may result in its release to the environment

through various waste streams. Linalool is found naturally in oils from herbs, leaves, flowers, and wood. Linalool has been detected in drinking water, mill effluent, wastewater treatment plant influent, foods, and household products. If released to soil, linalool will have very high mobility. Volatilization of linalool may be important from moist and dry soil surfaces. Insufficient data are available to determine the rate or importance of biodegradation of linalool in soil. If released to water, linalool may adsorb to suspended

Table 1. Linalool content in essential oils

Essential Oil	Percentage (%)
ho leaf	80-90
bois-de-rose	65-90
coriander	60-80
linaloe	30-70
sweet basil	30-50
lavandin	30-40
lavender	20-50
mentha citrate	20-50
spike lavender	20-40
petit grain	20-30
bergamot	10-30
clary sage	10-25
ylang ylang	10-15
geranium	8-15
sweet marjoram	3.0
laurel leaf	2.0
rosemary	2.0
lime	0.5
chamomile	0.3
anise	0.2
acacia	trace
cassis	trace
clove	trace
cumin	trace
nutmeg	trace

solids and sediment. Linalool may volatilize from water surfaces with estimated half-lives for a model river and model lake of 2.4 days and 21 days, respectively. An estimated BCF value of 106 suggests that linalool will bioconcentrate somewhat in aquatic organisms. Insufficient data are available to determine the rate or importance of biodegradation of linalool in water. If released to the atmosphere, linalool will exist in the vapor phase in the ambient atmosphere. Vapor-phase linalool is degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals; the half-life for this reaction in air is estimated to be about 3.2 hours. Vapor-phase linalool will also react with ozone in the atmosphere; the half-life for this reaction in air is estimated to be about 38 minutes. Due to its use and natural occurrence, the general population can be exposed to linalool through foodstuffs (NLM, 1997b).

Linalool has been qualitatively identified in one out of 10 secondary effluent samples from municipal and industrial wastewater treatment plants (Ellis *et al.*, 1982). Linalool has also been qualitatively identified in mill effluent from an aerated stabilization basin in Springfield, OR (Hrutfiord *et al.*, 1975). Linalool has been detected in two secondary effluent samples at Fort Polk, LA, November 4-5, 1980, at concentrations of 0.25 and 0.11 ug/L (Hutchins *et al.*, 1983). At a municipal wastewater infiltration system, linalool was detected in the basin influent at a concentration of 2.42 ug/L (Bedient *et al.*, 1983).

Linalool has been detected as a volatile component of pineapple guava (2.67 ug/g), in three different varieties of nectarines (<10 ppb, 10 ug/kg, and 500 ug/kg), edible Korean chamchwi, apricots (671, 365, and 150 ug/kg), plums (18 and 8 ug/kg), Harvester peaches, orange essences, unpasteurized orange juices, chicken, and Kogyoku apple juice (Binder & Flath, 1988; Engel *et al.*, 1988; Chung *et al.*, 1993; Gómez *et al.*, 1993; Meredith *et al.*, 1989; Moshonas & Shaw, 1990, 1994; Shahidi *et al.*, 1986; Takeoka *et al.*, 1988; Yajima *et al.*, 1984).

Linalool has been qualitatively identified in the headspace of the following household products: liquid wax for marble, ceramic, linoleum, plastic, and varnished wood floors and detergent (Knöppel & Schauenburg, 1989). Linalool has also been qualitatively identified in perfumes, colognes, bar soaps, shampoo, solid deodorant, hand lotion, nail enamel remover, detergent powder, bleach powder, fabric softener, and liquid air freshener (Wallace *et al.*, 1991).

Linalool has been detected in emissions from the 30 agricultural and natural plant types (crops and vegetation) found in California's Central Valley (Winer *et al.*, 1992).

Regulatory Status: No standards or guidelines have been set by NIOSH or OSHA for occupational exposure to or workplace allowable levels of linalool. The American Conference of Governmental Industrial Hygienists (ACGIH) has not recommended a threshold limit value (TLV) or biological exposure index (BEI) for linalool. Linalool is a "generally recognized as safe" (GRAS) substance approved by the FDA as a direct food additive (synthetic flavoring substance) for human and animal consumption (FDA, 1996).

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological or case reports investigating the association of exposure to linalool and cancer risk in humans were identified in the available literature. Despite the widespread exposure to linalool, few studies of its effects on humans have been conducted. One exception is dermal irritancy and sensitization. In a study of 39 oils and perfumes, 32% solutions of linalool were described as moderately irritating to 50 adult male volunteers (Motoyoshi *et al.*, 1979). FEMA summarizes several studies of persons with eczema or dermatitis attributed to cosmetics. Very few who received patch testing to diagnose the cause of the disease responded to linalool solutions ranging from 5 to 20% (FEMA, 1997).

DeGroot and Liem (1983) noted that many cosmetic reactions are not recognized as such when the reaction involves the face. Their review of the literature suggested, however, that sensitization to linalool is probably rare. Linalool was removed from the standard series at one clinic after only a 0.5% incidence of positive reactions had been observed in 792 patients with eczema. In another study, patch testing of 149 of 487 patients with cosmetic dermatitis revealed no cases of contact sensitivity to linalool.

Animal Data:

Acute. Acute systemic toxicity from linalool is associated with its central depressive effects. Clinical signs include ataxia, a decrease in spontaneous motor activity, lateral recumbency, narcosis, and respiratory disturbances leading to death (Powers & Beasley, 1985). Table 2 presents acute toxicity data for linalool. Information on insects was

included because it shows the effectiveness of linalool as a pesticide when contrasted against the mammalian data.

Animal models have been used to study linalool as an irritant and sensitizer. Linalool was one of 39 oils and perfumes included in a comparative study on dermal irritancy. Undiluted linalool was severely irritating to rabbits, moderately irritating to guinea

Table 2. Acute toxicity data for linalool

Route	Species	Toxicity value
gavage	Osborne-Mendel rat	LD_{50}=2.8 g/kg
oral	mouse	LD_{50}=2.2-3.5 g/kg
skin	rabbit	LD_{50}=8 g/kg
skin	fly	LD_{50}=189 _g
inhalation	mite	ED_{50}=1.633 _l
inhalation	house fly	LC_{50}=6.8 _g/cm^3
inhalation	red flour beetle	LC_{50}>1730 _g/cm^3
intramuscular	mouse	LD_{50}=8 g/kg
subcutaneous	mouse	LD_{50}=1.47 g/kg
intraperitoneal	mouse	LD_{50}=0.34 g/kg
intraperitoneal	CD-1 mouse	LD_{50}=0.2 g/kg
intraperitoneal	rat	LD_{50}=0.31 g/kg

Jenner *et al.* (1963); FEMA (1997)

pigs, and not reactive on the shaved skin of miniature swine (Motoyoshi *et al.,* 1979). In a modified Draize procedure using guinea pigs, linalool did not induce sensitization (Sharp, 1978).

Subacute/Subchronic Studies. Most subacute and subchronic studies of linalool have been directed at specific endpoints. An exception was a study in which strain-dependent toxicity was seen in rats receiving multiple doses of 0.25 to 4 g/kg of linalool via skin absorption. Wistar rats receiving this regimen for 29 days lost weight and experienced discomfort, piloerection, lethargy, and ataxia. Clinical chemistry tests showed dose-related increases in alkaline phosphatase and increased glucose and cholesterol at the 4 g/kg dose. Sprague-Dawley rats were similarly exposed for 91 days. Even at 0.25 g/kg, depressed activity was evident. At the highest dose, 11 of 40 animals died. In addition, squamous epithelial hyperplasia developed at the application site and liver and kidney weights were increased (Moreno, 1980).

Several plant species rich in linalool are used as anticonvulsants by practitioners of traditional medicine in the Brazilian Amazon (Elisabetsky *et al.*, 1995). Thus, it is not surprising that depressed activity was observed in the Moreno study. In mice, linalool also diminished caffeine-induced hyperactivity and showed anticonvulsive activity against pentylenetetrazole and strychnine (Atanassova-Shopova *et al.*, 1973; Buchbauer, 1991). Glutamatergic transmission plays a role in the anticonvulsant actions of linalool (Elisabetsky *et al.*, 1995). Linalool caused a dose-related inhibition of [^{3}H]-glutamate binding in CNS membranes from the cortex of male Wistar rats; 6500 _mol of linalool produced approximately the same inhibition as 430 _mol of phenobarbital.

Chronic/Carcinogenicity Studies. No 2-year carcinogenicity studies of linalool in animals were identified in the available literature. Specialized tests in strain A mice and tests of linalool as a tumor inhibitor have been conducted.

Linalool was one of 41 food additives examined for their ability to induce lung tumors in strain A mice (Stoner *et al.*, 1973). The animals received intraperitoneal (ip) injections of each compound for eight weeks and were killed at 24 weeks after the first injection. Linalool was negative in this test, as were some compounds now shown to be liver carcinogens.

Linalool did not inhibit the formation of 7,12-dimethylbenz[a]anthracene (DMBA) induced mammary tumors in rats. Mammary tumors were induced in 55-day-old female Sprague-Dawley rats with a single gastric intubation of 65 mg/kg of DMBA in sesame oil. A diet containing 1% linalool (w/w) was started two weeks before DMBA administration and continued for 20 weeks until the end of the experiment. The 50 rats in the linalool group developed a total of 96 tumors, with an average of 1.9 tumors per rat. The 51 positive control animals developed 119 tumors, with an average of 2.3 tumors per rat. The median tumor latency for the linalool group was 84 days compared with 56 days for the control group. These differences show a trend but were not statistically significant (Russin *et al.*, 1989).

The inhibitory capacity of linalool on intestinal neoplasia induced by azoxymethane (AOM) was examined. Male F344 rats (19 per group) were given six subcutaneous (sc) doses of AOM (15 mg/kg twice a week for 3 weeks). Three days later, the experimental group was placed on a diet containing 5 mg linalool/gram of food. The rats were fed this diet for 22 weeks when they were killed. The gastrointestinal tract was opened and

the presence of tumors recorded. Complete autopsies were also done and pathological tissues taken for histological study. Linalool produced no effect on the number of tumors of the large bowel. A modest decrease in adenocarcinomas of the duodenum, from 50% in AOM-only rats (0.6 tumors/rat) to 26% in linalool-fed rats (0.3 tumors/rat) occurred, but was not statistically significant (Wattenberg, 1991).

Short-Term Tests: Table 3 presents data on the genotoxicity of linalool. Linalool possesses antimicrobal and antifungal activity, which may explain the consistently negative findings in the Ames assay. Results in other test systems are mixed. However, the mutagenic activity of linalool differs completely from allyl compounds possessing strong leaving groups; these compounds (e.g., allyl bromide, allyl methane sulfonate) tend to be alkylating agents and direct mutagens (Lutz *et al*., 1982).

Linalool has been examined for potential antimutagenic and antitumorigenic activity. At 200µg/ml linalool was not effective against the activity of 4-nitroquinoline 1-oxide in *Escherichia coli* strain WP2s (Ohta *et al.,* 1986). In *Drosophila melanogaster,* linalool did not affect tumor expression in the melanotic strain, tu bw;+s-tu, but it caused retardation of development (FEMA, 1997).

Table 3. *In vitro* genotoxicity of linalool

Test system/strain or cell line (locus)	Dose; study details (activation, solvent, dose, schedule....)	Result	Reference
	Endpoint: Mutation		
S. typhimurium TA98, TA100, TA1535, TA1537 & TA1538	10 mg/plate; with or without rat liver S9	-	Heck *et al.*, 1989
S. typhimurium TA100	Plate test, with or without activation, concentration not given	-	Lutz *et al.*, 1982
S. typhimurium TA92, TA94, TA98, TA100, TA1535, TA1537 & TA2637	1 mg/plate; with or without S9	-	Ishidate *et al.*, 1984
S. typhimurium TA98 & TA100	0.05-300 _l of urine from rats administered 0.5 ml of linalool by gavage, with rat liver S9 or _-glucuronidase	-	Rockwell & Raw, 1979
Mouse lymphoma L5178Y TK+ cells	150 & 200 _g/ml; with or without rat liver S9, 4-hr exposure to linalool, 10-14 days growth	+ w/o S9, w+ with S9	Heck *et al.*, 1989
E. coli WP2 uvrA	0.125-1.0 mg/plate, mutation frequency of trp+ revertants	-	Yoo, 1986
	Endpoint: Chromosomal Aberrations		
CA/Chinese hamster fibroblasts	Highest dose was 0.25 mg/ml; DMSO vehicle, no metabolic activation	-	Ishidate *et al.*, 1984
SCE in CHO K-1 cells	Doses of 33.3 to 1000 _mol per plate	-	Sasaki *et al.*, 1989
	Endpoint: DNA damage		
B. subtillus M45 (rec-) & H17 (rec+)	Maximum of 10 _l per disk, spore rec- assay with DMSO vehicle	+	Yoo, 1986
DNA repair (UDS)/Rat hepatocytes	Highest dose was 0.50 ug	-	Heck *et al.*, 1989

CA = chromosome aberration, SCE= sister chromatid exchange, CHO=Chinese hamster ovary,
UDS=unscheduled DNA synthesis.

Metabolism: The metabolic activity of linalool appears to be a balance between biliary excretion of polar conjugates with _-glucuronidase and the formation of 4-hydroxylated products, a reaction mediated by microsomal cytochrome P450.

Linalool contains a polar structure, the hydroxyl group, and does not have to undergo Phase I metabolism before conjugation. When 500 mg/kg of radiolabeled linalool was given intragastrically to Wistar rats, there was no significant delay between dosing and

appearance of radioactivity in the urine (Parke *et al.*, 1974a). After several hours, substantial amounts of radiolabeled carbon dioxide appeared in the respired air, suggesting that linalool was entering pathways of intermediary metabolism. Fecal excretion was delayed, occurring mainly between 36 and 48 hours after dosing, partly because of extensive biliary excretion and reabsorption of partially hydrolyzed glucuronidase and sulfatase conjugates. After 72 hours, 3% of the radioactivity remained in the tissues, mainly in the liver, gut, skin, and skeletal muscle.

After 72 hours, about 58% of the dose was excreted in the urine, 25% in the air, and 16% in the feces (Chadra & Madyastha, 1984). About 10% of the administered dose was radiolabeled urea in the urine. Substantial amounts of dihydrolinalool and tetrahydrolinalool (free and conjugated) were also detected.

Repeated administration of linalool over one week produced different results, suggesting that repeated dosing induces oxidative metabolic pathways. The major metabolites detected in the urine of male rats administered 600 mg/kg of linalool orally each day for six days were 8-hydroxylinalool and 8-carboxylinalool, products of C-8 methyl oxidation. Dihydrolinalool and tetrahydrolinalool were not observed (Chada & Madyastha, 1984).

Over much longer periods, cytochrome P450 levels showed a complex response to the administration of linalool. When 500 mg/kg of linalool was administered by gastric intubation to Wistar rats, an initial increase in P450 occurred. P450 levels became depressed by day seven. By day 30, however, P450 levels were elevated 50%, and they remained that way throughout the 64-day study (Parke *et al.*, 1974b).

Linalool was also administered to male Wistar rats by intragastric intubation at 500 mg/kg per day (Parke *et al.*, 1974b). Animals were killed at 0, 3, 7, 14, 30, and 64 days to determine liver weights and enzyme activities. A slight but a significant increase in liver weight was observed only on the 64th day. Cytochromes P450 and b_5 concentrations were biphasic, eventually increasing to a plateau. Biphenyl 4-hydroxylase activity was unaffected. Alcohol dehydrogenase activity showed initial changes and returned to normal by the 14th day. 4-Methylumbelliferone glucuronyl transferase increased dramatically, rising to 150% of normal values by the 64th day ($P<0.001$), an apparent physiological adaptation to the increased metabolic demand and an indication that conjugation with glucuronides remains an important metabolic pathway.

Another effect of linalool administration on the drug-metabolizing liver enzymes was discovered by Roffey and coworkers (1990). For five days, 1.5 g/kg of linalool was administered to male Wistar rats by gastric intubation. Absolute and relative liver weights were increased in rats killed 24 hours after the final linalool dose and cytochrome P450 levels were slightly elevated. Linalool caused an increase in the level of liver peroxisomal bifunctional enzyme and induction of palmitoyl CoA _-oxidation; together the results suggested that linalool is a weak peroxisome proliferator.

Other Biological Effects: Lewis and coworkers (1994) evaluated the spatial and electronic parameters of 19 acyclic terpenes, including linalool, to predict their metabolic activation or detoxification by the cytochrome P450 family of enzymes. Linalool did not have a shape or electronic parameters appropriate for metabolic activation by P450 1A2, so the authors believed that linalool would not be mutagenic. Linalool was also an unlikely substrate of P450 2E so the authors concluded that it would be unlikely to initiate or promote malignancy through the formation of reactive oxygen species. The acyclic terpenes, including linalool, had a molecular pattern similar to phenobarbitone, a P450 2B substrate. The authors noted the discrepancy between their calculations for linalool and the findings of Roffey and coworkers, which showed linalool to be a weak peroxisome proliferator.

Structure/Activity Relationships: Linalool is generally found as a racemic mixture. It has several freely rotating bonds and can achieve a conformation that resembles cyclic ring terpenes suggesting that its toxicity may share some similarities with such compounds. The presence of the hydroxy group on linalool also appears important since it enhances the excretion of linalool. Considering these features led to the selection of four other spice ingredients for the structure/activity analysis.

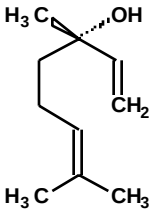
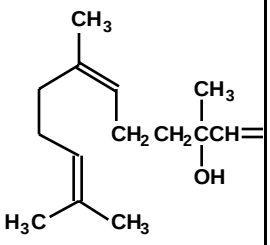
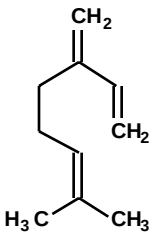
The NTP has conducted chronic carcinogenicity studies on the spice ingredients d-limonene, and geranyl acetate (NTP 1987, 1990). d-Limonene has become the lead compound for a mechanism believed to produce renal tubule toxicity and/or tumors in male rats. This mechanism requires the compound or a metabolite to bind tightly to the male rat protein, $\__{2u}$ -globulin. To do this, the compound must have two features, the right size and shape to fit into the receptor pocket and the ability to bind to specific amino acids contained within the $\__{2u}$ -globulin structure.

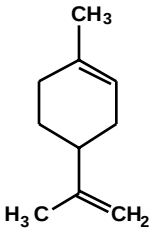
The geranyl acetate study might have provided more information to help define the male rat kidney effect. Food grade geranyl acetate contains 71% geranyl acetate and 29% citronellyl acetate. Both of these compounds are racemic mixtures with structural similarities to linalool. Renal tubular cell adenomas were found in two low-dose male rats, an incidence above historical controls. No renal tumors were found in the high-dose group, but only 36% of them lived to the end of the study. All high-dose male and female mice were dead by week 91 because of a dosing error, further limiting the negative findings of the study (NTP, 1987).

Two additional compounds, myrcene and nerolidol, were also selected. Myrcene is closely related to linalool except that it does not contain a polar substituent. Thus, myrcene should have toxicologic and therapeutic profiles similar to linalool but the effects might be more pronounced at the same dosage since myrcene is probably retained in the body longer than linalool. Nerolidol is a racemic mixture similar to linalool but the bulky side chain argues against any ability to bind to $_{-2u}$ -globulin.

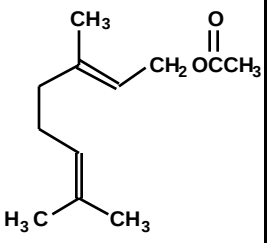
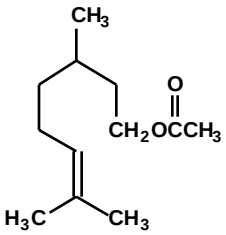
Table 4 summarizes carcinogenicity and mutagenicity data on these chemicals as well as linalool.

Table 4. Summary of information on linalool and structurally related compounds

Chemical [CAS No.]	Carcinogenicity data	Mutagenicity data
Linalool [78-70-6] 	negative in strain A mouse lung adenoma assay (Stoner *et al*., 1973) oral administration did not inhibit AOM-induced duodenal adenocarcinomas in male F344 rats or DMBA-induced mammary tumors in female Sprague-Dawley rats (Russin *et al*., 1989; Wattenberg, 1991)	negative in *S. typhimurium* TA92, TA97, TA98, TA100, TA102, TA1535, TA1537, TA1538, or TA2637 with or without metabolic activation (Rockwell & Raw, 1979; Ishidate *et al*., 1984; Heck *et al*., 1989; Fujita *et al.*, 1992) weakly positive with S9 in mouse lymphoma L5178 TK+ cells (Heck *et al*., 1989) positive in *B. subtillus* N45 & H17 rec- assay (Yoo, 1986) negative in *E. coli* WP2 uvrA (Yoo, 1986) negative for chromosomal aberrations in Chinese hamster lung fibroblasts (Ishidate *et al*., 1984) and SCEs in CHO K-1 cells (Sasaki *et al*., 1989) did not induce UDS in rat hepatocytes (Heck *et al*.,1989)
Nerolidol [7212-44-4] 	oral administration significantly inhibited AOM-induced large bowel neoplasms and slightly decreased AOM-induced duodenal adenocarcinomas in male F344 rats (Wattenberg, 1991)	NDF
Myrcene [123-35-3] 	oral administration did not inhibit the production of DMBA-induced mammary tumors in Sprague-Dawley rats (Russin *et al*., 1989)	negative in the Chinese hamster V-79/6-thioguanine assay with or without S9 (CCRIS, 1997) negative for chromosomal aberrations and SCEs in human lymphocytes and for mutation at the HPRT locus in V79 cells (Roscheisen *et al*., 1992a)

		negative in the *in vivo* bone marrow chromosome aberration test with rats (Roscheisen *et al*., 1992a) reduced SCE-induced S9-activated cyclophosphamide in human lymphocytes and V79 cells; also inhibited SCEs in V79 cells induced by aflatoxin B1 but not BAP or DMBA (Roscheisen *et al*., 1992b)
d-Limonene [5989-27-5] 	**Mouse** no evidence for carcinogenic activity in male B6C3F_1 mice administered 250 or 500 mg/kg or in female B6C3F_1 mice administered 500 or 1000 mg/kg by gavage, 5 days a week for 2 years (NTP, 1990) **Rat** clear evidence of carcinogenic activity (increased incidences of tubular cell hyperplasia and kidney tumors) in male F344/N rats that received 75 or 150 mg/kg but no evidence in female F344/N rats that received 300 or 600 mg/kg by gavage, 5 days a week for 2 years (NTP, 1990) kidney tumors in male F344 rats but not in _-$_{2U}$ globulin-deficient male NCI Black Reiter rats given 150 mg/kg of d-limonene 5 days a week for 30 weeks following administration of EHEN for two weeks (Dietrich & Swenberg, 1991)[1] inhibition of mammary tumors produced by DMBA or n-nitrosomethyl urea in Sprague-Dawley or Wistar rats; results are not completely consistent, but several regimens (for short periods before and after DMBA, for short periods after DMBA, and for long periods) produced significant	negative in *S. typhimurium* TA98, TA100, TA102, TA1535, TA1537, UTH8413, and YTH8414 in the presence or absence of S9 (CCRIS, 1997; NTP, 1990) negative in the L5178Y/TK+/- assay in the presence or absence of S9 (NTP, 1990) negative for chromosomal aberrations or SCEs in cultured CHO cells in the presence or absence of S9 (NTP, 1990) no antimutagenic activity toward NNK in *S. typhimurium* strain TA1535 (Teel, 1993)[1]

[1]EHEN= n-ethyl-n-hydroxyethylnitrosamine; NNK=(methylnitrosamino)-1-(3-pyridyl)-1-butanone

	decreases in incidence and/or multiplicity and/or significant increases in latency (CCRIS, 1997)	
Geranyl acetate [*cis*=141-12-8] [*trans*=105-87-3] Food grade geranyl acetate contains 29% citronellyl acetate  *trans*-geranyl acetate  c itronellyl acetate	**Mouse** no evidence of carcinogenic activity in male and female B6C3F$_1$ mice gavaged with 500 or 1000 mg/kg (food grade) 5 times a week for up to 2 years; survival of high-dose males and females (91 weeks) and of low dose females may have been inadequate for detection of late appearing tumors (NTP, 1987) **Rat** no evidence of carcinogenic activity in male and female F344/N rats gavaged with 1000 or 2000 mg/kg (food grade) 5 times a week for 2 years; reduced 2-year survival in high- dose males (18/50) lowered sensitivity and the the marginal increases of squamous cell papillomas of the skin and renal tubular cell adenomas observed in low-dose male rats may have been related to administration of geranyl acetate (NTP, 1987)	negative in a *Bacillus subtilis* rec-assay (NTP, 1987) negative in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 with or without S9 (NTP, 1987)

REFERENCES

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 terpineol. *Izv. Inst. Fiziol., Sof.,* **15**, 149-156 [cited in: FEMA, 1997]

Bauer, K., Garbe, D. & Surburg, H. (1988) Flavors and Fragrances. In: Gerhartz, W., Yamamoto, Y.S., Elvers, B., Rounsaville, J.F. & Schulz, G., eds., *Ullmann's Encyclopedia of Industrial Chemistry*, 5th rev. ed., Vol. A11, New York, VCH Publishers, pp. 156-157

Buchbauer, G., Jirovetz, L., Jager, W., Dietrich, H., Plank, C. & Karamat, E. (1991) Aromatherapy: Evidence for sedative effects on the essential oil of lavender after inhalation. Z. *Naturf., C: Biosciences,* **46**(11-12), 1067-1072

Bedient, P.B., Springer, N.K., Baca, E., Bouvette, T.C., Hutchins, S.R. & Tomson, M.B. (1983) Ground-water transport from wastewater infiltration. *J. Environ. Eng. (N.Y.),* **109**(2), 485-501

Bedoukian, P.Z. (1985) *Perfumery and Flavoring Synthetics*, 3rd. rev. ed., Wheaton, IL, Allured Publishing Corp., pp. 267-282

Binder, R.G. & Flath, R.A. (1988) Volatile components of pineapple guava. *J. Agric. Food Chem.*, **37**, 734-736

CCRIS (1997) *Chemical Carcinogenesis Research Information System*, National Library of Medicine, Bethesda, MD, searched May 1997

Chadha, A. & Madyastha, K.M. (1984) Metabolism of geraniol and linalool in the rat and effects on liver and lung microsomal enzymes. *Xenobiotica*, **14**(5), 365-374

Chung, T.Y., Eiserich, J.P. & Shibamoto, T. (1993) Volatile compounds isolated from edible Korean chamchwi (*Aster scaber* Thunb). *J. Agric. Food Chem.*, **41**, 1693-1697

Clark, G.S. (1988) A profile: An aroma chemical - Linalool. *Perfumer Flav.*, **13**(8-9), 49-54

deGroot, A.C. & Liem, D.H. (1983) Facial psoriasis caused by contact allergy to linalool and hydroxycitronellal in an after-shave. *Contact Dermatitis*, **9**(3), 230-232

Dietrich, D.R. & Swenberg, J.A. (1991) The presence of alpha 2u-globulin is necessary for d-limonene promotion of male rat kidney tumors. *Cancer Res.*, **51**, 3512-3521

Elisabetsky, E., Marschner, J. & Souza, D.O. (1995) Effects of linalool on glutamatergic system in the rat cerebral cortex. *Neurochemical Res.*, **20**(4), 461-465

Ellis, D.D., Jone, C.M., Larson, R.A. & Schaeffer, D.J. (1982) Organic constituents of mutagenic secondary effluents from wastewater treatment plants. *Arch. Environ. Contam. Toxicol.*, **11**, 373-382

Engel, K.H., Flath, R.A., Buttery, R.G., Mon, T.R., Ramming, D.W. & Teranishi, R. (1988) Investigation of volatile constituents in nectarines. 1. Analytical and sensory characterization of aroma components in some nectarine cultivars. *J. Agric. Food Chem.*, **36**, 549-553

FDA (1996) Food and Drugs. *Code Fed. Regul.*, Title 21, Parts 172.515, 182.60, 582.60, pp. 51-58, 425-426, 526-527

FEMA (1997) *FEMA Database: Linalool (FEMA No. 2635)*, Washington, DC, Flavor and Extract Manufacturers' Association, 53 pp.

Fujita, H., Sami, C. & Sasaki, M. (1992) Mutagenicity test of food additives with *S. typhimurium* TA97 and TA102 (VII) (Jpn.). *Ann. Rep. Tokyo Metc. Res. Lab.* P.H., **43**, 219-227

Gómez, E., Ledbetter, C.A. & Hartsell, P.L. (1993) Volatile compounds in apricot, plum, and their interspecific hybrids. *J. Agric. Food Chem.*, **41**, 1669-1676

Heck, J.D., Vollmuth, T.A., Cifone, M.A., Jagannath, D.R., Myhr, B. & Curren, R.D. (1989) An evaluation of food flavouring ingredients in a genetic toxicity screening battery. *Toxicologist,* **9**(1), 257 [cited in: FEMA, 1997]

Hrutfiord, B.F., Friberg, T.S., Wilson, D.F. & Wilson, J.R. (1975) Organic compounds in aerated stabilization basin discharge. *Tappi,* **58**(10), 98-100

Hutchins, S.R., Tomson, M.B. & Ward, C.H. (1983)Trace organic contamination of ground water from a rapid infiltration site: A laboratory-field coordinated study. *Environ. Toxicol. Chem.,* **2**, 195-216

Ishidate, M., Jr., Safune, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M. & Matsuoka, A. (1984) Primary mutagenicity screening of food additives currently used in Japan. *Food Chem. Toxicol.*, **22**(8), 623-636

Jenner, P.M., Hagan, E.C., Taylor, J.M., Cook, E.L. & Fitzhugh, O.G. (1964) Food flavourings and compounds of related structure. I. Acute oral toxicity. *Food Cosmet. Toxicol.*, **2**, 327-343

Knöppel, H. & Schauenburg, H. (1989) Screening of household products for the emission of volatile organic compounds. *Environ. Internat.*, **15**, 413-418

Koch, R.B. & Desaiah, D. (1974) Preliminary studies on rat olfactory tissue: Effects of odorants on Na+-K+ ATPases activity. *Life Sci.,* **15**, 1005-1015

Lewis, D.F.V., Ioannides, C., Walker, R. & Parke, D.V. (1994) Safety evaluations of food chemicals by "COMPACT" 1. A study of some acyclic terepenes. *Food Chem. Toxicol.*, **32**(11), 1053-1059

Lide, D.R., ed. (1995) *CRC Handbook of Chemistry and Physics*, 76th ed., Boca Raton, FL, CRC Press, p. 3-229

Lutz, D., Eder, E., Neudecker, T. & Henschler, D. (1982) Structure-mutagenicity relationship in _,_- unsaturated carbonylic compounds and their corresponding allylic alcohols. *Mutat. Res.*, **93**, 305- 315

Meredith, F.I., Robertson, J.A. & Horvat, R.J. (1989) Changes in physical and chemical parameters associated with quality and postharvest ripening of Harvester peaches. *J. Agric. Food Chem.*, **37**, 1210-1214

Millenium Specialty Chemicals (1995a) *Product Data Sheet: Linalool 925*, Jacksonville, FL

Millenium Specialty Chemicals (1995b) *Product Data Sheet: Linalool Coeur*, Jacksonville, FL

Millenium Specialty Chemicals (1995c) *Product Data Sheet: Linalool Extra*, Jacksonville, FL

Millenium Specialty Chemicals (1995d) *Product Data Sheet: Linalool Pure, FCC*, Jacksonville, FL

Millenium Specialty Chemicals (1995e) *Product Data Sheet: Linalool Supra, FCC*, Jacksonville, FL

Millenium Specialty Chemicals (1997) *Product Data Sheet: Linalool Special*, Jacksonville, FL

Moreno, O.M., Ratcliffe, H.R. & Moreno, M.T. (1980) *90 Day Subacute Dermal Toxicity with Linalool in Rats*, report to RIFM, unpublished [cited in: FEMA, 1997]

Moshonas, M.G. & Shaw, P.E. (1994) Quantitative determination of 46 volatile constituents in fresh, unpasteurized orange juices using dynamic headspace gas chromatography. *J. Agric. Food Chem.*, **42**, 1525-1528

Moshonas, M.G. & Shaw, P.E. (1990) Flavor evaluation of concentrated aqueous orange essences. *J. Agric. Food Chem.*, **38**, 2181-2184

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. *Cosmet.Toilet.*, **94**, 41-48

NLM (1997a) *RTECS (Registry of Toxic Effects of Chemical Substances)*, Bethesda, MD, National Library of Medicine, searched 5/97 [Record No. 53763]

NLM (1997b) *HSDB (Hazardous Substances Data Bank)*, Bethesda, MD, National Library of Medicine, searched 5/97 [Record No. 645]

Northover, B.J. & Verghese, J. (1962) The pharmacology of certain terpene alcohols & oxides. *J. Sci. Industr. Res.*, **21C**, 342-345

NTP (1987) *Toxicology and Carcinogenesis Studies of Food Grade Geranyl Acetate (71% Geranyl Acetate, 29% Citronellyl Acetate) (CAS No. 105-87-3) in F344/N Rats and B6C3F$_1$ Mice (Gavage Study) (Technical Report Series No. 252; NIH Publ. No. 88-2508)*, Research Triangle Park, NC, National Toxicology Program

NTP (1990) *Toxicology and Carcinogenesis Studies of d-Limonene (CAS No. 5989-27-5) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies) (Technical Report Series No. 347; NIH Publ. No. 90- 2802)*, Research Triangle Park, NC, National Toxicology Program

Ohta, T., Watanabe, M., Watanabe, K. & Shirasu, Y. (1986) Inhibitory effects of flavourings on mutagenesis induced by chemicals in bacteria. *Fd. Chem. Toxic.*, **24**(1), 51-54

Parke, D.V., Rahman, Kh.J.Q. & Walker, R. (1974b) Effect of linalool on hepatic drug-metabolizing enzymes in the rat. *Biochem. Soc. Transact.*, **2**, 615-618

Parke, D.V., Rahman, Kh.J.Q. & Walker, R. (1974a) The absorption, distribution and excretion of linalool in the rat. *Biochemical Society Transactions*, **2**, 612-615

Powers, K.A. & Beasley, V.R. (1985) Toxicologic aspects of linalool: A review. *Vet. Hum. Toxicol.,* **27**(6), 484-485

Rockwell, P. & Raw, I. (1979) A mutagenic screening of various herbs, spices, and food additives. *Nutr. Cancer,* **1**(4), 10-15

Roffey, S.J., Walker, R. & Gibson, G.G. (1990) Hepatic peroxisomal and microsomal enzyme induction by citral and linalool in rats. *Food Chem. Toxicol.,* **28**(6), 403-408

Roscheisen, C., Zamith, H., Vidal, M., Paumbartten, F.J. & Speit, G. (1992a) Antimutagenic effects of beta-myrcene. *Mutat. Res.,* **271**(2), 180 [Abstract]

Roscheisen, C., Zamith, H., Paumbartten, F.J. & Speit, G. (1992b) Myrcene: a specific inhibitor of the cytochrome P450 system? *Mutagenesis,* **7**(2), 166-167 [Abstract]

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**(11), 2161-2164

Sasaki, Y.F., Imanishi, H., Ohta, T. & Shirasu, Y. (1989) Modifying effects of components of plant essence on the induction of sister chromatid exchanges in cultured Chinese hamster ovary cells. *Mutat. Res.,* **226**, 103-110

Shahidi, F., Rubin, L.J. & D'Souza, L.A. (1986) Meat flavor volatiles: A review of the composition, techniques of analysis, and sensory evaluation. *Crit. Rev. Food Sci. Nutr.,* **24**(2), 141-243

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. & Gori, G.B. (1973) Test for carcinogenicity of food additives and chemotherapeutic agents by the pulmonary tumor response in strain A mice. *Cancer Res.,* **33**, 3069-3085

Takeoka, G.R., Flath, R.A., Güntert, M. & Jennings, W. (1988) Nectarine volatiles: Vacuum steam distillation versus headspace sampling. *J. Agric. Food Chem.,* **36**, 553-560

Teel, R.W. (1993) Effect of phytochemicals on the mutagenicity of the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pridyl)-1-butanone (NNK) in *Salmonella typhimurium* strain TA1535. *Phytother. Res.,* **7**(3), 248-251

US Environmental Protection Agency (1997) *USEPA/OPP's Chemical Ingredients Database,* Washington, DC, Office of Pesticide Programs, searched 6/6/97

Wallace, L.A., Nelson, W.C., Pellizzari, E., Raymer, J.H. & Thomas, K.W. (1991) *Identification of Polar Organic Compounds in Consumer Products and Common Microenvironments (EPA/600/D-91/074; NTIS PB91-182865),* Research Triangle Park, NC, Research Triangle Institute, 16 pp.

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**(1), 151-152

Winer, A.M., Arey, J., Atkinson, R., Aschmann, S.M., Long, W.D., Morrison, C.L. & Olszyk, D.M. (1992) Emission rates of organics from vegetation in California's Central Valley. *Atmos. Environ.*, **26A**(14), 2647-2659

Yajima, I., Yanai, T., Nakamura, M., Sakakibara, H. & Hayashi, K. (1984) Volatile flavor components of Kogyoku apples. *Agric. Biol. Chem.*, **48**, 849-855

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