SUMMARY OF DATA FOR CHEMICAL SELECTION

β-CITRONELLOL
CAS NO. 106-22-9

BASIS OF NOMINATION TO THE CSWG

The nomination of citronellol to the CSWG is based on high production volume, widespread human exposure, and an unknown potential for adverse health effects from long-term administration. Citronellol 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, citronellol is found in 17 different spices. It is also a common flavoring in beverages and foods and is one of the most widely used fragrance materials, having the sweet aroma of rose. Occupational exposure to citronellol in the United States is significant, estimated to be over 160,000 workers in 62 industries. Citronellol is present in high concentrations in citronella, geranium, and rose oils, accounting for additional human exposure. It is also closely related to citronellal and seven esters also having "GRAS" status.

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: Moderate

Rationale/Remarks:

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

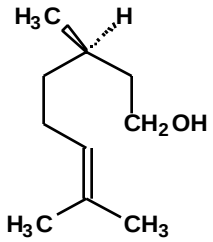
INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

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 citronellol 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 citronellol.

CHEMICAL IDENTIFICATION

CAS Registry Number: 106-22-9

Chemical Abstracts Service (8CI,9CI) Name: 6-Octen-1-ol, 3,7-dimethyl-



Synonyms and Trade Names: Cephrol; citronellol; β-citronellol; *dl*citronellol; −-citronellol; Rhodinol; Rodinol

Structural Class: Acyclic, unsaturated, monoterpenoid tertiary, allylic alcohol

Structure, Molecular Formula and Molecular Weight:

$C_{10}H_{20}O$ Mol. wt.: 156.27

Chemical and Physical Properties:

Natural citronellol consists solely of the β form although α-citronellol has been prepared (Bedoukian, 1985).

Description: Colorless, oily liquid with a rose-like odor (FEMA, 1997)

Boiling Point: 224%C (Lide, 1995)

Vapor pressure: ~0.009 mm Hg at 20%C (FEMA, 1997)

Refractive index: 1.4543 at 20%C (Lide, 1995)

Flash Point: >93%C (CC) (FEMA, 1997)

Density: 0.8560 g/cm^3 at 20%C (Lide, 1995)

Solubility: Very slightly soluble in water; miscible with alcohol, ether (Budavari, 1996)

Technical Products and Impurities: Citronellol is available in several grades (purity): Citronellol Terpenes (2.0-20.0%), Citronellol Select (20.0-25.0%), Citronellol 80 (80.0-85.0%), Citronellol Prime (85.0-87.0%), and Citronellol AJ, FCC (94.0-96.0%) (Millenium Specialty Chemicals, 1995a,b,c,d,e).

EXPOSURE INFORMATION

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

For citronellol, the method of production is closely related to usage. Premium quality citronellol used in expensive perfumes is organoleptically controlled (Millenium Speciality Chemicals, 1995b). (-)-Citronellol is still obtained mainly from geranium oil by saponification followed by fractional distillation. Much larger quantities of (+)- and (Å)-citronellol are used and are prepared by partial or total synthesis. The following methods have been reported for the production of citronellol: (1) synthesis of (+)- and (Å)-citronellol from the citronellal fraction of essential oils; (2) synthesis of (Å)-citronellol from geraniol fractions of essential oils; (3) synthesis of (Å)-citronellol from synthetic geraniol-nerol or citral; and (4) preparation of (-)-citronellol from optically active pinenes (Bauer *et al.*, 1988).

In the first method, (+)-citronellal is obtained by distillation of Java citronella oil and is hydrogenated to (+)-citronellol in the presence of a catalyst (e.g., Raney nickel). Similarly, (Å)-citronellol is prepared from the (Å)-citronellal fraction of *Eucalyptus citriodora* oil. In the second method, citronellol is produced by catalytic hydrogenation of saponified geraniol fractions obtained from *Java citronella* oil, followed by fractional distillation. Selective hydrogenation of the double bond in the 2-position of geraniol in geraniol-citronellol mixtures isolated from essential oils can be achieved by using Raney cobalt as a catalyst. In the third method, a considerable amount of commercial synthetic (Å)-citronellol is produced by partial hydrogenation of synthetic geraniol and/or nerol. Another starting material is citral, which can be hydrogenated, e.g., in the presence of a catalyst system consisting of palladium, ruthenium, and trimethylamine. In the fourth method, (+)-cis-pinane obtained from pinene is pyrolyzed to give (+)-3,7-dimethyl-1,6-octadiene; this is converted into (-)-citronellol (97% purity) by reaction with triisobutylaluminum or diisobutylaluminum hydride, followed by air oxidation and hydrolysis of the resulting aluminum alcoholate (Bedoukian, 1985; Bauer *et al.*, 1988).

Recent import data indicate that 202,000 and 109,000 kg of citronellol were imported into the U.S. from the UK, France, Germany, Switzerland, China, and Japan in 1995 and 1996, respectively (Anon., 1997).

Use Pattern: Citronellol is one of the most widely used fragrance materials, particularly for rose notes (aroma) and for floral compositions in general. As a flavor material,

citronellol is added for bouquetting purposes to citrus compositions. It is the starting material for numerous citronellyl esters and for hydroxydihydocitronellol, an intermediate in the production of hydroxydihydrocitronellal, and it may be added directly to soaps and detergents (Bauer *et al.*, 1988; Millenium Speciality Chemicals, 1995b).

The bulk of citronellol used in industry is derived from pinene, however, considerable quantities of natural citronellol isolated from essential oils are used by perfumers. Because of the varying quantities of geraniol and trace impurities present, the natural citronellol possesses a distinctive olfactory characteristic. Reduction of citronellal also yields a type of citronellol preferred by some perfumers. The annual consumption of citronellol by perfumers in the U.S. was estimated to be around 200,000 lbs. in the 1980s (Bedoukian, 1985).

Numerous natural and artificial flavorings in alcoholic and nonalcoholic beverages (1-4 ppm), hard and soft candies (2-18 ppm), chewing gum (8-9 ppm), ice creams (1-40 ppm), gelatin puddings (2-6 ppm), and baked goods (6-20 ppm) contain various amounts of citronellol. The GRAS list of flavoring ingredients published in 1965 includes citronellol and seven of its common esters (Bedoukian, 1985; FEMA, 1997).

Citronellol has been detected as a volatile component of orange juice (0.015-0.08 ppm), lemon peel oil, bilberry (0.001 ppm), guava (0.06-0.82 ppm), nutmeg (trace), beer (0.01 ppm), white wine (trace), red wine (0.02-0.04 ppm), black tea (2-10 ppm), green tea (1 ppm), mango, star anise (500-800 ppm), and plum brandy (0-16 mg/l) (De Vincenzi *et al.*, 1987; FEMA, 1997).

Human Exposure: There is potential for widespread, low level exposures to citronellol in general and to consumer populations resulting from its presence as a flavoring agent in foods and as a fragrance material. 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 163,706 workers in 62 industries, including 87,309 female employees, were potentially exposed to citronellol 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: In many natural products, citronellol occurs as a mixture of its two enantiomers; the pure (+)-citronellol [1117-61-9] and (-)-citronellol [7540-51-4]

form are seldom found (Bauer *et al.*, 1988). Citronellol has been reported in nearly a hundred essential oils. It is interesting that rose oils yield the practically pure (-)-form whereas geranium oils give a mixture of both with the (-)-form predominating (Bedoukian, 1985).

Citronellol was identified in influent wastewater during a screening for non-regulated organic compounds in municipal wastewater in Göteborg, Sweden (Paxéus & Schröder, 1996).

Citronellol has also been qualitatively identified in perfumes, shampoo, after-shave lotion, nail enamel remover, and fabric softener (Wallace *et al.*, 1991).

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

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposure to citronellol and cancer risk in humans were identified in the available literature.

Animal Data: No 2-year carcinogenicity studies of citronellol in animals were identified in the available literature. Toxicity information identified was limited to acute and subchronic studies. Acute toxicity values are shown in Table 1.

Table 1. Acute toxicity data for citronellol

Route	Species	LD_{50} (mg/kg)	Reference
Oral	Rat	3450	Moreno, 1973
Intramuscular	Mouse	4000	Northover & Verghese, 1962
Subcutaneous	Mouse	880	Nozawa, 1952
Dermal	Rabbit	1780-3520	Moreno, 1973

No adverse effects were reported when citronellol, as part of a 50:50 mixture with linaloo1, was added to the diet of rats for 12 weeks at a level calculated to provide an average daily intake of 50 mg/kg. A slight retardation of growth rate and decreased food efficiency uptake in males were attributed to unpalatability of the test diet (Oser, 1967).

The ability of citronellol to inhibit azoxymethane (AOM) induced neoplasia has been assessed. Male F344 rats (18-19 rats per group) were administered subcutaneous AOM doses of 15 mg/kg bw twice a week for 3 weeks followed by 5 mg citronellol/g of diet for 22 weeks. Citronellol administration resulted in a modest decrease in the number of adenocarcinomas of the duodenum which was not statistically significant. Incidence in the control and citronellol-treated rats was 50% and 26%, respectively; multiplicity was 0.6 and 0.4 tumors/rat, respectively. Citronellol had no effect on tumors of the large bowel (Wattenberg, 1991).

Short-Term Tests: At concentrations of 8-16 ppm, citronellol was not mutagenic in *Salmonella typhimurium* strains TA98 or TA100. Strain TA98 was tested with and without S9 while TA100 was only tested without activation (Kono *et al.*, 1995). Rockwell and Raw (1979) also reported negative results in strains TA98 and TA100 when citronellol was tested at 0.05-100 &l with S9. Urine samples from rats administered 0.5 ml of citronellol were also negative when assayed with strains TA98 and TA100 (Rockwell & Raw, 1979).

Citronellol (17 &g/disk) was negative in the rec-assay in *Bacillus subtilis* strains H17 and M45 (Oda *et al.*, 1978).

Metabolism: Available information on the metabolism, retention, and excretion of citronellol is extremely limited.

FEMA (1994) speculates that citronellol will be metabolized in humans principally by alcohol oxidation and 4-oxidation to yield 2,6-dimethyl-6-octendioic acid. This acid would be excreted primarily in the urine as an unspecified glucuronic acid conjugate. FEMA bases these speculations on studies of citronellal and on branched-chain aliphatic alcohols and related aldehydes, overall.

Citing studies by Parke (1974), Phillips and coworkers (1976), and Diliberto and coworkers (1988), FEMA notes that branched-chain aliphatic alcohols are rapidly

absorbed from the gastrointestinal tract. Once absorbed, FEMA notes that metabolic pathways available to form oxygenated polar metabolites include 4-oxidation, alcohol oxidation, hydration, selective hydrogenation, and conjugation. Based on the work of Chadha and Madyastha (1982, 1984) and Ishida and coworkers (1989), FEMA speculates that 4-oxidation of citronellal to yield diols will compete favorably with oxidation of citronellol to yield citronellal. This would lead to the formation of 2,6-dimethyl-2-octendioic acid (reduced Hildebrandt's acid). FEMA supports the plausibility of this metabolic pathway by noting that 2,6-dimethyl-2-octendioic acid (Asano & Yamakawa, 1950) and an alcohol precursor, 8-hydroxy-3,6-dimethyl-6-octenoic acid (Fischer & Beilig, 1940) have been reported as urinary excretion products of *d*-citronellol.

While the metabolic pathway described above is plausible, it is unlikely that it is the only one. Ishida and coworkers (1989) found an acidic metabolite in the urine of rabbits administered citronellal. They also found three neutral metabolites, (-)- and (+) *p*-menthane-3,8-diols and isopregol. The *p*-menthane diols were also formed when rabbit gastric juice was mixed with citronellal. It also has been shown that rabbits can metabolize citronellol to reduced Hildebrandt acid and a 7-hydroxymethyl precursor. Together these two compounds accounted for only 10% of the administered dose (Lewis *et al.,* 1994).

Citronellal can be metabolized in rabbits by undergoing a proton-catalysed cyclization and conjugation with glucuronic acid (Lewis *et al.*, 1994). Citronellol, the corresponding alcohol, does not undergo cyclization. How these differences influence uptake, excretion, and metabolism is not known.

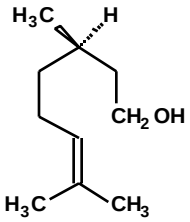
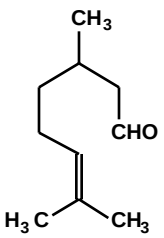
Certain other spice components are known to induce liver enzymes, an important consideration in their metabolism and potential toxicity. Very little information was found on citronellol. Chadha and Madyastha (1984), citing previous work, noted that rat liver and lung microsomal preparations catalyze the hydroxylation of citronellol to form 4- oxidation products.

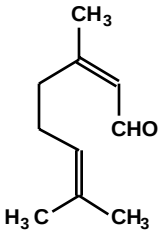
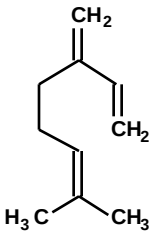
<u>Other Biological Effects</u>: Citronellol was one of 19 acyclic terpenes evaluated for potential toxicity/carcinogenicity by "Computer Optimized Molecular Parametric Analysis of Chemical Toxicity" (COMPACT) which uses molecular orbital determinations of a chemical's spatial and electronic parameters for prediction of its

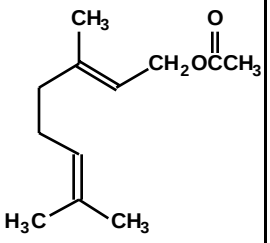
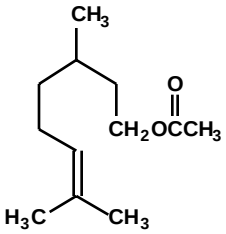
metabolic activation or detoxification by the cytochrome P-450 (CYP) super family of mixed-function oxidase enzymes. Previous studies characterized the spatial dimensions of the CYP1K1, 1A2, and 2E1 enzymes which are known to activate mutagens and carcinogens. None of the terpenes was found to have shape or electronic parameters appropriate for metabolic activation by CYP1A1 or 1A2. In addition, none of the chemicals had spatial parameters critical for substrates of CYP2E, and are therefore unlikely to induce formation of reactive oxygen species (ROS) or to initiate or promote malignancy or toxicity by mechanisms involving ROS (Lewis *et al*., 1994).

Structure Activity Relationships: Citronellol was chosen as a representative of the various impure oils (mixtures), spices, flavorings, fragrances, and household products that contain some form of citronella. As structurally related compounds, food grade geranyl acetate, which contains 29% citronellyl acetate, and the closely related citronellal were obvious choices. Other compounds selected were citral and myrcene, two spice components that like citronellol have an acyclic structure that can fold into an open ring-like configuration. Citral, a mixture of geraniol and nerol, is on test at NTP. It has a polar substituent that may provide an active site. Myrcene, which does not contain a polar substituent, is the simplest member of the structurally related group. A summary of information found in the available literature is presented in Table 2.

Table 2. Summary of information on citronellol and structurally related compounds

Chemical Name	Carcinogenicity Data	Mutagenicity Data
Citronellol [106-22-9]  	modest inhibition of AOM-induced adenocarcinomas of the duodenum (Wattenberg, 1991) unlikely to be carcinogenic in a Computerized Optimized Molecular Parametric Analysis of Chemical Toxicity (COMPACT) evaluation (Lewis *et al*., 1994)	negative in *S. typhimurium* strains TA98 and TA100 with or without S9 (Kono *et al*., 1995; Rockwell & Raw, 1979) negative in *B. subtilis* rec assay (Oda *et al*., 1978)
Citronellal [106-23-0]  	unlikely to be carcinogenic in a COMPACT evaluation (Lewis *et al*., 1994)	negative in *S. typhimurium* strains TA98 and TA100 with or without S9 (Kasamaki *et al*., 1982) induced chromosomal aberrations in Chinese hamster B241 cells (Kasamaki *et al*., 1982) posttreatment did not influence mitomycin C-induced sister

		chromatid exchanges in Chinese hamster ovary cells (Sasaki *et al.*, 1989)
Citral [5392-40-5]  	NTP prechronic studies in rats and mice (microencapsulation in feed) have been completed, and citral is on test in rats and mice (NTP, 1997) Several studies have predicted the carcinogenic activity of citral in the NTP bioassay. Six predicted it to be noncarcinogenic: evaluation by COMPACT, CASE/MULTICASE, rule learning (RL), and DEREK as well as two on chemical structure, genotoxicity, and rodent toxicity considerations. Three predicted it to be carcinogenic based on chemical structure, genotoxicity, and rodent toxicity considerations. Equivocal results were predicted by the Rapid Screening of Hazard (RASH) method (Ashby, 1996; Benigni *et al.*, 1996; Bootman, 1996; Huff *et al.*, 1996; Jones & Easterly, 1996; Lee *et al.*, 1996; Lewis *et al.*, 1996; Marchant & The DEREK Group, 1996; Tennant & Spalding, 1996; Zhang *et al.*, 1996) inhibited tumor promotion in a two-stage skin-carcinogenesis study in hairless mice (Connor, 1991)	negative in *S. typhimurium* strains TA92, TA1535, TA100, TA1537, TA94, and TA98 with or without S9 (Lutz *et al.*, 1982; Ishidate *et al.*, 1984; Zeiger *et al.*, 1987) did not demonstrate antimutagenic potential against the activity of several chemical mutagens in *S. typhimurium* and *E. coli* or against UV-induced mutagenesis in *E. coli* (Ohta *et al.*, 1986a,b) negative for chromosomal aberrations in Chinese hamster fibroblast cells without S9 (not tested with S9) (Ishidate *et al.*, 1984) induced DNA repair in *B. subtilis* (NLM, 1997b) negative for chromosome aberrations and positive for sister chromatid exchanges in Chinese hamster ovary cells (Givaudan Corp., 1985)
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 SCEs-induced by S9-activated cyclophosphamide in human lymphocytes and V79 cells;

		also inhibited SCEs in V79 cells induced by aflatoxin B1 but not by BAP or DMBA (Roscheisen *et al.*, 1992b)
Geranyl acetate [*cis*=141-12-8] [*trans*=105-87-3] Food grade geranyl acetate contains 29% citronellyl acetate [150-84-5]  *trans*-geranyl acetate  citronellyl 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 two 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 two years; reduced 2-year survival in high dose males (18/50) lowered sensitivity and 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 *B. subtilis* rec-assay (NTP, 1987) negative in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 with or without S9 (NTP, 1987)

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