SCREENING-LEVEL HAZARD CHARACTERIZATION
Terpenoid Primary Alcohols and Related Esters Category

SPONSORED CHEMICALS
dl-Citronellol (CASRN 106-22-9)
Geraniol (CASRN 106-24-1)
Nerol (CASRN 106-25-2)
Acetylated myrcene (mixture) (CASRN 68412-04-4)

SUPPORTING CHEMICALS
Geranyl acetate (CASRN 105-87-3)
Citronellyl acetate (CASRN 150-84-5)
Linalyl acetate (CASRN 115-95-7)
Citral (CASRN 5392-40-5)
Linalool (CASRN 78-70-6)
Citral diethyl acetal (CASRN 7492-66-2)

The High Production Volume (HPV) Challenge Program[1] was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to "SIDS" (Screening Information Data Set[1,2]) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency's Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance[2,3] and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor's responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including

[1] U.S. EPA. High Production Volume (HPV) Challenge Program; http://www.epa.gov/chemrtk/index.htm.
[2] U.S. EPA. HPV Challenge Program – Information Sources; http://www.epa.gov/chemrtk/pubs/general/guidocs.htm.
[3] U.S. EPA. Risk Assessment Guidelines; http://cfpub.epa.gov/ncea/raf/rafguid.cfm.

Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT's focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

Chemical Abstract Service Registry Number (CASRN)	**Sponsored Chemicals** **106-22-9** **106-24-1** **106-25-2** **68412-04-4** **Supporting Chemicals** **5392-40-5** **150-84-5** **139-70-8** **78-70-6** **7492-66-2**
Chemical Abstract Index Name	**Sponsored Chemicals** **6-Octen-1-ol, 3,7-dimethyl-** **2,6-Octadien-1-ol, 3,7-dimethyl-, (2E)-** **2,6-Octadien-1-ol, 3,7-dimethyl-, (2Z)-** **1,6-Octadiene, 7-methyl-3-methylene-, acetylated** **Supporting Chemicals** **2,6-Octadienal, 3,7-dimethyl-** **6-Octen-1-ol, 3,7-dimethyl-, acetate** **Benzeneacetic acid, 3,7-dimethyl-6-octenyl ester** **1,6-Octadien-3-ol, 3,7-dimethyl-** **2,6-Octadiene, 1,1-diethoxy-3,7-dimethyl-**
Structural Formula	see Section 1

Summary

The category members are liquids with moderate water solubilities and moderate vapor pressures. They are expected to have high mobility in soil, with the exception of CASRN 68412-04-4, which is expected to have moderate mobility in soil. Volatilization of these chemicals from water and moist soils is considered moderate based on their Henry's Law constants. The rate of hydrolysis is considered negligible. The rate of atmospheric photooxidation is considered rapid. The substances in this category are considered to be readily biodegradable. These chemicals are expected to have low persistence (P1) and low bioaccumulation potential (B1).

Acute toxicity of the category members via oral exposure in rats and dermal exposure in rabbits is low. Three category members showed moderate to severe skin irritation in humans, rabbits and/or guinea pigs. CASRN 106-22-9 was irritating to rabbit eyes. CASRN 106-24-1 was a skin sensitizer in humans and mice. No systemic toxicity was observed during repeated oral exposures of rats to CASRN 106-22-9 at 50 mg/kg-day (as a mixture with supporting chemical CASRN 78-70-6) or to a mixture of CASRNs 106-22-9 and 106-24-1 at 500 mg/kg-day (highest doses tested). Repeated oral exposure of rats and mice to a mixture of supporting chemicals CASRNs 105-87-3 and 150-84-5 resulted in mortality, kidney effects and decreased body weights (both species) and stomach inflammation, and histopathological effects in the liver and myocardium (mice) at 2000 mg/kg-day; the NOAEL was 1000 mg/kg-day. Chronic repeated oral exposures of mice to the supporting chemical CASRN 5392-40-5 resulted in nephropathy

and irritation (oral ulcers) at site of administration at 60 mg/kg-day; no NOAEL was established. In an oral combined reproductive/developmental toxicity screening test in rats, supporting chemical CASRN 5392-40-5 showed histopathological changes in the stomach in parents at 1000 mg/kg-day and increased parental mortality and body weight gain at 160 mg/kg-day in an oral rat reproductive toxicity study. The reproductive NOAEL was 1000 mg/kg-day based on no effects; decreased pup body weights were seen at 500 mg/kg-day resulting in a developmental NOAEL of 160 mg/kg-day. In an oral combined reproductive/developmental toxicity screening study in rats, CASRN 7492-66-2 resulted in reduced maternal body weights and weight gains at 250 mg/kg-day; no reproductive toxicity was observed but reduced pup body weights at 500 mg/kg-day resulted in a developmental NOAEL of 250 mg/kg-day. In an inhalation prenatal developmental toxicity study, supporting chemical CASRN 5392-40-5 resulted in deaths and decreased body weights of dams at 0.43 mg/L-day but no developmental toxicity, resulting in maternal and developmental NOAELs of 0.21 and 0.43 mg/L-day (highest dose tested), respectively. The category members and supporting substances did not induce gene mutations *in vitro* or *in vivo*. Some positive results were seen for the supporting chemical CASRN 105-87-3 in *in vivo* chromosomal aberrations tests and in an *in vitro* mouse lymphoma assay. A mixture of the supporting chemicals with CASRNs 105-87-3 and 150-84-5 was not carcinogenic in rats or mice. The supporting chemical CASRN 5392-40-5 was equivocal for carcinogenicity in female mice.

The measured 96-hour LC_{50} for the primary terpenols and related esters category members for fish ranged from 6.12 to 14 mg/L, the measured 48-hour EC_{50} for aquatic invertebrates ranged from 7.75 to 15 mg/L, and the measured 72-hour EC_{50} for aquatic plants ranged from 2.38 to 62 mg/L (growth), and 3.32 to 16 mg/L (biomass).

No data gaps have been identified under the HPV Challenge Program.

The sponsor, the Flavor and Fragrance High Production Volume Consortia, submitted a Test Plan and Robust Summaries for the Terpenoid Primary Alcohols and Related Esters Category to EPA on December 27, 2000. EPA posted the submission on the ChemRTK HPV Challenge website on March 20, 2001 (http://www.epa.gov/chemrtk/pubs/summaries/terprial/c12965tc.htm). EPA comments on the original submission were posted to the website on July 25, 2001. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on May 1, 2004, which were posted to the ChemRTK website on September 9, 2004. This category consists of the following members:

dl-Citronellol	CASRN 106-22-9
Geraniol	CASRN 106-24-1
Nerol	CASRN 106-25-2
Acetylated myrcene[4]	CASRN 68412-04-4

Category Justification

Three members of the category (citronellol, geraniol and nerol) are terpenoid acyclic aliphatic primary alcohols and are likely to undergo similar metabolism. The fourth member (acetylated myrcene), is a mixture of terpenoid esters (primarily geranyl and neryl acetates) and alcohols, and is expected to hydrolyze rapidly *in vivo* to yield the corresponding alcohol category members geraniol and nerol, plus acetic acid (CASRN 64-19-7). Although the sponsor's quantitative information on metabolic similarities was limited, EPA considered this grouping acceptable for the purposes of the HPV Challenge Program.

Justification for Supporting Chemicals

The sponsor provided additional data for the aquatic toxicity and human health endpoints using the supporting chemicals listed below (see appropriate section).

Environmental Effects – Aquatic Toxicity

Geranyl acetate – acute toxicity to fish
Linalyl acetate – acute toxicity to invertebrates and aquatic plants

EPA agreed with using these data for the ecological endpoints because physical-chemical properties of these chemicals are expected to be similar and estimated values for ecological effects are similar.

Human Health Effects

Geranyl acetate (component of acetylated myrcene; when used as "food grade" product, it is a 50:50 mixture with citronellyl acetate) – acute, repeated-dose and genetic toxicity

[4]Acetylated myrcene is a mixture of primarily geranyl and neryl acetates (CASRNs 105-87-3 and 141-12-8). Minor components include limonene, nerol, geraniol and linyl acetate.

Citral (mixture of geranial – CASRN 141-27-5; and neral – CASRN 106-26-3) – repeated-dose and reproductive/developmental toxicity. This mixture has been reviewed in the OECD HPV Chemicals Program and the final documents can be found at the following website: http://www.chem.unep.ch/irptc/sids/OECDSIDS/5392-40-5.pdf.

Linalool (used in a 50:50 mixture with citronellol) – repeated-dose toxicity. Linalool has been reviewed in the OECD HPV Chemicals Program and the final documents can be found at the following website: http://www.chem.unep.ch/irptc/sids/OECDSIDS/78706.pdf.

Citral diethyl acetal – reproductive/developmental toxicity

EPA agreed with using these data for human health endpoints. For example, geranyl acetate is a component of one of the category members (acetylated myrcene). Also, geranial and neral are metabolized by similar alcohol and *omega*-oxidation pathways as geraniol. Further, geranial is assumed to be reduced to geraniol, based on the formation of analogous urinary metabolites.

1 Chemical Identity

1.1 Identification and Purity

The structures of the category chemicals are provided in Table 1.

Table 1. Terpenoid Primary Alcohols and Related Esters Category Sponsored and Supporting Chemical Structures

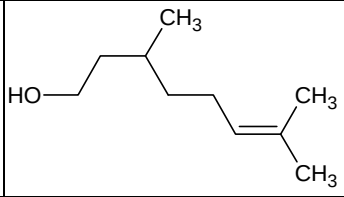
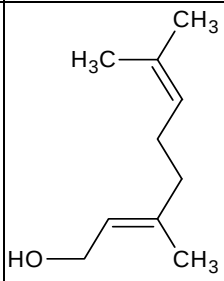
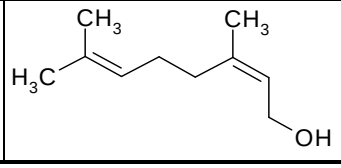
Sponsored Chemicals		
Chemical Name	**CASRN**	**Structure**
3,7-Dimethyl-6-octen-1-ol (dl-Citronellol)	106-22-9	
trans-3,7-Dimethyl-2,6-octadien-1-ol (Geraniol)	106-24-1	
cis-3,7-Dimethyl-2,6-octadien-1-ol (Nerol)	106-25-2	

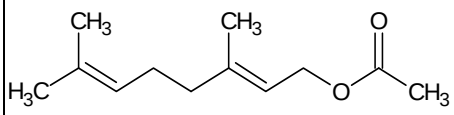
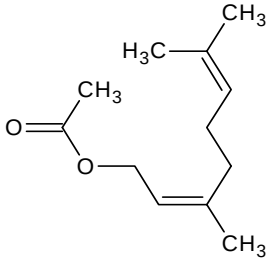
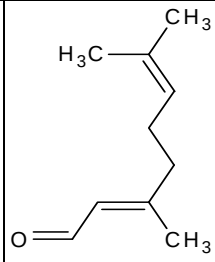
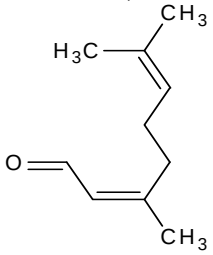
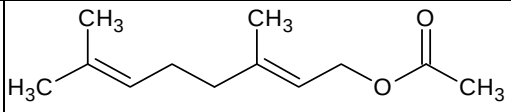
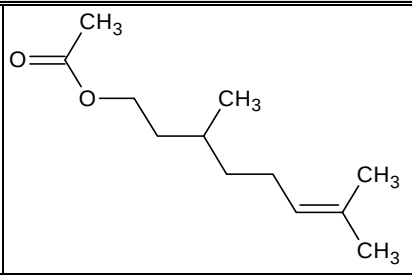
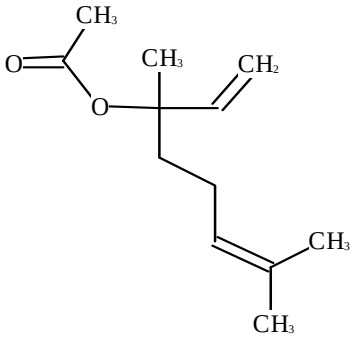
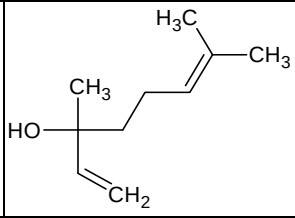
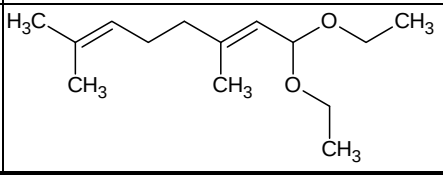
Table 1. Terpenoid Primary Alcohols and Related Esters Category Sponsored and Supporting Chemical Structures		
Acetylated myrcene* *Composition:* 60–65% geranyl and neryl acetates; 10% limonene; 2.5% nerol and geraniol; 2.5% linalyl acetate (a terpenoid ester); < 3% each of other components *Only structures of major components are shown	68412-04-4	 Geranyl acetate (also a supporting chemical)  Neryl acetate (CASRN 141-12-8)
Supporting Chemicals		
Chemical Name	**CASRN**	**Structure**
Citral (mixture of geranial and neral in varying ratios)	5392-40-5	 Geranial (CASRN 141-27-5)  Neral (CASRN 106-26-3)
Geranyl acetate	105-87-3	 Also see acetylated myrcene

Table 1. Terpenoid Primary Alcohols and Related Esters Category Sponsored and Supporting Chemical Structures		
Citronellyl acetate (‘food grade’ purity of geranyl acetate includes 21% citronellyl acetate)	150-84-5	
Linalyl acetate	115-95-7	
Supporting Chemicals		
Chemical Name	**CASRN**	**Structure**
Linalool (as 50:50 mixture with citronellol)	78-70-6	
Citral diethyl acetal	7492-66-2	

1.2 Physical-Chemical Properties

The physical-chemical properties of the category members are summarized in Table 2. The category members are liquids with moderate water solubilities and moderate vapor pressures.

Table 2. Physical-Chemical Properties of Terpenoid Primary Alcohols and Related Esters[1]

	Sponsored Chemicals				Supporting Chemicals					
Property	**dl-Citronellol**	**Geraniol**	**Nerol**	**Acetylated myrcene**	**Geranyl acetate**	**Citronellyl acetate**	**Linalyl acetate**	**Citral**	**Linalool**	**Citral diethyl acetal**
CASRN	**106-22-9**	**106-24-1**	**106-25-2**	**68412-04-4**	**105-87-3**	**150-84-5**	**115-95-7**	**5392-40-5**	**78-70-6**	**7492-66-2**
Molecular Weight	156.27	154.25	154.25	196.29	196.29	198.31	196.29	152.24	154.25[2]	226.36
Physical State	Liquid	Liquid	Liquid	Liquid	Liquid	Liquid	Liquid	Liquid	Liquid[2]	Liquid[3]
Melting Point	<25°C (measured)[2]	<-15°C (measured)[4]	<15°C (measured)[4]	No data	<25°C (measured)[2]	No data	<25°C (measured)[2]	<10°C (measured)	<25°C (measured)[2]	5 °C (estimated)[5]
Boiling Point	225°C (measured)	230°C (measured)	225°C (measured)	231°C (measured for neryl acetate); 244°C (measured for geranyl acetate)	240°C (measured)[2,5]	115°C at 10 mm Hg (measured)[2,4]; 239°C at 760 mm Hg (estimated)[6] 233.9°C at 760 mm Hg (measured)[7]	213°C (measured); 220°C (measured)[5]	227°C (measured)[2,5]; 230°C (measured)	198°C (measured)[2]	269.7°C (estimated)[5]
Vapor Pressure	0.071 mm Hg at 30°C (measured); 0.0441 mm Hg at 25°C (measured)[2]	0.023 mm Hg at 20°C (estimated); 0.03 mm Hg at 25°C (measured)[2]	0.060 mm Hg at 20°C (estimated); 0.03 mm Hg at 25°C (measured)[2]	0.03 mm Hg at 25°C (estimated for geranyl acetate); 0.02 mm Hg at 25°C (estimated for neryl acetate)	0.033 mm Hg at 25°C (measured)[2]	0.041 mm Hg at 25°C (estimated from reduced boiling point)[6]	0.07 mm Hg at 20°C (estimated); 0.111 mmHg (measured)[5]	0.068 mm Hg at 20°C (estimated); 1.0 mm Hg at 62°C (measured)[9]; 0.085 mm Hg at 25°C (measured)[6]	0.16 mm Hg at 25°C (measured)[2]	0.016 mm Hg at 25°C (estimated)[5]
Water Solubility	211 mg/L (estimated); 300 mg/L (measured)	256 mg/L (estimated); 600 mg/L (measured); 100 mg/L (measured)[2]	256 mg/L (estimated); 531 mg/L (measured)[2]	6.9 mg/L at 25°C (estimated for geranyl acetate); 6.9 mg/L at 25°C (estimated for neryl acetate)	18.24 mg/L at 25°C (estimated)[5]	5.7 mg/L at 25°C (estimated)[5]	20.12 mg/L at 25°C (estimated)[5]; 140 at 20°C (measured)	1,340 mg/L at 37°C (measured)[2, 4]	1,590 mg/L at 25°C (measured)[2]	2.45 mg/L at 25°C (estimated)[2]
Dissociation Constant (pK_a)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Henry's Law Constant	5.68×10^{-5} atm-m^3/mole (estimated)[5]	6.09×10^{-5} atm-m^3/mole (estimated)[5]	1.15×10^{-5} atm-m^3/mole (estimated)[5]	1.74×10^{-3} atm-m^3/mole (estimated)[5]	2.42×10^{-3} (estimated)[2,5]	2.33×10^{-3} atm-m^3/mole (estimated)[5]	1.74×10^{-3} (estimated)[5]	3.76×10^{-4} atm-m^3/mole (estimated)[5]	2.15×10^{-5} atm-m^3/mole (measured)[2]	1.23×10^{-3} atm-m^3/mole (estimated)[2]

Table 2. Physical-Chemical Properties of Terpenoid Primary Alcohols and Related Esters[1]

	Sponsored Chemicals				Supporting Chemicals					
Property	**dl-Citronellol**	**Geraniol**	**Nerol**	**Acetylated myrcene**	**Geranyl acetate**	**Citronellyl acetate**	**Linalyl acetate**	**Citral**	**Linalool**	**Citral diethyl acetal**
Log K_{ow}	3.1 (measured); 3.91 (measured)[2]	3.47 (estimated); 3.56 (measured)[2]	3.47 (estimated); 3.47 (measured)[2]	4.48 (estimated for neryl acetate); 4.48 (estimated for geranyl acetate)	4.04 (measured)[5]	4.56 (estimated)[2,5]	3.93 (measured)[5]	3.45 (estimated)[5]	2.97 (measured)[2]	4.82 (estimated)[2]

[1]Terpene Consortium. July 16, 2004. Revised Robust Summary for Terpenoid Primary Alcohols and Related Esters. http://www.epa.gov/HPV/pubs/summaries/terprial/c12965tc.htm.
[2]SRC. 2008. The Physical Properties Database (PHYSPROP). Syracuse, NY: Syracuse Research Corporation. Available from http://www.srcinc.com/what-we-do/free-demos.aspx as of September 17, 2008.
[3]CambridgeSoft Corporation. 2008. Chemfinder.com. Available at http://chemfinder.cambridgesoft.com/reference/chemfinder.asp.
[4]Lide, D.R. 2005. CRC Handbook of Chemistry and Physics 86TH Edition 2005–2006. CRC Press, Taylor & Francis, Boca Raton, FL.
[5]US EPA. 2008. Estimation Programs Interface Suite™ (version 3.20). United States Environmental Protection Agency, Washington, DC, USA Available online at: http://www.epa.gov/opptintr/exposure/pubs/episuite.htm with entered measured data points where applicable.
[6] NOMO5, 1987. Programs to Enhance PC-GEMS Estimates of Physical Properties for Organic Compounds. The Mitre Corp.
[7] Privi Organics Limited products datasheet, http://www.privi.com/product.asp?cno=C11820004
[8] INOUE Perfumery MFG. Co. LTD., Product Identification of Geraniol, http://chemicalland21.com/specialtychem/perchem/GERANIOL.htm
[9] MSDS data for Citral, http://msds.chem.ox.ac.uk/CI/citral.html

2 General Information on Exposure

2.1 Production Volume and Use Pattern

Each of the four category chemicals had an aggregated production and/or import volume in the United States between 10 million and 50 million pounds.

Non-confidential information in the IUR for category members indicated that the industrial processing and uses of the chemicals include intermediates or odor agents in a variety of industries. Non-confidential information in the IUR for three of the four chemicals indicated that the commercial and consumer products containing the chemicals include polishes and sanitation goods, soaps and detergents or "other." The HSDB information for CASRN 106-24-1 states that the chemical is used primarily in fragrance materials, beverages, foods, soaps, cosmetics, and as an intermediate in the manufacture of geranyl esters, and CASRNs 106-22-9 and 5392-40-5. The HPV submission states that the category chemicals are used as flavoring substances.

2.2 Environmental Exposure and Fate

No quantitative information is available on releases of these chemicals to the environment. There is generally a high potential for environmental releases to water for chemicals used in cleaning products, soaps and detergents.

Environmental fate properties are provided in Table 3. The category members are expected to have high mobility in soil, with the exception of acetylated myrcene, which is expected to have moderate mobility in soil. The rate of volatilization of these chemicals from water and moist soils is considered moderate based on their estimated Henry's Law constant, and the rate of atmospheric photooxidation is considered rapid. The rate of hydrolysis is considered negligible under environmental conditions. The substances in this category are considered to be readily biodegradable. The category members are expected to have low persistence (P1) and low bioaccumulation potential (B1).

Table 3. Environmental Fate Characteristics of Terpenoid Primary Alcohols and Related Esters[1]

	Sponsored Chemicals				Supporting Chemicals					
Property	**dl-Citronellol**	**Geraniol**	**Nerol**	**Acetylated myrcene**	**Geranyl acetate**	**Citronellyl acetate**	**Linalyl acetate**	**Citral**	**Linalool**	**Citral diethyl acetal**
CASRN	**106-22-9**	**106-24-1**	**106-25-2**	**68412-04-4**	**105-87-3**	**150-84-5**	**115-95-7**	**5392-40-5**	**78-70-6**	**7492-66-2**
Photodegradation Half-life	1.3 hours (estimated)	0.71 hours (estimated)	0.713 hours (estimated)	0.721 hours (estimated for geranyl acetate)	0.721 hours (estimated)[2]	1.34 hours (estimated)[2]	1.1 hours (estimated)[2]	0.944 hours (estimated)[2]	1.07 hours (estimated)[2]	0.655 hours (estimated)[2]
Hydrolysis Half-life	Stable	Stable	Stable	23.14 days at 25°C and pH 8 (estimated for geranyl acetate); 231.4 days at 25°C and pH 7 (estimated for geranyl acetate)	23 days at pH 8; 231 days at pH 7 (estimated)[2]	<1 hour at 37°C (measured in simulated intestinal fluid)	174 days at pH 8; 4.7 years at pH 7 (estimated)[2]	Stable	Stable	Stable
Biodegradation	80–90% after 28 days (measured); 65% after 28 days (measured); 100% after 15 days (measured) (readily biodegradable)	100% after 28 days (measured; 50% geraniol, 26% nerol, 18% citronellol); 100% after 15 days (>70% geraniol, <30% nerol) (readily biodegradable)	100% after 28 days (measured; 50% geraniol, 26% nerol, 18% citronellol); 100% after 15 days (>70% geraniol, <30% nerol) (readily biodegradable)	82.2% after 28 days (measured, readily biodegradable)	No data	82.2% after 28 days (measured for member acetylated myrcene) (readily biodegradable)	75% after 28 days (readily biodegradable)	92.1% after 28 days (measured 44% *cis*-neral, 50% *trans*-geranial); 99.5% after 19 days (measured, readily biodegradable)	90% after 28 days (measured, readily biodegradable)[3]	No data (likely biodegradable)
Bioconcentration	BCF = 204.5 (estimated)[2]	BCF = 110 (estimated)[2]	BCF = 93.7 (estimated)[2]	BCF = 509 (estimated)[2]	BCF = 235 (estimated)[2]	BCF = 648 (estimated)[2]	BCF = 211 (estimated)[2]	BCF = 89.7 (estimated)[2]	BCF = 38.63 (estimated)[2]	BCF = 1,020 (estimated)[2]
Log K_{oc}	1.85 (estimated)[2]	1.85 (estimated)[2]	1.85 (estimated)[2]	2.80 (estimated)[2]	2.78 (estimated)[2]	2.78 (estimated)[2]	2.71 (estimated)[2]	2.17 (estimated)[2]	1.75 (estimated)[2]	2.13 (estimated)[2]

Table 3. Environmental Fate Characteristics of Terpenoid Primary Alcohols and Related Esters[1]

	Sponsored Chemicals				Supporting Chemicals					
Property	**dl-Citronellol**	**Geraniol**	**Nerol**	**Acetylated myrcene**	**Geranyl acetate**	**Citronellyl acetate**	**Linalyl acetate**	**Citral**	**Linalool**	**Citral diethyl acetal**
Fugacity (Level III Model)										
Air (%)	0.855	0.0429	0.0529	0.0427	0.04	0.0769	0.0507	0.0563	0.0258	0.0177
Water (%)	39.8	39.3	36	35.9	17.8	15.6	10.5	22.8	18.6	7.98
Soil (%)	59.6	59.7	63.1	57.5	80.0	77.5	87.4	76.3	81	79.7
Sediment (%)	0.5	0.88	0.838	6.51 (data for geranyl acetate)	2.17	6.81	2.1	0.913	0.396	12.3
Persistence[4]	P1 (low)	P1 (low)	P1 (low)	P1 (low)	P1 (low)	P1 (low)	P1 (low)	P1 (low)	P1 (low)	P1 (low)
Bioaccumulation[4]	B1 (low)	B1 (low)	B1 (low)	B1 (low)	B1 (low)	B1 (low)	B1 (low)	B1 (low)	B1 (low)	B2 (moderate)

[1]Terpene Consortium. July 16, 2004. Revised Robust Summary for Terpenoid Primary Alcohols and Related Esters. http://www.epa.gov/HPV/pubs/summaries/terprial/c12965tc.htm.

[2] US EPA. 2008. Estimation Programs Interface Suite™ (version 3.20). United States Environmental Protection Agency, Washington, DC, USA Available online at: http://www.epa.gov/opptintr/exposure/pubs/episuite.htm with entered measured data points where applicable.

[3]National Institute of Technology and Evaluation. 2002. Biodegradation and Bioconcentration of Existing Chemical Substances under the Chemical Substances Control Law. http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html.

[4]Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

3. Human Health Effects

A summary of health effects data submitted for SIDS endpoints is provided in Table 4. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

Acute Oral Toxicity

Citronellol (CASRN 106-22-9)
Rats (10/dose, species and sex not specified) were administered single doses of the test substance ranging from 2050 – 5000 mg/kg-bw and observed for 14 days. The numbers of deaths per dose were 1, 0, 7, 6 and 8 at 2050, 2560, 3200, 4000 and 5000 mg/kg, respectively.
LD_{50} = 3450 mg/kg

Geraniol (CASRN 106-24-1)
Osborne-Mendel rats (5/sex) were administered the test substance via oral gavage (doses not specified). Time of death was between 4 and 18 hours although the number of deaths per dose was not reported.
LD_{50} = 3600 mg/kg

Nerol (CASRN 106-25-2)
Wistar rats (10 males/dose) were administered the test substance at 2560 – 9800 mg/kg and observed for 14 days. The numbers of deaths per dose were 1, 4, 7 and 10 at 2560, 4000, 6250 and 9800 mg/kg-bw, respectively. All deaths occurred within two days of dose administration.
LD_{50} = 4500 mg/kg

Geranyl acetate (CASRN 105-87-3, supporting chemical -- major component of acetylated myrcene)
Osborne-Mendel rats (5/sex) were administered the test substance orally via gavage (doses not specified) and observed for 2 weeks. Deaths occurred between 4 and 96 hours following dosing. The number of deaths per dose was not reported.
LD_{50} = 6330 mg/kg

Acute Dermal Toxicity

Citronellol (CASRN 106-22-9)
New Zealand white rabbits (5/dose; sex not specified) were administered the test substance at 1250, 2500 or 5000 mg/kg. No information was provided on exposure duration, post-exposure observation period, or whether test substance was occluded when administered. The numbers of deaths per dose were 0, 2, and 5 at 1250, 2500 and 5000 mg/kg, respectively.
LD_{50} = 2650 mg/kg

Nerol (CASRN 106-25-2)
New Zealand white rabbits (sex not specified) were dermally administered the test substance at 5000 mg/kg to clipped, abraded skin for 24 hours and observed for 7 days. There was one death at 5000 mg/kg.
LD_{50} > 5000 mg/kg

Repeated-Dose Toxicity

Mixture of citronellol (CASRN 106-22-9) and linalool (CASRN 78-70-6, supporting chemical)
Rats (strain, number and sex distribution unspecified) were administered a 50:50 mixture of these chemicals via the diet at 100 mg/kg-day (~ 50 mg/kg-day of each) for 12 weeks. The control group received the diet without the test substance. The urine of 3 animals per sex was examined for the presence of sugar and albumin. Blood hemoglobin levels were determined, and autopsies were performed. Although growth was slightly retarded and food efficiency was decreased in males at 100 mg/kg-day, these effects were attributed to the decreased palatability of the diet. No other adverse effects were noted.
NOAEL ~ 50 mg/kg-day citronellol (only dose tested)

Mixture of citronellol (CASRN 106-22-9) and geraniol (CASRN 106-24-1)
In an FDA screening study, Osborne-Mendel rats (5/sex/dose) were administered this mixture (percentages of each component not given) via the diet at 1000 or 10,000 ppm (approximately 50 or 500 mg/kg bw/day) for 189 – 196 or 112 days, respectively. Controls were used. Weekly measurements of body weight, food consumption and general condition of animals from the treated groups were comparable to the control group. At study termination, no effects were seen on hematological parameters, organ weights or during gross examination. Histopathology of limited organs/tissues (liver, kidney, spleen, heart and testes) showed no treatment-related lesions.
NOAEL ~ 500 mg/kg-day (highest dose tested)

Mixture of geranyl acetate (CASRN 105-87-3, supporting chemical - major component of acetylated myrcene) and citronellyl acetate (CASRN 150-84-5, supporting chemical)
(1) In a 17-week screening study using FDA guidelines, Osborne-Mendel rats (10/sex/dose) were administered the test substance (percent composition not available) in the diet at 1000, 2500 or 10,000 ppm (reported as approximately 500 mg/kg-day at the highest dose). There was no effect on body weight, food consumption, general conditions or hematological parameters. Macroscopic examination of all tissues and histopathological examination of liver, kidneys, spleen, heart and testes the controls and high-dose groups showed no adverse effects.
NOAEL ~ 500 mg/kg-day (highest dose tested)

(2) In an NTP study, F344/N rats (10/sex/dose) were administered a mixture of 71% geranyl acetate and 29% citronellyl acetate[5] in corn oil via oral gavage at 0, 250, 500, 1000, 2000 or 4000 mg/kg-day, 5 days/week for 13 weeks. Clinical signs and body weights were recorded. Necropsies were performed and tissues examined in high dose groups and controls. At 4000 mg/kg-day, 1 female and 2 males died and mean body weight gain was depressed in males by

[5] This percent composition is described as 'food-grade' geranyl acetate

19% and in females by 8%. No treatment-related histopathological changes were seen (NTP, 1987).
LOAEL = 4000 mg/kg-day (based on mortality and decreased body weight gain)
NOAEL = 2000 mg/kg-day

(3) In an NTP study, B6C3F1 mice (10/sex/dose) were administered a mixture of 71% geranyl acetate and 29% citronellyl acetate in corn oil via oral gavage at 0, 125, 250, 500, 1000 or 2000 mg/kg-day, 5 days/week for 13 weeks. Clinical signs and body weights were recorded. Necropsies were performed and tissues examined in high dose groups and controls. At 2000 mg/kg-day, seven males and nine females died, and body weights of males were decreased compared with controls. At this dose, inflammation or edema was seen in the stomach and cytoplasmic vacuolization (lipidosis) was seen in liver, kidney, and myocardium. No other effects were reported (NTP, 1987).
LOAEL = 2000 mg/kg-day (based on mortality, vacuolization, stomach lesions and decreased body weights)
NOAEL = 1000 mg/kg-day

(4) In an NTP study, F344/N rats (50/sex/group) were administered a mixture of 71% geranyl acetate and 29% citronellyl acetate in corn oil via oral gavage at 1000 or 2000 mg/kg-day, 5 days/week for 103 weeks. The control group received corn oil. Body weight was measured, animals necropsied and histopathology on major tissues and organs was performed. No compound-related clinical signs were seen. At 2000 mg/kg-day, survival was significantly decreased in males ($p < 0.001$). Mean body weights and body weight gains were depressed in high-dose males and in females at both doses after week 40. Body weights were lower than controls by more than 10% only at the high dose. In high-dose females, incidence of nephrosis was 63% compared to 26% in controls; in high-dose males, incidence of nephrosis was 90% compared to 80% in controls (NTP, 1987). Tumor findings are described below under *Additional Information – Carcinogenicity.*
LOAEL = 2000 mg/kg-day (based on decreased survival in males, increased incidence of nephropathy, decreased body weight)
NOAEL = 1000 mg/kg-day

Citral (CASRN 5392-40-5, supporting chemical)
(1) In a 14-week toxicity study by NTP, F344/N rats (10/sex/dose) were administered microencapsulated citral (2:1 mixture of geranial and neral - CASRNs 141-27-5 and 106-26-3) in the diet at 0, 3900, 7800, 15,600 and 31,300 ppm (approximately 0, 345, 820, 1785 and 1585 mg/kg-day for males and 0, 335, 675, 1330 and 2125 mg/kg-day for females). Control groups received untreated feed or feed with microcapsule placebos. Food and water was available *ad libitum*. In the 31,300 ppm group, rats were listless, had hunched postures, poor reflexes and dull eyes and were sacrificed in the 2nd week. There was a dose-related and statistically significant ($p < 0.01$ or 0.05) reduction in body weight in males and females in animals that survived to the end of the study at all doses. Changes in several hematology and clinical chemistry parameters were seen at one or more time points at two or three highest doses, and occasionally (e.g., increased mean cell volume at week 14) at all doses, although effects usually were not observed after Day 22, and some changes may have been related to decreased food and water consumption. Alterations in albumin, total protein, and urea nitrogen, although possibly

related to dehydration, could indicate decreased glomerular filtration rates as a result of renal damage. In males, minimal to mild nephropathy was seen in 3/10 animals at 3900 ppm, 10/10 animals at 7800 ppm and 8/10 animals at 15,600 ppm with presence of granular casts in the renal tubules; both kidney effects were significant at the two highest doses ($p \leq 0.01$). The incidence of hyaline droplets in the proximal renal tubule epithelium was not increased; therefore, the renal lesions were considered unlikely to be mediated by alpha 2µ-globulin. Bone marrow atrophy was noted in 7/10 males and 8/10 females at 15,600 ppm ($p \leq 0.01$), and in 10/10 males and 4/10 females at 31,300 ppm ($p \leq 0.01$ or 0.05), accompanied by bone marrow hemorrhage in 10/10 males and 9/10 females. Forestomach epithelial hyperplasia and hyperkeratosis with thickening of the stratified squamous epithelium and mucosa were seen in both sexes at 31,300 ppm. Thymic atrophy was observed at the highest dose (NTP, 2003).
LOAEL ~ 345 mg/kg-day (based on kidney toxicity in males and related clinical effects)
NOAEL = Not established

(2) In a 14-week toxicity study by NTP, B6C3F1 mice (10/sex/dose) were administered microencapsulated citral (2:1 mixture of geranial and neral) in the diet at 0, 3900, 7800, 15,600 and 31,300 ppm (corresponding to approximately 745, 1840, 3915 and 8110 mg/kg-day in males and 0, 790, 1820, 3870 and 7550 mg/kg-day in females). Control groups received untreated feed or feed with microcapsule placebos. At 31,300 ppm, rats were listless, had hunched postures, poor reflexes, and dull eyes and were sacrificed in the 2nd week. Statistically significant decreases ($p \leq 0.01$) in body weight gains and final body weights (more than 10% lower than controls) were seen in males and females at all concentrations. Although food consumption was decreased in the first week, it was greater in all exposed groups than controls by the end of the study. Lymphocyte counts were decreased at all doses in males and at the two highest doses in females ($p \leq 0.01$ or 0.05). Differences in absolute and/or relative organ weights were statistically significant at several doses at either $p \leq 0.01$ or 0.05, including relative increases in heart, kidney, liver, lung, and thymus. However, these changes were considered primarily related to differences in body weights and were not considered toxicologically significant. Many males and females exhibited thickened forestomach walls and mucosa with minimal hyperkeratosis at 15,600 and 31,300 ppm, considered a result of contracted forestomachs. Ovarian atrophy was increased in females at 15,600 ppm (7/10 animals; moderate severity) and 31,300 ppm (10/10 animals; marked severity), based on absence of or reduction in the number of corpora lutea (NTP, 2003).
LOAEL ~ 745/790 mg/kg-day (male/female; based on decreased body weights)
NOAEL = Not established

(3) In an NTP study, F344/N rats (50/sex/concentration) were administered 0, 1000, 2000 or 4000 ppm (corresponding to approximately 0, 50, 100 or 210 mg/kg-day) microencapsulated citral (63% geranial and 37% neral, purity of 94%) in the diet continuously for 2 years. Control groups received untreated feed or feed with microcapsule placebos. Animals were evaluated for clinical signs, changes in body weight, complete necropsies and histopathology. Survival was increased by the end of the study at all doses ($p < 0.05$) compared with the vehicle control. A decrease in body weight was seen in males and females at 4000 ppm. There were no differences in feed consumption between dosed groups and controls. In males, dose-related increases in kidney mineralization were evident. The incidences were 42/50 (84%) in the vehicle control, 45/50 (90%) at 50 mg/kg-day, 48/50 (96%) at 100 mg/kg-day and 50/50 (100%) at 210 mg/kg-day and the severity was increased at the two highest concentrations compared with the vehicle control (NTP, 2003). The renal changes were considered to be of minimal toxicological significance; only doses showing somewhat greater severity (and incidence) were designated as adverse for this assessment.
LOAEL ~ 100 mg/kg-day (based on severity of mineralization in kidneys of male rats)
NOAEL ~ 50 mg/kg-day

(4) In an NTP study, $B6C3F_1$ mice (50/sex/dose) were administered 0, 500, 1000 or 2000 ppm (approximately 60, 120 or 260 mg/kg-day) microencapsulated citral (63% geranial and 37% neral, purity of 94%) in the diet continuously for 2 years. Control groups received untreated feed or feed with microcapsule placebos. Animals were evaluated for clinical signs, changes in body weight, complete necropsies and histopathology. Survival was similar in dosed groups compared with controls. Mean body weights at 2000 ppm were generally lower throughout the study compared with the vehicle controls. At 1000 ppm, a decrease in body weights was seen during the second year in males and from week 14 to the end of the study in females. At 500 ppm, females had lower body weights starting at week 30. Mean body weights during the second year of the study were only decreased by more than 10% at 1000 ppm (females) and 2000 ppm (both sexes). Food consumption was similar between dosed groups and controls. Incidence of minimal or mild inflammation and ulcers of the oral mucosa was higher in females at all doses ($p \leq 0.01$ or 0.05) and in males at 2000 ppm compared with vehicle controls. Bone fibrosis was observed at incidences of 11/49, 22/50, 21/50 and 18/50 at 0, 60, 120 and 260 mg/kg-bw, with unknown significance. Increased incidence of minimal nephropathy was observed in females at 2000 ppm; significantly increased incidences of minimal renal tubule mineralization were observed at 500 and 1000 ppm ($p \leq 0.01$ or 0.05). In males, increased adrenal cortical focal hyperplasia was significantly increased at 2000 ppm (NTP, 2003).
LOAEL ~ 60 mg/kg-day (based on increased kidney mineralization with nephropathy at the highest dose; oral ulcers in females)
NOAEL ~ Not established

(5) In a 13-week screening study using FDA guidelines, Osborne-Mendel rats (10/sex/dose) were administered citral (percent of geranial and neral not given) in the diet at 0, 1000, 2500 or 10,000 ppm for 13 weeks. The highest dose corresponded to 200 mg/kg bw/day based on an assumed intake of 50 g food/kg bw. There was no effect on body weight, food consumption and general condition and hematological parameters. Macroscopic examination of all tissues and

histopathological examination of liver, kidneys, spleen, heart and testes were conducted on animals from the controls and high-dose groups. No adverse effects were observed in the study. **NOAEL = 200 mg/kg-day (**highest dose tested)

Reproductive Toxicity

Evaluation of reproductive organs in the repeated-dose toxicity studies discussed above revealed no effects on reproductive organs. Reproductive toxicity studies are available for the supporting chemicals citral and citral diethyl acetal.

Citral (CASRN 5392-40-5, supporting chemical)
(1) Citral (55% geranial; 44% neral) was administered via oral gavage in a combined reproductive/developmental toxicity screening test at 0, 40, 200 and 1000 mg/kg-day to Cij:CD (SD) rats (12/sex/dose) from 14 days prior to and during mating (males) or from 14 days prior to mating through lactation day 3 (females). In parents, general condition, body weight, food consumption, and weight/microscopy of testes, epididymis, and ovaries were evaluated. In addition, the liver of one female at 1000 mg/kg-bw was examined microscopically. Several mating and reproductive indices were evaluated. At the highest dose, some thickening of the mucosal layer in the stomach was observed in female parents and squamous hyperplasia, ulcers and granulation in the lamina propria were seen in both parental sexes. No statistically-significant effects on reproductive parameters were observed. This summary is based on the OECD HPV submission (http://www.chem.unep.ch/irptc/sids/OECDSIDS/5392-40-5.pdf).
LOAEL (parental systemic toxicity) = 1000 mg/kg-day (based on histopathological changes in the stomach)
NOAEL (parental systemic toxicity) = 200 mg/kg-day
NOAEL (reproductive toxicity) = 1000 mg/kg-day (highest dose tested)

(2) Citral (percent geranial and neral not available) was administered orally at doses of 0, 50, 160 and 500 mg/kg-day to 30 female Sprague-Dawley rats for 14 days prior to cohabitation with males and through day 20 of gestation. Approximately half of the rats were Caesarean-sectioned on day 20 of gestation and the remaining rats were dosed through parturition and a 21 day lactation period. In the dams, clinical observations, estrus cycle, body weight and body weight gains, mating and fertility, duration of gestation, delivery, maternal behavior, reproductive indices and gross necropsy were evaluated. At 160 and 500 mg/kg-day, dams showed dose-dependent increases in mortality, clinical signs of toxicity, and decreased body weight gain. No effects on estrous cycling, mating, fertility or gestation time were noted (Hoberman et al, 1989).
LOAEL (maternal systemic toxicity) = 160 mg/kg-day (based on increased mortality and decreased body weight gain)
NOAEL (maternal systemic toxicity) = 50 mg/kg-day
NOAEL (reproductive toxicity) = 500 mg/kg-day (highest dose tested)

Citral diethyl acetal (CASRN 7492-66-2, supporting chemical)
In a combined reproductive/developmental toxicity screening test, this chemical was administered orally via gavage at 0, 125, 250 and 500 mg/kg-day to female Sprague-Dawley rats (numbers not provided) 7 days prior to cohabitation and through cohabitation, gestation, delivery and day 4 of lactation. Corn oil or methylcellulose was used as the vehicle. Clinical signs, body

weight and food consumption were monitored. Dams were necropsied and examined for gross lesions. Pups that were delivered were sacrificed on day 4 postpartum; pups that died during lactation were necropsied. Dams showed clinical signs and lower body weights and body weight gains than controls at 250 and 500 mg/kg-day.
LOAEL (maternal systemic toxicity) = 250 mg/kg-day (based on reduced body weight and body weight gains)
NOAEL (maternal systemic toxicity) = 125 mg/kg-day
NOAEL (reproductive toxicity) = 500 mg/kg-day (highest dose tested)

Developmental Toxicity

Developmental toxicity studies are not available for the category members. However, studies are available for supporting chemicals citral and citral diethyl acetal.

Citral (CASRN 5392-40-5, supporting chemical)
(1) Twenty-five pregnant Sprague-Dawley rats were exposed by inhalation to vapors of commercially available citral (55% geranial and 35% neral; purity ~ 90%) at 0, 10, or 35 ppm or a combination of vapor/aerosol at 85 ppm for 6 hours/day during gestation days 6 – 15. Measured concentrations were 10.2, 34.4 and 68 ppm or 0.06, 0.21, and 0.43 mg/L/day. Dams were sacrificed on day 20. The number of corpora lutea, implantations, and resorptions were recorded. Also, fetal viability, litter size, sex ratio and body weight changes were determined. Fetuses were examined for gross, visceral and skeletal malformations. At 68 ppm, dams exhibited trouble breathing, nasal discharge, salivation, red and opaque eyes, discolored fur and rough hair coat. One dam aborted on GD 10, and one was killed on GD 17, both at 68 ppm; overall, there were two mortalities in dams. At 68 ppm, mean body weights of the dams were decreased by 39% during gestation when compared with controls ($p \leq 0.05$). Some increases in fetal abnormalities were seen at the highest dose, but none were statistically different from controls (Gaworski et al., 1992).
LOAEL (maternal toxicity) = 0.43 mg/L/day (based on decreased body weights, mortality)
NOAEL (maternal toxicity) = 0.21 mg/L/day
NOAEL (developmental toxicity) = 0.43 mg/L/day (highest dose tested)

(2) In the combined reproductive/developmental toxicity screening test described in the *Reproductive Toxicity* section, citral was administered via oral gavage at 0, 40, 200 and 1000 mg/kg-day to Cij:CD (SD) rats (12/sex/dose) from 14 days prior to mating (males) or from 14 days prior to mating to lactation day 3 (females). Parental evaluations were described above. Offspring were examined macroscopically and for clinical signs. In dams at the highest dose, some thickening of the mucosal layer in the stomach and squamous hyperplasia, ulcers and granulation in the lamina propria were seen. Pup body weights were decreased from day 0 to 4 at the highest dose. No other effects were observed in the offspring. This summary is based on the OECD HPV submission (http://www.chem.unep.ch/irptc/sids/OECDSIDS/5392-40-5.pdf).
LOAEL (maternal toxicity) = 1000 mg/kg-day (based on histopathological signs in the stomach)
NOAEL (maternal toxicity) = 200 mg/kg-day
LOAEL (developmental toxicity) = 1000 mg/kg-day (based on decreased pup body weights)
NOAEL (developmental toxicity) = 200 mg/kg-day

(3) In the second citral study described in the *Reproductive Toxicity* section, the test substance was administered orally at doses of 0, 50, 160 and 500 mg/kg-day to 30 female Sprague-Dawley rats for 14 days prior to mating, during gestation and through day 21 of lactation. Fetuses were examined for fetal wastage, body weight, sex and gross external changes. Pups were examined for clinical signs, body weight changes and gross necropsy. At 160 and 500 mg/kg-day, dams showed dose-dependent increases in mortality, clinical signs of toxicity, decreased body weight and decreased food consumption. A slight (not statistically significant) decrease in fetal body weight was evident. In pups, body weight was significantly decreased in the 500 mg/kg-day group ($p < 0.05$) (Hoberman et al., 1989).
LOAEL (maternal toxicity) = 160 mg/kg-day (based on increased mortality and decreased body weight/food consumption)
NOAEL (maternal toxicity) = 50 mg/kg-day
LOAEL (developmental toxicity) = 500 mg/kg-day (based on decreased pup body weights)
NOAEL (developmental toxicity) = 160 mg/kg-day

Citral diethyl acetal (CASRN 7492-66-2, supporting chemical)
In the reproductive/developmental toxicity screening test described previously, dams showed clinical signs and lower body weights and body weight gains than controls at 250 and 500 mg/kg-day. In offspring, lower body weight compared to controls was observed only at 500 mg/kg-day.
LOAEL (maternal toxicity) = 250 mg/kg-day (based on reduced body weight)
NOAEL (maternal toxicity) = 125 mg/kg-day
LOAEL (developmental toxicity) = 500 mg/kg-day (based on decreased body weights)
NOAEL (developmental toxicity) = 250 mg/kg-day

Genetic Toxicity – Gene Mutations

In vitro
Citronellol (CASRN 106-22-9)
In a reverse bacterial mutation assay, *Salmonella typhimurium* strains TA98 and TA100 were exposed to concentrations ranging from 0.05 to 100 µL/plate, in the presence and absence of metabolic activation. Because only two strains were used, the study is limited in its ability to assess the potential of this chemical to cause gene mutations. These results are corroborated in the *Summary of Data for Chemical Selection,* available at the NTP website (http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumPdf/Citronellol.pdf).
Citronellol was not mutagenic in this assay.

Geraniol (CASRN 106-24-1)
In a bacterial reverse mutation assay, *S. typhimurium* strains TA92, TA94, TA98, TA100, TA1535 and TA1537 were exposed to this chemical at six concentrations up to 500 µg/plate with and without metabolic activation. No information on the use of positive controls was given.
Geraniol was not mutagenic in this assay.

Acetylated myrcene (CASRN 68412-04-4)
S. typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to CASRN 68412-04-4 (composition not given) at a concentration of 20,000 µg/plate in the presence of metabolic activation. No evidence of gene mutations was seen. No information was given on use of positive controls or criteria for judging the positive response.
Acetylated myrcene was not mutagenic in this assay.

In vivo
Geranyl acetate (CASRN 105-87-3, supporting chemical – major component of acetylated myrcene)
(1) In a reciprocal translocation/sex-linked recessive lethal assay, this chemical was administered to *Drosophila* at 250 ppm in feed or 50,000 ppm by injection. Mortality was 50% when administered in feed. The compound was negative by both routes of administration (http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=drosophila.slrlStudySummary&study_no=686825&cas_no=105-87-3&endpointlist=DL).
Geranyl acetate was not mutagenic in this assay.

Genetic Toxicity – Chromosomal Aberrations

In vivo
Mixture of 79% geranyl acetate (CASRN 105-87-3) and 21% citronellyl acetate (CASRN 150-84-5), supporting chemicals
(1) In a mouse micronucleus assay, the test substance was administered by intraperitoneal injection at 0, 450, 900 or 1800 mg/kg-bw for three consecutive days. Positive and negative controls were used in the study. The numbers of micronucleated polychromatic erythrocytes (MN-PCEs) per 1000 PCEs in bone marrow or peripheral blood were not statistically increased at any dose by trend or pair-wise comparison tests, using a p-level of 0.05. Information was obtained from the sponsor's submission and NTP (http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=micronucleus.micronucleusData&cas_no=105%2D87%2D3&endpointlist=MN).
This test substance did not induce chromosomal aberrations or micronuclei in this assay.

Geranyl acetate (CASRN 105-87-3, supporting chemical – major component of acetylated myrcene)
(1) In a bone marrow cytogenetics study, geranyl acetate was administered by intraperitoneal injection to B6C3F1 mice (8 males/dose) at 0, 425, 850 and 1700 mg/kg-bw. Bone marrow samples were taken at 17 hours. Dimethylbenzanthracene was used as the positive control and exhibited expected results. The trend test was positive for chromosomal aberrations ($p < 0.01$), and incidence of chromosomal aberrations was higher at 1700 mg/kg ($p < 0.01$) compared with the vehicle control. No information on cytoxicity was provided (http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=invivoca.casummary&study_no=125080&cas_no=105%2D87%2D3&endpointlist=CA).
Geranyl acetate induced chromosomal aberrations in this assay.

(2) In a bone marrow cytogenetics study, the test substance was administered by intraperitoneal injection to B6C3F1 mice (8 males/dose) at 0, 1275 and 1700 mg/kg-bw. Bone marrow samples

were taken at 17 hours. Dimethylbenzanthracene was used as the positive control and exhibited expected results. The trend test was positive for chromosomal aberrations ($p < 0.01$), and the incidence of chromosomal aberrations was higher at 1700 mg/kg ($p < 0.01$) compared with the vehicle control. No information on cytoxicity was provided (http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=invivoca.casummary&study_no=125080&cas_no=105%2D87%2D3&endpointlist=CA).
Geranyl acetate induced chromosomal aberrations in this assay.

(3) In a bone marrow cytogenetics assay, B6C3F1 mice (8/dose) were administered this chemical at 0, 250, 500 or 1000 mg/kg (8/dose) by intraperitoneal injection (http://ntp.niehs.nih.gov/index.cfm?objectid=BCC27274-123F-7908-7B058FF982D55347). Bone marrow samples were taken at 17 hours. Dimethylbenzanthracene was used as the positive control and exhibited expected results.
Geranyl acetate did not induce chromosomal aberrations in this assay.

Genetic Toxicity – Other

Geranyl acetate (CASRN 105-87-3, supporting chemical – major component of acetylated myrcene)
This chemical was tested in a mouse lymphoma assay both with and without activation. Negative and positive controls were used (http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=mouselymphoma.studyDetails&study_no=340860&cas_no=105-87-3&endpointlist=ML,ML-N). The test substance was equivocal in one trial and negative in three trials when tested without activation, and the substance was positive in three trials and negative in one trial with activation. No details were available to determine whether the effects reflected increased gene mutations or increased chromosomal aberrations.
Geranyl acetate was mutagenic in this assay.

Additional Information

Carcinogenicity

Citral (CASRN 5392-40-5, supporting chemical)
This chemical did not exhibit carcinogenic potential in male rats, female rats or male mice up to the dose levels tested. In female mice, a positive trend was seen in the incidence of hepatocellular adenomas (3/49, 2/50, 8/50, 8/50), but pairwise comparisons and trend analyses were not significant. In female mice, the overall number of animals with malignant lymphomas of those necropsied was increased (3/49 = 6% in vehicle controls; 5/50 = 10% at 500 ppm; 9/50 = 18% at 1000 ppm; and 12/50 = 24% at 2000 ppm). The first lymphoma incidences observed were at day 719 in vehicle controls, day 733 (terminal sacrifice) at 500 ppm, day 469 at 1000 ppm, and day 491 at 2000 ppm. Other than these earlier lymphomas and one seen at day 523 (in the 2000 ppm concentration), all other lymphomas were seen at the end of the study. The lymphomas occurred primarily in the spleen, mesenteric lymph node, thymus and less commonly in the ovary. There was a positive dose-response trend ($p < 0.01$) and the number of lymphomas was significantly increased at 2000 ppm ($p < 0.05$). Therefore, NTP concluded that this increase

may have been related to this chemical in the diet. However, NTP also noted that the evidence in female mice is equivocal because malignant lymphomas are common in mice, the increased incidence in this study was within historical control ranges, and the concurrent vehicle control incidence was at the low end of the historical control range (NTP, 2003).
Evidence of carcinogenicity of citral in female mice was equivocal.

Mixture of 79% geranyl acetate (CASRN 105-87-3) and 21% citronellyl acetate (CASRN 150-84-5), supporting chemicals
NTP concluded that this mixture was not carcinogenic in F344/N rats or $B6C3F_1$ mice of either sex in 2-year gavage studies at 1000 or 2000 mg/kg-day in rats and 500 or 1000 mg/kg bw/day in mice. However, the authors noted that reduced survival in high-dose male rats, high-dose male mice and high- and low-dose female mice lowered the sensitivity to detect neoplastic lesions. Male rats showed marginal increases in squamous cell papillomas of the skin and tubular cell adenomas in the kidney (NTP, 1987).
This mixture was not carcinogenic in rats or mice, although sensitivity of the study was limited due to low survival.

Skin Irritation

Citronellol (CASRN 106-22-9)

Adult male volunteers with no known allergic reactions were patch-tested on their back for 48 hrs with 32% citronellol. After 48 hrs, patches were removed and the skin was cleaned of any residual test material. Moderate irritation was observed. In Albino angora rabbits and male Hartley guinea pigs, hair was clipped and animals were exposed to 100% compound (unoccluded) for 24, 48 or 72 hours. Severe irritation was observed in rabbits and guinea pigs. Miniature swine (hair clipped) were exposed to 100% citronellol for 48 hrs; no irritation was observed (Motoyoshi et al., 1979).
Citronellol resulted in moderate skin irritation in humans, severe irritation in rabbits and guinea pigs, and no irritation in swine.

In rabbits, 0.42% applied to skin for 4 hrs resulted in moderate irritation (RTECS). No additional details are available from RTECS.
Citronellol was moderately irritating to rabbits.

Geraniol (CASRN 106-24-1)
In humans, 32% geraniol resulted in severe irritation, 100% applied to rabbits and guinea pigs resulted in severe irritation, and 100% applied to swine was not irritating (Motoyoshi et al., 1979).
Geraniol resulted in severe skin irritation in humans, rabbits and guinea pigs and no irritation in swine.

Nerol (CASRN 106-25-2)
In rabbits, 500 mg applied to skin for 24 hrs resulted in moderate irritation (RTECS). No further details are available from RTECS.
Nerol resulted in moderate skin irritation in rabbits.

Eye Irritation

Citronellol (CASRN 106-22-9)
In rabbits, 0.42% applied to eyes resulted in moderate irritation (RTECS). No further details are available from RTECS.
Citronellol resulted in moderate eye irritation in rabbits.

Skin Sensitization

Geraniol (CASRN 106-24-1)
Data collected from 1996 to 2002 showed that of 1083 to 1924 persons/year who exhibited positive patch test reactions to fragrance mixes and were subsequently tested with single chemicals, 5.9% exhibited positive patch test reactions to 1% geraniol (Schnuch et al., 2004).
Geraniol was associated with positive patch test reactions in ~ 6 percent of individuals with positive reactions to fragrance mixtures.

In the local lymph node assay (LLNA), geraniol was administered to the skin of 4 female CBA/Ca mice at concentrations of 0, 2.5, 5.0, 10, 25 or 50% w/v in 1:3 ethanol:diethylphthalate for 3 consecutive days and then rested for 2 days. On day 6, the tails of all mice were injected with [^{3}H] methyl thymidine, and after five hours, the mice were euthanized and the auricular lymph nodes were excised and cells were processed; radioactivity was measured by disintegrations per minute (dpm) and a stimulation index (SI) was determined by dividing the dpm of the dose group by the dpm of the control. The test substance was considered to be a sensitizer if the SI was 3 or higher. This chemical resulted in SIs of 1.7, 2.4, 2.8, 4.8 and 5.0 at concentrations of 2.5, 5.0, 10, 25 and 50%; an SI of 3 is expected at a concentration of 11.4% (Lalko and Api, 2006).
Geraniol is a skin sensitizer in mice at $\geq$ 11.4% w/v concentration.

Conclusion: Acute toxicity of the category members via oral exposure in rats and dermal exposure in rabbits is low. Three category members showed moderate to severe skin irritation in humans, rabbits and/or guinea pigs. CASRN 106-22-9 was irritating to rabbit eyes. CASRN 106-24-1 was a skin sensitizer in humans and mice. No systemic toxicity was observed during repeated oral exposures of rats to CASRN 106-22-9 at 50 mg/kg-day (as a mixture with supporting chemical CASRN 78-70-6) or to a mixture of CASRNs 106-22-9 and 106-24-1 at 500 mg/kg-day (highest doses tested). Repeated oral exposure of rats and mice to a mixture of supporting chemicals CASRNs 105-87-3 and 150-84-5 resulted in mortality, kidney effects and decreased body weights (both species) and stomach inflammation, and histopathological effects in the liver and myocardium (mice) at 2000 mg/kg-day; the NOAEL was 1000 mg/kg-day. Chronic repeated oral exposures of mice to the supporting chemical CASRN 5392-40-5 resulted in nephropathy and irritation (oral ulcers) at site of administration at 60 mg/kg-day; no NOAEL was established. In an oral combined reproductive/developmental toxicity screening test in rats, supporting chemical CASRN 5392-40-5 showed histopathological changes in the stomach in parents at 1000 mg/kg-day and increased parental mortality and body weight gain at 160 mg/kg-day in an oral rat reproductive toxicity study. The reproductive NOAEL was 1000 mg/kg-day based on no effects; decreased pup body weights were seen at 500 mg/kg-day resulting in

developmental NOAEL of 160 mg/kg-day. In an oral combined reproductive/developmental toxicity screening study in rats, CASRN 7492-66-2 resulted in reduced maternal body weights and weight gains at 250 mg/kg-day; no reproductive toxicity was observed but reduced pup body weights at 500 mg/kg-day resulted in a developmental NOAEL of 250 mg/kg-day. In an inhalation prenatal developmental toxicity study, supporting chemical CASRN 5392-40-5 resulted in deaths and decreased body weights of dams at 0.43 mg/L-day but no developmental toxicity, resulting in maternal and developmental NOAELs of 0.21 and 0.43 mg/L-day (highest dose tested), respectively. The category members and supporting substances did not induce gene mutations *in vitro* or *in vivo*. Some positive results were seen for the supporting chemical CASRN 105-87-3 in *in vivo* chromosomal aberrations tests and in an *in vitro* mouse lymphoma assay. A mixture of the supporting chemicals with CASRNs 105-87-3 and 150-84-5 was not carcinogenic in rats or mice. The supporting chemical CASRN 5392-40-5 was equivocal for carcinogenicity in female mice.

Table 4. Summary of Human Health Data									
	Sponsored Chemicals				Supporting Chemicals				
Endpoints	**dl-Citronellol (106-22-9)**	**Geraniol (106-24-1)**	**Nerol (106-25-2)**	**Acetylated myrcene (68412-04-4)**	**Geranyl acetate[1] (105-87-3)**	**Citronellyl acetate[2] (150-84-5)**	**Citral[3] (5392-40-5)**	**Linalool (78-70-6)**	**Citral diethyl acetal (7492-66-2)**
Acute Oral Toxicity LD_{50} (mg/kg-bw)	**3450**	**3600**	**4500**	No data 6330 (RA)	**6330**	—	—	—	—
Acute Dermal Toxicity LD_{50} (mg/kg-bw)	**2650**	No data > 5000 (RA)	**> 5000**	No data 2650 – > 5000 (RA)	—	—	—	—	—
Repeated-Dose Toxicity NOAEL/ LOAEL (mg/kg-day)	**NOAEL = 50[4] (only dose tested) (12-wk; rat)** **NOAEL = 500[5] (hdt) (16-28 wk; rat)**	No data NOAEL = NE LOAEL ~ 345 (RA) NOAEL = NE LOAEL ~ 745 - 790 (RA) NOAEL ~ 50 LOAEL ~ 100 (RA) NOAEL = NE LOAEL ~ 60 (RA) NOAEL =~200 (RA)	No data NOAEL = NE LOAEL ~ 345 (RA) NOAEL = NE LOAEL~ 745 – 790 (RA) NOAEL ~ 50 LOAEL ~ 100 (RA) NOAEL = NE LOAEL ~ 60 (RA) NOAEL =~ 200 (RA)	No Data NOAEL = 2000 LOAEL = 4000 (RA) NOAEL =1000 LOAEL = 2000 (RA) NOAEL = 500 (RA)	**NOAEL = 2000 LOAEL = 4000 (13-wk; rat)** **NOAEL = 1000 LOAEL = 2000 (13-wk; rat, mouse)** **NOAEL = 500 (hdt) (17-wk; rat)**	—	**NOAEL = NE LOAEL ~ 345 (14-wk; rat)** **NOAEL = NE LOAEL ~ 745 - 790 (14-wk; mice)** **NOAEL ~ 50 LOAEL ~ 100 (2-yr; rat)** **NOAEL = NE LOAEL ~ 60 (2-yr; mice)** **NOAEL ~200 (hdt) (13-wk; rat)**	—	—

Table 4. Summary of Human Health Data									
	Sponsored Chemicals				Supporting Chemicals				
Endpoints	**dl-Citronellol (106-22-9)**	**Geraniol (106-24-1)**	**Nerol (106-25-2)**	**Acetylated myrcene (68412-04-4)**	**Geranyl acetate[1] (105-87-3)**	**Citronellyl acetate[2] (150-84-5)**	**Citral[3] (5392-40-5)**	**Linalool (78-70-6)**	**Citral diethyl acetal (7492-66-2)**
Reproductive Toxicity NOAEL/ LOAEL (mg/kg-day)	No Data	No Data	No Data	No Data	—	—		—	
Systemic Toxicity				NOAEL = 125 LOAEL = 250 (RA)			**(1)** **NOAEL = 200** **LOAEL = 1000**		**NOAEL = 125** **LOAEL = 250**
Reproductive Toxicity				NOAEL = 500 (RA)			**NOAEL = 1000** **(hdt)**		**NOAEL = 500** **(hdt)**
Systemic Toxicity	NOAEL = 50 LOAEL = 160 (RA)	NOAEL = LOAEL = 160 (RA)	NOAEL = 50 LOAEL = 160 (RA)				**(2)** **NOAEL = 50** **LOAEL = 160**		
Reproductive Toxicity	NOAEL = 500 (RA)	NOAEL = 500 (RA)	NOAEL = 500 (RA)				**NOAEL = 500** **(hdt)**		
Developmental Toxicity (Oral) (mg/kg-day)	No Data	No Data	No Data	No Data	—	—		—	
Maternal	NOAEL = 125 LOAEL = 250	NOAEL = 125 LOAEL = 250	NOAEL = 125 LOAEL = 250	NOAEL = 125 LOAEL = 250			**(1)** **NOAEL = 200** **LOAEL = 1000**		
Developmental	NOAEL = 250 LOAEL = 500 (RA)	NOAEL = 250 LOAEL = 500 (RA)	NOAEL = 250 LOAEL = 500 (RA)	NOAEL = 250 LOAEL = 500 (RA)			**NOAEL = 200** **LOAEL = 1000**		
Maternal							**(2)** **NOAEL = 50** **LOAEL = 160**		**NOAEL = 125** **LOAEL = 250**
Developmental							**NOAEL = 160** **LOAEL = 500**		**NOAEL = 250** **LOAEL = 500**

Table 4. Summary of Human Health Data									
	Sponsored Chemicals				Supporting Chemicals				
Endpoints	**dl-Citronellol (106-22-9)**	**Geraniol (106-24-1)**	**Nerol (106-25-2)**	**Acetylated myrcene (68412-04-4)**	**Geranyl acetate[1] (105-87-3)**	**Citronellyl acetate[2] (150-84-5)**	**Citral[3] (5392-40-5)**	**Linalool (78-70-6)**	**Citral diethyl acetal (7492-66-2)**
Developmental Toxicity (Inhalation) (mg/L/day)	No Data	No Data	No Data	No Data	—	—		—	—
Maternal	NOAEL = 0.21 LOAEL = 0.43	NOAEL = 0.21 LOAEL = 0.43	NOAEL = 0.21 LOAEL = 0.43	NOAEL = 0.21 LOAEL = 0.43			**NOAEL = 0.21** **LOAEL = 0.43**		
Developmental	NOAEL = 0.43 (RA)	NOAEL = 0.43 (RA)	NOAEL = 0.43 (RA)	NOAEL = 0.43 (RA)			**NOAEL = 0.43 (hdt)**		
Genetic Toxicity – Gene Mutations ***In vitro***	**Negative**	**Negative**	No data Negative (RA)	**Negative**	—	—	—	—	—
Genetic Toxicity – Chromosomal Aberrations ***In vivo***	No data Positive (RA)	No data Positive (RA)	No data Positive (RA)	Positive (RA)	**Positive**	—	—	—	—
Skin Irritation	**Moderate (humans)**	**Severe (humans, rabbits, guinea pigs)**	**Moderate (rabbits)**						
Eye Irritation	**Moderate (rabbits)**								
Skin Sensitization		**Positive (humans; local lymph node assay in mice)**							

RA = Read Across; NE = Not established; hdt = highest dose tested; [1]Component of acetylated myrcene; sometimes a mixture of 79% geranyl acetate and 21% citronellyl acetate; [2]Only as a component of food-grade geranyl acetate —See column for geranyl acetate for data; [3] Mixture of geranial and neral; [4]Mixture with linalool; [5]Mixture with geraniol (percentages not stated)

4. Environmental Effects – Aquatic Toxicity

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 5. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

Acute Toxicity to Fish

Citronellol (CASRN 106-22-9)
Golden Orfe (*Leuciscus idus*) were exposed to nominal concentrations of 0, 4.64, 10, 21.5, 46.4 or 100 mg/L of this chemical under static conditions for 96 hours. No mortalities were seen in the control and 4.64 mg/L groups. At 10 mg/L, apathy was noted up to 24 hours, but no mortalities were noted at 96 hours. At 21.5, 46.4 and 100 mg/L, 100% mortality was seen 1 hour after exposure.
96-h LC_{50} > 10 mg/L

Geraniol (CASRN 106-24-1)
Zebrafish (*Brachydanio rerio*) were exposed to nominal concentrations of 0, 11, 16, 22 or 31 mg/L under semi-static conditions (renewal every 24 hours) for 96 hours. Test concentrations were analytically measured.
96-h LC_{50} = 14.0 mg/L

Geranyl acetate (CASRN 105-87-3, supporting chemical – major component of acetylated myrcene)
Fathead minnows (*Pimephales promelas*) were exposed to measured concentrations of 0, 1.0, 1.76, 2.61, 4.54 or 8.25 mg/L under semi-static conditions (renewal every 24 hours) in sealed vessels for 96 hours.
96-h LC_{50} = 6.12 mg/L

Acute Toxicity to Aquatic Invertebrates

Geraniol (CASRN 106-24-1)
Daphnia magna (10/concentration) were exposed to measured concentrations of 0, 3.43, 5.90, 9.72, 16.5, 27.8 or 47.3 mg/L under semi-static conditions (renewal at 24 hours) in sealed containers for 48 hours.
48-h EC_{50} = 7.75 mg/L

Linalyl acetate (CASRN 115-95-7, supporting chemical)
Daphnia (20/concentration) were exposed to measured concentrations of 0, 2, 15.5, 26.3, 48.7 or 87.9 mg/L under static conditions in sealed containers for 48 hours. Immobility, sublethal effects and mortality were monitored.
48-h EC_{50} = 15 mg/L

Toxicity to Aquatic Plants

Citronellol (CASRN 106-22-9)
Green algae (*Selenastrum subspicatus*) were exposed to seven nominal concentrations ranging from 0.195 – 12.5 mg/L for 72 hours.
72-h EC_{50} (growth) = 2.38 mg/L

Geraniol (CASRN 106-24-1)
Green algae (*Pseudokirchneriella subcapitata*) were exposed to measured concentrations of 0, 0.467, 1.03, 1.93, 3.93 or 7.77 mg/L for 72 hours. Area under the curve was used to determine changes in biomass. The pH was adjusted to 7.5.
72-h EC_{50} (growth) = 5.93 mg/L
72-h EC_{50} (biomass) = 3.32 mg/L

Linalyl acetate (CASRN 115-95-7, supporting chemical)
Green algae (*S. subspicatus*) were exposed to measured concentrations of 0, 2.3, 4.7, 11.6, 15.9 or 75.5 mg/L for 72 hours. The pH was adjusted to 7.9. Biomass was measured as area under the curve.
72-h EC_{50} (biomass) = 16 mg/L
72-h EC_{50} (growth) = 62 mg/L

Conclusion: The measured 96-hour LC_{50} for the primary terpenols and related esters category members for fish ranged from 6.12 to 14 mg/L, the measured 48-hour EC_{50} for aquatic invertebrates ranged from 7.75 to 15 mg/L, and the measured 72-hour EC_{50} for aquatic plants ranged from 2.38 to 62 mg/L (growth), and 3.32 to 16 mg/L (biomass).

Table 5. Summary of Environmental Effects – Aquatic Toxicity Data						
	Sponsored Chemicals				Supporting Chemicals	
Endpoints	**dl-Citronellol (106-22-9)**	**Geraniol (106-24-1)**	**Nerol (106-25-2)**	**Acetylated myrcene (68412-04-4)**	**Geranyl acetate (105-87-3)**	**Linalyl acetate (115-95-7)**
Fish 96-h LC_{50} (mg/L)	**> 10 (m)**	**14.0 (m)**	No data 14.0 (RA)	No data 6.12 (RA)	**6.12 (m)**	—
Aquatic Invertebrates 48-h EC_{50} (mg/L)	No data 7.75 (RA)	**7.75 (m)**	No data 7.75 (RA)	No data 15 (RA)	—	**15 (m)**
Aquatic Plants 72-h EC_{50} (mg/L)			No data	No data		
(growth)	**2.38 (m)**	**5.93 (m)**	5.93	62	—	**62 (m)**
(biomass)	—	**3.32 (m)**	3.32 (RA)	16 (RA)		**16 (m)**

(m) = measured data (i.e., derived from testing); (e) = estimated data (i.e., derived from modeling); (RA) = Read Across; - the endpoint was not measured

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