SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

CHEMICAL CATEGORY NAME
Terpenoid Primary Alcohols and Related Esters

SPONSORED CHEMICALS

dl-Citronellol (CAS No. 106-22-9)
[9th CI Name: 6-Octen-1-ol, 3,7-dimethyl]
Geraniol (CAS No. 106-24-1)
[9th CI Name: 2,6-Octadien-1-ol, 3,7-dimethyl, (2E)-]
Nerol (CAS No. 106-25-2)
[9th CI Name: 2,6-Octadien-1-ol, 3,7-dimethyl, (2Z)-]
Acetylated myrcene (CAS No. 68412-04-4)
(mixture containing *trans*- and *cis*-3,7-dimethyl-2,6-octandien-1-yl acetate (i.e., geranyl and neryl acetates) and other components)
[9th CI Name:1,6-Octadiene, 7-methyl-3methylene-,acelated]

SUPPORTING CHEMICALS

Geranyl acetate (CAS No. 105-87-3)
[9th CI Name: 2,6-Octadien-1-ol, 3,7-dimethyl-, acetate, (E)-]
Citronellyl acetate (CAS No. 150-84-5)
[9th CI Name: 6-Octen-1-ol, 3,7-dimethyl-, acetate]
Citral (CAS No. 5392-40-5)
[9th CI Name: 2,6-Octadienal, 3,7-dimethyl-]
Linalool (CAS No. 78-70-6)
[9th CI Name: 1,6-Octadien-3-ol, 3,7-dimethyl-]
Citral diethyl acetal (CAS No. 7492-66-2)
[9th CI Name:2,6-Octadiene,1,1-diethoxy-3,7-dimethyl-]

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INTERIM

Prepared by

High Production Volume Chemicals Branch
Risk Assessment Division
Office of Pollution Prevention and Toxics
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001

SCREENING-LEVEL HAZARD CHARACTERIZATION OF HIGH PRODUCTION VOLUME CHEMICALS

The High Production Volume (HPV) Challenge Program[1] is 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 sponsor chemicals; sponsorship entails the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data do 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. OPPT is using a hazard-based screening process to prioritize review of the submissions. The hazard-based screening process consists of two tiers described below briefly and in more detail on the Hazard Characterization website[3].

Tier 1 is a computerized sorting process whereby key elements of a submitted data set are compared to established criteria to "bin" chemicals/categories for OPPT review. This is an automated process performed on the data as submitted by the sponsor. It does not include evaluation of the quality or completeness of the data.

In Tier 2, a screening-level hazard characterization is developed by EPA that consists of an objective evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. The evaluation is performed according to established EPA guidance[2,4] and is based primarily on hazard data provided by sponsors. EPA may also include additional or updated hazard information of which EPA, sponsors or other parties have become aware. The hazard characterization may also identify data gaps that will become the basis for a subsequent data needs assessment where deemed necessary. Under the HPV Challenge Program, chemicals that have similar chemical structures, properties and biological activities may be grouped together and their data shared across the resulting category. This approach often significantly reduces the need for conducting tests for all endpoints for all category members. As part of Tier 2, evaluation of chemical category rationale and composition and data extrapolation(s) among category members is performed in accord with established EPA[2] and OECD[5] guidance.

The screening-level hazard characterizations that emerge from Tier 2 are important contributors to OPPT's existing chemicals review process. These hazard characterizations are technical documents intended to support 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. The public, including sponsors, may offer comments on the hazard characterization documents.

The screening-level hazard characterizations, as the name indicates, do not evaluate the potential risks of a chemical or a chemical category, but will serve as a starting point for such reviews. In 2007, EPA received data on uses of and exposures to high-volume TSCA existing chemicals, submitted in accordance with the requirements of the Inventory Update Reporting (IUR) rule. For the chemicals in the HPV Challenge Program, EPA will review the IUR data to evaluate exposure potential. The resulting exposure information will then be combined with the screening-level hazard characterizations to develop screening-level risk characterizations[4,6]. The screening-level risk characterizations will inform EPA on the need for further work on individual chemicals or categories. Efforts are currently underway to consider how best to utilize these screening-level risk characterizations as part of a risk-based decision-making process on HPV chemicals which applies the results of the successful U.S. High Production Volume Challenge Program and the IUR to support judgments concerning the need, if any, for further action.

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[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. HPV Chemicals Hazard Characterization website (http://www.epa.gov/hpvis/abouthc.html).
[4] U.S. EPA. Risk Assessment Guidelines; http://cfpub.epa.gov/ncea/raf/rafguid.cfm.
[5] OECD. Guidance on the Development and Use of Chemical Categories; http://www.oecd.org/dataoecd/60/47/1947509.pdf.
[6] U.S. EPA. Risk Characterization Program; http://www.epa.gov/osa/spc/2riskchr.htm.

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

Introduction

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 February 26, 2001. 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. The terpenoid primary alcohols and related esters category consists of the following members:

dl-Citronellol	(CAS No. 106-22-9)
Geraniol	(CAS No. 106-24-1)
Nerol	(CAS No. 106-25-2)
Acetylated myrcene	(CAS No. 68412-04-4)
[mixture containing *trans*- and *cis*-3,7-dimethyl-2,6-octandien-1-yl acetate (i.e., geranyl and neryl acetates) and other components]	

This screening-level hazard characterization is based primarily on the review of the Test Plan and Robust Summaries of studies submitted by the sponsor(s) under the HPV Challenge Program. 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. The structures of the sponsored chemical(s) are included in Appendix. Summary tables of SIDS endpoint data are included in the document. The screening-level hazard characterization for environmental and human health toxicity is based largely on SIDS endpoints and is described according to established EPA or OECD effect level definitions and hazard assessment practices.

Category Justification

Three members of the terpenoid primary alcohols and related esters category (dl-citronellol, geraniol and nerol) are terpenoid acyclic aliphatic primary alcohols and the fourth member, acetylated myrcene, is a mixture of terpenoid esters and alcohols. One of the primary components of the mixture is geranyl acetate. The mixture of esters is included in the category because it is expected to hydrolyze rapidly *in vivo* to yield two of the category members, geraniol and nerol, as well as acetic acid. The chemicals in this category can be grouped and evaluated together based on similarities in chemical structure, physical-chemical and toxicological properties.

Terpenes are naturally occurring in plants and oxygenated terpenes (dl-citronellol, geraniol, nerol, citral and geranyl acetate) are ubiquitous in the plant kingdom. Citral is a mixture of geranial and neral. All of these category chemicals are common components of traditional foods or used as food additives. The U.S. Food and Drug Administration (FDA) recognized citronellol, geraniol, and nerol, and gernyl acetate as GRAS (generally regarded as safe) for their intended use as flavoring substances.

Justification for Supporting Chemicals

The sponsor provided additional data using the following supporting substances or components of acetylated myrcene for several health effects endpoints:

Geranyl acetate CAS No. 105-87-3, food-grade geranyl acetate, a mixture of 71% geranyl acetate and 29% citronellyl acetate); available data for acute toxicity, repeated-dose toxicity and chromosomal aberrations

Citronellyl acetate (CAS No.150-84-5, 29% of food-grade geranyl acetate); available data for repeated-dose toxicity and chromosomal aberrations

Citral (CAS No. 5392-40-5, mixture of geranial and neral); available data for repeated-dose toxicity and reproductive/developmental toxicity

Linalool (CAS No.78-70-6, a mixture of 50% linalool and 50% citronellol); available data for repeated-dose toxicity

Citral diethyl acetal (CAS No. 7492-66-2); available data for reproductive/developmental toxicity

The supporting chemicals have similar chemical structures and are expected to metabolize in ways similar to the sponsored category members. EPA considered the supporting data to be acceptable.

For ecological effects endpoints the sponsor provided fish acute toxicity data for geranyl acetate and acute toxicity data for aquatic invertebrates and algae on linalyl acetate to represent acetylated myrcene. EPA agreed with using these additional 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.

Summary-Conclusion

The log K_{ow} value of primary terpenoid alcohols indicates that their potential to bioaccumulate is expected to be low, except for the major components of acetylated myrcene (geranyl acetate and neryl acetate) whose log K_{ow} value indicates a high potential for bioaccumulation. All category members are readily biodegradable, indicating that they are not expected to persist in the environment.

The evaluation of available toxicity data for fish, aquatic invertebrates and aquatic plants indicates that the potential acute hazard of the terpenoid primary alcohols and related esters to aquatic organisms is moderate.

The acute oral and dermal toxicity of in the terpenoid primary alcohols and related esters category members is low. Repeated exposure of citronellol showed no effects up to the levels tested. Repeated exposures to citral (geranial:neral, 2:1) resulted in minimal to mild nephropathy in male rats. In mice, decreased body weight and body weight gain were seen. Other effects included bone marrow atrophy (rats) and effects on forestomach mucosa and ovarian atrophy (mice). Acetylated myrcene caused decreased survival and body weights, lipidosis and stomach lesions in mice following 13-weeks of exposure. In 2-year NTP bioassays in rats and mice, citral resulted in decreased body weights, dose-related kidney toxicity (mineralization and/or nephropathy) of minimal severity and fibrosis in bones. Increased survival was seen in male rats, and some decreases in benign tumors were also observed. In 2-year studies in rats with geranyl acetate, decreased body weights, and increased incidence of nephropathy and pheochromocytomas of the adrenal gland were seen. Decreased incidences of benign tumors were also observed. Citral and citral diethyl acetal did not affect fertility or reproduction parameters, but decreased fetal body weights at high doses. Repeated-dose studies did not result in any appreciable toxicity to male reproductive organs. The developmental toxicity studies of citral via oral route decreased maternal body weight and decreased pregnancy rate, increased resorptions and skeletal abnormalities (delayed ossification) and decreased fetal body weight at high doses. No effects were observed in an inhalation developmental toxicity study using citral.
The majority of gene mutation and chromosomal aberration assays using category members and supporting substances were negative, although some positive results have been reported by NTP with geranyl acetate in chromosomal aberrations tests. The weight of evidence suggests that the chemicals in this category do not induce gene mutation or chromosomal aberrations or micronuclei. Food-grade geranyl acetate was not carcinogenic in rats or mice of either sex in 2-year studies. 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. Marginal increases in squamous cell papillomas of the skin and tubular cell adenomas in the kidney were noted in male rats. Citral-treated female mice showed an increased incidence of lymphomas.

The potential health hazard of chemicals in this category is moderate, based on the repeated-dose, reproductive and developmental toxicity.

No data gaps have been identified under the HPV Challenge Program
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1. Physical-Chemical Properties and Environmental Fate

A summary of physical-chemical properties and environmental fate data submitted is provided in Table 1. For the purpose of the screening-level hazard characterization, the review and summary of these data was limited to the octanol-water partition coefficient and biodegradation endpoints as indictors of bioaccumulation and persistence, respectively.

Octanol-Water Partition Coefficient

dl-Citronellol (CAS No. 106-22-9)
Log K_{ow}: 3.1 (measured)

Geraniol (CAS No. 106-24-1)
Log K_{ow}: 3.47 (estimated)

Nerol (CAS No. 106-25-2)
Log K_{ow}: 3.47 (estimated)

Geranyl acetate (CAS No. 105-87-3, supporting chemical)
Log K_{ow}: 4.48 (estimated)

Neryl acetate (CAS No. 141-12-8, supporting chemical)
Log K_{ow}: 4.48 (estimated)

Biodegradation

dl-Citronellol (CAS No. 106-22-9)
In a Modified MITI test using activated sludge from two sewage treatment plants and soil from the Rhone River the inoculum, 65% dl-Citronellol had degraded after 28 days.
dl-Citronellol is readily biodegradable.

Mixture of Citronellol (CAS No. 106-22-9; 18%), Geraniol (CAS No. 106-24-1; 50%) and Nerol (CAS No. 106-25-2; 26%)
In a study that measured CO_2 evolution from a test substance using secondary effluent from sewage sludge as the inoculum, 100% of the mixture had degraded after 28 days.
The mixture of cironellol, geraniol and nerol is readily biodegradable.

Acetylated myrcene (CAS No. 68412-04-4)
In a study that measured the CO_2 evolution from the test substance using secondary effluent from sewage sludge as the inoculum, 82.2% acetylated myrcene had degraded after 28 days.
Acetylated myrcene is readily biodegradable.

Conclusion: The log K_{ow} values of dl-citronellol, geraniol and nerol indicate that their potential to bioaccumulate is expected to be low. The log K_{ow} values of the major components of acetylated myrcene (geranyl acetate and neryl acetate) indicate that for acetylated myrcene the potential to bioaccumulate is expected to be high. All category members are readily biodegradable, indicating that they are not expected to persist in the environment.

Table 1. Summary of Physical-Chemical Properties and Environmental Fate Data

Endpoints	dl-Citronellol (106-22-9)	Geraniol (106-24-1)	Nerol (106-25-2)	Acetylated myrcene (68412-04-4)	Geranyl acetate (supporting chemical) (105-87-3)	Citronellyl acetate (supporting chemical) (150-84-5)	Citral (supporting chemical) (5392-40-5)	Linalool (supporting chemical) (78-70-6)	Citral diethyl acetal (supporting chemical) (7492-66-2)
Melting Point (°C)	-12.16 (e)	-10.78 (e)	-10.78 (e)	No Data -6.10 (e)[1]	-6.10 (e)	—	—	—	—
Boiling Point (°C)	**225 (m)**	**230(m)**	**225 (m)**	**231 (m)** **244(m)[1]**	—	—	—	—	—
Vapor Pressure (hPa at 25°C)	**0.095 (m)**	0.03 (e)	0.08 (e)	0.03 (e) 0.04 (e)[1]	0.04 (e)	—	—	—	—
Log K_{ow}	**3.1**	3.47 (e)	3.47 (e)	—	4.48 (e)	—	—	—	—
Water Solubility (mg/L at 25°C)	**300 (m)**	**600 (m)**	256 (e)	6.9 (e)[1]	—	—	—	—	—
Direct Photodegradation	—	—	—	—	—	—	—	—	—
Indirect (OH^-) Photodegradation ($t_{1/2}$)	1.3(e)	0.71(e)	0.71 (e)	No Data 0.72 (e)[1]	0.72 (e)	—	—	—	—
Stability in Water (Hydrolysis) ($t_{1/2}$) (days)	Stable in water and not subject to hydrolysis at environmentally relevant pH values and time periods			No Data 231 at pH 7 (e)[1] 23.1 at pH 8(e)[2]	231 at pH 7 (e)[1]	—	—	—	—
Fugacity (Level III Model)	(e)	(e)	(e)	(e)	—	—	—	—	—
Air (%)	0.86	0.04	0.05	0.04					
Water (%)	39.8	39.3	36.0	35.9					
Soil (%)	59.6	59.7	63.1	57.5					
Sediment (%)	0.5	0.88	0.84	0.65					
Biodegradation at 28 days (%)	**65 (m)** Readily biodegradable	**100 (m)[2]** Readily biodegradable	No data	**82.2 (m)** Readily biodegradable	—	—	—	—	—

(m) = measured data (i.e., derived from experiment); (e) = estimated data (i.e., derived from modeling); [1]Values for acetylated myrcene are for two major components of the mixture – neryl acetate and geranyl acetate; [2]Value for test substance with following composition: 50% geraniol, 26% nerol and 18% citronellol

2. Environmental Effects – Aquatic Toxicity

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 2. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

Acute Toxicity to Fish

dl-Citronellol (CAS No. 106-22-9)
Golden Orfe (*Leuciscus idus*) were exposed to nominal concentrations of 0, 4.64, 10, 21.5, 46.4 and 100 mg/L dl-citronellol 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 at 96 hours. At 21.5, 46.4 and 100 mg/L, 100% mortality was seen 1 hour after exposure.
10 < 96-h LC_{50} < 22 mg/L

Geraniol (CAS No. 106-24-1)
Zebrafish (*Brachydanio rerio*) were exposed to nominal concentrations of 0, 11, 16, 22 and 31 mg/L under semi-static conditions for 96 hours. Solutions were renewed every 24 hours. Test concentrations were analytically measured.
96-h LC_{50} = 14.0 mg/L

Geranyl acetate (CAS No. 105-87-3, supporting chemical)
Fathead minnows (*Pimephales promelas*) were exposed to measured concentrations of 0, 1.0, 1.76, 2.61, 4.54 and 8.25 mg/L geranyl acetate, a component of acetylated myrcene, 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 (CAS No. 106-24-1)
Daphnia magna (10/concentration) each were exposed to measured concentrations of geraniol at 0, 3.43, 5.90, 9.72, 16.5, 27.8 and 47.3 mg/L in sealed vials, under static conditions for 48 hours with renewal at 24 hours.
48-h EC_{50} = 7.75 mg/L

Linalyl acetate (CAS No. 115-95-7, supporting chemical)
Daphnia magna (20/concentration) were exposed to the test substance at the measured concentrations of 0, 0.2, 8.2, 15.5, 26.3, 48.7 and 87.9 mg/L in sealed containers for 48 hours. Immobility, sublethal effects and mortality were monitored.
48-h EC_{50} = 15 mg/L

Toxicity to Aquatic Plants

dl-Citronellol (CAS No. 106-22-9)
Selenastrum subspicatus were exposed to seven nominal concentrations ranging from 0.195 – 12.5 mg/L of dl-citronellol for 72 hours.
72-h EC_{50} (growth) = 2.38 mg/L

Geraniol (CAS No. 106-24-1)
Pseudokirchneriella subcapitata were exposed to measured concentrations of 0, 0.467, 1.03, 1.93, 3.93 and 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) = 3.32 mg/L
72-h EC_{50} (biomass) = 5.93 mg/L

Linalyl acetate (CAS No. 115-95-7, supporting chemical)
Selenastrum subspicatus were exposed to the measured concentrations of 0, 2.3, 4.7, 11.6, 15.9 and 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
72-h NOEC (biomass) = 2.3 mg/L
72-h NOEC (growth) = 4.7 mg/L

Conclusion: The evaluation of available aquatic toxicity data for fish, aquatic invertebrates and aquatic plants indicates that the potential hazard of the terpenoid primary alcohols and related esters to aquatic organisms is moderate.

Table 2. Summary of Environmental Effects – Aquatic Toxicity Data

Endpoints	dl-Citronellol (106-22-9)	Geraniol (106-24-1)	Nerol (106-25-2)	Acetylated myrcene (68412-04-4)	Geranyl acetate (supporting chemical) (105-87-3)	Citronellyl acetate (supporting chemical) (150-84-5)	Citral (supporting chemical) (5392-40-5)	Linalool (supporting chemical) (78-70-6)	Citral diethyl acetal (supporting chemical) (7492-66-2)
Fish **96-h LC_{50} (mg/L)**	**> 10 and < 22 (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)** **(growth)** **(biomass)**	**2.38 (m)** —	**5.93 (m)** **3.32 (m)**	No data 5.93 3.32 (RA)	No data 62 16 (RA)	—	—	—	**62 (m)** **16 (m)**	—

(m) = measured data (i.e., derived from testing); (e) = estimated data (i.e., derived from modeling); (RA) = Read Across

3. Human Health Effects

A summary of health effects data submitted for SIDS endpoints is provided in Table 3. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

Acute Oral Toxicity

dl-Citronellol (CAS No. 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. Spontaneous activity was reduced 10 to 30 minutes after dose administration, peaked at 4 to 60 hours and returned to normal at 48 hours.
LD_{50} = 3450 mg/kg-bw

Geraniol (CAS No. 106-24-1)
Osborn-Mendel rats (5/sex) were administered the test substance via gavage (doses not specified). Toxic signs were depression, coma and wet fur. Time of death was between 4 and 18 hours.
LD_{50} = 3600 mg/kg-bw

Nerol (CAS No. 106-25-2)
Male rats (10) were administered the test substance ranging from 2560 – 9800 mg/kg-bw and observed for 14 days. Clinical signs of toxicity included axophthalmia, hyperreflectiveness, restlessness, lethargy and the loss of righting reflex. Deaths occurred within two days of dose administration.
LD_{50} = 4500 mg/kg-bw

Geranyl acetate (CAS No. 105-87-3, supporting chemical)
Osborne-Mendel rats (5/sex) were administered the test substance orally via gavage (doses not specified) and observed for 2 weeks. Signs of depression were noted. Deaths occurred between 4 and 96 hours following dosing.
LD_{50} = 6330 mg/kg-bw

Acute Dermal Toxicity

dl-Citronellol (CAS No. 106-22-9)
Rabbits (5/dose) were administered the test substance at 1.25, 2.5 or 5.0 mg/kg-bw. Signs of toxicity included ataxia and papillary dilation.
LD_{50} = 2650 mg/kg-bw

Nerol (CAS No. 106-25-2)
New Zealand White rabbits were dermally administered the test substance at 5000 mg/kg-bw to clipped, abraded skin.
LD_{50} > 5000 mg/kg-bw

Repeated-Dose Toxicity

dl-Citronellol (CAS No. 106-22-9)
Rats (strain unspecified) were administered a mixture containing 50% citronellol and 50% linalool via the diet at 100 mg/kg-bw/day (~ 50 mg/kg-bw/day citronellol and 50 mg/kg-bw/day linalool). The control group received the diet without the test substance. Urine 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 50 mg/kg-bw/day (citronellol level), these effects were attributed to the decreased palatability of the diet. No other adverse effects were noted.
LOAEL > 50 mg/kg-bw/day (based on no effects at the only dose tested)
NOAEL = 50 mg/kg-bw/day

Mixture of Citronellol (CAS No. 106-22-9) and Geraniol (CAS No. 106-24-1)
In an FDA screening study, Osborne-Mendel rats (5/sex/dose) were administered a mixture containing geraniol and citronellol (composition not given) via the diet at 1000 or 10,000 ppm (approximately 500 mg/kg bw/day) for 189 –

196 or 112 days, respectively. 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 and gross examination. Histopathology of limited organs/tissues showed no treatment-related lesions.
LOAEL > ~ 500 mg/kg-bw/day (based on no effects at the highest dose tested)
NOAEL ~ 500 mg/kg-bw/day

Citral (CAS No. 5392-40-5, mixture of geranial and neral, supporting chemical)
(1) In a 14-week toxicity NTP study (study was not included in the submission), F344 rats (10/sex/group) were administered microencapsulated citral (geranial:neral, 2:1) in the diet at 3900, 7800, 15,600 and 31,300 ppm (corresponding to approximately 345, 820, 1785 and 3585 mg/kg-bw/day for males and 335, 675, 1330, and 2125 mg/kg-bw/day for females). Control groups received untreated feed or feed with microcapsule placebos. In the 31,300 ppm group, rats were listless, had hunched postures, poor reflexes and dull eyes and were sacrificed moribund in the 2nd week. There was a dose-related and statistically significant ($p < 0.01$) reduction in body weight and body weight gain in males and females. Changes in several hematology and clinical chemistry parameters were seen at one or more time points. Bone marrow atrophy ($p < 0.01$) was noted at 15,600 ppm in 7/10 males and 8/10 females. In males, nephropathy (minimal to mild) was seen in 3/10 animals at 3900 ppm, 10/10 animals at 7800 ppm and 8/10 animals at 15,600 ppm with a presence of granular casts in the renal tubules; both kidney effects were significant at the two highest doses ($p \leq 0.01$).
LOAEL ~ 345 mg/kg-bw/day (based on kidney toxicity in males and related clinical effects)
NOAEL = Not established

(2) In a 14-week toxicity NTP study (study was not included in the submission), B6C3F1 mice (10/sex/group) were administered microencapsulated citral (geranial:neral, 2:1) in the diet at 3900, 7800, 15,600 and 31,300 ppm (corresponding to approximately 745, 1840, 3915 and 8110 mg/kg-bw/day in males and 790, 1,820, 3870 and 7550 mg/kg-bw/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 moribund in the 2nd week. Statistically significant decrease ($p \leq 0.01$) in final body weights were seen in males and females at all concentrations. 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, they were considered related to differences in body weights and were not considered toxicologically significant. Many males and females had effects on the forestomach at 15,600 and 31,300 ppm. Ovarian atrophy was markedly increased in females at 15,600 ppm (moderate in 7/10 animals) and 31,300 ppm (marked in 10/10 animals), based on absence of or reduction in the number of corpora lutea with no other effects (on primary, secondary, or antral follicles).
LOAEL ~ 745 mg/kg-bw/day (males, based on decreased body weights)
LOAEL ~ 790 mg/kg-bw/day (females, based on decreased body weights).
NOAEL = Not established

(3) In a 2-year NTP study, F344/N rats (50/sex/group) were administered 1000, 2000 or 4000 ppm (approximately 50, 100 or 210 mg/kg-bw/day) micro-encapsulated citral (63% geranial and 37% neral) in the diet continuously for 2 years. Control groups received untreated feed or feed with microcapsule placebos. A decrease in body weight was seen in males and females at 4000 ppm. 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-bw/day, 48/50 (96%) at 100 mg/kg-bw/day and 50/50 (100%) at 210 mg/kg-bw/day and the severity increased at the two highest concentrations compared with the vehicle control. Although mineralization in kidneys is a spontaneously occurring lesion in aging rats, the incidence was exacerbated by treatment with citral. The sponsor considered this effect of limited toxicological significance.
LOAEL ~ 100 mg/kg-bw/day (based on severity of mineralization in kidneys of male rats)
NOAEL ~ 50 mg/kg-bw/day

(4) In a 2-year NTP study, B6C3F$_1$ mice (50/sex/dose) were administered 500, 1000 or 2000 ppm (approximately 60, 120 or 260 mg/kg-bw/day) microencapsulated citral (63% geranial and 37% neral, overall purity of 94%) in the diet continuously for 2 years. Control groups received untreated feed or feed with microcapsule placebos. 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 in males was seen during the second year or from week 14 to the end of the study. At 500 ppm, females had lower body weights starting at week 30.
LOAEL ~ 60 mg/kg-bw/day (based on decreased body weight)
NOAEL = Not established

(5) In a 13-week screening study using FDA guidelines, Osborne-Mendel rats (10/sex/dose) were administered citral (composition of geranial and neral not available) in the diet at 0, 1000, 2500 or 10,000 ppm for 13 weeks. Determination of dietary concentration of citral revealed a weekly loss of 58%; therefore, average daily dose received was estimated (only for the highest dose) to be 200 mg/kg bw/day. There was no effect on body weight, food consumption and general condition and hemoglobin 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.
LOAEL > 200 mg/kg-bw/day (based on no effects at the highest dose tested)
NOAEL = 200 mg/kg-bw/day

Mixture of Geranyl acetate (CAS No. 105-87-3, supporting chemical) and Citronellyl acetate (CAS No.150-84-5, supporting chemical)
In a 17-week screening study using FDA guidelines, Osborne-Mendel rats (10/sex/group) were administered in the diet a mixture of geranyl acetate and citronellyl acetate (71:29) at 1000, 2500 or 10,000 ppm (approximately 500 mg/kg-bw/day—determined only for the highest dose). There was no effect on body weight, food consumption, general conditions and hematology parameters. Macroscopic and 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.
LOAEL > 500 mg/kg-bw/day (based on no effects at the highest tested dose)
NOAEL = 500 mg/kg-bw/day

Geranyl acetate (CAS No. 105-87-3, supporting chemical)
(1) In an NTP study, F344/N rats (10/sex/group) were administered food-grade geranyl acetate (a mixture of geranyl acetate and citronellyl acetate, 71:29) in corn oil via oral gavage 5 days/week, at 0, 250, 500, 1000, 2000 or 4000 mg/kg-bw/day 5/days/week for 13 weeks. At 4000 mg/kg-bw/day, three rats died, mean body weight was depressed at the highest dose in males and females; three male rats had reddened stomach mucosa. No histopathological effects were observed at necropsy.
LOAEL = 4000 mg/kg-bw/day (based on mortality and decreased body weights in male rats)
NOAEL = 2000 mg/kg-bw/day

(2) In an NTP study, B6C3F1 mice (10/sex/group) were administered food-grade geranyl acetate (a mixture of geranyl acetate and citronellyl acetate, 71:29) in corn oil via oral gavage at 0, 125, 250, 500, 1000 or 2000 mg/kg-bw/day 5 days/week for 13 weeks. At 2000 mg/kg-bw/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.
LOAEL = 2000 mg/kg-bw/day (based on mortality, lipidosis, stomach lesions and decreased body weights)
NOAEL = 1000 mg/kg-bw/day

(3) In an NTP study, F344/N rats (50/sex/group) were administered food-grade geranyl acetate (a mixture of geranyl acetate and citronellyl acetate, 71:29) in corn oil via oral gavage at 1000 or 2000 mg/kg-bw/day 5 days/week for 2 years. No compound-related clinical signs were seen. At 2000 mg/kg-bw/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. Decrease body weights greater than 10% occurred only at 2000 mg/kg-bw/day. In females, there was an increased incidence of nephropathy in the high dose (63%) compared to controls (26%). The incidence of nephropathy in the high-dose males was 90% compared to 80% in controls)
LOAEL = 1000 mg/kg-bw/day (based on decreased body weight)
NOAEL = Not established

Reproductive Toxicity

Reproductive toxicity studies are not available for the category members, but studies are available for the supporting chemicals citral and citral diethyl acetal. These reproductive toxicity studies did not evaluate male-related reproductive toxicity. However, no effects on reproductive organs were observed in repeated-dose toxicity studies discussed above that evaluated such effects. Although a positive trend ($p < 0.001$) in increased interstitial cell adenomas of the testes was observed in the 2-year bioassay with geranyl acetate administered by oral gavage to rats (43/50 in controls, 44/50 at 1000 mg/kg-bw/day, and 44/49 at 2,000 mg/kg-bw/day), the effect was likely to have reflected decreased survival at the highest dose

Citral (CAS No. 5392-40-5, supporting chemical)
In a two-generation reproductive toxicity study, citral (a mixture of geranial and neral) was administered orally at doses of 0, 50, 160 and 500 mg/kg-bw/day to 30 female Sprague-Dawley rats. The test substance was given for 14 days prior to cohabitation with males, from days 0 through 25 of presumed gestation and days 1 – 21 of lactation. In the dams, clinical observations, estrus cycle, body weight and body weight gains, mating and fertility, duration of gestation, delivery, maternal behavior, reproductive effects and gross necropsy were evaluated. Fetuses were examined for fetal wastage, body weight, sex and gross external changes. Clinical observations, body weight changes and gross necropsy were evaluated in the pups. At 160 and 500 mg/kg-bw/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 ($p < 0.05$).
LOAEL (systemic toxicity) = 160 mg/kg-bw/day (based on increased mortality and decreased body weight/food consumption)
NOAEL (systemic toxicity) = 50 mg/kg-bw/day
LOAEL (reproductive toxicity) = 500 mg/kg-bw/day (based on decreased pup body weights)
NOAEL (reproductive toxicity) = 160 mg/kg-bw/day

Citral diethyl acetal (CAS No. 7492-66-2, supporting chemical)
In a combined reproductive/developmental toxicity screening test, citral diethyl acetal was administered orally via gavage at 0, 125, 250 and 500 mg/kg-bw/day to female Sprague-Dawley rats 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. Dams showed clinical signs and lower body weights than controls at 250 and 500 mg/kg-bw/day. At 500 mg/kg-bw/day, decreased body weight gain was also observed. In pups, lower body weight compared to controls was observed only at 500 mg/kg-bw/day.
LOAEL (systemic toxicity) = 250 mg/kg-bw/day (based on clinical signs and reduced body weight)
NOAEL (systemic toxicity) = 125 mg/kg-bw/day
LOAEL (reproductive toxicity) = 500 mg/kg-bw/day (based on decreased pup body weights)
NOAEL (reproductive toxicity) = 250 mg/kg-bw/day

Developmental Toxicity

Developmental toxicity studies are not available for the category members. However, studies available for supporting chemicals include developmental toxicity tests—two studies for citral and one combined reproductive/developmental toxicity screening test for citral diethyl acetal.

Citral (CAS No. 5392-40-5, supporting chemical)
(1) Female Wistar rats received the test substance at 0, 60, 125, 250, 500 and 1000 mg/kg daily by oral gavage during days 6 – 15 of gestation. The number of resorptions and implantation sites were determined. Body weights of fetuses were reported and they were evaluated for external, visceral and skeletal malformations. Dams showed statistically significant decreases in pregnancy weight gain (minus uterus weight) at 500 and 1000 mg/kg-bw/day ($p < 0.05$). Body weight reductions were observed at all doses; reductions at lower doses were likely to be due to reduced gravid uterine weights. Fetal body weight was decreased ($p < 0.05$) at 125, 250 and 500 mg/kg-bw/day. Delayed ossifications of fetuses were also seen at 125 and 250 mg/kg-bw/day ($p < 0.05$). Increased numbers of fetuses with skeletal abnormalities were seen at 125, 250 and 1000 mg/kg-bw/day. Spleen weights were increased at doses of 250 mg/kg-bw/day and higher. The incidence of hematomas was increased at 250, 500 and 1000 mg/kg-bw/day ($p < 0.05$). Increased resorptions per implantation were observed at 60 and 125 mg/kg-bw/day and at 250 mg/kg-bw/day and higher, a dose-dependent reduction in the ratio of pregnant animals to mated animals was observed. Corpora lutea graviditas were seen in most sperm-positive-treated rats without implantation sites.
LOAEL (maternal toxicity) = 60 mg/kg-bw/day (based on reduced pregnancy weight gain)
NOAEL (maternal toxicity) = Not established
LOAEL (developmental toxicity) = 60 mg/kg-bw/day (based on increased resorptions)
NOAEL (developmental toxicity) = Not established

(2) Pregnant Sprague-Dawley rats were exposed by inhalation to vapors of commercially available citral (55% geranial and 35% neral) at 0, 10, 35 or 85 ppm for 6 hours/day during gestation days 6 – 15. Measured concentrations were 10.2, 24.4 and 68 ppm or 0.063.5, 0.152 and 0.423 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 showed clinical sings (clinical signs not stated in the robust summary). Body weight and/or body weight gain was also reduced at this concentration compared with controls ($p < 0.05$). The incidence of hypoplastic lumbar and pubis bones in the fetuses was increased slightly at 68 ppm (423 mg/L) compared with the controls.
LOAEL (maternal toxicity) = 0.423 mg/L/day (based on clinical signs and decreased body weights/body weight gains)
NOAEL (maternal toxicity) = 0.152 mg/L/day
LOAEL (developmental toxicity) > 0.423 mg/L/day
NOAEL (developmental toxicity) = 0.423 mg/L/day (based on no effects at the highest dose tested)

Citral diethyl acetal (CAS No. 7492-66-2, supporting chemical)
In the reproductive/developmental toxicity screening test described previously, dams showed clinical signs and lower body weights than controls at both 250 and 500 mg/kg-bw/day. At 500 mg/kg-bw/day, decreased body weight gain was also observed. In pups, lower body weight compared to controls was observed only at 500 mg/kg-bw/day.
LOAEL (maternal toxicity) = 250 mg/kg-bw/day (based on clinical signs and reduced body weight)
NOAEL (maternal toxicity) = 125 mg/kg-bw/day
LOAEL (developmental toxicity) = 500 mg/kg-bw/day (based on decreased pup body weights)
NOAEL (developmental toxicity) = 250 mg/kg-bw/day

Genetic Toxicity – Gene Mutation

In vitro
dl-Citronellol (CAS No. 106-22-9)
A reverse bacterial mutation assay, *Salmonella typhimurium* strains TA98 and TA100 were exposed to dl-citronellol concentrations ranging from 0.05 to 100 µL/plate, in the presence of metabolic activation system. Because only two strains were used, the study is somewhat limited in its ability to assess the potential of dl-citronellol to cause gene mutations. However, the results are corroborated in the *Summary of Data for Chemical Selection*, available at the National Toxicology Program (NTP) website (http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumPdf/Citronellol.pdf) and the NTP summary also reported a second study using the above two strains with and without metabolic activation and showing the compound to be negative for gene mutations.
dl-Citronellol was not mutagenic in this assay.

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

Acetylated myrcene (CAS No. 68412-04-4)
Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 were exposed to acetylated myrcene (composition not defined) at a concentration of 2000 µg/plate was tested in the presence metabolic activation system. No evidence of mutagenicity 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.

Genetic Toxicity – Chromosomal Aberrations

In vivo
Geranyl acetate (CAS No. 105-87-3, supporting chemical)
In a mouse micronucleus assay, food-grade geranyl acetate (79% geranyl acetate; 21% citronellyl acetate) was administered by intraperitoneal injection at 0, 450, 900 or 1800 mg/kg-bw for three consecutive days and mice were sacrificed 48 hours after the last treatment. Positive and negative controls were used in the study. The number of micronucleated polychromatic erythrocytes (MN-PCEs) per 1000 PCEs was not statistically increased at any dose by trend or pair-wise comparison tests ($p = 0.05$).
Geranyl acetate did not induce chromosomal aberration or micronuclei in this assay.

NTP studies with geranyl acetate (http://ntp.niehs.nih.gov/index.cfm?objectid=071455D7-E77F-FD02-2F03AF57EC9CED66) showed negative results in a nonstandard assays but positive results in another chromosomal aberrations assay. It is not clear whether the studies were conducted *in vitro* or *in vivo*. The compound was negative in one sister chromatid exchange assay but weakly positive in a second assay. Two reports of micronucleus assays were negative. No further details are available about these studies, nor is it known whether the study submitted by the sponsor is included in the NTP summary.

The weight of evidence from the submitted data and additional NTP data indicates geranyl acetate does not induce chromosomal aberrations.

Additional Information

Carcinogenicity

Citral (CAS No. 5392-40-5, supporting chemical)
Citral did not show carcinogenic potential in male rats, female rats or male mice up to the dose levels tested. In female mice, however, an increase in the incidence of lymphomas may have been related to citral in the diet.

Geranyl acetate (CAS No. 105-87-3, supporting chemical)
Geranyl acetate (79% geranyl acetate; 21% citronellyl acetate) showed evidence of carcinogenicity in F344/N rats or $B6C3F_1$ mice of either sex in 2-year gavage studies at doses up to 2000 mg/kg-bw/day in rats and 1000 mg/kg bw/day in mice. The authors noted, however, 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.

Conclusion: The acute oral and dermal toxicity of in the terpenoid primary alcohols and related esters category members is low. Repeated exposure of citronellol showed no effects up to the levels tested. Repeated exposures to citral (geranial:neral, 2:1) resulted in minimal to mild nephropathy in male rats. In mice, decreased body weight and body weight gain were seen. Other effects included bone marrow atrophy (rats) and effects on forestomach mucosa and ovarian atrophy (mice). Acetylated myrcene caused decreased survival and body weights, lipidosis and stomach lesions in mice following 13-weeks of exposure. In 2-year NTP bioassays in rats and mice, citral resulted in decreased body weights, dose-related kidney toxicity (mineralization and/or nephropathy) of minimal severity and

fibrosis in bones. Increased survival was seen in male rats, and some decreases in benign tumors were also observed. In 2-year studies in rats with geranyl acetate, decreased body weights, and increased incidence of nephropathy and pheochromocytomas of the adrenal gland were seen. Decreased incidences of benign tumors were also observed. Citral and citral diethyl acetal did not affect fertility or reproduction parameters, but decreased fetal body weights at high doses. Repeated-dose studies did not result in any appreciable toxicity to male reproductive organs. The developmental toxicity studies of citral via oral route decreased maternal body weight and decreased pregnancy rate, increased resorptions and skeletal abnormalities (delayed ossification) and decreased fetal body weight at high doses. No effects were observed in an inhalation developmental toxicity study using citral. The majority of gene mutation and chromosomal aberration assays using category members and supporting substances were negative, although some positive results have been reported by NTP with geranyl acetate in chromosomal aberrations tests. The weight of evidence suggests that the chemicals in this category do not induce gene mutation or chromosomal aberrations or micronuclei. Food-grade geranyl acetate was not carcinogenic in rats or mice of either sex in 2-year studies. 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. Marginal increases in squamous cell papillomas of the skin and tubular cell adenomas in the kidney were noted in male rats. Citral-treated female mice showed an increased incidence of lymphomas.

The potential health hazard of chemicals in this category is moderate, based on the repeated-dose, reproductive and developmental toxicity.

Table 3. Summary of Human Health Data

Endpoints	dl-Citronellol (106-22-9)	Geraniol (106-24-1)	Nerol (106-25-2)	Acetylated myrcene (68412-04-4)	Geranyl acetate (supporting chemical) (105-87-3)	Citronellyl acetate (supporting chemical) (150-84-5)	Citral (supporting chemical) (5392-40-5)	Linalool (supporting chemical) (78-70-6)	Citral diethyl acetal (supporting chemical) (7492-66-2)
Acute Oral Toxicity LD_{50} (mg/kg-bw)	**3450**	**3600**	**4500**	No data[1] 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-bw/day)	**NOAEL = 50** **LOAEL > 50** **NOAEL = 500**[3,4] **LOAEL > ~ 500**	No data[5] NOAEL = NE LOAEL ~ 345 (RA) NOAEL = NE LOAEL = 745 - 790 (RA) NOAEL = 50 LOAEL = 100 (RA) NOAEL = NE LOAEL = ~ 60 (RA) NOAEL =~200 LOAEL >~ 200 (RA)	No data[5] NOAEL = NE LOAEL ~ 345 (RA) NOAEL = NE LOAEL = 745 – 790 (RA) NOAEL = 50 LOAEL = 100 (RA) NOAEL = NE LOAEL = 60 (RA) NOAEL =~ 200 LOAEL >~ 200 (RA)	No Data[2] NOAEL = 2000 LOAEL = 4000 (RA) NOAEL =1000 LOAEL = 2000 (RA) NOAEL = NE LOAEL = 1000 (RA) NOAEL ~ 500 LOAEL > ~ 500 (RA)	**NOAEL = 2000** **LOAEL = 4000** **NOAEL = 1000** **LOAEL = 2000** **NOAEL = NE** **LOAEL = 1000**	—	**NOAEL = NE** **LOAEL ~ 345** **NOAEL = NE** **LOAEL = 745 - 790** **NOAEL = 50** **LOAEL = 100** **NOAEL = NE** **LOAEL ~ 60** **NOAEL ~200** **LOAEL > ~ 200**	—	—

Table 3. Summary of Human Health Data

Endpoints	dl-Citronellol (106-22-9)	Geraniol (106-24-1)	Nerol (106-25-2)	Acetylated myrcene (68412-04-4)	Geranyl acetate (supporting chemical) (105-87-3)	Citronellyl acetate (supporting chemical) (150-84-5)	Citral (supporting chemical) (5392-40-5)	Linalool (supporting chemical) (78-70-6)	Citral diethyl acetal (supporting chemical) (7492-66-2)
Reproductive Toxicity NOAEL/ LOAEL (mg/kg-bw/day)	No Data[5]	No Data[5]	No Data[5]	No Data[5]	—	—		—	
Systemic Toxicity	NOAEL = 50 LOAEL = 160 (RA)	NOAEL = 50 LOAEL = 160 (RA)	NOAEL = 50 LOAEL = 160 (RA)	NOAEL = 125 LOAEL = 250 (RA)			**NOAEL = 50 LOAEL = 160**		**NOAEL = 125 LOAEL = 250**
Reproductive Toxicity	NOAEL = 160 LOAEL = 500 (RA)	NOAEL = 160 LOAEL = 500 (RA)	NOAEL = 160 LOAEL = 500 (RA)	NOAEL = 250 LOAEL = 500 (RA)			**NOAEL = 160 LOAEL = 500**		**NOAEL = 250 LOAEL = 500**
Developmental Toxicity (Oral) (mg/kg-bw/day)	No Data[5]	No Data[5]	No Data[5]	No Data[5]	—	—		—	
Maternal	NOAEL = NE LOAEL = 60	NOAEL = NE LOAEL = 60	NOAEL = NE LOAEL = 60	NOAEL = NE LOAEL = 60			**NOAEL = NE LOAEL = 60**		
Developmental	NOAEL = NE LOAEL = 60 (RA)	NOAEL = NE LOAEL = 60 (RA)	NOAEL = NE LOAEL = 60 (RA)	NOAEL = NE LOAEL = 60 (RA)			**NOAEL = NE LOAEL = 60**		
Maternal	NOAEL = 125 LOAEL = 250	NOAEL = 125 LOAEL = 250	NOAEL = 125 LOAEL = 250	NOAEL = 125 LOAEL = 250					**NOAEL = 125 LOAEL = 250**
Developmental	NOAEL = 250 LOAEL = 500 (RA)	NOAEL = 250 LOAEL = 500 (RA)	NOAEL = 250 LOAEL = 500 (RA)	NOAEL = 250 LOAEL = 500 (RA)					**NOAEL = 250 LOAEL = 500**

Table 3. Summary of Human Health Data

Endpoints	dl-Citronellol (106-22-9)	Geraniol (106-24-1)	Nerol (106-25-2)	Acetylated myrcene (68412-04-4)	Geranyl acetate (supporting chemical) (105-87-3)	Citronellyl acetate (supporting chemical) (150-84-5)	Citral (supporting chemical) (5392-40-5)	Linalool (supporting chemical) (78-70-6)	Citral diethyl acetal (supporting chemical) (7492-66-2)
Developmental Toxicity (Inhalation) (mg/L/day)	No Data	No Data	No Data	No Data	—	—		—	—
Maternal	NOAEL = 0.152 LOAEL = 0.423	NOAEL = 0.152 LOAEL = 0.423	NOAEL = 0.152 LOAEL = 0.423	NOAEL = 0.152 LOAEL = 0.423			**NOAEL = 0.152** **LOAEL = 0.423**		
Developmental	NOAEL = 0.423 LOAEL > 0.423 (RA)	NOAEL = 0.423 LOAEL > 0.423 (RA)	NOAEL = 0.423 LOAEL > 0.423 (RA)	NOAEL = 0.423 LOAEL > 0.423 (RA)			**NOAEL = 0.423** **LOAEL > 0.423**		
Genetic Toxicity – Gene Mutation ***In vitro***	**Negative**	**Negative**	No data Negative (RA)	**Negative**	—	—	—	—	—
Genetic Toxicity – Chromosomal Aberrations ***In vivo***	No data Negative (RA)	No data Negative (RA)	No data Negative (RA)	**Negative**[2,6]	**Negative**	—	—	—	—

RA = Read Across; NE = Not established; [1]Supporting chemical (component of acetylated myrcene): geranyl acetate (purity not stated); [2]Supporting chemical: 79% geranyl acetate and 21% citronellyl acetate; [3]Supporting chemical: mixture of citronellol and geraniol (percentages not stated); [4]Dose level identified in NTP (1997); the sponsor's submission states only that the NOAEL is 100 mg mixture/kg-bw/day; [5]Supporting chemical: citral (mixture of geranial and neral) and citral diethyl acetal; [6]Weight of evidence suggests the compound is negative for chromosomal aberrations

4. Hazard Characterization

The log K_{ow} value of primary terpenoid alcohols indicates that their potential to bioaccumulate is expected to be low, except for the major components of acetylated myrcene (geranyl acetate and neryl acetate) whose log K_{ow} value indicates a high potential for bioaccumulation. All category members are readily biodegradable, indicating that they are not expected to persist in the environment.

The evaluation of available toxicity data for fish, aquatic invertebrates and aquatic plants indicates that the potential acute hazard of the terpenoid primary alcohols and related esters to aquatic organisms is moderate.

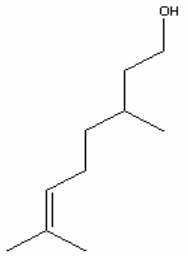
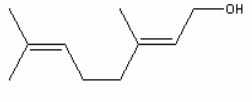
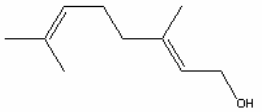
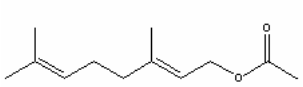
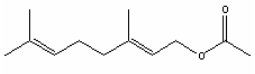
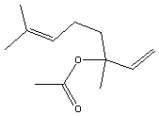
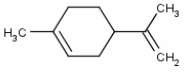
The acute oral and dermal toxicity of in the terpenoid primary alcohols and related esters category members is low. Repeated exposure of citronellol showed no effects up to the levels tested. Repeated exposures to citral (geranial:neral, 2:1) resulted in minimal to mild nephropathy in male rats. In mice, decreased body weight and body weight gain were seen. Other effects included bone marrow atrophy (rats) and effects on forestomach mucosa and ovarian atrophy (mice). Acetylated myrcene caused decreased survival and body weights, lipidosis and stomach lesions in mice following 13-weeks of exposure. In 2-year NTP bioassays in rats and mice, citral resulted in decreased body weights, dose-related kidney toxicity (mineralization and/or nephropathy) of minimal severity and fibrosis in bones. Increased survival was seen in male rats, and some decreases in benign tumors were also observed. In 2-year studies in rats with geranyl acetate, decreased body weights, and increased incidence of nephropathy and pheochromocytomas of the adrenal gland were seen. Decreased incidences of benign tumors were also observed. Citral and citral diethyl acetal did not affect fertility or reproduction parameters, but decreased fetal body weights at high doses. Repeated-dose studies did not result in any appreciable toxicity to male reproductive organs. The developmental toxicity studies of citral via oral route decreased maternal body weight and decreased pregnancy rate, increased resorptions and skeletal abnormalities (delayed ossification) and decreased fetal body weight at high doses. No effects were observed in an inhalation developmental toxicity study using citral.
The majority of gene mutation and chromosomal aberration assays using category members and supporting substances were negative, although some positive results have been reported by NTP with geranyl acetate in chromosomal aberrations tests. The weight of evidence suggests that the chemicals in this category do not induce gene mutation or chromosomal aberrations or micronuclei. Food-grade geranyl acetate was not carcinogenic in rats or mice of either sex in 2-year studies. 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. Marginal increases in squamous cell papillomas of the skin and tubular cell adenomas in the kidney were noted in male rats. Citral-treated female mice showed an increased incidence of lymphomas.

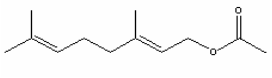
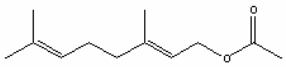
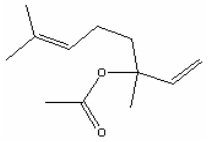
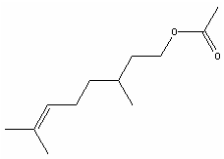
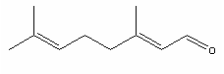
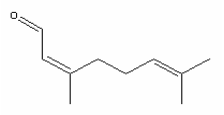
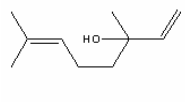
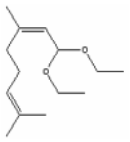
The potential health hazard of chemicals in this category is moderate, based on the repeated-dose, reproductive and developmental toxicity.

5. Data Gaps

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

Appendix

Terpenoid Primary Alcohols and Related Esters Category		
CAS No.	**Chemical Name**	**Structure**
SPONSORED CHEMICALS		
106-22-9	dl-Citronellol 3,7-Dimethyl-6-octen-1-ol	 $C_{10}H_{20}O$
106-24-1	Geraniol *trans*-3,7-Dimethyl-2,6-octadien-1-ol	 $C_{10}H_{18}O$
106-25-2	Nerol c*is*-3,7-Dimethyl-2,6-octadien-1-ol	 $C_{10}H_{18}O$
68412-04-4	Acetylated myrcene (mixture of geraniol and nerol, gernayl acetate, neryl acetate, linalyl acetate, limonene, and unidentified components) [Typical composition: 60 – 65% geranyl acetate (*trans*-3,7-dimethyl-2,6-octadien-1-yl acetate) and neryl acetate (*cis*-3,7-dimethyl-2,6-octadien-1-yl acetate); 2.5% geraniol and nerol; .5% linalyl acetate; 10% limonene; 20 – 25% other components (each ≤ 3% of total)]	Geranyl acetate (*trans*-3,7-dimethyl-2,6-octadien-1-yl acetate; CAS No. 105-87-3)  $C_{12}H_{20}O_2$
		Neryl acetate (trans-3,7-dimethyl-2,6-octadien-1-yl acetate; CAS No. 141-12-8)  $C_{12}H_{20}O_2$
		Linalyl acetate (CAS No. 115-95-7)  $C_{12}H_{20}O_2$
		Limonene (CAS No. 138-86-3)  $C_{10}H_{16}$

Terpenoid Primary Alcohols and Related Esters Category		
CAS No.	**Chemical Name**	**Structure**
SUPPORTING CHEMICALS		
105-87-3	Geranyl acetate (*trans*-isomer) (component of acetylated myrcene; also 71% of food-grade geranyl acetate]	 $C_{12}H_{20}O_2$
141-12-8	Neryl acetate (*cis*-isomer) (component of acetylated myrcene)	 $C_{12}H_{20}O_2$
115-95-7	Linalyl acetate	 $C_{12}H_{20}O_2$
150-84-5	Citronellyl acetate (29% of food-grade geranyl acetate)	 $C_{12}H_{22}O_2$
141-27-5	Geranial (component of citral, CAS No. 5392-40-5)	 $C_{10}H_{16}O$
106-26-3	Neral (component of citral, CAS No. 5392-40-5)	 $C_{10}H_{16}O$
78-70-6	Linalool (50% in mixture with citronellol)	 $C_{10}H_{18}O$
7492-66-2	Citral diethyl acetal (diethyl acetal of geranial)	 $C_{14}H_{26}O_2$