Integrated Laboratory Systems

β-Myrcene
[123-35-3]

Review of Toxicological Literature

Prepared for

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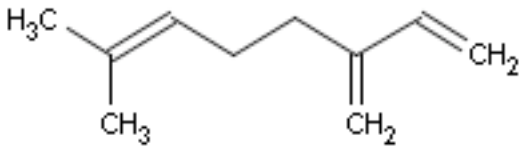
1.0 INTRODUCTION

1.1 Chemical Identification

β-Myrcene
[123-35-3]



β-myrcene ($C_{10}H_{16}$, mol. wt. = 136.24) is also called:

1,6-Octadien, 7-methyl-3-methylene- (8CI9CI)
2-Methyl-6-methylene-2,7-octadiene
7-Methyl-3-methylene-1,6-octadiene
3-Methylene-7-methyl-1,6-octadiene
2-Methyl-6-methylene-2,7-octadiene
Myrcene
Myrcene 85

1.2 Physical-Chemical Properties

Property	Information	Reference
Color	Colorless	The Good Scents Company (1996)
Physical State	Oil	Budavari (1996)
Boiling Point, °C	167	Weast and Astle (1980)
Density at 20°C	0.7601	Weast and Astle (1980)
Odor	Fresh, peppery, terpy, spicy, balsam, and plastic	The Good Scents Company (1996)
Solubility:		
Water	Practically insoluble	Budavari (1996)
Organic Solvents	Soluble in: alcohol, chloroform, ether, and glacial acetic acid	Weast and Astle (1980)

A polymerization inhibitor such as buytlhydroxytoluene or tenox propyl gallate is normally added to crude or high purity myrcene, respectively, during shipment or extended storage (Gorman, 1996). On prolonged heating at moderate temperatures (140-270 oC), b-myrcene readily dimerizes (Grayson, 1983).

2.0 PRODUCTION PROCESSES AND ANALYSES

The only important commercial source of β–myrcene is the pyrolysis of β–pinene at 550-600°C (Gorman, 1996). Typical crude pyrolyzate contains 75 to 77% myrcene, 9% limonene, approximately 2% PSI-limonene, and minor cracking products. It is thought that the reaction proceeds through allylic diradicals. Not typical free radicals; allylic diradicals rearrange intramolecularly because of their proximity to one another, and as a result, little polymerization occurs during pyrolysis. Fractional distillation is used to produce high purity myrcene, with precautions taken to prevent polymerization (Grayson, 1983). A polymerization inhibitor such as butylhydroxytoluene or tenox propyl gallate is normally added to crude or high purity myrcene, respectively, during shipment or extended storage (Gorman, 1996). On prolonged heating at moderate temperatures, β–myrcene readily dimerizes (Grayson, 1983). [For example, at 140 °C for 48 h under nitrogen] (Hayashi and Komae, 1982).

3.0 PRODUCTION AND IMPORT VOLUMES

In 1976, Opdyke reported that the amount of β–myrcene used in fragrances in the US amounted to approximately 2000 lb/yr. In the initial TSCA Inventory ca. 1977, six producers and three importers of β–myrcene were mentioned (TSCAAP, 1983). Two of the producers reported annual production volumes of <1,000 lb (<0.45 metric tons [Mg]) and from 1,000 to 10,000 lb (0.45 to 4.5 Mg). Grayson (1983) reported that the production volume of myrcene is large but that reliable production and cost figures for crude myrcene were unavailable. Most recently, SRI International (1996) listed SCM Glidco Organics, Jacksonville, Florida, as the only current producer of β–myrcene in the U.S. Production volumes are withheld when there is only one producer (USITC, 1994).

4.0 USES

Summary: The greatest use of β−myrcene is as an intermediate in the commercial production of terpene alcohols, which serve as intermediates for the production of large-volume aroma and flavor chemicals. β−Myrcene and essential oils containing this monoterpene have been widely used as scenting agents in cosmetics, soaps, and as detergents. β−Myrcene is also used as raw material for finer grade aromatic production, and copolymerization and condensation. β−Myrcene is a peripheral analgesic substance and the active ingredient in lemongrass tea.

β−Myrcene has been in public use since the 1950s (Opdyke, 1976). The greatest use of myrcene is as an intermediate in the commercial production of terpene alcohols: geraniol, nerol, and linalool, which serve as intermediates for the production of large-volume aroma and flavor chemicals. It is also used in large quantities in the manufacture of specialty aroma compounds (myrcenol and its derivatives) (Grayson, 1987; Kuney, 1994). It is found in verbena oil, galbanum oil, and Formosan and West Indian lemongrass oil (Guenther, 1949; cited by Opdyke, 1976), and is the major constituent of hop and bay oils which are used in the manufacture of alcoholic beverages (Madyastha and Srivatsan, 1987). Depending on variety, β−myrcene generally accounts for 40 to 70% of the total oil content but is readily oxidized and lost after harvest. β−Myrcene and essential oils containing this monoterpene have been widely used as scenting agents in cosmetics, soaps, detergents, and as flavoring additives in food and beverages (Lorente et al., 1989; Delgado et al., 1993b). Lorenzetti et al. (1991) reported that myrcene is a peripheral analgesic substance and the active ingredient in lemongrass (*Cymbopogon citratus*) tea. This potion is widely used in Brazilian folk medicine to treat gastrointenstinal disturbances and as a sedative and antipyretic (Carlini et al., 1986; cited by Delgado et al., 1993a).

5.0 ENVIRONMENTAL OCCURRENCE

Summary: β−Myrcene is present at a low relative abundance in the environment. It has been identified in over 200 plants, and was detected in the emissions of two representative plywood veneer dryers in the U.S. Myrcene is 1 of 9 major monoterpenes emitted into the atmosphere by many tree species in the U.S. It has also been identified in the headspace of biodegradable and mixed household waste at concentrations at least three times those found in control air samples, and was present at a low level in the indoor air of 4 of 26 houses (15%) in Helsinki, Finland.

5.1 Plant Sources of Myrcene

See the **Appendix** for a list of plants containing myrcene.

The myrcene concentrations in emission samples taken from 3 plywood stacks located at the green, middle, and dry end of one representative plywood veneer dryer in Southern U.S. were found to be 38.6, 22.2, and 7.0 mg/m^3 (283, 163, and 51 μmol/m^3, respectively), or approximately 1.8%, 2.0%, and 2.1% of the total terpene concentrations at these sites (Cronn et al., 1983). The concentration of myrcene in gaseous emissions from one Pacific Northwest U.S. plywood veneer dryer (middle plywood stack) was 0.38 mg/m^3 (2.79 μmol/m^3) or approximately 0.6% of all terpenes detected (66.2 mg/m^3) (Cronn et al., 1983).

β−Myrcene at concentrations between 0.8 and 1.4 μg/m^3 (0.006 - 0.010 μmol/m^3) was identified as 1 of 7 major monoterpenes detected during two summer nights at a sampling site inside a young planted forest of Scots Pine (*Pinus silvestris*) in Sweden (Petersson, 1988). Guenther et al. (1994) reported that typical rates for monoterpene emissions (with myrcene listed as 1 of 9 major monoterpenes being emitted) from many tree species in the U.S. (including representatives of all of the U.S. tree genera) under standard conditions ranged from 0.1 to 3 μg/g/h. On an area-weighted basis, the U.S. average total volatile organic compounds (VOCs) emission rate of 5.1 mg/m^3/h for all woodlands is comprised of 18% monoterpenes (including myrcene), 24% other VOCs, and 58% isoprene (Guenther et al., 1993; cited by Guenther et al., 1994). Long-term variations in monoterpene emissions are a function of ambient humidity, monoterpene solubility and vapor pressure, leaf temperature, morphology and resin content (Tingey et al., 1991; cited by Guenther et al. 1994), while short-term variations in monoterpene emission are controlled by leaf temperature (Guenther et al., 1993; cited by Guenther et al.,

1994).

5.2 Litter Concentrations

β–Myrcene was detected as 1 of 9 monoterpenes found in single-leaf pinyon (*Pinus monophylla* Frem.) litter from two stands growing on the western edge of the Great Basin (Western Utah to Southeastern California) (Wilt et al., 1988). Mean monoterpene concentrations for β–myrcene and β–pinene combined was 5.3 μg/g air dry weight (adw), while the total mean monoterpene concentration was 340 μg/g adw. Variation in the concentrations of monoterpenes in litter samples was thought to correspond with the amount of woody material in the samples and the degree of weathering. On the average, monoterpene levels in soil samples collected at both sites were 50 times less than those found in the litter samples.

5.3 Biodegradable and Mixed Household Waste

Myrcene was detected as 1 of 90 VOCs in the headspace of biodegradable and mixed household waste at concentrations (values not given) at least three times those found in control air samples. The concentrations of all the individual components in these samples were well below their threshold limit values (Wilkins, 1994). In a second, related study, β–myrcene was reported to be one of 200 volatile (micro)biological compounds present in household waste, building waste materials infected with microbial growth, kitchen waste exudate, stored food exudate, or garden waste (Wilkins and Larsen, 1995).

5.4 Indoor Air Concentrations

Over 200 VOCs, including β–myrcene, were identified in the indoor air of 26 houses in Helsinki, Finland (Kostiainen, 1995). β–Myrcene was detected at a low relative abundance in 4 (15%) of the homes investigated. The most common compounds in the indoor air were terpenes, C_1-C_4 alkylbenzenes, alkanes, aliphatic aldehydes, some cycloalkanes, and some halogenated compounds.

6.0 HUMAN EXPOSURE

6.1 Consumer Products

β–Myrcene is found in cosmetics, soaps, air freshners, detergents, and as a flavoring additive in food and beverages (Lorente et al., 1989; Delgado et al., 1993b; Cooper et al., 1995).

6.2 Occupational Exposure

The total number of employees exposed to β–myrcene in 14 occupational settings in the U.S. was 25,154 (NOES, 1983; cited by RTECS, 1996). Table 6-1 provides information on exposure to β–myrcene by occupation while Table 6-2 provides exposure information by industry.

Table 6-1. Exposure To β–Myrcene by Occupation[a]

Occupation	Plants	Total Employees	Female Employees
Managers and Administrators, N.E.C.	785	2356	
Registered Nurses	17	3999	3875
Pharmacists	164	1215	715
Physical Therapists	12	62	62
Clinical Laboratory Technologists and Technicians	83	167	167
Sales Workers, Other Commodities	329	1315	1315
Traffic, Shipping, and Receiving Clerks	122	245	
Health Aides (Nurses exempt)	97	1267	729
Nursing Aides, Orderlies, and Attendants	17	597	597
Maids and Housemen	85	1325	1001
Janitors and Cleaners	7	96	
Hairdressers and Cosmetologists	298	1785	1785
Groundskeepers and Gardeners (except farms)	162	487	
Automobile Mechanics	460	2761	
Mechanics and Repairers (not specified)	58	267	
Painters, Construction, and Maintenance	3	34	
Supervisors, Production Occupations	33	495	
Machinists	155	707	
Stationary Engineers	19	769	
Pressing Machine Operators	329	657	657
Laundering and Dry Cleaning Machine Operators	785	785	329
Packaging and Filling Machine Operators	7	827	276
Mixing and Blending Machine Operators	57	811	50
Crushing and Grinding Machine Operators	177	177	
Photographic Process Machine Operators	329	657	657
Production Inspectors, Checkers, and Examiners	329	329	329
Stock Handlers, and Baggers	7	138	
Machine Feeders and Offbearers	26	26	26
Laborers (except construction)	336	795	329
Total	5288	25,154	12,898

Table 6-2. Exposure To β–Myrcene by Industry[a]

Industry	Plants	Total Employees	Female Employees
Special Trade Contractors	174	1042	
Food and Kindred Products	24	95	
Furniture and Fixtures	12	60	
Primary Metal Industries	57	703	7
Fabricated Metal Products	548	8444	2760
Machinery (except electrical)	22	316	
Electric and Electronic Equipment	188	868	6
Instruments and Related Products	9	3035	1801
Miscellaneous Manufacturing Industries	103	1802	181
Transportation By Air	3	162	
Total	1139	16,527	4755

[a]National Occupational Survey as of December 12, 1996

7.0 REGULATORY ACTION

Regulatory Action	Effect of Regulation/Other Comments
21 CFR 172.510, Subpart F, Flavoring Agents and Related substances. 21 CFR 172.515, Subpart F, Synthetic Flavoring Substances and Adjuvants. 21 CFR 121.1164, Synthetic flavoring limitations.	β–Myrcene may be added to food as one or more flavoring substances or adjuvants generally recognized as safe in food, previously sanctioned for such use, or regulated by an appropriate section in 21 CFR 172. It must also be used in the minimum quantity required to produce its technical or physical effect and in accordance with all the principles of good manufacturing practice.

The EPA under 40 CFR 414.101 (Toxic pollutant effluent limitations and standards for direct discharge point sources that do not use end-of-pipe biological treatment) does not regulate β–myrcene directly but does regulate the amount of chromium released in waste streams resulting from the hydrogen chloride treatment of β–myrcene.

8.0 TOXICOLOGICAL DATA

Summary: In humans, dermatitis, conjunctivitis, and somnolence have all been reported following exposure to β−myrcene. In a single case report, chronic exposure to β−myrcene fumes caused severe and lingering asthma-like symptoms in hops inspector for a brewery.

In regard to disposition, metabolism, and toxicokinetics, β−myrcene when administered by gavage to rabbits was oxidized to 10-hydroxylinalool, 7-methyl-3methylene-oct-6-ene-1,2-diol, and uroterpineol. Following gastric intubation, rats metabolized β−myrcene to 10-hydroxylinalool, 7-methyl-3methylene-oct-6-ene-1,2-diol, 1-hydroxymethyl-4-isopropenyl cyclohexanol, 10-carboxylinalool, and 2-hydroxy-7-methyl-3-methylene-oct-6-enoic acid. Microsomal P-450 is involved in the metabolism of β−myrcene to 10-hydroxylinalool and β−myrcene induces the phenobarbital-inducible cytochrome P-450. The elimination half-life of β−myrcene in rats after oral administration was 285 min, with the compound being concentrated in adipose tissue and in many organs including the brain, liver, kidneys, and testes.

The acute oral toxicity of myrcene was low in mice and rats, with an approximate lethal dose (ALD) of greater than 5.06 g/kg bw (37100 μmol/kg bw) and 11.39 g/kg bw (83600 μmoles/kg bw), respectively. The ALD for treatment by intraperitoneal (i.p.) injection in mice and rats was 2.25 g/kg bw (16500 μmoles/kg bw) and 5.06 g/kg bw (37100 μmoles/kg bw), respectively. The lower ALD for this route likely resulted from drug-induced chemical peritonitis. No data were found on the toxic effects of β−myrcene when administered subchronically or chronically.

β−Myrcene, when administered orally to pregnant Wistar rats, induced a significant reduction in maternal weight gain beginning at 1.2 g/kg bw/day (8800 μmol/kg bw/day) and induced maternal mortality at 1.5 g/kg bw/day (11000 μmol/kg bw/day). β−Myrcene also adversely affected rat embryo-fetal development; the no-observable-adverse-effect level (NOAEL) for embryo-fetotoxicity was 0.5 g β−myrcene/kg bw/day (3600 μmol/kg bw/day), while the NOAEL for peri- and post-natal developmental toxicity was 0.25 g/kg bw/day (1800 μmol/kg bw/day).

No carcinogenicity data on β−myrcene were located.

β−Myrcene was generally negative for genotoxic activity in a limited number of lower eukaryotic and mammalian *in vitro* and *in vivo* genetic toxicology test systems. In the absence or presence of metabolic activation, it was negative for the induction of sister chromatid exchanges (SCE) in Chinese hamster V79 cells and human lymphocytes, mutations at the *hprt* locus in Chinese hamster V79 cells, and chromosome aberrations in human lymphocytes. However, β−myrcene was reported to induce a slight increase in SCE in cultured hepatic tumor cells. *In vivo*, β−myrcene did not induce chromosome aberrations in bone marrow cells of male and female Wistar rats.

In regard to other toxicological effects, β−myrcene demonstrates antinociceptive activity (i.e., induces insensitivity to pain) in rodents. The analgesic activity of myrcene acts at both central and peripheral sites and may involve the mediation of endogenous opioids. In rodents, β−myrcene does not appear to effect exploratory and emotional behavior,

anxiolytic activity in a plus maze, or inhibition of conditioned avoidance. β−Myrcene also does not protect against pentylenetetrazol-induced seizures in mice.

β−Myrcene was found to exhibit antigenotoxic activity in several *in vitro* prokaryote and eukaryote genotoxicity assays, inhibiting the ability of several promutagens (e.g., aflatoxin, cyclophosphamide) to induce mutations and/or DNA damage in prokaryote and *in vitro* mammalian cells. This antigenotoxic activity appears to be due to the ability of β−myrcene to inhibit certain forms of the cytochrome P-450 enzymes.

8.1 Human Data

The chemistry of hops has been studied extensively (Stevens, 1967; cited by Newmark, 1978), and among its constituents are myrcene (Lewis and Elvin-Lewis, 1977; cited by Newmark, 1978). In humans, dermatitis, conjunctivitis, and somnolence have all been reported following exposure to hops (O□Donovan, 1924; Coca et al., 1931; Hunter, 1966; all cited by Newmark, 1978). In a single case study (Newmark, 1978), a male chemist employed by a brewery to inspect hops in the field and laboratory, a task which involved crushing and rubbing the hops cones in his hands and comparing the aroma with that for pure β−myrcene, was reported to have experienced symptoms over a 3-year period progressing from slight sneezing and itching to wheezing, abdominal bloating, shortness of breath, watering eyes, and irregular heartbeat. The symptoms appeared to have been caused by the inhalation of β−myrcene fumes and it was concluded by Newmark (1978) that terpene sensitivity and hops allergy may well be added to the list of causes of occupational asthma reported by Karr et al. (1978; cited by Newmark, 1978).

8.2 General Toxicology

8.2.1 Chemical Disposition, Metabolism, and Toxicokinetics

Structures of the β−myrcene metabolites discussed below are shown in the metabolic pathways depicted in **Figure 8-1**. The studies discussed in this subsection are summarized in **Table 8-1**.

Valette and Cavier (1954; cited by Opdyke, 1976) reported that β−myrcene was well absorbed through the skin of rats.

Ishida et al. (1979, 1981) studied the metabolism of β−myrcene (670 mg/kg bw; 4900 μmol/kg bw) in rabbits and found that the monoterpene was oxidized to 10-hydroxylinalool, 7-methyl-3methylene-oct-6-ene-1,2-diol, and uroterpineol. The dose was administered via gavage

and urine was collected daily for 3 days after administration of the dose.

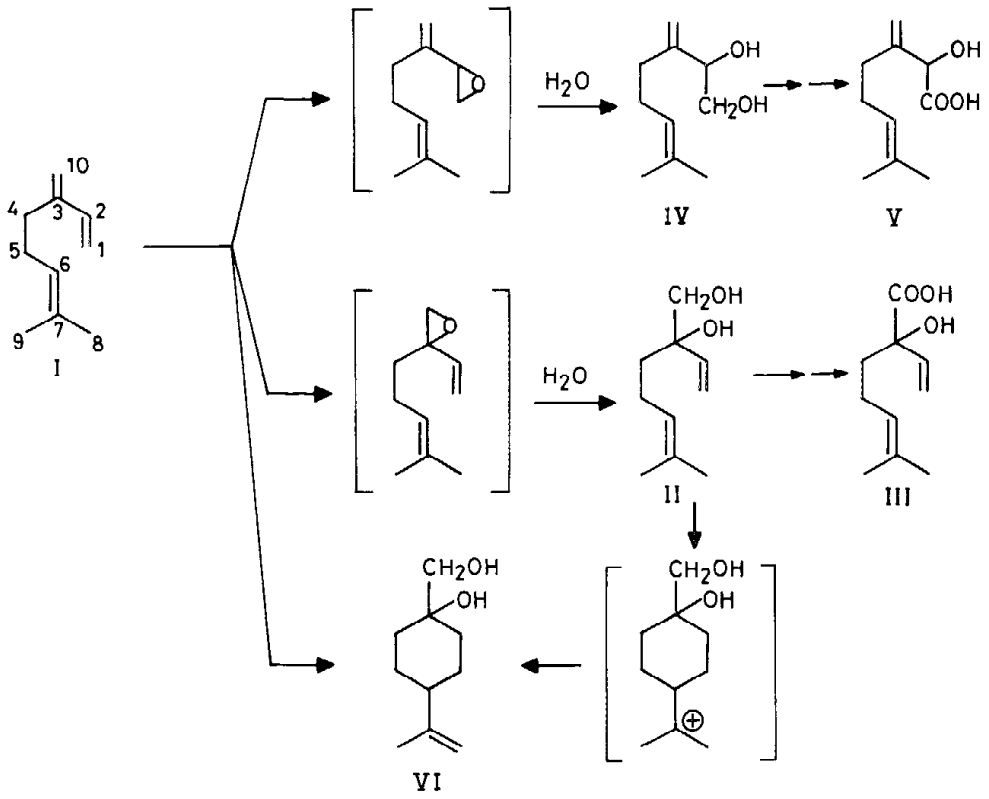
Following gastric intubation of β–myrcene (5900 μmol/kg bw/day) in 1% methanol cellulose solution for 20 days to male IISc. rats, several metabolites were identified in the urine. 10-hydroxylinalool, 7-methyl-3methylene-oct-6-ene-1,2-diol, 1-hydroxymethyl-4-isopropenyl cyclohexanol, 10-carboxylinalool, and 2-hydroxy-7-methyl-3-methylene-oct-6-enoic acid (Madyastha and Srivatsan, 1987). Based on their findings, Madyastha and Srivatsan (1987) postulated that the biotransformation of β–myrcene in rats involved epoxidation of the 1,2- and 3,10-double bonds, followed by hydration to yield 7-methyl-3methylene-oct-6-ene-1,2-diol and then 10-hydroxylinalool (the major metabolite; possibly mediated by a form of phenobarbital-induced cytochrome P450), followed by progressive oxidation of the primary alcoholic group in these diols, producing their respective aldehydes and subsequent formation of hydroxy acids. Formation of the minor metabolite 1-hydroxymethyl-4-isopropenyl cyclohexanol could have resulted from acid-catalyzed cyclization of 10-hydroxylinalool (Madyastha and Srivatsan, 1987). Similar metabolites were identified in rabbits by Ishida et al. (1979)

In vitro studies conducted by Madyastha and Srivatsan (1987) indicated that microsomal P-450 (extracted from 3-methylcholanthrene [3-MC] or phenobarbital [PB]-induced rats) was involved in the metabolism of β–myrcene to 10-hydroxylinalool. The greatest affinity of β–myrcene was for PB-induced microsomes, with approximately 12% of the cytochrome P-450 being converted to its nonphysiological form (Madyastha and Srivatsan, 1987). The inactivation of P-450 occurred without an accompanying decrease in microsomal heme (Madyastha et al., 1985).

Freitas et al. (1993) studied the effects of β–myrcene on pentobarbital (PT) sleeping in rats, and concluded that β–myrcene induced the PB-inducible cytochrome P-450 (P-450 IIB subfamily). This provides additional support that monoterpenes are natural inducers of cytochrome P-450-dependent liver enzymes.

In a pharmacokinetic study (J. Webb et al., unpublished data; cited by Delgado et al., 1993a), blood levels as high as 14.1 ± 3.0 μg/mL β–myrcene (peak value) were detected sixty minutes after oral administration of 1.0 g/kg bw (7300 μmol/kg bw) β–myrcene to female rats.

The elimination half-life of β–myrcene at this concentration was 285 min, with the compound being concentrated in adipose tissue and in many organs, including the brain, liver, kidneys, and testes.



I β-myrcene
II 10-hydroxylinalool
III 10-carboxylinalool
IV 7-methyl-3-methylene-oct-6-ene-1,2-diol
V 2-hydroxy-7-methyl-3-methylene-oct-6-enoic acid
VI 1-hydroxymethyl-4-isopropenyl cyclohexanol

Figure 8-1. Metabolic Fate of β–Myrcene in Rat. Figure taken from Madyastha and Srivatsan (1987).

Table 8-1. Summary of β–Myrcene Metabolic Studies.

Name; Number[a]	In Vivo	In Vitro	Reaction/Enzymes	Comments
Parent Compound				
β–Myrcene (I)	Rats (Madyastha and Srivatsan, 1987)		Metabolism of β–myrcene begins with direct oxidation of the terminal double bonds (Madyastha and Srivatsan, 1987).	
Metabolite				
10-Hydroxylinalool (II)	Rats (Madyastha and Srivatsan, 1987) Rabbits (Ishida et al., 1979 & 1981)	PB-induced rat liver microsomes (Madyastha and Srivatsan, 1987)	Epoxidation of the 3,10-double bonds and subsequent hydration yields II; catalyzed by microsomal P-450 (Madyastha and Srivatsan, 1987).	Major metabolite identified *in vitro* and *in vivo* studies (Madyastha and Srivatsan, 1987).
10-Carboxylinalool (III)	Rats (Madyastha and Srivatsan, 1987)		Progressive oxidation of II to an aldehyde and then to a hydroxy acid yields III (Madyastha and Srivatsan, 1987).	To facilitate the elimination of β–myrcene, the compound is functionalized by epoxidation of the 1,2- and 3,10-double bonds in the rat (Madyastha and Srivatsan, 1987).
7-Methyl-3-methylene oct-6-ene-1,2-diol (IV)	Rats (Madyastha and Srivatsan, 1987) Rabbits (Ishida et al., 1979 & 1981)	PB-induced rat liver microsomes (Madyastha and Srivatsan, 1987)	Epoxidation of the 1,2-double bonds and subsequent hydration yields IV (Madyastha and Srivatsan, 1987).	
2-Hydroxy-7-methyl-3-methylene oct-6-enoic acid (V)	Rats (Madyastha and Srivatsan, 1987)		Progressive oxidation of IV to an aldehyde and then to a hydroxy acid yields V (Madyastha and Srivatsan, 1987).	
1-Hydroxymethyl-4-isopropenylcyclohexamol (VI)	Rats (Madyastha and Srivatsan, 1987)		Acid-catalyzed II to form VI (see figure 8-1).	

[a]Number corresponds to Roman numeral assigned to parent compound or metabolite identified in **Figure 8-1.**

8.2.2 Acute Exposures

In mice and rats, the acute oral toxicity of myrcene was low, with an ALD of greater than 11.39 g/kg bw (836000 μmoles/kg bw) for rats and 5.06 g/kg bw (37100 μmols/kg bw) for mice (Paumgartten et al., 1990). Histopathology findings in mice suggested that the liver and stomach were the target organs while no organ-specific effects were detected in rats. Myrcene was found to be highly irritant to the peritoneum, and deaths after intraperitoneal (i.p.) injection of the terpene in mice (ALD = 2.25 g/kg bw; 16500 μmoles/kg bw) and rats (ALD = 5.06 g/kg bw; 37100 μmols/kg bw) likely resulted from drug-induced chemical peritonitis.

8.2.3 Short-Term and Subchronic Exposures

No data were found.

8.2.4 Chronic Exposures

No data were found.

8.2.5 Reproductive Toxicology

8.2.5.1 Maternal Toxicity

A summary of the results and experimental procedures discussed below are presented in **Table 8-2**.

β–Myrcene (0.25, 0.5, or 1.2 g/kg bw/day; 1800, 3700, or 8800 μmol/kg bw/day) was administered by gavage to Wistar rats from days 6 through 15 of pregnancy to determine possible adverse effects on embryo-fetal development (FDA segment II study) (Delgado et al., 1993a). Two control groups were included: one of which received the vehicle only and another that received no treatment. The data for these two control groups were pooled for all statistical analyses due to the lack of a statistically significant difference in the parameters measured. No difference in maternal weight gain was observed in the low- and mid-dose groups during the treatment period or for total pregnancy (day 0 to 20) when compared to controls. In the high

dose group, however, a significant reduction in maternal weight gain was observed during the first 5 days of treatment (day 6 to 11). Delgado et al. (1993a) concluded that the reduction in maternal weight gain was a sign of maternal toxicity, since the weight of the embryos is negligible during this period. The death of 1 of 29 high dose dams was considered additional evidence that β–myrcene was maternally toxic. Gross pathological alterations were not found in the maternal organs of any group at the time of caesarean section (Delgado et al., 1993a).

In a related study conducted by Delgado et al. (1993b) that evaluated the peri- and postnatal developmental toxicity of β–myrcene (FDA segment III study), Wistar rats were gavaged with β–myrcene (0.25, 0.5, 1.0, and 1.5 g/kg bw/day; 1800, 3700, 7300, and 11000 μmol/kg bw/day, respectively) in corn oil from day 15 of pregnancy up to weaning (postnatal day 21) of their offspring. The highest dose tested (1.5 g/kg bw/day; 11000 μmol/kg bw/day) was maternally toxic as demonstrated by the death of 5 of the 15 treated dams within the first 4 days of treatment, and a reduction in body weight at term (pregnancy day 20) that persisted until after delivery (postnatal day 1). No maternal deaths occurred in the second highest dose group (1.0 g/kg bw/day; 7300 μmol/kg bw/day), either before or after delivery, and the weight deficit observed at term was not detectable on the day following parturition. It was concluded that fetotoxicity could have accounted for the deficit in pregnancy weight gain observed in this dose group. No signs of maternal toxicity or a deficit in pregnancy weight gain were observed in the two lowest dose groups (0.25 and 0.5 g/kg bw/day; 1800 and 3700 μmol/kg bw/day, respectively). Apart from the finding of hyperkeratosis in the forestomach of most of the dams treated with the two highest doses, a necropsy of dams that died during the treatment period or those that were killed at weaning did not reveal any significant finding (Delgado et al., 1993b).

8.2.5.2 Embryo-Fetal Toxicity and Developmental Effects

A summary of the results and experimental procedures discussed below are presented in **Table 8-3**.

In the study discussed above, Delgado et al. (1993a) found that oral administration of β–myrcene to Wistar rats at doses up to 0.5 g/kg bw/day (3700 μmol/kg bw/day) did not induce

embryo-fetotoxicity, and oral administration of doses up to 1.2 g/kg bw/day (8800 μmol/kg bw/day) β–myrcene did not induce major gross structural abnormalities in rat fetuses. When fetal weight was analyzed using litter mean fetal weight as a statistical unit, no significant effect of treatment was observed in any of the treatment groups. A marginally significant reduction in fetal weight (< 6%) was found in the high dose group when individual fetuses were taken as the unit of analysis. Delgado et al. (1993a) concluded that the borderline weight reduction was questionable.

The only externally visible abnormalities observed by Delgado et al. (1993a) upon examination of control and β–myrcene-exposed fetuses following Caesarean section on day 20 of pregnancy were edema, kinky tail, and irregular position of the hind paws. Only the rate of irregular positioning of the hind paws was increased in the high dose group (1.9%) when compared to controls (0.6%). The statistical significance of the finding was not given. Visceral examination of 256 fetuses showed 4 with signs of abnormal development of internal organs: Enlarged ureters associated with an enlarged renal pelvis were found in 1 control fetus and 1 high dose fetus, and a shorter ureter was found in 1 control fetus and 1 low dose fetus. Three low dose fetuses showed an accessory (seventh) lobe in the liver. When the sum of structural variations of each treatment group (low dose, 4 [5.1%]; mid dose, 0; high dose, 2 [3.8%]) was compared to the sum found for the control group (1 [1.7%]), increased rates of structural variations were found for the low dose and high dose treatment groups. High dose fetal skeletons showed an increased incidence (21.5%) in the signs of delayed ossification (not ossified, poorly ossified, and irregular spongy bones) when compared to controls (1.7%): caudal vertebrae (controls, 7% vs. high dose, 37.8%); metacarpus (2.6% vs. 9.1%); metatarsus (5.3% vs. 29.2%); skull bones (4.4% vs. 9.6%) (Delgado et al., 1993a). No significant difference in frequency of gross structural skeletal anomalies was observed in the low and mid dose groups when compared to controls (Delgado et al., 1993a)

Delgado et al. (1993a) concluded that β–myrcene adversely affects embryo-fetal development in the rat and that the no-observable-adverse-effect level (NOAEL) for embryo-fetotoxicity was 0.5 g β–myrcene/kg bw (3700 μmol/kg bw).

In a related study (Delgado et al., 1993b), β–myrcene (0.25, 0.5, 1.0, or 1.5 g/kg bw/day; 1800, 3600, 7300, or 11000 μmol/kg bw/day, respectively) was administered in corn oil to Wistar rats via gavage from day 15 of pregnancy up to weaning (postnatal day 21) of the offspring. No adverse developmental effects (ear unfolding, incisor eruption, fur development, and eye opening) were seen in the offspring of the low dose group. However, the day of first detection of primary coat was significantly delayed in the 3 highest dose groups when compared to the control group on postnatal day 6. In the control group, 90.0% of the mice had their primary coat; while only 62.4%, 39.2%, and 61.2% of mice at 0.5 g/kg bw/day (3700 μmol/kg bw/day), 1.0 g/kg bw/day (7300 μmol/kg bw/day), and 1.5 g/kg bw/day (11000 μmol/kg bw/day) had their primary coat. The day of ear unfolding was significantly delayed in the two highest dose groups on postnatal day 4 when compared to the control group: 98% in the control versus 76.5% and 88.5% at 1.0 g/kg bw/day (7300 μmol/kg bw/day) and 1.5 g/kg bw/day (11000 μmol/kg bw/day), respectively. Delayed eye opening, another physical sign of delayed postnatal development, was significantly increased also in these same two high dose groups when compared to the control group on postnatal day 15: 39.4% in the control versus 19.8% and 20.0% at 1.0 g/kg bw/day (7300 μmol/kg bw/day) and 1.5 g/kg/day (11000 μmol/kg bw/day), respectively (Delgado et al., 1993b).

The offspring mortality in low dose group did not differ from that (1.8%) in the control group receiving 2.5 mg/kg bw/day corn oil only. However, mortality was significantly increased in the groups treated with higher doses, with 14.4% mortality at 0.5 g/kg bw/day (3700 μmol/kg bw/day), 24.4% mortality at 1.0 g/kg bw/day (7300 μmol/kg bw/day), and 16.8% mortality at 1.5 g/kg bw/day (11000 μmol/kg bw/day).

When the exposed offspring were approximately 120 days old, fertility tests were conducted. Delgado et al. (1993b) concluded that treatment with high doses of β–myrcene during the third week of gestation and the entire lactation period adversely affected fertility. For instance, the percentage of female offspring that mated for the first time/number giving birth was significantly less than the control group (92.6%) for rats treated with 0.5 (79.1%), 1.0 (66.7%), and 1.5 (73.1%) g/kg bw/day (3700, 7300, 11000 μmol/kg bw/day, respectively). In addition,

when the number of female rats that mated for the first and second time were added and then divided by the number giving birth, Delgado et al. (1993b) found that the percentage in the 1.0 and 1.5 g/kg bw/day (7300, 11000 μmol/kg bw/day, respectively) dose groups were significantly lower (79.2% and 76.9%, respectively) than that in the control group (98.2%). In males, no effect of β–myrcene treatment was found either on the weight of testes, prostate, and caudal epididymis, or on the sperm count in the testes and caudal epididymis.

Delgado et al. (1993b) concluded that the NOAEL for β–myrcene-induced peri- and postnatal developmental toxicity was 0.25 g/kg bw/day (1800 μmol/kg bw/day). This dose level is half the NOAEL determined for myrcene-induced fetotoxicity in the same strain (Delgado et al., 1993a), suggesting that rats are more susceptible to myrcene-induced adverse effects during late pregnancy and the neonatal period than earlier during prenatal development (Delgado et al., 1993b). The NOAEL derived from the study conducted by Delgado et al. (1993b) is approximately 15 times higher than the ED_{50} for analgesia (16 mg/kg bw; 117 μmol/kg bw; Lorenzetti et al., 1991) for the same strain of rat.

8.2.6 Carcinogenicity

No data were found.

8.2.6.1 Inhibition of Carcinogenesis

β–Myrcene had no significant chemopreventive activity when administered to 6-wk-old female Sprague-Dawley rats (Russin et al., 1989). Rats were fed a control diet or a diet containing 1% β–myrcene for two weeks. Mammary tumors were induced in the 55-day-old rats with a single intubation of 65 mg/kg 7,12-dimethylbenz[*a*]anthracene (DMBA) in sesame oil. The dietary regimens were continued throughout the remaining 18 week of the 20-week study. The effectiveness of β–myrcene was evaluated on the basis of the time to the appearance of the first tumor (tumor latency). Total tumors were compared, adjusted for total number of days at risk. By the end of the 20-week study, a total of 72 mammary tumors had formed in the experimental group (average of 2.3 tumors/rat) fed 1% β–myrcene in their diet and 81 mammary

tumors were found in the control group (average of 2.6 tumors/rat). The median tumor latency was 77 days for β–myrcene-treated rats and 70 days for the control group. Thus, myrcene did not significantly extend mammary tumor latency and did not significantly reduce the total number of mammary tumors in rats when compared to controls (Russin et al., 1989).

Table 8-2. Summary of Acute Toxicity Studies

Age, Strain, Species	No./Sex Exposed	Controls	Chemical Form and Purity	Dose	Duration of Exposure	Results/Comments	Reference
Wistar rats	24F low dose (LD) 24F mid dose (MD) 36F high dose (HD)	22F	β–myrcene, 90% pure	0.25, 0.5, or 1.2 g/kg/bw/day (1800, 3700, or 8800 μmol/kg bw/day) in corn oil by gavage	Days 6 through 15 of pregnancy	**Maternal toxicity:** Positive for a reduction of maternal weight gain. Maternal weight gain was significantly decreased in the HD group when compared to controls: 17.3 ± 7.2 g vs. 3.2 ± 13.2 g, respectively, during the first 5 days of treatment (day 6 to 11). The reduction in maternal weight gain was considered indicative of maternal toxicity Positive for maternal death: The death of 1/29 dams in the HD group was considered indicative of maternal toxicity. Positive for the reduction of pregnant uterus weight: HD (48.2 ±□14.4 g/kg bw) vs. controls (57.0 ± 12.2 g/kg bw).	Delgado et al. (1993a)
Wistar rats	12F LD 18F MD-1 14F MD-2 15F HD	20F (vehicle only)	β–myrcene, 90% pure	0.25, 0.5, 1.0, or 1.5 g/kg bw/day (1800, 3700, 7300, or 11000 μmol/kg bw/day) in corn oil by gavage	Day 15 of pregnancy through postnatal day 21 (weaning)	**Maternal toxicity:** Positive for the reduction of maternal weight gain. Maternal weight gain was significantly decreased in the HD group at term (pregnancy day 20) and persisted until after delivery (postnatal day 1): pregnancy day 20, HD, 288.4 ± 29.4 g vs. controls, 314.4 ± 19.2 g bw; postnatal day 1, HD, 223.8 ± 17.9 g bw vs. controls, 240.1 ± 15.7 g bw. Positive for maternal death: 5/15 HD dams died within the first 4 days of treatment. The statistical significance of the finding was not given. Apart from the finding of hyperkeratosis in the forestomach of most of the dams treated with the two highest doses, a necropsy of dams that died during treatment period or those that were killed at weaning did not reveal any prominent finding.	Delgado et al. (1993b)

Table 8-3. Summary of Fetal Toxicity and Developmental Effects

Age, Strain, Species	No./Sex Exposed	Controls	Chemical Form and Purity	Dose	Duration of Exposure	Results/Comments	Reference
Wistar rats	24F low dose 24F mid dose 36F high dose	22F	β–myrcene, 90% pure	0.25, 0.5, or 1.2 g/kg/bw (1800, 3700, or 8800 μmol/kg bw) in corn oil by gavage	Days 6 through 15 of pregnancy	**Fetal weight reduction:** When individual fetuses were taken as the unit of analysis, □□□questionable□□significant fetal weight reduction (<6%) was found in the HD group when compared to controls (3.4 ±□0.4 g vs. 3.6 ±□0.5 g for controls). **Externally visible abnormalities:** Positive for irregular positioning of hind paws. The rate of irregular positioning of hind paws was increased in the HD group when compared to controls: HD, 1.9% vs. controls, 0.6%. **Other Abnormalities:** Positive for reduction in implantation sites and live fetuses. Significant decreases in implantation sites (10.2 ± 2.9 in HD vs. 12.6 ± 2.2 in controls) and live fetuses (9.3 ±□2.8 in HD vs. 10.9 ± 2.0 in controls). **Visceral Malformations:** Positive for abnormal development of internal organs. Increased rates of structural variations were found for the LD and HD treatment groups when the sum of structural variations of each group was compared to the sum found for the control group: 5.1% LD (4: shorter ureter in 1 fetus; 3 fetuses with an accessory lobe in liver), 3.8% HD (2: enlarged renal pelvis in 1 fetus; shorter ureter in 1 fetus) vs. 1.7% control (1: enlarged renal pelvis in 1 fetus). Structural variations were not detected in MD group. **Ossification:** Positive for signs of delayed ossification (not ossified, poorly ossified, and irregular spongy bones. HD skeletons showed an increased incidence in the signs of delayed ossification when compared to controls: caudal vertebrae (37.8% vs. controls at 7%); Metacarpus (9.1% vs. controls at 2.6%); metatarsus (29.2% vs. controls at 5.3%); skull bones (9.6% vs. controls at 4.4%). An increased incidence in skeletal gross structural abnormalities was observed in the HD group: 21.5% vs. control at 1.7%. It was concluded that β–myrcene adversely affects embryo-fetal development in the rat at doses higher than 500 mg/kg bw (3700 μmol/kg bw), doses which led to maternal toxic effects (see **Table 8-1**).	Delgado et al. (1993a)

Table 8-3. Summary of Fetal Toxicity and Developmental Effects continued

Age, Strain, Species	No./Sex Exposed	Controls	Chemical Form and Purity	Dose	Duration of Exposure	Results/Comments	Reference
Wistar rats	12F LD 18F MD-1 14F MD-2 15F HD	20 F (vehicle only)	β–myrcene, 90% pure	0.25, 0.5, 1.0, and 1.5 g/kg bw/day (1800, 3700, 7300, and 11000 μmol/kg bw/day) in 2.5 mL/kg bw corn oil by gavage	Day 15 of pregnancy up to weaning of the offspring	**Perinatal:** Litter size (live pups plus stillbirths) was unaffected by treatment in any dose group. Positive for decrease in newborn weight. A significant decrease in birth weight was observed for the MD and HD groups when compared to controls: MD-1 = 5.5 ± 0.74 g, MD-2 = 5.2 ± 0.94 g, and HD = 4.9 ± 0.90 g vs. controls at 6.1 ± 0.35 g. **Postnatal day 1 to 21:** Any newborn death recorded during postnatal day 1 was considered a stillbirth. On postnatal days 6, 11, 16, and 21, weight gain of the litter was recorded. Pups were examined for signs of physical development (ear unfolding, incisor eruption, development of fur, and eye opening) and the days on which developmental milestones appeared. **Offspring mortality:** Positive for an increase in offspring mortality. Offspring mortality from postnatal day 2 to 90 was significantly increased in the MD and HD groups when compared to controls: MD-1 = 14.4%, MD-2 = 24.4%, and HD = 16.8% vs. controls at 1.8%. Positive for the delay of first detection of primary coat. The day of first detection of primary coat was delayed significantly in the 3 highest dose groups when compared to the control group on postnatal day 6: MD-1 = 62.4%, MD-2 = 39.2%, HD = 61.2% vs. control at 90%. Positive for the delay of ear unfolding. The day of ear unfolding was significantly delayed in the 1.0 and 1.5 -g/kg bw groups (7300 and 11000 μmol/kg bw/day) when compared to controls on postnatal day 4: 1.0 = 76.5%, 1.5 = 88.5% vs. control at 98%. Positive for delayed eye opening. Delayed eye opening was significantly increased in the 1.0 and 1.5 g/kg bw groups (7300 and 11000 μmol/kg bw/day) when compared to the control group on postnatal day 15: 1.0 = 19.8%, 1.5 = 20.0% vs. control at 39.4%.	Delgado et al. (1993b)

Age, Strain, Species	No./Sex Exposed	Controls	Chemical Form and Purity	Dose	Duration of Exposure	Results/Comments	Reference
Table 8-3. Summary of Fetal Toxicity and Developmental Effects continued							
f_1 Wistar rats	1st mating: 31F LD 43F MD-1 24F MD-2 26 HD 2nd mating: LD NG 9F MD-1 8F MD-2 7F HD 1st + 2nd mating: 31F LD 43F MD-1 24F MD-2 26F HD	1st mating: 54F 2nd mating: 4F 1st + 2nd mating: 54F	β–myrcene, 90% pure	in utero exposure (see above)	in utero exposure (see above)	**Postnatal day 120:** Weaning and fertility tests were conducted on the offspring: Three females and 1 male from the same treatment group, but different litters, were housed together for a mating period of 15 days. On postnatal day 4, the numbers of male and female live pups per litter were counted, and the mothers examined for the number of implantation sites. A second mating period was conducted for females that did not give birth within 24 days after the end of the first mating period. Except for the use of untreated males of proven fertility, the second mating period was similar to the first. In addition, males that were unable to impregnate at least two females during the first mating period were also submitted to a second mating period of 15 days with untreated females. In males, no effect of treatment was found on the weight of testes, prostate, and cauda epididymis, or on the sperm count in the testes and the cauda epididymis. Positive (for a decrease in offspring that mated for the first time/number giving birth). Female exposed offspring that mated for the first time/the number giving birth was significantly decreased in the 3 highest dose groups when compared to controls: MD-1 = 79.1%, MD-2 = 66.7%, and HD = 73.1% vs. controls at 92.6%. When the number of female rats that mated for the first and second time were added and then divided by the number giving birth, a significant decrease was found in the 2 highest dose groups when compared to controls: MD-2 = 79.2%, HD = 76.9% vs. controls at 98.2%. It was concluded that the no-observed-adverse-effect level (NOAEL) for β–myrcene-induced peri- and postnatal developmental toxicity was 0.25 g/kg bw (1800 µmol/kg bw). This dose level is half the NOAEL determined for β–myrcene-induced fetotoxicity in the same rat strain (Delgado et al., 1993a; see above), suggesting that rats are more susceptible to myrcene-induced adverse effects during late pregnancy and the neonatal period than earlier in prenatal development.	Delgado et al. (1993b)

NG: Not given

8.3 Genetic Toxicology

Genotoxicity studies with β–myrcene are summarized in **Table 8-4.**

8.3.1 Mammalian Systems *In Vitro*

8.3.1.1 DNA Damage

Roscheisen et al. (1991) reported that β–myrcene at 100 to 500 μg/mL (730 to 3700 μM) for 2 hours did not induce SCE in Chinese hamster V79 cells in either the presence or absence of metabolic activation. Roscheisen et al. (1991) also stated that cultured hepatic tumor cells (metabolically competent cells, species not provided) exposed to β–myrcene at 100 to 500 μg/mL (730 to 3700 μM) for 20 hours in the absence of metabolic activation exhibited an increase in SCE frequency. The lowest effective dose (LED) was 100 μg/mL (730 μM).

Kauderer et al. (1991) reported that SCE were not induced in human peripheral blood lymphocytes treated *in vitro* with β–myrcene. Doses of 100 to 1000 μg/mL (730 to 7300 μM) were tested for 24 hours in the presence and 2 hours in the absence of S9.

8.3.1.2 Gene Mutations

Kauderer et al. (1991) concluded that β–myrcene was negative for the induction of point mutations *in vitro* at the *hprt* locus in Chinese hamster V79 cells. The doses tested ranged from 100 to 1000 μg/mL (730 to 7300 μM) for 3 hours in both the presence and absence of metabolic activation.

8.3.1.3 Chromosomal Damage

Kauderer et al. (1991) reported that β–myrcene did not induce chromosomal aberrations in cultured human peripheral blood lymphocytes. The doses tested were 100 to 1000 μg/mL (730 to 7300 μM) for 24 hours in the absence and 2 hours in the presence of S9 metabolic activation.

8.3.2 Mammalian Systems *In Vivo*

Zamith et al. (1993) stated that β–myrcene failed to induce chromosome aberrations in

rat bone marrow cells. Male and female Wistar rats were treated orally with 100 to 1000 mg/kg (730 to 7300 μmol/kg bw) β–myrcene and sacrificed 24 and 48 hours later. A dose-related increase in the mitotic index at 24 hours was the only effect observed.

Table 8-4. Summary of β–Myrcene Genotoxicity Studies

Test System	Biological Endpoint	S9 Metabolic Activation	Purity	Doses Used	Endpoint Response	Comments	Reference
8.3.1 Mammalian Systems *In Vitro*							
8.3.1.1 DNA Damage							
Chinese hamster V79 cells	sister chromatid exchanges (SCE)	-/+	n.p.	00 to 500 μg/mL (730 to 3700 μM) for 2 h with or without S9	negative/ negative	+/-S9 HID = 500 μg/mL (3700 μM)	Roscheisen et al. (1991)
hepatic tumor cells (species not provided)	SCE	NA	n.p.	100 to 500 μg/mL (730 to 3700 μM) for 20 h	positive	Cells reported as metabolically competent. A slight increase in SCE was induced (LED = 100 μg/mL; 730 μM).	Roscheisen et al. (1991)
human peripheral blood lymphocytes	SCE	-/+	n.p.	100 to 1000 μg/mL (730 to 7300 μM) for 24 h -S9 and 2 h +S9	negative/ negative	+/- S9 HID = 1000 μg/mL (7300 μM)	Kauderer et al. (1991)
8.3.1.2 Gene Mutations							
Chinese hamster V79 cells	*hprt* gene mutations	-/+	n.p.	100 to 1000 μg/mL (730 to 7300 μM) for 3 h with or without S9	negative/ negative	+/- S9 HID = 1000 μg/mL (7300 μM)	Kauderer et al. (1991)
8.3.1.3 Chromosomal Damage							
human peripheral blood lymphocytes	chromosome aberrations	-/+	n.p.	100 to 1000 μg/mL (730 to 7300 μM) for 24 h -S9 and 2 h +S9	negative/ negative	+/- S9 HID = 1000 μg/mL (7300 μM)	Kauderer et al. (1991)
8.3.2 Mammalian Systems *In Vivo*							
Male and female Wistar rats	bone marrow chromosome aberrations	NA	n.p.	100 to 1000 mg/kg (730 to 7300 μmol/kg bw) orally for 24 and 48 h	negative	A dose- related increase in mitotic index at 24 h was the only effect observed.	Zamith et al. (1993)

Notes: HID = highest ineffective dose; LED = lowest effective dose; n.p. = purity not provided; n.g. = doses not given; NA = not applicable

8.4 Immunotoxicity

No data were found.

8.5 Other Toxic Effects

Other toxic effects attributed to β−myrcene include the following.

8.5.1 Antinociceptive (Insensitivity to Pain) Activity

Rao et al. (1990) found an increased antinociception (insensitivity to pain) effect in male Swiss mice treated with β−myrcene by i.p. or subcutaneous injection. The antinociceptive activity was measured using a low temperature hot plate method (Eddy and Leimbach, 1953; cited by Rao et al., 1990) and by the acetic acid-induced writhing test of Koster et al. (1959; cited by Rao et al., 1990). For the hot plate test, the reaction time was determined on the hot plate surface at 15 min intervals for a total of 120 min after administration of myrcene. The results showed that i.p. administration of β−myrcene at 10 (73) or 20 mg (150 μmol)/kg bw produced a dose related elevation in the reaction time which lasted ~120 min with the peak effect occurring at between 45 and 60 min. The antinociceptive activity observed in the 20 mg (150 μmol)/kg myrcene dose group was partially attenuated by simultaneous injection of nalaxone (1 mg/kg). Simultaneous administration of β−myrcene and yohimbe (2 mg/kg bw) almost completely reversed the monoterpene□s antinociceptive effect (Rao et al., 1990).

Intraperitoneal administration of β−myrcene produced a dose-dependent reduction in the mean number of writhes/mouse in the acetic acid writhing test (controls, 59.3 ± 4.8) vs. 39 ±□3.2 and 27 ± 2.4 at 20 (73) and 40 mg (150 μmol)/kg bw, respectively. Simultaneous administration of yohimbe or nalaxone with 40 mg/kg (150 μmol/kg) myrcene completely reversed the analgesic effect of myrcene (Rao et al., 1990).

As shown by an increase in reaction time of mice to thermal stimuli in the hot plate test and the decrease in the number of writhes to chemical stimuli in the acetic acid test, the analgesic response of β–myrcene works by acting at both central and peripheral sites (Rao et al., 1990). The analgesic effect of β–myrcene was reversed by simultaneous treatment with nalaxone, suggesting the mediation of endogenous opioids in its mechanism (see Pettibone and Mueller, 1981, Hart et al., 1983, Abiati et al., 1985, Yeh, 1986, Takahashi and Paz, 1987; all cited by Rao et al., 1990). Yohimbe effectively blocked the analgesic effect of myrcene, suggesting that presynaptic α_2-adrenoceptors are involved in its action (see Fielding et al., 1978, Pettibone and Mueller, 1981, Bentley et al., 1983, Portugal-Santana and Nakamura, 1987, Nakamura and Ferreira, 1988; all cited by Rao et al., 1990). When the analgesic effect of myrcene at 10 (73) or 20 mg (150 μmol) mg/kg bw was compared to that of morphine (5 mg/kg bw), Rao et al. (1990) concluded that the antinociceptive effect of myrcene was □inferior□ to that of morphine.

8.5.2 Neurobehavioral Activity

β–Myrcene at 1 g/kg bw (7300 μmol/kg bw) had no effect on exploratory and emotional behavior, had no anxiolytic activity in a plus maze, and did not inhibit conditioned avoidance in mice or rats following oral administration 1 hr before evaluation (da-Silva et al., 1991). β–Myrcene did not protect against pentylenetetrazol-induced seizures in mice (da-Silva et al., 1991). As suggested by these data, β–myrcene has no benzodiazepine-like anxiolytic activity and that antipsychotic or antidepressive activity on the central nervous system is unlikely (da-Silva et al., 1991).

8.6 Antigenotoxicity

Studies of the antimutagenic effects of β–myrcene are summarized in **Table 8-5**.

8.6.1 Prokaryotic Systems

Kim et al. (1992) reported that β–myrcene, isolated from Korean raw, roasted mugwort leaves, showed anti-mutagenic activity in *S. typhimurium*. β–Myrcene at 1.5 and 3.0% (specific dose not given) was tested with 1.0 μg/plate aflatoxin B_1 in the presence of rat liver S9 using strain TA100 and the pre-incubation method. Both doses showed inhibitory effects with inhibition ratios for 1.5 and 3.0% of 65 and 73%, respectively.

8.6.2 Mammalian Systems *In Vitro*

8.6.2.1 DNA Damage

Roscheisen et al. (1991) reported that β–myrcene (100 to 500 μg/mL; 730-3700 μM), when co-administered with rat liver S9, inhibited the ability of CP (2.5 and 5.0 μM) and AFB (0.1 and 0.2 μM) (LED = 250 μg/mL; 1830 μM) but not of benzo[*a*]pyrene (BP)(10 and 50 μM) or dimethylbenzanthracene (5.0 and 7.5 μM) to induce SCE in cultured V79 cells.

Roscheisen et al. (1991) also stated that simultaneous treatment of cultured hepatic tumor cells (metabolically competent; species not provided) with β–myrcene (500 μg/mL; 3700 μmol/L) inhibited the ability of CP (500 and 1000 μM) to induce SCE. Based on the literature and the responses obtained, these authors concluded that the antigenotoxic activity was due to the ability of β–myrcene to inhibit the metabolic activation of some promutagens via certain forms of the cytochrome P-450 enzymes.

Kauderer et al. (1991) also found that under co-treatment conditions, 100 and 500 μg/mL (730 and 3700 μmol/L) β–myrcene inhibited the ability of CP (20 and 50 μM, +S9) but not that of ethyl methanesulfonate (1000 and 2000 μM, -S9) or BP (100 and 200 μM, +/-S9) to induce SCE in cultured human lymphocytes.

8.6.2.2 Gene Mutations

Kauderer et al. (1991) reported that β–myrcene (500 μg/mL; 3700 μM/L) inhibited the ability of CP (20 and 50 μM) to induce mutations at the *hprt* locus in V79 cells, when tested together in the presence of rat liver S9.

Table 8-5. Summary of β–Myrcene Antigenotoxicity Studies

Test System	Biological Endpoint	S9 Metabolic Activation	Purity	Doses Used	Endpoint Response	Comments	Reference
8.6.1 Prokaryotic Systems							
Salmonella typhimurium strain TA100	inhibition of mutation induction (pre-incubation method)	+	n.p.	1.5 and 3.0% plus 1 μg/plate aflatoxin B_1	positive	Both doses showed inhibitory effects with inhibition ratios for 1.5 and 3.0% myrcene of 65 and 73%, respectively. β–Myrcene was collected from Korean raw, roasted mugwort leaves.	Kim et al. (1992)
8.6.2 Mammalian Systems *In Vitro*							
8.6.2.1 DNA Damage							
Chinese hamster V79 cells	inhibition of induction of SCE	+	n.p.	100 to 500 μg/mL (730-3700 μM) for 2 h plus either 2.5 & 5.0 μM cyclophosphamide (CP), 0.1 & 0.2 μM aflatoxin B1 (AFB), 10 & 50 μM benzo[*a*]pyrene (BP), or 5.0 & 7.5 μM dimethyl benzanthracene (DMBA)	positive	Inhibited SCE induction (LED = 250 μg/mL; 1800 μM) by both doses of CP and AFB but not BP or DMBA.	Roscheisen et al. (1991)
hepatic tumor cells (species not provided)	inhibition of induction of SCE	NA	n.p.	500 μg/mL (3700 μM) for 20 h plus either 500 or 1000 μM CP	positive	Cells reported to be metabolically competent. At both doses, inhibited SCE induced by CP.	Roscheisen et al. (1991)
human peripheral blood lymphocytes	inhibition of induction of SCE	-/+	n.p.	100 & 500 μg/mL (730-3700 μM) for 24 h -S9 and 2 h +S9 plus 20 & 50 μM CP, 100 & 200 BP, or 1000 & 2000 μM ethyl methanesulfonate (EMS)	negative/ positive	Reduced SCE induced by CP (+S9) (LED = 100 μg/mL; 730 μM) but did not effect the genotoxicity of EMS (-S9) or BP (+/-S9).	Kauderer et al. (1991)
8.6.2.2 Gene Mutations							
Chinese hamster V79 cells	inhibition of induction of *hprt* gene mutations	+	n.p.	500 μg/mL (3700 μM) for 3 h ±S9 with 20 or 50 μM CP	positive	At both doses, reduced the cytotoxic and mutagenic activity of CP.	Kauderer et al. (1991)

Notes: LED = lowest effective dose; n.p. = purity not provided; n.g. = doses not given; NA = not applicable

9.0 STRUCTURE-ACTIVITY RELATIONSHIPS

Summary: CASE found no structural basis for classifying myrcene as a carcinogen. The structure-activity relationships observed among several monoterpene isoprenylation inhibitors were in agreement with a role for small G proteins in cell proliferation. The structurally related monoterpene *d*-Limonene induced tumors in the kidneys of male rats in association with hyaline droplet nephropathy, but was negative in the presence or absence of metabolic activation for mutagenicity in *S. typhimurium* and the mouse lymphoma assay, for the induction of SCE and chromosomal aberrations in CHO cells; and for *in vivo* mutagenicity at toxic doses in the mammalian spot test.

9.1 Structure Alerts

Rozenkranz and Klopman (1990) applied CASE, an artificial intelligence structure-activity evaluation method, to the prediction of the carcinogenicity of a group of plant-derived carcinogens, including myrcene. CASE fragments the molecules of a learning set into all of the possible overlapping fragments consisting of 2 to 10 atoms (not including hydrogens), and then selects those fragments that have a significant probability of being associated (biophores) or a lack of association (biophobe) with carcinogenicity. CASE did not identify any biophores or biophobes for myrcene, which thus assumed the substance to be inactive since there was no structural basis for classifying it as a carcinogen (Rosenkranz and Klopman, 1990).

9.2 Ability of Limonene-Like Monoterpenes to Inhibit Post-Translational Isoprenylation

Crowell et al. (1994) studied the relative abilities of 26 limonene-like monoterpenes, including β–myrcene, to inhibit post-translational isoprenylation of small G proteins and cell proliferation. Inhibition of post-translational isoprenylation of p21*ras* and other small G proteins is thought to aid in the chemoprevention and therapy of chemically induced rodent cancers (Crowell et al., 1994). As a consequence of inhibition of post-translational isoprenylation, unfarnesylated *ras* proteins do not associate with plasma membrane and, contrary to *ras* proteins that are isoprenylated, are incapable of cellular transformation (Willumsen and Norris, 1984; Kato et al., 1992; both cited by Crowell et al., 1994). When β–myrcene (1 or 3 mM) was incubated with HT-29 colon carcinoma cells labeled with [2-^{14}C]-mevalonate (metabolizes to isoprenoid groups that attach to protein groups in the presence or absence of monoterpenes) for an unspecified time period, a 20% (1 mM) and 18% (3 mM) inhibition of 21-26 kDa protein (a family of isoprenylated proteins consisting of the *ras* superfamily of small G proteins)

isoprenylation were observed when compared to the intensity of the signal relative to that of a monoterpene negative control (Crowell et al., 1994). The relative potency of limonene-derived monoterpenes was found to be: monohydroxyl =ester = aldehyde > thiol > acid = diol = epoxide > triol = unsubstituted (Crowell et al., 1994).

Crowell et al. (1994) stated that the structure-activity relationships observed among the monoterpene isoprenylation inhibitors were in agreement with a role for small G proteins in cell proliferation, and warrant further investigation of limonene-derived monoterpenes as antitumor agents (Crowell et al., 1994).

9.3 Carcinogenicity and Genotoxicity of the Monoterpene*d*-Limonene

Due to the absence of carcinogenicity data on β–myrcene, information on the carcinogenicity and genotoxicity of a structurally-related monoterpene, *d*-Limonene, is included.

d-Limonene was found to induce tumors in the kidneys of male rats in association with hyaline droplet nephropathy (NTP, 1990; reviewed by Whysner and Williams, 1996).

In genotoxicity tests, *d*-limonene and its metabolites (1,2- or 8,9-epoxides) were concluded to be negative for mutagenicity in *S. typhimurium* TA98, TA100, TA1535, TA1537, and TA1538 in the presence or absence of activation by rat liver S9 (Watabe et al., 1980, 1981; cited by Whysner and Williams, 1996). Haworth et al. (1983; cited by Whysner and Williams, 1996) reported a similar negative mutagenicity finding for *d*-limonene alone using the same *Salmonella* strains in the presence or absence of either rat or Syrian hamster liver S9. In the presence or absence of S9, *d*-limonene did not induce mutations in mouse lymphoma L5178Y/TK +/- cells or chromosomal aberrations or SCE in CHO cells (NTP, 1990). *In vivo*, *d*-limonene was reported as negative at toxic doses in the mammalian spot test (Fahrig, 1982; cited by Whysner and Williams, 1996).

10.0 ONLINE DATABASES AND SECONDARY REFERENCES SEARCHED

10.1 Online Databases

Chemical Information System Files

SANSS (Structure and Nomenclature Search System)
TSCAPP (Toxic Substances Control Act Plant and Production)
TSCATS (Toxic Substances Control Act Test Submissions)

DIALOG Files

359 Chemical Economics Handbook
669 Federal Register 1988-1996
302 Kirk-Othmer Encyclopedia of Chemical Technology, 3rd and 4th editions

Internet Databases

Code of Federal Regulations full text. 1996 versions of various titles via GPO Gate, a gateway by the Libraries of the University of California to the GPO Access service of the Government Printing Office, Washington, DC. Internet URL http://www.gpo.ucop.edu/

Phytochemeco Database, Agricultural Research Service. Listed as Beckstrom-Sternberg and Duke (1996) in Section 11.

National Library of Medicine Databases

EMIC and EMICBACK (Environmental Mutagen Information Center)
TRI

STN International Files

BIOSIS (Biological Abstracts)
CA File (Chemical Abstracts)
CANCERLIT
CSNB (Chemical Safety News Base)
EMBASE (Excerpta Medica)
HSDB (Hazardous Substances Data Bank)
IPA (International Pharmaceutical Abstracts)
MEDLINE
Registry File
RTECS (Registry of Toxic Effects of Chemical Substances)

TOXLINE
TOXLIT

TOXLINE includes the following subfiles, often just the toxicology information from the databases named:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicology Research Projects	CRISP
NIOSHTIC□	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

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Appendix
Plants Containing Myrcene

Apium graveolens L. - Celery (Fruit Essent. Oil) 2,000-61,000 ppm
Pimenta racemosa (MILL.) J. W. MOORE - Bayrum Tree (Leaf) 3,160-23,800 ppm
Apium graveolens L. - Celery (Pericarp Essent. Oil) 18,000 ppm
Apium graveolens L. - Celery (Root Essent. Oil) 18,000 ppm
Apium graveolens L. - Celery (Leaf Essent. Oil) 14,000 ppm
Citrus limon (L.) BURMAN f. - Lemon (Leaf Essent. Oil) 13,000 ppm
Artemisia salsoloides WILLD. (Shoot) 7,000 ppm
Canarium indicum L. - Java-Olive (Essential Oil) 2,400-6,000 ppm
Myristica fragrans HOUTT. - Mace (Seed) 740-5,920 ppm
Rosmarinus officinalis L. - Rosemary (Plant) 25-5,605 ppm
Elettaria cardamomum (L.) MATON - Cardamom (Fruit) 336-3,000 ppm
Foeniculum vulgare MILLER - Fennel (Fruit) 100-2,700 ppm
Pycnanthemum tenuifolium SCHRAD. - Slenderleaf Mountain Mint (Shoot) 16-2,560 ppm
Mentha arvensis L. - Cornmint (Leaf) 10-2,485 ppm
Origanum sipyleum L. - Bayircayi (Shoot) 1,950 ppm
Monarda fistulosa L. - Wild Bergamot (Plant) 3-1,860 ppm
Juniperus communis L. - Common Juniper (Fruit) 110-1,800 ppm
Petroselinum crispum (MILLER) NYMAN ex A. W. HILL - Parsley (Seed) 168-1,680 ppm
Sideritis germanicolpitana BORNM (Plant) 1,285-1,625 ppm
Carum carvi L. - Caraway (Fruit) 180-1,560 ppm
Mentha spicata L. - Spearmint (Plant) 21-1,350 ppm
Citrus limon (L.) BURMAN f. - Lemon (Essential Oil) 65-1,270 ppm
Citrus aurantifolia (CHRISTM.) SWINGLE - Lime (Fruit) 70-1,030 ppm
Artemisia dracunculus L. - Tarragon (Shoot) 80-1,000 ppm
Sideritis athoa PAPANIKOLAOU ET KOKKINI - Kedi Kuyrugu Cayi (Shoot) 975 ppm
Anethum graveolens L. - Dill (Fruit) 84-924 ppm
Salvia triloba L. - Greek Sage (Plant) 150-900 ppm
Thymus orospedanus H. del VILLAR - Orosped Thyme (Plant) 858 ppm
Cymbopogon citratus (DC. ex NEES) STAPF - West Indian Lemongrass (Plant) 240-800 ppm
Citrus reticulata BLANCO - Mandarin (Fruit) 46-760 ppm
Pycnanthemum loomisii NUTT. - Loomis' Mountain Mint (Shoot) 495-756 ppm
Origanum syriacum L. - Za'Atar (Shoot) 750 ppm
Thymus vulgaris L. - Common Thyme (Plant) 36-676 ppm
Cunila origanoides (L.) BRITTON - Mountain Dittany (Shoot) 672 ppm
Origanum vulgare L. var hirtum (LINK) IETSWAART - Istanbul Kekigi (Plant) 645 ppm
Mentha pulegium L. - European Pennyroyal (Plant) 27-600 ppm
Satureja thymbra L. - Goat Oregano (Shoot) 590 ppm
Origanum vulgare ssp hirtum (LINK) IETSWAART - Greek Oregano (Shoot) 585 ppm
Origanum syriacum L. - Za'Atar (Shoot) 565 ppm
Citrus aurantium L. - Petitgrain (Leaf) 130-550 ppm
Mentha longifolia (L.) HUDS. - Biblical Mint (Shoot) 17-550 ppm
Umbellularia californica (HOOK. & ARN.) NUTT. - California Bay (Plant) 130-520 ppm
Monarda didyma L. - Beebalm (Plant) 10-485 ppm
Ocimum gratissimum L. - Agbo (Plant) 15-480 ppm
Hedeoma reverchonii GRAY - Reverchon's Pennyroyal (Plant) 461 ppm
Origanum sipyleum L. - Bayircayi (Shoot) 445 ppm
Satureja cuneifolia TEN. - Cuneate Turkish Savory (Shoot) 50-420 ppm
Pycnanthemum pycnanthemoides (LEAVENW.) FERNALD - Typical Mountain Mint (Shoot) 273-406 ppm
Hyssopus officinalis L. - Hyssop (Shoot) 27-400 ppm
Angelica archangelica L. - Garden Angelica (Root) 130-380 ppm
Bursera delpechiana POISS. - Lignaloe (Wood) 75-360 ppm
Pycnanthemum clinopodioides TORR. & GRAY - Clinopod Mountain Mint (Shoot) 84-352 ppm

Pycnanthemum setosum NUTT. - Setose Mountain Mint (Shoot) 40-341 ppm
Salvia officinalis L. - Sage (Plant) 0-336 ppm
Origanum onites L. - Oregano (Shoot) 330 ppm
Laurus nobilis L. - Bay (Leaf) 33-320 ppm
Satureja obovata LAG. - Iberian Savory (Leaf) 305 ppm
Apium graveolens L. - Celery (Seed) 190-300 ppm
Micromeria fruticosa - Tasnanesi (Leaf) 300 ppm
Satureja montana L. - Winter Savory (Plant) 7-295 ppm
Coridothymus capitatus (L.) REICHB. F. - Spanish Oregano (Shoot) 285 ppm
Thymus funkii COUSS. - Funk's Thyme (Shoot) 280 ppm
Agastache urticifolia (BENTH.) KUNTZE - Nettle-Leaf Giant Hyssop (Plant) 266 ppm
Pycnanthemum virginianum (L.) DURAND & JACKSON - Virginia Mountain Mint (Shoot) 6-261 ppm
Thymus funkii COUSS. - Funk's Thyme (Shoot) 260 ppm
Daucus carota L. - Carrot (Seed) 10-250 ppm
Hedeoma drummondii BENTH. - Drummond's Pennyroyal (Plant) 6-232 ppm
Thymus serpyllum L. - Creeping Thyme (Plant) 13-229 ppm
Origanum minutiflorum O. SCHWARZ & P.H. DAVIS - Small-Flowered Oregano (Shoot) 40-220 ppm
Rosmarinus officinalis L. - Rosemary (Leaf) 215 ppm
Satureja obovata LAG. - Iberian Savory (Leaf) 215 ppm
Thymus riatarum HUMBERT & MAIRE - 'Moroccan' Thyme (Shoot) 215 ppm
Cistus ladaniferus L. - Ambreine (Leaf) 3-210 ppm
Citrus sinensis (L.) OSBECK - Orange (Fruit) 69-210 ppm
Monarda citriodora CERV. EX LAGASCA - Lemon Mint (Flower) 205 ppm
Illicium verum HOOK. f. - Star-Anise (Fruit) 40-200 ppm
Melaleuca linariifolia SMITH - Paperbark Tea_tree (Leaf) 150-200 ppm
Pycnanthemum muticum (MICHX.) PERS. - Muticous Mountain Mint (Shoot) 29-200 ppm
Thymus zygis ssp sylvestris - 'Portuguese' Thyme (Shoot) 0-200 ppm
Citrus paradisi MacFAD. - Grapefruit (Fruit) 72-190 ppm
Hyssopus officinalis L. ssp aristatus (GODR.) BRIQ. - Hyssop (Shoot) 180 ppm
Thymus capitatus (L.) HOFFM. - 'Sicilian' Thyme (Plant) 150-180 ppm
Micromeria teneriffae (Leaf) 170 ppm
Origanum onites L. - Oregano (Shoot) 170 ppm
Thymus zygis L. - Spanish Thyme (Shoot) 170 ppm
Coriandrum sativum L. - Coriander (Fruit) 13-169 ppm
Hedeoma hispida PURSH. - Hispid Pennyroyal (Plant) 164 ppm
Picea mariana (MILLER) B.S.P. - Black Spruce (Twig) 161 ppm
Dracocephalum parviflora (NUTT.) BRITT. - Small-Flowered Moldavica (Plant) 160 ppm
Hyssopus officinalis L. ssp aristatus (GODR.) BRIQ. - Hyssop (Shoot) 160 ppm
Moldavica parviflora (NUTT.) BRITT. - Small-Flowered Moldavica (Plant) 160 ppm
Carum carvi L. - Caraway (Plant) 150 ppm
Hedeoma pulegioides (L.) PERS - American Pennyroyal (Plant) 30-150 ppm
Satureja cilicica P.H. DAVIS - Turkish Savory (Shoot) 150 ppm
Monarda media WILLD. - Mean Monarda (Plant) 140 ppm
Melaleuca alternifolia CHEEL - Tea-Tree (Leaf) 52-130 ppm
Pycnanthemum verticillatum (MICHX.) PERS. - Whorled Mountain Mint (Shoot) 126 ppm
Cuminum cyminum L. - Cumin (Fruit) 36-120 ppm
Eucalyptus citriodora HOOK. - Lemon Eucalyptus (Leaf) 1-120 ppm
Micromeria fruticosa (L.) DRUCE ssp barbata (BOISS. & KY.) P.H. DAVIS - Tea Hyssop (Shoot) 120 ppm
Trachyspermum ammi (L.) SPRAGUE ex TURRILL - Ajwan (Fruit) 90-120 ppm
Tsuga canadensis (L.) CARRIERE - Eastern Hemlock (Branches) 104-120 ppm
Thymus longicaulis C. PRESL - Kekik (Shoot) 115 ppm
Pycnanthemum incanum (L.) MICHX. - Hoary Mountain Mint (Shoot) 44-114 ppm
Rosmarinus x lavandulaceus DE NOE - Lavender Rosemary (Shoot) 19-110 ppm
Thymus broussonettii BOISS. - Moroccan Thyme (Shoot) 110 ppm
Pycnanthemum californicum TORR. - California Mountain Mint (Shoot) 108 ppm
Lavandula x hybrida BALB. EX GING. - Hybrid Lavender (Shoot) 70-105 ppm

Pycnanthemum pilosum NUTT. - Pilose Mountain Mint (Flower) 10-105 ppm
Pycnanthemum pilosum NUTT. - Pilose Mountain Mint (Leaf) 10-105 ppm
Satureja douglasii (BENTH.) BRIQ. - Douglas' Savory (Plant) 104 ppm
Origanum majorana L. - Marjoram (Plant) 18-103 ppm
Rosmarinus officinalis L. - Rosemary (Shoot) 50-100 ppm
Sideritis mugronensis (Flower) 15-100 ppm
Vitex agnus-castus L. - Chaste Tree (Leaf) 3-100 ppm
Cinnamomum camphora (L.) NEES & EBERM. - Camphor (Leaf) 48-96 ppm
Pycnanthemum torreyi BENTH. - Torrey's Mountain Mint (Shoot) 90 ppm
Thymus mastichina L. - Spanish Marjoram (Plant) 20-90 ppm
Lepechinia calycina EPLING - Epling's Lepechinia (Plant) 85 ppm
Ocimum basilicum L. - Basil (Leaf) 2-80 ppm
Rosmarinus tomentosus HUBER-MORATH & MAIRE - Hairy Rosemary (Shoot) 55-80 ppm
Ocimum gratissimum L. - Agbo (Shoot) 75 ppm
Lavandula latifolia MEDIK. - Aspic (Plant) 39-74 ppm
Rosmarinus eriocalyx JORDAN & FOURR. - Rosemary (Shoot) 38-70 ppm
Satureja obovata LAG. - Iberian Savory (Leaf) 70 ppm
Lavandula x intermedia EMERIC ex LOIS - Dutch Lavender (Plant) 47-65 ppm
Micromeria congesta BOISS. & HAUSSKN. - Kaya Yarpuzu (Leaf) 40-65 ppm
Pycnanthemum curvipes (GREENE) GRANT & EPLING - Curved Mountain Mint (Shoot) 63 ppm
Levisticum officinale KOCH - Lovage (Root) 6-60 ppm
Micromeria fruticosa (L.) DRUCE ssp barbata (BOISS. & KY.) P.H. DAVIS - Tea Hyssop (Shoot) 60 ppm
Rosmarinus eriocalyx JORDAN & FOURR. - Rosemary (Shoot) 33-60 ppm
Isanthus brachiatus (L.) BSP - False Pennyroyal (Plant) 58 ppm
Calamintha nepeta ssp. glandulosa (REQ.) P.W.BALL - Turkish Calamint (Leaf) 55 ppm
Rosmarinus x mendizabalii SAGREDO EX ROSUA - Mendizabali's Rosemary (Shoot) 4-55 ppm
Litsea glaucescens HBK var. glaucescens - Mexican bay (Shoot) 40-50 ppm
Thymus saturejoides - Moroccan Savory Thyme (Shoot) 50 ppm
Ocimum gratissimum L. - Agbo (Leaf) 24-47 ppm
Salvia sclarea L. - Clary Sage (Plant) 1-42 ppm
Thymus zygis L. - Spanish Thyme (Shoot) 42 ppm
Origanum onites L. - Oregano (Plant) 41 ppm
Monarda didyma L. - Beebalm (Leaf) 25-40 ppm
Nepeta cataria L. - Catnip (Plant) 8-40 ppm
Origanum sipyleum L. - Bayircayi (Shoot) 40 ppm
Teucrium cyprium BOISS. - 'Cyprus' Germander (Leaf) 39 ppm
Cymbopogon nardus (L.) RENDLE - Ceylon Citronella (Plant) 9-36 ppm
Abies alba MILLER - Silver-Fir (Leaf) 25-35 ppm
Micromeria dalmatica (Leaf) 35 ppm
Micromeria thymifolia (Leaf) 35 ppm
Origanum sipyleum L. - Bayircayi (Shoot) 35 ppm
Calamintha nepeta ssp. glandulosa (REQ.) P.W.BALL - Turkish Calamint (Shoot) 32 ppm
Agastache foeniculum (PURSH) KUNTZE - Giant Hyssop (Plant) 0-30 ppm
Monarda didyma L. - Beebalm (Flower) 30 ppm
Satureja obovata LAG. - Iberian Savory (Shoot) 0-30 ppm
Salvia gilliesii BENTH. - 'Cordoba' Sage (Shoot) 29 ppm
Pycnanthemum beadlei (SMALL) FERNALD - Beadle's Mountain Mint (Shoot) 28 ppm
Micromeria croatica (Leaf) 25 ppm
Pilocarpus jaborandi HOLMES - Indian Hemp (Leaf) 25 ppm
Elsholtzia polystachya BENTH. - Bush Mint (Leaf) 24 ppm
Nepeta racemosa LAM. - Catmint (Shoot) 24 ppm
Teucrium micropodioides ROUY - Small 'Cyprus' Germander (Leaf) 24 ppm
Aralia cordata L. - Udo (Root) 22 ppm
Satureja parvifolia (PHIL.) EPL. - Small-Leaf Pampa Savory (Shoot) 22 ppm
Sideritis pauli PAU - El Molinillo Sideritis (Shoot) 22 ppm
Thymus capitatus (L.) HOFFM. - 'Sicilian' Thyme (Shoot) 21 ppm

Achillea millefolium L. - Yarrow (Leaf) 0.5-20 ppm
Cinnamomum verum J. S. PRESL - Cinnamon (Bark) 5-20 ppm
Dracocephalum thymiflora RYDB. - Thyme-Flowered Moldavica (Plant) 20 ppm
Glechoma hederacea L. - Alehoof (Plant) 3-20 ppm
Moldavica thymiflora RYDB. - Thyme-Flowered Moldavica (Plant) 20 ppm
Pimenta dioica (L.) MERR. - Allspice (Leaf) 20 ppm
Sideritis mugronensis (Leaf) 15-20 ppm
Lycopus uniflorus MICHX. - One-Flowered Bugle (Plant) 12-18 ppm
Petroselinum crispum (MILLER) NYMAN ex A. W. HILL - Parsley (Leaf) 18 ppm
Monarda lindheimeri ENGL. & GRAY - Lindheimer's Monarda (Plant) 16 ppm
Pycnanthemum montanum MICHX. - Montane Mountain Mint (Shoot) 7-16 ppm
Acinos suaveolens (SIBT. & SMITH) G. DON F. (Shoot) 15 ppm
Monarda citriodora CERV. EX LAGASCA - Lemon Mint (Leaf) 15 ppm
Ocimum kilimandscharicum GUERKE - African Blue Basil (Leaf) 8-15 ppm
Teucrium divaricatum KOTSCHY var canescens (CELAK.) HOLMBOE - Hoary Divaricate Germander (Leaf) 15 ppm
Teucrium polium L. var valentinum - Iberian Golden Germander (Shoot) 15 ppm
Thymus longicaulis C. PRESL - Kekik (Shoot) 15 ppm
Lycopus virginicus L. - Bugle (Plant) 6-14 ppm
Rosmarinus officinalis L. - Rosemary (Shoot) 6-13 ppm
Salvia dorisiana STANDL. - 'Honduran' Sage (Shoot) 10.5-12.1 ppm
Hyptis suaveolens POIT. - Wild Hops (Shoot) 11 ppm
Elsholtzia pilosa GARKE - Hairy Mint Shrub (Shoot) 10 ppm
Mentha x piperita L. - Peppermint (Leaf) 1-10 ppm
Micromeria juliana (Leaf) 10 ppm
Monarda clinopodia L. - Clinopod Bergamot (Plant) 10 ppm
Ocimum gratissimum L. - Agbo (Flower) 8-10 ppm
Cleonia lusitanica (L.) L. - Spanish Heal-All (Leaf) 8 ppm
Melissa officinalis L. - Lemonbalm (Shoot) 1-8 ppm
Ocimum tenuiflorum L. - Anise-Scented Basil (Leaf) 8 ppm
Teucrium gnaphalodes L'HER. - Iberian Germander (Shoot) 8 ppm
Aloysia triphylla (L'HER.) BRITTON - Lemon Verbena (Plant) 1-7 ppm
Rosmarinus officinalis L. - Rosemary (Leaf) 7 ppm
Stachys germanica L. - Downy Woundwort (Plant) 7 ppm
Myrtus communis L. - Myrtle (Plant) 2-6 ppm
Origanum vulgare L. var gracile (C. KOCH) IETSWAART - Slender Turkish Oregano (Plant) 6 ppm
Origanum vulgare L. - Common Turkish Oregano (Plant) 6 ppm
Origanum vulgare L. var viride (BOISS.) HAYEK - Green Turkish Oregano (Plant) 5 ppm
Elsholtzia blanda BENTH. - Bantaluki (Shoot) 4 ppm
Satureja grandiflora (L.) SCHEELE - French Savory (Shoot) 4 ppm
Thymus longicaulis C. PRESL - Kekik (Shoot) 4 ppm
Teucrium oxylepis FONT QUER ssp oxylepis (Shoot) 2.02 ppm
Agastache nepetoides (L.) KUNTZE (Plant) 2 ppm
Pelargonium graveolens (L.) L'HER ex AIT. - Rose Geranium (Essential Oil) 1-2 ppm
Elsholtzia polystachya BENTH. - Bush Mint (Leaf) 1.6 ppm
Hyptis suaveolens POIT. - Wild Hops (Shoot) 1.5 ppm
Teucrium oxylepis FONT QUER ssp marianum RUIZ DE LA TORRE (Shoot) 1.48 ppm
Teucrium asiaticum L. (Shoot) 1.24 ppm

Recreated from Phytochemeco Database (Beckstrom-Sternberg and Duke, 1996).