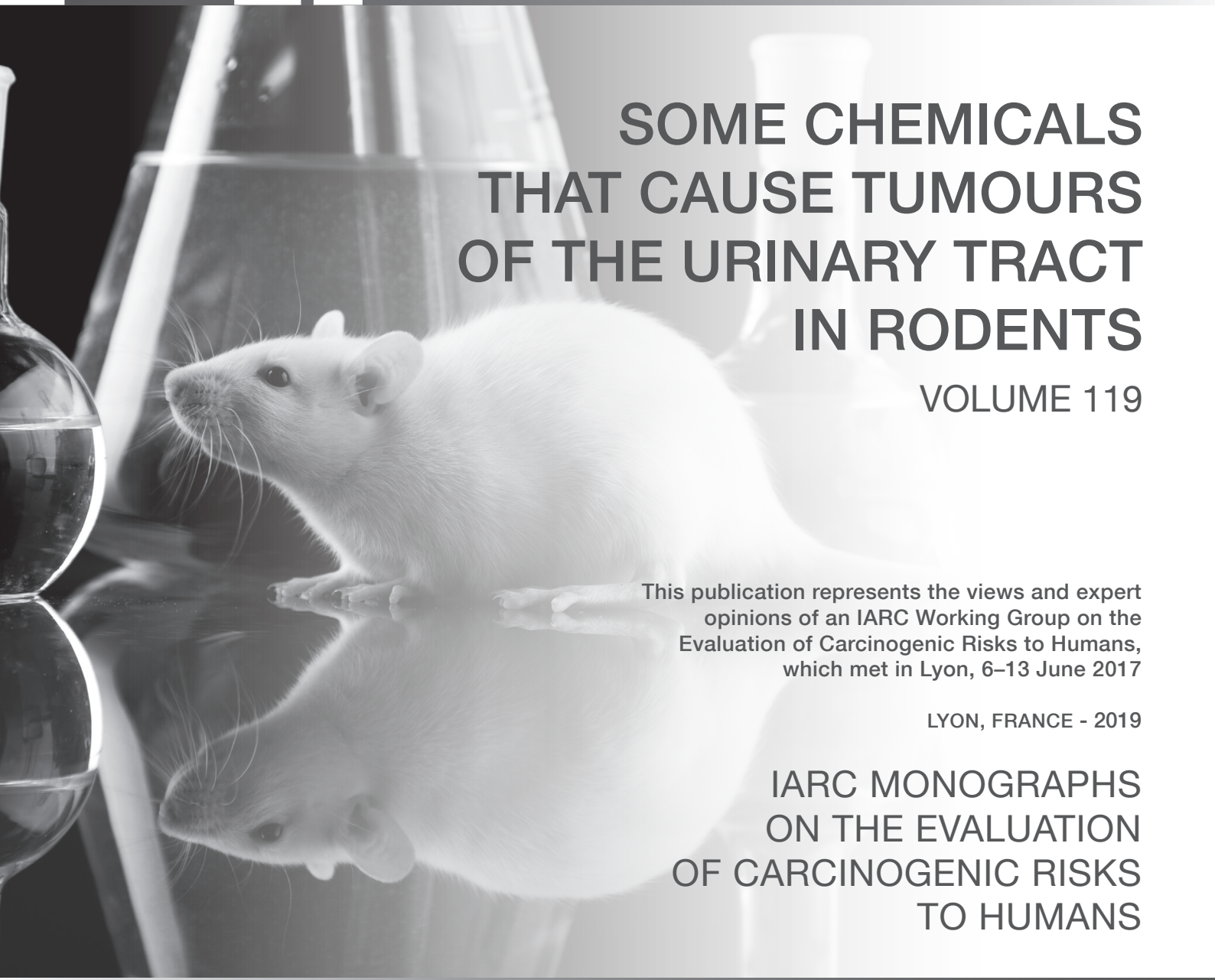
IARC MONOGRAPHS



SOME CHEMICALS THAT CAUSE TUMOURS OF THE URINARY TRACT IN RODENTS

VOLUME 119

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 6–13 June 2017

LYON, FRANCE - 2019

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

β-MYRCENE

1. Exposure Data

Myrcene exists as two isomers: the naturally occurring β-isomer, containing an isopropylidene group, and the isopropenyl form, often called the α-isomer (Behr & Johnen, 2009); however, the term "myrcene" in the literature may not exclusively refer to β-myrcene.

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 123-35-3

Chem. Abstr. Serv. name: 7-Methyl-3-methylene-1,6-octadiene

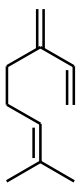
EC/List No.: 204-622-5

IUPAC systematic name: 7-Methyl-3-methylideneocta-1,6-diene

Synonyms: 2-Methyl-6-methylene-2,7-octadiene; 3-methylene-7-methyl-1,6-octadiene; myrcene; NSC No. 406264; β-geraniolene

From NTP (2010); Merck Index (2013); NCBI (2018)

1.1.2 Structural and molecular formulae, and relative molecular mass



Molecular formula: $C_{10}H_{16}$

Relative molecular mass: 136.24

1.1.3 Chemical and physical properties of the pure substance

Description: Yellow oily liquid with a characteristic pleasant terpene odour and citrus-like taste

Boiling point: 167 °C

Melting point: < –10 °C

Density: 0.794 g/cm³ at 20 °C

Octanol/water partition coefficient (P): log K_{ow}, 4.33

Refractive index: 1.4709 at 20 °C

Solubility: Practically insoluble in water; soluble in alcohol, chloroform, ether, and glacial acetic acid

Stability: Polymerizes spontaneously at room temperature, whether air is excluded or not

Conversion factor: 1 ppm = 5.57 mg/m³, at normal temperature (25 °C) and pressure (103.5 kPa)

From Merck Index (2013); NCBI (2018); Behr & Johnen (2009).

1.1.4 Impurities

Technical-grade β-myrcene has a purity of 75%, but rectification can achieve a purity of > 90%. Impurities include limonene, *psi*-limonene, *dl*-limonene, terpenes, β-pinene, dipentene from a cyclization reaction, and isomers and dimers of β-myrcene (Behr & Johnen, 2009; NTP, 2010). A polymerization inhibitor such as butylhydroxytoluene or tenox propyl gallate is normally added to crude or high-purity β-myrcene during shipment or extended storage (NTP, 2010). Most commercial preparations contain inhibitors of polymerization, such as tocopherol (Behr & Johnen, 2009).

1.2 Production and use

1.2.1 Production process

Monoterpenes such as β-myrcene are naturally formed in plants by stereospecific condensation of isopentenyl diphosphate with dimethylallyl diphosphate leading to geranyl diphosphate, which is hydrolysed to the monoterpene alcohol geraniol. β-Myrcene is then formed by dehydration and isomerization of geraniol (Eggersdorfer, 2012).

β-Myrcene occurs naturally in many organisms. It is a major component of essential oils of plants such as hops, bay leaf, and lemongrass, but since extraction is uneconomical, it is produced industrially by the pyrolysis of β-pinene, which is one of the key components of turpentine (Behr & Johnen, 2009; NTP, 2010; Eggersdorfer, 2012).

1.2.2 Production volume

β-Myrcene is listed in the USA as a chemical with a high production volume; > 1 million pounds [> 453 592 kg] were produced in or imported into the USA in 1990–1994 (NCBI, 2018). Aggregated national production volumes for β-myrcene reported under the inventory update rule show production in the range of > 10 million to < 50 million pounds [> 4536 to < 22680 tonnes] for the years 1986, 1990, 1994, 1998, 2002, and 2006 (HSDB, 2012).

The Joint Food and Agriculture Organization of the United Nations and World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA) reported annual production volumes of β-myrcene used as a flavouring agent of 58 076 kg for Europe and 1188 kg for the USA, while the annual volume of β-myrcene in naturally occurring foods was estimated as 66 842 kg for the USA (based on summarized data published between 1987 and 1999) (Pronk & Bend, 2006). Burdock (2010) reported an annual volume of 3500 pounds [1588 kg; presumably in the USA, date not specified].

β-Myrcene is listed as a chemical with a high production volume by the Organisation for Economic Co-operation and Development (OECD) (OECD, 2004). It was produced at a level of greater than 1000 tonnes per year in at least one member country or region of the OECD. β-Myrcene is manufactured and/or imported in the European Economic Area at a level of 0–100 tonnes per year (ECHA, 2017a).

The database Chemical Sources International (2017) listed 27 manufacturing companies worldwide, of which 10 are located in the USA, 12 in European countries, and 5 in Asia.

1.2.3 Use

One use of technically prepared β-myrcene is as a flavouring agent, for example, in foods and beverages. It is also used widely in cosmetics, soaps, and detergents as well as other fragranced products such as perfumes, air care products, polishes, wax blends, adhesives, disinfectants, biocides, paints, plasters, fuels, inks, and toners

(NTP, 2010; ECHA, 2017b), and electronic cigarette liquids (Yang et al., 2015). β-Myrcene is a starting material for a range of industrially important products such as menthol, geraniol, nerol, linalool, and isophytol (Behr & Johnen, 2009; Eggersdorfer, 2012). Besides its main use as an intermediate for the production of terpene alcohols, β-myrcene is also used in the production of terpene polymers, terpene–phenol resins, and terpene–maleate resins (Eggersdorfer, 2012).

β-Myrcene also occurs naturally in various plants (see Sections 1.4.1 and 1.4.2), and many plants and plant essential oils containing β-myrcene are used in medicinal, food, cosmetic, and other consumer products. For example, β-myrcene is a major constituent of hops used in the manufacture of beer (Okaru & Lachenmeier, 2017) (see Table 1.1; average, 37% of volatiles; Salanta et al., 2016).

1.3 Analytical methods

β-Myrcene is typically analysed along with various other compounds in assays for the characterization of terpenes and essential oils, which are predominantly based on hydrodistillation for sample preparation, followed by gas chromatography with flame ionization detection (GC-FID) or with mass spectrometry (GC-MS) (Okaru & Lachenmeier, 2017). The International Organization for Standardization (ISO) provides an international standard for the GC-FID analysis of essential oils, which includes β-myrcene as analyte (ISO, 1998). The various ISO standards for essential oils also contain representative gas chromatograms for each matrix (see summary in Section 1.5).

Another means of sample preparation is headspace solid-phase microextraction (Lachenmeier et al., 2006). For determination of the percentage of β-myrcene in mastic gum oil, a rapid procedure using Fourier transform Raman spectroscopy has been suggested (Daferera et al., 2002). Selected methods for the analysis of β-myrcene in various matrices are listed in Table 1.2.

No methods for analysis of β-myrcene in biological matrices in humans were reported.

1.4 Occurrence and exposure

1.4.1 Natural occurrence

β-Myrcene is a compound that occurs naturally in more than 200 plants, including verbena, lemongrass, hops, and bay (NTP, 2010; Merck Index, 2013). β-Myrcene has been reported qualitatively in more than 200 foods and beverages, including citrus peel oils and juices, apricot, sweet and sour cherry, berries, guava, pineapple, carrot, celery, potato, bell pepper, blackcurrants, anise, anise seed, cardamom, cinnamon, cassia, clove, capsicum varieties, ginger, *Mentha* oils, mace, parsley, thyme, cheeses, cream, pork, hop oil, beer, white wine, rum, cocoa, coffee, tea, mango, tamarind, coriander, gin, sweet bay, prickly pear, calamus, dill, lovage, caraway, buckwheat, corn, basil, fennel, kiwi fruit, rosemary, myrtle berry, turmeric, lemon balm, sage, pimento, angelica oil, Roman and German chamomile oil, eucalyptus and mastic gum oil (HSDB, 2012).

Table 1.1 and Table 1.3 provide a quantitative overview of the natural occurrence of β-myrcene in essential oils, some natural products, food, medicinal and related products.

While the highest concentrations of β-myrcene in natural materials have been detected in hops (up to 10 g/kg dry weight), the final concentration in beer was very low (0.4–80 µg/L) due to dilution, low extraction, and potential deterioration during processing (Kishimoto et al., 2005; Okaru & Lachenmeier, 2017).

β-Myrcene has been measured in air in forests in different parts of the world. Concentrations vary considerably by day and season, and by height of measurement in the forest. Measured concentrations of β-myrcene were often less than

Table 1.1 Relative concentrations of β-myrcene in essential oils and some natural products

Product	Average concentration[a]	Range	Unit	Year[b]	Country or region	Reference
Essential oils from *Distichoselinum tenuifolium*	67.2	47.7–84.6	%	2010	Portugal	Tavares et al. (2010)
Curcuma mangga	46.50	NR	%	2011	Malaysia	Wahab et al. (2011)
Essential oil of *Schinopsis brasiliensis*	45.12	NR	%	2011	Brazil	Donati et al. (2015)
Leaf volatiles of *Zanthoxylum gilletii*	42.87	NR	%	1997	Cameroon	Jirovetz et al. (1999)
Hops (n = 12)	37.90	23.29–52.63	% of volatiles	2011, 2012	Romania	Salanta et al. (2016)
Essential oil of *Cannabis sativa* (n = 5)	28.41	21.08–35.02	%	2001	Austria	Novak et al. (2001)
Essential oil of lemongrass (*Cymbopogon citratus*)	27.83	NR	%	2013	Benin	Gbenou et al. (2013)
Peel of pomelo (n = 4)	27.801	22.811–30.928	% of relative content	2014	China	Shao et al. (2014)
Mastic gum oil (n = 10)	24.5	4.5–57.9	% in oil	2002	Greece	Daferera et al. (2002)
Essential oil and the gum of *Pistacia lentiscus Var. chia* (n = 6)	15.6	7.8–25.0	%	2002	Greece	Koutsoudaki et al. (2005)
Essential oil of *Lippia alba*	15.0	NR	% of content	2002	Brazil	Oliveira et al. (2006)
Essential oil of *Thymus serpyllum* ssp. *serpyllum* (n = 52)	14.30	NR	%	1987	Finland	Stahl-Biskup & Laakso (1990)
Essential oil of *Artemisia annua*	12.6	0.0–37.7	%	2007	China	Yu et al. (2011)
Essential oil of *Santolina rosmarinifolia L. ssp. Rosmarinifolia* (n = 13)	11.8	0.3–15.5	% of content	1995–1996	Spain	Palá-Paúl et al. (2001)
Essential oil of *Houttuynia* Thunb.	11.51	2.58–18.47	%	2004	China	Lu et al. (2006)
Essential oil of Korean endemic citrus species (n = 14)	9.51	2.06–32.10	%	2005	Republic of Korea	Baik et al. (2008)
Essential oil of *Thymus serpyllum* ssp. *tanaensis* (n = 133)	9.1	NR	%	1987	Finland	Stahl-Biskup & Laakso (1990)
Essential oils of *Juniperus rigida* Siebold & Zucc.	9.0	0.0 (stems, needles) –27.00 (berries)	%	2014	China	Liu et al. (2016)
Essential oil of *Teucrium stocksianum* Bioss.	8.64	NR	%	2012	Pakistan	Shah et al. (2012)
Essential oil of juniper berry *(Juniperus communi* L.*)*	8.3	NR	%	2014	Bulgaria	Höferl et al. (2014)
Carrots (*Daucus carota*) (n = 7)	7.56	0.87–29.90	% of volatiles	2008	NR	Soria et al. (2008)
Essential oil of lemongrass (*Cymbopogon citratus*)	6.52	NR	%	2015	Cuba	Pinto et al. (2015)
Essential oil of thyme (*Thymus kotschyanus* and *Thymus persicus*)	6.46	0.26–12.65	%	2000	Iran (Islamic Republic of)	Rasooli & Mirmostafa (2003)

Table 1.1 (continued)

Product	Average concentration[a]	Range	Unit	Year[b]	Country or region	Reference
Essential oil of sweet fennel (*Ocimum gratissimum* L.)	6.4	NR	%	2013	Benin	Adjou et al. (2013)
Odorants in frankincense (*Boswellia sacra)* (*n* = 6)	6.3	2.8–8.0	% (total peak area)	2014	Oman and Somalia	Niebler & Buettner (2015)
Essential oil of *Thymus serpyllum L.* (*n* = 33)	6.2	0.0–20.2	% of content	2001–2004	Estonia	Paaver et al. (2008)
Essential oil of *Murraya koenigii* L.	6.12	NR	%	2014	India	Rajendran et al. (2014)
Evodia rutaecarpa fruits	5.83	NR	% of volatiles	2005	Japan	Pellati et al. (2005)
Essential oils of wild populations of *Stachys lavandulifolia* Vahl (Lamiaceae)	5.8	0.0–26.2	%	2011	Iran (Islamic Republic of)	Aghaei et al. (2013)
Essential oil of *Thymus serpyllum* L. (*n* = 20)	5.65	0.0–20.2	%	2002, 2003	Estonia	Raal et al. (2004)
Essential oil from *Stachys lavandulifolia* Vahl (*n* = 7)	5.49	0.52–15.87	%	2010	Iran (Islamic Republic of)	Pirbalouti & Mohammadi (2013)
Essential oils from *Gynura bicolour* DC	5.10	NR	%	2012	Japan	Miyazawa et al. (2016)
Oil from *Thymus serpylloides* ssp. *gadorensis* (*n* = 34)	5.0	0.13–30.39	%	1990–1993	Spain	Sáez (2001)
Essential oils of rosemary *(Rosmarinus officinalis, Lamiaceae)*	4.8	3.4–5.9	%	2008–2009	Serbia	Lakusić et al. (2013)
Japanese pepper *(Xanthoxylum piperitum* DC.*)*	4.41	1.75–7.08	%	2001	Japan	Jiang & Kubota (2004)
Essential oils from black pepper[c] (*Piper guineense*)	4.37	NR	% of content	2013	Nigeria	Oboh et al. (2013)
Essential oil of pineapple weed (*Chamomilla suaveolens*) (*n* = 2)	4.2	1.1–7.9	% of content	2007	Estonia	Orav et al. (2010)
Leaves from species of *Clausena* (Rutaceae)	4.0	0.1–14.3	%	2012	Viet Nam	Trung et al. (2014)
Essential oil from Danggui and Zhiqiao[d]	3.71	NR	%	2016	China	Wang et al. (2016)
Essential oil of carrot seeds (*Daucus carota*)	3.7	0.5–10.5	%	2014	Italy	Flamini et al. (2014)
Essential oil of wormwood (*Artemisia absintium)* (*n* = 15)	3.5	Trace – 9.2	% in oil	1999–2007	Lithuania	Judzentiene et al. (2009)
Essential oil of *Lippia alba* f. *intermedia*	3.5	NR	% of content	2002	Brazil	Oliveira et al. (2006)
Cardamom oil (*Elettaria cardamomum* (L.) Maton)	3.3	2.1–6.6	%	2004	Italy	Marongiu et al. (2004)

Table 1.1 (continued)

Product	Average concentration[a]	Range	Unit	Year[b]	Country or region	Reference
Essential oils of three *Thymus* species	2.8	0.6–6.8	%	2008	Iran (Islamic Republic of)	Asbaghian et al. (2011)
Essential oil from *Satureja intermedia* CA Mey	2.5	NR	%	2014	Iran (Islamic Republic of)	Sharifi-Rad et al. (2015)
Essential oils of ripe berries of *Juniperus oxycedrus* L. ssp. *macrocarpa* (S.&m) Ball	2.4	1.9–2.8	%	2007	Tunisia	Hanène et al. (2012)
Orange fruit juice (*Citrus sinensis*) L.	2.38	NR	% of volatiles	2008	China	Qiao et al. (2008)
Essential oils of herbs	2.26	0.11–6.29	%	2006	South-Western Rwanda	Qiao et al. (2008)
Peel oil of *Citrus natsudaidai* Hayata (Natsudaidai)	2.25	NR	% (w/w)	2002	Japan	Mukazayire et al. (2011)
Cardamom essential oil (*Elettaria cardamomum*)	2.2	NR	%	2016	Iran (Islamic Republic of)	Lan Phi et al. (2006)
Essential oil of *Citrus tamurana* Hort. ex Tanaka (Hyuganatsu)	2.20	2.11–2.28	% (w/w)	2000	Japan	Masoumi-Ardakani et al. (2016)
Essential oils of fennel fruits (n = 7)	2.15	1.48–3.00	%	2010	Romania	Choi & Sawamura (2000)
Orange peel oil (*Citrus sinensis* L.)	1.88	NR	% of volatiles	2008	China	Aprotosoaie et al. (2013)
Peel oil of kumquat *(Fortunella japonica* Swingle*)*	1.84	NR	%	2003	Republic of Korea	Choi (2005)
Essential oil of cardamom *(Amomum subulatum* Roxb.*)*	1.57	1.16–2.36	%	2013	India	Joshi et al. (2013)
Essential oil from ripe fruits of Jordanian *Pistacia palaestina* Boiss.	1.2	NR	%	2002	Jordan	Flamini et al. (2004)
Essential oil of *Origanum vulgare* L. (Lamiaceae) (n = 12)	1.1	0.0–3.4	%	2011	Europe	Lukas et al. (2015)
Essential oils of *Gynura bicolour* DC. Leaves	0.75	NR	%	2012	Japan	Miyazawa et al. (2016)
Essential oil of *Thymus serpyllum* L. (n = 7)	0.6	0.2–1.1	% of content	2001–2004	Armenia, Latvia, the Russian Federation	Paaver et al. (2008)
Essential oil of *Eucalyptus citriodora*	0.11	NR	%	2013	Benin	Gbenou et al. (2013)
Taperebá fruits	0.1–0.7	NR	% of volatiles	2002	Brazil	Ceva-Antunes et al. (2003)
Cajá fruits	38–41	NR	% of volatiles	2001	Brazil	Ceva-Antunes et al. (2003)

Table 1.1 (continued)

Product	Average concentration[a]	Range	Unit	Year[b]	Country or region	Reference
Essential oil of *Lingularia persica* Boiss.	0.5 (root) 2.0 (leaf) 2.8 (stem) 4.4 (flower)	NR	%	2012	Iran (Islamic Republic of)	Mohadjerani et al. (2016)
Essential oil of *Lavandula* L. *species*	0.3–7.5	NR	%	2012	Tunisia	Messaoud et al. (2012)
Essential oil of *Pistacia lentiscus* var. *chia*	8.34 (resin) 20.58 (leaves) 47.92 (twigs)	NR	%	1997	Greece	Magiatis et al. (1999)

[a] Calculated by the Working Group if not provided in reference; values below limit of quantification were calculated as zero
[b] Year of harvest/sampling; if not provided, year of publication
[c] Ashanti black pepper (*Piper guineense*)
[d] Radix *Angelica sinensis* and *Fructus aurantii*
NR, not reported; trace, traces below limit of quantification

Table 1.2 Selected methods for the analysis for β-myrcene

Sample matrix	Assay procedure	Limit of detection	Reference
Essential oils	GC-FID	NR	ISO (1998)
Beer	SBSE-GC/MS	0.001 µg/L	Kishimoto et al. (2005)
Hops and beer	HS trap-GC/MS	NR	Aberl & Coelhan (2012); Schmidt & Biendl (2016)
Cheese	HS-SPME-GC/MS	NR	Giuseppe et al. (2005)
Herbs	GC/MS	NR	Gherman et al. (2000)
Liver pâtés	SPME-GC/MS	NR	Estévez et al. (2004)
Tropical fruits	SPME-GC/MS	NR	Ceva-Antunes et al. (2003)
Orange juice	HS-SPME-GC/MS	NR	Lachenmeier et al. (2006)
Mastic gum oil	FT-Raman spectroscopy	NR	Daferera et al. (2002)
Tangerines	GC-O	NR	Miyazaki et al. (2012)
Pomelos	TDS-GC/MS	NR	Shao et al. (2014)

FT, Fourier transform; GC-FID, gas chromatography-flame ionization detection; GC/MS, gas chromatography-mass spectrometry; GC-O, gas chromatography-olfactometry; HS, headspace; NR, not reported; SPME, solid-phase microextraction; SBSE, stir bar-sorptive extraction; TDS, thermal desorption system

Table 1.3 Concentration of β-myrcene in foods, medicinal products, and related products

Product	Average concentration[a]	Range	Unit	Year[b]	Country or region	Reference
Alcoholic beverages	1.12	Max. 5.00	ppm [µg/L]	1994	USA	HSDB (2012)
Baked goods	10.05	Max. 14.92	ppm	1994	USA	HSDB (2012)
Beer (bottled and canned, *n* = 2)	25.0	8.9–41.0	µg/L	2016	Germany	Wietstock et al. (2016)
Beer (*n* = 2)	62.7	45.6–79.7	µg/L	2016	USA and Germany	Schmidt & Biendl (2016)
Beer (*n* = 3)	0.7	0.4–1.1	ppb	2005	Japan	Kishimoto et al. (2005)
Bullock's heart fruit (*Annona reticulata* L.) (*n* = 24)	16.24	12.62–20.06	mg/kg	2003	Cuba	Pino et al. (2003)
Carrots *(Daucus carota* L.*)*	125.25	80.0–219.0	ng/g	1999	Denmark	Kjeldsen et al. (2003)
Chewing gum	116.2	Max. 126.00	ppm	1994	USA	HSDB (2012)
Condiments, relishes	5.00	Max. 10.00	ppm	1994	USA	HSDB (2012)
Dekopon peel (*Shiranuhi mandarin*)	36.54	NR	mg/kg	2002	Japan	Umano et al. (2002)
Fennel fruits	1150	NR	µg/g	2006	Hungary	Zeller & Rychlik (2006)
Fennel tea (prepared)	140	NR	µg/L	2006	Hungary	Zeller & Rychlik (2006)
Frozen dairy	12.32	Max. 15.68	ppm	1994	USA	HSDB (2012)
Gelatins, puddings	19.96	Max. 22.91	ppm	1994	USA	HSDB (2012)
Hops (*n* = 12)	5489	2330–10 494	µg/g dw	2008	Germany	Aberl & Coelhan (2012)
Houttuynia cordata (*n* = 13)	138.0	57.68–271.2	µg/g	2010	China	Ji et al. (2011)
Italian lemon liquors (Limoncello) (*n* = 12)	12.2	3.0–31.0	mg/L	2003	Italy	Andrea et al. (2003)
Leaves and stalks of celery	31.5	8.0 (raw stalk)–73.0 (boiled leaves)	µg/kg	2006	Japan	Kurobayashi et al. (2006)
Mango	65.9	NR	µg/kg	2014	USA	Munafo et al. (2016)
Meat products	5.00	Max. 10.00	ppm	1994	USA	HSDB (2012)
Non-alcoholic beverages	7.72	Max. 11.15	ppm	1994	USA	HSDB (2012)
Soft candy	6.22	Max. 8.07	ppm	1994	USA	HSDB (2012)
Spanish pomegranates *(Punica granatum* L.*)*, sour cultivars (*n* = 2)	0.01	0.01–0.01	g/kg	2009	Spain	Calín-Sánchez et al. (2011)
Spanish pomegranates *(Punica granatum* L.*)*, sour-sweet cultivars (*n* = 3)	0.03	0.02–0.04	g/kg	2009	Spain	Calín-Sánchez et al. (2011)
Spanish pomegranates *(Punica granatum* L.*)*, sweet cultivars (*n* = 4)	0.03	0.01–0.07	g/kg	2009	Spain	Calín-Sánchez et al. (2011)

[a] Calculated by the Working Group if not provided in reference; values below limit of quantification were calculated as zero
[b] Year of harvest/sampling. If not provided, year of publication.
dw, dry weight; NR, not reported

Table 1.4 Exposure to β-myrcene in the general population

Region, country Year	Exposure (integrated/mixed exposure data)			
	Mean	Range	Comments	Reference
USA Before 2008	3 µg/kg bw per day	NR	Estimated daily per capita intake for eaters only; calculation based on annual volume of 1338 kg	Adams et al. (2011)
Europe Before 1999	138 µg/kg bw per day	NR	Estimation based on data sources 1989–1999 and an annual production of 58076 kg	Pronk & Bend (2006)
USA Before 1999	3 µg/kg bw per day	NR	Estimation based on data sources 1989–1999 and an annual production of 1188 kg	Pronk & Bend (2006)
USA NR	2.966 µg/kg bw per day	NR	Individual consumption based on annual consumption of 3500 lb [1587.5 kg]	Burdock (2010)

bw, body weight; NR, not reported

10 ppt during the day, rising to ppb levels during the night (Clement et al., 1990; Janson, 1992).

1.4.2 Exposure in the general population

The general population may be exposed to β-myrcene via ingestion of food and medicinal products containing β-myrcene, inhalation of ambient air in natural environments containing plants that emit β-myrcene, and dermal contact with products containing β-myrcene (HSDB, 2012). Inhalation exposure may also occur due to the emission of β-myrcene from various household products such as detergent, fabric deodorizer, or general purpose cleaner (Kwon et al., 2007). The United States consumer product information database lists five air freshener products containing β-myrcene (Household Products Database, 2017). [The Working Group noted that quantitative data for inhalation exposure, e.g. in households, were not unavailable.]

Since β-myrcene is an approved food flavouring additive, the greatest potential for exposure lies in the consumption of foods that naturally contain β-myrcene or to which β-myrcene has been added (HSDB, 2012).

JECFA estimated daily intakes of β-myrcene of 138 µg/kg body weight (bw) in Europe and 3 µg/kg bw in the USA (Pronk & Bend, 2006). More recently, the Flavour and Extract Manufacturers Association estimated daily per capita intake to be 3 µg/kg bw in the USA (assuming 10% of consumers of flavoured products only) (Adams et al., 2011), a value that is similar to other estimates (Burdock, 2010; Table 1.4).

[The Working Group noted that the available information on exposure was based on estimated use of β-myrcene as a food additive, and did not include exposure resulting from the natural occurrence of β-myrcene in food and beverages. Total diet estimations were not available.]

1.4.3 Occupational exposure

The only estimate of the number of workers (n = 25 154) exposed to this substance in the USA came from the National Occupational Exposure Survey (NOES) conducted in 1981–1983 (ILS, 1997).

In view of the extensive uses of β-myrcene, it is possible that workers may be exposed via dermal contact and inhalation (NTP, 2010).

[No data concerning exposure of workers were available to the Working Group].

1.5 Regulations and guidelines

The International Organization for Standardization (ISO) provided international standards with minimum and maximum percentages of β-myrcene in essential oils from various plant

Table 1.5 International standards regarding β-myrcene content in various plant essential oils

Common name	Botanical name	β-Myrcene content (% in essential oil)[a]		ISO norm no.
		Min.	Max.	
Bay	*Pimenta racemosa* (Mill.) JW Moore	20.0	30.0	3045:2004
Bergamot petitgrain	*Citrus bergamia* (Risso et Poit.)	1.2	1.8	8900:2005
Bitter fennel	*Foeniculum vulgare* Mill. ssp. *vulgare* var. *vulgare*	0.5	12.0	17 412:2007
Bitter orange	*Citrus aurantium* L.	1.5	3.0	9844:2006
Caraway	*Carum carvi* L.	0.2	0.7	8896:2016
Cardamom	*Elettaria cardamomum* (L.) Maton	Trace	2.5	4733:2004
Celery seed	*Apium graveolens* L.	0.3	1.4	3760:2002
Coriander fruits	*Coriandrum sativum* L.	0.5	1.5	3516:1997
Cumin seed	*Cuminum cyminum* L.	0.1	1.5	9301:2003
Dwarf pine	*Pinus mugo* Turra	3.0	11.0	21 093:2003
Galbanum	*Ferula galbaniflua* Boiss. et Buhse	2.5	3.5	14 716:1998
Grapefruit, obtained by expression	*Citrus x paradisi* Macfad.	1.5	2.5	3053:2004
Gum turpentine, Chinese	Mainly from *Pinus massoniana* Lamb.	Trace	1.5	21 389:2004
Juniper berry	*Juniperus communis* L.	3.0	22.0	8897:2010
Lavandin Grosso, French type	*Lavandula angustifolia* Mill. × *Lavandula latifolia* Medik.	0.3	1.0	8902:2009
Lime (cold pressed), Mexican type	*Citrus aurantifolia* (Christm.) Swingle	1.0	2.0	3809:2004
Lime distilled, Mexican type	*Citrus aurantifolia* (Christm.) Swingle	1.1	1.5	3519:2005
Lime expressed, Persian type	*Citrus latifolia* Tanaka	1.2	2.0	23 954:2009
Mandarin, Italian type	*Citrus reticulata* Blanco	1.4	2.0	3528:2012
Molle, Argentinean type	*Schinus areira* L.	1.0	14.0	16 385:2014
Neroli	*Citrus aurantium* L., syn. *Citrus amara* Link, syn. *Citrus bigaradia* Loisel, syn. *Citrus vulgaris* Risso	1.0	4.0	3517:2012
Oregano	*Origanum vulgare* L. subsp. *hirtum* (Link) letsw	0.5	3.0	13 171:2016
Origanum, Spanish type	*Coridothymus capitatus* (L.) Rchb.f.	1.0	3.0	14 717:2008
Petitgrain, Paraguayan type	*Citrus aurantium* L. var. Paraguay (syn. *Citrus aurantium* var. *bigaradia* Hook f.)	1.3	3.0	3064:2015
Rosemary	*Rosmarinus officinalis* L.	1.0	4.5	1342:2012
Sweet orange	*Citrus sinensis* (L.) Osbeck, obtained by physical extraction of the peel	1.5	3.5	3140:2011
Thyme containing thymol, Spanish type	*Thymus zygis* (Loefl.) L.	1.0	2.8	14 715:2010
Turpentine, Iberian type	*Pinus pinaster* Sol.	0.4	1.5	11 020:1998

[a] The widest possible minimum–maximum range is specified when the norm contained data on several subtypes
ISO, International Organization for Standardization
All ISO norms from ISO Standards (ISO, 2017)

species; these oils are widely used in the food and perfumery industries (ISO, 2017; Table 1.5).

β-Myrcene has been approved as a food additive by the United States Food and Drug Administration (FDA) (Behr & Johnen, 2009). According to FDA regulations, β-myrcene may be used as a flavouring substance or adjuvant in food in its natural form in essential oils (Code of Federal Regulations (CFR) 21, § 172.510), and as a synthetic substance (CFR 21, § 172.515) (NTP, 2010).

In 1974, the European Council included β-myrcene in the list of artificial flavouring substances that may be added to foodstuffs (Behr & Johnen, 2009), and β-myrcene is included in the most recent list of approved flavouring substances in the European Union according to Regulation No. 872/2012 (European Commission, 2012).

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

3.1 Oral administration

The results of studies of carcinogenicity in mice and rats treated with β-myrcene by gavage are summarized in Table 3.1 (NTP, 2010).

3.1.1 Mouse

Groups of 50 male and 50 female B6C3F$_1$ mice (age, 6–7 weeks) were given β-myrcene (purity, > 93%; impurity: *psi*-limonene, CAS No. 499-97-8, approx. 5%) at a dose of 0 (control), 0.25, 0.5, or 1 g/kg bw by gavage in corn oil, 5 days per week for 105 (males) or 104 (females) weeks (NTP, 2010). [The Working Group noted that this was a study of commercially available β-myrcene with a purity of > 93%. The major contaminant was *psi*-limonene and there had been no studies of carcinogenicity with this compound).]

Survival of male and female mice at 1 g/kg bw was significantly lower than that of mice in the vehicle-control groups: males: 35/50 (control), 35/50, 31/50, 21/50; females: 39/50 (control), 34/50, 35/50, 17/50. The cause of the early deaths was not determined. Mean body weights of males at 1 g/kg bw, females at 0.5 g/kg bw, and females at 1 g/kg bw were less than those of controls after weeks 8, 17, and 11, respectively. Because of the number of early deaths in male and female mice at 1 g/kg bw, these groups were not considered to contain enough animals for the carcinogenesis analysis, and were not included in the statistical evaluation for the treatment-related development of tumours.

In treated male mice, there were significant increases in the incidence of epithelial hepatocellular neoplasm and of hepatoblastoma [an embryonal tumour of the liver cells], with a significant positive trend for each. These included increases in the incidence of: hepatocellular adenoma (multiple); hepatocellular adenoma (including multiple); hepatocellular carcinoma (multiple); hepatocellular carcinoma (including multiple); and hepatoblastoma (including multiple). The incidence of the combination of hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma was also significantly increased, with a significant positive trend. In female mice, there were also increases in the incidence of hepatocellular tumours, but to a lesser extent than in male mice. The incidence of hepatocellular adenoma (including multiple), hepatocellular carcinoma, and hepatocellular adenoma or carcinoma (combined) was significantly increased at the lowest dose, without a significant positive trend.

[The Working Group noted this was a well-conducted study that complied with good laboratory practice (GLP), and was carried out in males and females. The Working Group also

Table 3.1 Studies of carcinogenicity in experimental animals treated with β-myrcene by gavage

Species, strain (sex) Age at start Duration Reference	Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Mouse, B6C3F$_1$ (M) 6–7 wk 105 wk NTP (2010)	Purity, > 93% Corn oil 0, 0.25, 0.5 g/kg bw 5 d/wk for 105 wk 50, 50, 50 35, 35, 31	*Liver* Hepatocellular adenoma (multiple): 15/50*, 31/50**, 30/50** Hepatocellular adenoma (includes multiple): 26/50*, 41/50**, 43/50** Hepatocellular carcinoma (multiple): 1/50*, 4/50, 9/50** Hepatocellular carcinoma (includes multiple): 14/50*, 20/50, 28/50** Hepatocellular adenoma or carcinoma (combined): 33/50*, 44/50**, 48/50*** Hepatoblastoma: 4/50*, 6/50, 11/50** Hepatocellular adenoma, carcinoma, or hepatoblastoma: 34/50*, 45/50**, 48/50***	*[$P = 0.002$ (trend, Cochran-Armitage test)], **$P \leq 0.01$ (poly-3 test) *$P < 0.001$ (trend, poly-3 test), **$P < 0.001$ (poly-3 test) * [$P = 0.024$ (trend, Cochran-Armitage test)], **$P \leq 0.01$ (poly-3 test) *$P = 0.003$ (trend, poly-3 test), **$P = 0.004$ (poly-3 test) *$P < 0.001$ (trend, poly-3 test), **$P = 0.003$, ***$P < 0.001$ (poly-3 test) *$P = 0.027$ (trend, poly-3 test), **$P = 0.041$ (poly-3 test) *$P < 0.001$ (trend, poly-3 test), **$P = 0.003$, ***$P < 0.001$ (poly-3 test)	Principal strengths: GLP study; study in males and females The dose of 1 g/kg bw was tested but not used for tumour analysis due to early death and effect on body weight

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Mouse, B6C3F$_1$ (F) 6–7 wk 104 wk NTP (2010)	Purity, > 93% Corn oil 0, 0.25, 0.5 g/kg bw 5 d/wk for 104 wk 50, 50, 50 39, 34, 35	*Liver* Hepatocellular adenoma (multiple): 0/50, 2/50, 0/50 Hepatocellular adenoma (includes multiple): 6/50, 13/50*, 6/50 Hepatocellular carcinoma: 1/50, 7/50*, 2/50 Hepatocellular adenoma or carcinoma (combined): 7/50, 18/50*, 8/50	 NS *P = 0.042 (poly-3 test) *P = 0.025 (poly-3 test) *P = 0.005 (poly-3 test)	Principal strengths: GLP study; study in males and females The dose of 1 g/kg bw was tested but not used for tumour analysis due to early death and effect (decrease) on body weight
Rat, F344/N (M) 5–6 wk 105 wk NTP (2010)	Purity, > 93% Corn oil 0, 0.25, 0.5 g/kg bw 5 d/wk for 105 wk 50, 50, 50 29, 36, 28	*Kidney, standard (single section) evaluation:* Renal tubule adenoma (multiple): 0/50, 2/50, 1/50 Renal tubule adenoma (includes multiple): 0/50*, 4/50, 8/50** Renal tubule carcinoma: 0/50, 3/50, 1/50 Renal tubule adenoma or carcinoma (combined): 0/50*, 7/50**, 9/50*** *Kidney, extended evaluation (step sections)* Renal tubule adenoma: 0/50*, 8/50**, 7/50***	 NS *P = 0.002 (trend, poly-3 test), **P = 0.003 (poly-3 test) NS *P = 0.002 (trend, poly-3 test), **P = 0.010, ***P = 0.002 (poly-3 test) *P = 0.013 (trend, poly-3 test), **P = 0.005, ***P = 0.007 (poly-3 test)	Principal strengths: GLP study; study in males and females The dose of 1 g/kg bw was tested but not used for tumour analysis due to early death and effect (decrease) on body weight Historical control incidence for renal tubule carcinoma (single section): gavage studies, 0/150; all routes, 1/1394 (0.1% ± 0.5%) [range, 0–2%]

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Tumour incidence	Significance	Comments
Rat, F344/N (M) 5–6 wk 105 wk NTP (2010) (cont.)		Renal tubule carcinoma:		
		0/50, 3/50, 0/50	NS	
		Renal tubule adenoma or carcinoma (combined):		
		0/50*, 10/50**, 7/50***	*P = 0.017 (trend, poly-3 test), **P < 0.001, ***P = 0.007 (poly-3 test)	
		Kidney, standard (single section) evaluation and extended evaluation (step sections) (combined)		
		Renal tubule adenoma:		
		0/50*, 12/50**, 13/50**	*P < 0.001 (trend, poly-3 test), **P < 0.001 (poly-3 test)	
		Renal tubule carcinoma:		
		0/50, 3/50, 1/50	NS	
		Renal tubule adenoma or carcinoma (combined):		
		0/50*, 14/50**, 13/50**	*P < 0.001 (trend, poly-3 test), **P < 0.001 (poly-3 test)	
Rat, F344/N (F) 5–6 wk 105 wk NTP (2010)	Purity, > 93% Corn oil 0, 0.25, 0.5, 1 g/kg bw 5 d/wk for 105 wk 50, 50, 50, 50 31, 33, 28, 33	*Kidney, standard (single section) evaluation*		Principal strengths: GLP study; study in males and females Historical control incidence for renal tubule adenoma (single section): gavage studies, 0/150; all routes, 1/1340 (0.1% ± 0.4%) [range, 0–2%]
		Renal tubule adenoma:		
		0/50, 1/50, 0/50, 2/50	NS	
		Kidney, standard (single section evaluation) and extended evaluation (step sections) (combined)		
		Renal tubule adenoma:		
		0/50, 2/50, 1/50, 3/50	NS	

bw, body weight; d, days; F, female; GLP, good laboratory practice; M, male; NS, not significant; wk, week

noted the poor survival of male and female mice at the highest dose.]

3.1.2 Rat

Groups of 50 male and 50 female F344/N rats (age, 5–6 weeks) were given β-myrcene (purity, > 93%; impurity: *psi*-limonene, CAS No. 499-97-8, approx. 5%) at a dose of 0 (control), 0.25, 0.5, or 1 g/kg bw by gavage in corn oil, 5 days per week for 105 weeks (NTP, 2010). All males in the group at 1 g/kg bw died before the end of the study as a result of renal toxicity, and this group was not included in the statistical evaluation for the treatment-related development of tumours (survival in males: 29/50 (control), 36/50, 28/50, 0/50). The mean body weights of males and females at 1 g/kg bw were less than those of controls after weeks 7 and 13, respectively. Survival of female rats was considered adequate for all exposed groups, and all three dose levels were included in the statistical analysis for tumour incidence.

Tumours of the renal tubules were seen in male and female treated rats; this tumour response was stronger in males than in females. The incidence of renal tubule adenoma in male rats at 0.5 g/kg bw was significantly increased, with a significant positive trend, compared with controls, and the incidence of renal tubule adenoma or carcinoma (combined) was significantly increased, with a significant positive trend, in male rats at 0.25 and 0.5 g/kg bw. These increases in the incidence of renal tubule tumours were confirmed by the extended evaluation (step section) of the kidneys.

According to the standard (single section) evaluation of the male rat kidney, the incidence of renal tubule tumours was: renal tubule adenoma: 0/50 (control), 4/50, 8/50; renal tubule carcinoma: 0/50 (control), 3/50 (6%), 1/50 (2%); and renal tubule adenoma or carcinoma (combined): 0/50 (control), 7/50, 9/50. According to the extended (step section) evaluation of the male rat kidney, the incidence of renal tubule tumours was: renal tubule adenoma: 0/50 (control), 8/50, 7/50; renal tubule carcinoma: 0/50 (control), 3/50, 0/50; and renal tubule adenoma or carcinoma (combined): 0/50 (control), 10/50, 7/50. According to the original (single section) and extended evaluation (step sections) (combined) of the male rat kidney, the incidence of renal tubule tumours was: renal tubule adenoma: 0/50 (control), 12/50, 13/50; renal tubule carcinoma: 0/50 (control), 3/50, 1/50; and renal tubule adenoma or carcinoma: 0/50 (control), 14/50, 13/50. In male rats, the historical incidence (mean ± standard deviation) of renal tubule carcinoma (single section) for gavage studies was: 0/150; all routes: 2/1394 (0.1% ± 0.5%); range, 0–2%.

The evaluations of the female rat kidney also demonstrated a treatment-related carcinogenic effect. In the standard (simple section) evaluation of the female rat kidney, the incidence of renal tubule adenoma (including multiple) was: 0/50 (control), 1/50 (2%), 0/50, 2/50 (4%). According to the original (single section) and extended evaluation (step sections) (combined) of the female rat kidney, the incidence of renal tubule adenoma (including multiple) was: 0/50 (control), 2/50, 1/50, and 3/50. In female rats, the historical incidence (mean ± standard deviation) of renal tubule adenoma (single section) for oral gavage studies was: 0/150; all routes, 1/1340 (0.1% ± 0.4%); range, 0–2%. [Thus, the 4% incidence of renal tubule adenoma (single section) in female rats at 1 g/kg bw was considered by the Working Group to be related to treatment with β-myrcene.] No malignant tumours of the kidney occurred in the treated groups of female rats.

Renal toxicity was seen in treated male and female rats, as demonstrated by the occurrence of several non-neoplastic kidney lesions. The incidence of renal tubule nephrosis was increased in groups of treated male and female rats. In addition, the incidence of papillary mineralization in treated male rats was increased. Nephropathy was increased in all groups of treated female rats. The incidence of hyperplasia of the transitional epithelium lining of the pelvis and overlying

the renal papilla was significantly increased in all treated groups of male and female rats. The incidence of focal suppurative inflammation was increased in treated male rats (NTP, 2010). [The Working Group noted that this was a well-conducted study that complied with GLP, and was carried out in males and females. The Working Group also noted the poor survival of male rats at the highest dose.]

3.2 Co-carcinogenicity studies

In a study on the chemopreventive effects of terpenoids (including β-myrcene) (Russin et al., 1989), groups of female Sprague-Dawley rats (age, 6 weeks) were fed diets containing β-myrcene (purity, 94.3%) at a concentration of 0% (control, n = 31) or 1% (n = 32) for up to 20 weeks. At week 2, the rats were given a single gavage dose of 7,12-dimethylbenz[*a*] anthracene (DMBA) at 65 mg/kg bw. Starting from 5 weeks after treatment with DMBA, the rats were palpated for mammary tumours at weekly intervals until week 20. All tumours were processed for histopathology (more than 95% were mammary carcinomas). There was a total of 81 mammary tumours in the DMBA-only control group (average, 2.6 mammary tumours per rat; mean tumour latency period, 70 days) versus 72 mammary tumours (average, 2.3 mammary tumours per rat; mean tumour latency period, 77 days) in the group treated with DMBA plus β-myrcene). While the number of tumours in the group treated with DMBA plus β-myrcene was lower than in the control group, this effect was not significant when using a χ^2 test adjusted for the total number of days at risk. β-Myrcene did not significantly extend tumour latency (Russin et al., 1989). [The Working Group noted that this was a study of chemoprevention and not a study of carcinogenicity.]

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

No data from exposed humans were available to the Working Group.

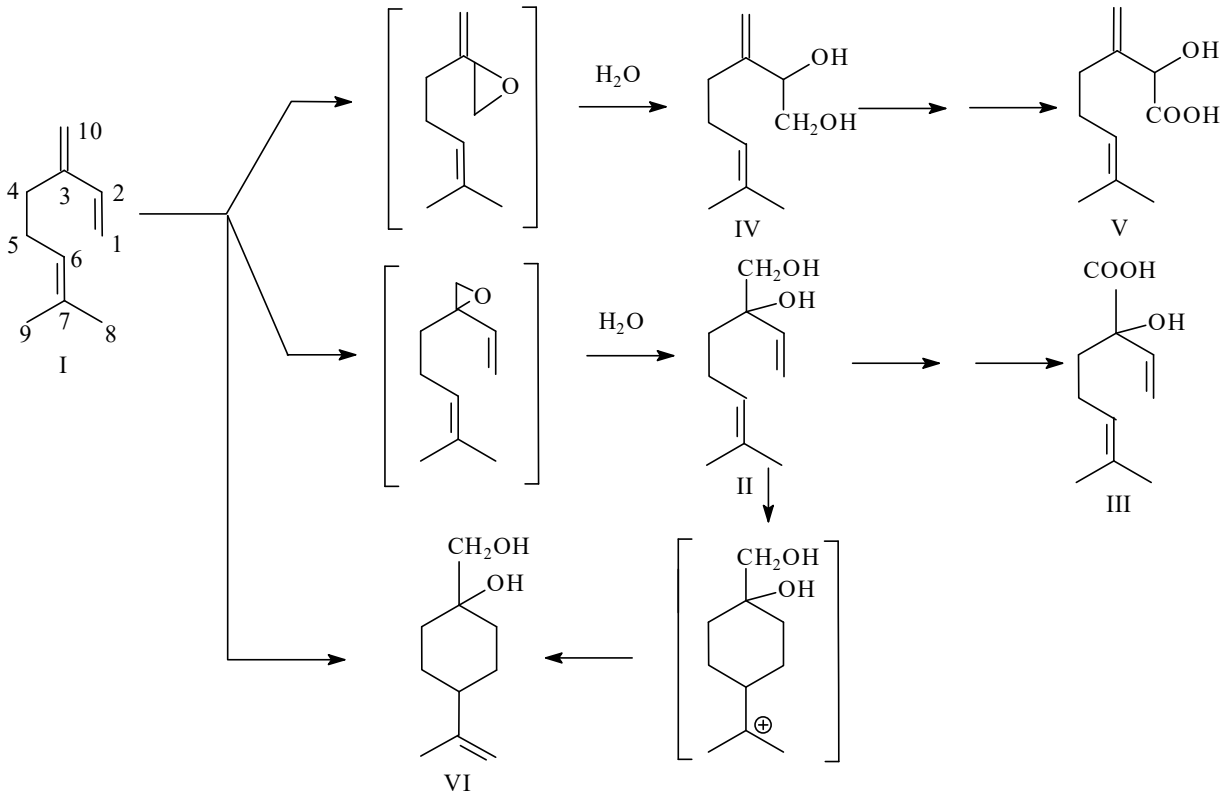
A study in vitro showed that β-myrcene permeates human skin (Schmitt et al., 2009). In a model of human intestinal absorption of xenobiotic compounds in vitro (human colon epithelial cancer cell line/Caco-2 cell monolayer), β-myrcene quickly established an equilibrium state of efflux and uptake by cells under the static conditions of the test system (Heinlein et al., 2014).

4.1.2 Experimental animals

(a) Absorption, distribution, and excretion

Few published data on the absorption, distribution, and excretion of β-myrcene in experimental animals were available to the Working Group. A study in rats indicated ready absorption through intact skin (Valette & Cavier, 1954). In rabbits and rats, β-myrcene is well absorbed after oral administration. Approximately 25% of the total dose (670 mg/kg bw per day for 2 days, by gavage) administered to male Japanese white rabbits was recovered in urine excreted over a period of 3 days after treatment (Ishida et al., 1981). In female rats treated orally with β-myrcene (1000 mg/kg bw, by gavage), blood concentrations as high as 14.1 ± 3.1 μg/mL were detected 60 minutes after treatment (Delgado et al., 1993a). In the same study, the elimination half-life of β-myrcene was 285 minutes, and the parent compound was concentrated in the adipose tissue and in organs including the brain, liver, kidney, and testis.

Fig. 4.1 Characterized metabolites of β-myrcene



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
Source: Madyastha & Srivatsan (1987). Metabolism of β-myrcene in vivo and in vitro: its effects on rat-liver microsomal enzymes, Madyastha KM, Srivatsan V, *Xenobiotica*, 1987, Taylor & Francis, by permission of the publisher (Taylor & Francis Ltd, http://www.tandfonline.com).

Urine was the predominant route of excretion of conjugated myrcene glycol/diol metabolites in rats and rabbits (Ishida et al., 1981). No studies examined the possibility of biliary excretion.

(b) Metabolism

The biotransformation of β-myrcene was studied in rabbits and rats (see Fig. 4.1). In male rabbits treated by gavage with β-myrcene, urinary excretion of the conjugates of two diols (10-hydroxylinalool and 7-methyl-3-methylene-oct-6-ene-1,2-diol) was observed. Their formation involved the corresponding epoxides as intermediates, and subsequent production of two hydroxyl acids (10-carboxylinalool and 2-hydroxy-7-methyl-3-methylene-oct-6-enoic acid) (Ishida et al., 1981; Ishida, 2005). Like in rabbits, male rats treated by gavage with β-myrcene (800 mg/kg bw per day) for 20 days excreted 10-hydroxylinalool, 7-methyl-3-methylene-oct-6-ene-1,2-diol, 1-hydroxymethyl-4-isopropenyl cyclohexanol, 10-carboxylinalool, and 2-hydroxy-7-methyl-3-methylene-oct-6-enoic acid in the urine (Madyastha & Srivatsan, 1987).

A similar pattern of biotransformation of β-myrcene was also observed in vitro with rat liver microsomal fraction (Madyastha & Srivatsan, 1987). The conversion of β-myrcene into 10-hydroxylinalool by rat liver microsomes was inhibited by several nonspecific inhibitors

of cytochrome P450 (CYP) (e.g. metyrapone, carbon monoxide, SK-525A, and *para*-chloromercuric benzoate). This indicated that the apparent oxidation of the β-myrcene carbon–carbon double bond to a 3,10-epoxide intermediate, which after hydrolysis gives rise to the corresponding 3,10-diol, is a CYP-catalysed reaction. Moreover, a higher rate of conversion of β-myrcene into 10-hydroxylinalool was seen using liver microsomal fractions from rats treated with phenobarbital than with liver microsomal fractions from rats that had or had not been treated with 3-methylcholanthrene, indicating that β-myrcene is preferentially metabolized by phenobarbital-inducible CYP forms (e.g. CYP2B) (Madyastha & Srivatsan, 1987).

The main urinary metabolites of orally administered β-myrcene found in the urine of rabbits and rats (after enzymatic hydrolysis of conjugates by treatment of urine samples with β-glucuronidase/arylsulfatase) were 10-hydroxylinalool and 7-methyl-3-methylene-oct-6-ene-1,2-diol (or myrcene-3,10-glyclol and 1,2-glycol, respectively), formed by hydrolysis of the respective 3,10- and 1,2- epoxide intermediates. In both species, the epoxidation of the 3,10 carbon–carbon double bond was apparently favoured over epoxidation of the 1,2 double bond, while epoxidation of the 6,7 double bond was not observed. Further oxidation of β-myrcene primary metabolites (diols) to carboxylic acids and cyclization products was also noted in rabbits and rats (Ishida et al., 1981; Madyastha & Srivatsan, 1987; Ishida, 2005). Formation of a single covalent bond linking carbons 1–6 in the β-myrcene acyclic structure results in ring closure and excretion of 1-hydroxymethyl-4-isopropenyl cyclohexanol (*para*-menth-8-ene-1,7-diol) or uroterpenol (4-menth-1-ene-8,9-diol) as a minor metabolite in the rat and rabbit urine, respectively (Ishida et al., 1981; Madyastha & Srivatsan, 1987).

4.2 Mechanisms of carcinogenesis

4.2.1 Genetic and related effects

The genotoxic potential of β-myrcene has been studied in different assays in vitro and in vivo that gave consistently negative results. Table 4.1 summarizes studies carried out in non-human mammals in vivo, and Table 4.2 summarizes studies in human cells and in various experimental systems in vitro.

(a) Humans

No data from exposed humans were available to the Working Group.

In lymphocytes isolated from nonsmoking donors (one male and one female), β-myrcene (100, 500, or 1000 μg/mL), did not induce chromosome aberrations or sister-chromatid exchange (Kauderer et al., 1991). β-Myrcene did not alter mitotic or proliferation indices.

(b) Experimental systems

(i) Non-human mammals in vivo

No changes in the incidence of metaphase cells with chromosome aberrations were detected in the bone marrow of male and female Wistar rats sampled 24 or 48 hours after oral administration of β-myrcene (0.1, 0.5, or 1.0 g/kg bw). Although not clastogenic, β-myrcene caused a dose-dependent increase in the mitotic index in bone marrow cells, indicating that the dose present in the target tissue was sufficient (Zamith et al., 1993).

No increase in the frequency of micronucleated normochromatic erythrocytes was noted at any dose level in mouse peripheral blood sampled within 24 hours after administration of the final dose in a 13-week study in which male and female B6C3F$_1$ mice were treated with β-myrcene (250–2000 mg/kg bw per day) by gavage (NTP, 2010).

Table 4.1 Genetic and related effects of β-myrcene in non-human mammals in vivo

End-point	Species, strain (sex)	Tissue	Results[a]	Dose (LED or HID)	Route, duration, dosing regimen	Reference
Chromosomal aberrations	Rat, Wistar, (M and F)	Bone marrow	–	1000 mg/kg bw	Gavage, 1×	Zamith et al. (1993)
Micronucleus formation	Mouse, B6C3F$_1$ (M and F)	Peripheral blood	–	1000 mg/kg bw per day	Gavage, 13 weeks	NTP (2010)

[a] –, negative; the level of significance was set at $P < 0.05$ in all cases
bw, body weight; F, female; HID, highest ineffective dose; LED, lowest effective dose; M, male

Table 4.2 Genetic and related effects of β-myrcene in experimental systems in vitro

End-point	Species, tissue, cell line	Results[a]		Concentration (LEC or HIC)	Comments	Reference
		Without metabolic activation	With metabolic activation			
Hprt mutation	Chinese hamster, lung, V79	–	–	1000 µg/mL		Kauderer et al. (1991)
Reverse mutation	*Salmonella typhimurium*, TA97a, TA98, TA100, TA1535	–	–	5000 µg/plate (–S9) 1500 µg/plate (+S9)		Gomes-Carneiro et al. (2005)
Reverse mutation	*Salmonella typhimurium*, TA97, TA98, TA100, TA1535, *Escherichia coli* WP2 uvrA	–	–	10 000 µg/plate		NTP (2010)
Chromosomal aberrations, sister-chromatid exchange	Human, lymphocytes	–	–	1000 µg/mL		Kauderer et al. (1991)
Sister-chromatid exchange	Chinese hamster, lung, V79	–	–	500 µg/mL		Röscheisen et al. (1991)
Sister-chromatid exchange	Rat, hepatocellular carcinoma, HTC cells	±	±	100 µg/mL	Slight, reproducible increase, not concentration-related	Röscheisen et al. (1991)

[a] –, negative; ±, equivocal, variable response in several experiments within an adequate study; the level of significance was set at $P < 0.05$ in all cases
HIC, highest ineffective concentration; LEC, lowest effective concentration; S9, 9000 × *g* supernatant

(ii) Non-human mammalian cells in vitro

β-Myrcene did not increase mutation frequencies at the hypoxanthine-guanine phosphoribosyl transferase (*Hprt*) locus or induce sister-chromatid exchange in hamster V79 cells, in the absence or presence of metabolic activation (Kauderer et al., 1991; Röscheisen et al., 1991). In a metabolically competent rat hepatocellular carcinoma cell line, β-myrcene produced a slight increase in sister-chromatid exchange at 100–250 μg/mL, but with no concentration–response relationship (Röscheisen et al., 1991).

(iii) Non-mammalian systems

In bacterial test systems, β-myrcene was not mutagenic. Two assays conducted by the National Toxicology Program (NTP) did not reveal any mutagenic activity with β-myrcene (doses ranging from 33 up to 10 000 μg/plate) in any of the *Salmonella typhimurium* strains tested (TA97, TA98, TA100, and TA1535) or in *Escherichia coli* (strain WP2 *uvr*ApKM101), either in the presence or in the absence of exogenous metabolic activation (S9 fraction from Aroclor 1254-induced rat or hamster liver) (NTP, 2010). In another study, β-myrcene (10–5000 μg/plate, without metabolic activation; 1–1500 μg/plate, with metabolic activation) gave negative results in four *S. typhimurium* strains (TA100, TA98, TA97a and TA1535) (Gomes-Carneiro et al., 2005).

4.2.2 Oxidative stress

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

No study reported β-myrcene-mediated enhancement of oxidative stress in mammalian cells or tissues. Several experimental studies, however, have provided evidence that β-myrcene has antioxidant activity. In the liver of female Sprague-Dawley rats treated by gavage with β-myrcene at a dose of up to 200 mg/kg bw per day for 30 or 60 days, there was an increase in the levels of reduced glutathione, and increases in the activities of catalase, glutathione peroxidase, and superoxide dismutase, as well as a decline in the formation of thiobarbituric acid reactive substances (lipid peroxidation) (Ciftci et al., 2011a). Moreover, Ciftci et al. (2011a) also demonstrated that concomitant administration of β-myrcene counteracted the enhancement of oxidative stress mediated by 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (2 μg/kg bw per week by gavage) in the rat liver. Another study suggested that oral administration of β-myrcene (7.5 mg/kg bw) in male Wistar rats protected against ethanol-induced gastric ulcers, and increased the activities of glutathione reductase and glutathione peroxidase, while decreasing levels of malondialdehyde in the gastric tissue (Bonamin et al., 2014). A study in C57Bl/J6 mice showed that β-myrcene (200 mg/kg bw per day, intraperitoneal dose), given for 10 days after transient surgical occlusion of the carotid artery, attenuated the cerebral ischaemia and reperfusion-mediated enhancement of oxidative stress in brain tissue (increase in the formation of thiobarbituric acid reactive substances, and decrease in glutathione levels and activities of glutathione peroxidase and superoxide dismutase), and also attenuated the increase in incidence of histopathological damage and apoptosis induced by ischaemia (Ciftci et al., 2014).

4.2.3 Inflammation and immunosuppression

(a) Humans

No data in exposed humans were available to the Working Group.

In a primary culture of human chondrocytes, β-myrcene (25–50 μg/mL) decreased interleukin IL-1β-induced nuclear factor-κB (NF-κB), jun terminal kinase (JNK) and p38 activation, and the expression of inflammatory inducible nitric oxide synthase (*iNOS*) and catabolic genes

(matrix metalloprotease *MMP1* and *MMP13*), while increasing the expression of anti-catabolic genes (tissue inhibitor of metalloproteases *TIMP1* and *TIMP3*) (Rufino et al., 2015).

(b) Experimental systems

β-Myrcene and nine other monoterpenoid compounds found in essential oils were tested in the rat popliteal lymph node assay (PLNA), a screening test for allergic and autoimmune-like reactions in humans (Friedrich et al., 2007). In the primary (direct) PLNA, β-myrcene induced a clear (positive) immuno-stimulatory response due to its irritant properties, but it gave a negative result and proved not to be a sensitizing agent in the secondary PLNA (a T-cell priming test) (Friedrich et al., 2007). In female Wistar rats, oral administration of β-myrcene (200 mg/kg bw per day, for 30 or 60 days) reduced (flow cytometric analysis) the percentage of $CD8^+$ cells in the blood, while increasing the percentages of $CD3^+$, $CD4^+$, $CD161^+$, CD45RA, $CD4^+CD25^+$, and the populations of total lymphocyte cells (Ciftci et al., 2011b). In the same study, β-myrcene (200 mg/kg bw per day) counteracted the immunosuppressive effects induced by 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (2 µg/kg bw per week by gavage) when administered concomitantly (Ciftci et al., 2011b).

In BALB/c mice, β-myrcene (0.8 mg/dose, injected intraperitoneally) mixed with ovalbumin or Ag85B (a protective antigen for tuberculosis) enhanced the specific antibody response to immunization with ovalbumin or Ag85B. Administration of β-myrcene alone did not enhance levels of T-helper Th1 and Th2 cytokines, nor did it cause any increase in immunoglobulin IgG subtypes (Uyeda et al., 2016).

4.2.4 Other mechanisms

In human hepatoma HepG2 cells, β-myrcene (7.4 µM) did not alter the process of repair of *tert*-butyl hydroperoxide-induced DNA damage, as shown by data from the alkaline comet assay, performed every 30 minutes for 2.5 hours (Mitić-Culafić et al., 2009).

β-Myrcene (100, 500, or 1000 mg/kg bw, by gavage) caused a dose-dependent increase in the mitotic index in Wistar rat bone marrow cells (Zamith et al., 1993).

In cell culture, β-myrcene (1 mM and 3 mM) was more potent than limonene in inhibiting protein isoprenylation, an effect positively correlated with inhibition of cell proliferation (Crowell et al., 1994). Nonetheless, in a model of DMBA-induced mammary carcinogenesis, β-myrcene and other acyclic monoterpenes (in contrast to limonene-like monocyclic monoterpenes) did not extend mammary tumour latency and did not reduce the total number of mammary tumours in Sprague-Dawley rats fed a diet containing β-myrcene (1%) when compared with controls (Russin et al., 1989).

4.3 Data relevant to comparisons across agents and end-points

For the results of high-throughput screening assays of the Toxicity Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes of the government of the USA, see Section 4.3 of the *Monograph* on 1-*tert*-butoxypropan-2-ol in the present volume.

4.4 Susceptibility to cancer

No data were available to the Working Group.

4.5 Other adverse effects

4.5.1 Humans

No data were available to the Working Group.

4.5.2 Experimental systems

In male and female Wistar rats treated orally with β-myrcene for 91 days, the highest dose (500 mg/kg bw, by gavage) induced small (approximately 10%) increases in liver and kidney weights (Paumgartten et al., 1998). In male and female F344/N rats, a 14-week (GLP-compliant) study of toxicity with β-myrcene found dose-related increases in liver and kidney weights. Renal tubule necrosis, the severity of which increased in a dose-dependent manner, was augmented in all treated groups compared with control groups. The incidence of nephrosis (restricted to the outer stripe of the outer medulla) was higher in rats treated with doses of > 1000 mg/kg bw (NTP, 2010). In $B6C3F_1$ mice, β-myrcene (up to 1000 mg/kg bw per day, by gavage, for 14 weeks) increased liver weight in males (up to 17%) and females (up to 21%), and also increased kidney weight in females (18%) (NTP, 2010).

IARC has established seven criteria that need to be fully met in order to conclude that an agent induces tumours of the kidney by a α_{2u}-globulin-associated response (IARC, 1999). Three criteria were met for the present agent, specifically: (1) induction of the characteristic sequence of histopathological changes associated with α_{2u}-globulin accumulation; (2) identification of the accumulating protein as α_{2u}-globulin (Cesta et al., 2013); and (3) absence of genotoxicity (see Section 4.2.1). However, four of these criteria were not met for β-myrcene (NTP, 2010), specifically: (1) male rat specificity for nephropathy and renal tumorigenicity (tumours and nephropathy were induced by β-myrcene in female rats); (2) reversible binding of the chemical or metabolite to α_{2u}-globulin (no data were available on the binding of β-myrcene or its metabolites to α_{2u}-globulin); (3) induction of sustained increase in cell proliferation in the renal cortex was not demonstrated; and (4) similarities in dose–response relationships of the tumour outcome with histopathological end-points associated with α_{2u}-globulin nephropathy (hyaline droplets were not seen at the highest dose, and α_{2u}-globulin protein was not quantified).

5. Summary of Data Reported

5.1 Exposure data

β-Myrcene is found in a wide variety of plants. It is not commonly extracted from natural materials, but is generally manufactured via the pyrolysis of β-pinene. The main use of β-myrcene is as a raw material in the manufacture of other chemicals such as menthol, although it is also used as a flavouring material in foods and cosmetics. Reliable information about global production volume was not available, but less than 100 tonnes were reported to be manufactured or imported into the European Union. The general population is mainly exposed by ingestion of foods and medicinal products containing β-myrcene, either from plant ingredients or manufactured additives. The estimated human intake from food additives is 3–138 μg/kg bw per day. People may also be exposed by inhalation of air in forests and other natural environments containing plants that emit β-myrcene, and from inhalation of and dermal contact with consumer products containing β-myrcene. Workers may be exposed to β-myrcene by inhalation and dermal contact.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

In one well-conducted study that complied with good laboratory practice (GLP) in male and female mice treated by gavage, β-myrcene caused a significant increase, with a significant

positive trend, in the incidence of hepatocellular adenoma, hepatocellular carcinoma, hepatocellular adenoma or carcinoma (combined), hepatoblastoma, and the combination of these three tumours in males; and a significant increase in the incidence of hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma or carcinoma (combined) in females.

In a well-conducted GLP study in male and female rats treated by gavage, β-myrcene caused a significant increase, and a significant positive trend, in the incidence of renal tubule adenoma, and renal tubule adenoma or carcinoma (combined) in males; and rare renal tubule adenomas were also observed in treated females.

A study in rats given β-myrcene in combination with 7,12-dimethylbenz[*a*]anthracene gave negative results.

5.4 Mechanistic and other relevant data

In rabbits and rats, β-myrcene is well absorbed after oral administration, being converted into conjugated metabolites found in the urine. The parent compound undergoes oxidation by cytochrome P450 2B to 1,2- and 3,10-epoxide intermediates, with subsequent hydrolysis to diols.

No data on the absorption, metabolism, distribution, or excretion of β-myrcene in humans were available.

With respect to the key characteristics of carcinogens, it was consistently demonstrated in bacterial and mammalian assays, including tests in vivo and in vitro, that β-myrcene is not genotoxic.

Few other data on the key characteristics were available. Experimental studies demonstrated antioxidant activity.

In a long-term bioassay in rodents, the primary toxic effects were seen in the kidney. Four of the seven criteria established by IARC for concluding that an agent induces tumours of the kidney by an α_{2u}-globulin-associated response have not been met.

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of β-myrcene.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of β-myrcene.

6.3 Overall evaluation

β-Myrcene is *possibly carcinogenic to humans (Group 2B).*

References

Aberl A, Coelhan M (2012). Determination of volatile compounds in different hop varieties by headspace-trap GC/MS–in comparison with conventional hop essential oil analysis. *J Agric Food Chem*, 60(11):2785–92. doi:10.1021/jf205002p PMID:22352993

Adams TB, Gavin CL, McGowen MM, Waddell WJ, Cohen SM, Feron VJ, et al. (2011). The FEMA GRAS assessment of aliphatic and aromatic terpene hydrocarbons used as flavor ingredients. *Food Chem Toxicol*, 49(10):2471–94. doi:10.1016/j.fct.2011.06.011 PMID:21726592

Adjou ES, Kouton S, Dahouenon-Ahoussi E, Soumanou MM, Sohounhloue DC (2013). Effect of essential oil from fresh leaves of *Ocimum gratissimum* L. on mycoflora during storage of peanuts in Benin. *Mycotoxin Res*, 29(1):29–38. doi:10.1007/s12550-012-0150-y PMID:23334722

Aghaei Y, Hossein Mirjalili M, Nazeri V (2013). Chemical diversity among the essential oils of wild populations of *Stachys lavandulifolia* VAHL (Lamiaceae) from Iran. *Chem Biodivers*, 10(2):262–73. doi:10.1002/cbdv.201200194 PMID:23418173

Andrea V, Nadia N, Teresa RM, Andrea A (2003). Analysis of some Italian lemon liquors (limoncello). *J Agric Food Chem*, 51(17):4978–83. doi:10.1021/jf030083d PMID:12903956

Aprotosoaie AC, Spac A, Cioancă O, Trifan A, Miron A, Hăncianu M (2013). The chemical composition of essential oils isolated from sweet fennel fruits available as herbal tea products. *Rev Med Chir Soc Med Nat Iasi*, 117(3):819–24. PMID:24502057

Asbaghian S, Shafaghat A, Zarea K, Kasimov F, Salimi F (2011). Comparison of volatile constituents, and antioxidant and antibacterial activities of the essential oils of *Thymus caucasicus*, *T. kotschyanus* and *T. vulgaris*. *Nat Prod Commun*, 6(1):137–40. PMID:21366065

Baik JS, Kim SS, Lee JA, Oh TH, Kim JY, Lee NH, et al. (2008). Chemical composition and biological activities of essential oils extracted from Korean endemic citrus species. *J Microbiol Biotechnol*, 18(1):74–9. PMID:18239420

Behr A, Johnen L (2009). Myrcene as a natural base chemical in sustainable chemistry: a critical review. *ChemSusChem*, 2(12):1072–95. doi:10.1002/cssc.200900186 PMID:20013989

Bonamin F, Moraes TM, Dos Santos RC, Kushima H, Faria FM, Silva MA, et al. (2014). The effect of a minor constituent of essential oil from *Citrus aurantium*: the role of β-myrcene in preventing peptic ulcer disease. *Chem Biol Interact*, 212:11–9. doi:10.1016/j.cbi.2014.01.009 PMID:24480520

Burdock GA (2010). Myrcene. Fenaroli's handbook of flavor ingredients. 6th ed. Boca Raton (FL), USA: CRC Press; pp. 1447–8. doi:10.1201/NOE0849309465

Calín-Sánchez A, Martínez JJ, Vázquez-Araújo L, Burló F, Melgarejo P, Carbonell-Barrachina AA (2011). Volatile composition and sensory quality of Spanish pomegranates (*Punica granatum* L.). *J Sci Food Agric*, 91(3):586–92. doi:10.1002/jsfa.4230 PMID:21218496

Cesta MF, Hard GC, Boyce JT, Ryan MJ, Chan PC, Sills RC (2013). Complex histopathologic response in rat kidney to oral β-myrcene: an unusual dose-related nephrosis and low-dose alpha2u-globulin nephropathy. *Toxicol Pathol*, 41(8):1068–77. doi:10.1177/0192623313482057 PMID:23531794

Ceva-Antunes PM, Bizzo HR, Alves SM, Antunes OA (2003). Analysis of volatile compounds of taperebá (*Spondias mombin* L.) and cajá (*Spondias mombin* L.) by simultaneous distillation and extraction (SDE) and solid phase microextraction (SPME). *J Agric Food Chem*, 51(5):1387–92. doi:10.1021/jf025873m PMID:12590486

Chemical Sources International (2017). Myrcene [123-35-3]. Chem Sources-Online [online database]. Available from: http://www.chemsources.com/chemonline.html.

Choi HS (2005). Characteristic odor components of kumquat (*Fortunella japonica* Swingle) peel oil. *J Agric Food Chem*, 53(5):1642–7. doi:10.1021/jf040324x PMID:15740053

Choi HS, Sawamura M (2000). Composition of the essential oil of *Citrus tamurana* Hort. ex Tanaka (Hyuganatsu). *J Agric Food Chem*, 48(10):4868–73. doi:10.1021/jf000651e PMID:11052747

Ciftci O, Ozdemir I, Tanyildizi S, Yildiz S, Oguzturk H (2011a). Antioxidative effects of curcumin, β-myrcene and 1,8-cineole against 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced oxidative stress in rats liver. *Toxicol Ind Health*, 27(5):447–53. doi:10.1177/0748233710388452 PMID:21245202

Ciftci O, Oztanir MN, Cetin A (2014). Neuroprotective effects of β-myrcene following global cerebral ischemia/reperfusion-mediated oxidative and neuronal damage in a C57BL/J6 mouse. *Neurochem Res*, 39(9):1717–23. doi:10.1007/s11064-014-1365-4 PMID:24972849

Ciftci O, Tanyildizi S, Godekmerdan A (2011b). Curcumin, myrecen and cineol modulate the percentage of lymphocyte subsets altered by 2,3,7, 8-tetracholorodibenzo-p-dioxins (TCDD) in rats. *Hum Exp Toxicol*, 30(12):1986–94. doi:10.1177/0960327111404909 PMID:21450899

Clement B, Riba ML, Leduc R, Haziza M, Torres L (1990). Concentration of monoterpenes in a maple forest in Quebec. *Environment Part A*, 24(9):2513–6. doi:10.1016/0960-1686(90)90342-K

Crowell PL, Ren Z, Lin S, Vedejs E, Gould MN (1994). Structure-activity relationships among monoterpene inhibitors of protein isoprenylation and cell proliferation. *Biochem Pharmacol*, 47(8):1405–15. doi:10.1016/0006-2952(94)90341-7 PMID:8185648

Daferera D, Pappas C, Tarantilis PA, Polissiou M (2002). Quantitative analysis of α-pinene and β-myrcene in mastic gum oil using FT-Raman spectroscopy. *Food Chem*, 77(4):511–5. doi:10.1016/S0308-8146(01)00382-X

Delgado IF, Carvalho RR, Nogueira AC, Mattos AP, Figueiredo LH, Oliveira SH, et al. (1993a). Study on embryo-foetotoxicity of beta-myrcene in the rat. *Food Chem Toxicol*, 31(1):31–5. doi:10.1016/0278-6915(93)90175-X PMID:8444385

Donati M, Mondin A, Chen Z, Miranda FM, do Nascimento BB Jr, Schirato G, et al. (2015). Radical scavenging and antimicrobial activities of *Croton zehntneri*, *Pterodon emarginatus* and *Schinopsis brasiliensis* essential oils and their major constituents: estragole, trans-anethole, β-caryophyllene and myrcene. *Nat Prod Res*, 29(10):939–46. doi:10.1080/14786419.2014.964709 PMID:25280163

ECHA (2017a). 7-Methyl-3-methyleneocta-1,6-diene. Substance information. Helsinki, Finland: European Chemicals Agency. Available from: https://echa.europa.eu/substance-information/-/substanceinfo/100.004.203.

ECHA (2017b). 7-Methyl-3-methyleneocta-1,6-diene. Consumer uses. Helsinki, Finland: European Chemicals Agency. Available from: https://echa.europa.eu/registration-dossier/-/registered-dossier/14795/3/1/6.

Eggersdorfer M (2012). Terpenes. In: Ullmann's encyclopedia of industrial chemistry. Weinheim, Germany: Wiley-VCH. 36:29–45.

Estévez M, Ventanas S, Ramírez R, Cava R (2004). Analysis of volatiles in porcine liver pâtés with added sage and rosemary essential oils by using SPME-GC-MS. *J Agric Food Chem*, 52(16):5168–74. doi:10.1021/jf0496705 PMID:15291492

European Commission (2012). Commission implementing regulation (EU) No. 872/2012 of 1 October 2012 adopting the list of flavouring substances provided for by Regulation (EC) No. 2232/96 of the European Parliament and of the Council, introducing it in Annex I to Regulation (EC) No 1334/2008 of the European Parliament and of the Council and repealing Commission Regulation (EC) No 1565/2000 and Commission Decision 1999/217/EC. *Off J Eur Union L*, 267(1):1161.

Flamini G, Bader A, Cioni PL, Katbeh-Bader A, Morelli I (2004). Composition of the essential oil of leaves, galls, and ripe and unripe fruits of Jordanian *Pistacia palaestina* Boiss. *J Agric Food Chem*, 52(3):572–6. doi:10.1021/jf034773t PMID:14759150

Flamini G, Cosimi E, Cioni PL, Molfetta I, Braca A (2014). Essential-oil composition of *Daucus carota* ssp. major (Pastinocello Carrot) and nine different commercial varieties of *Daucus carota* ssp. sativus fruits. *Chem Biodivers*, 11(7):1022–33. doi:10.1002/cbdv.201300390 PMID:25044588

Friedrich K, Delgado IF, Santos LM, Paumgartten FJ (2007). Assessment of sensitization potential of monoterpenes using the rat popliteal lymph node assay. *Food Chem Toxicol*, 45(8):1516–22. doi:10.1016/j.fct.2007.02.011 PMID:17383062

Gbenou JD, Ahounou JF, Akakpo HB, Laleye A, Yayi E, Gbaguidi F, et al. (2013). Phytochemical composition of *Cymbopogon citratus* and *Eucalyptus citriodora* essential oils and their anti-inflammatory and analgesic properties on Wistar rats. *Mol Biol Rep*, 40(2):1127–34. doi:10.1007/s11033-012-2155-1 PMID:23065287

Gherman C, Culea M, Cozar O (2000). Comparative analysis of some active principles of herb plants by GC/MS. *Talanta*, 53(1):253–62. doi:10.1016/S0039-9140(00)00458-6 PMID:18968110

Giuseppe Z, Manuela G, Marta B, Vincenzo G (2005). Application of artificial neural network on mono- and sesquiterpenes compounds determined by headspace solid-phase microextraction-gas chromatography-mass spectrometry for the Piedmont ricotta cheese traceability. *J Chromatogr A*, 1071(1–2):247–53. doi:10.1016/j.chroma.2004.11.083 PMID:15865200

Gomes-Carneiro MR, Viana ME, Felzenszwalb I, Paumgartten FJ (2005). Evaluation of beta-myrcene, alpha-terpinene and (+)- and (-)-alpha-pinene in the *Salmonella*/microsome assay. *Food Chem Toxicol*, 43(2):247–52. doi:10.1016/j.fct.2004.09.011 PMID:15621337

Hanène M, Ameur E, Larbi KM, Piras A, Porcedda S, Falconieri D, et al. (2012). Chemical composition of the essential oils of the berries of *Juniperus oxycedrus* L. ssp. rufescens (L. K.) and *Juniperus oxycedrus* L. ssp. macrocarpa (S. & m.) Ball. and their antioxidant activities. *Nat Prod Res*, 26(9):810–20. doi:10.1080/14786419.2011.558014 PMID:21999482

Heinlein A, Metzger M, Walles H, Buettner A (2014). Transport of hop aroma compounds across Caco-2 monolayers. *Food Funct*, 5(11):2719–30. doi:10.1039/C3FO60675A PMID:24977259

Höferl M, Stoilova I, Schmidt E, Wanner J, Jirovetz L, Trifonova D, et al. (2014). Chemical composition and antioxidant properties of juniper berry (*Juniperus communis* L.) essential oil. Action of the essential oil on the antioxidant protection of *Saccharomyces cerevisiae* model organism. *Antioxidants*, 3(1):81–98. doi:10.3390/antiox3010081 PMID:26784665

Household Products Database (2017). Myrcene. Bethesda (MD), USA: United States National Library of Medicine. Available from: https://householdproducts.nlm.nih.gov/cgi-bin/household/brands?tbl=chem&id=4051&query=myrcene&searchas=TblChemicals, accessed 13 July 2018.

HSDB (2012). Myrcene. Hazardous Substances Data Bank. Bethesda (MD), USA: United States National Library of Medicine. Available from: https://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm.

IARC (1999). Consensus report. In: Capen CC, Dybing E, Rice JM, Wilbourn JD, editors. Species differences in thyroid, kidney and urinary bladder carcinogenesis. IARC Scientific Publication No. 147; pp. 1–14. Available from: http://publications.iarc.fr/302.

ILS (1997). β-Myrcene [123-35-3]. Review of toxicological literature. Research Triangle Park (NC), USA: Integrated Laboratory Systems.

Ishida T (2005). Biotransformation of terpenoids by mammals, microorganisms, and plant-cultured cells. *Chem Biodivers*, 2(5):569–90. doi:10.1002/cbdv.200590038 PMID:17192005

Ishida T, Asakawa Y, Takemoto T, Aratani T (1981). Terpenoids biotransformation in mammals III: biotransformation of alpha-pinene, beta-pinene, pinane, 3-carene, carane, myrcene, and p-cymene in rabbits. *J Pharm Sci*, 70(4):406–15. doi:10.1002/jps.2600700417 PMID:7229954

ISO (1998). International Standard ISO 11024-1. Essential oils – general guidance on chromatographic profiles – part 1: preparation of chromatographic profiles for presentation in standards. Geneva, Switzerland: International Organization for Standardization.

ISO (2017). ISO standards. Geneva, Switzerland: International Organization for Standardization. Available from: https://www.iso.org/standards.html.

Janson R (1992). Monoterpene concentrations in and above a forest of Scots pine. *J Atmos Chem*, 14(1–4):385–94. doi:10.1007/BF00115246

Ji W, Bi K, Chen Q, Jiang L, Liang K, Li Q (2011). Simultaneous determination of eight active components in *Houttuynia cordata* injection and its quality control in productive process. *J Sep Sci*, 34(21):3053–60. doi:10.1002/jssc.201100457 PMID:21972174

Jiang L, Kubota K (2004). Differences in the volatile components and their odor characteristics of green and ripe fruits and dried pericarp of Japanese pepper (*Xanthoxylum piperitum* DC.). *J Agric Food Chem*, 52(13):4197–203. doi:10.1021/jf030663aPMID:15212469

Jirovetz L, Buchbauer G, Fleischhacker W, Ngassoum MB (1999). Analysis of leaf volatiles of *Zanthoxylum gillettii* used in folk medicine of Cameroon. *Planta Med*, 65(2):181–3. doi:10.1055/s-2006-960463 PMID:17260255

Joshi R, Sharma P, Sharma V, Prasad R, Sud RK, Gulati A (2013). Analysis of the essential oil of large cardamom (*Amomum subulatum* Roxb.) growing in different agro-climatic zones of Himachal Pradesh, India. *J Sci Food Agric*, 93(6):1303–9. doi:10.1002/jsfa.5886 PMID:23023817

Judzentiene A, Tomi F, Casanova J (2009). Analysis of essential oils of *Artemisia absinthium* L. from Lithuania by CC, GC(RI), GC-MS and ^{13}C NMR. *Nat Prod Commun*, 4(8):1113–8. PMID:19768995

Kauderer B, Zamith H, Paumgartten FJ, Speit G, Holden HE (1991). Evaluation of the mutagenicity of beta-myrcene in mammalian cells in vitro. *Environ Mol Mutagen*, 18(1):28–34. doi:10.1002/em.2850180106 PMID:1864266

Kishimoto T, Wanikawa A, Kagami N, Kawatsura K (2005). Analysis of hop-derived terpenoids in beer and evaluation of their behavior using the stir bar-sorptive extraction method with GC-MS. *J Agric Food Chem*, 53(12):4701–7. doi:10.1021/jf050072f PMID:15941303

Kjeldsen F, Christensen LP, Edelenbos M (2003). Changes in volatile compounds of carrots (*Daucus carota* L.) during refrigerated and frozen storage. *J Agric Food Chem*, 51(18):5400–7. doi:10.1021/jf030212q PMID:12926889

Koutsoudaki C, Krsek M, Rodger A (2005). Chemical composition and antibacterial activity of the essential oil and the gum of *Pistacia lentiscus* Var. chia. *J Agric Food Chem*, 53(20):7681–5. doi:10.1021/jf050639s PMID:16190616

Kurobayashi Y, Kouno E, Fujita A, Morimitsu Y, Kubota K (2006). Potent odorants characterize the aroma quality of leaves and stalks in raw and boiled celery. *Biosci Biotechnol Biochem*, 70(4):958–65. doi:10.1271/bbb.70.958 PMID:16636464

Kwon KD, Jo WK, Lim HJ, Jeong WS (2007). Characterization of emissions composition for selected household products available in Korea. *J Hazard Mater*, 148(1–2):192–8. doi:10.1016/j.jhazmat.2007.02.025 PMID:17376591

Lachenmeier K, Musshoff F, Madea B, Lachenmeier DW (2006). Application of experimental design to optimise solid-phase microextraction of orange juice flavour. *Electron J Environ Agric Food Chem*, 5:1380–8.

Lakusić D, Ristić M, Slavkovska V, Lakusić B, Lakusić B (2013). Seasonal variations in the composition of the essential oils of rosemary (*Rosmarinus officinalis*, Lamiaceae). *Nat Prod Commun*, 8(1):131–4. PMID:23472478

Lan Phi NT, Nishiyama C, Choi HS, Sawamura M (2006). Evaluation of characteristic aroma compounds of *Citrus natsudaidai* Hayata (Natsudaidai) cold-pressed peel oil. *Biosci Biotechnol Biochem*, 70(8):1832–8. doi:10.1271/bbb.50705 PMID:16926494

Liu Q, Li D, Wang W, Wang D, Meng X, Wang Y (2016). Chemical composition and antioxidant activity of essential oils and methanol extracts of different parts from *Juniperus rigida* Siebold & Zucc. *Chem Biodivers*, 13(9):1240–50. doi:10.1002/cbdv.201600048 PMID:27448278

Lu H, Wu X, Liang Y, Zhang J (2006). Variation in chemical composition and antibacterial activities of essential oils from two species of *Houttuynia* THUNB. *Chem Pharm Bull (Tokyo)*, 54(7):936–40. doi:10.1248/cpb.54.936 PMID:16819207

Lukas B, Schmiderer C, Novak J (2015). Essential oil diversity of European *Origanum vulgare* L. (Lamiaceae). *Phytochemistry*, 119:32–40. doi:10.1016/j.phytochem.2015.09.008 PMID:26454793

Madyastha KM, Srivatsan V (1987). Metabolism of beta-myrcene in vivo and in vitro: its effects on rat-liver microsomal enzymes. *Xenobiotica*, 17(5):539–49. doi:10.3109/00498258709043961 PMID:3604259

Magiatis P, Melliou E, Skaltsounis AL, Chinou IB, Mitaku S (1999). Chemical composition and antimicrobial activity of the essential oils of *Pistacia lentiscus* var. chia. *Planta Med*, 65(8):749–52. doi:10.1055/s-2006-960856 PMID:10630120

Marongiu B, Piras A, Porcedda S (2004). Comparative analysis of the oil and supercritical CO_2 extract of Elettaria cardamomum (L.) Maton. *J Agric Food Chem*, 52(20):6278–82. doi:10.1021/jf034819i PMID:15453700

Masoumi-Ardakani Y, Mandegary A, Esmaeilpour K, Najafipour H, Sharififar F, Pakravanan M, et al. (2016). Chemical composition, anticonvulsant activity, and toxicity of essential oil and methanolic extract of *Elettaria cardamomum*. *Planta Med*, 82(17):1482–6. doi:10.1055/s-0042-106971 PMID:27433883

Merck Index (2013). The Merck index: an encyclopedia of chemicals, drugs, and biologicals. Whitehouse Station (NJ), USA: Merck & Co., Inc.

Messaoud C, Chograni H, Boussaid M (2012). Chemical composition and antioxidant activities of essential oils and methanol extracts of three wild *Lavandula* L. species. *Nat Prod Res*, 26(21):1976–84. doi:10.1080/14786419.2011.635343 PMID:22117129

Mitić-Culafić D, Zegura B, Nikolić B, Vuković-Gacić B, Knezević-Vukcević J, Filipic M (2009). Protective effect of linalool, myrcene and eucalyptol against t-butyl hydroperoxide induced genotoxicity in bacteria and cultured human cells. *Food Chem Toxicol*, 47(1):260–6. doi:10.1016/j.fct.2008.11.015 PMID:19049815

Miyazaki T, Plotto A, Baldwin EA, Reyes-De-Corcuera JI, Gmitter FG Jr (2012). Aroma characterization of tangerine hybrids by gas-chromatography-olfactometry and sensory evaluation. *J Sci Food Agric*, 92(4):727–35. doi:10.1002/jsfa.4663 PMID:22413143

Miyazawa M, Nakahashi H, Usami A, Matsuda N (2016). Chemical composition, aroma evaluation, and inhibitory activity towards acetylcholinesterase of essential oils from *Gynura bicolor* DC. *J Nat Med*, 70(2):282–9. doi:10.1007/s11418-015-0961-1 PMID:26758617

Mohadjerani M, Hosseinzadeh R, Hosseini M (2016). Chemical composition and antibacterial properties of essential oil and fatty acids of different parts of *Ligularia persica* Boiss. *Avicenna J Phytomed*, 6(3):357–65. PMID:27462560

Mukazayire MJ, Tomani JC, Stévigny C, Chalchat JC, Conforti F, Menichini F, et al. (2011). Essential oils of four Rwandese hepatoprotective herbs: gas chromatography-mass spectrometry analysis and antioxidant activities. *Food Chem*, 129(3):753–60. doi:10.1016/j.foodchem.2011.05.016 PMID:25212295

Munafo JP Jr, Didzbalis J, Schnell RJ, Steinhaus M (2016). Insights into the key aroma compounds in mango (*Mangifera indica* L. 'Haden') fruits by stable isotope dilution quantitation and aroma simulation experiments. *J Agric Food Chem*, 64(21):4312–8. doi:10.1021/acs.jafc.6b00822 PMID:27167034

NCBI (2018). Myrcene. Compound summary for CID 31253. PubChem Open Chemistry Database. Bethesda (MD), USA: National Center for Biotechnology Information, United States National Library of Medicine. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/31253, accessed 28 March 2018.

Niebler J, Buettner A (2015). Identification of odorants in frankincense (*Boswellia sacra* Flueck.) by aroma extract dilution analysis and two-dimensional gas chromatography-mass spectrometry/olfactometry. *Phytochemistry*, 109:66–75. doi:10.1016/j.phytochem.2014.10.030 PMID:25468535

Novak J, Zitterl-Eglseer K, Deans SG, Franz CM (2001). Essential oils of different cultivars of *Cannabis sativa* L. and their antimicrobial activity. *Flavour Fragrance J*, 16(4):259–62. doi:10.1002/ffj.993

NTP (2010). NTP technical report on the toxicology and carcinogenesis studies of β-myrcene (CAS No. 123-35-3) in F344/N rats and B6C3F1 mice (gavage studies). *Natl Toxicol Program Tech Rep Ser*, 557(557):1–163. PMID:21415873

Oboh G, Ademosun AO, Odubanjo OV, Akinbola IA (2013). Antioxidative properties and inhibition of key enzymes relevant to type-2 diabetes and hypertension by essential oils from black pepper. *Adv Pharmacol Sci*, 2013:926047. doi:10.1155/2013/926047 PMID:24348547

OECD (2004). The 2004 OECD list of high production volume chemicals. Paris, France: Environment Directorate, Organisation for Economic Co-operation and Development.

Okaru AO, Lachenmeier DW (2017). The food and beverage occurrence of furfuryl alcohol and myrcene - two emerging potential human carcinogens? *Toxics*, 5(1):9. doi:10.3390/toxics5010009 PMID:29051441

Oliveira DR, Leitão GG, Santos SS, Bizzo HR, Lopes D, Alviano CS, et al. (2006). Ethnopharmacological study of two *Lippia* species from Oriximiná, Brazil. *J Ethnopharmacol*, 108(1):103–8. doi:10.1016/j.jep.2006.04.018 PMID:16784826

Orav A, Sepp J, Kailas T, Müürisepp M, Arak E, Raal A (2010). Composition of essential oil of aerial parts of *Chamomilla suaveolens* from Estonia. *Nat Prod Commun*, 5(1):133–6. PMID:20184038

Paaver U, Orav A, Arak E, Mäeorg U, Raal A (2008). Phytochemical analysis of the essential oil of *Thymus serpyllum* L. growing wild in Estonia. *Nat Prod Res*, 22(2):108–15. doi:10.1080/14786410601035118 PMID:18075894

Palá-Paúl J, Pérez-Alonso MJ, Velasco-Negueruela A, Palá-Paúl R, Sanz J, Conejero F (2001). Seasonal variation in chemical constituents of *Santolina rosmarinifolia* L. ssp. rosmarinifolia. *Biochem Syst Ecol*, 29(7):663–72. doi:10.1016/S0305-1978(01)00032-1 PMID:11399354

Paumgartten FJ, De-Carvalho RR, Souza CA, Madi K, Chahoud I (1998). Study of the effects of beta-myrcene on rat fertility and general reproductive performance. *Braz J Med Biol Res*, 31(7):955–65. doi:10.1590/S0100-879X1998000700012 PMID:9698761

Pellati F, Benvenuti S, Yoshizaki F, Bertelli D, Rossi MC (2005). Headspace solid-phase microextraction-gas chromatography–mass spectrometry analysis of the volatile compounds of Evodia species fruits. *J Chromatogr A*, 1087(1–2):265–73. doi:10.1016/j.chroma.2005.01.060 PMID:16130723

Pino JA, Marbot R, Fuentes V (2003). Characterization of volatiles in bullock's heart (*Annona reticulata* L.) fruit cultivars from Cuba. *J Agric Food Chem*, 51(13):3836–9. doi:10.1021/jf020733y PMID:12797752

Pinto ZT, Sánchez FF, dos Santos AR, Amaral AC, Ferreira JL, Escalona-Arranz JC, et al. (2015). Chemical composition and insecticidal activity of *Cymbopogon citratus* essential oil from Cuba and Brazil against housefly.

Rev Bras Parasitol Vet, 24(1):36–44. doi:10.1590/S1984-29612015006 PMID:25909251

Pirbalouti AG, Mohammadi M (2013). Phytochemical composition of the essential oil of different populations of *Stachys lavandulifolia* Vahl. *Asian Pac J Trop Biomed*, 3(2):123–8. doi:10.1016/S2221-1691(13)60036-2 PMID:23593591

Pronk MEJ, Bend JR (2006). Aliphatic and alicyclic hydrocarbons. Safety evaluation of certain food additives. Prepared by the sixty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Food Additives Series: 54. Geneva, Switzerland: World Health Organization; pp. 235–89.

Qiao Y, Xie BJ, Zhang Y, Zhang Y, Fan G, Yao XL, et al. (2008). Characterization of aroma active compounds in fruit juice and peel oil of Jinchen sweet orange fruit (*Citrus sinensis* (L.) Osbeck) by GC-MS and GC-O. *Molecules*, 13(6):1333–44. doi:10.3390/molecules13061333 PMID:18596659

Raal A, Paaver U, Arak E, Orav A (2004). Content and composition of the essential oil of *Thymus serpyllum* L. growing wild in Estonia. *Medicina (Kaunas)*, 40(8):795–800. PMID:15300002

Rajendran MP, Pallaiyan BB, Selvaraj N (2014). Chemical composition, antibacterial and antioxidant profile of essential oil from *Murraya koenigii* (L.) leaves. *Avicenna J Phytomed*, 4(3):200–14. PMID:25050318

Rasooli I, Mirmostafa SA (2003). Bacterial susceptibility to and chemical composition of essential oils from *Thymus kotschyanus* and *Thymus persicus*. *J Agric Food Chem*, 51(8):2200–5. doi:10.1021/jf0261755 PMID:12670156

Röscheisen C, Zamith H, Paumgartten FJ, Speit G (1991). Influence of beta-myrcene on sister-chromatid exchanges induced by mutagens in V79 and HTC cells. *Mutat Res*, 264(1):43–9. doi:10.1016/0165-7992(91)90044-5 PMID:1908947

Rufino AT, Ribeiro M, Sousa C, Judas F, Salgueiro L, Cavaleiro C, et al. (2015). Evaluation of the anti-inflammatory, anti-catabolic and pro-anabolic effects of E-caryophyllene, myrcene and limonene in a cell model of osteoarthritis. *Eur J Pharmacol*, 750:141–50. doi:10.1016/j.ejphar.2015.01.018 PMID:25622554

Russin WA, Hoesly JD, Elson CE, Tanner MA, Gould MN (1989). Inhibition of rat mammary carcinogenesis by monoterpenoids. *Carcinogenesis*, 10(11):2161–4. doi:10.1093/carcin/10.11.2161 PMID:2509095

Sáez F (2001). Volatile oil variability in Thymus serpylloides ssp. gadorensis growing wild in Southeastern Spain. *Biochem Syst Ecol*, 29(2):189–98. doi:10.1016/S0305-1978(00)00040-5 PMID:11106847

Salanta LC, Tofana M, Socaci S, Mudura E, Pop C, Pop A, et al. (2016). Determination of volatiles in hops from Romania by solid phase fiber microextraction and gas chromatography-mass spectrometry. *Anal Lett*, 49(4):477–87. doi:10.1080/00032719.2015.1075129

Schmidt C, Biendl M (2016). Headspace Trap GC-MS analysis of hop aroma compounds in beer. *Brewing Sci*, 69:9–15.

Schmitt S, Schaefer UF, Doebler L, Reichling J (2009). Cooperative interaction of monoterpenes and phenylpropanoids on the in vitro human skin permeation of complex composed essential oils. *Planta Med*, 75(13):1381–5. doi:10.1055/s-0029-1185744 PMID:19507114

Shah SM, Ullah F, Shah SM, Zahoor M, Sadiq A (2012). Analysis of chemical constituents and antinociceptive potential of essential oil of *Teucrium Stocksianum* bioss collected from the North West of Pakistan. *BMC Complement Altern Med*, 12(1):244. doi:10.1186/1472-6882-12-244 PMID:23217213

Shao Q, Liu H, Zhang A, Wan Y, Hu R, Li M (2014). Analysis of volatile components extracted from the peels of four different Chinese pomelos using TDS-GC-MS. *J Sci Food Agric*, 94(15):3248–54. doi:10.1002/jsfa.6677 PMID:24683164

Sharifi-Rad J, Sharifi-Rad M, Hoseini-Alfatemi SM, Iriti M, Sharifi-Rad M, Sharifi-Rad M (2015). Composition, cytotoxic and antimicrobial activities of *Satureja intermedia* C.A.Mey essential oil. *Int J Mol Sci*, 16(8):17812–25. doi:10.3390/ijms160817812 PMID:26247936

Soria AC, Sanz J, Villamiel M (2008). Analysis of volatiles in dehydrated carrot samples by solid-phase microextraction followed by GC-MS. *J Sep Sci*, 31(20):3548–55. doi:10.1002/jssc.200800282 PMID:18830960

Stahl-Biskup E, Laakso I (1990). Essential oil polymorphism in Finnish *Thymus* species. *Planta Med*, 56(5):464–8. doi:10.1055/s-2006-961012 PMID:17221449

Tavares AC, Gonçalves MJ, Cruz MT, Cavaleiro C, Lopes MC, Canhoto J, et al. (2010). Essential oils from *Distichoselinum tenuifolium*: chemical composition, cytotoxicity, antifungal and anti-inflammatory properties. *J Ethnopharmacol*, 130(3):593–8. doi:10.1016/j.jep.2010.05.054 PMID:20538054

Trung HD, Thang TD, Ban PH, Hoi TM, Dai DN, Ogunwande IA (2014). Terpene constituents of the leaves of five Vietnamese species of *Clausena* (Rutaceae). *Nat Prod Res*, 28(9):622–30. doi:10.1080/14786419.2014.888555 PMID:24617735

Umano K, Hagi Y, Shibamoto T (2002). Volatile chemicals identified in extracts from newly hybrid citrus, dekopon (*Shiranuhi mandarin* Suppl. J.). *J Agric Food Chem*, 50(19):5355–9. doi:10.1021/jf0203951 PMID:12207474

Uyeda S, Sharmin T, Satho T, Irie K, Watanabe M, Hosokawa M, et al. (2016). Enhancement and regulation effect of myrcene on antibody response in immunization with ovalbumin and Ag85B in mice. *Asian Pac J Allergy Immunol*, 34(4):314–23. PMID:27543726

Valette G, Cavier R (1954). Absorption percutanée et constitution chimique. Cas des hydrocarbures, des alcools et des esters. *Archs Int Pharmacodyn Thér*, 97(2):232–240. [French]

Wahab IR, Blagojević PD, Radulović NS, Boylan F (2011). Volatiles of *Curcuma mangga* Val. & Zijp (Zingiberaceae) from Malaysia. *Chem Biodivers*, 8(11):2005–14. doi:10.1002/cbdv.201100135 PMID: 22083913

Wang Y, Yan J, Li S, Wang W, Cai X, Huang D, et al. (2016). Composition of the essential oil from Danggui-zhiqiao herb-pair and its analgesic activity and effect on hemorheology in rats with blood stasis syndrome. *Pharmacogn Mag*, 12(48):271–5. PMID:27867268

Wietstock PC, Glattfelder R, Garbe LA, Methner FJ (2016). Characterization of the migration of hop volatiles into different crown cork liner polymers and can coatings. *J Agric Food Chem*, 64(13):2737–45. doi:10.1021/acs.jafc.6b00031 PMID:26996287

Yang J, Duan Y, Zhao W, Yang L, Han J, Zhu D, et al. (2015). Analysis of volatile components in e-liquid by headspace solid phase microextraction-gas chromatography-mass spectrometry. *Tobacco Science & Technology*, 48(4):42–48. Available from: http://www.tobst.cn/yckj/EN/abstract/abstract5992.shtml.

Yu Z, Wang B, Yang F, Sun Q, Yang Z, Zhu L (2011). Chemical composition and anti-acetyl cholinesterase activity of flower essential oils of *Artemisia annua* at different flowering stage. *Iran J Pharm Res*, 10(2):265–71. PMID:24250353

Zamith HP, Vidal MN, Speit G, Paumgartten FJ (1993). Absence of genotoxic activity of beta-myrcene in the in vivo cytogenetic bone marrow assay. *Braz J Med Biol Res*, 26(1):93–8. PMID:8220273

Zeller A, Rychlik M (2006). Character impact odorants of fennel fruits and fennel tea. *J Agric Food Chem*, 54(10):3686–92. doi:10.1021/jf052944j PMID:19127745