The MAK Collection for Occupational Health and Safety

Turpentine Oil

MAK Value Documentation, addendum – Translation of the German version from 2017

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Keywords: turpentine oil; MAK value; maximum workplace concentration; peak limitation; skin absorption; skin sensitization; irritation; urinary bladder

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated turpentine oil, considering all toxicity endpoints.

Turpentine oil [8006-64-2] is a mixture of different terpenes, terpenoids and terpene hydrocarbons, mostly mono and bicyclic monoterpenes like pinene, camphene, dihydropinene, carene or dipentene (limonene) with the main component being alpha-pinene with 60 to 86%. In 14-week studies with alpha-pinene in rats and mice, the critical effect was hyperplasia of the epithelium of the urinary bladder in mice at 100 ml/m³ with a no observed adverse effect concentration (NOAEC) of 50 ml/m³. No irritation was observed up to the highest concentration of 400 ml/m³ in rats and mice. Taking into account that the systemic NOAEC might be lower after chronic exposure and with the increased breathing volume of workers, a maximum concentration at the workplace (MAK value) of 5 ml/m³ was derived for turpentine oil. This concentration is far below 80 ml/m³, at which changes in bronchoalveolar lavage fluid were observed in volunteers after short-term exposure to a mixture of alpha and beta-pinene and delta-carene and which is below the NOAEC for alpha-pinene of 40 ml/m³ for sensory irritation in humans.

The MAK value was derived from a systemic effect; therefore, turpentine oil is classified in Peak Limitation Category II with an excursion factor of 2.

Turpentine oil and its major constituents do not have genotoxic potential. There are no carcinogenicity studies available with turpentine oil or its major components. Results of a dermal initiation-promotion study with turpentine oil alone were negative; promoting activity was seen only after application of an initiator. Turpentine oil is no longer classified as carcinogenic to humans, based on the Commission's evaluation of this type of study.

A significant contribution to systemic toxicity was demonstrated in a model calculation of dermal absorption and turpentine oil is designated with an "H". Due to the data described in the evaluation of 1996, turpentine oil continues to be designated with an "Sh".

Valid developmental toxicity studies are lacking; therefore, turpentine oil is assigned to Pregnancy Risk Group D.

Keywords

turpentine oil; α-pinene; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; allergenic effects; developmental toxicity; genotoxicity; carcinogenicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Turpentine Oil

[8006-64-2]	turpentine oil
[80-56-8]	α-pinene
[127-91-3]	β-pinene
[79-92-5]	camphene
[13466-78-9]	δ-3-carene

Supplement 2017

MAK value (2016)	**5 ml/m³ (ppm) ≙ 28 mg/m³**
Peak limitation (2016)	**Category II, excursion factor 2**
Absorption through the skin (2016)	**H**
Sensitization (1969)	**Sh**
Carcinogenicity	**–**
Prenatal toxicity (2016)	**Pregnancy Risk Group D**
Germ cell mutagenicity	**–**
BAT value	**–**

Molar mass	136.24 g/mol (pinenes $C_{10}H_{16}$)
Boiling point at 1013 hPa	turpentine oil: 154–170 °C (ECHA 2016 a) α-pinene: 155–156 °C (ECHA 2016 c)
Density at 20 °C	turpentine oil: 0.864 g/cm³ (ECHA 2016 a) α-pinene: 0.859 g/cm³ (ECHA 2016 c)
Vapour pressure at 25 °C	turpentine oil: 26 hPa (calculated) (ECHA 2016 a) α-pinene: 8.5 hPa (ECHA 2016 c) (–)-α-pinene: 5.3 hPa (Terpene Consortium 2006)
log K_{OW}[1)]	turpentine oil: 0.8–6.3 (calculated for individual components) (ECHA 2016 a) (–)-α-pinene: 4.487 at 25 °C (ECHA 2016 c)

1) octanol/water partition coefficient.

Solubility	turpentine oil: at 20 °C 0.048–29 000 mg/l water (calculated) (ECHA 2016 a) (+)-α-pinene: 0.65 mg/l water (Terpene Consortium 2006) α-pinene: ≤ 0.04 mg/l at 20 °C and a pH of about 8 (ECHA 2016 c)
1 ml/m³ (ppm) ≙ 5.653 mg/m³ for pinenes	**1 mg/m³ ≙ 0.177 ml/m³ (ppm) for pinenes**

There is documentation available from 1996 for the designation of the substance with "Sh" (for substances which cause sensitization of the skin) (documentation "Turpentine" 2000) and a supplement with classification in Carcinogen Category 3A (supplement "Turpentine" 2002).

As the relevance of the mouse skin initiation–promotion model has been assessed by the Commission with regard to the carcinogenicity of the substance in humans (Schwarz et al. 2015), the data available for turpentine oil is re-evaluated here.

Turpentine oil is a mixture of different terpenes and terpenoids. The mixture listed by the ECHA (2016 a) with CAS number [8006-64-2] contains mainly bicyclic monoterpenes such as **α-pinene**, **β-pinene** and **δ-3-carene** and smaller concentrations of monocyclic monoterpenes (ECHA 2016 a). Further bicyclic terpenes are camphene, cis-pinane and dihydropinene, and the monocyclic terpenes include limonene, terpinene, terpinolene and phellandrene. These monocyclic terpenes have two double bonds, and as they form epoxides they can have effects that are somewhat different to those of bicyclic terpenes (Sagunski and Heinzow 2003).

The composition of turpentine oil is often around **59% α-pinene**, **24% β-pinene**, 5% dipentene (limonene), 2% each of β-phellandrene, α-terpineol and linalool, and about 1% each of methylchavicol, cis-anethole and trans-anethole (Terpene Consortium 2006). The composition of turpentine oil obtained from pine trees depends on the species of pine, the geographical location, and the time of harvesting. In the USA, turpentine oil consists of around **75% to 85% α-pinene** with varying amounts of β-pinene (up to 3%), camphene (4%–15%), limonene (5%–15%), δ-3-carene and terpinolenes (percentage not specified) (NIEHS 2002). In the case of D-limonene, the MAK value is 5 ml/m³, L-limonene is assigned to Section II b.

α-Pinene is the main component of turpentine oil and amounts to between 59% and 85% of its content. It can be present in the form of (+)-α-pinene and (–)-α-pinene. European pines contain more (–)-α-pinene, which, in accordance with its RD_{50} value, has a markedly lower irritant effect than the (+)-α-pinene mainly contained in American pines.

Some of the components of turpentine oil are able to form epoxides during metabolism, which are assumed to have a greater reactivity, but have not been extensively investigated. The assessment is therefore based on turpentine oil itself, and does not automatically include the metabolites of its components.

1 Toxic Effects and Mode of Action

Irritation of the mucous membranes occurred in volunteers even at the lowest **turpentine oil** concentration tested of about 100 ml/m^3.

In recent 14-week inhalation studies with **α-pinene**, hyperplasia of the transitional epithelium of the bladder was observed in mice at 100 ml/m^3 and increased liver weights without any histopathological correlate in rats at 400 ml/m^3. No irritation of the respiratory tract occurred in either species at concentrations of up to 400 ml/m^3.

Contact sensitization to **turpentine oil** was found in humans and in animals.

There are no valid studies available for effects on fertility and the developmental toxicity of **turpentine oil**.

Genotoxicity studies with **α-pinene** and **β-pinene**, **camphene** and **turpentine oil** in vitro, and in vivo micronucleus tests in the bone marrow of mice after 14-week inhalation of **α-pinene** or single gavage doses of **camphene** yielded negative results.

There are no carcinogenicity studies available. In the mouse skin initiation–promotion experiment, **turpentine oil** had a promoting effect after the administration of an initiator, but produced no tumours in the skin after single applications or in dilutions of up to 50%.

2 Mechanism of Action

It is assumed that the tumour-promoting effect on the skin of mice is induced by cumulative irritation with a resultant increase in tissue proliferation (supplement "Turpentine" 2002).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

Turpentine oil is absorbed well after inhalation, but is absorbed also after ingestion, it is distributed throughout the body and accumulates, in some cases transiently, in the brain and kidneys (supplement "Turpentine" 2002).

In a study, 4 volunteers were given a single oral dose of 10 mg **α-pinene**. The urine was collected and analysed prior to exposure and up to 24 hours after administration of the substance. In 2 of the volunteers, blood samples were taken at hourly intervals for 5 hours, and analysed by means of GC-MS or GC-PCI-MS/MS. Ingestion of α-pinene did not affect the health of any of the volunteers. All reported a characteristic aromatic odour in the exhaled air, starting one hour after administration of the substance and continuing for up to 3 hours. At none of these times was α-pinene found in the blood. The main metabolites myrtenol, cis-verbenol, trans-verbenol and myrtenic acid were detectable in all blood samples, with a maximum concentration after 1 to 3 hours. The maximum urinary elimination of the metabolites was reached after 1.6 hours and had decreased within 24 hours to the

pre-exposure level. The amounts renally eliminated were between 690 µg/l for myrtenol and 3200 µg/l for myrtenic acid, and the half-lives were 1.4 hours for myrtenic acid, 1.5 hours for myrtenol and 1.6 hours for verbenol (Schmidt and Göen 2015).

The dermal penetration of monoterpenes, including α-pinene and β-pinene, through the human skin was investigated in an in vitro model both under monoexposure conditions and with exposure to a mixture of substances. For this, heat-separated human epidermis was excised and exposed to undiluted α-pinene, undiluted β-pinene, a mixture of α-pinene, myrcene and phenylethanol (1:1:1) or to mixtures of α-pinene and myrcene (1:1), α-pinene and phenylethanol (1:1), β-pinene, geraniol and methyleugenol (1:1:1), β-pinene and geraniol (1:1) or β-pinene and methyleugenol (1:1), and the concentration of monoterpenes was determined in the acceptor solution (ethanol/water 50/50) up to 27 hours. For the dermal penetration of α-pinene, the following permeation coefficients (range) were obtained: $4.53–7.33 \times 10^{-5}$ cm/s for the α-pinene/myrcene/phenylethanol mixture, $9.46–10.6 \times 10^{-6}$ cm/s for the α-pinene/myrcene mixture, $4.53–5.69 \times 10^{-5}$ cm/s for the α-pinene/phenylethanol mixture and $5.41–7.14 \times 10^{-5}$ cm/s for the monoexposure. The following permeation coefficients were determined for the dermal penetration of β-pinene: $6.56–26.1 \times 10^{-6}$ cm/s for the β-pinene/geraniol/methyleugenol mixture, $5.16–14.8 \times 10^{-6}$ cm/s for the β-pinene/geraniol mixture, $3.09–3.75 \times 10^{-5}$ cm/s for the β-pinene/methyleugenol mixture and $4.00–5.31 \times 10^{-5}$ cm/s for the monoexposure (Schmitt et al. 2009). Average permeation coefficients of 6.3×10^{-5} cm/s for α-pinene and of 4.7×10^{-5} cm/s for β-pinene are assumed for exposure to turpentine oil containing 59% α-pinene (corresponding to 590 mg/ml) and 24% β-pinene (corresponding to 240 mg/ml), dermal penetration rates of 133 mg/cm² and hour for α-pinene or 40.6 mg/cm² and hour for β-pinene are obtained from the in vitro data. Assuming the exposure of 2000 cm² of skin for 1 hour, this would correspond to absorbed amounts of 266 g α-pinene and 81 g β-pinene, respectively.

The use of heat-separated epidermis leads to an overestimation of the fluxes compared with the results obtained with dermatomed skin (for example, for caffeine by a factor of 3; Atrux-Tallau et al. 2007).

In another in vitro study using flow through cells, human whole skin was exposed to 500 mg undiluted **α-pinene** or **β-pinene** over an area of 0.65 cm². The receptor phase (10 ml) consisted of isotonic phosphate buffer, which was recirculated and conducted through a constant reservoir of 5 ml methylene chloride in order to extract the terpene dissolved in the water. The skin was in contact with the aqueous phase only. The exposure duration was 1, 2 or 4 hours. At the end of the exposure, the site of application was washed and the stratum corneum removed by tape-stripping. Penetration into the methylene chloride could not be found. After one hour, amounts of 11 µg/cm² in the stratum corneum and of 66 µg/cm² in the epidermis were detected for α-pinene. In the case of β-pinene, 40 µg/cm² was found in the stratum corneum, and 89 µg/cm² in the epidermis. After longer exposure times, the concentrations in the epidermis increased markedly, though not those in the stratum corneum. From the quantities found in the epidermis, dermally absorbed amounts of 78 mg α-pinene and 43 mg β-pinene are calculated for the exposure of 2000 cm² of skin to 59% α-pinene and 24% β-pinene for one hour (Cal et al. 2006).

The terpenes are eliminated mainly with the urine in the form of glucuronic acid conjugates, and some of them are exhaled in unchanged form. After the inhalation exposure of volunteers to 450 mg turpentine oil/m^3 (80 ml/m^3) during physical exercise (50 watts), α-pinene, β-pinene and δ-3-carene were eliminated from the blood with initial half-lives of 3–5 minutes, mean half-lives of 33–41 minutes and terminal half-lives of 25–42 hours. Amounts of 60% to 70% were absorbed in the lungs (see supplement "Turpentine" 2002). After exposure to 10 mg α-pinene/m^3, the net uptake is only 40%, presumably due to adsorption in the humidity of the airways (Falk et al. 1990).

3.2 Metabolism

Studies of the metabolism are described in detail in the supplement of 2000 (supplement "Turpentine" 2002).

In the study described above in which 4 volunteers ingested 10 mg **α-pinene**, the metabolism was dominated by oxidation reactions at the methyl side-chains yielding in carboxylic acid structures. Of the administered dose, 1.5% was eliminated with the urine as myrtenol, 5.6% as cis-verbenol, 4.1% as trans-verbenol and 6.7% as myrtenic acid. A major portion of the 78% of the dose not recovered could have been exhaled, thus causing the aromatic odour in the exhaled air. This air was not analysed. There was no evidence of an oxidation reaction at the double bond (Schmidt and Göen 2015).

4 Effects in Humans

Short-term exposure

As described in the supplement of 2000 (supplement "Turpentine" 2002), the lowest investigated concentration of about 450 mg **turpentine oil**/m^3 (80 ml/m^3) produced slight mucosal irritation (5% of the scale) in 8 volunteers carrying out physical exercise (50 watts). In addition, the airway resistance increased significantly from 0.12 to 0.15 kPa × s/l. In another study, exposure to 450 mg δ-**3-carene**/m^3 (80 ml/m^3) under similar conditions was likewise slightly irritating (10%–20% of the scale), although no relevant irritation occurred at 225 mg/m^3. After exposure to 225 mg **α-pinene**/m^3 (40 ml/m^3) during physical exercise (50 watts), there was no irritation in 8 volunteers, but irritation occurred in the nose and eyes of 5/8 volunteers (10% of the scale) at 450 mg/m^3 (80 ml/m^3) (Falk et al. 1990), so that 40 ml α-pinene/m^3 can be regarded as the NOAEC (no observed adverse effect concentration) for short-term exposure.

When 8 volunteers were exposed to 450 mg/m^3 (80 ml/m^3) of a **mixture** of α-pinene, β-pinene and δ-3-carene (10:1:5) on 4 different days for 3 hours each (half of the time during physical exercise at 50 watts) within a 2-week period, the number of macrophages and mast cells in the bronchioalveolar lavage fluid had increased by about 50% 20 hours after the final exposure (Johard et al. 1993; supplement "Turpentine" 2002).

Repeated exposure

In 5 workers at a shoe polish factory, a sensation of dizziness and drunkenness occurred during the winter months when starting work every morning in insufficiently ventilated rooms; this decreased after airing the workplace. The urine was found to have a characteristic odour of violets and an increased glucuronic acid content. Three workers had cysto-urethritis and an increased urge to urinate, in two cases combined with microhaematuria and in one other combined with macrohaematuria. The increased urge to urinate was attributed to the α-pinene in the turpentine oil in particular, or to the direct use of (+)-α-pinene originating from America. In addition to 65% to 70% turpentine oil or α-pinene, the shoe polish contained 7% white spirit, 23% to 24% paraffin and waxes, 0.8% nigrosine and induline colourants as well as 0.4% diphenylamine and 0.3% perfume. Exposure to aniline from the colourants could not be demonstrated. At times with improved ventilation and measured terpene concentrations in the air of 100 to 350 mg/m^3, the workers had no symptoms. As no details were given for the duration and frequency of exposure, the terpene concentration and the concentrations of the remaining components in the closed (non-ventilated) rooms, an evaluation of the findings after repeated exposure is not possible. Furthermore, methaemoglobinaemia was observed. According to the authors, this might be attributable to oxidation products (peroxides) of the turpentine oil produced by the surrounding air (Nürnberger 1967). On the other hand, the turpentine oil also contained diphenylamine and aniline colourants, which might explain both the bladder findings and the formation of methaemoglobin.

Due to the lack of data, it is not possible to give a NOAEC for long-term exposure.

Local effects on skin and mucous membranes

As shown in the supplement of 2000 (supplement "Turpentine" 2002), turpentine oil vapour causes mucosal irritation in humans. Irritant reactions (erythema and oedema) were seen in tests with 70% to 80% preparations of freshly distilled non-oxidized terpenes (α-pinene, β-pinene, δ-3-carene and limonene) in olive oil, but not in tests with 20% to 34% preparations.

Allergenic effects

Since 1969, turpentine oil(s) have been designated with "Sh" (for substances which cause sensitization of the skin), and the contact sensitizing potential of turpentine oil was re-assessed extensively in 1996 (documentation "Turpentine" 2000). As before, turpentine oil is still included in the standard series of the German Contact Dermatitis Research Group (DKG). In systematic studies at the clinics of the Information Network of Departments of Dermatology (IVDK) carried out during the first half of the 1990s, a 10% preparation of turpentine oil (in petrolatum) produced a comparatively low and decreasing number of reactions in relation to the frequencies previously reported in other studies (documentation "Turpentine" 2000). However, during the subsequent period, a marked increase in the number of positive

reactions, although varying, but always amounting to more than 1%, was once more recorded (Treudler et al. 2000). In the meantime, also markedly higher numbers of reactions of up to more than 4% were found in the clinics of the IVDK. As a possible cause it has been suggested that exposure to terpenoid substances is generally higher and the resultant cross-reactions to turpentine oil are therefore more frequent. Nevertheless, on a long-term basis, there is no recognizable trend for the number of reactions to turpentine oil (for example Schnuch et al. 2008; Uter et al. 2015).

There are only very sporadic reports of cases of suspected allergic rhinitis or allergic bronchial asthma (documentation "Turpentine" 2000). Since the documentation of 1996, only one further report of such reactions in the airways to turpentine oil is available. The authors report the case of a female art painter, who developed a non-productive cough, dyspnoea and wheezing after using balsamic turpentine oil as a thinner for oil paints for approximately 5 years. The symptoms always occurred between 30 and 60 minutes after exposure to turpentine oil. The results of prick tests with common allergens and metal salt solutions were negative, including prick-to-prick skin tests with the oil-based paints and the turpentine oil. The FEV_1 (forced expiratory volume in one second) and forced vital capacity were in the normal range. In a bronchial provocation test, the patient painted linseed oil, the oil paint and turpentine oil on a board measuring 1 m^2 for 30 minutes with 7-day intervals. Five minutes after the exposure to turpentine oil she reported tightness in the chest. Non-productive coughing and moderate dyspnoea occurred after one hour. Wheezing and a decrease in the FEV_1 by 10% were diagnosed. A drop in the peak expiratory flow (PEF) by 15% in the 1st, 5th and 12th hour was observed. After 1 hour, the FEV_1 was reduced by a maximum of about 15% and after 4 hours there was a further reduction, finally amounting to a drop of around 25% after 5 hours. One day after the provocation with turpentine oil, but not after 4 hours, there was an increase (from 4% to 16%) in the number of eosinophils in the sputum. The non-specific bronchial hyperreactivity after provocation was not investigated (Dudek et al. 2009).

In a publication already mentioned, although not described in greater detail, in the 1996 documentation (documentation "Turpentine" 2000), the workplace-related respiratory symptoms of a toolsetter were attributed to aerosols from a coolant. Provocation tests, during which the patient stirred a terpene mixture ("pine oil") contained in the lubricant for 30 minutes and turpentine oil for 20 minutes, produced an immediate reaction with a drop in the FEV_1 by 40% and 37%, respectively, and a much less pronounced delayed reaction. The colophony contained in the coolant as an emulsifier was heated to 250 °C for 5 minutes, which produced a drop in the FEV_1 by 44%. However, details of the terpene concentrations in the lubricant and in the aerosol are lacking (Hendy et al. 1985).

The more recent studies do not contradict the previous assessment that turpentine oil has contact sensitization potential.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

In addition to the data reported in the supplement of 2000 (supplement "Turpentine" 2002), LC_{50} values for **turpentine oil** of 13 000 mg/m³ were given for Sprague Dawley rats and albino guinea pigs, and of 9000 mg/m³ for Swiss mice (Terpene Consortium 2006).

In OF1- and NIH/S mice, the RD_{50} for (+)-**α-pinene** is 1053–1107 ml/m³, and that for (+)-**β-pinene** 1279–1419 ml/m³. The (–) **isomers** are markedly less irritating, the (–)-**β** isomer about 4 times less so; the (–)-**α** isomer was not irritating in this comparison (Kasanen et al. 1998).

In another study, an RD_{50} of 1173 ml/m³ for **turpentine oil** and of 1345 ml/m³ for (+)-**δ-3-carene** in mice is given (Kasanen et al. 1999).

5.1.2 Oral administration

In addition to the values reported in the supplement of 2000 (supplement "Turpentine" 2002), LD_{50} values were given for **turpentine oil** of 3956 mg/kg body weight or < 5000 mg/kg body weight (mortality 6/10) in male Wistar rats and of 4953 mg/kg body weight in albino rats, for **β-pinene** of 3388 mg/kg body weight in Sprague Dawley rats, and for **camphene** of > 5000 mg/kg body weight in Wistar rats (Terpene Consortium 2006).

5.1.3 Dermal application

In a study dating from 1972 not mentioned in the supplement of 2000 (supplement "Turpentine" 2002), 2000 mg undiluted **turpentine oil**/kg body weight was applied occlusively to the dorsal skin of 10 New Zealand White rabbits for 24 hours. There were no signs of systemic toxicity and no animals died. In one animal there was moderate reddening, in 8 animals slight reddening of the skin on the first day after application. At the same time, one animal was found to have moderate oedema and 4 animals slight oedema. The oedema disappeared after 3 days, the reddening of the skin after 5 days. Necropsy did not reveal any treatment-related findings. The dermal LD_{50} is greater than 2000 mg/kg body weight (ECHA 2016 a). The oil consisted of about 59% α-pinene, 24% β-pinene, 5% dipentene, and 2% each of β-phellandrene, α-terpineol and linalool, and 1% each of methylchavicol, cis-anethole and trans-anethole (Terpene Consortium 2006).

Limit tests, in which 5000 mg **α-pinene** or **β-pinene**/kg body weight was applied for 24 hours to the dorsal skin of New Zealand White rabbits, caused no deaths (no data as to whether the skin was covered or not). An analogous study with camphene caused the death of 2 of the animals given 5000 mg/kg body weight (Terpene Consortium 2006).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

Inhalation studies with **α-pinene** in F344 rats and B6C3F1 mice have been performed under the NTP program. The NOAEC was 50 ml/m³ in mice and 200 ml/m³ in rats (not including the species-specific α-2u-nephropathy in the male rats at concentrations of 25 ml/m³ and above). At the LOAEC of 100 and 400 ml/m³, respectively, hyperplasia of the transitional epithelium of the bladder in mice and reduced body weight gains and mortality in rats were observed. Irritation of the respiratory tract did not occur in either species up to concentrations of 400 ml/m³ (Table 1; ECHA 2016 a; NTP 2006; Terpene Consortium 2006).

5.2.2 Oral administration

Gavage administration of 1000 mg **camphene**/kg body weight and day to Wistar rats for 28 days led to increased salivation, increased liver weights and an increase in vacuolation of the hepatocytes. The NOAEL (no observed adverse effect level) was 250 mg/kg body weight and day. Gavage administration of 10 mg **verbenone**/kg body weight and day to Sprague Dawley rats for 28 days did not cause any substance-related toxicity (Table 2; Terpene Consortium 2006).

5.2.3 Dermal application

Only data from initiation–promotion tests in mice are available (see Section 5.7).

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

Repeated dermal application of turpentine oil to the skin of mice led to ulcers. Individual components produced irritation in rabbits, but not in hairless mice or pigs (supplement "Turpentine" 2002).

In an in vitro study with human skin, δ-3-carene, α-pinene and β-pinene were regarded as irritating (ECHA 2016 a).

In an in vitro study using a three-dimensional human skin model, **α-pinene** with a purity of 96.6% (impurities: 1.7% camphene, 1.1% β-pinene and 0.1% α-fenchene) was regarded as irritating after non-occlusive 15-minute application of 10 µl undiluted solution, as the percentage of surviving cells was below 50%. The positive control led to the survival of 18.7%; in the case of α-pinene, 39.6% of the cells survived (ECHA 2016 c). In an analogous study, turpentine oil (purity 100%, CAS number [70750-57-1]) was regarded as "not irritating", as survival of the cells was 88.8%, that for the positive control 7.4% and that for the negative control 100% (ECHA 2016 b).

Table 1 Effects of turpentine oil and its components after repeated inhalation

Species, strain, number per group	Exposure	Findings	References
turpentine oil			
rat, Long Evans and Sprague Dawley, per strain 10 ♂, 10 ♀	**30 days**, 2400 mg/m³, 6 hours/day, 5 days/week	from 1964, no control group, **2400 mg/m³**: inactivity, organs histopathologically examined: lungs, kidneys, liver, heart, trachea, adrenal glands, mesenteric lymph nodes in 3 ♂ and 3 ♀	Terpene Consortium 2006
rat, Sprague Dawley, 10 ♂, 15 ♀	**90 days**, 4800 mg/m³, 6 hours/day, 5 days/week	from 1963, no control group, **4800 mg/m³**: ♂: inactivity, ♀: body weight gains ↓, mortality (all animals up to day 23 of exposure due to acute myocardial anoxia) organs histopathologically examined: lungs, kidneys, liver, heart, trachea	Terpene Consortium 2006
mouse, Swiss, 10 ♂, 10 ♀	**30 days**, 2400 mg/m³, 6 hours/day, 5 days/week	from 1964, no control group, **2400 mg/m³**: inactivity, organs histopathologically examined: lungs, kidneys, liver, heart, trachea, adrenal glands, mesenteric lymph nodes in 3 ♂ and 3 ♀	Terpene Consortium 2006
guinea pigs, English, 5 ♂, 5 ♀	**90 days**, 4800 mg/m³, 6 hours/day, 5 days/week	from 1963, no control group, **4800 mg/m³**: inactivity, organs histopathologically examined: lungs, kidneys, liver, heart, trachea	Terpene Consortium 2006
dog, Beagle, 1 ♂, 1 ♀	**90 days**, 4800 mg/m³, 6 hours/day, 5 days/week	from 1964, no control group, **4800 mg/m³**: ataxia and inactivity, organs histopathologically examined: lungs, kidneys, liver, heart, trachea	Terpene Consortium 2006

Table 1 (continued)

Species, strain, number per group	Exposure	Findings	References
α-Pinene			
rat, Fischer 344, 5 ♂, 5 ♀	**14 days**, 0, 100, 200, 400, 800, 1600 ml/m^3, 6 hours/day, 5 days/week	**no results published**	NTP 2006
rat, Fischer 344, 10 ♂, 10 ♀	**14 weeks**, 0, 25, 50, 100, 200, 400 ml/m^3, 6 hours/day, 5 days/week, purity > 97%	similar to OECD Test Guideline 413, deviation: no documentation of food consumption and some organ weights, no haematology, no ophthalmological examination; **25 ml/m^3 and above**: ♂: **LOAEC** body weight gains ↓, nephropathy, hyaline droplets; **50 ml/m^3 and above**: ♂: alanine aminotransferase ↓ without histopathological correlate, ♀: absolute and relative liver weights ↑ without enzyme changes or histopathological correlate; **100 ml/m^3 and above**: ♂: absolute and relative kidney weights ↑, alkaline phosphatase ↓ without histopathological correlate; **200 ml/m^3**: **NOAEC**, **200 ml/m^3** and above: alanine aminotransferase ↓ without histopathological correlate, ♂: absolute and relative liver weights ↑ (no other details); **400 ml/m^3**: body weight gains ↓, ♀: mortality 6/10, survivors: slight trembling, absolute and relative thymus weights ↓, relative lung weights ↑, inflammation in lungs, alkaline phosphatase ↓ without histopathological correlate, ♂: sorbitol dehydrogenase ↓, no substance-related histopathological findings	ECHA 2016 a; NTP 2006; Terpene Consortium 2006

Table 1 (continued)

Species, strain, number per group	Exposure	Findings	References
mouse, B6C3F1, 5 ♂, 5 ♀	**14 days**, 0, 100, 200, 400, 800, 1600 ml/m³, 6 hours/day, 5 days/week	**no results published**	NTP 2006
mouse, B6C3F1, 10 ♂, 10 ♀	**14 weeks**, 0, 25, 50, 100, 200, 400 ml/m³, 6 hours/day, 5 days/week, purity > 97%	similar to OECD Test Guideline 413, deviation: no documentation of food consumption and some organ weights, no haematology, no ophthalmological examination; **50 ml/m³**: **NOAEC**; **100 ml/m³ and above**: bladder: hyperplasia of the transitional epithelium, degree: minimal to moderate; **200 ml/m³ and above**: absolute and relative liver weights ↑; **400 ml/m³**: ♂: absolute and relative thymus weights ↓	ECHA 2016 a; NTP 2006; Terpene Consortium 2006

Table 2 Effects of turpentine oil components after repeated oral administration

Species, strain, number per group	Exposure	Findings	References
camphene			
rat, Wistar, 5 ♂, 5 ♀	**28 days**, daily, 0, 62.5, 250, 1000 mg/kg body weight and day in sesame oil, gavage	from 1991, according to OECD Test Guideline 407, **62.5 mg/kg body weight and above**: ♂: α-2u-globulin renal toxicity; **250 mg/kg body weight**: ♀: **NOAEL**; **1000 mg/kg body weight**: salivation, liver weights ↑ (no data as to whether relative or absolute), vacuolation of hepatocytes	Terpene Consortium 2006
verbenone			
rat, Sprague Dawley, 10 ♂, 10 ♀	**28 days**, daily, 0, 10 mg/kg body weight and day, gavage	from 2003, according to OECD Test Guideline 407, **10 mg/kg body weight**: **NOAEL**	Terpene Consortium 2006

5.3.2 Eyes

There were no data available about effects on the eyes for the supplement of 2000 (supplement "Turpentine" 2002).

No studies of the irritant effects of α-pinene in the eyes have been carried out; instead, those with β-pinene and δ-3-carene are referred to (ECHA 2016 c).

In an eye irritation study carried out according to OECD Test Guideline 405 in New Zealand White rabbits, 0.1 ml undiluted **β-pinene**, which was not rinsed out, was found to be slightly irritating. Slight redness (max. score 2 of 4 after 1 hour) and swelling (max. score 3 of 4 after 1 hour) of the conjunctiva occurred. The swelling had completely subsided within 3 days, the redness after 7 days. On the basis of these findings, classification according to EU criteria is unnecessary (ECHA 2016 a).

δ-3-Carene was likewise found to be slightly irritating. There was slight redness (max. score 2 of 4 after 1 hour) and swelling (max. score 3 of 4 after 1 hour) of the conjunctiva. Both findings had completely subsided within 7 days. On the basis of these findings, classification according to EU criteria is unnecessary (ECHA 2016 a).

5.4 Allergenic effects

5.4.1 Sensitizing effects on the skin

As described in the documentation of 1996 (documentation "Turpentine" 2000), turpentine oil caused sensitization in a maximization test with guinea pigs, as did δ-3-carene in domestic pigs.

Positive findings in the cumulative contact enhancement test were reported for **δ-3-carene**. In the case of **β-pinene**, a positive result with an EC_3 value of 29% was obtained in a local lymph node assay (ECHA 2016 a).

5.4.2 Sensitizing effects on the airways

There are no other data available.

5.5 Reproductive and developmental toxicity

5.5.1 Fertility

There are no other studies available.

5.5.2 Developmental toxicity

No valid studies of developmental toxicity were reported in the supplement of 2000 (supplement "Turpentine" 2002). Valid studies with turpentine oil are still not available.

In the publically available registration data of the REACH program (ECHA 2016 a, b, c), studies with the individual components of turpentine oil are reported. However, there are no valid developmental toxicity studies with the main components. These data are therefore not included in the evaluation.

5.6 Genotoxicity

5.6.1 In vitro

In the supplement of 2000 (supplement "Turpentine" 2002), **α-pinene** was reported not to be mutagenic in Salmonella typhimurium. The tests with **pinene epoxides** were questionably positive, as only a doubling of the number of revertants was produced.

In the meantime, further studies have become available.

For **turpentine oil** concentrations between 5 and 5000 µg/plate, negative test results were obtained in a study carried out according to OECD Test Guideline 471 in the Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537, both in the presence and absence of a metabolic activation system from rat liver. Cytotoxicity occurred at 500 µg/plate and above. The positive controls demonstrated the validity of the test system (ECHA 2016 a).

In various studies with **α-pinene**, both in the presence and absence of a metabolic activation system from rat liver, concentrations of 0.1, 1 to 1000, 4000 or 25 000 µg/plate were not mutagenic in the Salmonella typhimurium strains TA97a, TA98, TA100, TA1535, TA1537 and TA1538. Cytotoxicity was observed in each instance (Terpene Consortium 2006).

Studies with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538 yielded negative results for **β-pinene** concentrations of 0.01 to 5 µl/plate or

5000 µg/plate in the presence and absence of a metabolic activation system from rat liver (Terpene Consortium 2006).

No mutagenic effects were observed in studies with **camphene** in the presence and absence of a metabolic activation system from rat liver in the Salmonella typhimurium strains TA98 and TA100 at concentrations of 0.5 to 300 µl/plate. When camphene was administered to rats by gavage and the 24-hour urine was used for testing, the ether extract was found to be slightly mutagenic in TA100 in the presence of a metabolic activation system (Terpene Consortium 2006).

Studies with **camphene** in the presence and absence of a metabolic activation system from rat liver yielded negative results in the Salmonella typhimurium strains TA98, TA100, UTH8414 and UTH8413 at concentrations of 10 to 1000 µg/plate (Terpene Consortium 2006).

The results of an unscheduled DNA synthesis (UDS) test in hepatocytes using in situ perfusion in male Sprague Dawley or Fischer rats were negative at **α-pinene** concentrations of 0.001 to 10 µl/ml. No cytotoxicity occurred, and the positive controls demonstrated the validity of the test system (Terpene Consortium 2006).

Camphene and **β-pinene** did not induce sister chromatid exchange (SCE) in Chinese hamster ovary (CHO) cells at concentrations of 3.3 to 1000 µM (Terpene Consortium 2006).

In a study carried out according to OECD Test Guideline 473, **turpentine oil** did not increase chromosomal aberrations in human lymphocytes in either the presence or absence of a metabolic activation system in the concentration range of between 0.032 and 5.0 µl/ml. The positive control demonstrated the validity of the test system. Cytotoxicity was found at concentrations of 0.17 µl/ml and above with an exposure time of 22 hours (ECHA 2016 a).

A $TK^{+/-}$ test carried out according to OECD Test Guideline 476 in L5178Y mouse lymphoma cells yielded negative results for **turpentine oil** up to concentrations of 50 µg/ml in the presence of a metabolic activation system from rat liver and up to 45 µg/ml in the absence of a metabolic activation system after 4 and 24 hours. The positive controls demonstrated the validity of the test system. Cytotoxicity occurred at concentrations of 50 µg/ml and above in the presence of a metabolic activation system, so that no higher concentrations could be tested (ECHA 2016 a).

5.6.2 In vivo

α-Pinene did not induce micronuclei in a micronucleus test in the bone marrow of male and female B6C3F1 mice after inhalation exposure to concentrations of 0, 50, 100, 200 or 400 ml/m^3 for 6 hours a day, on 5 days a week for 14 weeks (Terpene Consortium 2006).

A micronucleus test carried out according to OECD Test Guideline 474 with NMRI mice yielded negative results after single **camphene** doses of 4000 mg/kg body weight administered by gavage (Terpene Consortium 2006).

5.7 Carcinogenicity

As described in the supplement of 2000 (supplement "Turpentine" 2002), **turpentine oil** was shown to have tumour-promoting effects when applied to mouse skin

after the administration of an initiator. When turpentine oil was applied alone or diluted (20%–50% solutions in acetone or mineral oil), no tumour-promoting activity could be demonstrated.

There are no long-term carcinogenicity studies available.

A carcinogenicity study with inhalation exposure to α-pinene in rats and mice is at present being carried out (NTP 2016).

6 Manifesto (MAK value/classification)

In humans, irritation is the main effect of turpentine oil. In medium-term studies in rodents with α-pinene, the main component of turpentine oil, the critical systemic effect in mice was epithelial hyperplasia of the bladder.

MAK value. For the irritant effect of turpentine oil observed in volunteers, no NOAEC is available for medium to long-term exposure. There are no valid animal studies with turpentine oil.

α-Pinene is the main component of turpentine oil and amounts to between 59% and 85% of its content. Under the NTP program, 14-week inhalation studies in rats and mice were carried out with α-pinene. These can be used for the evaluation. α-Pinene can be present in the form of (+)-α-pinene and (–)-α-pinene. European pines contain more (–)-α-pinene, which, in accordance with its RD_{50} value, is markedly less irritating than the (+)-α-pinene mainly contained in American pines. The NTP study presents a worst-case scenario as regards irritation, since American α-pinene, with its higher irritation potential, was very probably used. The NOAEC for irritation of the respiratory tract of rats and mice after 14-week exposure was the highest α-pinene concentration tested of 400 ml/m³. The NOAEC for its systemic effects is 50 ml/m³ in mice, as epithelial hyperplasia of the bladder occurred at a concentration of 100 ml/m³. Taking into consideration a possible increase in the effects over time (1:2), the extrapolation from animals to humans (1:2) and the increase in respiratory activity of humans at the workplace (1:2) (calculated according to Buist et al. 2012, the blood:air partition coefficient of α-pinene is 12.4), a MAK value of 5 ml/m³ has been established from the NOAEC of 50 ml/m³ and using the preferred value approach. This MAK value is markedly below the NOAEC of 40 ml α-pinene/m³ for sensory irritation in volunteers (Falk et al. 1990) and is lower by a factor of 16 than the LOAEC of 80 ml/m³ for a mixture of α-pinene, β-pinene and δ-carene for changes in the bronchoalveolar lavage fluid after short-term exposure of volunteers (Johard et al. 1993). Therefore, no effects on the respiratory tract are to be expected at a concentration of 5 ml turpentine oil/m³.

Peak limitation. Due to its systemic effects, turpentine oil is assigned to Peak Limitation Category II. The bladder is the target organ. Its half-lives in the kidneys are not known. Although the mean half-lives in the blood of volunteers are below 45 minutes for exposure to 80 ml/m³, which would result in an excursion factor of 1 (documentation "Limitation of exposure peaks and short-term exposures" 2011), the net absorption at the lower concentration of 10 mg α-pinene/m³ (1.7 ml/m³) is only 40% instead of the 60% at 80 ml/m³. Therefore, an excursion factor of 2 together with a MAK value of 5 ml/m³ is justified. The resultant peak concentration of

10 ml/m³ is markedly below the NOAEC of 40 ml/m³ for sensory irritation and the LOAEC obtained with a synthetic turpentine oil of 80 ml/m³ for alveolar inflammatory effects.

Prenatal toxicity. There are no valid studies available for the developmental toxicity of turpentine oil or any of its main components. Turpentine oil is therefore classified in Pregnancy Risk Group D.

Carcinogenicity. As described in the supplement of 2000 (supplement "Turpentine" 2002), **turpentine oil** promotes skin tumours in mice after the administration of an initiator. When turpentine oil alone is applied, it does not produce tumours within the same period. Further carcinogenicity studies are not available. There are also no studies which demonstrate that turpentine oil has a specific effect on the skin in the low dose range. The mouse skin initiation–promotion model was assessed by the Commission on the basis of the mechanistic data available at present with regard to its relevance for possible carcinogenic effects in humans (Schwarz et al. 2015). The Commission has come to the conclusion that any suspected carcinogenic activity in the human skin can be considered so slight that turpentine oil can be removed from category 3A.

Germ cell mutagenicity. The available studies of genotoxicity yielded negative results. Therefore, the substance is not classified in one of the categories for germ cell mutagens.

Absorption through the skin. The dermally absorbed quantities of α-pinene and β-pinene calculated from in vitro penetration experiments with human epidermis and whole skin diverge greatly from 78 mg to 266 g and 43 mg to 81 g, respectively, assuming one-hour exposure to turpentine oil of 2000 cm² of skin. It is unclear which of the two experiments is more relevant for the in vivo situation. An 8-hour exposure to the substance at the level of the MAK value (28 mg/m³) would result in the uptake of 280 mg turpentine oil, assuming complete absorption at a respiratory volume of 10 m³. Even taking the lower of the two values obtained for dermal absorption as a basis, the uptake of α-pinene and β-pinene through the skin is in sum more than 25% of the systemically tolerable amount, so that turpentine oil is designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. Since the evaluation of the sensitization potential in 1996, no additional data have appeared which would make a re-assessment necessary. Therefore, the designation of the substance with "Sh" (for substances which cause sensitization of the skin) has been retained, but not that with "Sa" (for substances which cause sensitization of the airways).

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