The MAK Collection for Occupational Health and Safety

1-Octanol

MAK Value Documentation, addendum – Translation of the German version from 2018

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1-Octanol / Octan-1-ol[1)]

MAK Value Documentation

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated 1-octanol [111-87-5] to derive a maximum concentration at the workplace (MAK value), considering all toxicity endpoints. Irritation is the critical effect. Neither appropriate data in humans nor inhalation or oral studies of 1-octanol with animals are available for derivation of a MAK value. An 8-week feeding study in Wistar rats with the structurally related 1-dodecanol resulted in a NOAEL of 100 mg/kg body weight and day for systemic toxicity. Additionally, a NOAEL of 125 mg/kg body weight and day for 2-ethylhexanol was obtained in a 90-day oral study in rats. Therefore, a NOAEL of approximately 100 mg/kg body weight and day was assumed for 1-octanol. From this NOAEL, the concentration in workplace air was calculated to be 245 mg 1-octanol/m^3 according to the Commission's procedure. However, 1-octanol can cause irritation. The RD_{50} values of 50 ml/m^3 and 45 ml/m^3 for 1-octanol and 2-ethylhexanol, respectively, suggest a similar irritating potency. Therefore, the MAK value for 1-octanol was set at 10 ml/m^3 by analogy with 2-ethylhexanol. As local effects are critical, the substance is assigned to Peak Limitation Category I and an excursion factor of 1 has been established by analogy with 2-ethylhexanol. From a synopsis of all data, 1-octanol is classified in Pregnancy Risk Group C. 1-Octanol is not mutagenic in bacteria. There are no long-term studies with 1-octanol. Skin absorption does not contribute significantly to systemic toxicity and 1-octanol is not expected to lead to contact sensitization.

Keywords

1-octanol; caprylic alcohol; n-octyl alcohol; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; allergenic effects; reproductive toxicity; fertility; 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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1) The substance can occur simultaneously as vapour and aerosol.

2140

1-Octanol[1)]

[111-87-5]

Supplement 2018

MAK value (2017)	**10 ml/m³ (ppm) ≙ 54 mg/m³**
Peak limitation (2017)	**Category I, excursion factor 1**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2017)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**

Synonyms	caprylic alcohol *n*-octyl alcohol
Chemical name (IUPAC)	octan-1-ol
CAS number	111-87-5
Structural formula	$CH_3–(CH_2)_7–OH$
Molecular formula	$C_8H_{18}O$
Molar mass	130.23 g/mol
Melting point	–16.3 °C (ECHA 2016 a)
Boiling point	195.1 °C (ECHA 2016 a)
Density at 25 °C	0.83 g/cm³ (ECHA 2016 a)
Vapour pressure at 25 °C	0.1 hPa (ECHA 2016 a)
maximum vapour concentration at 21–27 °C	about 70 ml/m³
log K_{OW}[2)] at 23 °C	3.5 (ECHA 2016 a)

1) The substance can occur simultaneously as vapour and aerosol.

2) octanol/water partition coefficient

Solubility at 23 °C	107 mg/l (ECHA 2016 a)

1 ml/m³ (ppm) ≙ 5.404 mg/m³ **1 mg/m³ ≙ 0.185 ml/m³ (ppm)**

In the documentation from 2000 the decreasing importance of 1-octanol as an additive (emulsifier) in metal-working fluids (≤ 5% in the concentrate) and its use as an emulsifier in anti-rust emulsions, in the perfume industry or also as an additive in foodstuffs were described. In the chemical industry, 1-octanol serves as the starting material for the synthesis of ethoxylates, alkyl sulfates and ether sulfates, and in petroleum chemistry as an anti-foaming agent. It is used as a solvent in paints, varnishes and surface coatings, and in agricultural chemistry, for example, to inhibit the excessive growth of tobacco plants (documentation "1-Octanol" 2003).

1-Octanol is a colourless liquid with a fresh orangey, rose-like smell and an oily, sweet, herbal taste (NLM 2016). At concentrations of 0.1 ml/m³ and above, the odour is described as unpleasant (van Thriel et al. 2003).

As a result of new data, it is investigated below whether a MAK value can be derived. Also studies of the analogous substances 2-ethylhexanol, 1-decanol and 1-dodecanol are included. The substance names in these studies are highlighted in bold type for better clarity.

Toxic Effects and Mode of Action

In rabbits, 1-octanol causes slight to moderate irritation of the skin. According to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) 1-octanol is classified as an eye irritant.

In rats, the inhalation of a 1-octanol concentration of 400 mg/m³ during pregnancy did not lead to any unusual findings for the number of resorptions and foetal weights, and there were no skeletal or visceral abnormalities on gestation day 20.

In Salmonella mutagenicity tests 1-octanol was not found to be mutagenic. In V79 cells it induces spindle disturbances (c mitoses and aneuploidies) at concentrations of about 0.1 mM (about 0.013 mg/ml) and above; this is explained as an unspecific (physical) mechanism.

There are no valid clinical or experimental findings for 1-octanol from which a contact-sensitizing effect can be derived.

There are no valid studies of the carcinogenicity of the substance.

Mechanism of Action

Narcotic effect

Like other alcohols, 1-octanol has an anaesthetic effect, as was demonstrated in an experiment with tadpoles by the loss of the righting reflex in an aqueous milieu. At an EC_{50} of 57 µM, tadpoles reacted 3.2 times more strongly to the narcotic effect of 1-octanol than to that of ethanol (Alifimoff et al. 1989). The narcotic effect is medi-

ated among other things by current-dependent calcium channels. T-type current-dependent calcium channels are found in large numbers, for example, in the neurons of the thalamus nuclei. They are the cellular targets of some anaesthetics. The T-type calcium channels react to low membrane tension with a transient calcium current, therefore the name T-type, and thus increase the dendritic signal. Investigations with brain slices from young rats showed that at subanaesthetic concentrations with an IC_{50} of about 4 µM 1-octanol inhibited the calcium current in the neurons of the nucleus reticularis thalami. This results in a shift in the polarization equilibrium from the activation of polarization to the inactive status of the channel. This 1-octanol-induced inhibition probably takes place via the impairment of protein kinase C signal transduction (Joksovic et al. 2010). 1-Octanol inhibited T-type calcium channels in various nerve cells, for example in cells of the dorsal root ganglions of adult rats (EC_{50} = 122 µM; Todorovic and Lingle 1998), in nerve cells of the hippocampus (EC_{50} not specified; Takahashi et al. 1989) or in relay neurons of the thalamus (EC_{50} not specified; Llinás et al. 2007). The inhibition of T-type calcium channels was demonstrated also in GH3 cells (EC_{50} = 244 µM; Herrington and Lingle 1992). 1-Octanol may also amplify the calcium currents controlled by the GABA-receptor (Franks and Lieb 1994).

Neurotoxic effects

In vitro, it was demonstrated that 1-octanol may be able to interfere with the development of the brain by changing the cell cycle of neural cells. During early embryogenesis, numerous nerve and glia cells develop within the ventricular layers from mitotic precursor cells. As a result of the migration of the neural cells to their target site and the subsequent differentiation of the cells, complex structures and connections are formed in the brain. After closure of the neural tube, the neural crest cells migrate from its dorsal section and form the sensory and motor neurons of the peripheral nervous system. The influence of the mitogenic fibroblast growth factor 2 (FGF-2) and of the anti-mitogenic 1-octanol were investigated in explants of the neural epithelium from the brain of mouse embryos. While in vivo all post-mitotic cells migrate from the ventricular layers, in the explants some cells remained behind and did not re-enter the S phase. It was therefore assumed that these cells were in a very long G1 phase or remained in the G0 state. As a result of 1-octanol, almost all of these cells remained in the explants, while as a result of FGF-2 migration took place (Goto et al. 2002).

Intracellular effects

The effects of 1-octanol on biological systems are ascribed to unspecific interaction with biological membranes; such effects are directly correlated with the partition coefficient (documentation "1-Octanol" 2003). In some cases the effects of 1-octanol can affect also the gap junction-mediated intercellular communication. The cellular response to the chemotherapeutic drug melphalan was investigated with adenocarcinoma cells (A2780 and COLO-316, from human ovaries) in the presence and absence of 1-octanol. In melphalan-sensitive A2780/S cells, 1.0 mM 1-octanol increased the inhibition of the gap junction-mediated intercellular communication induced by melphalan and also the lipid mobility in the plasma membranes of A2780/S and COLO-316/S cells. In melphalan-resistant cells (A2780/R and COLO-316/R) the resistance could be reversed by 1-octanol (Barhoumi et al. 1995).

It was also assumed that the gene expression profile caused by various straight-chain alcohols is closely associated with the inhibition of cell growth induced by these alcohols or the morphological changes. In yeast, lipophilic alcohols with high log K_{OW} values were more toxic than those with low log K_{OW} values. Morphological changes occurred after exposure to ethanol, 1-pentanol or 1-octanol, while *n*-pentane impaired only the surface of the external membrane, but had hardly any effect on the organelles. In cDNA microarrays, the results for the up-regulated gene categories caused by straight-chain alcohols were not uniform, such as those for "cell rescue, defence and virulence", and "energy" or "metabolism" (Fujita et al. 2004).

Toxicokinetics and Metabolism

Absorption, distribution, elimination

There are no studies available of the oral absorption of 1-octanol or by inhalation. After 24-hour skin contact with undiluted ^{14}C-labelled 1-octanol, a fraction of 50% of the dose was absorbed by hairless mice and exhaled mainly as CO_2 (documentation "1-Octanol" 2003; Iwata et al. 1987). Marked irritation was observed, and the data cannot, therefore, be used for a quantitative evaluation of the amount absorbed through the skin. After the application of diluted solutions, the amount absorbed was influenced by the concentration in the vehicle and the type of vehicle used. The amount absorbed reached a value of about 60% of the dose after the application of a 0.5% solution (corresponding to 5 g/l) of 1-octanol in squalene, which caused, at the most, only slight irritation. For a volume of 100 µl solution applied to 2 cm^2 of skin, a flux of 150 µg/cm^2 in 24 hours or 6.25 µg/cm^2 and hour is obtained (Iwata et al. 1987). On the basis of this flux, the exposure of 2000 cm^2 of skin for one hour would result in the absorption of 12.5 mg of the substance. In view of the better solubility of 1-octanol in squalene compared with that in water, the amount absorbed from a saturated aqueous solution, as is usually the case in the evaluation, would, however, probably be smaller.

In a diffusion chamber with human skin (dermis and epidermis, without subcutaneous adipose tissue), 1-octanol was demonstrated to penetrate the skin well if both the donor and receptor medium were physiological saline. In this system the permeability constant was 0.052 cm/hour (Blank 1964). This results in a flux of about 5.6 µg/cm^2 and hour for a saturated aqueous solution (107 mg/l).

Overall, both studies yield an absorbed amount of about 12 mg for exposure under standard conditions.

Metabolism

1-Octanol, as a primary alcohol, is oxidized mainly to the corresponding carboxylic acid and then further to CO_2 or, after conjugation with glucuronic acid, is eliminated as an ester glucuronide. The direct conjugation of 1-octanol to form octyl glucuronide, octyl sulfate or the glycine conjugate plays only a minor role (documentation "1-Octanol" 2003).

Effects in Humans

Single exposures

Neurobehavioural changes caused by 1-octanol were investigated in 24 healthy male volunteers in a "crossover design". On average, the subjects were 25.8 years old. Twelve of the students had reported enhanced chemical sensitivity, the other twelve were age-matched controls. Enhanced chemical sensitivity was regarded to be a strong physical reaction, such as nausea to chemicals, for example to varnish vapour or petrol. All the volunteers had an intact sense of smell. The odour threshold for butyl alcohol did not differ between the two groups of students. The exposure lasted for 4 hours to a constant 1-octanol concentration of 0.1 ml/m^3 or to an average 6.4 ml/m^3 with four peaks of about 12.5 ml/m^3. Neuropsychological tests were carried out at the beginning and end of the exposure. At both concentrations, the volunteers reported olfactory complaints (unpleasant odour) during the exposure that they did not experience before the exposure. These decreased with the increasing exposure duration. There was a statistically significant increase in the frequency of sensory irritation of the eyes and nose at 6.4 ml/m^3, but overall the severity was only slight (median score of 10 on a scale up to 100, 90% confidence interval (CI) 0–38,4; before exposure: median score of 0, 90% CI: 0–21). However, the complaints of the volunteers were only roughly recorded, the blinking frequency was not determined and the role of the exposure peaks in the sensory irritation was not investigated in detail. Only in persons with enhanced chemical sensitivity was there a marked increase in annoyance at both concentrations, and in tests in which divided attention was required the detection frequency was lower. The results for 1-octanol were not concentration-dependent. The unpleasant odour of 1-octanol might mask the sensory irritation and also hinder the attention of persons with enhanced chemical sensitivity in more demanding tasks. Overall, however, no acute neurotoxic effects occurred, as shown by the vigilance task, which is very sensitive as regards prenarcotic effects (van Thriel et al. 2003). The results of this study are not included in the evaluation of the irritant effects of 1-octanol in humans as the influence of the exposure peaks was not determined exactly, the complaints of the volunteers were only recorded roughly and the blinking frequency was not measured. In a follow-up study in which the respiratory and heart frequencies in these investigations were analysed, no effects resulting from the exposure to 1-octanol were found (Haumann et al. 2003). This method is not as sensitive as determining the blinking frequency, but marked physiological effects would have been apparent.

Local effects on skin and mucous membranes

1-Octanol caused irritant reactions in 5 of 28 test persons after occlusive application for 4 hours. The reaction was regarded as an irritant effect if the subject developed at least mild erythema or dryness over most of the application site 24, 48 or 72 hours after treatment. Irritant reactions to the 20% aqueous preparation of sodium dodecylsulfate included as standard were observed in 21 of the 28 persons (Basketter et al. 2004).

The occlusive application of 50% 1-octanol in petrolatum to the outside of the upper arm for 24 hours caused mild erythema and oedema in some of the 4 test persons (no other data) at the reading after removal of the plaster; the findings rapidly regressed (Kästner 1977).

The local irritation of the eyes caused by **2-ethylhexanol** in humans is described in detail in the supplement from 2006. 2-Ethylhexanol concentrations of 50 ml/m^3 were found to cause severe irritation in volunteers (supplement "2-Ethylhexanol" 2006, available in German only). The increased blinking frequency determined in volunteers was used as a physiological marker for sensory irritation in the derivation of the MAK value in 2012. Calculation of the benchmark dose (BMD) and the lower confidence limit (BMDL) for an increase in the blinking frequency by 5% yielded a BMDL of 14.7 ml/m^3 (supplement "2-Ethylhexanol" 2012, available in German only).

Undiluted **1-decanol** caused slight irritation of the skin after occlusive exposure for 4 hours (ECHA 2016 b; Robinson 2000, 2001, 2002; Robinson et al. 1998). After repeated exposure (75 mg 1-decanol applied intermittently for 3 days) to the undiluted substance, severe irritation was observed (no other details; IFA 2015).

In another study (see above) **1-decanol** caused irritant reactions in 24 of 159 test persons after occlusive application for 4 hours. Of the 159 subjects, 95 reacted to the 20% aqueous preparation of sodium dodecyl sulfate included as standard. Reactions to 1-dodecanol and tetradecanol were seen in 5 of 28 and none of the 29 subjects, respectively, and reactions to a 10% acetic acid solution were found in 6 of 63 persons (Basketter et al. 2004).

In a comparative test with 24-hour application of 50% preparations of the C6 to C18 alcohols in petrolatum, **1-decanol** led to slight irritant effects in some of the 4 test persons (class 3 on a scale from 1 to 5), which were, however, somewhat more pronounced than with the homologous C8 and C12 compounds (class 2), while the longer chained C14, C16 and C18 compounds had practically no irritant effects (class 1) (Kästner 1977).

Allergenic effects

In a maximization test in 25 test persons, no sensitization was induced by a 2% preparation of 1-octanol in petrolatum (no other details) (documentation "1-Octanol" 2003).

In an earlier study, various long-chain aliphatic alcohols were tested in 1664 patients. Reactions were observed in 11 persons to a 5% 1-octanol preparation, in 15 persons to 5% **1-decanol** in petrolatum/olive oil, in 22 persons to 10% **1-decanol** in petrolatum and to 5% preparations of **1-dodecanol** (4 patients) and **1-tetradecanol** (9 patients). 15 and 21 persons, respectively, reacted also to 10% preparations of **C12** or **C14 alcohols**. Reactions to 30% **1-hexadecanol** in petrolatum were observed in only 2 of the 1664 patients. The authors emphasized that the C8 to C14 alcohols are primarily irritants, and that the observed reactions can often not be distinguished from "genuine" eczematous reactions (Hjorth and Trolle-Lassen 1963). Also in a comment on these findings the opinion was expressed that 10% preparations of these alcohols, in particular of 1-dodecanol, often lead to irritant reactions in patch tests (Kligman 1983).

Animal Experiments and in vitro Studies

Acute toxicity

In rats exposed to a 1-octanol aerosol of ≥ 5600 mg/m³ for 4 hours, pulmonary oedema and haemorrhage were observed (Bingham et al. 2001). In mice an RD_{50} of 50 ml/m³ was determined (Muller and Greff 1984). For the structurally analogous **2-ethylhexanol** an RD_{50} of 45 ml/m³ was found in mice (documentation "2-Ethylhexanol" 2003).

Subacute, subchronic and chronic toxicity

Inhalation

After inhalation exposure to 1-octanol vapour at the concentration of 400 mg/m³ (74 ml/m³) for 6 hours a day on 19 days during gestation, no treatment-related effects on feed consumption, water intake or body weights were observed in 15 Sprague Dawley rats. Examination on day 20 of gestation did not yield any unusual findings in the foetuses (see Section 5.5). As a result of the low vapour pressure of 1-octanol, a higher vapour concentration could not be produced in the study. The nose and the nasal mucosa were not investigated (Nelson et al. 1990 a, b).

Oral administration

In a study of developmental toxicity carried out according to OECD Test Guideline 414, groups of 8 to 10 pregnant Wistar rats were given gavage doses of 1-octanol (in aqueous emulsion) of 0, 130, 650, 975 or 1300 mg/kg body weight and day from days 6 to 15 of gestation. 1-Octanol doses of 650 mg/kg body weight and day caused dose-dependent nasal discharge, inflammation of the lungs and decreased feed consumption, which was accompanied by a slight delay in body weight gains. There was evidence of slight transient depression of the central nervous system (no other details). The extent of the effects increased with the duration of pregnancy. The NOAEL (no observed adverse effect level) in this study was 130 mg 1-octanol/kg body weight and day. There are no details available of maternal organ toxicity or foetotoxicity (ECHA 2016 a).

A similar NOAEL for systemic effects of 125 mg/kg body weight and day was found for **2-ethylhexanol** in a 90-day study in rats (documentation "2-Ethylhexanol" 2003).

A NOAEL of 100 mg/kg body weight and day was found for **1-dodecanol** in Wistar rats in an 8-week feeding study. In this study, in which groups of 12 male and 12 female Wistar rats were given 1-dodecanol concentrations of 0, 1500, 7500 or 30 000 mg (purity 99%) per kg feed (doses of about 0, 100, 500 and 2000 mg/kg body weight and day) for 8 weeks, no changes in body weights, feed consumption or organ weights were found and no unusual findings were observed in the gross-pathological and histopathological examinations. An additional blood analysis was carried out only in the male animals. This revealed a dose-dependent decrease in the leukocyte count after doses of about 500 and 2000 mg/kg body weight and day and in the triglyceride level at about 2000 mg/kg body weight and day. The differential

blood picture did not reflect these changes. As a result of the reduced leukocyte count, the NOAEL in this study was 100 mg/kg body weight and day (documentation "1-Dodecanol" 2006).

Dermal application

In a 90-day study carried out according to OECD Test Guideline 411, an alcohol mixture made up of around 45% 1-octanol and around 50% 1-decanol was applied semiocclusively to the dorsal skin of groups of 10 male and 10 female Sprague Dawley rats on 5 days per week. After 6 hours the solution was removed with a moist paper towel. The doses were 0, 100, 300 or 1000 mg alcohol mixture/kg body weight and day. The animals emitted cries of pain, fought during the exposure (no other details) and were oversensitive to being touched. At the low dose of the alcohol mixture of 100 mg/kg body weight and day and above, marked skin irritation occurred, which increased with the duration of the treatment (see also Section "Local effects on skin and mucous membranes"). The reduced body weights and the reduced feed consumption were attributed to the irritant effect, and the effects on the leukocyte count and albumin and globulin levels (no other details) were regarded as a response to the dermal inflammation. An increased adrenal weight, which was not accompanied by pathological changes, was probably the result of the stress caused by the irritation. In this study the LOAEL (lowest observed adverse effect level) was 100 mg alcohol mixture/kg body weight and day for local irritation and its secondary systemic sequelae (ECHA 2016 a).

Local effects on skin and mucous membranes

Skin

Undiluted 1-octanol causes mild to moderate irritation on the intact skin of rabbits and guinea pigs, but severe irritation in hairless mice (documentation "1-Octanol" 2003).

In a 90-day study carried out according to OECD Test Guideline 411 (see also Section "Dermal application"), an alcohol mixture made up of around 45% 1-octanol and around 50% 1-decanol was applied semiocclusively to the dorsal skin of groups of 10 male and 10 female Sprague Dawley rats on 5 days per week. At the low dose of 100 mg alcohol mixture/kg body weight and day, marked skin irritation occurred. Very mild to severe erythema, very mild to moderate oedema, persistent desquamation, scab formation, sloughing, clear exudate and cracking of the skin were observed. The repeated dermal applications to the already damaged skin and also the duration of the treatment exacerbated the irritant effect (ECHA 2016 a).

Eyes

Amounts of 0.1 ml 1-octanol were instilled into the conjunctival sac of one eye of 3 New Zealand White rabbits according to OECD Test Guideline 405. The eyes were not rinsed. The average scores after 24, 48 and 72 hours were 1.7 (1, 2, 2) for corneal clouding, 0.7 (0, 1, 1) for iritis, 2.2 (1.7, 2.3, 2.7) for reddening of the

conjunctiva and 2.5 (1.7, 3.0, 2.7) for swelling of the conjunctiva. The overall score (MMAS = modified maximum average score) was 41, the maximum value was not given. The irritation had regressed in 1 animal after 7 days and in 2 animals only after 14 days. 1-Octanol was classified as irritating to the eyes according to the GHS (ECHA 2016 a).

In a study with 1-octanol carried out according to OECD Test Guideline 405 in 3 New Zealand White rabbits, the following irritant effects were observed: iritis, slight to moderate inflammation of the conjunctiva and very mild to mild corneal clouding. The average irritation scores after 24, 48 and 72 hours were 2, 1 and 1 (maximum value 4) for the cornea, 1, 1 and 1 (maximum value 2) for the iris, 2.3, 1.7 and 1.3 (maximum value 3) for the conjunctiva and 1, 1.3 and 0.7 (maximum value 4) for swelling of the conjunctiva. The effects on the iris (1 rabbit) and conjunctiva (2 rabbits) had not yet completely regressed after 22 days. In this study 1-octanol was classified as irritating to the eyes according to the GHS and caused severe damage to the eyes according to the EU criteria (ECHA 2016 a).

Also in another study carried out in 6 New Zealand White rabbits according to OECD Test Guideline 405, 1-octanol was found to be irritating to the eyes according to the GHS. After 24, 48 and 72 hours the average irritation scores were 2.23 for the cornea, 0.7 for the iris, 2.57 for reddening of the conjunctiva and 1.9 for swelling of the conjunctiva. Individual values were not given (ECHA 2016 a).

In other publications it was reported that the instillation of 1-octanol into the conjunctival sac of rabbits caused transient changes to the cornea (no other details), which had regressed after 48 hours (Grant 1986), and that the scores for erythema were 2.54, for inflammation of the conjunctiva 1.83 and for corneal clouding 2.11 (Jacobs and Martens 1989).

In a Draize test in the rabbit eye, 50% 1-octanol in olive oil caused slight irritation (no other details) (documentation "1-Octanol" 2003).

For the structurally analogous substance **2-ethylhexanol** the average values were 2.56 of 3 for erythema, 0.78 of 4 for oedema of the conjunctiva, 1.44 of 4 for corneal clouding and 0.89 of 2 for iritis (documentation "1-Octanol" 2003).

In another study carried out in 4 New Zealand White rabbits according to OECD Test Guideline 405 with **2-ethylhexanol**, the average irritation scores after 24, 48 and 72 hours were 1.75 for the cornea, 0.67 for the iris, 2.08 for reddening of the conjunctiva and 1.92 for swelling of the conjunctiva. 2-Ethylhexanol was regarded as irritating to the eyes by the registrants (ECHA 2016 c).

Both 1-octanol and 2-ethylhexanol were therefore classified by the registrants according to the GHS as "causing severe eye irritation" (ECHA 2016 a, c).

Allergenic effects

Sensitizing effects on the skin

There are no data available for the sensitizing effects on the skin of 1-octanol.

In a Bühler test in 10 guinea pigs, in which the induction treatment was carried out with 0.4 ml undiluted **1-decanol** and the challenge treatment with 0.4 ml 25% 1-decanol in mineral oil (no other details), 1-decanol was not found to cause sensitization (ECHA 2016 b).

Sensitizing effects on the airways

There are no data available for the sensitizing effects on the airways of 1-octanol.

Reproductive and developmental toxicity

Fertility

There are no studies available of the effects on fertility after the administration of 1-octanol.

In a one-generation study, male and female Wistar rats were given 0, 1500, 7500 or 30 000 mg **1-dodecanol** (purity 99%) per kg feed (1-dodecanol doses of around 0, 100, 500 or 2000 mg/kg body weight and day) for 2 weeks. Over an investigation period of 8 weeks, the incidence of pregnancy, the duration of pregnancy, the number of offspring per litter, the weight and sex ratio of the offspring and the number of live births up to day 5 after birth were not significantly changed (documentation "1-Dodecanol" 2006).

Developmental toxicity

Inhalation

In 15 pregnant Sprague Dawley rats exposed by inhalation to a 1-octanol concentration of 400 mg/m^3 (highest possible vapour concentration at room temperature) daily for 6 hours a day during the first 19 days of gestation, no treatment-related effects occurred. Feed consumption, water intake and body weights were monitored (see also Section "Subacute, subchronic and chronic toxicity"); on day 20 of gestation the incidence of resorptions and the foetal weights were determined, and the foetuses were examined for skeletal and visceral malformations (Nelson et al. 1990 a, b). There were no concurrent controls in the study. The results for control animals from other studies of the research group carried out at a similar time (Nelson et al. 1990 a, b), however, provide a good overview of the foetotoxic parameters of untreated animals. In view of the study design and the good documentation, this study is regarded as valid.

1-Decanol was also investigated by the same authors with the same study design. No treatment-related effects occurred at the highest possible vapour concentration at room temperature of 100 mg/m^3 (Nelson et al. 1990 a, b).

Oral administration

In a study of developmental toxicity carried out according to OECD Test Guideline 414, groups of 8 to 10 pregnant Wistar rats were given gavage doses of 1-octanol (in aqueous emulsion) of 0, 130, 650, 975 or 1300 mg/kg body weight and day from days 6 to 15 of gestation. At 650 mg/kg body weight and day and above, 1-octanol caused dose-dependent nasal discharge, pulmonary inflammation and reduced feed consumption, accompanied by a slight delay in body weight gains. There was evidence of slight transient depression of the central nervous system (no other details). The severity of the effects increased with the duration of pregnancy. The NOAEL in this study was 130 mg 1-octanol/kg body weight and day. No data were given for

maternal organ toxicity or foetotoxicity. There were no toxic effects on development (ECHA 2016 a; Hellwig and Jäckh 1997).

In vitro

Mouse embryos at a stage in development of three to five somites were cultured for 6 hours in 3, 10 or 50 µM 1-octanol and subsequently for 20 hours in the control medium. At 10 µM 1-octanol and above, delays in somite formation occurred. The pronounced inhibition in growth that occurred in the same investigation system with ethanol could be reduced by 1-octanol (Chen et al. 2000).

Genotoxicity

In vitro

1-Octanol was not found to be mutagenic in Salmonella mutagenicity tests in the strains TA98, TA100, TA1535, TA1537 and TA1538 in either the presence or absence of a metabolic activation system in the concentration range from 4 to 2500 µg/plate. There are no data available for cytotoxicity (documentation "1-Octanol" 2003).

In V79 cells, 1-octanol concentrations of around 0.1 mM (about 0.013 mg/ml) and above induced spindle disorders (c mitoses and aneuploidies); the occurrence of such disorders was explained as an unspecific (physical) mechanism based on the distribution of the lipophilic compound in hydrophobic cell compartments. The authors noted that the concentrations may have been lower than those given as a result of the poor solubility of 1-octanol in water (documentation "1-Octanol" 2003).

In vivo

There are no data available.

Carcinogenicity

Relevant carcinogenicity studies are not available.

Manifesto (MAK value/classification)

The critical effect of 1-octanol is the irritation seen in the Draize test in the rabbit eye and which is evident from the low RD_{50} in mice and the corresponding data for the structurally similar 2-ethylhexanol.

MAK value. Relevant inhalation studies or even oral studies with 1-octanol in animals are not available; the evaluation of the systemic and local effects is therefore based on data for better-investigated structurally analogous substances. In an 8-week feeding study with 1-dodecanol in Wistar rats, a NOAEL of 100 mg/kg body weight and day was obtained. Also for 2-ethylhexanol, the NOAEL for systemic effects was 125 mg/kg body weight and day in a 90-day study with oral administration on 5 days a week, so that also for 1-octanol a NOAEL can be assumed in the

range of 100 mg/kg body weight and day. The following toxicokinetic data are taken into consideration for the extrapolation of an assumed NAEL (no adverse effect level) of 100 mg/kg body weight and day to a concentration in workplace air: the daily exposure of the animals in comparison with the 5 days per week exposure at the workplace (7:5), the corresponding species-specific correction value (1:4) for the rat, the assumed oral absorption (100%), the body weight (70 kg) and respiratory volume (10 m^3) of the person, and the assumed 100% absorption by inhalation. The concentration calculated from this is 245 mg 1-octanol/m^3 (45 ml/m^3). With 2-ethylhexanol, a concentration of 219 mg/m^3 (40 ml/m^3) is calculated. After 90-day inhalation exposure to 2-ethylhexanol, however, the NOAEC (no observed adverse effect concentration) for rats was the highest concentration tested of 120 ml/m^3; oral administration may therefore represent a worst case scenario.

As 1-octanol is classified as irritating to the eyes and an irritant effect on the airways is to be assumed, but there are no studies available with repeated inhalation exposure, the MAK value has been derived in analogy to the better-investigated structurally similar alcohol 2-ethylhexanol; irritation of the eyes is the main effect also for this substance. The RD_{50} (50% reduction in the respiratory frequency as a measure of sensory irritation) in mice is used as the basis for the comparison of these two substances. The RD_{50} for 1-octanol is 50 ml/m^3 and that for 2-ethylhexanol 45 ml/m^3. The RD_{50} values for alcohols decrease with increasing molar mass (Muller and Greff 1984) and thus the strength of the sensory irritation increases, so that the MAK values for short-chain alcohols, such as that of 20 ml/m^3 for the pentanols, cannot be applied for 1-octanol. 2-Ethylhexanol has the same molar mass as 1-octanol. For this reason 2-ethylhexanol is the best analogous substance for 1-octanol. As a result of the irritant effect observed in studies with volunteers, which was determined as an increase in the blinking frequency, a MAK value of 10 ml/m^3 was derived for 2-ethylhexanol in 2012. The blinking frequency has not been determined in volunteers exposed to 1-octanol. In view of the comparable strength of the irritation in the eye observed in the Draize test and the similar RD50 values, also the eye irritation caused by exposure to the two compounds in vapour form is expected to be similar and the MAK value for 1-octanol has therefore been set in analogy to 2-ethylhexanol at 10 ml/m^3. After applying a factor 2 for a possible increase in the effects over time and for the extrapolation of the results from animal experiments to humans, a value of 10 ml/m^3 is obtained also for the systemic effect. As for 2-ethylhexanol, this probably represents the worst case, however.

Peak limitation. As the MAK value for 1-octanol is derived on the basis of the irritant effect, the substance is classified in Peak Limitation Category I. In analogy to 2-ethylhexanol, an excursion factor of 1 has been set.

Prenatal toxicity. After inhalation exposure of pregnant Sprague Dawley rats to a 1-octanol concentration of 400 mg/m^3 for 19 days, no treatment-related effects were observed in the dams and foetuses. In the study, which is regarded as valid, the maximum possible vapour concentration of 400 mg 1-octanol/m^3 was used. The true concentration without effects could therefore be higher. As the blood:air partition coefficient of 1-octanol of 3.41 is below 5 (see also List of MAK and BAT Values, Section I b and I c), the higher respiratory volume at the workplace need not be

taken into consideration. The NOAEC of 400 mg/m³ is around 8 times higher than the MAK value of 54 mg/m³.

A NOAEL of 1300 mg/kg body weight and day was derived for developmental toxicity from an oral study with rats carried out according to OECD Test Guideline 414; this was the highest dose tested. The NOAEL for maternal toxicity was 130 mg/kg body weight and day. Taking into consideration the toxicokinetic data, the extrapolation of the NOAEL for developmental toxicity to a concentration in workplace air (see "MAK value" above for the conversion factors applied; adjustment for a five-day working week is not necessary) yields a concentration of 2275 mg 1-octanol/m³ or 421 ml/m³. The 42-fold margin between the calculated NAEC (no adverse effect concentration) for developmental toxicity and the MAK value of 10 ml/m³ is therefore sufficiently large also after oral administration. 1-Octanol is therefore classified in Pregnancy Risk Group C.

Carcinogenicity and germ cell mutagenicity. 1-Octanol is not mutagenic in bacteria. Valid long-term studies with 1-octanol are not available. As carcinogenic effects are not to be expected in view of the structure of the substance, 1-octanol is not classified in any of the categories for carcinogenicity or germ cell mutagenicity.

Absorption through the skin. On the basis of the experimental results, under standard conditions (exposure for one hour, an exposed area of 2000 cm² of skin) the amount dermally absorbed is calculated to be about 12 mg. By analogy with the NOAEL for 1-dodecanol (100 mg/kg body weight) and 2-ethylhexanol (125 mg/kg body weight), after toxicokinetic correction (1:4), extrapolation from subchronic to chronic exposure (1:2) and after taking into consideration the daily administration (7:5) and extrapolation of the data from animal experiments to humans (1:2) with a body weight of 70 kg, a tolerable dose of about 613 mg is calculated. The expected body burden after skin contact with the substance at the workplace is thus considerably below the tolerable body burden. 1-Octanol is therefore not designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

Sensitization. There are no valid positive clinical findings for the contact-sensitizing effects of 1-octanol. Regarding structure–activity relationships and comparison with the homologous alcohols, contact-sensitizing effects of 1-octanol are not to be expected. There are no animal studies of the contact-sensitizing effects or findings for sensitizing effects on the airways. 1-Octanol is therefore not designated with either "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

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