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4-Methyl-3-penten-2-one

MAK Value Documentation, supplement – Translation of the German version from 2016

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4-methyl-3-penten-2-one; irritation; olfactory epithelium; maximum workplace concentration; MAK value; peak limitation; toxicity

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum concentration at the work place (MAK value) for 4-methyl-3-pentene-2-one (mesityl oxide) of 5 ml/m^3, considering local and systemic toxicity as well as developmental toxicity. As described in the last evaluation from 2006, 4-methyl-3-pentene-2-one is irritating to eyes and skin. Starting at the lowest concentration of 31 ml/m^3 in a 49-day-inhalation-study with daily exposure, exudate in the olfactory epithelium is observed in 10 of 24 rats. A NAEC of 10 ml/m^3 is extrapolated. Since 2014, the Commission uses an empirical approach to set MAK values for substances with critical effects on the upper respiratory tract or the eyes. Taking into consideration exposure of rats took place 7 days a week and no chronic study is available, it is assumed, that the chronic NAEC is 5 ml/m^3. As olfactory epithelium is the target tissue, according to the empirical approach, the MAK-value is reduced to 2 ml/m^3. The assignment to Peak Limitation Category I, because local effects are critical, and the excursion factor of 2 are confirmed. As there are no developmental toxicity studies, the assignment to Pregnancy Risk Group D is confirmed.

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MAK value (2015)	**2 ml/m³ (ppm) ≙ 8.1 mg/m³**
Peak limitation (2006)	**Category I, excursion factor 2**
Absorption through the skin (2006)	**H**
Sensitization	–
Carcinogenicity	–
Prenatal toxicity (2006)	**Pregnancy Risk Group D**
Germ cell mutagenicity	–
BAT value	–
BAR/BLW/EKA	–
CAS number	141-79-7
Molar mass	98.14 g/mol
Vapour pressure at 25 °C	19.31 hPa (ECHA 2013)
log K_{OW}	1.37 (calculated) (Greim 2007; ECHA 2013)
Solubility at 20 °C	26.98 g/l water (ECHA 2013)
1 ml/m³ (ppm) ≙ 4.072 mg/m³	**1 mg/m³ ≙ 0.246 ml/m³ (ppm)**

Since 2014, the Commission has been using a procedure based on physiological and empirical aspects (Brüning et al. 2014) to derive MAK values for substances that act on the upper respiratory tract and the eyes, which also describes criteria for categorization as a sensory irritant. This procedure is used here to review the MAK value.

For 4-methyl-3-pentene-2-one a documentation is available from 2007 (Greim 2007, available in German only). In the meantime, new data for irritation but no new data for repeated inhalation toxicity and reproductive toxicity have become available.

Effects in Humans

As described in the documentation of 2007 (Greim 2007), volunteers were exposed to 4-methyl-3-pentene-2-one concentrations of 25 or 50 ml/m³ for 15 minutes. The majority of the persons reported slight eye irritation at 25 ml/m³; at 50 ml/m³ 4-methyl-3-pentene-2-one caused irritation also in the nasal region and had an unpleasant odour.

There are no data available for other end points.

Animal Experiments and in vitro Studies

Acute toxicity

Inhalation

In a newly available study to determine the RD_{50} value, the normal respiratory rate of Swiss-OF1 mice was determined in a plethysmograph and the animals were then exposed head-only to 4-methyl-3-pentene-2-one for 15 minutes (6 animals per concentration). The change in respiratory rate was evaluated as a measure of sensory irritation. The respira-

tory rate decreased in a concentration-dependent manner by 29%, 43%, 63% and 73% during exposure for 15 minutes to 4-methyl-3-pentene-2-one concentrations of 41, 48, 71 and 117 ml/m^3, respectively. In addition, a behavioural test was performed in which the immobility phase was determined in a swimming test after inhalation exposure of mice to 4-methyl-3-pentene-2-one. After inhalation exposure to the same concentrations for 4 hours, the immobility phase was extended by 31%, 34%, 60% and 67%, respectively. All the changes were significant ($p < 0.05$, Student's t-test). The RD_{50} value in this study was calculated to be 61 ml/m^3 (De Ceaurriz et al. 1984).

Oral administration

A study in female Sprague Dawley rats according to OECD Test Guideline 423 yielded an LD_{50} value for 4-methyl-3-pentene-2-one of above 300 mg/kg body weight (no mortality in 6 animals) and below 2000 mg/kg body weight (all 3 animals died within 2 days) (ECHA 2013). This is not contained in the documentation of 2007 (Greim 2007).

Dermal application

Also not mentioned in the documentation of 2007 (Greim 2007) is a dermal LD_{50} value of 5150 mg/kg body weight in rabbits (ECHA 2013).

Subacute, subchronic and chronic toxicity

Inhalation

As described in the documentation of 2007 (Greim 2007), in the study relevant to the MAK value, groups of 12 Sprague Dawley rats were exposed to 4-methyl-3-pentene-2-one concentrations of 0, 31, 103 or 302 ml/m^3 for 6 hours daily, on 7 days per week, for up to 49 days in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to OECD Test Guideline 422. At concentrations of 31 ml/m^3 and above, substance-related findings occurred; on the one hand a concentration-dependent reduction in feed intake, on the other hand increased nasal secretion and histopathological findings in the nose: exudate at the low concentration in the olfactory epithelium in 10 of 24 animals and at the middle concentration and above also in the respiratory epithelium as well as metaplasia in both types of epithelium; additionally at 302 ml/m^3 inflammation in the respiratory epithelium. In this study, the LOAEC (lowest observed adverse effect concentration) for the parent animals was 31 ml 4-methyl-3-pentene-2-one/m^3 (Greim 2007).

There are no other studies available.

Local effects on skin and mucous membranes

Skin

In a study carried out according to OECD Test Guideline 404 in New Zealand White rabbits, not included in the 2007 documentation (Greim 2007), 0.5 ml undiluted substance had an irritant effect on the dorsal skin after a semi-occlusive application for 4 hours and 14-day follow-up period; the individual variability was great. In one animal erythema was significantly more pronounced (with a maximum score of 3 out of 4 on day 15) than in the other two animals (with a maximum score of 1 after 24 hours or 7 days and complete regression by day 15) (ECHA 2013).

The new data confirm the marked irritant effect on the skin.

Eyes

In a study carried out according to OECD Test Guideline 437, not included in the 2007 documentation (Greim 2007), 0.75 ml undiluted 4-methyl-3-pentene-2-one was applied to the corneal epithelium of 3 isolated bovine eyes for 10 minutes and then observed for 2 hours. The positive control was 10% sodium hydroxide and the negative control was physiological saline. The mean opacity at the end of the experiment was 11, and 133 for the positive control and 0.3 for the negative control. After assessing the opacity, the cornea was treated with 0.4% sodium fluorescein to investigate changes in permeability. The results for 4-methyl-3-pentene-2-one ($OD_{490:}$ 2.01) and the positive control ($OD_{490:}$ 2.16) were similar. According to the evaluation system of this experiment, 4-methyl-3-pentene-2-one causes a slight change in opacity and a great change in the permeability in vitro of the cornea of bovine eyes. The IVIS (In Vitro Irritancy Score) as a measure of irritant intensity was given as 41.2; at 50 and above a substance is considered to be a strong irritant (ECHA 2013).

The new data confirm the irritant effect in the eye (Greim 2007).

Allergenic effects

Sensitizing effects on the skin

In a maximization test according to OECD Test Guideline 406 with 10 female and 10 male Dunkin Hartley guinea pigs, 4-methyl-3-pentene-2-one (purity: 96.63%) did not cause sensitization in any of the 20 animals. Intradermal induction treatment was performed with a 10% preparation in paraffin and epicutaneous induction treatment with the undiluted substance. A 10% preparation in petrolatum was used for the occlusive challenge treatment. As 4-methyl-3-pentene-2-one had proved to be non-irritant in a preliminary test, non-occlusive pre-treatment of the animals with 10% sodium lauryl sulfate in petrolatum was performed the day before. None of the animals produced a reaction 24 and 48 hours after the challenge treatment with undiluted 4-methyl-3-pentene-2-one (ECHA 2013).

Sensitizing effects on the airways

There are no data available.

Manifesto (MAK value/classification)

The critical effect of 4-methyl-3-pentene-2-one is the irritant effect on the eye, skin and respiratory tract.

MAK value. The effects observed after the exposure of rats to the LOAEC of 31 ml 4-methyl-3-pentene-2-one/m³ for 36 to 49 days were nasal secretion and exudate with a few leukocytes and granulocytes in the olfactory epithelium (Greim 2007). These effects are adverse and must be taken into consideration for the derivation of the MAK value. Although a NOAEC (no observed adverse effect concentration) was not obtained, the incidence of exudate in the olfactory epithelium is, at 10 animals out of 24, of a magnitude which allows a NAEC (no adverse effect concentration) to be extrapolated.

According to the procedure described by Brüning et al. (2014), from the LOAEC of 31 ml/m³ a NAEC of 10 ml/m³ can be calculated. The animals were exposed on 7 days per week, so that after 5 days there was no exposure-free interval for regeneration. As no long-term studies are available, it is assumed for long-term exposures, taking into account the daily exposure of the animals in comparison with the 5-day exposure per week at the workplace, that the NAEC decreases to 5 ml/m³. Since the findings occurred in the olfactory epithelium of the rat, a concentration of 2.5 ml/m³ is obtained for humans. The MAK value has therefore been lowered to 2 ml 4-methyl-3-pentene-2-one/m³.

Peak limitation. Peak Limitation Category I with an excursion factor of 2 has been retained. At this permissible concentration of 4 ml/m^3, eye irritation is not to be expected; this was not observed in volunteers until after exposure to 25 ml 4-methyl-3-pentene-2-one/m^3 for 15 minutes.

Prenatal toxicity. As there is still only a screening study of developmental toxicity in rats, carried out in accordance with OECD Test Guideline 422, and thus no studies of the teratogenic effects, the assignment of 4-methyl-3-pentene-2-one to Pregnancy Risk Group D has been retained.

Sensitization. There are still no clinical findings of contact sensitization, but a negative result in a valid maximization test is available. Data for respiratory sensitization are not available. 4-Methyl-3-pentene-2-one has therefore not been designated with "Sh" or "Sa" (for substances which cause sensitization of the skin or airways).

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