tert-Butyl alcohol / 2-Methylpropan-2-ol

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 re-evaluated the Pregnancy Risk Group of tert-butyl alcohol [75-65-0].
In rats, fetal weights were reduced at 2000 ml/m³, the LOAEC for developmental toxicity after inhalation. A 95% lower confidence limit of the benchmark dose for developmental toxicity of 1600 ml/m³ was calculated. After now considering the increased respiratory volume at the workplace (see List of MAK and BAT Values, Sections I b and I c) this concentration corresponds to 800 ml/m³ at the workplace. The difference to the MAK value of 20 ml/m³ is still sufficient so that damage to the embryo or foetus is unlikely when the MAK value is observed. tert-Butyl alcohol remains assigned to Pregnancy Risk Group C.
In a screening study based on OECD guideline 421 the NOAEL for fetotoxicity is 400 mg/kg body weight and day in rats. After toxicokinetic scaling this dose corresponds to a concentration of 230 ml/m³ at the workplace. The difference between the NOAEL for fetotoxicity for rats and the MAK value of 20 ml/m³ confirms the assignment to Pregnancy Risk Group C.
For mice, no NOAEL for developmental toxicity was obtained. At the LOAEL for developmental toxicity after gavage of 1600 mg/kg body weight and day, increased numbers of resorptions and reduced litter size, but no malformations occurred. After toxicokinetic scaling this dose corresponds to a concentration of 520 ml/m³ at the workplace. The difference between the LOAEL for developmental toxicity for mice and the MAK value does not contradict the retention of the assignment to Pregnancy Risk Group C, particularly as a bolus administration (gavage) is considered to be a worst case compared with a continuous exposure at the workplace.

Keywords

tert-butyl alcohol; 2-methylpropan-2-ol; developmental toxicity; prenatal toxicity; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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tert-Butyl alcohol

[75-65-0]

Supplement 2018

MAK value (1999)	**20 ml/m³ (ppm) ≙ 62 mg/m³**
Peak limitation (2002)	**Category II, excursion factor 4**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2006)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
1 ml/m³ (ppm) ≙ 3.076 mg/m³	**1 mg/m³ ≙ 0.325 ml/m³ (ppm)**

Documentation for *tert*-butyl alcohol was published in 1999 (documentation "tert-Butyl alcohol" 2003), followed by a supplement on developmental toxicity in 2007 (supplement "tert-Butyl alcohol" 2007) and another on a large number of end points in 2014 (supplement "tert-Butyl alcohol" 2014).

In 2016, the Commission began using a revised approach for assessing substances with a MAK value based on systemic effects and derived from inhalation studies in animals or studies with volunteers at rest; this new approach takes into account that the respiratory volume at the workplace is higher than under experimental conditions. However, this does not apply to gases or vapour with a blood:air partition coefficient < 5 (see List of MAK and BAT Values, Sections I b and I c). The experimentally derived blood:air partition coefficient of *tert*-butyl alcohol is 462 (documentation "tert-Butyl alcohol" 2003), a value that is significantly higher than 5. The increased respiratory volume does not apply in this case because the MAK value for *tert*-butyl alcohol was derived from a drinking water study. However, this supplement does take the increased respiratory volume into consideration when reassessing the classification of the substance in Pregnancy Risk Group C because the study that is relevant for the assessment is an inhalation study.

Developmental toxicity

Studies with rats and mice are available for the assessment of the toxic effects of *tert*-butyl alcohol on prenatal, perinatal and postnatal development (see supplement "tert-Butyl alcohol" 2007, supplement "tert-Butyl alcohol" 2014). In a study of the toxic effects on prenatal development in Sprague Dawley rats, inhalation exposure at the lowest concentration tested of 2000 ml/m³ still caused reduced foetal body weights. Concentrations of 3500 ml/m³ led to skeletal variations. Maternal toxicity, expressed as significantly reduced body weight development and reduced feed consumption, was first observed at 5000 ml/m³ (Nelson et al. 1989). A value of 1600 ml/m³ was determined as the lower limit of the relevant 95% confidence interval (95%-BMDL: benchmark dose lower confidence limit) for reduced foetal body weights.

In a modified screening study carried out according to OECD Test Guideline 421 in Sprague Dawley rats with gavage administration, perinatal mortality was increased and litter sizes reduced at 1000 mg/kg body weight and day. The NOAEL for foetal toxicity was 400 mg/kg body weight and day; this was accompanied by maternal toxicity in the form of effects on the nervous system that were expressed as lethargy and ataxia. The NOAEL for maternal toxicity was 160 mg/kg body weight and day (Propylene Carbonate/t-Butyl Alcohol HPV Committee 2004). In CBA/J and C57Bl/6 J mice and Swiss Webster mice, an increase in resorptions and reduced litter sizes were observed at the lowest doses tested of 1600 and 3110 mg/kg body weight and day; these exceed the recommended maximum dose of 1000 mg/kg body weight and day (limit dose) (Daniel and Evans 1982; Faulkner et al. 1989).

After prenatal exposure of Swiss Webster mice, postnatal toxicity was observed at the lowest dose of 3110 mg/kg body weight and day and above after oral administration (Daniel and Evans 1982). Postnatal toxicity was not observed in Sprague Dawley rats exposed to concentrations of up to 4000 ml/m³ in an inhalation study (Nelson et al. 1991). After oral administration of 1000 mg/kg body weight and day to Sprague Dawley rats beginning 2 weeks before gestation and continuing up to the end of lactation, perinatal mortality and reduced body weights were observed in the foetuses up to the end of lactation. In addition, reduced litter sizes were recorded on postnatal day 4. The NOAEL for the toxic effects on prenatal and postnatal development in rats was 400 mg/kg body weight and day (Propylene Carbonate/t-Butyl Alcohol HPV Committee 2004).

Manifesto (prenatal toxicity)

Prenatal toxicity. In a developmental toxicity study with exposure of Sprague Dawley rats to *tert*-butyl alcohol by inhalation, reduced foetal body weights were observed at the lowest concentration tested of 2000 ml/m³ and the incidence of skeletal variations (rudimentary cervical ribs) was found to be increased at 3500 ml/m³ and above (Nelson et al. 1989). The 95%-BMDL was 1600 ml/m³ (supplement "tert-Butyl alcohol" 2007). In a modified screening study carried out according to OECD Test Guideline 421, the NOAEL for foetal toxicity in rats after oral administration was 400 mg/kg body weight and day, which after toxicokinetic

extrapolation is equivalent to 230 ml/m³ (see List of MAK and BAT Values, Section I c) and is thus 12 times higher than the MAK value of 20 ml/m³. For mice, only a LOAEL after oral administration is available, which is above the recommended limit dose of 1000 mg/kg body weight and led to increased resorptions and reduced litter sizes, but no malformations. The LOAEL of 1600 mg/kg body weight and day (equivalent to 520 ml/m³ after toxicokinetic extrapolation; see List of MAK and BAT Values, Section I c) is 26 times higher than the MAK value, and thus supports continued classification in Pregnancy Risk Group C, particularly as oral administration in bolus form is to be considered the worst-case scenario in comparison with continuous exposure at the workplace (supplement "tert-Butyl alcohol" 2014). Taking into consideration the increased respiratory volume (1:2), there is a 40-fold difference between the 95%-BMDL for developmental toxicity in rats of 1600 ml/m³ after exposure by inhalation and the MAK value for *tert*-butyl alcohol of 20 ml/m³. Although in some cases developmental toxicity was observed at concentrations that were not toxic to the dams and that were 50 to 88 times the MAK value, this difference and the 12-fold difference to the calculated NOAEC for foetal toxicity after gavage administration in rats support continued classification in Pregnancy Risk Group C.

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