The MAK Collection for Occupational Health and Safety

tert-Butyl acetate

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

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tert-Butyl acetate

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 maximum concentration at the workplace (MAK value) and the Pregnancy Risk Group for *tert*-butyl acetate [540-88-5].
Critical effects are transient acute neurotoxic symptoms which are observed in a 90-day-study with mice with a NOAEC of 100 ml/m³. From this concentration the former MAK value of 50 ml/m³ was derived. It is now lowered to 20 ml/m³ taking into account the increased respiratory volume at the workplace because the blood:air partition coefficient of *tert*-butyl acetate is > 5 (see List of MAK and BAT Values, Sections I b and I c). This value also provides protection from irritation. Since a systemic effect is critical, Peak Limitation Category II is retained. The excursion factor of 2 is set in spite of the short half-life of *tert*-butyl acetate in blood as it is an acute effect for which an adaptation during subchronic exposure has been noticed. Therefore, peaks of exposure will not enhance the effect at chronic exposure. Furthermore, since the incidences after 90 days at 400 ml/m³ are low, the true NAEC might have been higher than 100 ml/m³.
tert-Butyl acetate had been classified in Pregnancy Risk Group C because the NOAEC for fetotoxicity is 1600 ml/m³ in a screening study in rats and taking into consideration the data for the metabolite *tert*-butyl alcohol. There is no new data on developmental toxicity. This classification is retained even considering the increased respiratory volume at the workplace.

Keywords

tert-butyl acetate; acetic acid tert-butyl ester; acetic acid 1,1-dimethylethyl ester; (sub)acute toxicity; (sub)chronic toxicity; genotoxicity; peak limitation; prenatal toxicity; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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tert-Butyl acetate

[540-88-5]

Supplement 2018

MAK value (2017)	**20 ml/m³ (ppm) ≙ 96 mg/m³**
Peak limitation (2013)	**Category II, excursion factor 2**
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2014)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value	**–**
Vapour pressure at 25 °C	62.66 hPa (SRC 2017)
log K_{OW} [1)]	1.76 (SRC 2017)
1 ml/m³ (ppm) ≙ 4.82 mg/m³	**1 mg/m³ ≙ 0.207 ml/m³ (ppm)**

Documentation was published for *tert*-butyl acetate in 1999 (documentation "*tert*-Butyl acetate" 2003), followed by a supplement on all end points in 2014 (supplement "*tert*-Butyl acetate" 2014). Reviews of the studies cited in these documents, some of which had not been published, have in the meantime become available (Bus et al. 2015; Faber et al. 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 vapours if their blood:air partition coefficient is < 5 (see List of MAK and BAT Values, Sections I b and I c). The blood:air partition coefficient calculated according to the formula of Buist et al. (2012) is 31.5. This supplement reviews whether the MAK value and the Pregnancy Risk Group for *tert*-butyl acetate need to be amended as a result of the higher respiratory volume at the workplace.

1) octanol/water partition coefficient

Animal Experiments and in vitro Studies

Subacute, subchronic and chronic toxicity

Inhalation

After whole-body exposure in inhalation chambers for 6 hours a day for 14 days, the target organ in female CD1 mice at *tert*-butyl acetate concentrations of 375 ml/m^3 and above was found to be the liver, with hypertrophy of the centrilobular hepatocytes and increased liver weights. At 750 ml/m^3 and above, hyperactivity and excessive grooming were observed; these are both CNS effects. The highest concentration tested of 1500 ml/m^3 induced hyperactivity or hypoactivity and impaired equilibrium in mice of both sexes. The groups were composed of 5 animals per sex (Cruzan and Kirkpatrick 2006; Lyondell Chemical Company 2007; supplement "*tert*-Butyl acetate" 2014).

In a 13-week inhalation study carried out according to Test Guideline OPPTS 870.3465 of the US EPA with whole-body exposure of groups of 30 male and 30 female CD1 mice for 6 hours a day on 7 days a week, symptoms such as hyperactivity and increased grooming were observed during and particularly after exposure; these observations were assessed as acute neurotoxic effects. These symptoms were sporadically found in the animals exposed to a *tert*-butyl acetate concentration of 100 ml/m^3 and were clearly substance-related at 400 ml/m^3 and above. Likewise, symptoms that were associated with hyperactivity were sporadically observed in the females of the control group during the 6-hour exposure period. In the group exposed to 1600 ml/m^3, the absolute liver weights were increased in the females and the relative liver weights were increased in both males and females. Centrilobular hypertrophy of the liver was detected in one female. In addition, mild degeneration was observed in the adrenal cortex of the females (Bus et al. 2015; Faber et al. 2014; Lyondell Chemical Company 2006; supplement "*tert*-Butyl acetate" 2014). In the review of Bus et al. (2015) the observed hyperactivity was shown to be a plausible effect of *tert*-butyl acetate: the functional observational battery (FOB) tests, which yielded no changes, were carried out 15 minutes to 2.5 hours after the end of exposure, whereas the clinical observations were completed within the first hour after the end of exposure. The concentrations of *tert*-butyl acetate in the serum of rats reached their maximum at the end of exposure and rapidly decreased after the end of exposure; this also applied to the decrease in hyperactivity in mice. Similar toxicokinetics are assumed to apply for mice and rats. As the *tert*-butyl alcohol levels in the serum were still markedly increased during the period in which the FOB tests were carried out (no other details), these observations confirm the assumption that the neurotoxic effects were not caused by the metabolite *tert*-butyl alcohol (Bus et al. 2015).

Table 1 shows the incidences of hyperactivity in male and female CD1 mice on the basis of observations that were made 1 hour after the end of exposure (Bus et al. 2015). The original study reported hyperactivity that was sporadically observed also in the female control animals during exposure (Lyondell Chemical Company 2006).

Table 1 Incidences of hyperactivity in male and female CD1 mice after 13-week inhalation exposure established 1 hour after the end of exposure (Bus et al. 2015)

Exposure week	Incidences of hyperactivity ♂				Incidences of hyperactivity ♀			
	exposure concentration (ml/m³)				exposure concentration (ml/m³)			
	0	100	400	1600	0	100	400	1600
1	0/30	0/30	0/30	26/30	0/30	0/30	0/30	24/30
2	0/30	0/29	0/30	24/30	0/30	0/30	0/30	25/29
3	0/30	0/29	0/30	26/30	0/30	0/30	0/30	21/29
4	0/30	0/29	5/30	22/30	0/30	0/30	8/30	20/29
5	0/30	0/29	3/30	14/30	0/30	1/30	2/30	12/29
6	0/10	0/10	1/9	4/9	0/9	0/9	0/10	5/10
7	0/10	0/10	2/9	5/9	0/9	1/9	0/10	7/10
8	0/10	0/10	0/9	6/9	0/8	1/9	4/10	5/10
9	0/10	5/10	3/9	8/9	0/8	1/9	4/10	7/10
10	0/10	0/10	1/9	6/9	0/8	1/9	2/9	6/10
11	0/10	0/10	0/9	7/9	0/8	0/9	1/9	7/10
12	0/10	0/10	1/9	7/9	0/8	0/9	1/9	6/10
13	0/10	0/10	1/9	5/9	0/8	0/9	2/9	5/10

The time course of the incidences of hyperactivity shows that after exposure to a concentration of 400 ml/m³ the maximum was reached after about 4 to 5 weeks; no further increase was later observed. Thus, an intensification of the effects with an increase in the exposure duration is unlikely. Likewise, adaptation occurred after exposure to a concentration of 1600 ml/m³.

A 90-day inhalation study carried out according to OPPTS Test Guidelines 870.3465, 870.3650 and 870.7800 of the US EPA with whole-body exposure of groups of 10 male and 10 female Sprague Dawley rats for 6 hours a day on 7 days a week revealed increased motor activity of the males at 1600 ml/m³; this supports the assumption that *tert*-butyl acetate causes neurotoxic effects. The α2u-globulin nephropathy that was observed in the male rats at 100 ml/m³ and above is species-specific and sex-specific and is not considered to be of relevance for humans (Lyondell Chemical Company 2011; supplement "*tert*-Butyl acetate" 2014).

Summary:

In the 90-day inhalation studies with mice and rats, the acute effect on the CNS in CD1 mice was the most sensitive systemic end point for the derivation of a MAK value. The LOAEC (lowest observed adverse effect concentration) for this effect was 400 ml/m³ and the NOAEC (no observed adverse effect concentration) was 100 ml/m³ because only a few animals were affected at this concentration and also a number of females of the control group were found to have these symptoms during the exposure.

Reproductive and developmental toxicity

Developmental toxicity

No new data have been published for this end point since the supplement of 2014 (supplement "*tert*-Butyl acetate" 2014).

Genotoxicity

As described in the 2014 supplement (supplement "*tert*-Butyl acetate" 2014), *tert*-butyl acetate was not found to be mutagenic in bacteria. Likewise, the substance did not cause mutations in a mutation test with L5178Y mouse lymphoma cells up to concentrations of 1162 µg/ml in either the presence or absence of a metabolic activation system (ECHA 2016). Clastogenicity was not observed in vitro or in vivo (supplement "*tert*-Butyl acetate" 2014).

Manifesto (MAK value/classification)

The critical effect of *tert*-butyl acetate is transient hyperactivity in mice, which is interpreted as an acute effect on the CNS.

MAK value. The results of a 90-day study in mice are decisive for the level of the MAK value (Lyondell Chemical Company 2006). The transient acute CNS symptoms that were observed in the animals at concentrations of 400 and 1600 ml/m³ were clearly caused by the substance, and, at 400 ml/m³, reached the maximum incidence after 4 to 5 weeks. The NOAEC was 100 ml/m³ because only a few animals were affected at this concentration and also a number of females in the control group were found to have these symptoms during the exposure. A concentration of 35 ml/m³ is calculated on the basis of this NOAEC taking the following factors into consideration: exposure of the animals on 7 days a week (7:5), the extrapolation from animal studies to humans (1:2) and the increased respiratory rate of humans at the workplace compared with test animals at rest (1:2). The MAK value has been lowered to 20 ml/m³ in line with the preferred value approach. As none of the studies observed an intensification of the effects over the course of the exposure period, this does not have to be taken into account.

The MAK value of 20 ml/m³ also provides protection from irritation caused by *tert*-butyl acetate because irritation is not expected to occur up to a concentration of 100 ml/m³ (see supplement "*tert*-Butyl acetate" 2014).

Peak limitation. The MAK value for *tert*-butyl acetate was derived on the basis of systemic effects; therefore, the substance remains in Peak Limitation Category II. The clinical effects in mice were caused by the parent substance; it has a half-life of 45 minutes in rats (Groth and Freundt 1994). These effects were acute; however, as adaptation was observed also during subchronic exposure, the effects would not be intensified by the peak exposure concentrations during chronic exposure. In addition, as the incidence of these effects was low at the LOAEC, the actual NAEC (no

adverse effect concentration) may be higher than 100 ml/m³. Therefore, the excursion factor of 2 has been retained in spite of the short half-life.

Irritation is not expected to occur at the permitted concentration of 40 ml/m³ (see above).

Prenatal toxicity. Classification in Pregnancy Risk Group C has been confirmed as the MAK value has been lowered to 20 ml/m³ and there are no new data regarding developmental toxicity. Taking into account the increased respiratory volume (1:2) the 40-fold margin between the MAK value and the NOAEC of 1600 ml/m³ in a screening study in Sprague Dawley rats is sufficiently large, considering also the data for *tert*-butyl alcohol (see supplement "*tert*-Butyl acetate" 2014).

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