The MAK Collection for Occupational Health and Safety

Ethylbenzene

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

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The commission established rules and measures to avoid conflicts of interest.

Ethylbenzene

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 of ethylbenzene [100-41-4].

Critical effect is the liver toxicity, which is observed as centrilobular hypertrophy and liver weight increase resulting from the induction of enzymes and proliferation of hepatocytes, in long-term studies with rats and mice. In an oral 13-week study a NOAEL of 75 mg/kg bodyweight and day for rats and a NOAEC of 75 ml/m³ for liver cell proliferation in mice were established. Based on this data, a MAK value of 20 ml/m³ had been set. This value is now reaffirmed even considering the increased respiratory volume at the workplace for the cell proliferation study (see List of MAK and BAT Values, Sections I b and I c). Since a systemic effect is critical, Peak Limitation Category II is retained and since it is not clear whether the effects are due to the metabolites or ethylbenzene the default factor of 2 is confirmed.

The NOAEC for developmental toxicity in rats is 500 ml/m³ and after considering the increased respiratory volume at the workplace the difference to the MAK value is sufficient. Therefore, damage to the embryo or foetus is unlikely when the MAK value is observed and ethylbenzene remains in Pregnancy Risk Group C.

Keywords

ethylbenzene; peak limitation; prenatal toxicity; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance

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Ethylbenzene

[100-41-4]

Supplement 2018

MAK value (2011)	**20 ml/m³ (ppm) ≙ 88 mg/m³**
Peak limitation (2011)	**Category II, excursion factor 2**
Absorption through the skin (1985)	**H**
Sensitization	**–**
Carcinogenicity (2011)	**Category 4**
Prenatal toxicity (2011)	**Pregnancy Risk Group C**
Germ cell mutagenicity	**–**
BAT value (2015)	**250 mg mandelic acid plus phenyl glyoxylic acid/g creatinine**
1 ml/m³ (ppm) ≙ 4.41 mg/m³	**1 mg/m³ ≙ 0.227 ml/m³ (ppm)**

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 of < 5 (see List of MAK and BAT Values, Sections I b and I c). The blood:air partition coefficient of ethylbenzene is > 5 (Sato and Nakajima 1979). This supplement evaluates whether the MAK value and the pregnancy risk group for ethylbenzene need to be re-assessed as a result of the higher respiratory volume at the workplace.

Manifesto (MAK value/classification)

Liver cell proliferation is the critical effect.

MAK value and peak limitation. A MAK value of 20 ml/m³ was derived in 2011 from the data reported in two studies, one of which was a 5-day inhalation study in mice, the other an oral 13-week study in rats that focused on liver weight increases

and centrilobular hypertrophy resulting from enzyme induction and liver cell proliferation (supplement "Ethylbenzene" 2012).

The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL (no observed adverse effect level) of 75 mg/kg body weight and day obtained from the 13-week study with gavage administration in rats to a concentration in air: the species-specific correction value for the rat of 1:4, the assumed oral absorption of 100%, the body weight of the person of 70 kg, the respiratory volume of 10 m^3 and the measured absorption by inhalation of 64%. The workplace concentration calculated from this is 205 mg/m^3 or 45 ml/m^3. A lower NOAEL is not to be expected even after long-term exposure because the 28-day NOAEL was also 75 mg/kg body weight and day. After extrapolating the data from the animal study (1:2), the preferred value approach was applied to derive a MAK value of 20 ml/m^3 (supplement "Ethylbenzene" 2012).

Based on the NOAEC (no observed adverse effect concentration) of 75 ml/m^3 for liver cell proliferation that was obtained from the 5-day inhalation study in mice, a concentration of 18.5 ml/m^3 was determined after extrapolating the data of the animal study (1:2) and taking the increased respiratory volume (1:2) into consideration. As no increase in cell proliferation was observed at 750 ml/m^3 in a comparison of the 5-day and 28-day studies, an intensification of the effect over time is not to be expected. Therefore, the MAK value of 20 ml/m^3 can be retained even after taking the increased respiratory volume at the workplace compared with that in the animal study into consideration.

Ethylbenzene also remains classified in Peak Limitation Category II with an excursion factor of 2.

Prenatal toxicity. Investigations of the effects on prenatal development in rats did not reveal increased incidence of malformations. A reduction in body weight gains in the dams was accompanied by reduced foetal weights at ethylbenzene concentrations of 1000 ml/m^3 and above (Saillenfait et al. 2003). The NOAEC for the toxic effects of ethylbenzene on prenatal development was 500 ml/m^3. Postnatal investigations of the F1 offspring in a 2-generation study (Faber et al. 2006) and postnatal investigations of behavioural neurotoxicity in the F2 generation (Faber et al. 2007) did not reveal any relevant effects on the offspring up to the high concentration of 500 ml/m^3. Taking into consideration the increased respiratory volume of the person at the workplace in comparison with that of the laboratory animal at rest (1:2), this value is still 13 times higher than the MAK value. As ethylbenzene does not cause developmental toxicity, the 13-fold difference between the NOAEC for developmental toxicity and the MAK value of 20 ml/m^3 is sufficient. For this reason, ethylbenzene remains in Pregnancy Risk Group C.

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