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Toluene – Addendum: evaluation of a pregnancy risk group for the BAT values

Assessment Values in Biological Material – Translation of the German version from 2021

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Abstract

In 2020, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area evaluated toluene [108-88-3] regarding reproductive and developmental toxicity. Provided the maximum workplace concentration (MAK value) of 50 ml toluene/m^3 is observed, prenatal toxic effects are not to be expected. Toluene was therefore classified in Pregnancy Risk Group C in 1993, which was confirmed in 2020. The biological tolerance values (BAT values) of 600 µg toluene/l blood, 75 µg toluene/l urine and 1.5 mg o-cresol/l urine were based on the correlation to toluene uptake by inhalation at the MAK value. Therefore, Pregnancy Risk Group C is also valid for BAT values. If the BAT values for toluene are not exceeded, no prenatal toxic effects are to be expected.

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BAT value (2017)	**75 µg toluene/l urine** Sampling time: end of exposure or end of shift
BAT value (2009)	**600 µg toluene/l blood** Sampling time: immediately after the exposure
	1.5 mg o-cresol (after hydrolysis)/l urine Sampling time: end of exposure or end of shift; for long-term exposures: at the end of the shift after several previous shifts
MAK value (1993)	**50 ml/m³ ≙ 190 mg/m³**
Peak limitation (2020)	Category II, excursion factor 2
Absorption through the skin (1998)	H
Carcinogenicity	–
Prenatal toxicity (1993, 2020)	Pregnancy Risk Group C

When deriving BAT values, since 2019 the adoption of the pregnancy risk group derived for the respective MAK value is explicitly checked (DFG 2019). In 2020, Pregnancy Risk Group C was confirmed for the MAK value of toluene (Hartwig and MAK Commission 2021). This addendum examines whether Pregnancy Risk Group C can be adopted for the BAT values of toluene.

Re-evaluation

Due to the lack of data, it was not possible to derive BAT values for toluene based on relationships between internal exposure and relevant effect parameters. Therefore, the evaluation was performed via correlations between external and internal exposure. As parameters, toluene in blood and urine and excretion of o-cresol in urine were used. The BAT values of 600 µg toluene/l blood and 1.5 mg o-cresol (after hydrolysis)/l urine were established in correlation to the MAK value of 50 ml toluene/m³ (190 mg/m³) (translated in Angerer 2019). In addition, a BAT value of 75 µg toluene/l urine was derived in correlation to the MAK value (translated in Jäger et al. 2019).

Prenatal toxicity

The available literature on the developmental toxic effects of toluene has been re-evaluated (Hartwig and MAK Commission 2021). In the unborn child, toluene produces symptoms similar to the foetal alcohol syndrome caused by ethanol when women inhaled large amounts (4000 to 12 000 ml/m³) of toluene or other organic solvents during pregnancy. Depending on the concentration, embryonic lethality or developmental delay, growth retardation of the foetuses, and retarded development of the skeletal system may occur. However, toluene does not cause teratogenicity up to concentrations of 3500 ml/m³. Reliable studies in the low-dose range in humans are not available.

Developmental toxicity

The most sensitive end point for developmental toxicity is perinatal body weight reduction (Hartwig and MAK Commission 2021; Thiel and Chahoud 1997). There are no significant differences in the metabolism of humans and laboratory animals. The effects on body weight on the first postnatal day (8% decrease each) were only slight in the rat at 1000 and 1200 ml toluene/m³, reversible after two weeks and occurred only with simultaneous maternal toxicity. The NOAEC (no observed adverse effect concentration) for prenatal developmental toxicity is 600 ml toluene/m³ and the LOAEC (lowest observed adverse effect concentration) is 1000 ml/m³ based on these slight and reversible effects. Taking

into account the increased respiratory volume (1:2), NOAEC and LOAEC correspond to 6 and 10 times the MAK value of 50 ml/m^3, respectively. Therefore, due to the slight and reversible effects on the body weights of the offspring, prenatal toxic effects are not to be expected for exposures to toluene at the level of the MAK value of 50 ml/m^3.

Developmental neurotoxicity

Since 2016, a statement on developmental neurotoxicity in the foetus has been required for substances with MAK values derived from neurotoxic effects. For the rat, the NOAECs are 1200 and 2000 ml toluene/m^3 in the developmental neurotoxicity studies, so that even taking into account the increased respiratory volume (1:2), the margins to the MAK value are sufficiently large (12 and 20 times, respectively).

All in all, the NOAEC for developmental toxicity is lower than that for developmental neurotoxicity. Since prenatal toxic effects are not to be expected for exposures at the level of the MAK value, toluene remains assigned to Pregnancy Risk Group C. Since the BAT values were derived in correlation to the MAK value, prenatal toxic effects are not to be expected if the BAT values of 600 µg toluene/l blood, 75 µg toluene/l urine and 1.5 mg o-cresol (after hydrolysis)/l urine are not exceeded.

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

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