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1,4-Dichlorobenzene – Addendum: evaluation of a pregnancy risk group for the BAT value

Assessment Values in Biological Material – Translation of the German version from 2022

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Keywords

1,4-dichlorobenzene; biological tolerance value; BAT value; developmental toxicity; prenatal toxicity

Abstract

In 2017, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the maximum workplace concentration (MAK value) of 1,4-dichlorobenzene [106-46-7]. If the MAK value of 2 ml 1,4-dichlorobenzene/m^3 (12 mg/m^3) is not exceeded, prenatal toxic effects are not to be expected. Therefore, 1,4-Dichlorobenzene was classified in Pregnancy Risk Group C. In 2019, the biological tolerance value (BAT value) of 10 mg 2,5-dichlorophenol/l urine was derived in correlation to the MAK value. Therefore, Pregnancy Risk Group C is also valid for the BAT value. Adhering to the BAT value of 10 mg 2,5-dichlorophenol/l urine, prenatal toxic effects are not to be expected.

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BAT value (2019) **10 mg 2,5-dichlorophenol (after hydrolysis)/l urine**

BAR (2019) **25 µg 2,5-dichlorophenol (after hydrolysis)/l urine**

EKA (2019)

Air 1,4-dichlorobenzene		Urine 2,5-dichlorophenol (after hydrolysis)
[ml/m³]	[mg/m³]	[mg/l]
2	12	10
5	30.5	20
10	61	30
20	122	60
30	183	90

Sampling time: end of exposure or end of shift; at the end of shift, for long-term exposures after several previous shifts

MAK value (2017)	**2 ml/m³ ≙ 12 mg/m³**
Peak limitation (2017)	Category II, excursion factor 2
Absorption through the skin (2001)	H
Carcinogenicity (2017)	Category 4
Prenatal toxicity (2017)	Pregnancy Risk Group C

In 2017, a maximum workplace concentration (MAK value) of 2 ml/m³ was derived for 1,4-dichlorobenzene, and the substance was classified in Pregnancy Risk Group C (translated in Hartwig and MAK Commission 2019). In 2019, a biological tolerance value (BAT value) of 10 mg 2,5-dichlorophenol (after hydrolysis)/l urine was derived in correlation to this MAK value (translated in Schmitz-Spanke et al. 2020). When deriving BAT values, since 2019 the adoption of the pregnancy risk group derived for the respective MAK value is explicitly checked (DFG 2019). This addendum evaluates whether Pregnancy Risk Group C can be adopted also for the BAT value of 1,4-dichlorobenzene.

Prenatal toxicity

The available literature on the developmental toxic effects of 1,4-dichlorobenzene has been re-evaluated (Hartwig and MAK Commission 2019). Reliable studies in humans are not available.

In animal experiments, no prenatal developmental toxicity occurred in the rat **after inhalation exposure** up to the highest concentration tested of 500 ml 1,4-dichlorobenzene/m³ (ICI 1977). In rabbits, the number of resorptions was increased at concentrations of 300 ml 1,4-dichlorobenzene/m³ and above. The NOAEC (no observed adverse effect concentration) for developmental toxicity in this species is 100 ml 1,4-dichlorobenzene/m³. Taking into account the increased respiratory volume (1:2), the margins between these NOAECs and the MAK value of 2 ml 1,4-dichlorobenzene/m³ are 125- and 25-fold for rats and rabbits, respectively.

In rats **given gavage doses** of 500 mg 1,4-dichlorobenzene/kg body weight and day and above, the foetal weights were reduced and the number of skeletal anomalies increased. The NOAEL (no observed adverse effect level) for developmental toxicity was 250 mg 1,4-dichlorobenzene/kg body weight and day (Giavini et al. 1986). The toxicokinetic extrapolation of this NOAEL to a concentration in workplace air results in a concentration of 703 mg 1,4-dichlorobenzene/m³ (115 ml/m³) and thus in a 58-fold margin between this and the MAK value of 2 ml 1,4-dichlorobenzene/m³. Since no

malformations occurred in rats and rabbits, the sufficiently large differences between the NOAEC or NOAEL for developmental toxicity and the MAK value of 2 ml/m^3 allow the assignment of the substance to Pregnancy Risk Group C.

In **2-generation studies** in rats, litter sizes were reduced **after inhalation** exposure at concentrations of 538 ml 1,4-dichlorobenzene/m^3 (CMA 1989; Greim 2003) and foetal weights at birth were decreased **after gavage doses** of 90 mg 1,4-dichlorobenzene/kg body weight and day (Bornatowicz et al. 1994). The NOAEC and NOAEL for perinatal toxicity are 211 ml 1,4-dichlorobenzene/m^3 and 30 mg 1,4 dichlorobenzene/kg body weight and day, respectively. Taking into account the increased respiratory volume and the 7 days' treatment of the animals in comparison with the 5 days per week exposure of humans at the workplace, this results in 74- and 10-fold margins to the MAK value, respectively. Since the relevant form of exposure at the workplace is inhalation, the 2-generation inhalation study is of greater significance. Overall, the NOAEC and the NOAEL for perinatal toxicity from the 2-generation studies support the assignment of the substance to Pregnancy Risk Group C (Hartwig and MAK Commission 2019).

Based on the available data, prenatal toxic effects are not to be expected for exposures at the level of the MAK value of 2 ml 1,4-dichlorobenzene/m^3 (12 mg/m^3). 1,4-Dichlorobenzene has therefore been assigned to Pregnancy Risk Group C. Since the BAT value of 1,4-dichlorobenzene was derived in correlation to the MAK value,

prenatal toxic effects are not to be expected,
if the BAT value of 10 mg 2,5-dichlorophenol (after hydrolysis)/l urine is not exceeded.

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

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