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Ethylbenzene – Addendum: evaluation of a pregnancy risk group for the BAT value

Assessment Values in Biological Material – Translation of the German version from 2023

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Abstract

In 2011, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area re-evaluated the maximum workplace concentration (MAK value) of ethylbenzene [100-41-4]. If the MAK value of 20 ml ethylbenzene/m^3 (88 mg/m^3) is observed, no prenatal toxic effects are to be expected. Therefore, ethylbenzene was classified in Pregnancy Risk Group C. In 2015, the biological tolerance value (BAT value) of 250 mg mandelic acid plus phenylglyoxylic acid/g creatinine was derived in correlation to the MAK value. Pregnancy Risk Group C is therefore similarly valid for the BAT value. In adherence with the BAT value of 250 mg mandelic acid plus phenylglyoxylic acid/g creatinine, no prenatal toxic effects are to be expected.

BAT value (2015)	**250 mg mandelic acid plus phenylglyoxylic acid/g creatinine** Sampling time: immediately after exposure
MAK value (2011)	**20 ml/m³ ≙ 88 mg/m³**
Peak limitation (2011)	Category II, excursion factor 2
Absorption through the skin (1985)	H
Carcinogenicity (2011)	Category 4
Prenatal toxicity (2011)	Pregnancy Risk Group C

In 2011, a maximum workplace concentration (MAK value) of 20 ml/m³ (88 mg/m³) as well as assignment to Pregnancy Risk Group C was established for ethylbenzene (Hartwig 2014). This was also confirmed taking into account the increased respiratory volume at the workplace (Hartwig and MAK Commission 2018). In 2015, in correlation to this MAK value, a biological tolerance value (BAT value) of 250 mg mandelic acid plus phenylglyoxylic acid/g creatinine was derived (Reuter et al. 2018). When setting BAT values, as of 2019, the adoption of the pregnancy risk group valid for the respective MAK value is explicitly verified (DFG 2019). This addendum evaluates whether Pregnancy Risk Group C can similarly be adopted for the BAT value of ethylbenzene.

Prenatal toxicity

The available literature on the prenatal toxic effects has been re-evaluated (Hartwig 2014). Reliable human studies are not available.

Developmental toxicity

The MAK Documentation from 2001 describes a number of older studies from the 1980s which investigated the prenatal developmental toxicity of ethylbenzene in mice, rats, and rabbits (Hartwig and MAK Commission 2016). Newer valid studies have investigated the prenatal developmental toxicity of ethylbenzene alone (Saillenfait et al. 2003) or in combination with o-, m-, and p-xylene as well as technical xylene (Saillenfait et al. 2003), methyl ethyl ketone (Saillenfait et al. 2006), or n-butyl acetate (Saillenfait et al. 2007). In Sprague-Dawley **rats**, **inhalation exposure** to 1000 ml/m³ for 6 hours per day from day 6 to day 20 of gestation led to reduced maternal food consumption and weight gain as well as reduced foetal weights and to an increased proportion of foetuses with skeletal variations. There was no increase in malformations (Saillenfait et al. 2003, 2006, 2007). An NOAEC (no observed adverse effect concentration) for prenatal developmental toxicity of 500 ml/m³ can be derived.

Developmental neurotoxicity

When investigating the **developmental neurotoxicity** of the F2 offspring of the **two-generation study** in rats of Faber et al. (2006), a "functional observational battery", a test of motor activity, acoustic startle testing, a learning and memory test using a Biel-water maze, as well as morphometric and histological investigations of the brain and nervous system yielded no exposure-related changes up to the highest concentration of 500 ml ethylbenzene/m³ (Faber et al. 2007).

Evaluation of a pregnancy risk group for the BAT value

Animal studies showed no increased incidence of malformations in investigations of **prenatal developmental toxicity** in **rats** following inhalation exposure. Starting at a concentration of 1000 ml ethylbenzene/m^3, foetal weight was reduced in cases of reduced maternal weight gain and an increased proportion of foetuses with skeletal variations were observed (Saillenfait et al. 2003). An **NOAEC** for prenatal developmental toxicity of 500 ml ethylbenzene/m^3 was derived.

Investigations of the F1 offspring in a two-generation study (Faber et al. 2006) as well as investigations of **behavioural neurotoxicity** in the F2 generation (Faber et al. 2007) yielded no relevant effects on the offspring up to the highest tested concentration of 500 ml/m^3.

Taking into account the increased respiratory volume of humans at the workplace compared with experimental animals at rest (1:2), the **NOAEC** for developmental toxicity is 250 ml/m^3 and its margin to the MAK value is 13-fold.

Since ethylbenzene does not trigger any specific developmental toxic effects, the 13-fold margin between the NOAEC for developmental toxicity and the MAK value of 20 ml/m^3 is sufficient. Based on the available data, prenatal toxic effects are not to be expected for exposure at the level of the MAK value of 20 ml ethylbenzene/m^3 (≙ 88 mg/m^3). Ethylbenzene has therefore been assigned to Pregnancy Risk Group C. Since the BAT value was derived in correlation to the MAK value,

prenatal toxic effects are not to be expected,
if the BAT value of 250 mg mandelic acid plus phenylglyoxylic acid/g creatinine 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.

References

DFG (Deutsche Forschungsgemeinschaft), editor (2019) List of MAK and BAT Values 2019. Maximum Concentrations and Biological Tolerance Values at the Workplace. Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, report 55. Weinheim: Wiley-VCH. https://doi.org/10.1002/9783527826889

Faber WD, Roberts LSG, Stump DG, Tardif R, Krishnan K, Tort M, Dimond S, Dutton D, Moran E, Lawrence W (2006) Two generation reproduction study of ethylbenzene by inhalation in Crl-CD rats. Birth Defects Res B Dev Reprod Toxicol 77(1): 10–21. https://doi.org/10.1002/bdrb.20063

Faber WD, Roberts LSG, Stump DG, Beck M, Kirkpatrick D, Regan KS, Tort M, Moran E, Banton M (2007) Inhalation developmental neurotoxicity study of ethylbenzene in Crl-CD rats. Birth Defects Res B Dev Reprod Toxicol 80(1): 34–48. https://doi.org/10.1002/bdrb.20101

Hartwig A, editor (2014) Ethylbenzene. MAK Value Documentation, 2012. In: The MAK-Collection for Occupational Health and Safety. Part I: MAK Value Documentations. Weinheim: Wiley-VCH. https://doi.org/10.1002/3527600418.mb10041e5214

Hartwig A, MAK Commission (2016) Ethylbenzene. MAK Value Documentation, 2001. MAK Collect Occup Health Saf. https://doi.org/10.1002/3527600418.mb10041e3316

Hartwig A, MAK Commission (2018) Ethylbenzene. MAK Value Documentation, 2018. MAK Collect Occup Health Saf 3(4): 1889–1892. https://doi.org/10.1002/3527600418.mb10041e6418

Reuter U, Göen T, Drexler H, Hartwig A, MAK Commission (2018) Addendum to ethylbenzene. BAT Value Documentation, 2016. MAK Collect Occup Health Saf 3(3): 1528–1532. https://doi.org/10.1002/3527600418.bb10041e2218

Saillenfait A-M, Gallissot F, Morel G, Bonnet P (2003) Developmental toxicities of ethylbenzene, ortho-, meta-, para-xylene and technical xylene in rats following inhalation exposure. Food Chem Toxicol 41(3): 415–429. https://doi.org/10.1016/s0278-6915(02)00231-4

Saillenfait A-M, Gallissot F, Sabaté J-P, Bourges-Abella N, Cadot R, Morel G, Lambert AM (2006) Developmental toxicity of combined ethylbenzene and methylethylketone administered by inhalation to rats. Food Chem Toxicol 44(8): 1287–1298. https://doi.org/10.1016/j.fct.2006.02.006

Saillenfait A-M, Gallissot F, Sabaté J-P, Bourges-Abella N, Muller S (2007) Developmental toxic effects of ethylbenzene or toluene alone and in combination with butyl acetate in rats after inhalation exposure. J Appl Toxicol 27(1): 32–42. https://doi.org/10.1002/jat.1181